General Aspects of Primary Cancer Prevention

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Keywords

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Abstract

Background: Cancer is the second leading cause of death worldwide next to cardiovascular diseases. Despite the advancement in screening, early diagnosis, and development in treatment technology in last several decades, cancer incidence overall, particularly that of gastrointestinal (GI) cancers, is far from being controlled, and is expected to increase worldwide. **Summary:** Although numerous preclinical and population-based clinical studies have already made important progress in restraining the overall cancer incidence and mortality, the full potential of preventive strategy is still far from being realized, and remains at an early stage. There are several major challenges regarding this issue, and one of the crucial challenges is to maintain the balance between risks and benefits. As a result of past investments, primary prevention nowadays include the integration of various activities such as lifestyle changes to reduce risk, screening to detect early lesions, vaccines and preventive therapies aimed to actively interrupt the carcinogenic pathway. Long-term aspirin

use seems to have the largest potential effect on the general population on cancer incidence and mortality overall, especially GI cancers. *Helicobacter pylori* eradication reduces the risk for gastric cancer and is advocated regardless of the symptoms and stage of disease. Metformin and statins are promising in cancer prevention in patients with type 2 diabetes. Vitamin D supplementation is promising in the prevention of colorectal adenoma recurrence. **Key Message:** However, additional studies are warranted to establish the potential of various agents and to identify more specific and highly targeted new agents for chemoprevention in digestive oncology.

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Introduction

Despite the advancement in screening, early diagnosis, and progress in treatment technology, cancer still remains the second leading cause of death worldwide, next to cardiovascular diseases (CVDs) [1]. According to the global burden of disease study, in 2015, there were 17.5 million cancer cases worldwide and over 8.8 million deaths due

to cancer [2]. Between 2005 and 2015, cancer incidence increased by 33% at the global level, while most of this increase can be explained by an aging population and population growth. Thus, in 2015, colorectal cancer (CRC) was among the 3 most common incident cancers in both sexes, while the leading causes of deaths from cancer were stomach and liver cancer in men and CRC in women [1]. According to current data from the National Cancer Institute for cancer statistics in the United States, gastrointestinal (GI) cancers are in the top 10 cancers in the world. Additionally, the top 3 causes of death from GI disease are CRC, followed by pancreatic and liver cancers [3, 4]. Thus, GI cancer incidence is far from being controlled, and is expected to increase worldwide, even in countries with the advanced health care systems [1]. Consequently, chemoprevention appears to be the frontline strategy in fighting against cancers already, and is ranked as a prime importance to reduce the global burden of cancer.

Key Problems in Chemoprevention

The term “chemoprevention” was first introduced by Sporn in 1976, and refers to the use of nontoxic chemical substances, of either natural or synthetic origin to delay, retard, or reverse the carcinogenesis process [5]. Since then, efforts have been made to search for potential chemopreventive agents. Thus, numerous preclinical and population-based clinical studies have already made important progress in restraining cancer incidence and mortality [6–11]. However, the full potential of chemopreventive strategy is still far from being realized, and remains at an early stage. There are several major challenges regarding this issue, and one of the crucial challenges is to maintain the balance between risks and benefits. Indeed, cancer preventive therapies have been primarily intended for use in healthy individuals who may never actually develop cancer. Furthermore, targeting high-risk individuals for specific therapies to prevent cancer is essential to achieve a favorable benefit-risk ratio, and to avoid associated adverse effects or ineffective treatments [10, 11]. On the other hand, the nature of cancer still remains very complex and not fully understood, while potential biomarkers of susceptibility to specific cancer are either lacking or are not available for routine use in everyday clinical practice. In addition, specific factors that predict response to treatments are still poorly understood. For these reasons, further studies with a large number of participants are required to evaluate the potential new agents. These trials warranted long follow-up period, since preventive effects often take a long time to become

visible, as early stages of the carcinogenesis are targeted. Therefore, the focus of digestive oncology is to determine the individual risk of developing disease, to help improve patient’s health, and to predict the future development of disease. Moreover, the new concept of personalized medicine has been adopted also in digestive oncology. This concept represents treat to target concept, tailoring medicine to patient preferences, with the potential to identify treatments with the optimal response and highest safety in order to ensure better patient care. From this perspective, we will discuss here some of the most important challenges in primary GI cancer prevention and chemoprevention as well. The most common chemopreventive agents and potential effective preventive treatments in GI oncology are shown in Table 1.

Results

Treatments with Preliminary Evidence of Cancer Prevention

Today primary prevention is the strategy that comprises several preventive measures, such as lifestyle changes to reduce risk, screening to detect early lesions and preventive therapies aimed to actively interrupt the carcinogenic pathway – chemoprevention [10].

Diet and Lifestyle

GI cancers include cancers of the esophagus, stomach, intestine, colorectum, liver, and pancreas. A vast majority of the GI cancers have etiologic link with dietary and lifestyle factors, commonly named “Western lifestyle,” of which point is critical basis for prevention. Thus, in the last 30 years, many studies have shown that GI cancers, particularly CRC can be prevented by changing dietary habit and lifestyle [12–19]. Regarding lifestyle factors, there is convincing evidence, that abstinence from alcohol and smoking, physical activity and prevention of obesity can each have a positive effect on GI cancer prevention. A large cohort study of 43,479 participants showed that reasonable physical activity, specifically aerobic exercise of any intensity, is a common protective factor for GI cancers [18]. Many studies confirmed the presence of a protective effect of aerobic exercise to digestive tract cancers, in particular, for CRC [20–23]. Moreover, the association between CRC and high consumption of red meat, processed food, high fat dairy products, refined sugars and starches, is well known and has been shown in several studies [13–17]. Although many studies have provided some protective effect of

Table 1. Agents for treatment of precancerous lesions or cancer risk reduction

Study	Treatment offered/cancer site	Number of cases/controls		Design	Main results
<i>Aspirin and celecoxib trials</i>					
Flossmann and Rothwell [37], Lancet, 2007	Aspirin 300–1,200 mg/CRC	5,061	2,527	Meta analyses BDAT; UK-TIA	Aspirin use for 5 years is effective in primary prevention
Rothwell et al. [48], Lancet, 2010	Aspirin 75–1,200 mg/CRC	8,282	5,751	Meta analyses BDAT; UK-TIA; SALT; TPT	Aspirin reduced long-term incidence and mortality
Rothwell et al. [54], Lancet, 2011	Aspirin/all cancers	14,035	11,535	Meta analyses BDAT; TPT; UK-TIA; ETDRS;SAPAT; JPAD; POPADAD; AAA	Aspirin reduced deaths due to esophagealadenoCa, pancreatic, CRC, brain, lung adenoCa, stomach and prostate cancers. Benefits increased with the duration of treatment
Cao et al. [55], JAMA Oncol, 2015	Aspirin/all cancers	135,965		Two prospective cohort studies: Nurses Health Study; Health Professionals Follow-up Study	Aspirin modestly reduced the incidence of overall cancer, especially for GI cancers
Ye et al. [56], PLoS One, 2013	Aspirin/gastric cancer	6,868		Meta analyses; 15 studies	Long-term (4 years) aspirin useis associated with reduction in the risk of gastric cancer
Steinbah et al. [26], N Engl J Med, 2000	Celecoxib/FAP	62	15	RTC	Celecoxib leads to a significant reduction in the number of polyps in patients with FAP
Spence et al. [59], Gastroenterology, 2018	Aspirin/esophageal and gastric cancer	4,654 esophageal	3,240 gastric	Two population-based studies	Aspirin was not associated with increased survival
<i>H.pylorierdiction therapy</i>					
Nakamura et al. [62], Gut 2012	Gastric MALT lymphoma	420 gastric MALT		Multicenter cohort study	Excellent long-term outcome of gastric MALT lymphoma after H. pylori eradication
Ford et al. [64], BMJ 2014	Gastric cancer	3,294	3,203	Meta-analysis of RCT	Eradication therapy for H. pylori reduces the incidence of gastric cancer
Choi et al. [65], NEJM, 2018	Metachronous gastric cancer	470 early gastric cancer		RCT	H. pylori treatment prevents metachronous cancer in patients with early gastric cancer
<i>Metformin</i>					
Evans et al. [71], BMJ, 2005	Cancer risk in T2DM	983	1,846	Pilot case-control study	Metformin may reduce the risk of cancer in patients with T2DM
Currie et al. [72], Diabetologia, 2009	Cancer risk in T2DM	62,809 cases with T2DM		Cohort study	Metformin reduces risk of CRC and pancreas cancer
DeCensi et al. [73], Cancer Prev Res, 2010	Cancer risk in T2DM	4,042 cancer events		Meta-analysis	Metformin reduces cancer risk for 31%
Chang et al. [76], Transl Oncol, 2018	CRC risk in T2DM	47,597		Cohort study	Metformin significantly reduced the risk od CRC in dose-dependent manner
Zhang et al. [74], J Clin Endocrinol Metab, 2012	Liver cancer risk in T2DM	105,495 cases with T2DM		Meta-analysis	Metformin is associated with lower risk of liver cancer in patients with T2DM
<i>Vitamin D and calcium supplementation</i>					
Grau et al. [80], J Natl Cancer Inst, 2003	Colorectal adenoma	803		RCT	Calcium supplementation and vitamin D reduce the risk ofcolorectal adenoma recurrence
Wei et al. [81], Cancer Epidemiol Biomarkers Prev, 2008	Colorectal adenoma	6,869	68,223	Meta-analyses	Both, circulating 25(OH) D and vitamin D intake significant decreased risk of colorectal adenoma incidence and recurrence
<i>Statins</i>					
Aggarwal et al. [83], 2004	Cancer			Preclinical and clinical studies	Resveratrol can be used for the prevention and therapy of cancer
Chiu et al. [84], Am J Gastroenterol, 2011	Gastric cancer	337 gastric cancer	1,348	Population-based case-control study	Statins are associated with a reduced risk of gastric cancer
Poynter et al. [86], N Engl J Med, 2005	CRC	1,953 CRC	2,015	Population-based case-control study	Statins are associated with a 47% relative reduction risk of CRC

Table 1. (continued)

Study	Treatment offered/cancer site	Number of cases/controls		Design	Main results
Chiu et al. [85], Am J Gastroenterol, 2011	Liver cancer	1,166 liver cancers	1,166	Population-based case-control study	Statins may reduce the risk of liver cancer
<i>Proton pump inhibitors</i>					
Nguyen et al. [87], Gastroenterol, 2010	Esophageal carcinoma	1,182 Barret's esophagus	696	Observational case-control cohort study	PPI, NSAID/aspirin or statin therapy might reduce the risk of esophageal adenocarcinoma
Brusselsaers et al. [88], Cancer Epidemiol, 2018	Esophageal carcinoma	796,492		Population-based cohort study	Long-term use of PPIs is associated with increased risk of esophageal adenocarcinoma
Brusselsaers et al. [89], BMJ Open, 2017	Gastric cancer	797,067		Population-based cohort study	Long-term PPI use might be a risk factor for gastric cancer
Cheung et al. [90], Gut, 2018	Gastric cancer	63,397		Population-based cohort study	Long-term PPIs was associated with an increased risk for gastric cancer

RCT, randomised controlled trials; BDAT, British Doctors Aspirin Trial; UK-TIA, UK transient ischaemic attack trial; TPT, thrombosis prevention trial; SAPAT, Swedish Angina Pectoris Aspirin Trial; ETDRS, early treatment diabetic retinopathy study; JPAD, Japanese primary prevention of atherosclerosis with aspirin for diabetes; POPADAD, prevention of progression of arterial disease and diabetes; AAA, Aspirin for Asymptomatic Atherosclerosis; GI, gastrointestinal; CRC, colorectal carcinoma; FAP, familial adenomatous polyposis; MALT, mucosa associated lymphoid tissue; T2DM, type 2 diabetes mellitus; PPI, proton pump inhibitors.

consumption of fruits, vegetables, and vitamins, there is still no conclusive evidence for the benefit for GI cancers or any type of cancer in humans overall [24, 25]. However, modifying the dietary habit with food that has potential anti-inflammatory and anti-cancer characteristics like fish, poultry, fiber-rich diets, and unsaturated fats, has been commonly advocated [13, 14, 15]. Thus, future studies are needed to assess clinical benefits and harmful effects in humans.

Chemoprevention

Effective Preventive Treatments – Aspirin, NSAIDs, and COX-2 Selective Inhibitors

We have previously outlined in this article that there is substantial potential for primary prevention of CRC through modification of diet and lifestyle. Moreover, as many as 70% of the overall burden of CRC could be prevented through environmental changes. Among them, anti-inflammatory drugs such as aspirin, NSAIDs, and cyclooxygenase-2 (COX-2) selective inhibitors (COXIBs) are shown to be the most effective agents for GI cancer chemoprevention.

The first clinical study to investigate the chemopreventive effects of COXIBs was in high-risk patients with familial adenomatous polyposis, demonstrated reductions in the colorectal adenoma number of 28% with celecoxib at a dose of 400 mg BID for 6 months [26]. After the trial, in 2000, the US Food and Drug Administration approved celecoxib as a new adjunctive treatment for patients with familial adenomatous polyposis [27]. Later on, Food and Drug Administration voluntarily withdrew ap-

proval in 2011 due to challenges in confirmatory studies [28]. Thus, evidence from the studies in early 1990s and 2000s primarily demonstrated chemopreventive effects on colorectal adenoma. Subsequent randomised controlled trials and meta-analyses confirmed the beneficial effect of aspirin, non-aspirin NSAIDs, and COXIBs on the recurrence of adenomas [29]. However, adverse effects regarding bleeding, particularly for non-aspirin NSAIDs and COX-2, limited the potential for their use. Thus, further investigations have been focused on aspirin and they have found that the use of aspirin after diagnosis of CRC is associated with improved survival [30–32]. Moreover, it is well known that aspirin reduces the incidence of cardiovascular events by 12%, both in the general population and in high-risk groups [33]. Thus, aspirin was one of the first pharmacologic agents recommended by the US Preventive Services Task Force for chemoprevention of a CRC primarily in adults aged 50–59 years and possibly 60–69 years, who have a 10% or greater 10-year risk for CVD [34, 35]. Later on, accumulating evidence supports an effect of aspirin in reducing CRC incidence and mortality not only in individuals with CVD risk but also in individuals with an average risk [36, 37].

There have been several proposed mechanisms by which aspirin, NSAIDs, and COXIBs reduce risk of CRC. It seems that the most convincing hypothesis is related to the ability of these agents to inhibit COX-2, a key enzyme that promotes inflammation and cell proliferation [38–40]. COX-2 is a principal enzyme that produces proinflammatory prostaglandins, which increases cellular pro-

liferation and resistance to apoptosis and promotes angiogenesis. Angiogenesis is an important role of COX-2 in CRC and is supported by several studies, showing that COX-2, but not COX-1 is progressively over expressed in colorectal adenomas and cancers in humans [41, 42]. Moreover, aspirin and NSAIDs have other potential anti-inflammatory and anti-cancer mechanisms, including the inhibition of nuclear factor- κ B, DNA repair, polyamines metabolism, Wnt signaling, activation of p38 kinase, and induction of apoptosis [43–47].

Although several observational studies and randomised trials provided compelling evidence that aspirin does reduce CRC when administered as daily doses of 300–1,200 mg, adverse effects like bleeding complications, limited its potential for long-term prevention. Thus, the key study that confirmed the effect of low dose aspirin on CRC incidence and mortality in individuals with average risk was published in 2010 [48]. This study analyzed 5 randomized trials with 14,033 participants and established the effect of aspirin on risk of CRC over 20 years. The most important finding was that the long-term use of low-dose aspirin reduced CRC mortality by 30% and CRC incidence by about 28%. Moreover, the higher dose daily aspirin is shown to be as effective as 75 mg, but has the greater risk of GI ulceration and bleeding complications. In addition, aspirin might have a greater effect on cancer of the proximal colon, reducing the incidence by about 70%, but only about 5% in the rectum. Daily aspirin for at least 5 years reduced the risk of CRC after a latent period of about 7 years, while benefit increased with scheduled duration of treatment [48]. Another important meta-analysis investigated the effectiveness of aspirin versus screening for CRC and concluded that aspirin reduced CRC mortality by 19% compared to placebo [49]. Moreover, low-dose aspirin seems to be equally effective as flexible sigmoidoscopy or guaiac fecal occult blood test screening to reduce CRC incidence and mortality, while low-dose aspirin was more effective for cancers in the proximal colon [49]. However, aspirin is not effective in all individuals with an average risk for CRC. This can be interpreted by the fact that CRC represents a complex disease resulting from a multiple interplay of genetic and epigenetic factors that are driving forces of cancerogenesis [50–52]. One of the fundamental concepts in tumorigenesis of CRC is “the adenoma-carcinoma sequence” that was proposed in the 1978 [53]. Although the concept “adenoma-carcinoma sequence” has never been proven directly, it affords a means of preventing CRC by endoscopic removal of precursor lesions. Moreover, this concept provides an excellent model to

study the genesis of CRC. Since then, several genetic studies confirmed that the chromosomal instability pathway and microsatellite instability pathway are the 2 recognized pathways in tumorigenesis in CRC [50, 51]. Thus, according to genetic variation, the use of aspirin and/or NSAIDs has been differentially associated with CRC risk. In the investigations that followed, regular aspirin use might be associated with a lower risk of BRAF-wild-type CRC [50]. Furthermore, genome-wide investigation of gene-environment interactions showed that 2 single nucleotide polymorphisms at chromosome 12 and 15 might modify the chemopreventive effect of aspirin or NSAIDs on CRC in some individuals [52].

It seems that the role of aspirin in primary prevention is not only limited to CRC, but also to other types of cancer, particularly of the GI tract. The first reliable evidence came from the study with 25,570 patients from 8 eligible trials, which investigated the 20-year risk of death due to cancer [54]. This study demonstrated that long-term use of aspirin for 5–10 years would reduce the risk of death due to GI and non-GI solid cancers by about 20%, while benefits increased with the scheduled duration of treatment. Effects were greatest for GI cancer, particularly CRC and esophageal cancers. Furthermore, 2 large prospective cohort studies included 88,084 women and 47,881 men, for 32 years of follow-up and confirmed that regular use of low-dose aspirin for at least 6 years was associated with a 1.8% lower risk for overall cancer, 8% for GI cancers overall, and 10.8% for CRC. However, this study did not observe the presence of a significant association between aspirin and breast, advanced prostate or lung cancer [55]. Another meta analysis showed an overall 29% reduced risk of gastric cancer corresponding to long-term aspirin use (≥ 4 years) [56]. Thus far, the use of prophylactic aspirin for a minimum of 5 years at doses between 75 and 325 mg appears to have a favorable benefit-harm profile, and might reduce the incidence of cancer by 7% in women and 9% in men (relative reduction dependent on age and sex). Longer use is likely to have greater benefits. The predominant adverse event caused by aspirin is GI bleeding, and there appears to be no valid evidence that the overall frequency of fatal GI bleeding is increased by daily low-dose aspirin [36, 57, 58]. On the other hand, recent population-based study from the United Kingdom showed that low-dose aspirin was not associated with increased survival of patients diagnosed with esophageal or gastric cancer [59]. Thus, future studies would be of great interest to assess the exact effect of aspirin in the overall cancer incidence and mortality.

Helicobacter Pylori Infection Eradication Strategy

According to epidemiological data, gastric cancer is the fifth most common newly diagnosed cancer and the third leading cause of cancer-related death worldwide [1]. It is well established that *Helicobacter pylori* (*H. pylori*) infection is the major etiological factor for gastric cancer. Approximately 89% of gastric cancers worldwide are associated with chronic *H. pylori* infection [60, 61]. Moreover, localized stage gastric MALT lymphomas are strongly associated with *H. pylori* infection [62]. According to this hypothesis, the International Agency for Research on Cancer of the World Health Organization (WHO) classified *H. pylori* as a Group 1 carcinogen in 1994. Since then, important progress has been made in the management of *H. pylori*. The WHO published the strategy plan that includes *H. pylori* eradication, for preventing gastric cancer [63]. Furthermore, the working group in the Maastricht V/Florence Consensus reported that *H. pylori* is an infectious disease, and should be treated, irrespective of an individual's symptoms or stage of disease [60]. To this end, eradication of *H. pylori* and control of gastric inflammation induced by the pathogen are essential in the prevention of gastric cancer. Additionally, the risk of developing gastric cancer can be reduced more effectively by employing eradication treatment before the development of atrophy and intestinal metaplasia, which are 2 conditions considered preneoplastic lesions [61, 64]. Thus, patients with gastric cancer usually have glandular atrophy and are at high risk for metachronous development of new gastric cancer. Thus the long-term effects of *H. pylori* eradication in this particular group of patients might prevent the development of metachronous gastric cancer [65].

Vaccination and Antiviral Therapy

Primary liver cancer is the fifth most common cancer and the second leading cause of cancer-related death, accounting for 7% of all cancers worldwide [66]. Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers, and the incidence of HCC is increasing globally, this being among one of the leading causes of cancer death in the world. Cirrhosis is an important risk factor for HCC, and may be caused by chronic viral hepatitis B (HBV) and C, alcohol consumption, aflatoxin, and inherited metabolic diseases, such as non-alcohol fatty liver disease or genetic hemochromatosis. Overall, one third of cirrhotic patients will develop HCC, but the risk is higher in patients with chronic viral HBV and hepatitis C (HCV) [67]. Thus, the main goal of therapy for HBV and HCV infection is

reduction of infection globally, and consequently prevention of disease progression and HCC development [67–69]. Currently, HBV infection can be prevented by available safe and effective vaccine. Vaccination against HBV reduces the risk of HCC and is recommended for newborns and high-risk groups [68]. On the other hand, in individuals with infection, antiviral therapy for chronic HBV and HCV is beneficial in preventing progression, although does not eliminate the risk of HCC development. Antiviral therapies should follow the EASL guidelines and WHO targets for management of chronic HBV and HCV infection [68–70].

Metformin, Vitamin D, Statins, and Proton Pump Inhibitors

Several other agents including metformin, vitamin D, statins and proton pump inhibitors (PPIs) might have chemopreventive effects based on findings from several population-based observational studies. Thus, previous studies have shown an association between the long-term administration of metformin among patients with diabetes, and lower risks of cancer and cancer mortality, in general [71, 72]. Later on, a few meta-analyses have demonstrated the chemopreventive effect of metformin for cancer overall, particularly for liver cancer and among patients with type 2 diabetes mellitus (T2DM) [73, 74]. Thus, a 31% reduction in overall relative cancer risk was found in individuals taking metformin compared with other antidiabetic drugs, particularly for HCC and pancreatic cancer, while nonsignificant for breast, colon, and prostate cancer [73]. Moreover, metformin treatment seems to be associated with a lower risk for esophageal and gastric cancer [71]. Besides, the growing body of evidence suggests that patients with T2DM have an increased risk of CRC [75]. In addition, both CRC and T2DM share some of the same risk factors such as dietary habit, obesity, and physical inactivity. Yet, the national Taiwan cohort study that included 47,597 T2DM patients revealed that metformin use significantly reduces the risk of CRC in a dose-dependent manner [76].

A first studies with positive effect of vitamin D on CRC risk in rats was proposed more than 25 years ago [77]. Later on, many experimental studies and epidemiological investigations have shown that vitamin D can have an antineoplastic effect, inhibiting cell proliferation and promoting apoptosis [78, 79]. One of the key studies that included 803 individuals in the randomized, placebo-controlled, multi-center clinical trial in 2003 provided a strong indication that vitamin D and calcium have a joint

antineoplastic effect in the colon, reducing the risk of colorectal adenoma recurrence [80]. Nevertheless, further data and meta-analyses clearly suggest the potential for important chemopreventive effects of vitamin D and colorectal adenoma [81, 82].

On the other hand, large randomized controlled trials investigated the effects of statins to prevent CVD and to safety reasons analyzed whether statins increased cancer incidence and cancer mortality, and surprisingly showed that statins can actually prevent cancer. Consequently, observational studies and meta-analyses have shown that long-term statin use significantly reduces the incidence of GI cancer, particularly gastric cancer and CRC [83–86]. Furthermore, there is some evidence that statins might be useful in the prevention of liver cancer [85]. However, the beneficial effects of statins on inhibiting carcinogenesis should be clarified by ongoing and future studies within large prospective cohorts.

It is well known that PPIs are the most important pharmacological agents in the management of patients with Barrett's esophagus as they control symptoms, heal ulcerations, and prevent strictures. Moreover, observational studies demonstrated that PPIs effectively reduced the progression of non-dysplastic Barrett's esophagus to esophageal adenocarcinoma [87]. On the other hand, the population-based cohort study on 796,492 patients on long-term therapy with PPIs showed increased risk of esophageal adenocarcinoma [88]. It is well known that PPIs induced hypergastrinemia, while the patients with high gastrin values had increased risk of gastric cancer. Although there is some evidence for increased risk of gastric cancer in patients treated on long-term PPI after *H. pylori* eradication, the association between chronic PPI use and both gastric cancer and esophageal cancer risk is still controversial [87–90]. However, additional studies are warranted to establish the potential of metformin, vitamin D, statins, and PPIs in the chemoprevention of cancer overall.

Conclusion

Despite the developments in genetic studies, novel treatment approaches, and progressive interest in chemoprevention in the last several decades, GI cancers remain a source of considerable morbidity and mortality all over the world. As a result of past investments, current therapeutic GI cancer prevention include the integration of various activities such as lifestyle changes to reduce risk, vaccines, screening to detect early lesions

and preventive therapies aimed to actively interrupt the carcinogenic pathway. Long-term aspirin use seems to have the largest potential effect on the general population on cancer incidence and mortality overall. Aspirin taken for several years at doses of at least 75 mg daily, reduces long-term cancer incidence for 7–10%, overall, and appears to have a favorable benefit-harm profile. Moreover, aspirin is likely to have the greatest benefits for 3 common GI cancers: colon, gastric, and esophageal. *H. pylori* eradication reduces the risk for gastric cancer and is advocated, regardless of the symptoms and stage of disease. Metformin and statins are promising in cancer prevention in patients with T2DM. Numerous studies have shown that vitamin D intake is associated with a reduced risk of colorectal adenoma. In the future, the chemoprevention in digestive oncology will focus on better identification and individualize decision making to the specific patient in order to have great efficacy with fewer and tolerable risks. Thus, further studies with large prospective cohorts are warranted to establish the potential of various agents and to identify more specific and highly targeted new agents for the chemoprevention of cancer overall.

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Authors Contribution

M.N.K.: conceptualization. M.N.K. and T.M.: supervision. M.N.K., D.D.M., D.D.P., and A.P.M.: writing original draft. M.N.K., D.D.M., and T.M.: writing ± review and editing.

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