

The *Your Disease Risk* Index for Colorectal Cancer is an Inaccurate Risk Stratification Tool for  
Advanced Colorectal Neoplasia at Screening Colonoscopy

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Paul C. Schroy III<sup>1</sup>, Alison M. Coe<sup>1</sup>, Shamini R. Mylvanaman<sup>1</sup>, Lynne B. Ahn<sup>1</sup>, Maria A.  
Lydotes<sup>1</sup>, Patricia A. Robinson<sup>1</sup>, Julie T. Davis<sup>1</sup>, Clara A. Chen<sup>2</sup>, Jacqueline Ashba<sup>2</sup>  
Michael L. Atkinson<sup>3</sup>, Graham A. Colditz<sup>4</sup>, Timothy C. Heeren<sup>5</sup>.

<sup>1</sup> Department of Medicine, Boston University School of Medicine, Boston, MA.; <sup>2</sup> Data  
Coordinating Center, Boston University School of Public Health, Boston, MA; <sup>3</sup> Channing  
Laboratory, Dana Farber Cancer Institute, Boston, MA; <sup>4</sup> Prevention and Control  
Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO;  
<sup>5</sup> Department of Biostatistics, Boston University School of Public Health, Boston, MA

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Corresponding author:

Paul C Schroy III, M.D., M.P.H.

Boston Medical Center, 85 E. Concord St., Suite 7715, Boston, MA 02118

Phone: (617) 638-8335 ; Fax: (617) 638-6529 ; e-mail: paul.schroy@bmc.org

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### Abstract

*Background:* Tailoring the use of screening colonoscopy based on the risk of advanced colorectal neoplasia (ACN) could optimize the cost-effectiveness of colorectal cancer screening.

Our goal was to assess the accuracy of the *YourDiseaseRisk* (*YDR*) colorectal cancer risk index for stratifying average-risk patients into low versus intermediate/high risk categories for ACN.

*Methods:* The *YDR* risk assessment tool was administered to 3317 asymptomatic average-risk patients 50 to 79 years of age just prior to their screening colonoscopy. Associations between *YDR*-derived relative risk scores and ACN prevalence were examined using logistic regression and chi-square analyses. ACN was defined as a tubular adenoma  $\geq 1$  cm, tubulovillous or villous adenoma of any size, the presence of high grade dysplasia or cancer.

*Results:* The overall prevalence of ACN was 5.6%. Although *YDR*-derived relative risk scores were linearly associated with ACN after adjusting for age and gender ( $P=0.033$ ), the index was unable to discriminate “below average” from “above/average” risk patients (OR, 1.01; 95% CI, 0.75 -1.37). Considerable overlap in rates of ACN was also observed between the different *YDR* risk categories in our age and gender-stratified analyses.

*Conclusions:* The *YDR* index lacks accuracy for stratifying average-risk patients into low versus intermediate/high risk categories for ACN.

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### 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) Screening has been shown to be a cost-effective strategy for reducing the public health burden of this deadly disease and is now widely recommended by authoritative groups. Each of these groups endorse a menu-based approach for average risk patients 50 years of age and older that includes multiple screening options, ranging from colonoscopy, fecal occult blood testing, and flexible sigmoidoscopy with interval fecal occult blood testing by the US Preventive Services Task Force (2) to colonoscopy, fecal occult blood testing, flexible sigmoidoscopy, double contrast barium enema, CT colonography (“virtual colonoscopy”) and stool DNA testing by the American Cancer Society, US Multi-society Task Force on Colorectal Cancer and American College of Radiology (3). This menu-based approach reflects trade-offs between the relative strengths and weaknesses of each test with respect to accuracy, potential effectiveness, strength of supporting evidence, complexity, intervals, follow-up of positive tests, cost and availability.

Despite a lack of consensus regarding a single best option, the demand for screening colonoscopy has surged in recent years coincident with a decline in the use of the other screening options. Forecasting models based on decision analysis (4) and data from national surveys conducted by the National Cancer Institute (5) and Centers for Disease Control (6) suggest that the nation lacks the capacity to accommodate this growing demand. A potentially cost-effective solution is to reduce demand by tailoring the use of colonoscopy based on the risk of advanced colorectal neoplasia (ACN). Most authorities agree that ACN, defined as a tubular adenoma  $\geq 1$  cm in size, a tubulovillous or villous adenoma of any size, or adenomas harboring high grade dysplasia or invasive, is the appropriate target lesion for CRC screening (7, 8). Besides

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providing a cost-effective solution to the capacity issue, risk stratification for ACN would also be a useful adjunct when considering patient preferences for CRC screening within the context of shared decision-making. Implicit in this approach is the need for an accurate risk prediction model for ACN.

Investigators at the Harvard School of Public Health and Harvard Medical School have developed a risk index for CRC that generates personalized risk estimates relative to the general population (9). The revised version of the index incorporates 20 “definite” or “probable” factors positively or negatively associated with CRC risk. The model was validated using prospective data from the Nurses Health Study and the Health Professionals Follow-up Study (10). It is currently promoted as part of *Your Disease Risk (YDR)*, an interactive, web-based tool, which provides personalized risk estimates for several common chronic diseases, including various cancers, and tailored behavioral risk reduction messages to users (11). Its validity as a risk stratification tool for predicting the point prevalence of ACN at the time of screening colonoscopy is unknown. Hence, the primary objective of this study was to assess the validity of the *YDR* model for stratifying a diverse population of average risk patients due for colorectal cancer screening into low, intermediate and high risk categories for ACN after adjustment for age and gender.

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### Methods

#### *Patients*

The study population was drawn from the pool of asymptomatic, mostly English-speaking, average risk patients presenting to the endoscopy unit at Boston Medical Center or the Endoscopy Center at Brookline for a screening colonoscopy between March 22, 2005 and January 31, 2102. Patients were eligible for inclusion if the indication for the procedure was CRC screening, they were 50 to 79 years of age, the examination was complete as defined by documentation of cecal intubation, and the bowel preparation was deemed of adequate quality to warrant routine follow-up in accordance with current screening and surveillance 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 affecting a first-degree relative of any age or colorectal polyps affecting a first-degree relative before age 60 were also ineligible.

#### *Survey Methodology*

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

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### *Survey Instrument*

The risk assessment questionnaire incorporated all 20 items of the original *YDR* tool (11), including age, sex, previous diagnosis of cancer (other than non-melanoma skin cancer), family history of CRC, height and weight (to calculate body mass index), medical history (use of oral contraceptives, hormone replacement therapy, aspirin and history of longstanding inflammatory bowel disease), diet (consumption of red meat, alcohol, and use of multivitamins, calcium and vitamin D supplements), physical activity, and screening history (prior colonoscopy within 10 years; flexible sigmoidoscopy/barium enema/virtual colonoscopy/stool DNA testing within 5 years and fecal occult blood testing within one year). Items related to a family history of CRC, long-standing inflammatory bowel disease and prior screening behavior provided an internal check of eligibility status. Identical wording and formatting was used to ensure consistency with the web-based version. The age, height and weight items used a fill-in-the-blank format; all other items used a mostly dichotomous, tick box format.

A modified version of the risk assessment questionnaire was used beginning in July 2007 in accordance with the posting of a revised version of the *YDR* index. Relevant changes included omission of the vegetable intake item and addition of a dairy intake item. Prior screening behavior was also expanded 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 after the administration of either a polyethylene glycol lavage solution or an oral phosphosoda preparation. Endoscopic data, including the size (mm) and location of any polyps or masses, depth of scope insertion

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(defined by colonic segment), and quality of the bowel preparation were abstracted from the computerized colonoscopy reports. Polyp size was estimated based on clinical judgment. All retrieved polypoid lesions or biopsy specimens were reviewed by board-certified pathologists and classified according to World Health Organization histologic criteria as normal mucosa, hyperplastic, adenomas or invasive cancer (12). Adenomas were further classified as tubular, tubulovillous or villous with or without high grade dysplasia (12). An advanced colorectal neoplasm (ACN) was defined as a tubular adenoma  $\geq 1$  cm in size, a tubulovillous or villous adenoma of any size, high grade dysplasia or cancer (13). Serrated lesions with and without dysplasia were classified as adenomas and hyperplastic polyps, respectively; all dysplastic serrated lesions were classified as advanced.(14) Findings such as lipomas, lymphoid aggregates, nonspecific inflammation, and inflammatory or juvenile polyps were categorized as normal.

### *Risk Calculation*

The *YDR* risk calculation incorporates responses to each of the “definite” or “probable” factors positively or negatively associated with CRC risk listed in Table 1. Each has an assigned relative risk that was determined by a group consensus process after a comprehensive review of the relevant epidemiologic literature (9). The formula used to calculate an individual's relative risk (RR) of disease is as follows:

$$RR = \frac{RR_{11} * RR_{12} * \dots * RR_{1n}}{[(P_1 * RR_{C1}) + (1 - P_1) * 1.0] * [(P_2 * RR_{C2}) + (1 - P_2) * 1.0] * \dots * [(P_n * RR_{Cn}) + (1 - P_n) * 1.0]}$$

where  $RR_{1n}$  is the individual's assigned relative risk for each risk factor (based on its presence or absence),  $RR_{Cn}$  corresponds to the consensus-based relative risk and  $P_n$  represents the estimated

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prevalence of the risk factor among men and women in the general population.(10) The calculation assumes the relative risks of disease for risk factors do not vary substantially by age, gender, or other sociodemographic factors. The calculated relative risk (RR) is then expressed qualitatively as a relative risk category ranging from “very much below average risk” (RR,  $\leq 0.20$ ) to “much below average risk” (RR, 0.21 to  $\leq 0.50$ ), “below average risk” (RR, 0.51 to  $\leq 0.9$ ), “average risk” (RR, 0.91 to  $\leq 1.10$ ), “above average risk” (RR, 1.11 to  $\leq 2.10$ ), “much above average risk” (RR, 2.11 to  $\leq 5.1$ ) and “very much above average risk” (RR,  $> 5.10$ ). Also, because the original version of the *YDR* index lacked the dairy intake question, we arbitrarily assigned a RR of 1.0 in our primary analyses for patients enrolled prior to July 2007 (n=824) who did not use calcium supplements based on results for patients who completed the revised index, which demonstrated that only ~6% of respondents consumed 3 or more servings daily and were not taking calcium supplements. As a secondary analysis, we conducted a multiple imputation analysis to account for this missing data (discussed below under “Statistical Analyses”). Patients enrolled after July 2007 who failed to answer this question (n=2) or enrolled at any time who failed to answer any of the other questions in the revised index (n=149) were excluded from the primary analysis.

### *Sample Size and Power Estimates*

Our primary objective was to assess the validity of the *YDR* index for stratifying average risk patients into low and intermediate/high risk categories for ACN. Thus, to describe the adequacy of our sample, we examined the statistical power of detecting a difference in the odds of ACN for patients in the combined “below average” *YDR* risk categories vs. those in the combined “average/above average” *YDR* risk categories, controlling for age and sex through



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multiple logistic regression. Power was evaluated through simulation. We assumed an overall rate of ACN of 5% and that the effects of age, sex, and YDR risk category on ACN followed a logistic model with the observed age (per year odds ratio = 1.03) and sex (odds ratio = 1.70) effects (see Table 4). Given the study sample size (n=3317) and the age and sex distribution of the sample, we varied the underlying odds ratio for the YDR risk category to determine the OR detectable with 80% power, when testing at the two-tailed  $P < 0.05$  level, by running the logistic regression analysis on 1,000 simulated data sets. Based on these simulations, this study has >80% power of detecting an adjusted OR for the “below” vs. “average/above average” YDR risk category of 0.60.

### *Statistical Analyses*

Descriptive statistics were used to describe the study population with respect to demographic factors and findings at colonoscopy. Univariate associations between individual risk factors included in the YDR index and the prevalence of ACN were examined through chi-square analyses or Fisher’s exact test when sample size was small. Multiple logistic regression analysis was used to obtain adjusted odds ratios (OR) and 95% confidence intervals (CI) to describe the associations between YDR risk categories and ACN, controlling for age (as a continuous covariate) and sex. To account for missing data for the dairy consumption item for patients enrolled prior to 2007, we conducted a secondary multiple imputation analysis using ‘proc mi’ and ‘proc mianalyze’ in the SAS statistical software. Because responses to the dairy item are on a 4 point ordinal scale (corresponding to 0, 1, 2, or 3+ servings per day), missing data were imputed using a proportional odds logistic regression model for ordinal data, based on the participant’s age, sex, and response to non-missing YDR items. The results were based on

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pooled results across 5 different imputed data sets. Differences in the prevalence of ACN between “above average/average” and “below average” *YDR* risk categories were examined through chi-square analyses or Fisher exact tests after stratification by age and gender. The *YDR* index’s ability to discriminate between patients with and without ACN was assessed with the concordance (C) statistic, which estimates the area under the receiver operator characteristic (ROC) curve.(15) ; by convention, a C statistic of less than 0.6 suggests that the model has no clinical value, 0.6 to 0.7 limited value, 0.7 to 0.8 modest value and greater than 0.8 adequate value for discriminating those with and without the outcome of interest.(15) All statistical calculations were performed using SAS® Windows, Version 9.2 (Cary, NC) with significance being defined at the two-tailed  $P < 0.05$  level for all analyses.

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### Results

#### *Description of the Study Population*

More than 99% (n=3656) of the target sample agreed to participate in the study. The study population was comprised of 3317 patients who satisfied eligibility criteria and underwent a complete screening colonoscopy between March 22, 2005 and January 31, 2012. The remaining 339 (9%) patients were excluded from analysis because of missing *YDR* data other than dairy intake prior to 2007 (n=151), inadequate bowel preparation (n=131), incomplete colonoscopy for reasons other than poor bowel preparation (n=29), or failed polyp retrieval (n=28). There were no significant differences between patients in the study group and patients excluded due to missing data with respect to age, sex, race/ethnicity and rates of ACN (data not shown). As shown in Table 2, the study population was predominantly 50 to 59 years of age (75.3%) and non-Hispanic black (48.8%) with an equal percentage of males and females. The overall prevalence of ACN was 5.6%.

Table 3 provides overall prevalence rates for individual *YDR* risk factors in our cohort. Although overall rather than gender-specific rates are depicted, most approximate ( $\pm 20\%$ ) *YDR* prevalence estimates for the general population (Table 2). Notable exceptions included multivitamin use and calcium sufficiency, which were both substantially lower in our cohort (38% vs. 60% and 27% vs. 52%, respectively), and physical activity, which was substantially higher in our cohort (72% vs. 19%). The lower prevalence of calcium sufficiency is likely due in part to missing information on dairy intake for individuals enrolled prior to 2007 who completed the original *YDR* assessment tool.

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### *ACN and Individual YDR Risk Factors*

Associations between individual risk factors and presence of ACN are shown in Table 3. Although our study was not powered to validate the significance of individual risk factors, similar trends in association were observed for most variables (see Table 1 for relative risk multipliers). Factors positively associated with CRC risk, including height, consumption of  $\geq 3$  servings of red meat per week, consumption of  $\geq 2$  servings of alcohol daily and calcium “insufficiency” (consumption of  $<3$  servings of milk daily and no calcium supplementation) were positively associated with ACN risk; conversely, factors negatively associated with CRC risk, including regular aspirin use of  $> 15$  years, hormone replacement therapy for  $\geq 5$  years, use of vitamin D supplements and daily multivitamins were negatively associated with ACN risk. None of these associations achieved statistical significance, except height and alcohol consumption. No association was seen for use of birth control pills for  $\geq 5$  years or moderate physical activity for  $\geq 30$  minutes most days and an unexpected, albeit non-significant, inverse association was seen for body mass index.

### *YDR Relative Risk Scores and Prevalence of ACN*

Figure 1 depicts the distribution of calculated relative risk scores for the study. Overall, 1798 (54%) patients were categorized as “below average” risk with a mean (standard deviation) RR score of 0.46 (0.24) and median (range) RR score of 0.4 (0.1-0.90); the remaining 1519 (46%) patients were categorized as “above/average” risk with a mean RR score of 1.64 (0.59) and median RR score of 1.51 (0.90-4.89).

We first performed multiple logistic regression analyses to further examine the association between rates of ACN and YDR-derived relative risk scores using pooled data,

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controlling for gender and age as a continuous variable. The model demonstrated that the continuous *YDR*-derived relative risk scores were an independent determinant of ACN (OR, 1.23 per 1.0 increase in RR score; 95% CI, 1.02-1.49;  $P=0.033$ ). However, inclusion of RR scores expressed as a continuous variable in the adjusted logistic regression model did not enhance discriminative ability for ACN compared to age and gender alone ( $C=0.60$  vs.  $C=0.59$ ). As shown in Table 4, when expressed categorically (“much above average”, “above average”, “average”, “below average”, “much below average”, “very much below average”), the “much above average” group was significantly more likely to have ACN than the “average” group (OR 3.16, 95% CI 1.45-6.88,  $P=0.004$ ) but the same was true for the “very much below average” group (OR, 2.44, 95% CI 1.03-5.80,  $P=0.044$ ); conversely, no significant differences were noted for the other categories. Collapsing *YDR* categories into the more clinically useful “above average/average” versus “below average” risk groups did not improve the model’s ability to differentiate low from high/intermediate patients (OR, 1.01; 95% CI, 0.75-1.37;  $P=0.94$ ). There were no significant interactions between *YDR* category and gender or between *YDR* category and age.

The results were near identical when we used multiple imputation to account for missing data on dairy consumption for patients enrolled prior to 2007 ( $n=824$ ). Continuous *YDR* RR scores remained an independent determinant of ACN in the adjusted models (OR 1.23; 95% CI 1.02 – 1.49;  $P=0.03$ ) and “below average” patients were no less likely to have ACN than “above/average” risk patients (OR, 1.01; 95% CI, 0.74 – 1.36;  $P=0.94$ ).

We also compared rates of ACN for the collapsed *YDR* relative risk categories after stratification for gender and age using chi-square analyses (Table 5). No significant differences were observed for “above/average” versus “below average” risk males or females aged 50 to 59

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(6.7% vs. 6.4%,  $P=0.78$  and 3.4% vs. 4.7%,  $P=0.28$ , respectively), 60 to 69 (8.4% vs. 8.4%,  
 $P=1.00$  and 4.6% vs. 2.4%,  $P=0.35$ , respectively) and 70 to 79 (6.4% vs. 7.7%,  $P=1.00$  and 8.0%  
vs. 8.3%,  $P=1.00$ , respectively).

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### Discussion

Risk stratification for ACN provides a rational strategy for optimizing the cost-effectiveness of screening colonoscopy. An essential prerequisite to this approach is the availability of an accurate risk stratification tool. The overall objective of this study was to assess the utility of the *YDR* colorectal cancer index for stratifying average risk patients into low and intermediate/high risk categories for the presence of ACN. Our study finds that although *YDR*-derived relative risk values were an independent determinant of ACN at screening colonoscopy, the *YDR* index has limited ability to discriminate between average risk patients with and without ACN after adjustment for age and gender. Moreover, both our logistic regression models and stratified analyses found that the discriminative ability for identifying individuals at relatively low risk of ACN was poor. Since one of the primary objectives of risk stratification for average risk patients is to identify those at low risk of disease for whom screening approaches other than colonoscopy may be justifiable, we conclude that the *YDR* tool lacks precision for stratifying average risk patients into low versus intermediate/high risk groups.

One possible explanation for the index's limited discriminative ability relates to the validity of the variables included in the index. Because most colorectal cancers arise from pre-existing adenomatous polyps through a multi-stage process referred to as the adenoma-carcinoma sequence, it is biologically plausible that individual determinants of risk for adenoma development may differ from those associated with disease progression. Despite inherent biases related to case ascertainment, however, a majority of studies have observed few differences between risk factors for non-advanced adenomas, advanced adenomas and invasive cancers, suggesting that most influence adenoma formation *per se* and not disease progression (16, 17). The one notable exception is folic acid which appears to inhibit the formation of colorectal

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adenomas but has no impact on disease progression (18, 19). In the current study, similar trends in association were observed for the majority of *YDR* variables and rates of ACN. Possible explanations for the discrepancies with body mass index, physical activity and use of birth control pills could relate to small sample size, confounding, response bias, and/or diversity of the patient population. In the aggregate, it would appear that although many, if not all, of the variables included in the *YDR* index may be valid determinants of ACN, potential differences in the magnitude of the association for advanced adenomas versus cancers for individual variables might contribute to the lack of discriminating ability for ACN.

A second explanation could relate to the validity of the intervals of use defined for select chemopreventive agents in the *YDR* index. Microsimulation models estimate that it takes 7.6 to 24.2 years from adenoma incidence to preclinical cancer (adenoma dwell time) and an additional 1.6 to 4.0 years to cancer diagnosis (preclinical cancer dwell time or sojourn time) (20). It is therefore plausible that the duration of exposure necessary to alter the natural history for developing advanced adenomas may be different than that for invasive cancers. Supporting clinical evidence is derived from post-polypectomy chemoprevention trials demonstrating that regular use of aspirin can reduce the incidence of recurrent advanced adenomas within 1 to 3 years of use, whereas observational studies suggest that prolonged use for 10 to 15 years, as defined in the *YDR* index, may be necessary to reduce the incidence of colorectal cancer (21-23). Similarly, short-term, active use of hormone replacement therapy has been associated with a reduced risk of advanced adenomas whereas prolonged use for more than 5 years, as defined in the *YDR* index, may be required for a significant reduction in cancer risk (24, 25).

A third explanation relates to the notable absence of several important determinants of ACN risk absent from the *YDR* index. A recent meta-analysis of 42 studies found that cigarette



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smoking was strongly associated with an increased risk of advanced adenomas (current vs. never: relative risk [RR], 2.04; 95% CI, 1.56-2.66; ever vs. never: RR, 1.82; 95% CI, 1.65-2.00) and that this association was both dose- and time-dependent (26). Type 2 diabetes mellitus may also be associated with an increased risk of ACN but existing data are conflicting.(27, 28) Conversely, post-polypectomy chemoprevention trials have consistently observed a reduction in the incidence of recurrent advanced adenomas with both selective and non-selective non-aspirin NSAIDs (29). Although associations between race/ethnicity and risk of ACN are less well-defined, current data suggests that significant differences may exist (30). The extent to which genetic or biological factors versus disparities in access to screening account for these differences, however, remains debatable (31).

A fourth explanation relates to the exclusion of patients with a family history of colorectal cancer. By excluding individuals at familial risk, which has the highest assigned relative risk multiplier, we may have compromised the ability of the *YDR* index to discriminate between individuals at lower risk. We speculate that this is unlikely to be the sole explanation since existing evidence suggests that the index has validity for predicting CRC risk (as opposed to ACN risk) among both men and women lacking a family history of the disease. (10)

A number of other non-genetic prediction models for colorectal cancer or ACN have been proposed.(32) The most relevant of these from the perspective of the current study is a web-based model developed by the National Cancer Institute that provides absolute 10- and 20-year risk predictions for the development of colorectal cancer among average risk men and women 50 years of age and older (33, 34). Although its utility for predicting the point prevalence of ACN at screening colonoscopy is unknown, we speculate that the model may provide greater accuracy than the *YDR* index since it incorporates smoking and non-aspirin

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NSAID use in addition to many of the variables in the *YDR* index for which the evidence of an association with advanced adenoma risk is the strongest. The model's major limitation is that it employs relative risk estimates derived from studies that included mostly white non-Hispanic patients and thus its validity for other racial and ethnic groups is unknown. Several more simplified clinical scoring systems based on age, sex, family history alone or in combination with various environmental or lifestyle risk factors have been shown to be valid risk stratification tools for ACN among select patient groups but their validity among more diverse patient populations is unknown (35-38). Lastly, Imperiale and colleagues have proposed a clinical index for identifying patients at increased risk of advanced *proximal* neoplasia (39). The model incorporates age, gender and findings at sigmoidoscopy as key determinants of risk and hence has limited utility given the declining use of sigmoidoscopy as a screening test. Moreover, recent data suggest that the model exhibits limited accuracy for discriminating low from intermediate/high risk patients when tested among a racially diverse patient population (40).

Our study has several unique strengths. First, the racial, ethnic and socioeconomic diversity of our study population enhances the external validity of our findings. Boston Medical Center is the largest safety net hospital in New England and the demographics of the study population were similar to those of the general patient population. Second, our recruitment strategy enabled us to maximize our response rate and minimize selection bias. Third, 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.

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Our study also had several important limitations. First, the study lacked sufficient statistical power for validating the assigned relative risks for individual items in the *YDR* index and for comparisons across the full range of *YDR* RR categories. Second, like many such studies, including the National Polyp Study (13) and Collaborative Outcomes Research Initiative (30), we relied on the subjective judgment of multiple endoscopists to provide data about polyp size, thus raising the possibility of misclassification for ACN defined by size alone (41). Third, our reliance on self-reported data raises the possibility of social response bias. In general, however, the self-reported prevalence rates for individual *YDR* risk factors in our cohort were similar to *YDR* prevalence estimates for the general population. Lastly, our study lacked statistical power to determine whether the performance of the *YDR* varies by anatomic site of ACN (e.g., proximal versus distal vs. rectal).

In conclusion, our study finds that the *YDR* index lacks discriminative accuracy for stratifying average risk patients into low versus intermediate/high risk groups for the point prevalence of ACN at screening colonoscopy. Factors that may explain this lack of discriminative power include the exclusion of several key determinants of ACN, potential differences in duration of use for select chemopreventive agents necessary to alter the natural history of advanced adenomas compared to cancers, and potential differences in the assigned relative risks of certain exposures on disease progression from non-advanced to advanced adenomas versus cancer. Future prospective studies are needed to identify a unique risk prediction model for ACN that is not only valid and generalizable for diverse patient populations but easy to implement into clinical practice.

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Risk Stratification for Advanced Colorectal Neoplasia

**Table 1:** Prevalence and relative risk estimates used in the *YourDiseaseRisk* calculation.

| <b>Risk factor <sup>a</sup></b>                   | <b>Relative Risk Multiplier <sup>e</sup></b> | <b>Prevalence <sup>e</sup></b> |
|---|--|--------------------------------|
| Body mass index                                   |  |                                |
| Men ≤ 30  | 1.0  | 65%                            |
| Men > 30  | 1.5  | 35%                            |
| Women ≤ 30  | 1.0  | 60%                            |
| Women > 30  | 1.5  | 40%                            |
| Height  |  |                                |
| Men ≤ 5'10"                                       | 1.0  | 60%                            |
| Men > 5'10"                                       | 1.3  | 40%                            |
| Women ≤ 5'7"                                      | 1.0  | 90%                            |
| Women > 5'7"                                      | 1.3  | 10%                            |
| Aspirin use, most days > 15 years                 |  |                                |
| Men, No   | 1.0  | 89%                            |
| Men, Yes  | 0.7  | 11%                            |
| Women, No   | 1.0  | 87%                            |
| Women, Yes  | 0.7  | 13%                            |
| Duration of birth control pill use                |  |                                |
| Never/< 5 years                                   | 1.0  | 80%                            |
| ≥ 5 years   | 0.7  | 20%                            |
| Duration of hormone replacement therapy           |  |                                |
| Never/< 5 years                                   | 1.0  | 92.5%                          |
| ≥ 5 years   | 0.8  | 7.5%                           |
| Red meat intake, ≥ 3 servings a week              |  |                                |
| No  | 1.0  | 50%                            |
| Yes   | 1.2  | 50%                            |
| Servings of alcohol on a typical day              |  |                                |
| Men < 2   | 1.0  | 95%                            |
| Men ≥ 2   | 1.4  | 5%                             |
| Women < 2   | 1.0  | 98%                            |
| Women ≥ 2   | 1.4  | 2%                             |
| Multivitamin use 4 or more days a week            |  |                                |
| No  | 1.0  | 40%                            |
| Yes   | 0.5  | 60%                            |
| Calcium sufficiency <sup>b</sup>                  |  |                                |
| Yes   | 1.0  | 52%                            |
| No  | 1.3  | 48%                            |
| Daily vitamin D supplement ± calcium <sup>c</sup> |  |                                |
| No  | 1.0  | 99%                            |
| Yes   | 0.6  | 1%                             |
| Moderate physical activity ≥ 30 minutes daily     |  |                                |
| No  | 1.0  | 81%                            |
| Yes   | 0.6  | 19%                            |
| Parent or sibling with colorectal cancer          |  |                                |
| No  | 1.0  | 95%                            |
| Yes   | 1.8  | 5%                             |
| Prior screening <sup>d</sup>                      |  |                                |
| No  | 1.0  | 57%                            |
| Yes   | 0.67   | 43%                            |

## Risk Stratification for Advanced Colorectal Neoplasia

<sup>a</sup> Items related to age, sex and previous cancer are not included in the risk calculation.

<sup>b</sup> The relative risk calculation uses a calcium “sufficient” variable defined by daily use of a calcium supplement or daily intake of  $\geq 3$  servings of milk/dairy.

<sup>c</sup> The vitamin D group includes patients who either a took vitamin D supplement alone or a multivitamin on most days.

<sup>d</sup> Prior screening defined as a colonoscopy within 10 years, flexible sigmoidoscopy or barium enema within 5 years or fecal occult blood testing within 1 year.

<sup>e</sup> The relative risk multiplier ( $RR_{In}$ ) for the numerator of the formula depends on whether the risk factor is present or absent; the multiplier for the denominator ( $RR_{Cn}$ ) is the population-based relative risk estimate. Citations for the relative risk multiplier and prevalence estimates can be accessed at <http://www.yourdiseaserisk.wustl.edu> (11).

Risk Stratification for Advanced Colorectal Neoplasia

**Table 2:** Patient demographics and findings at screening colonoscopy (n=3317).

| <b>Variable</b>                         | <b>No. (%) Patients</b> |
|---|-------------------------|
| <b>Demographic characteristics</b>      |                         |
| <i>Age, yr</i>                          |                         |
| 50 – 59                                 | 2498 (75.3)             |
| 60 – 69                                 | 675 (20.4)              |
| 70 – 79                                 | 144 (4.3)               |
| <i>Sex</i>                              |                         |
| Men                                     | 1682 (50.7)             |
| Women                                   | 1635 (49.3)             |
| <i>Race/Ethnicity</i>                   |                         |
| White, non-Hispanic                     | 1173 (35.4)             |
| Black, non-Hispanic                     | 1618 (48.8)             |
| Hispanic                                | 267 (8.0)               |
| Other                                   | 238 (7.2)               |
| Missing                                 | 21 (0.6)                |
| <b>Colonoscopy findings<sup>a</sup></b> |                         |
| Normal                                  | 1919 (57.8)             |
| Hyperplastic polyps                     | 434 (13.1)              |
| Tubular adenomas < 10 mm                | 780 (23.5)              |
| Advanced neoplasia <sup>b</sup>         | 184 (5.6)               |

<sup>a</sup> Colonoscopic findings defined by most advanced lesion

<sup>b</sup> Advanced neoplasia defined as a tubular adenoma  $\geq$  1 cm in size, a tubulovillous or villous adenoma of any size, the presence of high grade dysplasia or cancer.

Note: Percentages for demographic characteristics may exceed 100% due to rounding.

Risk Stratification for Advanced Colorectal Neoplasia

**Table 3:** Associations between individual *YDR* risk factors and prevalence of ACN

| <b>Risk factor</b>                                | <b>No. (%) Patients</b> | <b>No. (%) Patients with ACN</b> | <b>OR (95% CI)</b> |
|---|-------------------------|----------------------------------|--------------------|
| Body mass index                                   |                         |                                  |                    |
| ≤ 30  | 2079 (63)               | 119 (5.7)                        | Referent           |
| > 30  | 1238 (37)               | 65 (5.2)                         | 0.9 (0.7-1.2)      |
| Height  |                         |                                  |                    |
| Men ≤ 5'10", Women ≤ 5'7"                         | 2542 (77)               | 123 (4.8)                        | Referent           |
| Men > 5'10", Women > 5'7"                         | 775 (23)                | 61 (7.9) <sup>a</sup>            | 1.7 (1.2-2.3)      |
| Aspirin use, most days > 15 years                 |                         |                                  |                    |
| No  | 3274 (99)               | 182 (5.6)                        | Referent           |
| Yes   | 43 (1)                  | 2 (4.6)                          | 0.8 (0.2-3.5)      |
| Duration of birth control pill use                |                         |                                  |                    |
| Never/< 5 years                                   | 1213 (74)               | 50 (4.1)                         | Referent           |
| ≥ 5 years   | 422 (26)                | 17 (4.0)                         | 1.0 (0.6-1.7)      |
| Duration of hormone replacement therapy           |                         |                                  |                    |
| Never/< 5 years                                   | 1570 (96)               | 65 (4.1)                         | Referent           |
| ≥ 5 years   | 65 (4)                  | 2 (3.1)                          | 0.7 (0.2-3.1)      |
| Red meat intake, ≥ 3 servings a week              |                         |                                  |                    |
| No  | 2309 (70)               | 120 (5.2)                        | Referent           |
| Yes   | 1008 (30)               | 64 (6.4)                         | 1.2 (0.9-1.7)      |
| Servings of alcohol on a typical day              |                         |                                  |                    |
| < 2   | 3022 (91)               | 152 (5.0)                        | Referent           |
| ≥ 2   | 295 (9)                 | 32 (10.8) <sup>a</sup>           | 2.3 (1.5-3.4)      |
| Multivitamin use 4 or more days a week            |                         |                                  |                    |
| No  | 2070 (62)               | 116 (5.6)                        | Referent           |
| Yes   | 1247 (38)               | 68 (5.4)                         | 1.0 (0.7-1.3)      |
| Calcium "sufficient" <sup>c, d</sup>              |                         |                                  |                    |
| Yes   | 893 (27)                | 46 (5.2)                         | Referent           |
| No  | 2424 (73)               | 138 (5.7)                        | 1.1 (0.8-1.6)      |
| Daily vitamin D supplement ± calcium <sup>e</sup> |                         |                                  |                    |
| No  | 2535 (77)               | 144 (5.7)                        | Referent           |
| Yes   | 769 (23)                | 39 (5.1)                         | 0.9 (0.6-1.3)      |
| Moderate physical activity ≥ 30 minutes daily     |                         |                                  |                    |
| No  | 914 (28)                | 51 (5.6)                         | Referent           |
| Yes   | 2403 (72)               | 133 (5.5)                        | 1.0 (0.7-1.4)      |

*YDR*, *YourDiseaseRisk*; ACN, advanced colorectal neoplasia; OR, odds ratio; CI, confidence interval

<sup>a</sup> The denominator is the number of patients with or without the risk factor.

<sup>b</sup>  $P < 0.002$  by chi-square analyses

<sup>c</sup> Calcium "sufficient" defined by daily use of a calcium supplement or daily intake of ≥ 3 servings of milk/dairy

<sup>d</sup> Data missing for 824 patients who completed prior version of *YDR* risk assessment tool

<sup>e</sup> Daily vitamin D group includes patients who took a multivitamin

**Table 4:** Prevalence and odds ratio estimates of ACN after adjustment for *YDR* relative risk category, age and sex

| <b>Effect</b>                  | <b>No. (%) Patients</b> | <b>No. (%) Patients with ACN</b> | <b>Adjusted OR for ACN (95% CI)<sup>a</sup></b> |
|--------------------------------|-------------------------|----------------------------------|---|
| <i>RR category</i>             |                         |                                  |   |
| Much above average             | 258 (7.8)               | 27 (10.5)                        | 3.16 (1.45 – 6.88)                              |
| Above average                  | 981 (29.6)              | 49 (5.0)                         | 1.40 (0.68 - 2.90)                              |
| Average                        | 280 (8.4)               | 9 (3.2)                          | Referent  |
| Below average                  | 643 (19.3)              | 38 (5.9)                         | 1.68 (0.80 - 3.54)                              |
| Much below average             | 947 (28.5)              | 47 (5.0)                         | 1.47 (0.71 - 3.04)                              |
| Very much below average        | 208 (6.3)               | 14 (6.7)                         | 2.44 (1.03 – 5.80)                              |
| <i>Age (per year increase)</i> |                         |                                  |   |
|                                | ---                     | ---                              | 1.02 (1.00 – 1.04)                              |
| <i>Sex</i>                     |                         |                                  |   |
| Male                           | 1682 (50.7)             | 117 (7.0)                        | 1.79 (1.30 -2.47)                               |
| Female                         | 1635 (49.3)             | 67 (4.1)                         | Referent  |
| <i>RR category (collapsed)</i> |                         |                                  |   |
| Above average/average          | 1519 (45.8)             | 85 (5.6%)                        | Referent  |
| Below average                  | 1798 (54.2)             | 99 (5.5%)                        | 1.01 (0.75 -1.37)                               |

ACN, advanced colorectal neoplasia; *YDR*, *YourDiseaseRisk*; OR, odds ratio; CI, confidence interval; RR, relative risk

**Table 5:** Rates of ACN for individual *YDR* relative risk categories stratified by age and gender

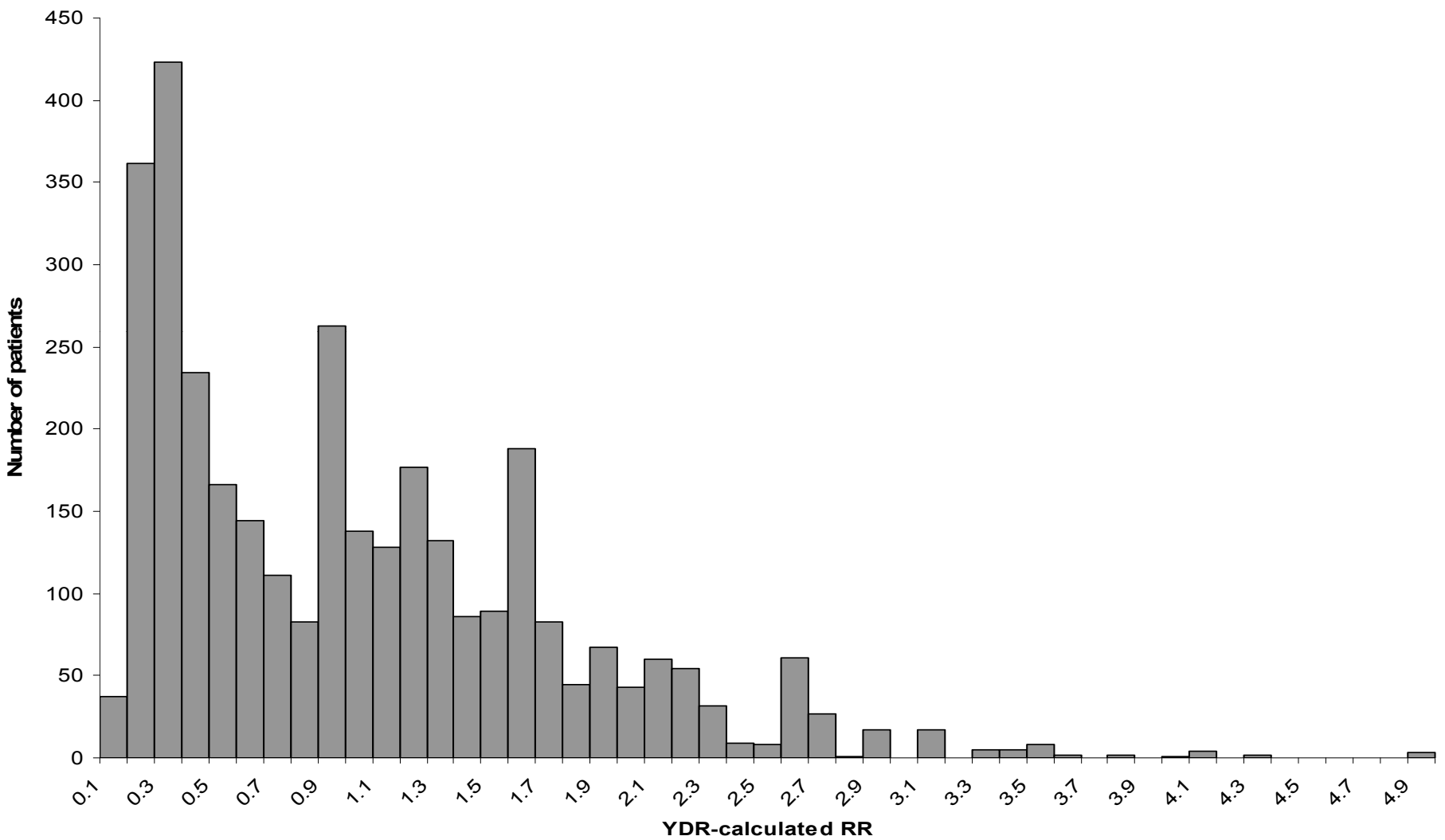
| Gender  | YDR Risk Category     | No. Patients with ACN, % (95% CI) <sup>a</sup> |                              |                             |
|---------|-----------------------|--|------------------------------|-----------------------------|
|         |                       | Age, 50-59 yrs                                 | Age, 60-69 yrs               | Age, 70-79 yrs              |
| Males   | Above average/average | 6.7 (4.8 – 8.7)<br>[n=653]                     | 8.4 (4.1 – 12.8)<br>[n= 154] | 6.4 (-2.2 – 15.1)<br>[n=31] |
|         | Below average         | 6.4 (4.4 – 8.3)<br>[n=614]                     | 8.4 (4.3 – 12.5)<br>[n=178]  | 7.7 (0.4 – 14.9)<br>[n=52]  |
|         |                       | <i>P</i> =0.78                                 | <i>P</i> =1.00               | <i>P</i> =1.00              |
| Females | Above average/average | 3.4 (1.9 – 5.0)<br>[n=524]                     | 4.6 (1.0 – 8.1)<br>[n=132]   | 8.0 (-2.6 – 18.6)<br>[n=25] |
|         | Below average         | 4.7 (3.1 – 6.2)<br>[n=707]                     | 2.4 (0.3 – 4.4)<br>[n=211]   | 8.3 (-0.7 – 17.4)<br>[n=36] |
|         |                       | <i>P</i> =0.28                                 | <i>P</i> =0.35               | <i>P</i> =1.00              |

*ACN*, advanced colorectal neoplasia; *YDR*, *YourDiseaseRisk*; *yrs*, years

<sup>a</sup> *P*-values from chi square analyses or Fisher’s exact test for each age stratum

## Figure Legend

**Figure 1.** Distribution of YDR-calculated Relative Risks (RR). RR  $\leq 0.20$  = very much below average risk; RR 0.21 to  $\leq 0.50$  = much below average risk; RR 0.51 to  $\leq 0.9$  = below average risk; RR 0.91 to  $\leq 1.10$  = average risk; RR 1.11 to  $\leq 2.10$  = above average risk; RR 2.11 to  $\leq 5.1$  = much above average risk; RR  $> 5.10$  = very much above average risk.





# Cancer Prevention Research

## The Your Disease Risk Index for Colorectal Cancer is an Inaccurate Risk Stratification Tool for Advanced Colorectal Neoplasia at Screening Colonoscopy

Paul C. Schroy III, Alison M. Coe, Shamini R. Mylvaman, et al.

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