Colon cancer and the epidermal growth factor receptor: Current treatment paradigms, the importance of diet, and the role of chemoprevention

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Author contributions: Konda VJ, Bissonnette M and Pabla B designed research; Pabla B performed research and analyzed data; Konda VJ, Bissonnette M and Pabla B wrote the paper.

Conflict-of-interest statement: None.

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Received: May 4, 2015
Peer-review started: May 5, 2015
First decision: June 3, 2015
Revised: June 8, 2015
Accepted: July 21, 2015
Article in press: July 23, 2015
Published online: October 10, 2015

Abstract
Colorectal cancer represents the third most common and the second deadliest type of cancer for both men and women in the United States claiming over 50000 lives in 2014. The 5-year survival rate for patients diagnosed with metastatic colon and rectal cancer is <15%. Early detection and more effective treatments are urgently needed to reduce morbidity and mortality of patients afflicted with this disease. Here we will review the risk factors and current treatment paradigms for colorectal cancer, with an emphasis on the role of chemoprevention as they relate to epidermal growth factor receptor (EGFR) blockade. We will discuss how various EGFR ligands are upregulated in the presence of Western diets high in saturated and N-6 polyunsaturated fats. We will also outline the various mechanisms of EGFR inhibition observed with several naturally occurring chemopreventative agents such as ginseng, green tea, and curcumin. Finally, we will discuss the current role of targeted chemotherapy in colon cancer and outline the limitations of our current treatment options, describing mechanisms of resistance and escape.

Key words: Chemoprevention; Colon cancer; Epidermal growth factor receptor; Western diet; Curcumin; Green tea; Ginseng

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Core tip: This review article will summarize the risk factors and current treatment paradigms for colorectal cancer, with an emphasis on the role of targeted chemotherapy and chemoprevention as they relate to epidermal growth factor receptor (EGFR) blockade. It will include an overview of the structure and function of EGFR as well as intracellular pathways regulated by its activity. It will discuss how various EGFR ligands are upregulated in the presence of Western diets that are high in saturated and N-6 unsaturated fat, and will outline the various mechanisms of EGFR inhibition observed with several naturally occurring
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chemopreventative agents including ginseng, green tea, and curcumin.

Pabla B, Bissonnette M, Konda VJ. Colon cancer and the epidermal growth factor receptor: Current treatment paradigms, the importance of diet, and the role of chemoprevention. World J Clin Oncol 2015; 6(5): 133-141. Available from: URL: http://www.wjgnet.com/2218-4333/full/v6/i5/133.htm DOI: http://dx.doi.org/10.5306/wjco.v6.i5.133

INTRODUCTION

A total of 1665540 new cancer cases and 585720 cancer deaths were projected to occur in the United States in 2014. Of these, colon and rectal cancer (CRC) will account for 8% of new cases, representing the third most common and the second deadliest type of cancer for both men and women[1], claiming over 50000 lives in 2014[2,3]. The 5-year survival rate for patients diagnosed with metastatic CRC is < 15%[4]. Early detection and treatment is crucial for the improvement in morbidity and mortality of patients afflicted with this disease.

Overexpression of epidermal growth factor receptor (EGFR) is common in many tumors. Specifically in CRC, EGFR is estimated to be overexpressed in 60%-80% of tumors, and is associated with a poor prognosis[5]. For these reasons EGFR has been targeted as a locus for treatment with small molecule inhibitors and monoclonal antibodies, with the latter playing a role in the treatment of metastatic disease. This review article will discuss risk factors and current treatment modalities for colorectal cancer and examine the roles of chemotherapy and chemoprevention.

RISK FACTORS FOR COLORECTAL CANCER

Many factors have been identified contributing to the risk of colon cancer. These risk factors are believed to increase the rate at which genetic mutations occur in various oncogenes and tumor suppressor genes, and/or result in growth-promoting epigenetic modifications. Generally, these factors can be classified into the following categories: germline genetic mutations, environmental exposures, personal or family history of CRC, associated diseases, and demographic considerations.

There are several germline genetic mutations that greatly increase the incidence of colon cancer through distinct molecular mechanisms. The two syndromes that account for most of the hereditary diseases are Lynch syndrome, and familial adenomatous polyposis (FAP) syndrome. Lynch syndrome accounts for approximately 3% of CRC cases, while FAP syndrome contributes an additional 0.01%-0.04%. Lynch syndrome is caused by mutations in one or more of the DNA mismatch repair genes MLH1, MSH2, MSH6, PMS2, and EPCAM. The two most common forms of FAP syndrome are a result of a germline mutation in the APC gene. Other germline - inherited colorectal cancer syndromes include MUTYH-associated polyposis, Cowden syndrome, Peutz-Jeghers syndrome, and juvenile polyposis syndrome.

Environmental exposures associated with an increased risk of CRC include a history of abdominal radiation, smoking, alcohol use, and diet[5-8]. Of particular interest with respect to the EGFR receptor is the role of a high fat Western diet, which has been shown to promote the development of experimental colon cancer via an EGFR-mediated mechanism. The role of this pathway will be discussed in detail later.

Personal history of CRC or large adenomatous polyps (> 1 cm) or polyps with villous features increase the risk of colorectal cancer[9]. Family history of colon cancer or adenomatous polyps confers an increased risk of disease, even if these histories do not meet the criteria for the syndromes discussed above. US guidelines reflect this increased risk, with the ACG recommending earlier screening if a single first-degree relative was diagnosed with CRC or had an advanced adenoma diagnosed at age < 60 years or if two first-degree relatives were diagnosed with CRC or advanced adenomas[10].

Disease states associated with an increased incidence of colon cancer include IBD (both ulcerative colitis and Crohn’s disease), diabetes, and obesity. As with many cancers, risk for CRC increases with age. CRC incidence is approximately equal in males and females, although there is an increased incidence and higher mortality rate among African Americans and an increased mortality among men. Recent studies suggest that testosterone effects in males rather the protective effects of estrogens in females account for increased male risk[11].

APPROACH TO CRC MANAGEMENT

The management of CRC includes screening, staging, and treatment with surgery, chemotherapy, and/or radiation. As more than 20% of patients with CRC will present with metastatic disease with a 5 year survival rate < 15%[1], prevention is critical in colorectal cancer. Colorectal cancer prevention is primarily based on screening methods, which include stool tests, radiographic imaging, and colonoscopy to identify adenomatous polyps, a precursor lesion for colon cancer. Colonic polyps may be identified through these screening methods and then may be removed during colonoscopy. Colorectal cancer, once diagnosed, is defined as either colon or rectal cancer based on the anatomical location of the lesion, with the rectum being defined as the region extending from the transitional mucosa of the anal dentate line to the sigmoid colon at the peritoneal reflection. Recent studies of CRC suggest that tumors arising in the proximal and distal colon have different
molecular phenotypes with different prognostic outcomes. Interestingly, rectal cancers and tumors in the distal colon share many molecular features.\(^{[12]}\)

Upon diagnosis of CRC, staging is primarily accomplished through CT (with certain situations calling for additional PET-CT) of the chest, abdomen, and pelvis, using the TMN system, with the goal of identifying tumors appropriate for resection. If amenable to resection, the tumor is removed. Pathological staging and subsequent assessment of high-risk features for systemic recurrence are performed to help guide the utility of adjuvant chemotherapy with 5-FU based chemotherapies. In this regard, determining the presence of nodal disease is of particular importance. For metastatic disease, assessment of RAS gene status (KRAS/NRAS) and BRAF status (if KRAS is WT) determines whether or not the tumor is likely to respond to anti-EGFR monoclonal antibodies such as panitumumab and cetuximab. The rationale for this treatment paradigm and the specific pathways involved will be discussed later. In addition to genetic testing for individuals with CRC at younger ages or with CRC positive family history, search for metastatic lesions must be pursued to determine if patients are likely to benefit from resection of isolated metastasis. The timing of colectomy with resection of metastasis, and the use of various 5-FU based chemotherapeutics as neoadjuvant forms of chemotherapy such as FOLFOX, FOLFIRI, and CapeOX, along with bevacizumab, panitumumab, or cetuximab, depend on the individual patient and tumor characteristics. If resection of metastatic disease is impossible, neoadjuvant chemotherapy should be administered first if there is no imminent risk of obstruction or significant bleeding. In addition, the patient should undergo periodic re-assessment regarding the resectability of metastatic lesions.\(^{[13]}\)

For rectal cancer, endorectal ultrasound is important to assess the presence of LN involvement. In clinical T1-T2 node negative rectal cancer, surgical management should be pursued with a pathological assessment of TMN stage. High grade T lesions or node positive disease should be treated with adjuvant chemotherapy and radiation. In advanced clinical stage disease (T3 or higher or any node positive disease), neoadjuvant chemoradiation should be offered with adjuvant chemotherapy. The chemotherapeutics recommended in rectal cancer include the 5-FU based agents with oxaliplatin. In metastatic disease, there is a role for panitumumab and cetuximab if the tumors are KRAS/NRAS WT. As with colon cancer, the goal in metastatic rectal cancer is to periodically reassess the potential for resection of metastases. Treatment regimens for rectal vs colon cancer share many similarities, with the major difference being the use of radiation therapy for rectal cancer as outlined above.\(^{[13]}\) There is, however, some data suggesting a benefit for adjuvant RT in colon cancer in select patients with high-risk features for local recurrence.\(^{[14]}\)

## EGFR Pathways in Colorectal Cancer

EGFR was one of the first targets to be exploited in cancer treatment. The receptor also known as HER (human EGF receptor) or c-erbB1, is a 170-kDa transmembrane protein with intrinsic protein tyrosine kinase activity. EGFR is one of four members of the c-erb subfamily of receptor protein tyrosine kinases. Two cysteine-rich domains comprise the ligand-binding region on the extracellular aspect of the cell. A single alpha-helical transmembrane domain connects the ligand-binding region to the intracellular receptor, which is comprised of three domains. One domain serves as a site for feedback attenuation by PKC and erk MAP kinases, another is a tyrosine kinase domain, and the third is a carboxy-terminal tail. EGFR is present on all epithelial and stromal cells, and is expressed on many glial and smooth muscle cells as well. It is a multifunctional receptor that plays a key role in cell division and apoptosis, cell differentiation and dedifferentiation, migration, and organogenesis.\(^{[15]}\) EGFR executes these functions by activation of multiple signaling pathways including PLC-gamma-1, RAS-RAF-MEK-MAPKs, phosphatidylinositol-3 kinase and Akt, Scc, the stress-activated protein kinases, PAK-JNK-JNK, and the signal transducers and activators of transcription. Binding of a diverse array of ligands (EGF, TGF, amphiregulin, heparin-binding EGF, betacellulin, or epiregulin) induces receptor homodimerization or heterodimerization with other ErBb2 members (Figure 1).

EGFR ligands are released from membrane bound proligand forms by membrane bound metalloprotease enzymes of the ADAM family. ADAM17 is a key enzyme regulating release of EGFR ligands: EGF, amphiregulin, and heparin-binding EGFR.\(^{[16]}\)

When liganded, the EGFR undergoes autophosphorylation in trans in the cytoplasmic kinase domain. Phosphorylated tyrosine residues function as docking sites that are recognized by adapter or effector proteins that contain src homology 2 domains or protein tyrosine binding domains. EGFR signal responses are cell-type specific and modulated by the specific activating EGFR ligand, the particular homo or heterodimeric ErB partners formed and the availability of downstream effector pathways.\(^{[17]}\)

EGFR is expressed in 60%-80% of CRCs.\(^{[2]}\) The mechanisms by which EGFR promotes tumorigenesis are diverse and involve both cell cycle dysregulation and the promotion of factors that aid in tumor survival. Studies in other tumors have dissected some of the mechanisms involved. In breast cancer cells, increased levels of EGFR have been associated with increased proliferative and angiogenic activity. Increased proliferation and angiogenesis are thought to be induced TGF, which correlates with increased mitotic activity. EGFR ligands TGFα and EGF have also been shown to function as chemoattractants for endothelial cells, with TGFα
animal fat and red meat. This association has been investigated in the azoxymethane (AOM) model of colon cancer that mimics many of the clinical, histological and molecular features of sporadic human colon cancer. AOM causes O6 methylation of DNA guanine bases resulting in activating mutations in K-ras and CTNNB1 (which codes for β-catenin). In this model, EGFR is required for tumor promotion by Western diet. To demonstrate EGFR requirement, mice with wild type Egfr and mice homozygous for loss-of-function Waved-2 Egfr mutations were fed standard vs high-fat diets and cancer was induced by treating with AOM, followed by tumor promoting dextran sulfate sodium. The Waved-2 Egfr lacks 90% of wild type receptor kinase activity. The Egfr wild type mice in the high-fat group had a significantly higher tumor incidence compared to mice on standard diet but this tumor promoting effect of high fat diet did not occur in mice with mutant Egfr.

The proto-oncogenes CTNNB1, MYC, CNND1, and PTGS2 and the EGFR ligand TGF-α were also found to be expressed at significantly higher levels in tumors from Egfr wild type mice treated with the high fat diet compared to tumors from mice with mutant Egfr.

In more recent preliminary studies we showed that Western diet increases ADAM17 expression and up-regulates EGFR ligands TGF-α and amphiregulin. Stroma-derived factor 1 alpha (Sdf1α) was also increased by WD. Sdf1α is a ligand for the G-protein coupled receptor CXCR4. In other preliminary colon cancer studies we showed that Sdf1α induces the activation of EGFR (EGFR transactivation) by stimulating ADAM17.
have demonstrated the anti-tumor effects of ginseng including antioxidant, anti-proliferative, pro-apoptotic and anti-inflammatory actions of ginseng and more recently EGFR inhibitory effects have been identified\(^{42-45}\). Additionally, in a mouse model of colitis-associated colon cancer, American ginseng was shown to inhibit inflammation and suppress EGFR signaling, effects that are postulated to contribute to ginseng’s anti-tumorigenic properties\(^{46}\) (Figure 1).

In studies of mice treated with a combination of Western diet alone or WD plus ginseng, colonic mucosal EGFR signals were noted to be increased in the Western diet group and Ginseng inhibited these increases. Ginseng also appears to inhibit tumorigenesis through other mechanisms, including the induction of apoptosis. Ginseng’s anti tumor effects likely require ginseng metabolite activation by the colonic microbiome as several biologically active metabolites of ginsenosides are synthesized by gut microbes. One metabolite in particular, 20-O-b-D glucopyranosyl)-20(S)-protopanaxadiol or compound K, was shown to suppress growth of colon tumor xenografts\(^{47}\).

**Green tea**

Several other naturally occurring products have been studied as potential chemopreventative agents and been shown to inhibit EGFR signals. A bioactive green tea polyphenol, epigallocatechin-3-gallate (EGCG), has been shown to selectively inhibit EGFR-dependent signaling in cervical cancer cells, leading to growth cessation and cell apoptosis. The mechanism of this selective inhibition was shown to involve suppression of EGFR-induced ERK1/2 (aka MAPK1 and 3) and AKT activation as well as direct suppression of ERK and AKT\(^{48}\) (Figure 1). These kinases have been implicated in cell cycle progression; ERK1/2 signals both activation of the intrinsic or extrinsic apoptotic pathway depending on the ligand and cell type, and AKT has been shown to regulate cell proliferation and survival, with constitutive up-regulation of activated AKT demonstrated in many types of human cancers\(^{49-51}\). The importance of these cellular pathways is underscored by the observation that only selective kinases downstream of EGFR were inhibited, but not others. Increasing concentrations of EGCG exerted both short term reversible effects on cell cycle progression and long term cellular changes with increased rates of apoptosis\(^{49}\).

**Curcumin**

Another naturally occurring substance that has drawn the attention of the scientific community is curcumin, the yellow pigment of turmeric found in curry. It is produced by the rhizome of the plant tumeric and has been safely consumed and utilized for its medicinal properties for centuries. This substance has been shown to inhibit the growth of cancer cells by suppressing gene expression of cyclinD1 and EGFR\(^{52}\). Recent studies have demonstrated that curcumin inhibits binding of the transcription factor
EGR-1 to the EGFR promoter as well as suppressing EGR-1 gene expression through the ERK signal pathway, thereby suppressing EGR-1 transactivation activity[53] (Figure 1). Of note, the concentrations required to achieve this growth suppression in vitro, are much higher than those normally achieved in blood and tissue in vivo following curcumin ingestion, but for colon cancer prevention colonic luminal concentrations may be more relevant. Recent developments of more stable curcumin analogues may also increase the efficacy of this compound[64].

EGFR AS A CHEMOTHERAPEUTIC TARGET

With the potential central role of EGFR in tumorigenesis, several groups have successfully developed neutralizing antibodies or kinase inhibitors. Of particular interest are the monoclonal antibodies cetuximab and panitumumab, as well as the small molecule inhibitors gefitinib and erlotinib. Cetuximab and panitumumab act by binding the extracellular domain of EGFR and thereby inhibiting ligand-dependent activation and receptor dimerization. Cetuximab also may induce an immune response by antibody-dependent cell-mediated cytotoxicity[55-58] (Figure 1). In colon cancer, cetuximab is currently FDA approved for EGFR-positive metastatic disease in patients who cannot tolerate irinotecan-based therapy, or in combination with oxaliplatin, irinotecan, and 5-FU. These recommendations are based on a 2009 study that examined the use of cetuximab as a first-line treatment with FOLFOX, with assessment of tumor response in KRAS wildtype vs KRAS mutant tumors. Tumors with KRAS mutations resulting in constitutively active GTP-binding protein were shown to be resistant to EGFR inhibitors[59,60]. This trial confirmed previous findings and demonstrated significant differences between tumor response and risk of disease progression in the KRAS mutant and KRAS WT groups with the addition of cetuximab, though a difference of progression-free survival was not detected[61]. Panitumumab is also used in metastatic CRC and also requires WT KRAS for efficacy[62]. More recently a study suggested that tumors with KRAS mutations in codon 13 may remain susceptible to Cetuximab, whereas those with KRAS codon 12 mutations did not[63].

Small molecule EGFR receptor tyrosine kinase inhibitors, gefitinib and erlotinib are not used in the treatment of CRC. Gefitinib was initially approved for third-line treatment of patients with non-small cell lung cancer (NSCLC) based on preliminary small clinical trials but later studies demonstrated conflicting results of its efficacy[64]. A phase II RCT of FOLFOX vs gefitinib plus FOLFIRI did not show any benefit and demonstrated high toxicity[65]. There have since been studies looking at the efficacy of gefitinib in select groups of patients, initially based on demographic considerations such as non-smokers, Asians, and women, and later based on specific activating mutations[66,67], underscoring the importance of careful patient selection in maximizing the success of these targeted agents. Erlotinib is currently approved for second-line treatment of patients with locally advanced or metastatic NSCLC and first-line treatment for patients with locally advanced, unresectable, or metastatic pancreatic cancer in combination with gemcitabine[55]. Recent studies have looked at the combination of cetuximab and erlotinib in the treatment of chemotherapy-refractory metastatic CRC with promising results. These studies demonstrated improvement in response rates and progression free survival in patients with tumors having wild type EGFR compared to failures in the patients with tumors having mutant EGFR[68].

These studies point to the importance of assessing the mutation status of EGFR and KRAS when using EGFR targeted therapies. It should be noted that there are many other factors that determine a given patient’s initial and subsequent response to therapy. This is highlighted by the fact that KRAS mutations only account for approximately 30%-40% of nonresponsive patients[50,69]. Mutations in other downstream signaling molecules such as BRAF have been shown to correlate with unresponsiveness to cetuximab and panitumumab[70]. Raf proteins are principal downstream effectors of KRAS in the RAS-RAF-MEK-MAPKs signaling cascade. They are activated directly by KRAS and serve to phosphorylate and activate the downstream kinase MEK, which phosphorylates ERK leading to numerous Ras-induced cellular responses[71,72]. Specifically, BRAF has a higher affinity for MEK leading to stronger MEK stimulation than A-Raf or c-Raf, and plays a critical role in promoting cell survival by activating the MAPK pathway[72]. The prognostic significance of these mutations with respect to survival is less clear, with some data indicating that gender may a role how these mutations affect tumor virulence. In one prospective cohort study, BRAF mutations were associated with a reduced cancer specific survival in men, particularly in lymph node positive disease, when compared to women. Additionally in microsatellite stable tumors, BRAF was found to be an independent predictor of poor prognosis in men[74]. The exact mechanisms of how gender may interact with BRAF mutation status are not yet clear. However, even when adjusting for BRAF mutant tumors to assess nonresponders to cetuximab and panitumumab, approximately 41% of nonresponders are left unaccounted for, suggesting the presence of other unknown mechanisms of resistance[70].

Responses even in selected groups of patients with wild type EGFR, KRAS, and BRAF alleles is not uniform, and all patients will ultimately develop acquired resistance to targeted therapy with monoclonal antibodies. Increased ERBB2 signaling has been shown to be one such mediator in resistant clones of previously cetuximab-sensitive cell lines via the up-regulation of ERK1/2 signaling[75]. This can occur through the amplification of ERBB2 itself or through the overexpression of herregulin,
one of the ERBB3 ligands. Increased C-Met signaling may be another mechanism for EGFR antibody resistance. Importantly, restoration of sensitivity to cetuximab has been demonstrated with the application of interfering RNA or small molecule inhibitors such as gefitinib, suggesting a potential valuable role of these small molecule kinase inhibitors in restoring efficacy of EGFR targeted therapies.

CONCLUSION
We have reviewed the risk factors and current treatment paradigm for colorectal cancer, with an emphasis on the role of targeted chemotherapy and chemoprevention as they relate to EGFR blockade. The complex interplay between other growth promoting pathways that cross talk with EGFR and downstream EGFR effectors that can be driven by activating mutations make strategies that target EGFR vulnerable to several escape mechanisms. The role of Western diet and the exciting field of chemoprevention offer opportunities to target EGFR signaling cascade which plays a critical role in tumor promotion and progression. Future development of anti-EGFR directed nanoparticles restricted to the gut that could inhibit over active EGFR signals might hold promise to safely reduce colorectal cancer risk.

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