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Familial Risk and Heritability of Colorectal Cancer in the Nordic Twin Study of Cancer

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BACKGROUND & AIMS: **We analyzed data from twins to determine how much the familial risk of colorectal cancer can be attributed to genetic factors vs environment. We also examined whether heritability is distinct for colon vs rectal cancer, given evidence of distinct etiologies.**

METHODS: **Our data set included 39,990 monozygotic and 61,443 same-sex dizygotic twins from the Nordic Twin Study of Cancer. We compared each cancer's risk in twins of affected co-twins relative to the cohort risk (familial risk ratio [FRR]). We then estimated the proportion of variation in risk that could be attributed to genetic factors (heritability).**

RESULTS: **From earliest registration in 1943 through 2010, there were 1861 individuals diagnosed with colon cancer and 1268 diagnosed with rectal cancer. Monozygotic twins of affected co-twins had an FRR for colorectal cancer of 3.1 (95% confidence interval [CI], 2.4–3.8) relative to the cohort risk. Dizygotic twins of affected co-twins had an FRR for colorectal cancer of 2.2 (95% CI, 1.7–2.7). We estimated that 40% (95% CI, 33%–48%) of the variation in colorectal cancer risk could be attributed to genetic factors; unique environment only accounted for the remaining liability. For colon cancer, the FRR was 3.3 (95% CI, 2.1–4.5) for monozygotic twins and 2.6 (95% CI, 1.7–3.5) for dizygotic twins. For rectal cancer, comparable estimates were 3.3 (95% CI, 1.5–5.1) for monozygotic twins and 2.6 (95% CI, 1.2–4.0) for dizygotic twins. Heritability estimates for colon and rectal cancer were 16% (95% CI, 0–46%) and 15% (95% CI, 0–50%), common environment estimates were 15% (95% CI, 0–38%) and 11% (95% CI, 0–38%), and unique environment estimates were 68% (95% CI, 57%–79%) and 75% (95% CI, 61%–88%), respectively.**

CONCLUSIONS: **Interindividual genetic differences could account for 40% of the variation in susceptibility to colorectal cancer; risk for colon and rectal cancers might have less of a genetic component than risk for colorectal cancer. Siblings, and particularly monozygotic co-twins, of individuals with colon or rectal cancer should consider personalized screening.**

Keywords: Biometric Modeling; Genetic Susceptibility; Zygosity; Concordance Relative Risk.

[a]Authors share co-first authorship.

Abbreviations used in this paper: A, additive genetic; C, common environmental; CI, confidence interval; D, dominant genetic; DZ, dizygotic; E, unique environmental; FRR, familial risk ratio; MZ, monozygotic.

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See editorial on page 1204.

Individuals with a first-degree relative affected by colorectal cancer have a 2- to 3-fold increased risk of disease themselves.[1] Although roughly 20% of colorectal cancer patients have an affected relative, less than 10% of colorectal cancers are inherited in an autosomal-dominant manner.[2] Familial clustering occurs even in the absence of defined Mendelian syndromes,[3] suggesting a potential role for inherited risk loci with low penetrance. Common risk loci explain up to 8% of colorectal cancer heritability,[4] and the more than 50 susceptibility variants that have been identified by genome-wide association studies (summarized by Schmit et al[5]) explain only 1% to 4% of the underlying genetic variation.[6] How much the remaining familial risk can be attributed to unknown heritable factors or environment remains unclear.

Prior twin studies of colorectal cancer have yielded heritability estimates between 9% and 35%.[7,8] More recently, our group used methods that account for censoring and the competing risk of death, and we estimated heritabilities of colon and rectal cancer to be 15% and 14%, respectively.[9] Given discrepancies across prior estimates, we aimed to estimate colorectal cancer heritability in total as well as proximal colon, distal colon, and rectal cancer heritability separately, and to investigate differences in heritability across sex and age. In support of these objectives, we estimated the cumulative incidence of the cancers of interest among monozygotic (MZ) and dizygotic (DZ) twins using the Nordic Twin Study of Cancer.

Materials and Methods

The Population-Based Twin Cohorts

The Nordic Twin Study of Cancer cohort aggregates the population-based twin registries from Denmark, Finland, Norway, and Sweden, and their respective national cancer and mortality registries. Follow-up evaluation for cancer incidence essentially is complete. For this study, we excluded twins of unknown zygosity (n = 57,057) and opposite-sex twins (n = 96,499). Analyses were based on 203,690 twins. The Supplementary Materials and Methods contain additional information about the cohort.

The ethical committees of each country approved this study.

Definitions

Heritability is defined as the proportion of variability in disease risk caused by genetic factors. Familial risk is defined as the risk of disease in a twin, given an affected co-twin. This estimate relative to the overall population risk (ie, the familial risk ratio [FRR]) estimates excess familial risk in twins compared with the general population. Differences in familial risks by zygosity help ascertain the contribution of genetic vs nongenetic familial (ie, shared environmental exposures) factors on disease risk.

Statistical Analysis

The statistical analyses we used have been described elsewhere.[10] Briefly, we estimated the overall and sex-specific risks of total colorectal cancer, colon cancer (as well as proximal and distal colon cancer), and rectal cancer using the Aalen–Johansen estimator.[11] For each cancer subtype, we then analyzed heritability and familial risk for same-sex twin pairs. In estimating the cumulative incidence, we accounted for left-censoring owing to variable initiation of cancer registration. For all estimates, we accounted for right-censoring resulting from the end of follow-up evaluation and competing risk of death.[12,13] We obtained familial risks by age and FRRs in MZ and DZ pairs separately.[14,15] We tested the similarity of familial risk curves for MZ and DZ pairs by age using Pepe and Mori's test,[13] which has been shown to be the most powerful among various tests when evaluated in a similar setting.[16]

We assessed the magnitude of genetic vs environmental influences on disease using quantitative models, decomposing the variation into the following components: additive genetic (A), dominant genetic (D), common (ie, shared) environmental (C), and unique (ie, nonshared) environmental (E) effects.[12,13,17–19] Because all 4 components cannot be estimated simultaneously owing to statistical issues,[18] a series of models are tested sequentially for the significance of specific parameters. Dominance effects are typically biologically implausible in the absence of additive effects, so the primary models are ACE and ADE, and their submodels AE and CE.

We assessed zygosity differences in disease prevalence by testing for equality of thresholds in MZ and DZ pairs. To test for variation in heritability by age at diagnosis, we estimated within-pair correlations for MZ and DZ pairs and the cumulative heritability of each cancer at each age. We then estimated differences in age at diagnosis within pairs as well as the mean and median differences in age at diagnosis for pairs in which both twins were diagnosed.

We investigated the colon and rectal cancer concordance relative risk to evaluate possible pleiotropy for colon and rectal cancer. At each age at which a twin was diagnosed with colon cancer whose co-twin already had been diagnosed with rectal cancer, or vice versa, we calculated the concordance risk. We then divided it by the marginal cumulative incidence of colon and rectal cancer. A relative risk of 1 would suggest that colon and rectal cancer are independent diagnoses, whereas relative risks greater than 1 would suggest familiality.

All statistical analyses were conducted using the package mets 1.1.0 (Copenhagen, Denmark) for R 3.1.3 (Vienna, Austria).[13] All tests were 2-sided with a P value less than .05 considered statistically significant.