Impact of Screening Colonoscopy on Outcomes in Colon Cancer Surgery

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IMPORTANCE Screening colonoscopy seemingly decreases colorectal cancer rates in the United States. In addition to removing benign lesions and preventing progression to malignancy, screening colonoscopy theoretically identifies asymptomatic patients with early-stage disease, potentially leading to higher survival rates.

OBJECTIVES To assess the effect of screening colonoscopy on outcomes of colon cancer surgery by reviewing differences in staging, disease-free interval, risk of recurrence, and survival and to identify whether diagnosis through screening improves long-term outcomes independent of staging.

DESIGN Retrospective review of prospectively maintained, institutional review board–approved database.

SETTING Tertiary care center with high patient volume.

PATIENTS All patients who underwent colon cancer surgery at Massachusetts General Hospital from January 1, 2004, through December 31, 2011.

INTERVENTION Colon cancer surgery.

MAIN OUTCOMES AND MEASURES Postoperative staging, death, and recurrence, measured as incidence and time to event.

RESULTS A total of 1071 patients were included, with 217 diagnosed through screening. Patients not diagnosed through screening were at risk for a more invasive tumor ($\geq$T3: relative risk [RR] = 1.96; P < .001), nodal disease (RR = 1.92; P < .001), and metastatic disease on presentation (RR = 3.37; P < .001). In follow-up, these patients had higher death rates (RR = 3.02; P < .001) and recurrence rates (RR = 2.19; P = .004) as well as shorter survival (P < .001) and disease-free intervals (P < .001). Cox and logistic regression controlling for staging and baseline characteristics revealed that death rate (P = .02) and survival duration (P = .01) were better stage for stage with diagnosis through screening. Death and metastasis rates also remained significantly lower in tumors without nodal or metastatic spread (all P < .001).

CONCLUSIONS AND RELEVANCE Patients with colon cancer identified on screening colonoscopy not only have lower-stage disease on presentation but also have better outcomes independent of their staging. Compliance to screening colonoscopy guidelines can play an important role in prolonging longevity, improving quality of life, and reducing health care costs through early detection of colon cancer.

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Since their introduction in 2000, National Institutes of Health–recommended screening colonoscopy guidelines seemingly have consistently decreased overall rates of colorectal cancer in the United States. The National Cancer Institute Surveillance Epidemiology and End Results database reported annual decreases in the incidence of colon cancer of 4.0% in 2002 to 2005 and 2.4% in 2005 to 2009.[1] As the vast majority of colorectal neoplasms arise from adenomas[2,3] and these precursor lesions are usually asymptomatic,[4] the increased detection is believed to contribute to the decrease of cancer diagnoses through detection of premalignant disease before it progresses to malignant disease.[5] In addition to removing benign lesions and preventing their progression to malignancy, screening colonoscopy can also identify asymptomatic patients with early-stage disease, potentially leading to higher survival rates.[6]

This study aims to assess the effect of screening colonoscopy on outcomes of patients with surgically treated colon cancer by reviewing differences in staging, disease-free interval, risk of recurrence, and survival. We also examine whether diagnoses made by screening colonoscopy have a better prognosis independent of tumor stage by comparing (disease-free) survival outcomes stage for stage in patients whose tumors were identified by screening and those whose tumors were not.

Methods

Patients

A retrospective review of an institutional review board–approved, prospectively maintained colon cancer database at Massachusetts General Hospital was performed. All patients treated surgically for colonic adenocarcinoma between January 1, 2004, and December 31, 2011, were reviewed for inclusion. We elected to include patients with colon cancer only because colon and rectal cancer differ in staging, treatment protocols, and stage-specific outcomes. Colon cancer was defined as any colonic tumor located proximal to the rectosigmoid junction.[7] Patients with a colon cancer diagnosed either through screening colonoscopy or through other means with perioperative pathological confirmation were included. Screening and nonscreening patients formed the 2 groups subsequently compared in this article.

The included population was controlled for the following baseline characteristics: age, sex, race, and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). Our primary outcomes were postoperative staging, survival, and disease-free interval. The 2 latter outcomes were expressed both as a time-related continuous number (duration in days) and as a dichotomous outcome (yes or no for recurrence or death). The screening and nonscreening groups were compared in terms of these primary outcomes as well as follow-up duration. Following this, survival and recurrence outcomes were compared pairwise, matching the subgroups stage for stage in their respective T, N, and M classifications, to assess whether there were any differences in the long-term outcomes within those stages. Kaplan-Meier sur-

Table 1. Distribution of Events Leading to Diagnosis

Event	No. (%) (N = 1071)
Screening	217 (20.3)
Nonscreening	854 (79.7)
Symptomatic	678 (63.3)
Hemoccult stool testing by FOBT	21 (1.9)
Suspect imaging	19 (1.8)
Asymptomatic anemia	42 (3.9)
Follow-up of polyps	49 (4.6)
Follow-up of earlier CRC	13 (1.2)
Other	32 (3.0)

Abbreviations: CRC, colorectal cancer; FOBT, fecal occult blood test.

vival curves stratified for these groups illustrated the differences visually. Lastly, these outcomes were verified for significant covariates in a multivariate model controlling for all encountered covariates.

Statistical Analysis

All statistical analysis was performed using the SPSS version 20.0 statistical software package (IBM SPSS Statistics for Windows; IBM Corp). $P < .05$ was considered statistically significant.

For continuous variables, normality of distribution was tested using a Shapiro-Wilk test. Normally distributed variables were compared using an independent samples t test, and nonnormal distributions used a Mann-Whitney U test to verify for any significant differences. We assessed the differences between ordinal variables using Cramér V. For nominal variables, we used χ^2 coefficients to assess for statistical significance of outcome differences. Kaplan-Meier survival curves and pairwise comparisons of staging used the log-rank (or Mantel-Cox) test to calculate the P values of differences between groups. Multivariate models used Cox regression.

Results

In total, 1071 patients were included, of whom 217 (20.3%) were diagnosed through screening colonoscopy and 854 (79.7%) were diagnosed through other means, including 678 (63.3%) presenting with symptoms. **Table 1** shows the detailed clinical presentation of these cases.

Baseline Characteristics

The baseline characteristics of both groups were as follows (**Table 2**). The nonscreening group had a higher rate of metastatic disease on presentation (relative risk [RR] = 3.37; 95% CI, 1.86-6.11; $P < .001$), was older (mean difference, 4.6 years; $P < .001$), and had a lower BMI (mean difference, 1.2; $P = .001$). Screening patients were more likely to be male ($P = .049$).

Direct Relationship With Outcomes

Table 3 and **Figure 1** demonstrate the distribution of patients according to TNM staging. On pathology, nonscreening patients compared with screening patients had a significantly

Table 2. Baseline Population Characteristics at Diagnosis

Characteristic	Screening (n = 217)	Nonscreening (n = 854)	P Value
Age, mean (SD), y	63.1 (10.4)	67.6 (14.6)	<.001
BMI, mean (SD)	28.6 (6.0)	27.4 (6.5)	.001
White, %	90.8	89.5	.57
Male, %	57.1	49.6	.049
Metastatic presentation, %	5.1	17.1	<.001
Preoperative chemotherapy, %	1.4	3.7	.08

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 3. Differences in Postoperative Staging

Staging	No. (%) Screening	No. (%) Nonscreening	P Value
T stage			
Tis	23 (10.6)	27 (3.0)	
T1	81 (37.3)	94 (11.0)	
T2	31 (14.3)	98 (11.5)	<.001
T3	65 (30.0)	404 (47.3)	
T4	31 (7.8)	232 (27.2)	
N stage			
N0	167 (77.0)	476 (55.7)	
N1	40 (18.4)	218 (25.5)	<.001
N2	10 (4.6)	160 (18.7)	
M stage			
M0	213 (98.2)	760 (89.0)	<.001

higher T stage (≥T3: 74.5% vs 37.8%, respectively; RR = 1.96; 95% CI, 1.65-2.35; $P < .001$), a higher risk of having nodal disease (44.2% vs 23.0%, respectively; RR = 1.92; 95% CI, 1.49-2.47; $P < .001$), and a higher risk of having stage M1 pathology (11.0% vs 1.8%, respectively; RR = 6.08; 95% CI, 2.26-16.36; $P < .001$).

Follow-up outcomes are shown in **Table 4**. Nonscreening patients compared with screening patients had significantly higher recurrence rates (13.1% vs 6.0%, respectively; RR = 2.19; 95% CI, 1.25-3.81; $P = .004$) and higher death rates (26.5% vs 8.8%, respectively; RR = 3.02; 95% CI, 1.94-4.71; $P < .001$) with shorter disease-free intervals (mean, 109 vs 150 weeks, respectively; $P < .001$) and survival duration (mean, 157.4 vs 196.1 weeks, respectively; $P < .001$). These differences were reflected in a shorter overall duration of follow-up (mean follow-up duration, 952 vs 1149 days, respectively; $P < .001$).

By plotting these outcomes on Kaplan-Meier survival curves (**Figure 2**), we illustrate the beneficial effects of a diagnosis through screening. A log-rank test confirms the visual pattern, which shows a significant, lasting gain in disease-free intervals ($P < .001$) and survival ($P < .001$). The curves also illustrate how the effect on both outcomes has the strongest effects within the first years of follow-up.

Stage-for-Stage Long-term Outcomes

The Kaplan-Meier curves in **Figure 3** show survival and disease-free survival over time, stage for stage, for both groups. A pattern of better outcomes in screening patients is observed throughout pathological stages, with the strongest differences manifesting in higher stages. **Table 5** lists the associ-

ated statistical measures of significance in stage-for-stage comparison. T stages largely fail to show statistical significance despite a clear pattern in the percentages; this could possibly be related to the dilution of the sample size of our relatively small screening population over 5 subgroups. N0 and M0 specimens show a highly significant difference ($P < .001$) between both groups in survival rate and metastasis-free portion, while screening diagnosis is also associated with better metastasis-free survival in N2 tumors ($P = .009$).

Multivariate Analysis

Our final analysis shows the effects of diagnosis type on the cumulative risks of death and recurrence as well as their cumulative survival and uses a model that corrects for T stage, N stage, metastatic presentation, BMI, and age where appropriate. Covariates that fit are detailed for each outcome in **Table 6**.

Body mass index was not a predictor in the multivariate models and was therefore kept out of the calculations. As expected, the difference in follow-up duration was no longer significant after correction for duration of survival. The survival and hazard curves in **Figure 4** show a trend in which the difference in terms of disease-free interval is strongest within the first few months and tends to stop diverging over time. The differentiating effect on overall survival, however, appeared to be lasting throughout the duration of follow-up as screening and nonscreening subsets diverged continuously. In terms of statistical significance, the multivariate models correcting for T, N, and M staging and age corroborated the independently predictive effect of screening diagnosis for lower death

Figure 1. Distribution of Staging
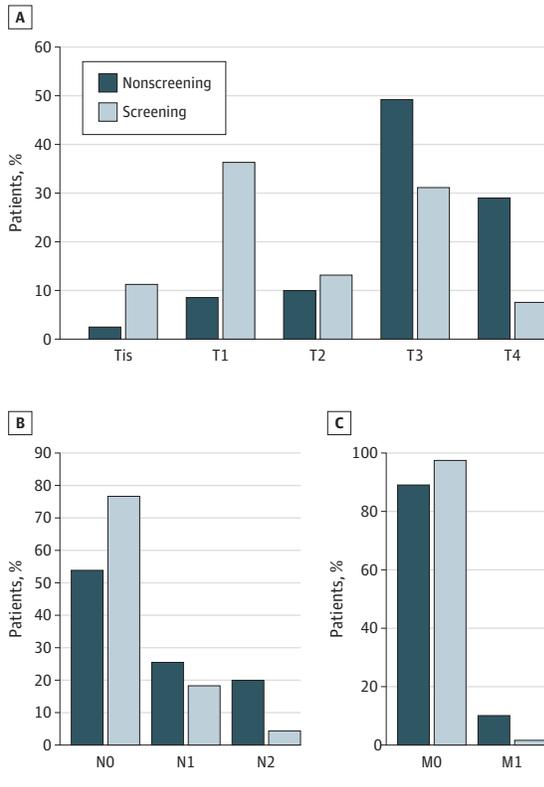
The distributions are shown according to T stage (A), N stage (B), and M stage (C).

Figure 2. Kaplan-Meier Curves for Survival and Disease-Free Interval
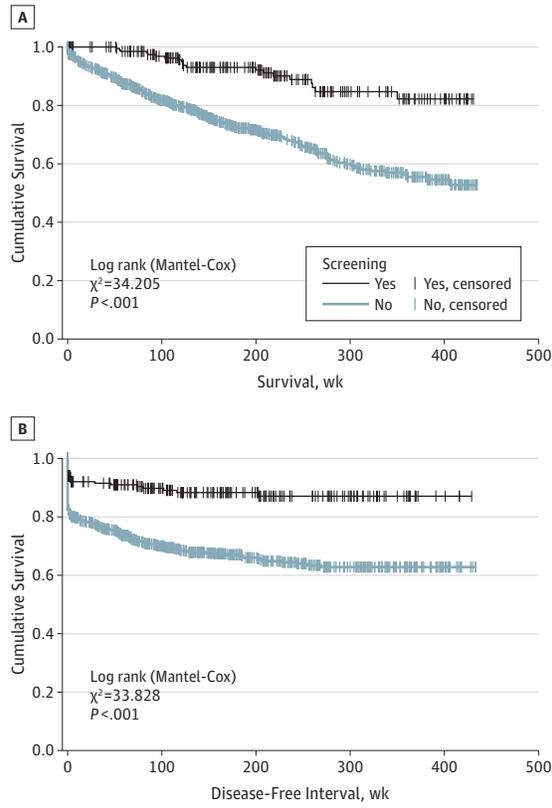
Kaplan-Meier curves for survival (A) and disease-free interval (B).

Table 4. Comparison of Follow-up and Long-term Outcomes for Screening and Nonscreening Groups

Outcome	Nonscreening	Screening	P Value
Follow-up, mean (SD), d	952 (782)	1149 (765)	<.001
Recurrence rate, %	13.1	6.0	.004
Disease-free interval, mean (SD), wk	109 (116)	150 (116)	<.001
Death rate, %	26.5	8.8	<.001
Survival, mean (SD), wk	157.4 (119.7)	196.1 (117.4)	<.001

rates (P = .02) and longer survival duration (P = .01). Disease-free survival (P = .16) and recurrence rates (P = .44), however, lose their significant difference between both groups after correction for T stage, N stage, and age.

Discussion

Screening colonoscopy is believed to be a major contributor to the consistent decline in the number of colorectal cancer diagnoses in the United States over the last decade.[8] As stated previously, this is likely to be related to earlier detection of asymptomatic premalignant tumors. Our hypothesis was that the current screening program has benefits beyond early detection of benign or premalignant disease and also contributes to earlier detection of malignant neoplasms, leading to significantly lower staging and perhaps better long-term outcome.

Our analysis attempted to quantify this beneficial effect in our population. We did so through a comparison of outcomes between patients who had their colon cancers detected during screening colonoscopy and the overall population diagnosed through other means.

In a review of baseline characteristics, patients diagnosed through screening were notably younger, had a higher BMI, and were more likely to be male. This younger age is easily explained as guidelines specifically recommended colonoscopies to be performed between the ages of 50 and 75 years. The narrower spread of ages in terms of standard deviation in screening patients supports this explanation. The difference in BMI can also be explained as an effect of the age difference, as older patients have a tendency to lose weight as they age.[9] The difference in sex distribution had no clear explanation and was borderline significant. Therefore, we chose to only account for age as a

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Figure 3. Kaplan-Meier Curves Displaying Stage-for-Stage Outcomes for Survival and Disease-Free Survival Divided by Screening and Nonscreening Groups
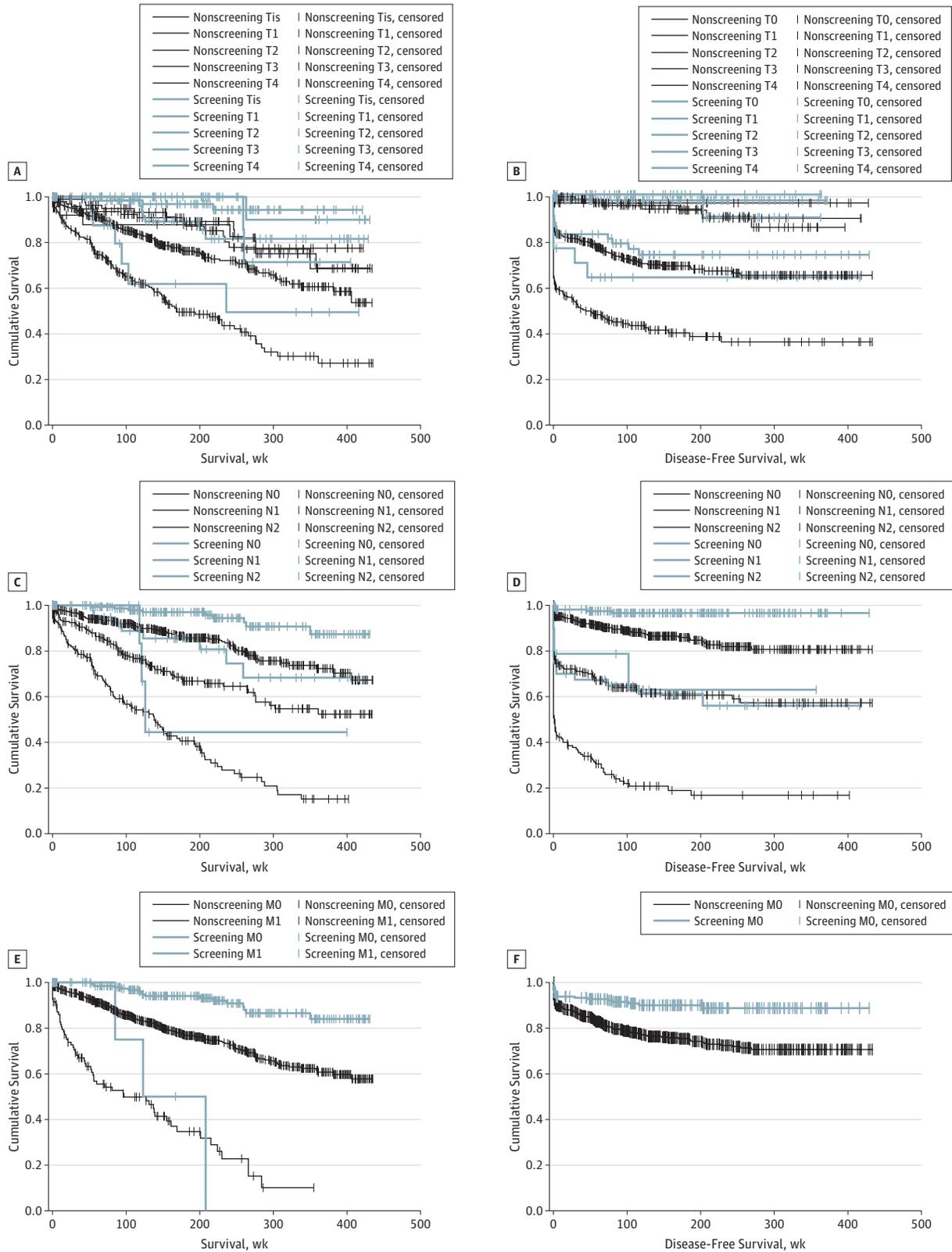
Survival is shown for T stage (A), N stage (C), and M stage (E), and disease-free survival is shown for T stage (B), N stage (D), and M stage (F).

Table 5. Stage-for-Stage Pairwise Comparison of Outcomes

Staging	Metastasis-Free Portion			Survival Rate		
	Screening, %	Nonscreening, %	P Value	Screening, %	Nonscreening, %	P Value
T stage						
Tis	100	96.3	.37	95.5	81.5	.18
T1	97.5	94.7	.50	96.3	89.4	.04
T2	96.8	92.9	.46	96.8	83.7	.10
T3	76.9	71.5	.34	89.2	76.5	.02
T4	64.7	44.0	.09	64.7	56.5	.27
N stage						
N0	97.0	87.4	<.001	95.2	84.9	<.001
N1	60.0	63.3	.88	80.0	70.6	.11
N2	70.0	26.2	.009	70.0	43.8	.24
M stage						
M0	90.6[a]	78.4[a]	<.001	92.5	77.4	<.001

[a] Denotes recurrence-free survival.

Table 6. Multivariate Comparison of Follow-up and Long-term Outcomes of Screening Diagnosis Relative to Other Diagnoses Corrected for Covariates and Staging

Model for Outcome (Covariates)	Statistic	P Value
Linear regression for follow-up duration (survival duration)	.016[a]	.23
Logistic regression for recurrence (N stage, T stage)	1.26[b]	.44
Logistic regression for death (metastatic presentation, N stage, T stage, age)	0.535[b]	.02
Cox regression for disease-free interval (T stage, N stage, age)	0.659[c]	.16
Cox regression for survival duration (metastatic presentation, T stage, N stage, age)	0.534[c]	.01

[a] Beta coefficient.

[b] Odds ratio.

[c] Hazard ratio.

covariate that needed to be accounted for in subsequent multivariate analysis after verifying whether sex or BMI had a relationship with any outcome or predictor.

After analysis of baseline pathology, it was revealed that symptomatic patients had more than twice the risk of having metastatic disease on presentation. This is an intuitive result, yet it is surprising in its magnitude and a clear illustration of the hypothesized contribution of screening colonoscopy to detecting disease early.

Differences in staging were also very significant throughout the TNM classification. Postoperative pathology reports from symptomatic cases had more invasive tumors, with screening patients being 3 times less likely to have T4 tumors, being half as likely to have nodal spread, and having a 5-fold lower risk of distant metastasis in surgical pathology. These differences are a clear indication that screening patients are at significantly lower risk for advanced disease and distant spread at diagnosis. Not surprisingly, these outcomes led to very significant differences in long-term outcomes. In nonscreening diagnoses, death and recurrence rates were higher and were more likely to appear sooner after the operation.

We then attempted to assess whether any of the effects of screening were independent of staging. Interestingly, after correction for cofactors found during baseline analysis and postoperative staging, screening patients were still at very significantly lower mortality risk in follow-up and also seemed to have independently lower risks of recurrence for certain pathological stages. This raised questions about the origin of these staging-independent differences in outcomes. Possible factors that could contribute to these more favorable recurrence and survival rates in patients who undergo regular screening are better access to health care, better socioeconomic status resulting in better compliance to screening, and possibly better overall general health. Also, even though we have reviewed the results stage for stage and have made stage-adjusted comparisons, lead-time bias may still be a source of advantages in the screening population by leading to subtle differences in disease progression within those stages.

Our initial findings were substantiated by multivariate analysis through Cox cumulative hazards models and survival curves. The curves showed a continuous divergence in risk of death between both groups, while differences in recurrence risk tended to stabilize over time, possibly contributing to the nonsignificant difference after correction for covariates. The curves appear to illustrate how patients diagnosed through screening are at lower risk for dying during follow-up, independent of their chances of recurrence. This seems to support the hypothesis that screening patients have better general lifestyle characteristics, especially as age differences have been taken into account in the Cox model.

A last possible factor to take into account in explaining the staging-independent difference in outcomes is that patients diagnosed outside screening programs are more likely to have more aggressive tumors; this effect is plausibly strong enough to even make a difference when patients have the same staging at baseline. This could especially be true if diagnosis was established between screening colonoscopies, implying that the tumor developed in the interval between 2 screenings.

A limitation of our study is the possibility that our center attracts more serious and advanced symptomatic cases of co-

Figure 4. Multivariate Cox Proportional Hazards Curves
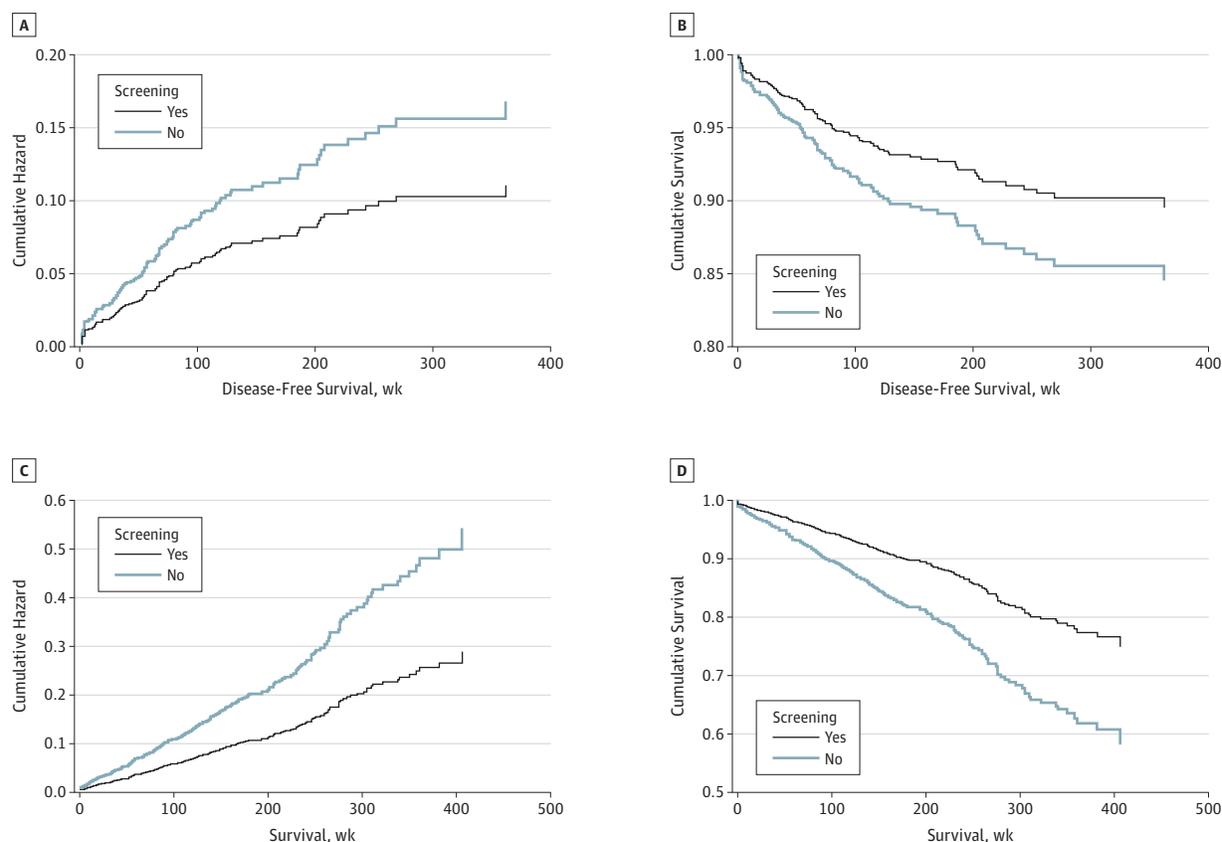
The cumulative hazard (A) and cumulative survival (B) are shown for disease-free interval, and the cumulative hazard (C) and cumulative survival (D) are shown for survival. The multivariate Cox proportional hazards curves control for T stage, N stage, metastatic presentation, and age at surgery.

lon cancer, as it is a highly specialized tertiary cancer center and a top-level referral destination for complicated surgical cases. This may result in inflation of the differences between screening diagnoses and the rest of our population. Because the proportion of our population fitting these criteria is small relative to the sample size, we do not expect this possible confounding effect to be of significant value. A last potential limitation is the effect of variability in treatment over time on outcomes, as the study spans a period that may have witnessed minor changes in treatment regimens and protocols. However, because the proportion of screening diagnoses has been constant over time, we believe that this effect, if at all existent, is negligible.

In conclusion, patients with colon cancer identified on screening colonoscopy are shown to have considerably better staging and outcomes than those with tumors identified through other means. In addition, this beneficial effect is not solely related to the lower postoperative staging. In fact, diagnosis through screening colonoscopy independently affected the long-term survival of patients with colon cancer. Despite that screening colonoscopy has now been a recommended preventive measure for more than a decade,[10] approximately 1 in 6 of all colon cancer diagnoses referred to our center for surgery are still found incidentally. Considering the tremendous effect early diagnosis through screening has for the prognosis of patients, this further emphasizes the important role compliance to screening colonoscopy guidelines can play in prolonging longevity, improving quality of life, and reducing health care costs through early detection of colon cancer.

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