Medical News

Lifestyle and Cancer Survival, the Best Time of Day for Treatment, and More—Highlights From ASCO

Rita Rubin, MA

Lifestyle changes to improve survival among patients with colon cancer and the benefits of receiving immunochemotherapy earlier in the day were among the topics covered at the recent annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago.

After the meeting, *JAMA* Associate Editor Kimmie Ng, MD, MPH, spoke with JAMA Medical News about new research presented on extending the lives of patients with cancer and optimizing late-phase clinical trials of cancer therapies. Ng is associate chief of the division of Gastrointestinal Oncology at the Dana-Farber Cancer Institute and an associate professor of medicine at Harvard Medical School.

Multimedia

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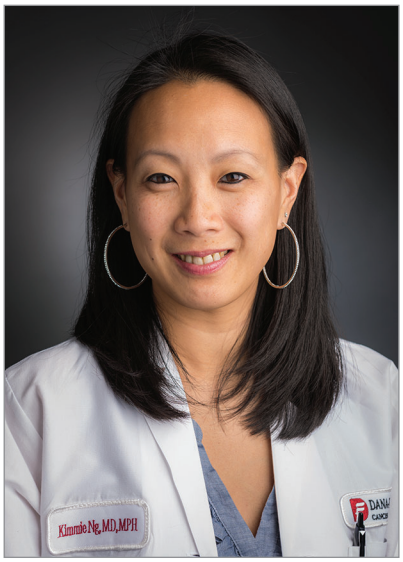
This interview has been edited for clarity and length.



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JAMA: Several interesting studies investigated the relationships between cancer and exercise, diet, and weight. One of these studies was the CHALLENGE [Colon Health and Lifelong Exercise Change] trial, the first randomized clinical trial of exercise that found a survival benefit. Trial participants had stage III or high-risk stage II colon cancer. What's the takeaway for clinicians and patients?

DR NG: I was extremely excited to hear the results of this study, which have been eagerly anticipated for many years. Many preclinical and observational studies have shown that higher levels of physical activity are associated with a decreased risk of cancer recurrence and improved survival in patients with colorectal cancer. But until this meeting there had not been causal evidence from a randomized clinical trial about the benefits of exercise.

In this study, which was run by the Canadian Cancer Trials Group and conducted in Canada and Australia, researchers enrolled nearly 900 patients with stage III [or high-risk stage II] colon cancer who had undergone surgery as well as chemotherapy. They were randomized to either a 3-year structured exercise program with health education materials or, in the control arm, just the health education materials. This structured exercise program was quite intensive. There were mandatory behavioral support and supervised exercise sessions, all conducted with a certified physical activity consultant. But they succeeded in increasing the amount of moderate aerobic exercise in the intervention group compared with the control group. The study showed a statistically significant benefit in the primary end point of disease-free survival with a hazard ratio of 0.72. So very exciting data, and, really, the benefit seen is equivalent to many [US Food and Drug Administration] FDA-approved drugs for this cancer in this space.

JAMA: Did they also look at whether the intense exercise contributed to weight loss?

DR NG: They did, and interestingly, there was no significant difference in body mass index or waist circumference measurements between the 2 arms. Largely the benefits were independent of weight loss. Some people may wonder whether the benefit of exercise on survival is due to improving other health outcomes, but actually it was really through improving cancer outcomes. It was mostly related to decreasing the risk of colon cancer recurrence and the incidence of second primary cancers. Exercise really affects cancer outcomes.

JAMA: That is very exciting. You're the senior author of an observational study that examined the relationship between a proinflammatory diet and outcomes for patients with stage III colon cancer. You also looked at whether exercise might attenuate the association. What is a proinflammatory diet and why might it lead to worse outcomes in people with colon cancer?

DR NG: We were also excited by the findings of this study, which support the CHALLENGE randomized trial that we just talked about. It's been known for a while that systemic inflammation is implicated in colorectal cancer pathogenesis, and it's been shown that certain dietary patterns and foods can also increase systemic inflammation. We calculated a score called the empirical dietary inflammatory pattern [EDIP] and tried to see if that score, which correlates intake of certain foods with levels of plasma inflammatory markers, is associated with outcomes in patients with stage III colon cancer who were enrolled in a national cooperative group clinical trial.

We found that people who consumed a more proinflammatory diet seemed to have worse survival compared with those who consumed a less inflammatory diet. We also found that those who consumed the least inflammatory diets and exercised the most had the best overall survival compared with people who ate more proinflammatory diets and had the least amount of exercise.

JAMA: What are some proinflammatory and anti-inflammatory foods?

DR NG: The EDIP score considered 9 food groups that are regarded as proinflammatory,

and they're the usual suspects: red and processed meats, energy drinks, refined grains. The EDIP score also considered 9 food groups that are considered anti-inflammatory, including vegetables, coffee, and tea.

JAMA: It seems like almost every week we hear about another potential use for GLP-1 [glucagon-like peptide-1] receptor agonists, the weight loss and type 2 diabetes drugs that seem to have taken the US by storm. An observational study presented at ASCO looked at the rates of 14 obesity-related cancers in 170 000 US adults with both obesity and diabetes. The researchers compared people treated with DPP-4 [dipeptidyl peptidase 4] inhibitors, a class of oral diabetes drugs not associated with weight loss, with patients who had been treated with GLP-1 receptor agonists. They found that the patients who had received GLP-1 receptor agonists were a little less likely to be diagnosed with or die of the obesity-related cancers.

What are some of the most common obesity-related cancers? Do you think weight loss might fully explain the modestly lower risk of these cancers in patients treated with GLP-1 receptor agonists? Or could there be something about the drugs themselves other than their effect on weight?

DR NG: We have been wanting data about whether these drugs can protect against the development of obesity-associated cancers for a long time. Some of the most common obesity-associated cancers are many gastrointestinal cancers, including colon cancer, rectal cancer, and pancreatic cancer, as well as endometrial cancer and breast cancer. Although the exact mechanisms of how obesity may lead to cancer are not known, theories include that it promotes inflammation, dysregulates hormones, causes an immunosuppressive environment, and may modulate the microbiome in unfavorable ways.

We saw from this study that there were modestly reduced risks of obesity-related cancers in users of GLP-1 receptor agonists compared with users of DPP-4 inhibitors. The association was largely driven by decreases in colorectal cancer, with a 16% decrease in colon cancer cases and a 28% decline in rectal cancer cases.

A subgroup analysis found that the benefit seemed to be greater among women using GLP-1 receptor agonists, particularly for all-cause death. But nobody yet knows whether these protective effects are true and, if so, whether they're due to decreasing obesity or an independent mechanism.

JAMA: The study was done in patients who had obesity as well as diabetes, so it doesn't say much about people who are taking these drugs for weight loss and don't have diabetes.

DR NG: That's right. A second study presented right after this one at the ASCO annual meeting looked at adults with obesity but not necessarily diabetes who were using GLP-1 receptor agonists. The results were different. There was an overall decreased risk of cancer, but they didn't see a significant decrease in colorectal cancer. There are many conflicting results out there, and I think that some of the limitations include numbers of cases of each of these cancers that are too small to make definitive conclusions about specific cancer types.

JAMA: Speaking of colorectal cancer, there was another really interesting study that was published in *JAMA* during the ASCO annual meeting and first reported earlier this year at the ASCO Gastrointestinal Cancer Symposium. That study examined the use of a blood test for circulating tumor DNA to screen for colorectal cancer. There's a great deal of interest in a screening blood test for colorectal cancer because, of course, it would be much less invasive than a colonoscopy. Could you tell us about the study, which is the largest to date of a blood-based colorectal cancer screening test?

DR NG: Colorectal cancer is unique in that there are effective screening tests for it, but there are barriers to many of them. As you mentioned, colonoscopies are invasive, and you need to get anesthesia and do a prep. And there are also many reasons why people may not be willing to do stool-based tests, which are also approved for colorectal cancer screening. So yes, there's a lot of enthusiasm about a blood-based test for colorectal cancer screening.

This study enrolled average-risk adults aged 45 to 85 years who were asymptomatic and were going to undergo a standard-of-care screening colonoscopy. All these individuals had a blood draw done for a circulating tumor DNA test from a company called Freenome. This test does next-generation sequencing and then uses artificial intelligence and machine learning–based models to detect a unique methylation signature associated with advanced colorectal neoplasia.

The primary end point was to clinically validate this test and look at sensitivity for colorectal cancer and specificity for advanced colorectal neoplasia as well as negative and positive predictive values for advanced colorectal neoplasia. And they did find that all of their end points met their prespecified thresholds with about a 79% sensitivity for detecting colorectal cancer and a 92% specificity for advanced colorectal neoplasia, which also includes high-risk polyps. So this does add to the armamentarium of tools for screening for colorectal cancer. It does seem pretty equivalent to other blood-based tests that are now FDA-approved for colorectal cancer screening as well as many of the stool-based tests. But it's probably not as good as some of the multitargeted stool detection tests that are out there and certainly not as good as colonoscopy still, particularly for discovering preneoplastic lesions, which is really how you enable colorectal cancer prevention and not just early detection.

JAMA: Will this test become another screening tool for colorectal cancer anytime soon?

DR NG: If regulatory authorities approve the test, it will become another way to do screening. The US Preventive Services Task Force realizes that there are a variety of different barriers for different individuals with any of these screening tests. And they really emphasize the need to have a menu of different options for patients to consider in terms of what is the best screening test for them. My takeaway has always been the best screening test is the one that gets done.

JAMA: There have been intriguing retrospective studies across 10 types of cancer that have suggested that infusing immunochemotherapy early in the day rather than later increased efficacy. At ASCO, results of the first randomized phase 3 clinical trial to examine this question were presented. This trial randomized 210 patients with non–small cell lung cancer to receive their initial 4 immunochemotherapy cycles either before or after 3 PM, an interesting cutoff for early vs late. After an average follow-up of 19 months, the researchers did find a difference in treatment efficacy depending on the time of day it was administered.

Could you provide a little more detail about what they found and why the time of day might make a difference in treatment efficacy?

DR NG: I found this study to be fascinating. There are a lot of preclinical data as well as observational data suggesting that circadian rhythms impact everything from sleep to disease incidence to treatment, and they may be associated with how well your immune system functions as well. Multiple retrospective studies and meta-analyses that have indicated better results with immunotherapy when these drugs are given earlier in the day.

You mentioned the cutoff of 3 PM, and that was a question posed to the authors at the ASCO annual meeting. They said that they did multiple sensitivity analyses looking at different time cutoffs for different times of day and found that the most promising results were associated with this 3 PM cutoff. I don't know that there's a biological rationale yet for that, but it was based on some preliminary analyses they did.

They found a doubling of the progression-free survival among patients who were receiving immunochemotherapy prior to 3 PM with an improvement from 5.7 months in the control group to 11.3 months in the early administration group. They also found significant improvements in the secondary end point of overall survival, again in favor of the patients who received these regimens earlier in the day.

And then what I found very interesting was that they also tried to correlate this with immune cell subsets in the peripheral circulation. So they drew blood samples in the morning from everybody on the study at baseline and then after 2 and 4 cycles. And what they found was increased peripheral circulating CD8-positive T cells among patients receiving these treatments earlier in the day and a decrease in CD4-positive T cells. And when they did flow cytometry, they showed that the ratio of activated vs exhausted CD8-positive T cells was greater among the early time administration group.

So that certainly lends some biological support that perhaps the timing of administration of immunotherapy may indeed be affecting the immune system function in these patients.

JAMA: You mentioned that the trial showed greater progression-free survival in the patients treated before 3 PM. That's a good segue to another study, one that was presented at the ASCO annual meeting and published simultaneously in *JAMA Oncology*. It suggested that surrogate end points such as progression-free survival in phase 3 randomized clinical trials of cancer treatments might not necessarily reflect what's most important to patients. What do the authors of that study conclude might be more meaningful end points for future late-phase cancer treatment trials?

DR NG: Alternative end points such as progression-free survival are on the rise for phase 3 clinical trials for many good reasons. You get results faster, and event rates are higher. You need to enroll fewer patients in these trials, which reduces the costs of conducting them, and, arguably, patients get access to effective therapies faster.

But they really honed in on the point that the end points that matter for patients are overall survival and quality of life. Many studies report positive results in terms of the [alternative] primary end point but do not subsequently show superiority in overall survival or quality of life. The authors found that only 28% of the trials that reported positive results also demonstrated an improvement in overall survival and only 11% demonstrated improvements in quality of life end points. And when you look at both of those important end points combined together, only 6% of those trials actually showed improvements in both.

Now, there are some caveats to this. Many studies that are powered for a progression-free survival primary end point are not necessarily powered to detect the overall survival end point, but it doesn't mean it's not there. This study highlights the importance of paying attention to these outcomes. I think it requires talking to regulatory authorities about how we may still be able to demonstrate improvement in these outcomes with these trials. ■

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Note: Source references are available through embedded hyperlinks in the article text online.