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Diet- and Lifestyle-Based Prediction Models to Estimate Cancer Recurrence and Death in Patients With Stage III Colon Cancer (CALGB 89803/Alliance)

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PURPOSE Current tools in predicting survival outcomes for patients with colon cancer predominantly rely on clinical and pathologic characteristics, but increasing evidence suggests that diet and lifestyle habits are associated with patient outcomes and should be considered to enhance model accuracy.

METHODS Using an adjuvant chemotherapy trial for stage III colon cancer (CALGB 89803), we developed prediction models of disease-free survival (DFS) and overall survival by additionally incorporating self-reported nine diet and lifestyle factors. Both models were assessed by multivariable Cox proportional hazards regression and externally validated using another trial for stage III colon cancer (CALGB/SWOG 80702), and visual nomograms of prediction models were constructed accordingly. We also proposed three hypothetical scenarios for patients with (1) good-risk, (2) average-risk, and (3) poor-risk clinical and pathologic features, and estimated their predictive survival by considering clinical and pathologic features with or without adding self-reported diet and lifestyle factors.

RESULTS Among 1,024 patients (median age 60.0 years, 43.8% female), we observed 394 DFS events and 311 deaths after median follow-up of 7.3 years. Adding self-reported diet and lifestyle factors to clinical and pathologic characteristics meaningfully improved performance of prediction models (c-index from 0.64 [95% CI, 0.62 to 0.67] to 0.69 [95% CI, 0.67 to 0.72] for DFS, and from 0.67 [95% CI, 0.64 to 0.70] to 0.71 [95% CI, 0.69 to 0.75] for overall survival). External validation also indicated good performance of discrimination and calibration. Adding most self-reported favorable diet and lifestyle exposures to multivariate modeling improved 5-year DFS of all patients and by 6.3% for good-risk, 21.4% for average-risk, and 42.6% for poor-risk clinical and pathologic features.

CONCLUSION Diet and lifestyle factors further inform current recurrence and survival prediction models for patients with stage III colon cancer.

INTRODUCTION

In 2021, an estimated of 149,500 new cases of colorectal cancer (CRC) will be diagnosed in the United States, and it is the fourth most common cancer diagnosed annually.[1] Advances in surgery and adjuvant chemotherapy over the past decades have improved 5-year overall survival (OS).[2,3] Nonetheless, approximately 36% of stage III patients will experience cancer recurrence following appropriate surgery and adjuvant therapy.[4-6] Thus, there remains a critical clinical need to define new methods to reduce cancer recurrence and mortality and improve patient outcome.

Current prediction tools in stage III colon cancer rely on clinical and pathologic characteristics, such as age, sex,

positive lymph nodes, and T stage, to predict survival outcomes.[7-14] However, recent prospective observational studies among patients with colon cancer suggest that diet and lifestyle factors may significantly influence the risk of colon cancer recurrence and death.[15-18] Given the growing body of evidence that post-diagnosis diet and lifestyle is associated with colon cancer survival, the inclusion of diet and lifestyle components into current prediction models may enhance model accuracy and assist clinicians and patients to better estimate cancer outcomes. To improve likelihood estimates of being disease-free and alive following cancer diagnosis and treatment, clinicians could provide additional diet and lifestyle interventions

CONTEXT

Key Objective

Increasing evidence suggests that diet and lifestyle habits are associated with survival after colon cancer diagnosis. Current clinically and pathologically based prediction models for survival outcomes for colon cancer do not incorporate diet and lifestyle habits.

Knowledge Generated

Using two cohorts derived from multicenter randomized trials, we developed and validated prediction models by clinical, pathologic, diet, and lifestyle characteristics of patients with colon cancer to estimate 5-year disease-free survival and overall survival. The addition of diet and lifestyle to established clinical and pathologic features improved the prediction of prognosis. Regardless of different risks in clinical and pathologic features, patients with healthy diet and lifestyle were predicted to experience improved survival and a reduction in the risk of cancer recurrence and death.

Relevance

These models could serve as important tools for personalized survival prediction. Through diet and lifestyle modifications, clinicians and patients could work together to meaningfully improve cancer outcome.

to patients. As such, we sought to develop prediction models for 5-year disease-free survival (DFS) and OS by clinical, pathologic, diet, and lifestyle characteristics among patients with stage III colon cancer.

METHODS

Study Population

Between April 1999 and April 2001, 1,264 patients with stage III colon cancer were enrolled in a National Cancer Institute–sponsored multicenter adjuvant chemotherapy trial in the Cancer and Leukemia Group B (CALGB), now Alliance for Clinical Trials in Oncology, 89803 study. Patients were randomly assigned for (1) once weekly fluorouracil and leucovorin or (2) once weekly irinotecan, fluorouracil, and leucovorin, and their clinical characteristics were collected. Additionally, a self-administered questionnaire was completed by patients to collect their demographics, anthropometrics, medication use, medical and family history, diet, and lifestyle during the period they were receiving adjuvant therapy (4 months following surgical resection), and again 6-8 months after completion of adjuvant therapy (14-16 months following surgical resection). The study was approved by institutional review boards of each participant institution. All patients signed informed written consent forms in compliance with well-accepted ethical guidelines. This analysis followed the reporting guideline of the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[19]

More details about the study protocol has been described previously.[20] The Data Supplement (online only) illustrates the derivation of the final study population of 1,024 patients. Briefly, 1,095 (87.0%) patients completed questionnaire 1 (Q1) once in the third cycle of their adjuvant chemotherapy course, and 978 (77.4%) patients completed the same questionnaire (Q2) 6 months after completing adjuvant therapy. For Q1, 1,062 (84.0%) questionnaires were considered valid after excluding the ones (N = 33) with ≥ 70 food items blank or unrealistic calorie intake (< 600 calories or > 4,200 calories per day for men, and < 500 calories or > 3,500 calories per day for women). Thirty-eight patients were further excluded because of recurrence or death within 90 days after completion of Q1.

Clinical and Pathologic Characteristics

Patients reported age, sex, ethnicity, height, weight, and family history of CRC via the questionnaires. Through clinical notes of participating institutions and Alliance Pathology Coordinating Laboratory, performance status, bowel wall invasion (T stage), bowel obstruction, positive lymph nodes ratio, and tumor location were carefully collected and confirmed.

Diet and Lifestyle

In line with other studies,[17,18,21-23] the following characteristics have been reported to be associated with improved DFS among patients with colon cancer in CALGB 89803: healthy diet (higher intake of coffee, nuts, dark meat fish, and lower intake of sugar-sweetened beverage and refined grains), aspirin and cyclooxygenase-2 (COX-2) inhibitor use, physical activity, higher vitamin D status, nonsmoking, and adequate body mass index (BMI).[24-33] Additionally, after exhaustively exploring the associations of all dietary components and lifestyle factors with survival in CALGB 89803, we found that higher intake of lycopene-rich vegetables had strong effects that few studies reported before. Thus, by a priori criteria and discovery in CALGB 89803, we considered the following diet and lifestyle factors for modeling: coffee, nuts, dark meat fish, sugar-sweetened beverage, refined grains, lycopene-rich vegetables, aspirin and COX-2 inhibitor use, physical activity, predicted 25-hydroxyvitamin D [25(OH)D] score, smoking behavior, and BMI.

Patients completed a validated semiquantitative food frequency questionnaire (FFQ) that assessed 131 self-reported food items, vitamin and mineral supplement use, and medication use in the past 3 months, with up to nine frequency choices ranging from never to six or more times per day.[34,35] Although self-reported diet and lifestyle exposures may not reflect the whole spectrum of true diet and lifestyle, we have validated this FFQ among patients with cancer receiving chemotherapy and found that it could act as an informative and practical tool.[36] Intake of coffee, nuts, dark meat fish, lycopene-rich vegetables, sugar-sweetened beverage and refined grains, and the use of aspirin and COX-2 inhibitors were assessed subsequently. Patients also reported average time per week during the past two months for nine common recreational activities (duration ranging from 0 to 11 or more hours per week).[30] We assigned a metabolic equivalent task (MET) score to each activity, multiplied the reported time engaged in that activity by its MET score, and then estimated total MET hours per week by summing all multiplication.[37] The predictive level of plasma 25(OH)D, a metabolite to reflect vitamin D status, was calculated using a robust regression model.[38] Details regarding tobacco use in the past and the present among patients were also collected via questionnaires, and further categorized into never, past, or current smoking.[32] BMI was derived using self-reported weight and height. We estimated diet and lifestyle exposures using cumulative averaging, as previous described,[20,39] and the categories of these exposures were constructed on the basis of the levels reported in previous publications.[24-33]

Outcome and Measures

The primary outcome was DFS, defined as time from the completion of Q1 to colon cancer recurrence, occurrence of a new primary colon cancer, or death from any cause. We also estimated OS, defined as time from the completion of Q1 to death from any cause.

Statistical Analysis

There was no statistically significant difference in OS or DFS in both arms of the randomized trial.[40] Therefore, patient data from both arms were combined and analyzed according to frequency categories of diet and lifestyle. In addition to descriptive analysis of the final study population (N = 1,024), we compared the demographic and clinical characteristics of included and excluded patients and found minor differences for most characteristics except T stage (Data Supplement).

For model parsimony and clinical applications, we did not include interaction terms and applied stepwise variable selection procedure for all diet and lifestyle variables at the significance level of 0.15,[41] resulting in exclusion of predicted 25(OH)D score and smoking behavior for final models. By including clinical and pathologic characteristics alone or in combination with selected diet and lifestyle variables, multivariable Cox proportional hazards regression and the

Breslow method were applied for DFS and OS to estimate hazard ratios of different characteristics and their corresponding coefficients.[42,43] Missing data were substituted with median values of continuous variables and most frequent values of categorical variables.[44] The Schoenfeld residuals method was used to test proportional hazards assumption and no violation was detected.[45] Visual nomograms of prediction models were subsequently constructed for DFS and OS with clinical, pathologic, diet, and lifestyle characteristics.[46,47] Among each characteristic, features with higher points would ultimately result in worse survival.

To further illustrate how diet and lifestyle may improve survival estimates, we proposed three hypothetical scenarios for patients with (1) good-risk, (2) average-risk, and (3) poor-risk clinical and pathologic features. We compared the changes in their survival estimates if such estimates were calculated on the basis of only clinical and pathologic features versus addition of most or least favored diet and lifestyle factors. Relative risks (RR) were derived accordingly, by treating predicted survival estimated with only clinical and pathologic features as the reference level. For clinical and pathologic features, good risk and poor risk referred to the level with the lowest point (ie, zero) and the highest point, respectively; whereas average risk corresponded to the most frequent level among each characteristic (Table 1). For this analysis, the characteristics of average-risk patients included age < 65 years, male, performance status as 0, T3 stage, no bowel obstruction, no family history of CRC, positive lymph nodes ratio as 0.2, and right-sided tumor location. For diet and lifestyle factors, most and least favored feature referred to the level with the lowest point (ie, zero) and the highest point, respectively.

To assess goodness of fit of modeling, we calculated the Gronnesby-Borgan test statistic, a more robust statistic for survival data than Hosmer-Lemeshow's statistic for calibration: P value < .05 suggests lack of fit.[48,49] The concordance index (c-index) was estimated to evaluate modeling performance to predict outcomes, and higher c-index indicates better performance.[46] The c-indices of prediction models comprising clinical characteristics alone or in combination with diet and lifestyle characteristics were compared with likelihood-ratio tests.[50] The models were further internally validated using bootstrapping to obtain optimism-corrected c-index and calibration curves,[46,51] and externally validated using another recent National Cancer Institute–sponsored adjuvant chemotherapy trial (CALGB/SWOG 80702) to evaluate discrimination and calibration.[52] Among CALGB/SWOG 80702, 2,526 patients with stage III colon cancer were enrolled between 2010 and 2015 and were followed up through 2020, and we observed 700 patients experiencing recurrence or death. Of these patients, the median age was 61.3 (interquartile range, 53.7-68.7) years, 44.9% were female, and 79.1% were White. CALGB 80702 had a similar study design as CALGB 89803 in collecting diet and lifestyle information; in each

TABLE 1. Characteristics of 1,024 Patients With Stage III Colon Cancer in CALGB 89803

Characteristic[a]	Included Patients (N = 1,024)
Age, years	
Median (IQR)	60.0 (51.0-69.0)
≥ 65, No. (%)	395 (38.6)
Female, No. (%)	448 (43.8)
Ethnicity	
White	909 (88.8)
Black	68 (6.6)
Other	47 (4.6)
ECOG performance status,[b] No. (%)	
0	750 (73.2)
1-2	253 (24.7)
Unknown	21 (2.1)
Bowel wall invasion by T stage, No. (%)	
T1-2	137 (13.4)
T3	793 (77.4)
T4	70 (6.8)
Unknown	24 (2.3)
Bowel obstruction, No. (%)	224 (21.9)
Positive lymph nodes ratio,[c] median (IQR)	0.2 (0.1-0.4)
Tumor location, No. (%)	
Left-sided	383 (38.2)
Right-sided	386 (38.5)
Multi	36 (3.6)
Transverse/flexure	198 (19.7)
Unknown	21 (2.1)
Family history of CRC, No. (%)	186 (18.2)
Treatment arm, No. (%)	
Fluorouracil + leucovorin	516 (50.4)
Irinotecan, fluorouracil, and leucovorin	508 (49.6)
Aspirin and COX-2 inhibitor use, No. (%)	149 (14.6)
Physical activity, MET-hours/week	
0-8.9	589 (57.5)
≥ 9	435 (42.5)
Predicted 25(OH)D score, ng/mL[d]	
Median (IQR)	27.6 (25.2-29.8)
> 30, No. (%)	204 (19.9)
Coffee (serving[e]/day), No. (%)	
0-1	640 (62.5)
2+	384 (37.5)
Nuts > 0 serving[e]/week, No. (%)	868 (84.8)
Dark meat fish > 1 serving[e]/month, No. (%)	434 (42.4)

(continued in next column)

TABLE 1. Characteristics of 1,024 Patients With Stage III Colon Cancer in CALGB 89803 (continued)

Characteristic[a]	Included Patients (N = 1,024)
Lycopene-rich vegetables ≥ 2 servings[e]/ week, No. (%)	617 (60.3)
SSB ≥ 3 servings[e]/week, No. (%)	448 (43.8)
Refined grains (serving[e]/day), No. (%)	
0-0.9	161 (15.7)
1-2.5	564 (55.1)
> 2.5	299 (29.2)
Smoking status, No. (%)	
Never	459 (44.8)
Current	114 (11.1)
Past	451 (44.0)
BMI, kg/m^2	
Median (IQR)	27.6 (24.4-31.7)
< 30, No. (%)	677 (66.1)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MET, metabolic equivalent task; SSB, sugar-sweetened beverage.

[a]Continuous variables were presented as median (IQR), and categorical variables as number (percentage). Percentages may not add up to 100% because of rounding.

[b]ECOG 0 indicates patients who are fully active, able to carry on all predisease performance without restriction. ECOG 1 indicates patients who are restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. ECOG 2 indicates patients who are ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

[c]Number of missing for positive lymph nodes ratio: 27.

[d]Predicted 25(OH)D score was computed using validated regression models proposed by the reference.[40]

[e]One serving was defined as follows: coffee (1 cup); nuts (1 oz); dark meat fish (3-5 oz); SSB (1 glass or bottle or can); refined grain (1-3 pieces). SSB included caffeine/caffeine-free cola, any carbonated beverage, and fruit drinks. Lycopene-rich vegetables included tomatoes, tomato juice, and tomato sauce. Nuts included peanuts, other nuts, and peanut butter. Dark meat fish included mackerel, salmon, sardines, bluefish, and swordfish. Refined grains included sweet rolls, cake desserts, white bread, pasta, English muffins, muffins, biscuits, refined grain cereals, white rice, pancakes, waffles, and pizza.

trial, two FFQs were similarly administered during and after adjuvant chemotherapy. The full description of this population could be further found from a recent publication.[52]

Data collection was conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. All statistical analyses were 2-sided and conducted at Yale and Dana-Farber Cancer Institute using SAS statistical software, version 9.4 (SAS Institute, Inc) and R, version 4.0.2
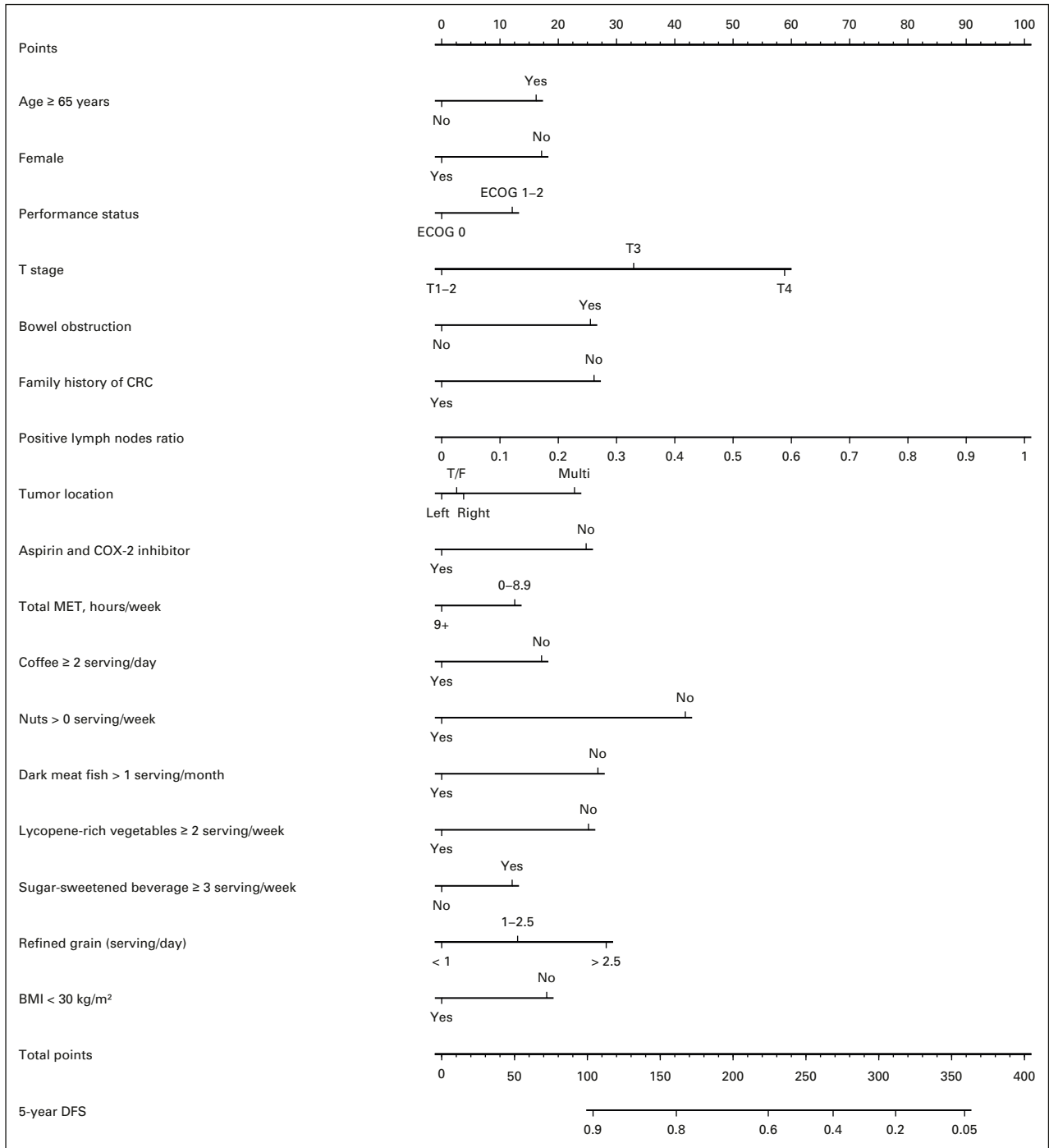
FIG 1. Nomogram for 5-year DFS. BMI, body mass index; COX-2, cyclooxygenase-2; CRC, colorectal cancer; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; MET, metabolic equivalent task; T/F, transverse/flexure.

(R Foundation for Statistical Computing) from March 23, 2019, to December 2, 2020. Estimates were presented with 95% CIs and P value < .05 was considered as statistically significant. Multiple comparisons were not adjusted.

RESULTS

Among 1,024 patients (median follow-up: 7.3 years), we observed 311 deaths, 350 recurrences, and 394 events for DFS. Of these patients, the median age was 60.0 (interquartile range, 51.0-69.0) years, 43.8% were female, and 88.8% were White. Baseline clinical and pathologic characteristics as well as data on dietary and lifestyle factors for the cohort are presented in Table 1.

Model Construction

When only clinical and pathologic characteristics were included into multivariable analyses for prediction models,
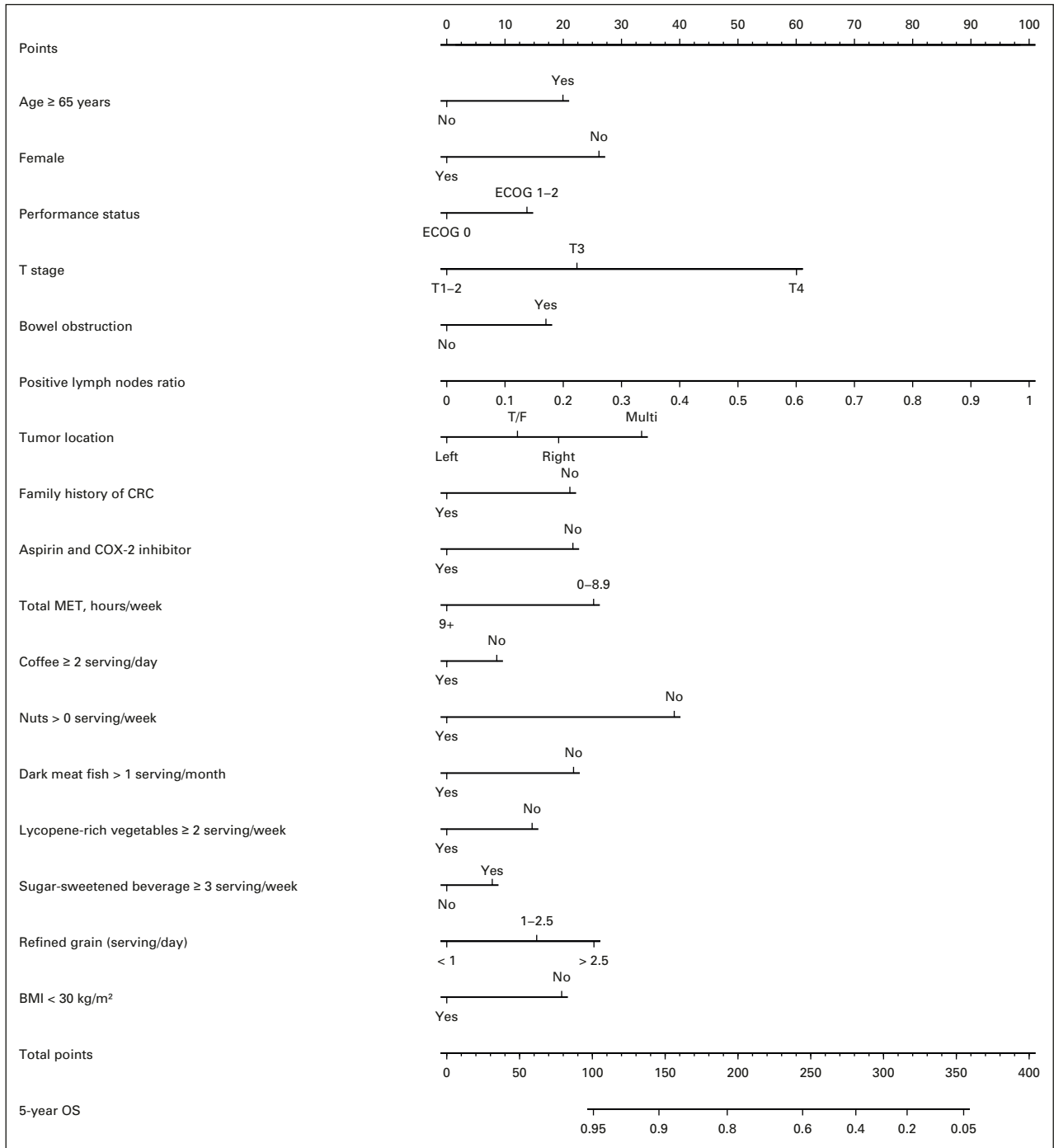
FIG 2. Nomogram for 5-year OS. BMI, body mass index; COX-2, cyclooxygenase-2; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; MET, metabolic equivalent task; OS, overall survival; T/F, transverse/flexure.

age, sex, and tumor location were not significantly associated with DFS, and all factors were significantly associated with OS except bowel obstruction and family history of CRC. After incorporating diet and lifestyle variables into the DFS prediction model, sex was significantly associated with DFS but age and tumor location remained not, and additionally, performance status was found to be not significantly associated with DFS. Furthermore, aspirin

and COX-2 inhibitor use, coffee, nuts, dark meat fish, lycopene-rich vegetables, and BMI were significantly associated with DFS in the DFS prediction model. For the OS prediction model, bowel obstruction and family history of CRC were found to be significantly associated with OS, whereas performance status and tumor location were not significantly associated with OS. Furthermore, physical activity, nuts, dark meat fish, and BMI were significantly

associated with OS. More details are presented in the Data Supplement.

Assessment of Prediction Model Performance

Including diet and lifestyle factors into the prediction model improved the c-index from 0.64 (95% CI, 0.62 to 0.67) to 0.69 (95% CI, 0.67 to 0.72) for DFS, and from 0.67 (95% CI, 0.64 to 0.70) to 0.71 (95% CI, 0.69 to 0.75) for OS. The performance improvement was significant ($P_{difference} < .001$) and aligned with optimism-corrected c-indices (Data Supplement). Additionally, the calibration curves of observed versus predicted 5-year DFS and OS demonstrated substantial prediction accuracy (Data Supplement). External validation for both models also indicated good performance of discrimination and calibration (Data Supplement).

Nomograms, Survival, and RRs

The nomograms for DFS and OS are presented as Figures 1 and 2. Predicted 5-year DFS and OS can be estimated by first determining the point value on the basis of the clinical, pathologic, diet, and lifestyle factors of the patient. The sum of the point values across all characteristics on the nomogram then defines the corresponding 5-year DFS or OS. In the Data Supplement, we proposed a hypothetical patient as an example to inform survival estimation with specific clinical, pathologic, diet, and lifestyle characteristics, and more instructions for nomogram application could be found in the corresponding footnotes.

Five-year predicted survival and RRs for patients with different clinical, pathologic, diet, and lifestyle characteristics were presented in Table 2 and Figures 3A and 3B. Beyond only considering clinical and pathologic features, adding most favored diet and lifestyle would improve DFS in all hypothetical scenarios. The increases were 6.3% for good-risk, 21.4% for average-risk, and 42.6% for poor-risk clinical and pathologic features, and the risk of colon cancer recurrence or death for all patients decreased at least by 44.0% (the corresponding RR: 0.56 [95% CI, 0.32 to 0.87]). By contrast, adding least favored diet and lifestyle would decrease DFS by 24.3% for good-risk, 46.9% for average-risk, and 2.1% for poor-risk clinical and pathologic

TABLE 2. Five-Year Predicted Survival Rates (%)[a] and Corresponding RRs (95% CI)[b] Among Patients With Different Clinical, Pathologic, Diet, and Lifestyle Characteristics

	DFS		OS	
Characteristics	**5-Year**	**RR**	**5-Year**	**RR**
Good-risk clinical and pathologic features[c]				
Alone	91.0 (86.9 to 95.2)	1.00	95.8 (93.6 to 98.1)	1.00
+ Diet and lifestyle (most favored)[d]	97.3 (95.6 to 99.1)	0.29 (0.17 to 0.45)	99.0 (98.2 to 99.8)	0.25 (0.13 to 0.40)
+ Diet and lifestyle (least favored)[e]	66.7 (52.7 to 84.4)	3.69 (2.71 to 5.12)	82.4 (72.6 to 93.5)	4.24 (2.95 to 6.09)
Average-risk clinical and pathologic features[f]				
Alone	69.1 (63.2 to 75.6)	1.00	78.0 (72.8 to 83.5)	1.00
+ Diet and lifestyle (most favored)[d]	90.5 (85.8 to 95.4)	0.31 (0.19 to 0.46)	94.3 (91.0 to 97.7)	0.26 (0.14 to 0.42)
+ Diet and lifestyle (least favored)[e]	22.2 (11.9 to 41.2)	2.52 (2.07 to 3.05)	33.1 (20.1 to 54.7)	3.04 (2.37 to 3.86)
Poor-risk clinical and pathologic features[g]				
Alone	2.1 (0.19 to 23.7)	1.00	1.3 (0.1 to 24.1)	1.00
+ Diet and lifestyle (most favored)[d]	44.7 (23.7 to 84.4)	0.56 (0.32 to 0.87)	45.8 (23.3 to 89.8)	0.55 (0.30 to 0.90)
+ Diet and lifestyle (least favored)[e]	0 (0 to 2.3)	1.02 (1.00 to 1.14)	0 (0 to 2.3)	1.01 (1.00 to 1.11)

Abbreviations: BMI, body mass index; CRC, colorectal cancer; DFS, disease-free survival; OS, overall survival; RR, relative risk.

[a]Survival rates were estimated using direct adjusted survival curves by averaging the estimated survival curves of patients with the same characteristics.

[b]Relative risks were calculated using (1 − survival rate of the index group of interest) divided by (1 − survival rate of the reference group). 95% CIs were estimated using bootstrapping with 1,000 replicates.

[c]Good-risk clinical and pathologic factors included age < 65 years, female, performance status as 0, T1-2 stage, no bowel obstruction, family history of CRC, positive lymph nodes ratio as 0, and left-sided tumor location.

[d]Most favored diet and lifestyle included aspirin and COX-2 inhibitor use, physical activity ≥ 9 MET-hour/week, coffee ≥ 2 servings/day, nuts > 0 serving/week, dark meat fish > 1 serving/month, lycopene-rich vegetables ≥ 2 servings/week, sugar-sweetened beverage < 3 servings/week, refined grain < 1 serving/day, and BMI< 30 kg/m^2.

[e]Least favored diet and lifestyle included no aspirin and COX-2 inhibitor use, physical activity 0-8.9 MET-hour/week, coffee < 2 servings/day, nuts < 0 serving/week, dark meat fish ≤ 1 serving/month, lycopene-rich vegetables < 2 servings/week, sugar-sweetened beverage ≥ 3 servings/week, refined grain > 2.5 serving/day, and BMI ≥ 30 kg/m^2.

[f]Average-risk clinical and pathologic factors included age < 65 years, male, performance status as 0, T3 stage, no bowel obstruction, no family history of CRC, positive lymph nodes ratio as 0.2, and right-sided tumor location.

[g]Poor-risk clinical and pathologic factors included age ≥ 65 years, male, performance status as 1-2, T4 stage, bowel obstruction, no family history of CRC, positive lymph nodes ratio as 0.8, and multi-sided tumor location.
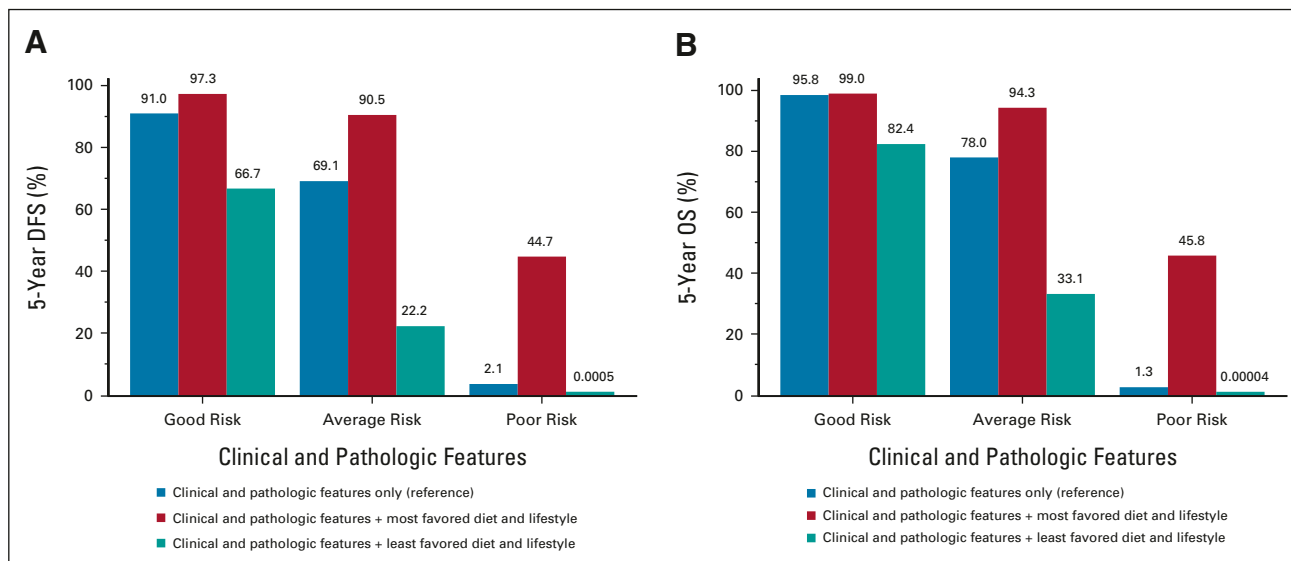
FIG 3. (A) Five-year predicted disease-free survival rates of patients with different clinical, pathologic, diet, and lifestyle characteristics. (B) Five-year predicted overall survival rates of patients with different clinical, pathologic, diet, and lifestyle characteristics. DFS, disease-free survival; OS, overall survival.

features, with RR for colon cancer recurrence or death increasing up to 3.69 (95% CI, 2.71 to 5.12). Similar patterns were observed for OS, although the magnitudes of RR were generally stronger.

DISCUSSION

In this prospective cohort of patients with stage III colon cancer, we found that compared with only considering established clinical and pathologic factors, patients who would maintain a healthy diet and lifestyle were predicted to experience improved survival and a reduction in the risk of cancer recurrence and death. Dietary and lifestyle components were associated with statistically significant higher c-index that indicates improvement of modeling performance. Models for DFS and OS were well calibrated and corresponding c-indices were 0.69 and 0.71 that were higher than the majority of prediction models on survival outcomes of CRC (median summarized c-index of 0.67),[7-13] indicating such improvement to be meaningful. External validation for both models also supports good performance of discrimination and calibration. To our knowledge, this is the first prediction model to assess DFS and OS on the basis of dietary and lifestyle factors in addition to clinical and pathologic characteristics.

Clinical decisions in estimating cancer recurrence or death following curative surgical resection generally focus on non-modifiable clinical and pathologic characteristics. By proposing three hypothetical scenarios for patients with (1) good-risk, (2) average-risk, and (3) poor-risk clinical and pathologic features, we demonstrated that the oversight of diet and lifestyle may misinform patients' survival estimates. Most favorable diet and lifestyle factors have demonstrated beneficial effects of reducing inflammation,[53,54] hypermethylation,[55] oxidation,[56] hyperglycemia,[57] hyperinsulinemia,[58] and insulin resistance,[59,60] which may lower cancer progression and contribute to

improved survival.[17,18] Especially among patients with poor-risk clinical and pathologic features, their 5-year DFS could be improved from 2.1% to 44.7% if patients would adhere to most favorable diet and lifestyle and such habits would be considered in survival prediction. By contrast, least favorable diet and lifestyle would result in worse survival via the reverse biologic pathway mentioned above, and decreased 5-year DFS from 69.1% to 22.2% among patients with average risk of clinical and pathologic features. Since clinicians may spend limited time assessing or advising patients to adopt healthy diet and lifestyles, their protective effects may not be fully understood by patients, resulting in poor adherence. Given that the prevalence of healthy diet and lifestyle in the United States is low and limited improvement has been observed over the past decade,[61-65] applications of our prediction models may facilitate clinicians in identifying patients at increased risk of cancer recurrence and death by virtue of less than optimal diet and lifestyle habits. Furthermore, this diet- and lifestyle-based tool enables clinicians to counsel patients on interventions toward healthier lifestyle approaches to prevent the development of cancer recurrence.

Our prediction models are not all-inclusive of all diet and lifestyle factors that may be predictive of cancer recurrence, but include most critical factors that could predict survival outcomes after colon cancer diagnosis. Given the fixed sample size, some dietary and lifestyle components were not statistically significantly associated with survival outcomes (P values > .05), indicating moderate loss of statistical precision because of more variables being incorporated into models.[46,51] However, higher intake of coffee, nuts, and dark meat fish, and lower intake of sugar-sweetened beverage and refined grains, aspirin and COX-2 inhibitor use, physical activity, and adequate BMI have been consistently associated with improved patient

outcome across multiple studies.[17,18,21-33] We relied on a relatively parsimonious diet and lifestyle model to assess cancer recurrence risk. Thus, clinicians only need to inquire six dietary components and three lifestyle relevant factors, rather than asking patients to fill long FFQs if all-inclusive prediction models are proposed. This will minimize the burden of information collect among clinicians and patients, help them rapidly inform personalized survival estimates in clinical practice, and decide their next step in cancer treatment, especially in diet and lifestyle modifications to improve survival estimates.

Our study has several strengths. First, to our knowledge, our prediction models are the first prediction tools including diet and lifestyle characteristics to predict survival after colon cancer diagnosis. Second, in contrast to the majority of prediction tools that did not adhere to appropriate statistical methodology,[13,14] our study strictly followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[66] Third, we developed models in a large randomized clinical trial where patient, disease, and treatment characteristics were well controlled, diet and lifestyle factors were well documented using extensively validated FFQs, and meticulous follow-up was uniformly conducted—contributing to improved prediction performance in theory. Furthermore, since CALGB 89803 is a multiple-center study enrolling patients across the United States and Canada[40] and external validation supports good performance in discrimination and calibration of our prediction models, we reasonably believe that our prediction models could be generalized to a broader population.

Several limitations should also be noted. First, because of data availability, some prognosis biomarkers were not included, but nomograms could be easily updated, which is one of the advantages of this type of prediction tool. Second, our prediction models may not reflect latest breakthroughs in colon cancer treatment, and thus, may underestimate survival rates. Nevertheless, our findings may still help clinicians and their patients optimistically evaluate survival expectations because patients' survival now should be, at least, higher than our estimates. Also, our findings convincingly encourage clinicians and their patients to incorporate diet and lifestyle modification into cancer treatment.

In conclusion, current prediction models for stage III colon cancer outcome rely exclusively on clinical and pathologic characteristics to estimate 5-year DFS and OS. In light of the growing body of evidence documenting the impact of postdiagnosis diet and lifestyle habits on the stage III colon cancer patient outcome, we derived prediction models that included diet and lifestyle factors, reporting that healthy diet and lifestyle were associated with a significantly lower risk of cancer recurrence and death, after adjusting for established clinical and pathologic features. These models could serve as an important tool for personalized cancer care, through diet and lifestyle modifications, and more efforts to meaningfully improve patient outcome. Given that such prediction models incorporating diet and other lifestyle factors are not available in other stages (I, II, and IV), further evaluation in other colon cancer populations is warranted.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Diet- and Lifestyle-Based Prediction Models to Estimate Cancer Recurrence and Death in Patients With Stage III Colon Cancer (CALGB 89803/Alliance)

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