Colorectal Cancer, Crohn-Like Lymphoid Reactions, Survival — And the Power of a Good Cup of Coffee!

“Never underestimate the power of a good cup of coffee.”

Indeed, over the past 40 years, coffee’s reputation has changed for the better. In 1981, a 369-patient case control study reported on an unforeseen “strong association between coffee consumption and pancreatic cancer.” Since then, other studies have cited uncontrolled for confounders to explain this earlier, unexpected observation, drawing very different conclusions of their own: coffee now seems to confer health benefits, reduce cancer risk, and improve cancer outcomes.

Such favorable observations are plausible. Coffee is one of the most widely consumed beverages in the world and serves as a rich source for 1000+ compounds, such as polyphenols, melanoidins, diterpenes, and caffeine, many of which could enhance health. Although type of bean, method and degree of roasting, brewing procedure, and quantity and frequency of consumption could modulate health benefits, a growing literature base suggests that, for colorectal cancer, these effects might be overall favorable. For example, in a case control study that included more than 9000 individuals, Schmit et al reported that more than 2.5 servings of coffee per day decreased the risk of colorectal cancer (odds ratio, 0.46; 95% CI, 0.39 to 0.54; P<.0001 with the referent <1 serving per day). Similarly, in a secondary analysis of a prospective trial, Mackintosh et al reported on more than 1000 patients with locally advanced or metastatic colorectal cancer and concluded that increased coffee consumption was associated with decreased cancer progression (hazard ratio [HR] for a 1 cup/day increment up to 4 cups per day, 0.95; 95% CI, 0.91 to 1.00; P=.04 for trend) and decreased risk of death (HR for a one cup per day increment, 0.93; 95% CI, 0.89 to 0.98; P=.004 for trend). By our quick and rough count, well over a dozen published studies have sought (and have often found) a direct association between coffee consumption and improved outcomes in patients with or at risk for colorectal cancer. Admittedly, these encouraging findings might be telling of nothing more than publication bias (studies that show no statistically significant findings often go unreported) and a dearth of prospective trials that have tested the salutatory effects of coffee as the primary outcome. Nonetheless, when viewed in aggregate, a growing body of literature suggests that coffee confers health benefits relevant to colorectal cancer.

Thus, in this issue of the Mayo Clinic Proceedings, the study from Ugai et al is provocative. Reporting findings from the Nurses’ Health Study and the Health Professionals Follow-Up Study, these investigators showed no association between coffee consumption and improved colorectal cancer-specific mortality. However, in non-primary, multivariable analyses, these investigators observed that with increasing coffee consumption, patients with high Crohn-like lymphoid reaction manifested a lower risk of death (HR, 0.55; 95% CI, 0.37 to 0.81; P=.002 [for trend]).

First described in 1990, Crohn lymphoid reaction is a peritumoral clustering of lymphocytes near the cancer’s border and can occur in the absence of Crohn disease. This clustering appears to unfold sequentially, manifesting a predominance of CD4+ T cells early on; an increase in B cells over time; and, eventually, a lymphoid structure that...
appears — and ostensibly is — functionally surveillant. Crohn-like lymphoid reaction has been associated with favorable outcomes in other studies, even in patients with deficient DNA mismatch repair cancers, which tend to carry a more favorable prognosis. Similar to Crohn lymphoid reaction, other patterns of lymphoid aggregates, including peritumoral lymphocytic reactions, intratumoral periglandular reactions, and tumor-infiltrating lymphocytes, have also been described as having prognostic significance.8

In this context, the study from Ugai et al7 is important because it merges epidemiological findings with mechanism-based observations, thus suggesting insights into how and why coffee might confer such benefits to patients with colorectal cancer.

What message can we glean from this study from Ugai et al7? Should we all start drinking coffee — or start drinking more coffee (but perhaps no more than 4 to 5 cups per day) — to prevent colorectal cancer? Should we advise patients with colorectal cancer to do the same? For at least three reasons, we believe the answers to these last two questions remain unknown. First, the findings from Ugai et al7, in some respects, run counter to earlier observations that coffee intake improves outcomes in colorectal cancer patients. These investigators “did not observe a significant association of coffee intake with colorectal cancer-specific mortality.” Further, even with respect to Crohn-like lymphoid reaction, the findings fell short of these investigators’ primary hypothesis, as the authors themselves explain in their Mayo Clinic Proceedings paper: “Although statistical significance was not reached at the stringent level (alpha = 0.005), the association of coffee intake with colorectal cancer-specific mortality differed by Crohn-like lymphoid reaction (P=0.007 [interaction]).” In short, this important study provides enticing observations but no definitive, clinically instructive conclusions. Second, this recent paper is not these investigators’ first foray into examining coffee intake and immune markers in patients with colorectal cancer. Earlier, Ugai et al9 examined immune cell densities in colorectal cancer tissue based on coffee consumption; they reported no association between coffee intake and colorectal cancer when these malignancies were classified based on intraepithelial or stromal T-cell densities, as derived from multiplex immunofluorescent assays of CD3, CD4, CD8, CD45RO, and FOXP3. Perhaps the key to understanding the inconsistency of findings reported earlier and those reported now is the recognition that these two studies used different methods to describe lymphocytic infiltration. An absence of a much-needed universal scoring system to denote the pattern and frequency of lymphocytic infiltrates in solid tumors might well account for these divergent findings. Nonetheless, the discrepant conclusions between these papers are noteworthy, leaving us still a bit puzzled about how coffee consumption might improve outcomes for patients with colorectal cancer.

Third and finally, colorectal cancer is now the second leading cause of cancer death in the United States. Rates appear to be declining in the general population, but for reasons that remain elusive this cancer is on the rise in young adults. And coffee consumption also seems to be on the rise in young adults.10 Based on the totality of published epidemiological studies and on temporal trends of potentially culpable explanatory factors and outcomes, it seems highly unlikely that coffee could be negatively implicated in this rise in cancer incidence in young adults. However, now more than ever before — we need more research to learn how to reverse these disturbing trends. The study from Ugai et al7 underscores the need to conduct carefully monitored clinical trials and other such research that tests mechanistically plausible lifestyle interventions — such as coffee consumption — with the goal of finding ways to decrease cancer risk and to improve cancer outcomes, particularly among those at inexplicably high risk. Before formally advising patients to start drinking coffee or to...
drink more of it, we need to know the results of such research. “The power of a good cup of coffee” might perhaps be harnessed to decrease the incidence of colorectal cancer and to improve outcomes in patients who have been diagnosed with this malignancy.

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