Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Chemoprevention of Colorectal Cancer***
-January 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed chemoprevention of colorectal cancer (CRC) at the 2023 Winter Meeting. This is the first therapeutic review of CRC for the NPTC. Current medication(s) listed on the IHS National Core Formulary (NCF) relevant to these conditions include aspirin, atorvastatin, metformin, pravastatin, rosuvastatin, and simvastatin. Following review, **no modifications** were made to the NCF.

In the United States (US), CRC is the fourth most common cause of cancer for both men and women, representing 7.9% of all new cancer cases.[1,2] However the American Indian/Alaska Native (AI/AN) population carries a significant burden of CRC second only to Non-Hispanic Blacks.[2] It is the second most diagnosed cancer among Alaska Native men and women.[1] CRC is the third leading cause of cancer-related deaths in the US annually.[1] From 2016-2020, Non-Hispanic Blacks had the highest death rates followed by AI/AN men and women.[2] CRC develops over decades for average risk individuals and can be influenced by certain risk factors.[1] The following are modifiable risk factors for CRC which can increase risk: alcohol intake (e.g. moderate drinking 12.6-49.9 grams ethanol/day, heavy drinking ≥50 grams ethanol/day increases risk by 52%), cigarette smoking, obesity (BMI >30), diet of red meat (100 grams/day), and processed meats (50 grams/day), and low vitamin D.[1,5,20] Uncontrolled blood sugar as seen with Type 2 Diabetes Mellitus (T2DM) and insulin resistance are also risk factors.[1] Protective factors that can decrease CRC risk are a diet of whole grains, vegetables, low fat dairy products, and increased physical activity.[1,20] Non-modifiable CRC risk factors include: increased age, family/personal history of CRC (first degree relative diagnosed before age 50) and/or certain hereditary conditions.[1,5,20]

CRC prevention strategies focus attention on early detection and management to prevent disease. Current US guidelines recommend screening average risk adults 45 years or older for CRC.[3,20] Although colonoscopies are the gold standard and a mainstay for CRC screening[3,20], 56% of AI/ANs overall are current for CRC screening versus 69% of Caucasians[1]. The 2021 Government Performance and Results Act screening outcomes for colorectal cancer indicate that IHS fell below the national target of 32.6% with a final aggregate result of 27.9%.[8]

Discussion:

Chemoprevention involves the long-term use of a variety of preferably oral agents that can delay, prevent or reverse the development of adenomas in the large bowel, thus interfering with progression from adenoma to carcinoma.[2,7,9] This effect is of particular importance to individuals with a hereditary predisposition to colorectal neoplasia.[7,9] Though the FDA had once approved aspirin and celecoxib for use of CRC prophylaxis[9], recent evidence no longer supports this recommendation. There is a range of medications and vitamin supplements (e.g. folic acid, vitamin d, calcium, Omega-3 polyunsaturated fatty acids) that have been studied. However current evidence does not show strong support for these medications and supplements.[5,7,9] For this review, certain agents that either show promise or were noted to no longer be considered will be highlighted.

Though there are not specific studies on vaccines vs. placebo for CRC prevention, it is important to note that vaccines targeting the human papillomavirus (HPV) can aid in preventing cancer of the anus, especially among those with history of sexual abuse.[9,10,11] The CDC recommends HPV vaccination routinely for those aged 11–12 years (can start at age 9 years especially if there is a known history of sexual abuse or assault) and for those who have immunocompromising conditions like HIV.[9.10.11]

Aspirin's exact mechanism of action is not clear but it appears to inhibit several pathways related to CRC proliferation such as prostaglandin synthesis, platelet activation, and Wnt signaling.[7] In 2022, the US Preventative Services Task Force (USPSTF) eliminated its 2016 recommendation of utilizing low-dose aspirin for primary prevention of CRC in adults ages 50 to 59 years who met specific criteria, citing new data which shows there is insufficient evidence to support using aspirin to reduce CRC incidence or mortality.[12] Pooled data from 4 RCTs showed no association between aspirin use and CRC incidence at 5 to 10 years of follow-up (OR 1.07, 95% CI: 0.92 to 1.24, p=0.20, I^2=36%).[12] However, in the Women's Health Study (n=39,876), patients randomly assigned to aspirin had a significantly lower incidence of CRC at 17.5 years when post-trial observational follow-up was included (OR, 0.82, 95% CI: 0.69 to 0.98).[12,19] A meta-analysis of 11 RCTs from 1993-2020 compared a range of aspirin doses (low-dose to high dose) to placebo in healthy people aged 17-66 years and showed that aspirin had a similar adverse event rate to placebo (RR=1.03, 95% CI: 0.77-1.37, p=0.81; I^2=84%) and also had a similar mortality rate to placebo (RR=0.95, 95% CI: 0.58-1.57, p=0.86; I^2=0%).[23]

Metformin's anti-cancer mechanisms involve multiple pathways including inhibiting mTOR pathways to hamper cell proliferation and slowing tumor growth which has shown to be beneficial to patients with T2DM.[6,17,18] In a meta-

analysis of 58 international studies of patients with T2DM, there was 23% decreased incidence of adenoma formation (RR=0.77, 95% CI: 0.67 to 0.88, p<0.001) and a 39% decreased incidence of advanced adenoma formation (RR=0.61, 95% CI: 0.42 to 0.88, p=0.008) in patients taking metformin vs not taking metformin.[17] Metformin may play a role in CRC by decreasing mortality in patients with T2DM and CRC. In a meta-analysis of 10 cohort studies (n=10,123) with international participants with T2DM and CRC comparing metformin vs. placebo, overall survival improved for the metformin group (OR 0.54, 95% CI: 0.47 to 0.63, I^2=50%, p=0.04).[18] Cancer-specific survival also improved in the metformin group (OR 0.59, 95% CI: 0.43 to 0.82, I^2=59%, p=0.002).[18]

Though statins are not recommended for primary prevention of CRC, there is evidence that this class may improve mortality outcomes in patients diagnosed with CRC.[7] In a meta-analysis of 14 studies (case-control and cohort), adults on statins before or after CRC diagnosis were compared to no statin use for all-cause mortality (ACM) or cancer-specific mortality (CSM).[25] For adults already on a statin before CRC diagnosis, statin use appeared to decrease ACM (HR 0.85, 95% CI: 0.79 to 0.92, p=0.346, I^2=5.7%) and also decrease CSM (HR 0.82, 95% CI: 0.79 to 0.86, p=0.519, I^2=0.0%).[25] For those adults who started taking a statin after CRC diagnosis, statin use also appeared to decrease ACM (HR 0.86, 95% CI: 0.76 to 0.98, p=0.00, I^2=75.3%) and also decreased CSM (HR 0.79, 95% CI: 0.79 to 0.89, p=0.028, I^2=55.3%).[25]

Findings:

The 2022 USPSTF guidelines do not recommend aspirin for CRC chemoprevention.[12] However, the NICE guidelines state to consider using aspirin for patients with Lynch syndrome (or carriers) for greater than 2 years, though the exact beneficial dose and duration is unknown.[15,16] The USPSTF states more research is needed to evaluate low-dose aspirin effects on CRC incidence and mortality over a greater span of time (i.e., >10 years) in primary prevention populations and in the context of current CRC screening practices.[12] Based on current available evidence, interventions with adequate evidence for decreased risk of CRC includes metformin in patients with diabetes. Current data supports the use of metformin in patients with diabetes and at high risk for CRC as it appears to decrease incidence of adenoma and advanced adenoma formation and also improve mortality rates for those with advanced CRC.[17,18] Celecoxib is no longer recommended for reducing adenomatous colorectal polyps for patients with FAP due to significant cardiovascular events and increased risk of GI side effects.[22] The class of non-aspirin NSAIDs is not favored because risks outweigh its benefit.[22,23] Current recommendation suggests a healthy diet over the use of OTC supplements such as calcium, vitamin D, or folic acid.[5] Literature on omega-3 fatty acids does not support their use as chemo-preventative agents due to lack of efficacy.[7,24] Further evidence on statins is needed, currently there is not enough data to recommend its use for those with CRC. However, there is some evidence this class may play a role in individuals with KRAS mutations who are unresponsive to monoclonal antibodies targeting epithelial growth factor receptor which should be further explored.[25] Promoting healthy lifestyle changes and encouraging increased use of current CRC screening modalities such as colonoscopy remain key prevention strategies for CRC.

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