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Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle, Environmental, and Genetic Factors

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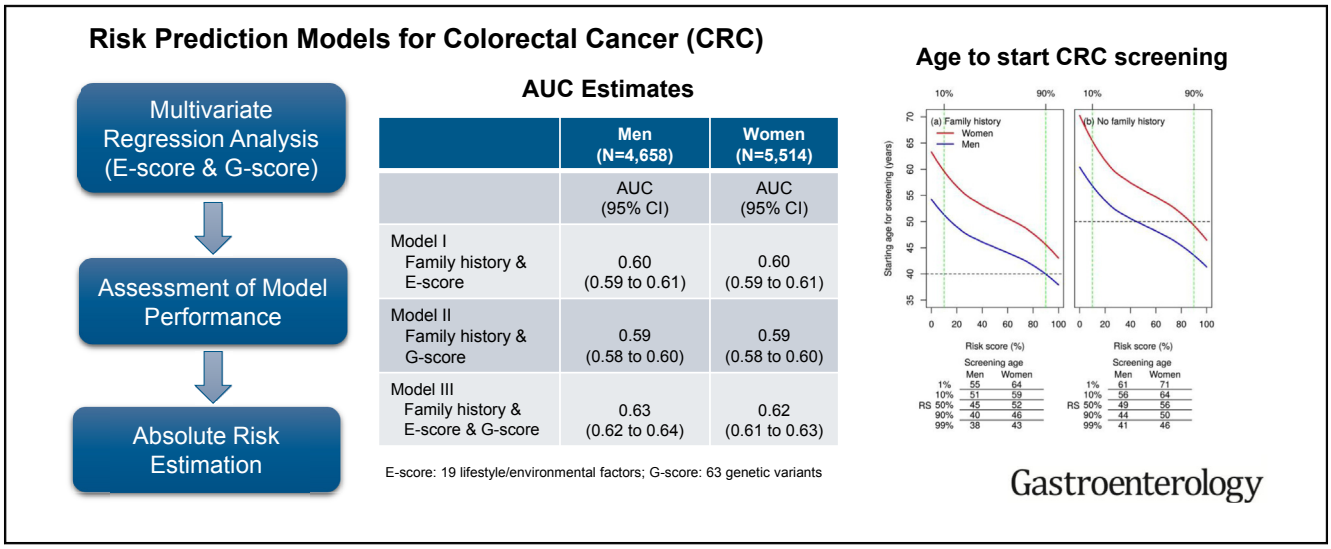
BACKGROUND & AIMS: Guidelines for initiating colorectal cancer (CRC) screening are based on family history but do not consider lifestyle, environmental, or genetic risk factors. We developed models to determine risk of CRC, based on lifestyle and environmental factors and genetic variants, and to identify an optimal age to begin screening. **METHODS:** We collected data from 9748 CRC cases and 10,590 controls in the Genetics and Epidemiology of Colorectal Cancer Consortium and the Colorectal Transdisciplinary study, from 1992 through 2005. Half of the participants were used to develop the risk determination model and the other half were used to evaluate the discriminatory accuracy (validation set). Models of CRC risk were created based on family history, 19 lifestyle and environmental factors (E-score), and 63 CRC-associated single-nucleotide polymorphisms identified in genome-wide association studies (G-score). We evaluated the discriminatory accuracy of the models by calculating area under the receiver operating characteristic curve values, adjusting for study, age, and endoscopy history for the validation set. We used the models to project the 10-year absolute risk of CRC for a given risk profile and recommend ages to begin screening in comparison to CRC risk for an average individual at 50 years of age, using external population incidence rates for non-Hispanic whites from the Surveillance, Epidemiology, and End Results program registry. **RESULTS:** In our models, E-score and G-score each determined risk of CRC with greater accuracy than family history. A model that combined both scores and family history estimated CRC risk with an area under the



receiver operating characteristic curve value of 0.63 (95% confidence interval, 0.62–0.64) for men and 0.62 (95% confidence interval, 0.61–0.63) for women; area under the receiver operating characteristic curve values based on only family history ranged from 0.53 to 0.54 and those based only E-score or G-score ranged from 0.59 to 0.60. Although screening is recommended to begin at age 50 years for individuals with no family history of CRC, starting ages calculated based on combined E-score and G-score differed by 12 years for men and 14 for women, for individuals with the highest vs the lowest 10% of risk. **CONCLUSIONS:** We used data from 2 large international consortia to develop CRC risk calculation models that included genetic and environmental factors along with family history. These determine risk of CRC and starting ages for screening with greater accuracy than the family history only model, which is based on the current screening guideline. These scoring systems might serve as a first step toward developing individualized CRC prevention strategies.

Keywords: Colon Cancer; GECCO; CORECT; Colonoscopy.

Despite progress in reducing colorectal cancer (CRC) incidence and mortality in recent decades in the United States, CRC remains the third leading cause of cancer death.[1] CRC is one of the most preventable and treatable cancers, if detected early.[2] Though screening for CRC is recommended for adults between age 50 and 75,[3] in 2013, only 58% were in compliance.[4] Currently screening guidelines are based only on age and family history; however, >80% of CRC cases have no family history. By evaluating the influence of multiple lifestyle, environmental,[5] and genetic risk factors, especially as genetic information will increasingly become a routine part of the medical record,[6,7] risk prediction models can be used to more accurately define low- and high-risk populations, which is the core of precision medicine. Improved risk stratification may also increase screening adherence and uptake, particularly for those at higher risk, as these individuals may be more likely to follow recommendations for prevention when aware of their heightened risk.[8–11] Furthermore, it can optimize the appropriate use of invasive technology.

Several models have been developed to determine the risk of CRC,[9,12–17] adenoma,[18,19] or colorectal neoplasia, including both CRC and adenoma,[20] most of which included only clinical, lifestyle, and environmental risk factors, while a few models have accounted for the then-known genetic variants[9,13] and one model included a limited number of lifestyle, environmental, and genetic factors.[17] However, thus far, no models have attempted to incorporate broad established and putative lifestyle risk factors with the growing number of common genetic variants.

While substantial progress has been made in understanding CRC risk factors, translating lifestyle, environmental, and genetic risk factor information into actionable clinical information is the next step in developing personalized prevention. We developed risk prediction models for CRC based on 19 lifestyle and environmental factors and 63 common genetic variants known to be associated with CRC risk using data from 14 population-based studies. We expanded the risk prediction analysis to define the optimal starting age for screening, demonstrating the potential utility of using a model to tailor screening recommendations according to one's personal risk profile.

Abbreviations used in this paper: **AUC, area under the receiver operating characteristic curve; CI, confidence interval; CRC, colorectal cancer; SNP, single-nucleotide polymorphism; OR, odds ratios; GWAS, genome-wide association study.**

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