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Risk of Advanced Neoplasia Using the National Cancer Institute's Colorectal Cancer Risk Assessment Tool

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Abstract

Background: There is no validated, discriminating, and easy-to-apply tool for estimating risk of colorectal neoplasia. We studied whether the National Cancer Institute's (NCI's) Colorectal Cancer (CRC) Risk Assessment Tool, which estimates future CRC risk, could estimate current risk for advanced colorectal neoplasia among average-risk persons.

Methods: This cross-sectional study involved individuals age 50 to 80 years undergoing first-time screening colonoscopy. We measured medical and family history, lifestyle information, and physical measures and calculated each person's future CRC risk using the NCI tool's logistic regression equation. We related quintiles of future CRC risk to the current risk of advanced neoplasia (sessile serrated polyp or tubular adenoma ≥ 1 cm, a polyp with villous histology or high-grade dysplasia, or CRC). All statistical tests were two-sided.

Results: For 4457 (98.5%) with complete data (mean age = 57.2 years, SD = 6.6 years, 51.7% women), advanced neoplasia prevalence was 8.26%. Based on quintiles of five-year estimated absolute CRC risk, current risks of advanced neoplasia were 2.1% (95% confidence interval [CI] = 1.3% to 3.3%), 4.8% (95% CI = 3.5% to 6.4%), 6.4% (95% CI = 4.9% to 8.2%), 10.0% (95% CI = 8.1% to 12.1%), and 17.6% (95% CI = 15.5% to 20.6%; $P < .001$). For quintiles of estimated 10-year CRC risk, corresponding current risks for advanced neoplasia were 2.2% (95% CI = 1.4% to 3.5%), 4.8% (95% CI = 3.5% to 6.4%), 6.5% (95% CI = 5.0% to 8.3%), 9.3% (95% CI = 7.5% to 11.4%), and 18.4% (95% CI = 15.9% to 21.1%; $P < .001$). Among persons with an estimated five-year CRC risk above the median, current risk for advanced neoplasia was 12.8%, compared with 3.7% among those below the median (relative risk = 3.4, 95% CI = 2.7 to 4.4).

Conclusions: The NCI's Risk Assessment Tool, which estimates future CRC risk, may be used to estimate current risk for advanced neoplasia, making it potentially useful for tailoring and improving CRC screening efficiency among average-risk persons.

The worldwide disease burden of colorectal cancer (CRC) is substantial, with 1.2 million new cases per year and more than 600 000 deaths (1), with corresponding US numbers of 142 000 and 53 000 (2). CRC biology lends itself toward interventions for early detection and prevention by removal of adenomatous polyps. The effectiveness and cost-effectiveness of screening have been well established, with several tests and strategies recommended (3–12). However, CRC screening has not achieved the

population penetration that breast, cervical, and prostate cancer screening have: Between 60% and 65% of the US population between age 50 and 80 years are current with screening, and 22 million have never been screened (13,14). Further, a screening program dominated by colonoscopy could be considered inefficient, as suggested by the relatively low yield for important neoplasia. Between 60% and 70% of persons who undergo screening colonoscopy have no neoplasia, and only 5% to 7% have

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advanced adenomatous polyps (15–18,21). Even though CRC screening is considered cost-effective, it is expensive, costing billions of dollars per year (19).

Tailoring screening based on individual patient risk is one way to improve efficiency (20–23). However, currently available risk stratification tools have substantial limitations, including lack of validation in relevant populations, modest discrimination, and difficulty measuring certain predictor variables. Tailoring is not new; it is done for high-risk groups, including persons with hereditary polyposis or nonpolyposis syndromes, inflammatory bowel disease, and a strong family history of colorectal cancer.

The National Cancer Institute's (NCI's) Colorectal Cancer (CRC) Risk Assessment Tool (24) uses demographics, family history, lifestyle factors, and personal medical history to estimate future absolute CRC risk. The tool has been validated on an independent cohort (25) and is available at <http://www.cancer.gov/colorectalcancerrisk/>. While it has been validated for predicting future CRC risk, the tool's clinical utility might be enhanced if it estimated current risk of a clinically important lesion (CRC, advanced precancerous polyps, or the combination). Knowing current risk may affect short-term decision-making more than knowing future risk. The objective of this study was to determine whether the NCI's Risk Assessment Tool ("tool") could estimate current risk for advanced neoplasia (ie, CRC and advanced, precancerous polyps) in an average-risk population.

Methods

This study was conducted at Indiana University Medical Center in Indianapolis and was approved without need for written informed consent by the institutional review board at Indiana University (Indianapolis, IN). Our reporting generally follows STROBE guidelines (26).

Study Population

Between December 2004 and September 2011, we enrolled persons age 50 to 80 years undergoing first-time screening colonoscopy. Study recruitment was initially targeted at two large corporations providing screening colonoscopy for their employees, retirees, and their dependents; these procedures were arranged by Indianapolis Gastroenterology Research Foundation (27,28) and scheduled at multiple contracted sites throughout the United States. During study years 4 and 5, recruitment was extended to Indianapolis Gastroenterology and Hepatology, a large single-specialty practice in Indianapolis, and to Wishard Memorial Hospital, the Richard L. Roudebush Veterans Affairs Medical Center, and Margaret Mary Community Hospital, affiliates of Indiana University Medical Center. Excluded were persons with previous colorectal neoplasia, inflammatory bowel disease, or familial or nonfamilial polyposis syndromes. Persons with a previous sigmoidoscopy or diagnostic colonoscopy were not excluded unless it had been performed within the previous five or 10 years, respectively, or resulted in surveillance colonoscopy (presumably for adenomatous polyps). The NCI's tool includes previous lower endoscopy and results, if known.

Study Procedures

Eligible subjects already scheduled for screening colonoscopy received a letter of introduction describing the study, a 12-page, 50-item, self-administered questionnaire, and 72-inch tape

measure. A follow-up telephone call clarified eligibility and answered questions about the study. Subjects completed the survey, including self-measure of height, weight, and waist and hip circumferences, and mailed it to the study center. Survey items included demographic variables, family history of CRC, personal medical history (including previous lower endoscopic procedure findings and nonendoscopic screening test results), lifestyle habits (diet, exercise, cigarette smoking, ethanol use), medication use (particularly aspirin, nonsteroidal anti-inflammatory drugs, and postmenopausal hormone replacement therapy), and physical measures. During the colonoscopy appointment, nursing personnel recorded physical measures (height, weight, and waist and hip circumference). These measures and subjects' survey responses were linked to endoscopic and pathological findings, which were categorized by the most advanced finding as no neoplasia, nonadvanced neoplasia, advanced adenomatous polyps (≥ 1 cm, villous histology, high-grade dysplasia), sessile serrated polyps ≥ 1 cm, or adenocarcinoma). Data collection began prior to the use of colonoscopy quality metrics such as withdrawal time and adenoma detection rate. We did not collect data on either preparation quality (as it was not uniformly available) or on extent of examination of the colon. Previous data from a large segment of participating endoscopists suggest very high rates of examinations to the cecum (29,30).

Data Management

Data were managed by the Department of Biostatistics, Indiana University School of Medicine (Indianapolis, IN). We limited the analytic dataset to those factors measured in the NCI's tool: age, sex, race; body mass index; the amount and number of servings of vegetables per week; a lower endoscopy within the previous 10 years; aspirin and NSAID use; physical activity; cigarette smoking, postmenopausal hormone replacement therapy, and CRC in one or more first-degree relatives. Because our data collection instrument was designed for a separate study involving risk prediction for advanced colorectal neoplasia (31), subject survey responses were categorized as closely as possible to those variable categories in the NCI's tool, with only minor differences. For example, the NCI's tool measures both number and size of vegetable servings per day, whereas our survey asked about number, but not size, of servings. We assumed average serving size for all subjects. The NCI's tool inquires about aspirin and NSAID use during the previous 30 days, whereas our survey did so over a range of less than one year to more than 20 years. We considered use of at least a year to reflect use within the previous 30 days.

The Risk Assessment Tool

The tool uses sex-specific multivariable risk equations to calculate a summary relative risk (24) and uses baseline age-specific cancer hazard rates from the Survey, Epidemiology, and End Results data, combining baseline hazard rate, competing risks because of comorbidity, and summary relative risk to estimate future CRC risk, given a set of risk factors. The tool and an accompanying SAS program found on the website computed estimated absolute CRC risk. We used the program to compute five-year, 10-year, and 20-year absolute risks.

Statistical Analysis

A nonparametric contingency table approach was used to test the association between the absolute future CRC risks

(estimated from the tool) and current risk (or prevalence) of advanced neoplasia. Specifically, each subject's five-, 10-, and 20-year estimated absolute CRC risk was categorized into risk quintiles. We calculated the mean predicted CRC risk for each quintile by taking the arithmetic mean of the individual predicted CRC risk of all persons in that quintile. The Spearman rank correlation test was used to test for differences among the quintiles. The quintiles were then tested for an ordinal association with the proportion (or prevalence) of persons in each quintile with advanced neoplasia using the Cochran-Armitage test for trend. We compared the current absolute risk of advanced neoplasia between persons above vs below the median lifetime CRC risk of 5% for each timeframe. We reported the relative risk of advanced neoplasia and the 95% exact binomial confidence interval for these dichotomized comparisons. As a complement to the primary results using the nonparametric quintile approach, we included a measure of discrimination using the area under the receiver operating characteristics curve (AUC), also known as the c-statistic, derived from a logistic regression model, for the five-, 10-, and 20-year timeframes. In the model, NCI tool-estimated future absolute CRC risk was the independent variable, and the observed current risk for advanced neoplasia was the dependent variable, dichotomized as present or absent. Sample size estimation was based on having a sufficient number of subjects with advanced neoplasia with which to derive and split-sample validate a model with up to 10 independent variables; the target sample size was 4500 to 5000 subjects. All statistical tests were two-sided, and a *P* value of less than .05 was considered statistically significant.

Results

The study population was comprised of 4526 subjects, of whom 4457 (98.5%) had complete data and were included in the analysis (Figure 1). The mean age was 57.2 years (SD=6.6 years); 51.7% were women, 94% were Caucasian, and 9.3% indicated having a family history of CRC. Nearly 34% had a body mass index of 30 kg/m² or greater; 41.1% were either current or former cigarette smokers. CRC and advanced neoplasia were present in 0.4% and 8.3%, respectively. There were no differences between the overall study population and included subjects on demographic features, risk factors, or prevalence of advanced neoplasia. Based on the NCI's tool, quintiles of estimated five-year, 10-year, and 20-year CRC risk were generated (Figure 1 and Table 1). The numbers of cancers in each quintile from lowest to highest were one, one, two, seven, and seven.

Table 1 and Figure 2 show the NCI tool's estimated five-year CRC risk in quintiles, along with the current risk (or prevalence) for advanced neoplasia with 95% confidence intervals. From the lowest to highest quintile, the estimated five-year CRC risks were 0.2%, 0.4%, 0.5%, 0.7%, and 1.5%, with corresponding risks for advanced neoplasia of 2.1% (95% confidence interval [CI] = 1.3% to 3.3%), 4.8% (95% CI = 3.5% to 6.4%), 6.4% (95% CI = 4.9% to 8.2%), 10.0% (95% CI = 8.1% to 12.1%), and 17.6% (95% CI = 15.5% to 20.6%; *P*_{trend} < .001 in risk for advanced neoplasia) (Table 1). The AUC from the logistic regression model was 0.71 (95% CI = 0.68 to 0.73), with no difference between men (AUC = 0.69, 95% CI = 0.66 to 0.73) and women (AUC = 0.69, 95% CI = 0.64 to 0.74). Supplementary Tables 1 and 2 (available online) show these results separately for women and men, respectively. Trends between quintile of future cancer risk and current risk for advanced neoplasia were statistically significant both overall and separately for men and women (*P* < .001). Estimated

Figure 1. Flow diagram for the study. NCI = National Cancer Institute.

absolute CRC risks were 26% to 70% higher for men than for women, while current risks for advanced neoplasia were 41% to 144% higher (Supplementary Tables 1 and 2, available online).

Table 1 and Figure 3 show the estimated 10-year absolute CRC risks and current absolute risks for advanced neoplasia by quintile of 10-year estimated absolute CRC risk. For the quintiles of estimated 10-year CRC risk, corresponding current risks for advanced neoplasia were 2.2% (95% CI = 1.4% to 3.5%), 4.8% (95% CI = 3.5% to 6.4%), 6.5% (95% CI = 5.0% to 8.3%), 9.3% (95% CI = 7.5% to 11.4%), and 18.4% (95% CI = 15.9% to 21.1%; *P* < .001). All lines show statistically significant trends in risk for both CRC and advanced neoplasia. The AUC was 0.70 (95% CI = 0.68 to 0.73), with no difference between men (AUC = 0.69, 95% CI = 0.65 to 0.72) and women (AUC = 0.69, 95% CI = 0.64 to 0.73). Similar to the five-year results, risks for both estimated future CRC and current advanced neoplasia were higher for men.

Table 1 and Figure 4 show the estimated 20-year absolute CRC risks and current absolute risks for advanced neoplasia by quintile of 20-year absolute CRC risk. The overall trend for future cancer risk was statistically significant (*P* = .045); however, neither of the sex-specific trends reached statistical significance because of the small number of cancers among men and women separately (Figure 4). The overall AUC was 0.67 (95% CI = 0.64 to 0.70), and was 0.67 (95% CI = 0.62 to 0.71) for women and 0.64 (95% CI = 0.60 to 0.68) for men. For current risk of advanced neoplasia by quintile of 20-year absolute CRC risk, however, both overall and sex-specific trends were statistically significant.

Table 2 shows current absolute and relative risks for advanced neoplasia (overall and sex-specific) according to whether the estimated five-year, 10-year, and 20-year CRC risks were above or below the median future cancer risk. The absolute risks for advanced neoplasia were consistently higher

Table 1. Estimated 5-, 10-, and 20-year colorectal cancer risk and current risk for advanced neoplasia: all subjects (n = 4457)*

Predicted future CRC risk and current risk of advanced neoplasia for each timeframe	Quintile 1 (n = 891)	Quintile 2 (n = 892)	Quintile 3 (n = 891)	Quintile 4 (n = 892)	Quintile 5 (n = 891)
5-y					
Predicted CRC risk, % (range†)	0.2 (0.1–0.3)	0.4 (0.3–0.4)	0.5 (0.4–0.6)	0.7 (0.6–0.9)	1.5 (0.9–5.6)
Current prevalence of advanced neoplasia, % (95% CI)	2.1 (1.3 to 3.3)	4.8 (3.5 to 6.4)	6.4 (4.9 to 8.2)	10.0 (8.1 to 12.1)	17.6 (15.5 to 20.6)
10-y					
Predicted CRC risk, % (range†)	0.5 (0.2–0.7)	0.9 (0.7–1.0)	1.2 (1.0–1.4)	1.7 (1.4–2.1)	3.0 (2.1–8.7)
Current prevalence of advanced neoplasia, % (95% CI)	2.2 (1.4 to 3.45)	4.8 (3.5 to 6.4)	6.5 (5.0 to 8.3)	9.3 (7.5 to 11.4)	18.4 (15.9 to 21.1)
20-y					
Predicted CRC risk, % (range†)	1.6 (0.6–2.1)	2.5 (2.1–2.9)	3.2 (2.9–3.6)	4.1 (3.6–4.7)	6.1 (4.7–15.2)
Current prevalence of advanced neoplasia, % (95% CI)	2.2 (1.4 to 3.5)	6.3 (4.8 to 8.1)	7.0 (5.4 to 8.8)	10.4 (8.5 to 12.6)	15.4 (13.1 to 17.9)

*P < .001 for differences among the quintile means for all future colorectal cancer risks using the two-sided Spearman rank correlation test and for trend in prevalence of advanced neoplasia using the two-sided Cochran-Armitage test. CI = confidence interval; CRC = colorectal cancer.

†Ranges come from the predicted values of future CRC risk for persons in each quintile.

Figure 2. Estimated five-year colorectal cancer (CRC) risk and current risk of advanced neoplasia by quintile of colorectal cancer risk. P values for five-year CRC risk are based on the two-sided Spearman rank correlation test; P values for current risk for advanced neoplasia are based on the two-sided Cochran-Armitage test for trend in risk among quintiles. CRC = colorectal cancer.

when CRC risk was above the median value. Among persons with an estimated five-year CRC risk above the median, current risk for advanced neoplasia was 12.8% compared with 3.7% among those below the median (relative risk = 3.44, 95% CI = 2.71 to 4.36). Absolute risks for current advanced neoplasia were higher in men (5.3%–7.3% when below the median future risk, 13.8%–15.8% when above the median) than in women

(3.4%–3.7% when below the median future risk, 8.5%– 8.9% when above the median).

Discussion

Our findings suggest that the NCI's Risk Assessment Tool, which estimates future CRC risk, effectively estimates current risk for

Figure 3. Estimated 10-year colorectal cancer (CRC) risk and current risk of advanced neoplasia by quintile of colorectal cancer risk. P values for 10-year CRC risk are based on the two-sided Spearman rank correlation test; P values for current risk for advanced neoplasia are based on the two-sided Cochran-Armitage test for trend in risk among quintiles. CRC = colorectal cancer.

advanced neoplasia, extending the tool's clinical utility. Such dual risk estimation has the potential to make the tool useful for improving screening efficiency. Discrimination is observed in the clinically and statistically significant spread of current risk for advanced neoplasia among quintiles of estimated future CRC risk. While the degree of discrimination observed in the five-year analysis (AUC = 0.71) is in the moderate-to-good range (32), these results are placed in context by two comparisons: the tool's AUC when applied to its original validation cohort (AUC = 0.61) (25,33) and that of the Gail Model when applied to an independent cohort to estimate five-year breast cancer risk (AUC = 0.58) (33).

The NCI's tool addresses limitations of currently available risk models by having more rigorous validation and greater relevance to the Caucasian segment of the US population. Few risk models are available to estimate future CRC risk (24,34,35); not all have been validated on independent populations. Further, the models are limited in generalizability because of the population from which they were derived. The NCI's tool was derived and validated on a nearly all-Caucasian population. Our study population closely reflects this demographic as it was 94% Caucasian, 3% black, 2% Asian, and 1% Hispanic.

In contrast to predicting future risk of CRC, several models estimate current risk for advanced neoplasia (36–42), but all

have limitations, including: 1) they are based on populations (eg, eastern Asian [38,40], Spanish [36], Polish [42]) with unclear generalizability to the more diverse US population [41]; 2) they demonstrate suboptimal model discrimination [37,38,41], meaning that they do not produce risk estimates that discriminate well enough to affect clinical decision-making (eg, to identify risk groups that are very high [37] or very low risk [41]) or that do not include a substantial proportion of the study population in those risk groups (42). Some models contain variables with little or no relevance to the US population (consumption of pickled foods, for example) (40). We have recently published a model for advanced colorectal neoplasia that has good discrimination (31); however, its uptake and clinical utility have yet to be determined. Further, it is not yet readily available, as is the NCI's tool. While the generalizability of the NCI's tool to non-Caucasian populations is uncertain, it is likely to generalize to US non-Caucasians to a greater extent than non-US models because of penetration of its variables into the US population independently of race.

There are several ways that the NCI's tool could improve screening. The tool may engage patients to consider screening and, for low-risk persons, provide rationale for a less invasive test than colonoscopy (21,22). The lowest-risk quintile's risk of

Figure 4. Estimated 20-year colorectal cancer (CRC) risk and current risk of advanced neoplasia by quintile of colorectal cancer risk. P values for 20-year CRC risk are based on the two-sided Spearman rank correlation test; P values for current risk for advanced neoplasia are based on the two-sided Cochran-Armitage test for trend in risk among quintiles. CRC = colorectal cancer.

Table 2. Absolute and relative risks of advanced neoplasia below vs above median estimated future CRC risk*

Study group	5-y CRC risk		10-y CRC risk		20-y CRC risk	
	Below median	Above median	Below median	Above median	Below median	Above median
All – absolute risk						
Total No.	2229	2228	2228	2229	2228	2229
No. (%) with advanced neoplasia	83 (3.7)	285 (12.8)	86 (2.9)	282 (12.6)	106 (4.8)	262 (11.8)
RR (95% CI)	3.4 (2.7 to 4.4)		3.2 (2.6 to 4.1)		2.5 (2.0 to 3.1)	
Men – absolute risk						
Total No.	1076	1076	1076	1076	1076	1076
No. (%) with advanced neoplasia	57 (5.3)	170 (15.8)	58 (5.4)	169 (15.7)	78 (7.3)	149 (13.8)
RR (95% CI)	3.0 (2.2 to 4.0)		3.0 (2.2 to 3.9)		1.9 (1.5 to 2.5)	
Women – absolute risk						
Total No.	1152	1153	1152	1153	1153	1152
No. (%) with advanced neoplasia	39 (3.4)	102 (8.9)	38 (3.3)	103 (8.9)	43 (3.7)	98 (8.5)
RR (95% CI)	2.6 (1.8 to 3.7)		2.6 (1.8 to 3.8)		2.3 (1.6 to 3.2)	

*CI = confidence interval; CRC = colorectal cancer; RR = relative risk.

2.13% for current advanced neoplasia may be “low enough” to warrant less-aggressive screening as only one cancer was present in each of the two lowest-risk quintiles and both were located in the distal colon. The choice of a less-invasive option fits within recommendations of the US Preventive Services Task Force for persons and subgroups within the average-risk group. Further, for some persons nonadherent with screening, learning that they have high current risk for advanced neoplasia (even though they are part of the “average-risk” population) might convince them to get screened with any test if not with colonoscopy. On the other hand, those with low current risk for advanced neoplasia may elect to have a noninvasive test or less invasive test such sigmoidoscopy. In this latter circumstance, having a choice based on a quantitative prediction of risk may increase uptake of screening (43).

Another reason to consider using the NCI’s tool is because CRC screening, despite being cost-effective, is still quite expensive, costing the United States tens of billions of dollars per year (19,44,45). If screening were more efficient, it would allow resources to be used elsewhere. The majority of persons who undergo screening do not derive any direct benefit from it but, rather, only incur its risks and inconveniences, including the risk of a false-positive test, perforation, hemorrhage, and preparing for and undergoing the screening test. Use of a risk prediction tool mitigates the intrinsically unfavorable balance of benefit and risk associated with screening.

Tailoring screening based on risk prediction also has potential disadvantages. Patients and providers may feel that tailoring makes screening more complicated, which may preclude making any choice. A second drawback may be the perception that tailoring is “rationing” of screening services. That any risk prediction tool is an aid to clinical judgment and patient preference, not a substitute for either, must be made clear. Third, all risk prediction tools operate under less-than-ideal conditions as overall risk for a group or subgroup may not reflect the risk of each of the individuals comprising the group (46).

This analysis has limitations, one of which is the generalizability of our findings. The NCI’s tool was derived and validated on non-Hispanic white men and women age 50 to 84 years. While our study group was closely aligned to these demographic features, the degree of generalizability of our findings beyond these features is not known. Given the paucity of well-validated and available models, this limitation might be addressed in the future. A second limitation is the uncertainty of whether knowing future CRC risk or current risk for advanced neoplasia has any effect on either the uptake of screening or choice of a screening test by patients or providers. Subsequent research is needed to quantify these effects. Third, our data collection instrument was designed for a separate study (31) involving prediction of advanced neoplasia. Thus, subjects’ responses to the NCI tool’s questions were based on our instrument rather than the Web site itself. That we achieved clinically meaningful risk stratification despite minor differences in some response choices attests to the robustness of the NCI’s tool.

In conclusion, the NCI’s Risk Assessment Tool, created to estimate future CRC risk, estimates current risk of advanced neoplasia among average-risk persons for whom the US Preventive Services Task Force currently recommends, without preference, any of several testing strategies (3). Compared with existing tools, the NCI’s tool has the advantage of providing greater separation of risk, has been validated on a target population that represents a substantial proportion of the population eligible for screening, is more generalizable, and is available and accessible, thus filling gaps left by other prediction tools. Last, it has been

validated to predict future CRC risk and now current risk of advanced neoplasia. With additional information about current risk of advanced neoplasia, the tool may increase the uptake of screening and facilitate tailoring of screening according to these risks. Increasing uptake would further decrease CRC morbidity and mortality, while tailoring would make screening, particularly the use of screening colonoscopy, more efficient. Subsequent research is needed to validate these findings in a more racially and ethnically heterogeneous population and to determine the effect of risk information about future CRC risk and current risk of advanced neoplasia on patient and provider decision-making about screening.

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