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A Risk Prediction Index for Advanced Colorectal Neoplasia at Screening Colonoscopy

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Abstract

Background—Eliciting patient preferences within the context of shared decision-making has been advocated for colorectal cancer screening. Risk stratification for advanced colorectal neoplasia (ACN) might facilitate more effective shared decision-making when selecting an appropriate screening option. Our objective was to develop and validate a clinical index for estimating the probability ACN at screening colonoscopy.

Methods—We conducted a cross-sectional analysis of 3,543 asymptomatic, mostly average risk patients 50–79 years of age undergoing screening colonoscopy at two urban safety net hospitals. Predictors of ACN were identified using multiple logistic regression. Model performance was internally validated using bootstrapping methods.

Results—The final index consisted of 5 independent predictors of risk (age, smoking, alcohol intake, height and a combined sex/race/ethnicity variable). Smoking was the strongest predictor (net reclassification improvement [NRI], 8.4%) and height the weakest (NRI, 1.5%). Using a simplified weighted scoring system based on 0.5 increments of the adjusted odds ratio, the risk of ACN ranged from 3.2% (95% CI, 2.6 to 3.9) for the low-risk group (score ≤ 2) to 8.6% (95% CI,

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7.4–9.7) for the intermediate/high-risk group (score 3–11). The model had moderate to good overall discrimination (C-statistic, 0.69; 95% CI, 0.66–0.72) and good calibration (*P*=0.73 to 0.93).

Conclusions—A simple 5-item risk index based on readily available clinical data accurately stratifies average-risk patients into low- and intermediate/high-risk categories for ACN at screening colonoscopy. Uptake into clinical practice could facilitate more effective shared decision-making for CRC screening, particularly in situations where patient and provider test preferences differ.

Introduction

Colorectal cancer (CRC) remains the third most commonly diagnosed cancer among men and women and the second overall leading cause of cancer-related death in the United States (1). Sufficient evidence has accumulated to suggest that screening is the most effective strategy for reducing the public health burden of this deadly disease and is now widely recommended by most authoritative groups (2–5). Each of these groups endorses a menu-based approach for average risk patients 50 years of age that includes some combination of colonoscopy, fecal occult blood testing, flexible sigmoidoscopy, double contrast barium enema, CT colonography ("virtual colonoscopy") or stool DNA testing. Although screening rates have steadily increased in recent years, approximately one-third of age-eligible Americans remain unscreened (6).

Eliciting patient preferences within the context of shared decision-making has been endorsed as an appropriate and potentially effective strategy for increasing CRC screening rates (2–5). CRC screening is ideally suited for this approach given the availability of multiple options with distinct advantages and disadvantages, the lack of consensus regarding an optimal cost-effective strategy, and limited effectiveness of the more traditional paternalistic approach where primary care providers assume full responsibility for the decision-making process. Nevertheless, existing data suggest that many providers are reluctant to comply with patient preferences (7, 8). A reliable risk index for estimating individual probability of advanced colorectal neoplasia (ACN), the target lesion for CRC screening (9), would provide clinicians with objective decisional support when considering patient preferences and thereby potentially enhance the effectiveness of SDM. Although a number of prediction models have been proposed for ACN, the majority were developed and validated in select patient populations and/or included individuals at increased risk of disease because of a family history (10). Hence, the principal objective of this study was to develop and validate a simple risk index for ACN based on readily available clinical data that accurately stratifies a diverse average-risk patient population into low- and intermediate/high-risk categories for ACN.

Methods

Study Design

We conducted a cross-sectional study of consecutive asymptomatic, mostly English-speaking, average risk patients presenting to the endoscopy unit at Boston Medical Center

and Tufts Medical between March 22, 2005 and January 31, 2012. Potential study participants were identified from the appointment logs and assessed for eligibility by one of the study coordinators in the endoscopy unit just prior to their scheduled procedure. The study protocol was approved by the Boston University Medical Campus and Tufts Medical Center Institutional Review Boards.

Setting and Participants

Boston Medical Center (BMC) is a private, community-based, academic medical center and the largest safety net hospital in New England. Approximately 70% of BMC's patients are from low-income, minority groups (35% black, 19% Hispanic, 4% Asian, and 11% other) and rely on government payors for their coverage. Tufts Medical Center is also an urban private, academic medical center that cares for a diverse patient population (70% white, 10% black, 10% Asian and 9% Hispanic). Tufts was added as a second study site in September 2009 to bolster recruitment and increase the representation of Asian patients in the study population. More than 95% of patients from both sites have medical insurance as a result of the Massachusetts Health Reform Law.

Patients were deemed eligible for this analysis if they were 50 to 79 years of age and due for CRC screening in accordance with current guidelines. Patients with indications other than screening, such as the presence of lower gastrointestinal symptoms, iron deficiency anemia, positive fecal occult blood testing or surveillance because of a personal history of colorectal neoplasia or chronic inflammatory bowel disease, were ineligible. Patients undergoing screening because of a family history of CRC or colorectal polyps affecting a first-degree relative before age 60 were also ineligible, on grounds that most authoritative groups endorse colonoscopy as their preferred screening strategy for these high-risk groups rather than an option-based approach driven by patient preferences (2).

Survey Methodology

The risk assessment questionnaire was self-administered to consenting patients with adequate literacy skills using a scannable, paper-based data collection form devoid of patient identifiers. A trained interviewer technique was used for patients with low literacy skills. The survey took ~ 5 minutes to complete.

Details of our survey instrument have been previously published (11). The questionnaire initially included all 21 items of the original *YourDiseaseRisk* (*YDR*) index for CRC, a web-based adaptation of the validated Harvard Cancer Risk Index (12, 13), and 15 additional items related to other putative risk factors for ACN (Supplement 1). In July 2007, the questionnaire was modified to reflect changes in the *YDR* index (Supplement 2) (14), specifically omitting the vegetable intake item, adding a dairy intake item and expanding prior screening behavior to include virtual colonoscopy and stool-based DNA testing.

Colonoscopy findings and histology

All screening colonoscopies were performed by board-certified attending gastroenterologists alone or assisted by a gastroenterology fellow. Endoscopic data, including the size (mm) and location of any polyps or masses, depth of scope insertion, and quality of the bowel

preparation were abstracted from the computerized colonoscopy reports. All retrieved polypoid lesions or biopsy specimens were reviewed initially by board-certified pathologists and classified according to World Health Organization histologic criteria (15); each also underwent a second review by a gastrointestinal pathologist with expertise in colorectal neoplasia. The GI pathologist re-reviewed any variances in classification to establish the final determination. An advanced colorectal neoplasm was defined as a tubular adenoma ≥ 10 mm in size, an adenoma of any size with villous features or high grade dysplasia, a dysplastic serrated lesion of any size, or invasive cancer (16, 17). Patients with multiple polyps submitted individually or collectively in a single specimen container were classified on the basis of their most advanced histology.

Outcome

The primary outcome was prevalence of ACN, defined as the proportion of evaluable patients with ACN. Patients with incomplete examinations due to poor bowel preparation or failure to reach the cecum for reasons other than a poor bowel preparation or obstructing neoplasm were excluded from analysis if they did not undergo a complete examination within 1 year. Patients with unretrieved polyp specimens were also excluded.

Statistical Analyses

All statistical analyses were done using SAS, version 9.4, software (SAS institute Inc., Cary, NC, USA.)

Sample Size and Power Estimates

Power considerations focused on identifying independent dichotomous predictors in a multivariable logistic regression model for ACN. Assuming an overall prevalence of ACN of 4.6% (18) and a low correlation between the predictor and other covariates in the model (R^2 =0.10), a sample of 4000 patients would provide 80% power of detecting an adjusted odds ratio of 1.65 or 0.61 (testing at the two-tailed 0.05 level) for a predictor with prevalence of 20% and 1.58 or 0.63 for a predictor with prevalence of 40% (19). Based on a revised estimate of the overall prevalence of ACN of 5.5%, which was less than the final prevalence of 5.7%, it was determined that a sample of 2,952 would provide similar power.

Model Development

Although data for primary risk factors were missing on only 5.6% of the observations for the primary modeling variables, this proportion was similar to the observed event rate for ACN. Thus, the Expectation-Maximization (EM) algorithm was used to obtain estimates of the variance-covariance matrix and model coefficients for logistic regression models predicting ACN (20). Estimation and testing of model coefficients was done across 5 imputed datasets, each containing substituted values for missing data that reflected estimates derived from other observations in the original dataset. The variance estimates for testing and confidence intervals accounted for the variability between values on the imputed datasets (21). Imputed values were used directly in the model development without any rounding for binary variables.

Simple associations of patient risk factors with the presence of ACN were tested using logistic regression models on the imputed data. Associations were summarized by the odds ratio for ACN and associated 95% confidence intervals. Candidate predictors with *P* values less than 0.20 in the univariable analyses were included into a multivariable logistic regression. Backward selection was used to remove variables with insignificant ($P \geq 0.05$) contributions to multivariable model fit. Based on published data (11, 22), an interaction between race/ethnicity and sex was tested. Internal validity for selected variables was summarized by the percentage of times that each variable was statistically significant ($P<0.05$) and would have been scored (with an odds ratio greater than 1.25) on 1000 bootstrap samples of 3453 patients per sample with replacement from the original imputed study dataset.

The Net Reclassification Improvement (NRI) was used to summarize the improvement in classification when a predictor identified in the multivariable logistic model was added to the model (23, 24). Patients were classified as predicted to have ACN if their predicted probability from the model was greater than 5.7%, the mean overall prevalence of ACN in the dataset. The NRI is estimated by calculating the net percentage of patients with ACN that were reclassified from low-risk to intermediate/high-risk added to the percent of subjects without ACN that were reclassified from intermediate/high-risk to low-risk when the predictor was added to the regression model. Thus, higher NRI values are associated with greater improvement in appropriate classification of subjects. The calculated NRI value should not be interpreted an estimate of proportional risk for the outcome of interest.

Model Performance

Model performance was assessed by the C-statistic for discrimination by calculating the area under the receiver-operating characteristic (ROC) curve and by plots of model calibration. Confidence limits for the area under the ROC curve were generated from the 2.5% and 97.5% percentiles from prediction on regression models generated on the 1000 imputed bootstrap datasets to provide estimates of precision and internal validity. Model calibration comparing observed and predicted ACN rates across deciles of predicted risk were checked on each of the 5-imputed datasets and tested for statistical significance using the Hosmer and Lemeshow goodness-of-fit test.

ACN Scoring Algorithm

Points were assigned to each predictor based on the number of 0.5 levels above the referent odds of 1.0, rounded to the nearest level. Individual risk estimates were based on the sum of weighted scores for each variable. To create an easy to use two-tier risk stratification index, individual cumulative scores were collapsed into low- and intermediate/high-risk categories based on the corresponding observed rates of ACN. Adjusted 95% confidence intervals for the rate of ACN were generated for each risk category using the bootstrap methods described above. The actual cut-point was optimized to insure that: (1) the prevalence of ACN in the low-risk group was sufficiently low (range, 2–3% (25)) to influence provider decision-making, and (2) the proportion of patients categorized as low-risk was large enough to be clinically relevant, recognizing that approximately 30 to 60% of patients may prefer tests other than colonoscopy (8, 26, 27).

Results

Patient Characteristics

Figure 1 depicts the number of pre-screen eligible patients who declined to participate, deemed ineligible based on inclusion/exclusion criteria, or excluded because of inadequate bowel preparation, incomplete examination for reasons other than an inadequate bowel preparation, or failed polyp retrieval for each sample. Table 1 presents the ccharacteristics of the 3,543 participants included in the study with 98.4% enrolled at BMC, 74.7% aged 50 to 59 years, 50.5% black with an equal percentage of males and females. The mean overall rate of ACN was 5.7% (95% CI, 5.0–6.6%).

Model Composition

Univariable associations between potential risk factors and ACN are presented in Table 1. Age as a continuous variable, height, smoking behavior, alcohol intake, NSAID use, red meat consumption and family history of CRC affecting a first-degree relative at age ≥60 had *P* values less than 0.20 and were included as covariates in the multivariable logistic regression models. Results from a logistic regression model with terms for sex and race/ethnicity supported the inclusion of an interaction term for race/ethnicity by sex (P<0.001). Multivariable model coefficients, odds ratio estimates and 95% confidence intervals for the imputed datasets are given in Table 2. After adjustment, only age, a combined sex/race/ethnicity variable, smoking, alcohol intake, and height remained significant (*P*<0.05) and were included in the final model. Each of the selected variables had positive NRIs and was significant (odds ratio > 1.25) in more than 50% of bootstrap samples with repeated sampling (Table 2). Conversely, NSAID use, meat consumption and family history were excluded since they were not statistically significant after adjustment for the other covariates in the model, had low or negative NRIs, and were statistically significant in less than 50% of samples with repeated sampling.

Model Performance and Validation

The final model demonstrated moderate to good discrimination (c-statistic, 0.69; 95% CI, 0.66–0.72) on the imputed dataset. Performance varied by race and ethnicity with the strongest discrimination for whites (C=0.73; 95% CI, 0.68–0.77) followed by Hispanics (C=0.66; 95% CI, 0.53–0.78), blacks (C=0.63; 95% CI, 0.57–0.69) and others (C=0.59; 95% CI, 0.44–0.74), but these differences did not achieve significance because of overlapping confidence internals. Performance also varied by sex with stronger discrimination for males (C=0.69; 95% CI, 0.65–0.73) than females (C=0.66; 95% CI, 0.60–0.71), but these differences were again non-significant. As shown in Figure 2, there were no systematic biases in agreement with observed and predicted rates of ACN across deciles of predicted risk (Hosmer-Lemeshow test, *P*=0.73 to 0.92). The NCI, reflecting the improvement in appropriately identifying individuals with ACN as intermediate/high or low risk, was strongest for the smoking variable for which there was a net improvement of 8.4% in classification when compared to a model lacking this variable (Table 2). The net improvement in classification for inclusion of the other variables was 2.2% for the race/ethnicity by sex interaction, 1.7% for both age and alcohol, and 1.5% for height.

ACN Scoring Algorithm

Each of the 5 predictors were assigned a point value based on the number of 0.5 levels above the referent odds of 1.0, rounded to the nearest level (Table 3). For the combined sex/race/ethnicity variable, white males were assigned a score of 2 based on the observed odds ratio of 1.79 (P=0.022); scores of 0 were assigned to each of the other groups, except black males, since none of the adjusted odds ratios were significant. Black males were assigned a 1-point score based on published data demonstrating significantly higher rates of ACN compared to non-Hispanic white women (11, 22, 28, 29). Summing the points yielded total risk scores that ranged from 1 to 11 with the higher scores indicating greater predicted risk for ACN. Mean ACN rates for each of these scoring categories are shown in Table 4. Scores were collapsed into two categories, scores 1 to 2 or greater than 3, to identify potential low-risk and intermediate/high-risk individuals, respectively. The mean ACN rate in the low risk-group was 3.2% (95% CI, 2.6–3.9%) and 8.6% (95% CI, 7.4–9.7%) for the intermediate/high-risk group. The proportion of patients with ACN identified as intermediate/high-risk was 70.1% (95% CI, 63.6–76.3) and the proportion without ACN with estimated low-risk was 54.4% (95% CI, 52.7–56.0).

Discussion

Risk stratification for ACN provides a rational strategy for facilitating shared-decision making when selecting an appropriate CRC strategy and for improving the cost-effectiveness of screening colonoscopy. An essential prerequisite to this approach is the availability of an accurate risk assessment tool. Our study finds that a simple, user-friendly index, hereafter referred to as the Advanced Colorectal Neoplasia Index (ACNI), comprised of five predictors of risk (age, a combined sex/race/ethnicity variable, smoking, alcohol consumption and height) accurately stratifies a diverse population of average-risk patients for CRC into low- and intermediate/high risk groups for the presence of ACN at screening colonoscopy.

One measure of the likely validity of a risk index relates to the evidence base for the key predictors. Each of the ACNI predictors is an established risk factor for both advanced adenomas and invasive cancer. Positive associations with increasing age (30), male sex (31), alcohol use (32, 33), long-term exposure to cigarette smoke (34) and tallness (35, 36) have been affirmed by numerous observational studies. Data regarding associations between race/ethnicity and ACN, however, have been more conflicting and appear to vary on the basis of age and sex (22, 28, 29, 37, 38). After controlling for other determinants of risk and the interaction between sex and race/ethnicity, we observed significantly higher rates of ACN among non-Hispanic white males than other racial groups, including blacks, as previously reported (11). We speculate that selection bias related to access to screening colonoscopy and failure to account for differential exposure to modifiable risk factors for ACN, including prior colonoscopy, might account for the much of the variance between our findings and studies that find similar (29, 37, 38)or higher (22, 28) rates of ACN among black males compared to white males. Population-based data demonstrating that non-Hispanic white males also had the highest incidence rates of CRC in the 1980s prior to the surge in screening lends credence to our findings (39). Although absolute rates of disease varied

among males and females for the other racial and ethnic groups studied, no significant difference were observed, presumably due to the relatively low prevalence of ACN and small sample size. Even if significant differences were observed in a larger study, existing prevalence data would suggest that the magnitude of difference is unlikely to warrant a change in the weighted score. The sole exception would be black males for whom there is compelling evidence of increased risk compared to non-Hispanic white women to warrant our assignment of 1 point in our scoring system (11, 22, 28, 29). The exclusion of many other candidate predictors from our model (e.g., BMI) in no way refutes their importance as risk factors for ACN, since our study has insufficient power for validating the significance of factors with low exposure rates or low attributable risk in the general population.

Besides including credible predictors, an index should meet performance standards related to discrimination (ability to distinguish low from high risk individuals), calibration (agreement between observed and predicted outcomes) and internal validity. Although our index demonstrated only moderate to good discriminative ability, its performance compares favorably with the discriminative ability of other existing models for both average (10) and high-risk patients (40). Nevertheless, extrapolation of our findings suggest that as many as 30% of patients without ACN will be misclassified as “intermediate/high-risk” (false positives) that as many as 45% of patients with ACN may be misclassified as “low-risk” (false negatives). Nevertheless, even poorly discriminating models may have clinical utility in situations where the clinical decision is a “toss up” as in the case of CRC screening test selection (41), or where there is a lack of consensus regarding a single best option (42, 43). The variable performance of the model as a function of sex and race/ethnicity suggests that other risk factors not included the model may be important predictors of ACN in select patient populations. Nevertheless, the model was well calibrated and internally validated using bootstrapping methods. Although internal validation methods are more prone to overfitting than external validation, the use of bootstrapping is more efficient than split-sample validation and provides more stable estimates with less bias than cross-validation methods (44).

Our index addresses many of the limitations of previously described prediction models for colorectal neoplasia. First, our index provides real-time estimates of risk for existing ACN rather than projections for the future development of CRC (14, 45, 46), thus enhancing its potential utility for facilitating effective shared decision-making for individual patients. Second, our index targets both advanced adenomas and cancers rather than just cancers. Although most studies have observed few differences between risk factors for non-advanced adenomas, advanced adenomas and invasive cancers, we have previously shown that the *Your Disease Risk* index lacks accuracy for discriminating those at low versus intermediate or high risk for ACN at screening colonoscopy (47). Third, unlike the risk index proposed by Imperiale and colleagues (48), our index provides risk estimates for ACN arising anywhere in the large bowel rather than just the proximal colon and also obviates the need for flexible sigmoidoscopy. Fourth, the inclusion of a racially and ethnically diverse patient population enhances the generalizability of our index and differs from other prediction models (49–52), which were mostly derived and validated in select patient groups. Lastly,

our model employs a relatively simple scoring system compared to recent models (53), thus increasing the likelihood of uptake in clinical practice.

Our study has several unique strengths. The racial, ethnic and socioeconomic diversity of our study population satisfies a National Cancer Institute recommendation and enhances the generalizability of our findings (54). Our recruitment strategy enabled us to maximize our response rate and minimize selection bias. Our study protocol minimized recall bias, since patients completed the questionnaire prior to undergoing their screening colonoscopy and thus were unaware of the findings of their examination. Lastly, we restricted our analyses to patients with complete examinations with adequate preparations and complete retrieval of all polyp specimens to minimize misclassification.

Our study also had several important limitations. First, we failed to validate the performance on our index on an external dataset, so concerns about overfitting and generalizability are warranted. Second, although patients were recruited consecutively and enrollment was high, the use of a convenience sample also raises concern about potential selection bias. Third, despite the large number of candidate predictors examined, we failed to consider other putative anthropomorphic (e.g., hip-to-waist circumference) or biological (e.g., C-reactive protein levels) determinants of risk. Although the inclusion of such predictors might have enhanced the discriminative ability of our index, we speculated that logistical challenges related to real-time measurement during the clinician-patient encounter might deter adoption into clinical practice. Similarly, we also opted to exclude potential socioeconomic determinants of risk because the content of our questionnaire and setting captured the likely mediators of the increased risk of CRC among disadvantaged populations, namely adverse health behaviors (e.g., obesity, smoking, unhealthy diet and physical activity) and poor access to screening (55, 56). Fourth, we relied on the subjective judgment of multiple endoscopists to provide data about polyp size, thereby raising the possibility of misclassification for ACN defined by size alone (57). Fifth, our reliance on self-reported data raises the possibility of social response bias, particularly with respect to BMI, alcohol consumption and smoking history. Lastly, the model was derived based on a cross-sectional analysis of patients willing to undergo screening colonoscopy and hence its validity among patients unwilling or unable to undergo screening colonoscopy is unknown.

Despite the limitations, our index provides a clinically useful tool for facilitating shared decision-making related to colorectal cancer screening, particularly in situations in which provider and patient preferences differ. Conceptually, providers who prefer colonoscopy may be more willing to comply with patient preferences for tests other than colonoscopy for individuals at low risk; alternatively, patients who prefer tests other than colonoscopy may be more receptive to colonoscopy if informed that they are increased risk. We have previously reported that most primary care providers were willing to use such a tool, assuming that it minimized disruptions to workflow, was easy to use and required minimal time to complete (25). The ACNI's simple scoring algorithm using readily available clinical information satisfies these prerequisites, especially if adapted into an electronic format and automated within electronic health records.

In conclusion, we have developed and internally validated a new risk prediction index for ACN that stratifies average-risk patients into low- and high-risk categories for ACN at screening colonoscopy. Although performance varied on the basis of sex and race/ethnicity, we believe that the index has adequate discriminative ability to facilitate shared decision-making related to screening test selection and individualized risk assessment, particularly in situations where patient and provider preferences differ. Future studies are needed to externally validate the performance of the index among diverse populations and to determine the extent to which providers are willing to incorporate such a tool into clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

What is current knowledge

- Eliciting patient preferences for a particular colorectal cancer (CRC) screening option might increase adherence.
- Patient and provider preferences for CRC screening tests often vary.
- Risk stratification for the presence of advanced colorectal neoplasia (ACN) provides a rational means of reconciling these differences.

WHAT IS NEW HERE

- A simple 5-item risk index based on readily available clinical data accurately stratifies average-risk patients into low- and high-risk categories for ACN at screening colonoscopy.
- Uptake of this novel risk index into clinical practice could facilitate more effective shared decision-making related to CRC screening.

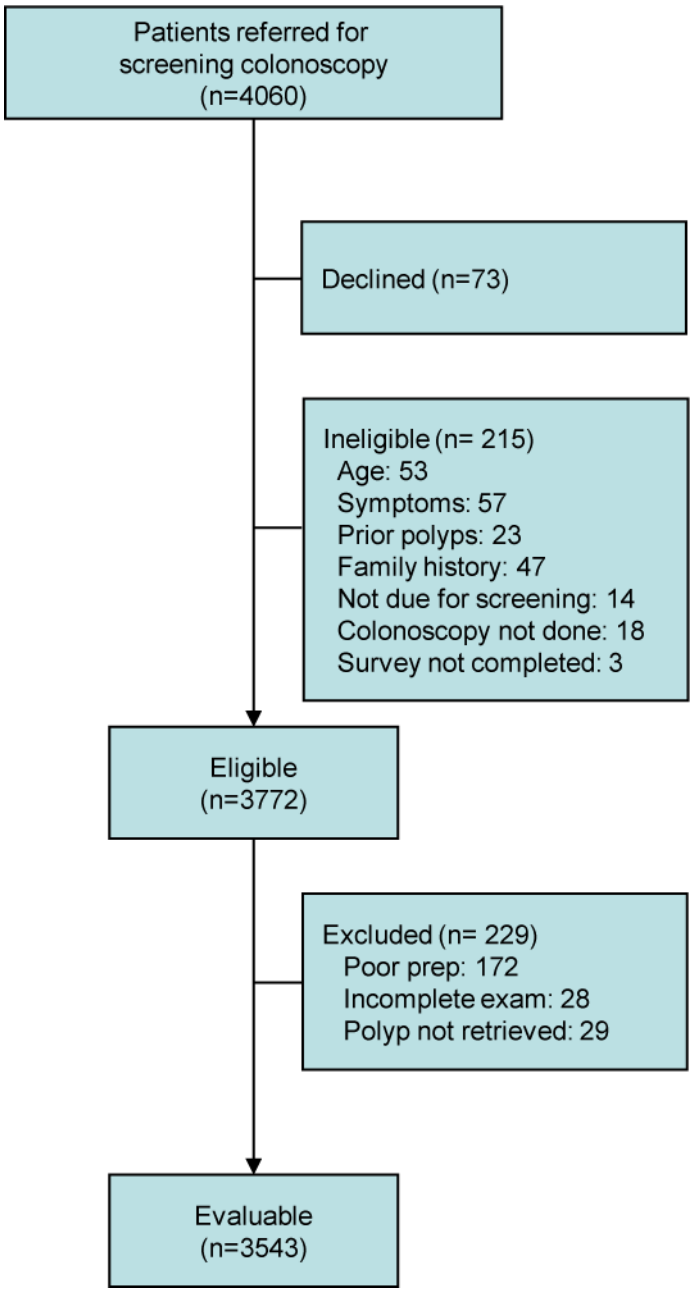

Figure 1.
Study flow diagram.

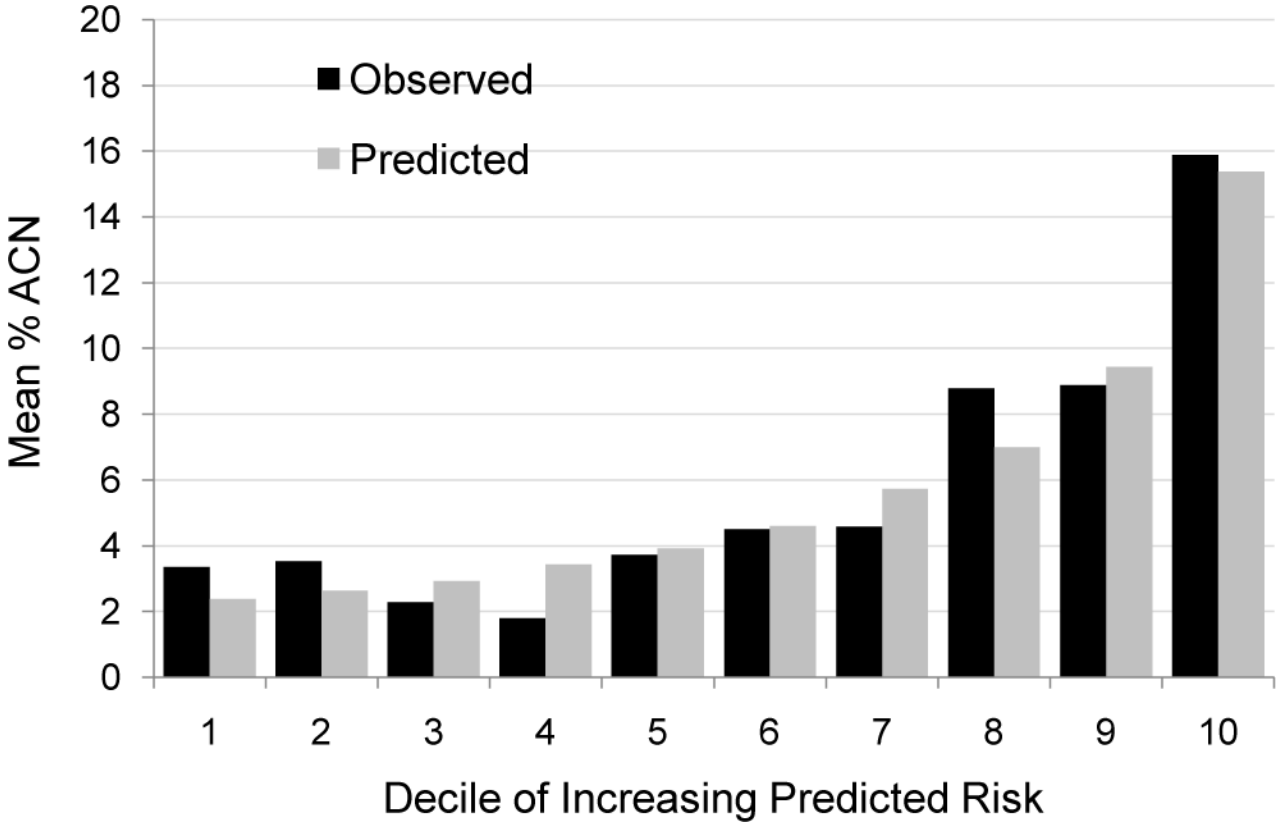

Figure 2.

Model calibration. Patients were ranked by their predicted probability and divided into 10 equal groups. The gray shaded bars represent the mean probabilities for each of the 10 groups and the black bars represent the observed proportions with ACN in each of these same groups.

Table 1

Patient Characteristics and Univariable Associations between Putative Risk Factors and Advanced Colorectal Neoplasia*

	No. Patients			
Categorical Risk Factors	**Total, N**	**ACN, n (%)**	**OR (95% CI)**	***P* value †**
Site				
Boston Medical Center	3487	200 (5.7)	1.00	0.90
Tufts Medical Center	56	3 (5.4)	0.93 (0.29–3.00)	
Age				
50–59y	2646	144 (5.4)	1.00	0.170
60–69y	741	45 (6.1)	1.12 (0.80–1.59)	
70–79y	156	14 (9.0)	1.71 (0.97–3.04)	
Sex				
Female	1751	75 (4.3)	1.00	<0.001
Male	1789	128 (7.2)	1.72 (1.29–2.31)	
Race/Ethnicity				
White	1273	92 (7.2)	1.00	0.027
Black	1788	88 (4.9)	0.67 (0.49–0.90)	
Hispanic	343	14 (4.1)	0.55 (0.31–0.97)	
Other	137	9 (6.6)	0.90 (0.44–1.83)	
Race\Ethnicity * Sex				
White female	560	24 (4.3)	1.00	Reference
White male	713	68 (9.5)	2.36 (1.46–3.80)	<0.001
Black female	950	39 (4.1)	0.96 (0.57–1.61)	0.87
Black male	838	49 (5.8)	1.39 (0.84–2.29)	0.20
Hispanic female	172	8 (4.7)	1.09 (0.48–2.47)	0.83
Hispanic male	171	6 (3.5)	0.81 (0.33–2.02)	0.65
Other female	69	4 (5.8)	1.37 (0.46–4.09)	0.57
Other male	67	5 (7.5)	1.80 (0.66–4.89)	0.25
Body Mass Index				
> 30 kg/m^2	1294	68 (5.3)	1.00	0.43
≤ 30 kg/m2	2169	128 (5.9)	1.13 (0.84–1.53)	
Height				
Men ≤ 1.78 m, Women ≤ 1.70 m	2676	133 (5.0)	1.00	<0.001
Men > 1.78 m, Women > 1.70 m	804	66 (8.2)	1.71 (1.26–2.32)	
Smoking				
Never	1845	69 (3.7)	1.00	<0.001
< 20 y	742	35 (4.7)	1.27 (0.84–1.93)	

Categorical Risk Factors	No. Patients Total, N	ACN, n (%)	OR (95% CI)	*P* value †
≥ 20 y	936	98 (10.5)	3.01 (2.19–4.14)	
Daily servings of alcohol				
< 2	3106	159 (5.1)	1.00	<0.001
≥ 2	318	38 (12.0)	2.52 (1.73–3.66)	
Aspirin use, most days > 15y				
No	3472	198 (5.7	1.00	0.87
Yes	48	3 (6.3)	1.10 (0.34–3.58)	
NSAID use				
Ever	1660	111 (6.7)	1.00	0.033
Never	1825	91 (5.0)	0.73 (0.5–0.97)	
Use of birth control pills				
Never/< 5 years	683	33 (4.8)	1.00	0.74
≥ 5 years	453	20 (4.4)	0.91 (0.52–1.61)	
Use of hormone replacement therapy				
Never/< 5 years	1678	73 (4.4)	1,00	0.51
≥ 5 years	73	2 (2.7)	0.62 (0.15–2.57)	
Red meat intake				
< 3 servings per week	2459	129 (5.3)	1.00	0.060
≥ 3 servings a week	1081	74 (6.9)	1.33 (0.99–1.78)	
Multivitamin use				
< 4 days a week	2221	120 (5.8)	1.00	0.78
≥ 4 days a week	1316	74 (6.0)	1.04 (0.78–1.40)	
Calcium "sufficient" ‡				
No	2720	161 (5.9)	1.00	0.49
Yes	797	42 (5.3)	0.88 (0.62–1.25)	
Daily vitamin D supplement ± calcium §				
No	2677	154 (5.8)	1.00	0.82
Yes	830	46 (5.5)	0.96 (0.69–1.35)	
Moderate physical activity ≥ 30 minutes daily				
No	972	58 (6.0)	1.00	0.69
Yes	2562	144 (5.6)	0.94 (0.69–1.29)	
Diabetes mellitus				
No	2194	133 (6.1)	1.00	0.78
Yes	453	29 (6.4)	1.06 (0.70–1.61)	
Family history of CRC ≥ age 60				

	No. Patients			
Categorical Risk Factors	**Total, N**	**ACN, n (%)**	**OR (95% CI)**	***P* value** †
No	2525	150 (5.0)	1.00	0.087
Yes	86	9 (10.5)	1.86 (0.91–3.78)	
Prior colonoscopy (> 10 years)				
No	2459	154 (6.3)	1.00	0.34
Yes	197	9 (4.6)	0.72 (0.36–1.43)	
	Mean (SD)			
Continuous Risk Factors	**ACN**	**No ACN**	**OR (Change of 10)**	***P* value** *
Age, ***y***	57.2 (6.8)	56.0 (6.1)	1.34 (1.08–1.66)	0.007
Body mass index, kg/m^2	29.1 (5.9)	29.2 (6.3)	0.98 (0.77–1.24)	0.85

ACN, advanced colorectal neoplasia; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval; CRC, colorectal cancer; FDR, first-degree relative; SD, standard deviation.

*Non-imputed dataset (N=3543)

†Chi-square analysis for categorical variables and t-tests for continuous variables

‡Calcium “sufficient” defined by daily use of a calcium supplement or daily intake of ≥ 3 servings of milk/dairy

§Daily vitamin D group includes patients who took a multivitamin

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Table 2

Univariable and Multivariable Predictors of Advanced Colorectal Neoplasia.

	Univariable Associations*			Multivariable Associations				
Variable	**Model Coefficient**	**Unadjusted OR (95% CI)**	***P* value**	**Model Coefficient**	**Adjusted OR† (95% CI)**	***P* value**	**NRI, %**	**% OR >1.25‡**
Age (10 y increments)	0.292	1.34 (1.08–1.66)	0.007	0.293	1.34 (1.08–1.67)	0.008	1.7	71
Race/Ethnicity*Sex			<0.001			<0.001	2.2	
White Female	—	1.00	—	0.000	1.00	—		
White Male	0.858	2.36 (1.46–3.81)	<0.001	0.583	1.79 (1.09–2.95)	0.022		65
Black Female	−0.043	0.96 (0.57–1.61)	0.87	0.117	1.12 (0.66–1.90)	0.66		
Black Male	0.329	1.39 (0.84–2.29)	0.198	0.112	1.12 (0.69–1.87)	0.67		
Hispanic Female	0.088	1.09 (0.48–2.48)	0.83	0.415	1.51 (0.66–3.47)	0.33		
Hispanic Male	−0.206	0.81 (0.33–2.02)	0.66	−0.140	0.87 (0.35–2.18)	0.76		
Other Female	0.320	1.38 (0.46–4.09)	0.57	0.637	1.89 (0.63–5.68)	0.26		
Other Male	0.590	1.80 (0.67–4.90)	0.25	0.724	2.06 (0.75–5.66)	0.159		
Smoking (≥20y vs. never/<20y)	1.027	2.79 (2.10–3.72)	<0.001	0.925	2.52 (1.87–3.39)	<0.001	8.4	100
Alcohol intake (≥2 vs. <2 drinks daily)	0.935	2.55 (1.74–3.72)	<0.001	0.695	2.00 (1.34–2.98)	<0.001	1.7	90
Height (Men >1.78m or Women >1.70m vs. shorter)	0.545	1.72 (1.27, 2.34)	<0.001	0.359	1.43 (1.03–2.00)	0.035	1.5	54

Variable	Univariable Associations*			Multivariable Associations				
	Model Coefficient	Unadjusted OR (95% CI)	*P* value	Model Coefficient	Adjusted OR† (95% CI)	*P* value	NRI, %	% OR >1.25‡
Variables not included in final multivariable model								
NSAID use (Never vs. ever)	0.312	1.37 (1.03–1.82)	0.032	0.280	1.32 (0.98–1.78)	0.066	−1.3	42
Red meat intake (<3 vs. 3+ servings a week)	0.282	1.33 (0.99–1.78)	0.061	0.072	1.07 (0.79–1.46)	0.65	−0.1	6
Family history CRC ≥ age 60 (Yes vs. No)	0.685	1.98 (1.03–3.84)	0.042	0.602	1.83 (0.92–3.61)	0.084	−0.9	32

ACN, advanced colorectal neoplasia; NSAID, non-steroidal anti-inflammatory drugs; OR, odds ratio; CI, confidence interval; NRI. Net reclassification improvement; CRC, colorectal cancer;

*Associations based on results of analyses conducted across 5 imputed datasets.

†All logistic regression models included adjustments for the variables in the final model (age, the race/ethnicity by sex interaction, smoking, alcohol intake, and height)

‡Percent of bootstrap samples a variable would be given a score or 1 or greater and be statistically significant ($P<0.05$).

Table 3

Scoring Algorithm

Risk Factor	Points Assigned*
Age	
50–59	1
60–69	2
70–79	3
Race/ethnicity by sex	
White males	2
Black males	1
Others	0
Cigarette smoking history	
≥ 20 years	3
Never/< 20 years	0
Alcohol intake, servings per day	
≥ 2	2
None/< 2	0
Height	
Men > 1.78 m. Women > 1.70 m	1
Men ≤ 1.78 m, Women ≤ 1.70 m	0

* Points were assigned based on the number of 0.5 levels above the referent odds of 1.0, rounded to the nearest level, with the exception of black males who received 1 point based on published literature {Lebwohl, 2012 #176;Friedenberg, 2012 #158;Schroy, 2013 #195;Lieberman, 2014 #184}

Table 4

Prevalence of Advanced Colorectal Neoplasia by Score and Risk Category

Score*	% Individuals with Designated Score (N=17,715)†	Mean Prevalence of ACN, %	Risk Category	Mean Prevalence of ACN, % (CI)
1	34.9	3.2	Low	3.2 (2.6–3.9)
2	17.8	3.0		
3	10.4	4.6	Intermediate/High	8.6 (7.4–9.7)
4	15.9	6.9		
5	8.2	6.2		
6	6.8	12.3		
7	3.5	21.3		
8 – 11	2.6	15.9		

ACN, advanced colorectal neoplasia

*Cumulative scores were defined by the sum of individual scores for each risk factor

†Percent of individuals in the 5 combined imputed datasets with designated score (3543*5 = 17,715).