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Derivation and validation of a scoring system to stratify the risk of advanced colorectal neoplasia in asymptomatic adults

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Abstract

Background—Several methods are recommended equally strongly for colorectal cancer screening in average-risk persons. Risk stratification would enable tailoring of screening within this group, with less invasive tests (sigmoidoscopy or occult blood tests) for lower-risk persons and colonoscopy for higher-risk persons.

Objective—To create a risk index for advanced neoplasia (colorectal cancer and adenomas or serrated polyps ≥ 1.0 cm, villous histology, or high-grade dysplasia) anywhere in the colorectum, using the most common risk factors for colorectal neoplasia.

Design—Cross-sectional study.

Setting—Multiple endoscopy units, primarily in the Midwest.

Patients—Persons aged 50 to 80 years undergoing initial screening colonoscopy (December 2004 to September 2011).

Measurements—Derivation and validation of a risk index based on points from regression coefficients for age, sex, waist circumference, cigarette smoking, and family history of colorectal cancer.

Results—Among 2993 persons in the derivation set, prevalence of advanced neoplasia was 9.4%. Risks for advanced neoplasia in persons at very low, low, intermediate, and high risk were 1.92% (95% CI, 0.63% to 4.43%), 4.88% (CI, 3.79% to 6.18%), 9.93% (CI, 8.09% to 12.0%), and 24.9%

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Statistical Code: Available to interested readers by contacting Dr. Imperiale at timperia@iu.edu Data: not available

(CI, 21.1% to 29.1%), respectively ($P < 0.001$). Sigmoidoscopy to the descending colon in the low-risk groups would have detected 51 of 70 (73% [CI, 61% to 83%]) advanced neoplasms. Among 1467 persons in the validation set, corresponding risks for advanced neoplasia were 1.65% (CI, 0.20% to 5.84%), 3.31% (CI, 2.08% to 4.97%), 10.9% (CI, 8.26% to 14.1%), and 22.3% (CI, 16.9% to 28.5%), respectively ($P < 0.001$). Sigmoidoscopy would have detected 21 of 24 (87.5% [CI, 68% to 97%]) advanced neoplasms.

Limitations—Split-sample validation; results apply to first-time screening.

Conclusion—This index stratifies risk for advanced neoplasia among average-risk persons by identifying lower-risk groups for which noncolonoscopy strategies may be effective and efficient and a higher-risk group for which colonoscopy may be preferred.

Keywords

colorectal cancer; cancer screening; risk stratification

In the United States, colorectal cancer is a significant cause of morbidity and mortality among men and women, accounting for nearly 140 000 new cases and 55 000 deaths per year (1). The natural history of colorectal neoplasia, which usually involves a slow progression from precancerous polyp to cancer, lends itself to screening. Screening for colorectal cancer with any of several tests and strategies has been found to be effective (2–3) and cost-effective (4–7) and is supported by guidelines from several organizations (8–10). Foremost among them is the U.S. Preventive Services Task Force (10), which recommends any of several screening tests and strategies with no preference for any single strategy based on direct evidence and quantitative modeling (11–12).

Despite the favorable biology, test options, and evidence to support screening, it is underused, costly, and inefficient. Nearly 22 million U.S. residents aged 50 to 75 years have never been screened, and just 60% to 65% have had lower endoscopy of any kind for any reason within the past 10 years (13). Although screening is cost-effective, it is estimated to cost billions of dollars per year (14–15). In addition to its high total cost, screening is conducted inefficiently; low-risk persons may receive colonoscopy with low yield and little benefit, and high-risk persons may receive noninvasive testing with missed opportunity for benefit.

Tailoring of colorectal cancer screening based on risk could improve the overall uptake and efficiency of screening. Among average-risk persons not current with screening, knowledge of their personal risk for colorectal cancer or advanced neoplasia might affect how they choose to be screened. For lower-risk persons within the average-risk group, screening could be done with stool-based occult blood tests or sigmoidoscopy (or both), which are less invasive, less risky, and less costly than colonoscopy. For higher-risk persons, initial colonoscopy might be the preferred test.

Several risk prediction models for either colorectal cancer (16–18) or advanced neoplasia (19–24) (colorectal cancer plus advanced, precancerous polyps) may not be clinically useful for several reasons. Models predicting risk for advanced neoplasia either show limited performance in risk stratification (that is, "high risk" and "low risk" are not far from average

risk) or are based on populations with unclear generalizability to the U.S. population. Further, all models are limited in their degree of validation. In this study, we developed and validated a risk stratification tool for advanced neoplasia anywhere in the colon and rectum using the most commonly identified risk factors for colorectal cancer and advanced adenomas. We included advanced adenomas because they are believed to be immediate precursor lesions to most colorectal cancer (25), even though their natural history is unknown.

Methods

This study was conducted at the Indiana University Medical Center in Indianapolis, Indiana, and was approved by the Institutional Review Board of Indiana University at Indianapolis. We report methods and results in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) guidelines (26–27). Between December 2004 and September 2011, we enrolled consecutive eligible and consenting persons aged 50 to 80 years who were scheduled to have their first screening colonoscopy. We initially recruited patients from endoscopy units participating in either of 2 company-based colorectal cancer prevention programs, one of which was based in central Indiana and the other in northeastern Ohio. Because of low uptake in these programs, we expanded recruitment to include general endoscopy practices and units within central Indiana, including those affiliated with Indiana University Medical Center. At all sites and throughout the study, we excluded persons with inflammatory bowel disease, those with a high-risk family history (polyposis or nonpolyposis colorectal cancer syndrome), and those reporting a history of polyps that required follow-up colonoscopy.

Before having colonoscopy, enrolled participants were asked to complete a comprehensive survey that asked about candidate risk factors, including family history; sociodemographic factors; and lifestyle factors, including previous and current cigarette smoking. Participants were also asked to measure and record current height, weight, and waist and hip circumference; a tape measure was provided for the circumferential measurements. On the day of their screening colonoscopy, participants' physical measures were collected by medical personnel just before the procedure. In analysis, physical measures recorded by medical personnel were used unless they were unavailable, in which case self-reported measures were used.

All surveys were reviewed for completeness by trained study personnel, who contacted participants by telephone for clarification or completion of survey items. Colonoscopy and pathology reports were reviewed and coded by trained personnel who were blinded to survey information. The most advanced findings in the colorectum were coded for both proximal (which includes the splenic flexure) and distal segments. Colonoscopies with no pathology report were assumed to show no neoplasia, provided that the colonoscopy report did not specify that a tissue specimen had been obtained (biopsy or polypectomy). After review, completion, and coding, all data were scanned into a deidentified database with unique identifier numbers.

Statistical Analysis

Study sample size was based on both prevalence of advanced neoplasia from a previous study of screening colonoscopy among average-risk persons (28) and a goal of ensuring an adequate number of persons with advanced neoplasia for derivation and split-sample validation. In analysis, a stratified random sample comprising two thirds of the original sample was obtained using PROC SURVEYSELECT in SAS, version 9.3 (SAS Institute). Strata were created using the following variables: advanced neoplasia, sex, family history of cancer, and body mass index (BMI). Participants in this data set were used as the derivation set, and the other one third of participants were used as a validation set. The data set was divided in this way to ensure a random but equal distribution of sex and most advanced findings. The goal of the analysis was to determine model performance using 5 factors that are most commonly associated with colorectal neoplasia in the published literature: age, sex, cigarette smoking, body fat, and a family history of colorectal cancer. For cigarette smoking, which was measured in pack-years, we considered different cutoffs to categorize exposure. For measures of body fat, we considered BMI, waist circumference, and waist-to-hip ratio. Categories for measures of body fat were determined a priori based on published literature that related each physical factor to risk for either colorectal cancer or advanced adenoma (29–31). For family history of colorectal cancer, we considered first-degree relatives only and both first- and second-degree relatives, and we considered ages for both categories. For family history, cigarette smoking, and measures of body fat, we used age- and sex-adjusted logistic regression models to quantify the most discriminating variable (in the case of body fat) or to compare different ways of categorizing them, as determined by the Wald test and odds ratio for the variable itself and the omnibus likelihood ratio test for the model (32) (Appendix Table 1). The outcome (dependent) variable was advanced neoplasia, which included adenocarcinoma of the colon or rectum, a tubular adenoma or sessile serrated adenoma or polyp with a greatest dimension of at least 1 cm, or an adenomatous polyp with villous histology or high-grade dysplasia.

We used statistical metrics and clinical judgment to choose the optimal format for cigarette smoking, family history of colorectal cancer, and body fat measurement. We then included them in a model along with age and sex and determined performance of the full model in the derivation set by measuring calibration with the Hosmer–Lemeshow test and discrimination with the c-statistic (32). The log-odds coefficients from each variable were subsequently incorporated into a points system, an approach described by Sullivan and colleagues (33). Coefficients were translated into risk categories for advanced neoplasia, with 0 points representing the lowest-risk group for each variable. Points were rounded to the nearest integer and were scaled such that a single point was equivalent to the increase in risk for advanced neoplasia associated with a 5-year increase in age (Appendix Table 2). On the basis of previous work (34), we planned to create risk categories by collapsing scores with clinically similar risk estimates. We used a chi-square test for trend for risk for (or prevalence of) advanced neoplasia across categories, and we tested performance of the model and the risk score classification table by using the same cutoffs and categories on the validation set, which contained the remaining one third of the study participants. SAS, version 9.3, was used for all analyses. For each risk group within the derivation and

validation sets, we calculated likelihood ratios, defined as the proportion of persons with advanced neoplasia divided by the proportion without.

Results

A total of 4500 eligible consenting persons were enrolled into the study between December 2004 and September 2011. Demographic and clinical features of the derivation ($n = 3025$) and validation ($n = 1475$) sets were similar, including the proportion of participants with complete data who were used in subsequent analyses (Table 1). Ninety-four percent of persons in the cohort were white.

Results of age- and sex-adjusted models for family history of colorectal cancer, cigarette smoking, and body fat measurement are shown in Table 2 and are based on the derivation set. The presence versus absence of 1 or more first-degree relatives with colorectal cancer was used on the basis of practical consideration of reporting accuracy, statistical metrics (Appendix Table 1), and published literature (35). For cigarette smoking, cutoffs of 0 and 30 pack-years were chosen on the basis of the number of categories and statistical discrimination (Appendix Table 1). Among the physical measures of body fat, waist circumference, which was categorized as small (<95.0 cm for men or <87.9 cm for women) (29), medium, or large (119.9 cm for men or 110.0 cm for women), was more discriminating than either BMI or waist-to-hip ratio.

Multivariable odds ratios and 95% CIs based on the derivation set are shown in Table 3. The model was well-calibrated ($P = 0.42$) and showed good discrimination (c-statistic = 0.72). Points given to the different values for each of the 5 variables are shown in Appendix Table 2. The score was the sum of points for age (0 for <55 years, 1 for 55 to <60 years, 2 for 60 to <65 years, 3 for 65 to <70 years, or 4 for ≥70 years), sex (0 for female or 1 for male), first-degree relative with colorectal cancer (1 for 1 relative or 0 for other), cigarette smoking (0 for 0 pack-years, 2 for >0 to <30 pack-years, or 4 for ≥30 pack-years), and waist circumference (0 for small, 1 for medium, or 2 for large). Scores for the risk index ranged from 0 to 13. We computed the risk for advanced neoplasia for each score and collapsed scores with clinically similar risks into risk categories.

On the basis of the risk for (or prevalence of) advanced neoplasia and the risk score (Appendix Table 3), we identified 4 risk groups (very low, low, intermediate, and high) within the derivation set, with risks for advanced neoplasia that ranged from 1.92% (95% CI, 0.63% to 4.43%) among the nearly 9% considered to be at very low risk to 24.9% (CI, 21.1% to 29.1%) among the 15.5% who were at high risk ($P < 0.001$ for trend) (Table 4). The 1591 total persons in the very-low-risk and low-risk groups represented 53% of the derivation set. Five adenocarcinomas were detected in this combined subgroup, all of which were located in the distal colon. If this subgroup had undergone sigmoidoscopy with detection of any distal polyp resulting in a diagnostic colonoscopy, 51 of 70 (73% [CI, 61% to 83%]) advanced neoplasms would have been detected; 19 persons had advanced proximal adenomas without a distal sentinel lesion.

In the validation set, the risks for advanced neoplasia were similar to those in the derivation subgroup, ranging from 1.65% (CI, 0.20% to 5.84%) among participants in the very-low-risk group to 22.3% (CI, 16.9% to 28.5%) in the high-risk group (Table 4). Risk for (or prevalence of) advanced neoplasia for each score from 0 to 12 in the validation set is shown in Appendix Table 3. The 786 total persons in the very-low-risk and low-risk groups represented slightly more than 53% of the validation set. No cancer cases were detected in this combined subgroup. Further, 21 of 24 (87.5% [CI, 68% to 97%]) advanced neoplasms would have been detected if sigmoidoscopy had been performed with subsequent colonoscopy for a finding of a distal polyp.

Discussion

Colorectal cancer screening is effective and cost-effective, but it is also underused, potentially risky, and costly. Colonoscopy is the predominant screening test used in the U.S. health care system (1), even though no comparative outcomes studies have been done and quantitative modeling shows that alternative strategies may—when a less sensitive test is applied more frequently over time—be at least as effective as a colonoscopy-based strategy (11–12). In addition, studies of colonoscopy capacity in the United States (15, 36) and other countries (37) suggest that it is a limited resource (38–39). The ability to accurately and reliably estimate and stratify risk for colorectal cancer and advanced precancerous polyps among persons currently classified as average-risk could help guide choice among several available test options for patients and providers. In the larger picture, such risk stratification and resultant tailoring within the average-risk group would make screening more efficient by targeting colonoscopy toward higher-risk persons and away from lower-risk persons, who could be effectively screened with less invasive tests, all of which are recommended by the U.S. Preventive Services Task Force (12).

Our model identified 4 risk groups, with risk for advanced neoplasia ranging from less than 2% among very-low-risk persons to 22% to 25% among high-risk persons. The model could be used to tailor screening on the basis of risk for advanced neoplasia. Persons at very low or low risk could be screened effectively and efficiently with strategies other than colonoscopy, including sigmoidoscopy every 5 years, fecal immunochemical testing annually, both strategies combined, or another less invasive strategy. For persons at high risk, screening with colonoscopy seems to be warranted. Persons at intermediate risk, who have the same risk as that observed in large-scale screening studies (40–41), could continue to choose from the available tests. Such risk-based tailored screening has the potential to increase the uptake and efficiency of colorectal cancer screening.

Over the past decade, several risk models for advanced colorectal neoplasia have been developed in the screening setting (19–20, 22, 24, 34, 42). The clinical and methodological variation in both model performance and extent of validation has precluded selection of any of them for use in decision making about colorectal cancer screening. The models vary in important features, including the outcome predicted (advanced neoplasia vs. advanced proximal neoplasia), demographic characteristics of the study population, risk factors, ability to achieve clinically meaningful risk stratification, degree of discrimination, and extent of validation. A summary of the published risk prediction models for advanced adenoma or

advanced neoplasia is shown in Appendix Table 4. All of the models shown have limitations that require consideration, including the ability to reliably and accurately measure the variables contained in the model, clinical importance of the magnitude of the risk gradient, proportion of the study population found to be at low or high risk, and applicability of the findings beyond the population from which the model was derived.

For the U.S. population, in which colonoscopy dominates screening (1), the model we describe seems to have the greatest potential for clinical application because it contains 5 factors that can be easily and reliably measured and that are likely to be present in medical records. The model itself is simple to use; it was derived from and validated in a cohort of average-risk U.S. persons aged 50 to 80 years who were having their first screening colonoscopy. The model distributes persons more evenly among its risk categories than do other models. Also, both the degree of discrimination (as measured by the c-statistic) and the risk gradient are greater than those of the other models, suggesting a more robust and clinically meaningful separation of risk for advanced neoplasia across the 4 risk groups.

In several cross-sectional screening studies, age and sex accounted for much of the variation in prevalence of advanced neoplasia (28, 34, 40–41, 43–44). Our risk score may have particular importance among women aged 50 to 59 years, who have been identified as a low-risk subgroup for whom screening may be performed noninvasively or possibly deferred (42, 45). The current study included 1108 women in this age group with a 5.2% prevalence of advanced neoplasia, which is lower than that of the entire cohort. Application of the risk score to this subgroup would have categorized 85% of these women as very-low-risk or low-risk, with risks for advanced neoplasia from the lowest- to highest-risk groups of 1.92%, 5.02%, 11.3%, and 0%, respectively ($P < 0.001$). This shows that the risk score provides incremental discrimination within this large low-risk subgroup, for which non-colonoscopy-based screening may be most efficient. Understanding the differences in outcomes and costs between tailored screening and colonoscopy for all persons, particularly in women aged 50 to 59 years, requires formal modeling to quantify these tradeoffs (46).

Our model may have strengths compared with a similar model derived from and internally validated in the screening setting. Kaminski and colleagues (21) derived a model containing age, sex, family history of colorectal cancer, cigarette smoking, and BMI to identify low- and high-risk groups in nearly 36 000 persons aged 40 to 66 years who had screening colonoscopy (Appendix Table 4). Although the risks for advanced neoplasia in the validation set of 17 939 persons were 2.49% and 19.44% in the low- and high-risk groups, respectively, these risk extremes represented only 1% of the sample when combined, whereas in our model the risk extremes represented between 22.9% and 24.2%. Further, the comparability of this model and ours is uncertain because of differences in the physical measure used (BMI vs. waist circumference) and the difference in age range between the study cohorts (Appendix Table 4). We tested Kaminski and colleagues' model on our cohort, and its discrimination was inferior to that of our model (data not shown).

This study has strengths, including the relatively large sample size, uniformity of data collection across sites, and completeness of data collection from study participants, all of which allowed for a robust analysis. However, the study also has limitations. First, the

variables used for this model were chosen on the basis of the published literature (that is, they were predetermined). Other variables might have better discrimination, but we suggest that the performance of these variables in the validation set, using the cut points derived in the derivation set, is substantially stronger than in other models. A strength of using these variables is that they are easily measured, and all except waist circumference are likely to be easily identifiable from the medical record. Although other models containing a greater number of factors that are less easily measured may perform better, more complex models may be less useful from practical and clinical perspectives. Second, the prediction equation has imperfect discrimination; some patients with advanced neoplasia would be categorized as low-risk, including those with colorectal cancer. Detection of these lesions would depend on which less invasive strategy was used (sigmoidoscopy; fecal immunochemical or other stool-based testing; both tests; or other tests, such as computed tomographic colonography). Of note, the model quantifies the prevalence of advanced neoplasia anywhere in the colorectum; it does not distinguish between proximal and distal disease and therefore cannot determine which less invasive test may be preferred. Nonetheless, the 5 cancer cases in the low-risk subgroups of the derivation set were within reach of a sigmoidoscope; no cancer was found in the low-risk groups of the validation set. This post hoc observation, in particular, requires validation in independent cohorts. Use of sigmoidoscopy alone in the low-risk groups would have detected 73% to 87.5% of all advanced neoplasia in a single application. If fecal immunochemical testing were used as well, additional advanced neoplasms would probably have been detected. Further, because of transition rates from advanced adenoma to cancer of less than 3% in low-risk patients (25), subsequent screening with fecal immunochemical testing, sigmoidoscopy, or both would provide additional opportunity for detection of advanced neoplasia. Third, this model was validated using the split-sample method, which is a relatively simple way to test for overfitting (47–48) but does not determine the generalizability to independent cohorts. The transportability of the model beyond the type of population studied has not yet been established. Fourth, the study cohort comprised predominantly white persons, and whether the findings are generalizable to a more racially diverse population is uncertain. Although black persons are believed to be at higher risk for colorectal neoplasia, recent studies have shown no clinically important differences in prevalence of neoplasia between black and white persons (49–52). Further study of this issue is required. Finally, an important practical consideration of any validated model is quantification of its clinical and economic impact—in this case, on screening uptake, adherence, and efficiency. These effects remain to be determined.

In conclusion, this 5-variable risk index may help decision making about colorectal cancer screening for persons currently considered to be at average risk, for whom several test options are equally strongly recommended. The index identified both lower-risk groups that may be screened with strategies other than colonoscopy and a higher-risk group for which colonoscopy may be preferable in terms of yield and efficiency. If this index is further validated externally in independent cohorts, it could increase the uptake and efficiency of colorectal cancer screening in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Steele CB, Rim SH, Joseph DA, King JB, Seeff LC. Centers for Disease Control and Prevention (CDC). Colorectal cancer incidence and screening—United States, 2008 and 2010. *MMWR Surveill Summ.* 2013; 62(Suppl 3):53–60.
2. Zauber AG, Lansdorp-Vogelaar I, Knudsen AB, Wilschut J, vanBallegooijen M, Kuntz KM. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2008; 149:659–69. [PubMed: 18838717]
3. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2008; 149:638–58. [PubMed: 18838718]
4. Heitman SJ, Manns BJ, Hilsden RJ, Fong A, Dean S, Romagnuolo J. Cost-effectiveness of computerized tomographic colonography versus colonoscopy for colorectal cancer screening. *CMAJ.* 2005; 173:877–81. [PubMed: 16217110]
5. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA.* 2000; 284:1954–61. [PubMed: 11035892]
6. Parekh M, Fendrick AM, Ladabaum U. As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia. *Aliment Pharmacol Ther.* 2008; 27:697–712. [PubMed: 18248653]
7. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *Am J Gastroenterol.* 2013; 108:120–32. [PubMed: 23247579]
8. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, et al. American Cancer Society Colorectal Cancer Advisory Group. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology.* 2008; 134:1570–95. [PubMed: 18384785]
9. Rex DK, Johnson DA, Anderson JC, Schoenfeld PS, Burke CA, Inadomi JM. American College of Gastroenterology. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol.* 2009; 104:739–50. [PubMed: 19240699]
10. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 2008; 149:627–37. [PubMed: 18838716]
11. Pignone M, Russell L, Wagner J. Economic Models of Colorectal Cancer Screening in Average-Risk Adults: Workshop Summary. Washington, DC: National Academies Press; 2005.
12. Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002; 137:132–41. [PubMed: 12118972]
13. Centers for Disease Control and Prevention (CDC). Vital signs: colorectal cancer screening test use—United States, 2012. *MMWR Morb Mortal Wkly Rep.* 2013; 62:881–8. [PubMed: 24196665]
14. Tangka FK, Subramanian S, Beebe MC, Hoover S, Royalty J, Seeff LC. Clinical costs of colorectal cancer screening in 5 federally funded demonstration programs. *Cancer.* 2013; 119(Suppl 15): 2863–9. [PubMed: 23868481]
15. Seeff LC, Richards TB, Shapiro JA, Nadel MR, Manninen DL, Given LS, et al. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. *Gastroenterology.* 2004; 127:1670–7. [PubMed: 15578503]
16. Freedman AN, Slaterry ML, Ballard-Barbash R, Willis G, Cann BJ, Pee D, et al. Colorectal cancer risk prediction tool for white men and women without known susceptibility. *J Clin Oncol.* 2009; 27:686–93. [PubMed: 19114701]

17. Park Y, Freedman AN, Gail MH, Pee D, Hollenbeck A, Schatzkin A, et al. Validation of a colorectal cancer risk prediction model among white patients age 50 years and older. *J Clin Oncol*. 2009; 27:694–8. [PubMed: 19114700]
18. Driver JA, Gaziano JM, Gelber RP, Lee IM, Buring JE, Kurth T. Development of a risk score for colorectal cancer in men. *Am J Med*. 2007; 120:257–63. [PubMed: 17349449]
19. Betés M, Muñoz-Navas MA, Duque JM, Angós R, Macías E, Sútil JC, et al. Use of colonoscopy as a primary screening test for colorectal cancer in average risk people. *Am J Gastroenterol*. 2003; 98:2648–54. [PubMed: 14687811]
20. Cai QC, Yu ED, Xiao Y, Bai WY, Chen X, He LP, et al. Derivation and validation of a prediction rule for estimating advanced colorectal neoplasm risk in average-risk Chinese. *Am J Epidemiol*. 2012; 175:584–93. [PubMed: 22328705]
21. Kaminski MF, Polkowski M, Kraszeńska E, Rupinski M, Butruk E, Regula J. A score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy. *Gut*. 2014; 63:1112–9. [PubMed: 24385598]
22. Lin OS, Kozarek RA, Schembre DB, Ayub K, Gluck M, Cantone N, et al. Risk stratification for colon neoplasia: screening strategies using colonoscopy and computerized tomographic colonography. *Gastroenterology*. 2006; 131:1011–9. [PubMed: 17030171]
23. Tao S, Hoffmeister M, Brenner H. Development and validation of a scoring system to identify individuals at high risk for advanced colorectal neoplasms who should undergo colonoscopy screening. *Clin Gastroenterol Hepatol*. 2014; 12:478–85. [PubMed: 24022090]
24. Yeoh KG, Ho KY, Chiu HM, Zhu F, Ching JY, Wu DC, et al. Asia-Pacific Working Group on Colorectal Cancer. The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. *Gut*. 2011; 60:1236–41. [PubMed: 21402615]
25. Brenner H, Altenhofen L, Stock C, Hoffmeister M. Natural history of colorectal adenomas: birth cohort analysis among 3.6 million participants of screening colonoscopy. *Cancer Epidemiol Biomarkers Prev*. 2013; 22:1043–51. [PubMed: 23632815]
26. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007; 147:573–7. [PubMed: 17938396]
27. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med*. 2015; 162:55–63. [PubMed: 25560714]
28. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med*. 2000; 343:169–74. [PubMed: 10900275]
29. Wang Y, Jacobs EJ, Patel AV, Rodríguez C, McCullough ML, Thun MJ, et al. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. *Cancer Causes Control*. 2008; 19:783–92. [PubMed: 18322811]
30. Giacosa A, Franceschi S, LaVecchia C, Favero A, Andreatta R. Energy intake, overweight, physical exercise and colorectal cancer risk. *Eur J Cancer Prev*. 1999; 8(Suppl 1):S53–60. [PubMed: 10772419]
31. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med*. 1995; 122:327–34. [PubMed: 7847643]
32. Hosmer, DW.; Lemeshow, S. *Applied Logistic Regression*. 2. New York: J Wiley; 2000.
33. Sullivan LM, Massaro JM, D'Agostino RB Sr. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med*. 2004; 23:1631–60. [PubMed: 15122742]
34. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Using risk for advanced proximal colonic neoplasia to tailor endoscopic screening for colorectal cancer. *Ann Intern Med*. 2003; 139:959–65. [PubMed: 14678915]

35. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: a constellation approach. *Gastroenterology*. 2010; 138:877–85. [PubMed: 19932107]
36. Seeff LC, Manninen DL, Dong FB, Chattopadhyay SK, Nadel MR, Tangka FK, et al. Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? *Gastroenterology*. 2004; 127:1661–9. [PubMed: 15578502]
37. Steele RJ, McDonald PJ, Digby J, Brownlee L, Strachan JA, Libby G, et al. Clinical outcomes using a faecal immunochemical test for haemoglobin as a first-line test in a national programme constrained by colonoscopy capacity. *United European Gastroenterol J*. 2013; 1:198–205.
38. Ballew C, Lloyd BG, Miller SH. Capacity for colorectal cancer screening by colonoscopy, Montana, 2008. *Am J Prev Med*. 2009; 36:329–32. [PubMed: 19285198]
39. Rodríguez-Moranta F, Trapero-Bertran M, Castells A, Mas-Canal X, Balaguer F, Pellisé M, et al. Endoscopic requirements of colorectal cancer screening programs in average-risk population. Estimation according to a Markov model. *Gastroenterol Hepatol*. 2008; 31:405–12. [PubMed: 18783684]
40. Regula J, Rupinski M, Kraszevska E, Polkowski M, Pachlewski J, Orlowska J, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med*. 2006; 355:1863–72. [PubMed: 17079760]
41. Ferlitsch M, Reinhart K, Pramhas S, Wiener C, Gal O, Bannert C, et al. Sex-specific prevalence of adenomas, advanced adenomas, and colorectal cancer in individuals undergoing screening colonoscopy. *JAMA*. 2011; 306:1352–8. [PubMed: 21954479]
42. Park HW, Han S, Lee JS, Chang HS, Lee D, Choe JW, et al. Risk stratification for advanced proximal colon neoplasm and individualized endoscopic screening for colorectal cancer by a risk-scoring model. *Gastrointest Endosc*. 2012; 76:818–28. [PubMed: 22884098]
43. Imperiale TF, Glowinski EA, Lin-Cooper C, Ransohoff DF. Tailoring colorectal cancer screening by considering risk of advanced proximal neoplasia. *Am J Med*. 2012; 125:1181–7. [PubMed: 23062404]
44. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med*. 2000; 343:162–8. [PubMed: 10900274]
45. Hassan C, Pooler BD, Kim DH, Rinaldi A, Repici A, Pickhardt PJ. Computed tomographic colonography for colorectal cancer screening: risk factors for the detection of advanced neoplasia. *Cancer*. 2013; 119:2549–54. [PubMed: 23754679]
46. Lansdorp-Vogelaar I, vanBallegooijen M, Zauber AG, Boer R, Wilschut J, Winawer SJ, et al. Individualizing colonoscopy screening by sex and race. *Gastrointest Endosc*. 2009; 70:96–108. [PubMed: 19467539]
47. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med*. 1999; 130:515–24. [PubMed: 10075620]
48. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med*. 2000; 19:453–73. [PubMed: 10694730]
49. Schroy PC 3rd, Coe A, Chen CA, O'Brien MJ, Heeren TC. Prevalence of advanced colorectal neoplasia in white and black patients undergoing screening colonoscopy in a safety-net hospital. *Ann Intern Med*. 2013; 159:13–20. [PubMed: 23817700]
50. Levitzky BE, Brown CC, Heeren TC, Schroy PC 3rd. Performance of a risk index for advanced proximal colorectal neoplasia among a racially/ethnically diverse patient population (risk index for advanced proximal neoplasia). *Am J Gastroenterol*. 2011; 106:1099–106. [PubMed: 21326221]
51. Kwah J, Schroy PC 3rd, Jacobson BC, Calderwood AH. Whites and blacks have similar risk of metachronous advanced colorectal neoplasia. *Dig Dis Sci*. 2014; 59:2264–71. [PubMed: 24700155]
52. Friedenberg FK, Singh M, George NS, Sankineni A, Shah S. Prevalence and distribution of adenomas in black Americans undergoing colorectal cancer screening. *Dig Dis Sci*. 2012; 57:489–95. [PubMed: 22052446]

Table 1

Description of demographic and clinical factors in derivation and validation sets.

Variable	Derivation set*	Validation set
Number of individuals	3025	1475
Age (mean $\pm$ SD)	57.3 $\pm$ 6.6 years	57.2 $\pm$ 7.0 years
Women	51.6%	51.5%
Caucasian	94.6%	94.4%
First-degree relative with CRC	9.6%	9.2%
Lifetime nonsmoker [‡]	60.3%	60.5%
Body mass index [§] (mean $\pm$ SD)	28.6 $\pm$ 5.7	28.8 $\pm$ 5.9
Waist circumference (mean $\pm$ SD)	36.4 $\pm$ 5.3 in.	36.5 $\pm$ 5.5 in.
Advanced neoplasia	9.4%	8.5%
N (%) with complete data	2993 (98.9%)	1467 (99.5%)

* Missing data: cigarette smoking, n=20 (0.66%); waist circumference, n=12 (0.39%)

[‡] Missing data: cigarette smoking, n=6 (0.41%); waist circumference, n=2 (0.14%)

[‡] Defined either as never having smoked or having smoked less than 100 cigarettes lifetime.

[§] Units are weight in kilograms /height in meters²

Table 2

Age- and sex-adjusted logistic regression models of advanced neoplasia for categorical factors *

Variable	Categories	Odds Ratio [†] (95% CI)	P-value
1 or more first-degree relatives with colorectal cancer	No	---	0.107
	Yes	1.37 (0.94 – 2.00)	
Cigarette smoking	Non-smoker	---	<0.0001
	> 0 to < 30 pack-years	2.06 (1.52 – 2.80)	
	30 pack-years	3.39 (2.47 – 4.66)	
Waist circumference [‡]	Small	---	0.003
	Medium	1.44 (1.11 – 1.88)	
	Large	2.01 (1.23 – 3.29)	

* Based on a derivation set of 2993

[†] Odds ratios represent the age-and sex-adjusted odds of advanced neoplasia. An odds ratio > 1 indicated an increased risk of advanced neoplasia

[‡] Small: < 37.4 inches for men, < 34.6 inches for women; Medium: 37.4–47.2 inches for men, 34.6–43.3 inches for women; Large: 47.2 inches for men, 43.3 inches for women

Table 3

Multivariable regression model of advanced neoplasia and resulting scores for each variable *

Variable	Odds Ratio (95% CI)	Log Odds Coefficient	Score
Age (per year increase)	1.06 (1.04–1.08)	0.0592	0 to 4 †
Sex			
Women	Reference group		0
Men	1.69 (1.30–2.20)	0.5225	1
1 First-degree relative with colorectal cancer	1.39 (0.94–2.04)	0.3259	1
Waist circumference ‡			
small	Reference group		0
medium	1.41 (1.08–1.84)	0.3426	1
large	1.88 (1.14–3.09)	0.6313	2
Cigarette smoking			
0 pack-years	Reference group		
>0 to <30 pack years	2.07 (1.52–1.84)	0.7250	2
30 pack-years	3.33 (2.43–4.58)	1.2042	4

* Based on a derivation set of 2993

† 0 points for age < 55 years; 1 point for 55 to <60 years; 2 points for 60 to < 65 years; 3 points for 65 to <70 years; 4 points for ≥ 70 years

‡ Small: < 37.4 inches for men, < 34.6 inches for women; Medium: 37.4–47.2 inches for men, 34.6–43.3 inches for women; Large: ≥ 47.2 inches for men, ≥ 43.3 inches for women

Table 4

Risk of advanced neoplasia and likelihood ratios in each risk group within derivation and validation sets

Risk Group	Score*	Derivation set (N=2993)				Validation set (N=1467)			
		N	% of Subgroup	Risk (%) CI	Likelihood Ratio (CI)	N	% of Subgroup	Risk (%) CI	Likelihood Ratio (CI)
Very low	0	260	8.7	1.92 (0.63 – 4.43)	0.19 (0.08– 0.46)	121	8.2	1.65 (0.20 – 5.84)	0.18 (0.05–0.73)
Low	1–3	1331	44.5	4.88 (3.79 – 6.18)	0.50 (0.40– 0.62)	665	45.3	3.31 (2.08 – 4.97)	0.37 (0.25–0.55)
Intermediate	4–6	937	31.3	9.93 (8.09 – 12.0)	1.07 (0.90– 1.28)	466	31.7	10.9 (8.26 – 14.1)	1.34 (1.07–1.68)
High	> 6	465	15.5	24.9 (21.1 – 29.1)	3.23 (2.73– 3.83)	215	14.7	22.3 (16.9 – 28.5)	3.14 (2.42–4.08)

*. Score is the sum of points for age (0 for age < 55; 1 for age 55 to < 60; 2 for 60 to < 65; 3 for 65 to < 70; 4 for 70); Sex (0 for women; 1 for men); Family history of colorectal cancer (1 for 1 first-degree relative with colorectal cancer; 0 for other); smoking (0 for lifetime non-smoker; 2 for > 0 to < 30 pack-years; 4 for 30 pack-years; waist circumference (0 for small; 1 for medium; 2 for large). Likelihood ratios for each risk group calculated as the percent of all advanced neoplasia divided by the percent of all without non-advanced neoplasia.