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REVIEW

Surveillance for gastrointestinal malignancies

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Abstract

Gastrointestinal (GI) malignancies are notorious for frequently progressing to advanced stages even in the absence of serious symptoms, thus leading to delayed diagnoses and dismal prognoses. Secondary prevention of GI malignancies through early detection and treatment of cancer-precursor/premalignant lesions, therefore, is recognized as an effective cancer prevention strategy. In order to efficiently detect these lesions, systemic application of screening tests (surveillance) is needed. However, most of the currently used non-invasive screening tests for GI malignancies (for example, serum markers such as alpha-fetoprotein for hepatocellular carcinoma, and fecal occult blood test, for colon cancer) are only modestly effective necessitating the use of highly invasive endoscopy-based procedures, such as esophagogastroduodenoscopy and colonoscopy for screening purposes. Even for hepatocellular carcinoma where non-invasive imaging (ultrasonography) has become a standard screening tool, the need for repeated liver biopsies of suspicious liver nodules for histopathological confirmation can't be avoided. The invasive nature and high-cost associated with these screening tools hinders implementation of GI cancer screening programs. Moreover, only a small fraction of general population is truly predisposed to developing GI malignancies, and indeed needs surveillance. To spare the average-risk individuals from superfluous invasive procedures and achieve an economically viable model of cancer prevention, it's important to identify cohorts in general population that are at substantially high risk of developing GI malignancies (risk-stratification), and select suitable screening tests for surveillance in these cohorts. We herein provide a brief overview of such high-risk cohorts for different GI malignancies, and the screening strategies that have commonly been employed for surveillance purpose in them.

Key words: Gastrointestinal malignancies; Surveillance; Screening; Biomarkers; Cancer prevention

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INTRODUCTION

Malignancies originating in the gastrointestinal (GI) tract are responsible for about one third of global cancer burden[1]. In the United States, of estimated 1 529 560 new cancer cases and 569 490 cancer deaths in 2010, approximately 274 330 new cases (approximately 18% of total) and 139 580 deaths (approximately 25% of total) could be attributed to GI malignancies[2]. One of the reasons behind relatively high mortality rate for GI cancers is their visceral location, which requires highly invasive endoscopy to directly visualize early-stage lesions, leading to diagnoses at advanced incurable stages in most cases.

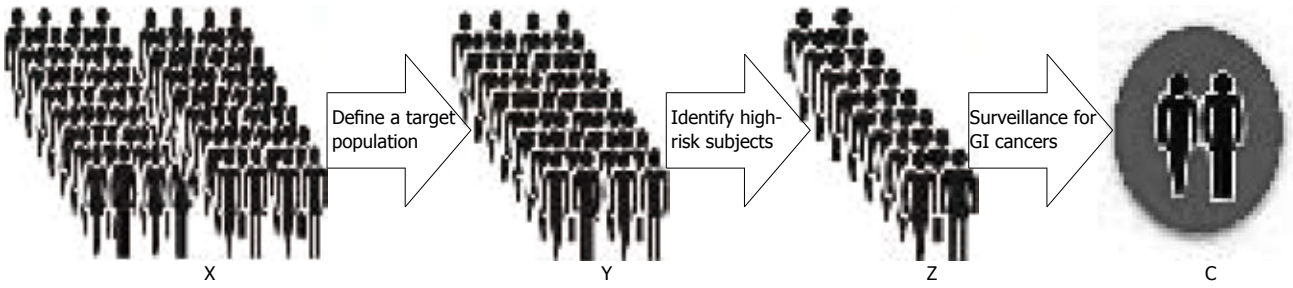

Figure 1 Risk stratification is a step-wise approach towards identifying high-risk individuals where surveillance for gastrointestinal cancers is truly needed in order to detect any neoplastic growth at early stages. The initial step is to define a target population (Y) in the general population (X) where screening strategies would be applied. Based upon findings of the screening tests in target population, subjects deemed to be at high-risk for developing a gastrointestinal (GI) malignancy (Z) would need repeated screening tests at suitable intervals (surveillance), and this would result in detection of potentially curable early stage cancerous lesions in certain individuals (C).

Secondary prevention through systemic application of screening tests (surveillance) to detect cancer-precursor/premalignant lesions is regarded an effective prevention strategy, and arguably also promotes positive life-style changes[3]. However, only a small proportion of total population is indeed at a credible risk of developing GI malignancy in future and needs surveillance. Identifying these high-risk cohorts (risk-stratification) is therefore crucial for the success of any surveillance program[4] (Figure 1). Such an approach is not only mandatory from an economic perspective but also spares the general population of repeated invasive screening tests to detect cancer precursor lesions. Screening tests detect the end-point of increased genetic/environmental predisposition (that is precursor lesions), and therefore constitute the most important arm of any risk-stratification strategy.

CANCER BIOMARKERS, SURROGATE MARKERS, LEAD-TIME BIAS AND OVERDIAGNOSIS BIAS

Biomarker is a variable that directly relates to cancer progression and/or final biological outcome (such as death), and is measured by a screening test[5]. The ease of procuring the material for biomarker analysis is an important question for visceral organs such as those in GI tract. Intraepithelial neoplasia or dysplasia remains the most reliable marker of impending malignancy, but is associated with a number of inherent limitations, including the need for invasive procedures to obtain tissue and inter-pathologist variability in interpretation of histopathological features[6]. Moreover, although endoscopic techniques have evolved over the years[7], their regular use for risk-stratification in average risk populations is economically unviable at this point. Surrogate markers, which variably correlate with cancer progression, can usually be measured through non-invasive means such as in serum or stool and therefore represent attractive tools for screening, but have limitations such as poor sensitivity and/or specificity[8]. It should be noted that surveillance programs are recommended only if an effective treatment is known to exist should any precursor/premalignant lesion be detected upon screening. This is important in order to avoid the possibility of lead-time bias (early diagnosis of cancerous lesions leading to increased number of years patient survives without actual shift in age at death) and overdiagnosis bias (diagnosis of cancerous lesions that won't have progressed, meaning they won't have caused death in first place)[9].

ESOPHAGEAL CANCER

In the United States, more than four fifth of patients diagnosed with esophageal cancer in 2010 are estimated to have a cancer death[2]. Esophageal adenocarcinoma (EA) and squamous cell carcinoma (ESCC) together account for more than 95% of esophageal cancer cases: ESCC being responsible for the bulk of cases worldwide and EA being more common in western countries, particularly among Caucasian males[10]. Due to such stark differences in the epidemiology of ESCC and EA, there is greater emphasis on risk-stratification for ESCC in developing countries, as compared to EA and its precursor lesion, Barrett's esophagus (BE), in developed countries. However, with increasing westernization of developing countries, the incidence of EA is surely on the rise in these countries too.

EA

Nearly all the cases of EA evolve through BE→Dysplasia→EA sequence[11]; and therefore, BE subjects represent a high-risk cohort where surveillance could be considered depending upon mucosal changes detected on endoscopic biopsy (reviewed in detail in reference[12]). The challenging part, however, is to identify individuals who could have BE in first place. Long-standing gastroesophageal reflux disease (GERD) patients are clearly at-risk for developing BE, but a significant proportion of BE cases can exist and progress to EA even without GERD symptoms. Furthermore, high prevalence of GERD symptoms in general populations (> 20% of adult population[13]) and extremely low rate of progression from GERD to BE to EA (approximately 0.5% and 1.0% per year respectively[14,15]) means that endoscopic screening for BE in all GERD patients would not be cost-effective[16]. However, certain subsets of GERD patients can clearly benefit from screening for BE on

an individual basis; for example, first-degree relatives of BE patients are more likely to harbor BE in presence of GERD symptoms as compared to other GERD patients with no such family history[17,18]. This increased risk could be related to genetic polymorphism of cyclin D1 and glutathione S-transferase genes which have been implicated in development of BE[19-21]. However, it's important to emphasize that there is no evidence of clear benefit of screening in asymptomatic persons (no GERD symptoms) with a positive family history of BE/EA. Overall, screening recommendations for BE remain controversial, and > 95% of EA cases are still diagnosed in patients without any prior diagnosis of BE[22]. The risk of EA (as well as ESCC) is also increased in hereditary conditions such as Peutz-Jeghers syndrome (PJS), but endoscopic surveillance in such cases is recommended for the whole upper GI tract and is not esophagus-specific.

A recent single cohort study demonstrated promising results of non-endoscopic screening for BE using an ingestible esophageal sampling device (Cytosponge) coupled with immunocytochemistry for trefoil factor 3[23]. However, non-endoscopic screening is still tested only on a limited scale, and serum markers have not been shown to be effective for screening for BE/EA as yet. Therefore, standard endoscopy with biopsy remains the "gold" standard for detecting BE. However, apart from the need of invasive endoscopy, low positive predictive value (about 34%) associated with index endoscopy[24] and need for multiple biopsies (at least 8 biopsies[25]) to diagnose metaplasia needed to define BE have been major drawbacks of endoscopy based screening. Recent advancements in endoscopic GI mucosa imaging (reviewed in reference[26]) have largely improved lesion detection capabilities, and enabled targeted biopsy of the dysplastic areas. Current recommendations for the need and frequency for EA surveillance in BE patients are largely based upon the degree of dysplasia in the BE mucosa (reviewed in detail by Badreddine *et al*[12]). In summary, after screening endoscopy in suspected BE patients (such as GERD patients over 50), detection of no dysplasia leads to repeat confirmatory endoscopy after 6-12 mo followed by endoscopic surveillance every 3 years; detection of low grade dysplasia leads to repeat confirmatory endoscopy in 6 mo followed by yearly endoscopic surveillance; and detection of high grade dysplasia needs confirmation by two expert pathologists and either 3 monthly surveillance combined with multiple biopsies spaced at every 1 cm *vs* endoscopic ablation *vs* esophageal resection.

ESCC

Currently, surveillance for ESCC is mandated only in two conditions-Tylosis palmaris (an obscure skin condition often associated with internal malignancies) and Lye ingestion[27]. However, co-existence of multiple ESCC risk factors could prompt surveillance in certain circumstances. For example, alcohol, smoking, flushing response to alcohol, Asian ethnicity, inactivating aldehyde dehydrogenase 2 allele polymorphism and personal history of any other malignancy of aerodigestive tract (UADT-which includes oral cavity, larynx, pharynx and esophagus) are all independent risk factors for ESCC[28-31]; and although none of them warrants surveillance for ESCC on its own, it would be worthwhile to consider screening for precursor lesions in persons with multiple risk factors, especially in case of Asian ethnicity, on an individualized basis. Some other conditions such as achalasia and Plummer-Vinson syndrome that are known to increase the risk of ESCC warrant endoscopic interventions for symptomatic treatment (such as for dysphagia) but not for screening[32]. Most of the reports on the impact of screening on ESCC incidence and mortality, and associated cost-effectiveness analyses have come from geographically high-risk countries. In two such studies conducted in China, investigators concluded that screening general population with exfoliative balloon cytology (EBC) was an effective tool for risk stratification and could have favorable impact on ESCC incidence and mortality[33,34]. However, United States-based Veterans' Affairs (VA) studies conducted in relatively high-risk population due to personal history and (or) symptoms produced conflicting results; and it was concluded that because of the low prevalence of ESCC in the United States and the difficulty of diagnosing malignancy in the setting of active esophagitis, EBC was probably not a cost-effective screening strategy in Western world[35]. Therefore, internationally, endoscopy aided biopsy therefore remains the standard test for ESCC screening and surveillance currently, albeit only in a limited cohort of subjects at high-risk for ESCC.

GASTRIC CANCER

Gastric cancer (GC) is the second leading cause of cancer deaths worldwide, and remains a major public health burden in Asia-pacific countries such as China, Japan and Korea where the age-standardized incidence rate for GC is > 20 per 100 000 subjects (defining criterion for high-risk areas)[1]. Gastric adenocarcinoma is the most common gastric malignancy (> 90% cases), with two subtypes: Intestinal (more common form and prevalent in high-risk areas) and diffuse type. Due to stark geographical differences in the prevalence of gastric cancer worldwide, the strategies and significance attached with screening for this cancer are highly variable.

The individuals migrating from high-risk areas remain at-risk even in low-risk countries such as the United States; however, their offspring tend to have risk levels comparable to that of the local population[36]. Geographical origin and location is therefore an extremely important consideration for any surveillance strategy against GC. Universal screening for GC has been considered only in certain high-risk countries such as Japan, South Korea and Matsu Island in Taiwan (China)[37]. On the other hand in average/low-risk countries, screening is recommended only in the presence of a well-characterized familial predisposition to GC (responsible for 1%-3% of GC cases), such as in case of hereditary

diffuse gastric cancer (HDGC) syndrome, familial adenomatous polyposis (FAP), PJS and Lynch syndrome. HDGC is the most common inherited form arising due to germline mutation in *E-cadherin* gene (*CDH1*) with the carrier of the mutations having more than 80% lifetime risk of developing GC[38]. However, surveillance or genetic testing is not considered for poorly-characterized familial cases (responsible for 8%-10% of GC cases) which are believed to be associated with more common but less penetrant defects such as polymorphism in pro-inflammatory interleukin-1 (*IL-1*) gene clusters and toll-like receptors 4 (TLR 4) + 896A > G[37,39,40]. Additionally, TLR 4 + 896A > G polymorphisms in TLR 4, a pattern recognition receptor that activates pro-inflammatory signaling pathways in response to microbes, has been associated with presence of GC and its precursors which indicates the relevance of TLR 4 polymorphism during gastric carcinogenesis[41]. A meta analysis of the role of IL-1b and IL-1 receptor antagonist gene polymorphisms in gastric cancer risk showed an association in Caucasians, but not in Asians[40]. Similarly, a metaanalysis by Huang *et al*[42] concluded that *cag A* seropositivity significantly increased the risk for gastric cancer and could be used for identifying populations at risk for GC. However, despite high prevalence of *cagA* in Asia-Pacific regions, the currently known *cagA* genotypes in Asia are not associated with increased GC risk[43]. Other high-risk subgroups considered for screening on a case-to-case basis are elderly patients with atrophic gastritis or pernicious anemia, patients with partial gastrectomy, patients with the diagnosis of sporadic adenomas, and immigrant ethnic populations from GC high-risk countries.

Over ninety percent of GC cases are sporadic, and most are linked to *Helicobacter pylori* (*H. pylori*) infection[44,45]. A meta-analysis of six major studies on *H. pylori* eradication demonstrated that *H. pylori* "screen-and-treat" strategy reduced the incidence of GC[46]. Based on this, the Asia-Pacific Gastric Cancer Consensus Conference in 2008 concluded that it might perhaps be the right time for a population-based screening and treatment of *H. pylori* infection (by using locally approved screening tests for *H. pylori,* such as serum or stool antibody/antigen detection), particularly in high-risk areas as a part of GC prevention program[37]. Interestingly, Ford *et al*[47] have proposed that even in western countries where better sanitation, low-salt intake and effective treatment of *H. pylori* infection has led to gradual decline in GC incidence over decades, a "screen and treat" strategy for *H. pylori* could reduce the dyspepsia-related health care costs over a longer (10 years or more) follow-up duration. However, prospective trials on a global scale are needed to validate such observations; and currently, no screening for *H. pylori* is recommended for asymptomatic individuals in geographically low/average-risk areas. Gastric cancer phenotype initiated due to *H. pylori* is characterized structurally by a corpus predominant gastritis, multifocal gastric atrophy, intestinal metaplasia, and physiologically by high gastrin, low acid secretion, low pepsinogen I and pepsinogen I / Ⅱ ratio, and hypo-and achlorhydria[48-50]. All these findings have been used to design screening tests for GC, such as serum pepsinogen I levels and pepsinogen I / Ⅱ ratios that have been investigated in high-risk areas, but have limited usefulness on a global scale[51]. Currently, endoscopy aided with advanced imaging techniques and biopsy (at least 5) to look for precursor lesions remains the main tools for screening and surveillance for GC.

PANCREATIC CANCER

Pancreatic cancer (PC) is the most aggressive GI malignancy that silently progresses to untreatable metastatic disease in most cases, and is generally fatal within six mo of diagnosis[2]. However, interestingly, a study from Japan has demonstrated that resection of all pancreatic lesions < 1 cm in size can achieve about 100% cure rates[52], suggesting that a thorough surveillance program for PC could potentially be useful. However, this approach leads to unnecessary high-risk surgical resection of many benign lesions that won't have progressed to malignancy in first place. Therefore, identifying high-risk cohorts where such pancreatic lesions are more likely to be malignant is definitely a better-refined strategy for prevention. Such high-risk cohorts for PC (defined as having > 10-fold increased risk of PC as compared to the general population) include familial and/or syndromic cases (3%-16% of total cases) where screening is routinely recommended (Figure 1)[53-56]. However, screening strategy for individuals at 5- to 10-fold increased risk of pancreatic cancer (e.g., those with just one or two affected first-degree relatives) is unclear. Clearly, in such cases, most centers take individualized approaches depending upon the cost and other considerations. Future studies are needed to establish the risk threshold at which screening is likely to be most cost-effective.

Notably, conditions such as chronic pancreatitis, diabetes mellitus and smoking history have strong associations with PC, but none of them increases the risk to an extent that could warrant screening.

Screening for PC faces a unique challenge in terms of incidental radiological findings in the pancreas due to rampant use of computerised tomography (CT) scan in patient-care. Because many of these lesions are non-lethal, it's important to establish their malignancy potential in order to guide their management and avoid over-enthusiastic and sometimes unwarranted surgeries that could ensue otherwise[57]. The most common of these lesions are intraductal papillary mucinous neoplasms (IPMNs). IPMNs which involve the main duct have a 70% risk of containing a malignancy at the time of diagnosis and need to be resected[58], while those involving the branch ducts have 25% risk of containing malignancy and 15% risk of malignant transformation during follow-up, and they can be safely observed with continued surveillance[57,58]. Certain other features however necessitate immediate resection, such as diameter ⩾ 3 cm, a mural nodule appearance, main pancreatic duct dilation ⩾ 6 mm, progressively changing lesion characteristics,

or presence of symptoms[57,58]. In general, the approach is usually much more aggressive if such lesions are present in high-risk individuals[55].

Another variety of PC precursor lesions, although not detectable by routine imaging tests in a clinical setting, are pancreatic intra-epithelial neoplasia (PanIN)[59]. PanIN is a histological diagnosis where pro-cancerous genetic and epigenetic aberrations have been noticed. PanIN-3 lesions are essentially treated as PC and resected whereas PanIN-1 lesions have very small risk of malignancy, and can be safely followed-up[60]. The management of PanIN-2 lesions is controversial and recommendations depend upon co-existing conditions and cost-considerations.

Currently, endoscopic ultrasonography (EUS) is most efficient screening test for PC; it accurately identifies pancreatic cysts and IPMNs, and has the advantage of detecting structural changes somehow predictive of PanIN lesions[61]. Other screening modalities like CT and endoscopic retrograde cholangiopancreatography have fallen out of favor mainly due to low sensitivity and radiation exposure and high incidence of pancreatitis respectively. However, magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRCP), especially secretin-enhanced MRCP, is still an acceptable alternative to EUS[62]. In the absence of any clear guidelines for the frequency and starting age for screening for pancreatic cancer, recommendations are highly institutionalized based upon factors such K-ras mutations, family history *etc*.[63-66].

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, and is increasing in incidence in the United States[2]. In general, 5-year survival is less than 10% if diagnosed in symptomatic patients, but HCC diagnosis prior to appearance of symptoms offers the curative opportunities through resection of tumor[67]. Although extremely rare in asymptomatic populations, HCC is a dreaded long-term complication of most chronic liver diseases (CLD); and therefore, CLD patients constitute the obvious target population for risk-stratification. However, the level of HCC risk varies in different CLDs; and due to the generally protracted course of CLDs and high cost of repeated screening, cost-considerations are very important in formulating surveillance strategies in these patients. Among CLD patients, diagnosis of cirrhosis is a strong predictor of the risk of progression to HCC, and advent of cirrhosis often marks the starting point for surveillance recommendations in these patients. Chronic viral hepatitis (hepatitis B and C) is the most common etiology behind HCC. Hepatitis B and C carriers have an HCC incidence rate of 0.2%-0.6% per year, and 3%-11% per year respectively[68,69]. Hepatitis B can particularly be deceptive because HCC can occur even in non-cirrhotic hepatitis B virus (HBV) carriers, and the risk seems to be variable. Asian ethnicity, viral replication status, and seropositivity for hepatitis B surface antigen and anti-HBe antigen differentially influence the risk of development of HCC in HBV carriers, and therefore have an important impact on surveillance program (reviewed in references[70-73]). On the other hand, the risk of HCC in long-term hepatitis C carriers is independent of factors such as ethnicity and viral replication status[71,74], and largely depends upon the extent and severity of cirrhosis. Based upon this, the first European association for study of the liver conference on HCC recommended screening for HCC in chronic hepatitis C patients with at least stage 3 fibrosis (METAVIR)[75]. Another puzzling question is whether surveillance for HCC should continue in successfully treated chronic viral hepatitis patients? Evidence has been conflicting for hepatitis B carriers with mostly Western and some Asian studies suggesting a significant reduction in HCC risk after successful treatment[76-78], and a non-randomized, but match controlled Asian study following a large cohort for longer periods suggesting continued risk of HCC post treatment[79]. Thus, given the higher risk associated with Asian ethnicity, it seems prudent to continue HCC surveillance in Asian hepatitis B carriers with cirrhosis even after successful seroconversion. However, the same can't be said about non-cirrhotic western populations. In contrast, continued surveillance for HCC is recommended for hepatitis C infected population because even after successful treatment (i.e., sustained virological response), the risk of HCC in cirrhotic hepatitis C carriers remains sufficiently high to warrant surveillance[74]. Additionally, co-existing risk factors like old age, viral genotype, viral replication status, aflatoxin exposure, co-infection and other CLDs, diabetes and human immunodeficiency virus also need to be taken into account in deciding the surveillance protocol for HCC in viral hepatitis carriers. Additionally, there are some non-viral cirrhotic conditions as well where surveillance could be considered (Table 1).

For screening purposes, ultrasonography (USG) and serum alpha-fetoprotein levels are often used. Serial USG (at 6-12 mo interval[80,81]) has by far been superior to any other screening test for HCC (65%-80% sensitivity and 90% specificity), and can detect nodules of 1 cm size, which are essentially curable[82]. However, USG needs to be aided with biopsies to differentiate between benign cirrhotic and dysplastic/malignant nodules. Conversely, evidence suggests that serum alpha-fetoprotein measurement has no role in HCC screening (although it can still have some utility in HCC diagnosis and follow-up), and should be no longer used for screening purposes. Other serological markers such as alpha flucosidase, glypican-3 and desgamma carboxyprothombin have already been discredited[83].

COLORECTAL CANCER

Colorectal cancer (CRC) is the third most common cancer in both men and women[2]. Over the years, its incidence has constantly been decreasing, largely due to colonoscopic screening. As less than one third of CRC cases are as-

Table 1 At-risk cohorts for considering surveillance for gastrointestinal malignancies

Esophageal cancer
Barrett's esophagus
Tylosis palmaris
Lye ingestion
Head and Neck tumors patients with flushing response/inactive ALDH1 allele
Gastric cancer
Hereditary diffuse gastric cancer
Lynch syndrome
Peutz-Jeghers syndrome
Juvenile polyposis syndrome
Li-Fraumeni syndrome
Atrophic gastritis/pernicious anemia
Post-partial gastrectomy
Sporadic adenoma
18-60 yr old Inhabitants of high-risk areas
Pancreatic cancer
Hereditary pancreatitis
Peutz-Jeghers syndrome
Familial pancreatic cancer kindred (≥ 1 first-degree relative and ≥ 3 first, second or third degree relative with pancreatic cancer)
Familial atypical multiple mole melanoma
Familial breast-ovarian cancer
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)
Familial adenomatous polyposis (FAP)
Cystic fibrosis
Fanconi anemia
Ataxia telangiectasia
Incidentally discovered IPMN/PanIN lesions
Hepatocellular carcinoma
Hepatitis B carriers (Asians and Africans)
Hepatitis B cirrhosis
Family history of HCC (mainly Asians and Africans)
Treated hepatitis B cirrhosis (Asians)
Hepatitis C cirrhosis
Treated hepatitis C cirrhosis
Alcoholic cirrhosis
Genetic hemochromatosis
Alfa1-antitrypsin deficiency
Primary biliary cirrhosis
Colorectal cancer
Familial adenomatous polyposis
Attenuated FAP (AFAP)
Hereditary nonpolyposis colorectal cancer (Lynch syndrome)
Peutz-Jeghers syndrome
Juvenile polyposis syndrome
MUTYH-associated polyposis
Hyperplastic polyposis
Patients with long-standing IBD
Acromegaly patients
Positive findings on index colonoscopy (at 50 yr) such as three or more tubular adenomas, tubular adenoma > 10 mm, adenoma with villous histology, adenoma with high-grade dysplasia, after surgical removal of invasive cancer, incomplete removal of neoplastic lesion

IPMN: Intraductal papillary mucinous neoplasms; PanIN: Pancreatic intraepithelial neoplasia; HCC: Hepatocellular carcinoma; IBD: Inflammatory bowel disease; ALPH1: Aldehyclen dehydrogenase 1; MUTYH: Human MutY homolog.

sociated with any kind of familial predisposition and even lesser proportions (< 5%) belong to well-defined inherited syndromes (such as Lynch syndrome, FAP *etc*.[84]), screening colonoscopy at age 50 (also called index colonoscopy) is the main tool of CRC risk-stratification in general[85]. Presence of adenomas on index colonoscopy is a strong predictor of the risk of development of additional adenomas (30%-50% detection rate at follow up after clearance colonoscopy[86]) and CRC in future. However, most adenomas don't progress to cancer (the life-time cumulative incidence of CRC is 5.5%, and prevalence of colonic adenomas at age 60 is 30%-40%[87]), and therefore their size, numbers, morphology and histopathological characteristics are used to assess the relative risk of progression to cancer and the need of follow-up surveillance/treatment strategies.

In individuals with familial predisposition, the average life-time risk of CRC varies from 100% in FAP to 20% in persons with first and/or second degree relatives with CRC[88], due to difference in penetrance of the inherited genetic defects. It is estimated that only 5% of CRC cases are associated with highly penetrant inherited mutations with well-characterized clinical presentation such as FAP, Lynch syndrome *etc*. whereas rest belong to less penetrant but far more common genetic defects such a polymorphisms in CYP450 family, glutathione-S-transferase family, insulin-like growth factor binding protein-3, ornithine decarboxylase-1 and transforming growth factor-beta receptor 1 genes[84]. However, currently the genetic testing is recommended only if a well-characterized familial syndrome (e.g., Lynch syndrome, FAP) is suspected, because the epidemiological data of the relative-risk of CRC associated with gene polymorphisms is still limited.

Two other well-established high-risk cohorts where surveillance for CRC is recommended are patients with long standing inflammatory bowel disease (IBD) and acromegaly patients. Recent reports suggest that both ulcerative colitis and Crohns' disease patients are at comparable cumulative risk of CRC if the extent and duration of the disease are the same (in case of ulcerative colitis, risk of CRC stands at 1.6% at 10 years, 8.3% at 20 years and 18.4% at 30 years[89,90]). For IBD patients with colonic disease, screening is recommended after 10 years of disease history, and involves endoscopic evaluation of inflammatory changes in the mucosa combined with multiple biopsies to detect dysplasia[91]. Acromegaly patients, on the other hand, seem to have increased incidence as well as propensity for malignant transformation of adenomas, especially right-sided ones, as compared to the general population (odds ratio: 2.4 for adenoma, 7.4 for CRC[92]). This could possibly be attributed to the presence of elevated serum insulin growth factor-1 level (seen in > 90% of acromegaly patients), which has been shown to increase the risk of CRC in non-acromegalic population[93]. Additionally, colonoscopic screening starting at age 40 is recommended to detect precursor lesions in such patients.

From a screening test perspective, non-invasive screening tests such as stool tests (occult blood and DNA tests), imaging (CT, Barium enema) and sigmoidoscopy are only occasionally used, and a full-length colonoscopy despite its several limitations remains the most effective and preferred screening test for CRC (reviewed in details in reference[85]). Current guidelines recommend

screening colonoscopy in average risk individuals at age 50, a significant deviation from earlier practice of colonoscopic screening only in high-risk individuals[94]. The rationale for colonoscopic surveillance has always been based on the high detection rate of colorectal adenomas at follow up (30%-50%) after a complete clearance colonoscopy[86]. However, the main object of colonoscopic surveillance is the prevention of subsequent colorectal cancer rather than the detection and removal of adenomas, most of which will not become malignant. Adenomas with advanced pathology (> 1 cm, with villous elements or severe dysplasia) have a much higher malignant potential, and the main objective of screening is to ensure that such lesions are detected before they become invasive. Therefore, individuals with 1-2 small polyps < 1 cm size and no villous morphology at index colonoscopy are considered low-risk and need no modification in surveillance protocol. However, certain findings on index colonoscopy (as mentioned in the Table 1) indicate high-risk of CRC and necessitate enhanced surveillance.

FUTURE PERSPECTIVE

Currently, surveillance for GI malignancies is challenging because of the general lack of inexpensive screening tests and potent biomarkers that could efficiently identify high-risk cohorts. Recently, there has been a surge in interest in using a panel of biomarkers (gene expression signatures) for screening purposes, but their impact on cancer mortality remains to be tested in large-scale studies[95,96]. Another new class of biomarkers under investigation these days are miRNAs, a type of non-coding RNAs that are endogenous silencers of target genes[97,98]. Unfortunately, many biomarkers/screening tests with initial promise indeed fail to meet the Early Detection Research Network-outlined criteria for their validation[99], and therefore are not used clinically. From a futuristic perspective, we are standing at the crossroads of a major change in our approach towards cancer prevention. With completion of the human genome project, rapid advances in deep sequencing technology and better understanding of the genetic landscape of different tumors (including GI cancers), it is being expected that it would be possible to assess the cumulative predisposition to different cancers in every individual in a cost-effective manner, leading to a highly individualized treatment and preventive care (Personalized Medicine) in coming years[100].

SEARCH STRATEGY AND SELECTION CRITERIA

References for this review were identified through searches of PubMed with the following search terms: "Gastrointestinal malignancies", "risk stratification", "gastrointestinal cancer screening/surveillance", "cancer biomarker", and "cancer prevention" published before December 2011. Articles were also identified through searches of the authors' own files. The final reference list was generated on the basis of relevance to the broad scope of this review; and only articles published in English were reviewed, and considered for inclusion in the reference list based upon the further reading opportunity they offered.

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