

CRC IN FOCUS

Current Developments in the Management of Colorectal Cancer

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What Should We Tell Our Patients With Colorectal Cancer About Diet, Supplements, and Lifestyle?



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H&O What would prompt you to discuss diet and lifestyle changes with a patient who has colorectal cancer (CRC)?

JM Patients will often initiate the discussion, which may occur at varying times depending on their disease stage at diagnosis and where they are in their treatment. Some patients will ask about diet and lifestyle during their initial consultation. If patients do not ask, I bring it up during the course of treatment. For patients with early-stage disease, I bring up the topic again at the completion of treatment as part of the survivorship plan. However, I think it is best as a continual discussion with patients throughout their treatment course.

H&O What are the general areas in which diet and lifestyle have the potential to make a difference in a patient with CRC?

JM The 4 areas in which these changes have the potential to make a difference are in disease recurrence or progression, survival, quality of life, and tolerance to chemotherapy. For example, changes in diet can make a tremendous difference in how well a patient undergoing chemotherapy tolerates treatment. Certain dietary changes can reduce the risk of diarrhea, for example. Physical activity also has been shown to help patients with CRC tolerate treatment. Regarding the bigger picture of how cancer behaves, we have good data in early-stage disease—and emerging data in metastatic disease—that diet and lifestyle can affect recurrence, progression, and survival rates.

H&O How have diet and lifestyle been shown to affect primary prevention?

JM Most of the initial studies of diet and lifestyle changes in CRC, which took place over several decades, were focused on primary prevention. Large prospective cohort studies have shown a fairly consistent association between physical activity, avoidance of obesity, and certain dietary factors—particularly a lower intake of red and processed meat—with a reduced risk of developing CRC. Smoking also is associated with increased risk of developing CRC. In terms of chemoprevention, both observational and randomized studies have shown that aspirin and cyclooxygenase 2 (COX-2) inhibitors can lower the risk of polyps and/or colorectal cancer.

H&O Could you talk about some of the specific studies of diet and lifestyle in people diagnosed with CRC?

JM In the past decade, we have begun to see a sizable number of observational studies looking at these factors in patients already diagnosed with the disease.

Regarding diet, I was an investigator in a study of 1009 patients with stage III colon cancer that was published in the *Journal of the American Medical Association* in 2007. We found that patients who followed a Western-pattern diet had reduced disease-free survival, recurrence-free survival, and overall survival compared with those who followed a prudent diet. The Western diet was characterized by a high intake of meat, fat, refined grains, and dessert, whereas the

prudent diet was rich in fruits, vegetables, poultry, and fish. We subsequently published studies showing that higher-glycemic-load diets and intake of sugar-sweetened beverages were associated with an increased risk of recurrence in stage III colon cancer survivors, whereas coffee intake was associated with a reduced risk of recurrence.

Numerous observational studies have found that people who are more physically active have a reduced risk of recurrence and increased tolerance to chemotherapy. More than a dozen studies have linked increased physical activity—either prior to or after diagnosis—to a decreased risk of cancer recurrence in patients with stage I, II, and III CRC. In addition, a meta-analysis of 7 studies by Je and colleagues that was published in the *International Journal of Cancer* in 2013 found that patients with a high level of physical activity after diagnosis had significantly better mortality than those with a low level of physical activity.

Several studies have found that people with CRC who have lower levels of vitamin D—which reflects sunlight exposure, diet, and supplements—have an increased risk of recurrence or cancer progression. In one study, we looked at 1043 patients with metastatic CRC who were enrolled in CALGB/SWOG (Cancer and Leukemia Group B/Southwest Oncology Group) 80405. Dr Kimmie Ng presented our results at the most recent annual meeting of the American Society of Clinical Oncology. We found that median overall survival was significantly better in patients whose serum vitamin D level was in the highest quintile compared with those whose level was in the lowest quintile, after adjustment for pathologic and clinical prognostic factors (32.6 months vs 24.5 months, respectively).

Dr Ng was also the first author on 2 published papers on vitamin D and CRC outcomes. In a study published in 2008 in the *Journal of Clinical Oncology*, we looked at 304 patients with CRC in the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS). We found that after adjusting for confounding factors, overall mortality was nearly halved for those with the highest levels of vitamin D before diagnosis compared with those who had the lowest levels.

In the second study, published in the *British Journal of Cancer* in 2009, we looked at 1017 patients with CRC in the NHS and HPFS. Here, we found an association between higher predicted vitamin D levels after a diagnosis of CRC and improved survival.

H&O What is the relationship between body weight and CRC?

JM We know that the risk of CRC increases along with increasing body mass index (BMI). The data on how weight affects outcomes in people diagnosed with CRC are somewhat mixed. Several studies have suggested an obesity

paradox, in which patients with CRC who are overweight or mildly obese have slightly better outcomes than those of normal weight. Patients who are more obese, however—with a BMI of 35 or greater—seem to have worse outcomes.

Of course, BMI is a highly imperfect measure of weight because it does not account for body composition. As a result, ongoing studies are looking at the relationship between CRC recurrence and progression and body composition, including the ratio of muscle mass to fat mass. This measure may be more closely tied than BMI to outcomes.

H&O What are some of the specific studies of supplements or other agents in people diagnosed with CRC?

JM Studies have looked at the association between aspirin or COX-2 inhibitors and disease onset or recurrence in people who have had polyps or CRC. Randomized trials by Baron and colleagues in *Gastroenterology* and the *New England Journal of Medicine*, by Sandler and colleagues in the *New England Journal of Medicine*, and by Bertagnolli and colleagues in the *Journal of the National Cancer Institute* have found that aspirin and COX-2 inhibitors can reduce the risk of developing further polyps in people who have had polyps.

An observational study of 843 patients with stage III CRC by Dr Kimmie Ng that was published in the *Journal of the National Cancer Institute* looked at the relationship between use of aspirin or COX-2 inhibitors and survival. We found that patients who used COX-2 inhibitors had a trend toward better relapse-free survival, disease-free survival, and overall survival after adjusting for multiple variables.

Finally, CALGB/SWOG 80702 from the National Cancer Institute's Alliance and SWOG Cooperative Groups is looking at the use of celecoxib for 3 years in patients undergoing chemotherapy for stage III colon cancer. This study is nearing completion of accrual and should have results in the next 3 to 4 years (NCT01150045).

H&O Are certain groups of patients more or less likely to benefit from daily aspirin?

JM We do not know for sure which is the right group to receive aspirin as part of their treatment program. In one observational study of 964 patients with CRC from the NHS and HPFS that was published in the *New England Journal of Medicine* in 2012, Liao and colleagues found that regular use of aspirin after diagnosis was associated with longer survival among patients who had *PIK3CA*-mutated colorectal cancer, but not among patients with *PIK3CA* wild-type cancer. These findings were confirmed in an analysis by Domingo and colleagues of the VICTOR (Vioxx in Colorectal Cancer Therapy: Definition of

Optimal Regime) trial, which was a randomized trial of 2 doses of rofecoxib or placebo in patients with stage II or III colorectal cancer that was terminated prematurely because of the worldwide withdrawal of rofecoxib from the market due to toxicity. Although *PIK3CA* mutation status did not predict benefit from rofecoxib, patients with *PIK3CA*-mutated tumors had significantly benefited from low-dose aspirin, whereas those without *PIK3CA* mutations did not. In contrast, a different observational study by Kothari and coinvestigators from the Moffitt Cancer Center in the United States and Royal Melbourne Hospital in Australia did not corroborate that finding. Therefore, some uncertainty remains about exactly which tumor types may benefit the most from aspirin.

H&O If a patient does have CRC, is there any reason to not take a low-dose aspirin?

JM We do have to balance the potential benefit with the risk of ulcers or gastrointestinal bleeding, so that is an important discussion for us to have with our patients. Several ongoing studies should give us more information about the benefits and risks, including a study from Singapore in which patients who have completed therapy for stage II and III disease and are being randomly assigned to receive aspirin or placebo (NCT00565708), the SWOG S0820 study of sulindac and eflornithine to prevent high-risk adenomas and second primary colorectal cancers in stage 0 to III colorectal cancer survivors (NCT01349881), and a study from the United Kingdom called Add-Aspirin that will soon begin enrollment for stage II and III colorectal cancer survivors (www.addaspirintrial.org).

H&O Have any randomized trials looked at diet or lifestyle changes in CRC?

JM None that have been reported yet. There is a large study called CHALLENGE (Colon Health and Life-Long Exercise Change) that is being conducted by the NCIC Clinical Trials Group in Canada and led by Dr Kerry Courneya. In this study, approximately 1000 survivors of high-risk stage II or stage III CRC in Canada and Australia are being randomly assigned to standard treatment or a 3-year supervised intervention to boost physical activity. The primary endpoint of the study is 3-year disease-free survival. Quality of life, anxiety, depression, sleep, and physical function also will be measured.

H&O What lifestyle factors have not been shown to affect outcomes?

JM One of the larger studies on smoking and outcomes in CRC, by Nadine Jackson McCleary and colleagues in 2010,

found no relationship between smoking and CRC. Another large study, which was published in the *Journal of Clinical Oncology* in 2015 with Yang as the first author, did find a modest association. Because of these mixed results, we do not know whether smoking may affect patient survival.

Alcohol has not been shown to affect recurrence or survival either way, although alcohol use during treatment with drugs that are processed in the liver could enhance certain toxicities. We also do not have any good evidence that foods or supplements such as calcium, folic acid, vitamin E, or fiber affect outcomes.

Suggested Readings

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