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

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Abstract

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Author Contributions: REG, SM, and JBH analyzed and interpreted the data, and drafted the manuscript. All authors were involved in conceptualizing and designing the study, acquiring data, critically revising the manuscript for important intellectual content, and/or obtaining funding.

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, 1861 individuals were diagnosed with colon cancer and 1268 with rectal cancer. Monozygotic twins of affected co-twins had an FRR for colorectal cancer of 3.1 (95% 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.

Conclusion—Inter-individual 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

INTRODUCTION

Individuals with a first-degree relative affected by colorectal cancer have a two- to three-fold increased risk of disease themselves.[1] While 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 greater than 50 susceptibility variants that have been identified by genome-wide association studies (GWAS; summarized in ref. 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 estimated between 9 and 35%.[7,8] More recently, our group employed 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 (NorTwinCan).

MATERIALS AND METHODS

The population-based twin cohorts

The NorTwinCan cohort aggregates the population-based twin registries from Denmark, Finland, Norway, and Sweden, and their respective national cancer and mortality registries. Follow-up for cancer incidence is essentially 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 due to 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 (i.e., the *familial risk ratio*; FRR) estimates excess familial risk in twins compared to the general population. Differences in familial risks by zygosity help ascertain the contribution of genetic versus non-genetic familial (i.e., 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 due to variable initiation of cancer registration. For all estimates, we accounted for right-censoring resulting from the end of follow-up 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 most powerful among various tests when evaluated in a similar setting.[16]

We assessed the magnitude of genetic versus environmental influences on disease using quantitative models, decomposing the variation into components: additive genetic (A), dominant genetic (D), common (i.e., shared) environmental (C), and unique (i.e., non-shared) environmental (E) effects.[12,13,17–19] Because all four components cannot be simultaneously estimated due to statistical issues,[18] a series of models are sequentially tested 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 sub-models 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 difference 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 had already 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 one would suggest that colon and rectal cancer are independent diagnoses, whereas relative risks greater than one would suggest familiality.

All statistical analyses were conducted using the package mets 1.1.0 for R 3.1.3.[13] All tests were 2-sided with $P < 0.05$ considered statistically significant.

RESULTS

Among 203,690 same-sex twins, 3,094 were diagnosed with colorectal cancer during follow-up (Table 1). Roughly half of colorectal cancers occurred in males, and approximately three-fifths originated from the colon. Among 1,532 colon cancers that could be further classified by subsite, just over half were proximal. There were 60 twin pairs (31 MZ and 29 DZ) concordant for colorectal cancer but discordant for colon or rectal subsite. Among 40 twin pairs (22 MZ) concordant for colon cancer with proximal versus distal information, 12 pairs (6 MZ) were discordant for subsite.

Figure 1 displays the cumulative incidence of colorectal cancer by subsite, sex, country, and zygosity. The lifetime risk of colon cancer was 2.7% and that of rectal cancer was 1.8% (Figure 1A). Stratification by colon cancer subsite revealed that the lifetime risk of proximal disease (1.0%) was slightly higher than that of distal disease (0.69%). The lifetime risk of colorectal cancer was similar across sexes (4.8% for men versus 4.4% for women, Figure 1B); women were slightly more likely to be diagnosed with colon cancer (2.6% for men versus 2.8% for women), whereas rectal cancer was more common among men (2.2% for men versus 1.4% for women). The cumulative incidence of colorectal cancer overall was slightly higher in Denmark and Norway than in Sweden and Finland (Figure 1C). Estimates of cumulative incidence were similar among MZ and DZ twins (Figure 1D). Supplementary Table S1 shows within-pair concordances for vital status at the end of follow-up for each cancer subsite.

Table 2 presents the cancer subsite-specific results for lifetime risk of disease, familial risks by zygosity, and estimates of the genetic, common, and unique environmental variance components underlying variation in disease liability. Because models without dominant genetic effects best fit the data and we favored consistency in interpretation, we present

estimates from ACE models only. Where alternative models better fit, we mention as such in the text. There were some minor violations of the equal thresholds assumption in MZ and DZ pairs, noted in Supplementary Table S2, but models run without the assumption returned materially unchanged results (data not shown). Supplementary Table S3 provides estimates from AE and CE sub-models, and Supplementary Table S4 provides relative fit statistics for all models.

The overall lifetime risk of colorectal cancer was 4.6% and the familial risk was 18.1% among MZ and 9.9% among DZ twins. The FRR of colorectal cancer was 3.1 (95% CI: 2.4–3.8) for MZ and 2.2 (95% CI: 1.7–2.7) for DZ twins. Estimates of the proportion of disease variance based on the ACE model were 40% (95% CI: 33%–48%) for heritability and zero for common environment; the AE model best fit the data. Sex-stratified analyses yielded evidence that genetic effects explain more variation in disease liability in females than males. Specifically, heritability under the ACE model among women was estimated at 45% (95% CI: 35%–55%) and common environment did not contribute to variation in disease liability. For men, heritability was estimated at 28% (95% CI: 0%–61%) and common environment at 7% (95% CI: 0%–30%). The best fitting models for males and females respectively were AE and ACE.

The lifetime risk of colon cancer was 2.7% overall and the familial risk was 10.6% among MZ and 7.8% among DZ twins. The FRR of colon cancer was 3.3 (95% CI: 2.1–4.5) for MZ and 2.6 (95% CI: 1.7–3.5) for DZ twins. Quantitative modeling estimated heritability at 16% (95% CI: 0%–46%) and common environment at 15% (95% CI: 0%–38%). Again there was evidence of greater heritability among women (40%; best-fit model AE) than men (0%; best-fit model CE); precision of the estimates, however, was limited. The familial risks for proximal colon cancer (MZ: 10.9%, DZ: 4.8%) exceeded their counterparts for distal colon cancer (MZ: 6.6%, DZ: 2.5%). Estimates of heritability for both subsites, however, were 38% with an AE best-fit model. Findings from exploratory analyses of the sex-specific heritability of proximal and distal colon cancer suggested that heritability was larger among females for both subsites, particularly for proximal colon cancer (data not shown).

The lifetime risk of rectal cancer was 1.8% overall, and the familial risks were 6.4% and 4.6% for MZ and DZ twins respectively. The FRR of rectal cancer was 3.3 (95% CI: 1.5–5.1) for MZ and 2.6 (95% CI: 1.2–4.0) for DZ twins. Heritability accounted for 15% (95% CI: 0%–50%) of the variation in liability while common environment explained 11% (95% CI: 0%–38%). Once again, there was a clear difference in the estimates by sex; heritability was estimated at 24% for women with an AE best-fit model and 8% for men with a CE best-fit model, again with limited precision.

Figure 2 presents the familial risk of colorectal cancer across the lifespan. At every age, the risk of colorectal cancer for DZ twins of affected co-twins was higher than the overall risk in the twin population (i.e., the marginal estimate). The risk for MZ twins of affected co-twins was yet higher than the corresponding risk for DZ twins (P_{diff} <0.001). The relative magnitude of familial risks for MZ versus DZ twins was largely consistent starting at age 65 for both male and female twin pairs, even while absolute risks increased over time.

Among concordant twin pairs, the mean time between diagnoses of colorectal cancer were 10.5 years (SE: 1.0) for MZ pairs and 9.9 years (SE: 1.1) for same-sex DZ pairs (P_{diff} = 0.70). Corresponding median times were 9.3 years for MZ pairs and 6.1 years for same-sex DZ pairs (P_{diff} = 0.21). Estimates of mean and median times between diagnoses for twin pairs concordant for colon cancer and, separately, rectal cancer, showed no significant differences by zygosity (data not shown).

Figure 3 depicts the cumulative heritability for colorectal cancer liability by five-year intervals of age at diagnosis as derived from the quantitative modeling. Within-pair correlations remained relatively constant across the lifespan for both MZ and DZ pairs. The type and magnitude of the genetic and common environmental contribution did not appreciably change with increasing age.

Figure 4 demonstrates the concordance relative risks of colon and rectal cancer for (A) 32 MZ pairs, and (B) 28 DZ pairs in which one twin was diagnosed with colon cancer and the other was diagnosed with rectal cancer. Individuals with co-twins who developed colon cancer had a substantial excess risk of developing rectal cancer, and vice versa, particularly at younger ages. Excess risks were especially apparent for MZ twin pairs.

DISCUSSION

We found that twins of affected co-twins were at a substantially increased risk of colorectal cancer relative to the general population. We also found that genetic factors explain two-fifths of the variation in liability to the disease. Heritability was greater among women than men, and greatest when colorectal cancer combining all subsites together was analyzed. The concordance relative risk for colon and rectal cancer was higher for MZ than DZ twins, suggesting that colon and rectal cancer may share inherited genetic risk factors.

Screening endoscopy has been shown to prevent against colorectal cancer occurrence and deaths.[20] Twins of affected co-twins might particularly benefit from diligent screening given their excess risk relative to the general population. They might also especially benefit from colonoscopy over sigmoidoscopy; while both screening tests are valuable with respect to distal colon and rectal cancer, only colonoscopy has been shown to reduce proximal colon cancer risk and mortality.[20] Clinicians bear a large part of responsibility in determining screening practices. They might consider that twins of affected co-twins, and even siblings (who are as genetically similar as dizygotic twins) of affected individuals, should be encouraged toward routine screening. A complete family history is of utmost importance and may help guide decisions around screening methods and intervals.

Colorectal cancer heritability was previously estimated at 35% within the twin cohorts.[8] More recently, these analyses were updated with larger sample sizes, longer follow-up, and more robust statistical methods, and estimates of colon (15%) and rectal (14%) cancer heritability separately were lower.[9] Our results for colon and rectal cancer heritability were comparable, despite using a slightly different cohort subset. Our heritability estimate of 40% for total colorectal cancer is consistent with the Lichtenstein findings, and lacking censoring or competing risk of death, our methods would have been comparable.[17,18] However, our

study was less prone to bias since we accounted for censoring and the competing risk of death. It also included more than three times the number of twin pairs, an additional ten years of follow-up, the Norwegian cohort, and thus more than 2,300 additional colorectal cancer cases. We were thus able to examine proximal colon, distal colon, and rectal cancer heritability separately, which is key given accumulating evidence that their etiologies and familial risks may be distinct.[21–23]

There are thought to be three primary tumorigenic pathways in colorectal carcinogenesis: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP).[24] CIN seems to be the predominant mechanism in distal colon and rectal carcinogenesis,[25,26] whereas the overlapping MSI and CIMP pathways more often predispose to proximal colon cancers.[27,28] The latter two pathways are also more often implicated in hereditary cancer,[26,29–31] and family history seems most strongly associated with sporadic proximal colon cancer.[21,23] The sum of these parts renders it somewhat surprising that our results did not more strongly suggest that proximal colon cancer is more heritable than distal colon cancer and that colon cancer overall is more heritable than rectal cancer. The ACE models did not indicate such relative magnitudes of heritability, though models that excluded the common environment component were more indicative of the expected results. Notably, a previous family study from Sweden also found that colon and rectal cancer were roughly equally heritable.[32]

Heritability estimates were greater for colorectal cancer overall than for colon or rectal cancer individually. These differences could reflect limited power, but could also indicate shared genetic factors contributing to both sites. That the concordance relative risk for colon and rectal cancer was higher for MZ than DZ twins supports the latter explanation. This finding is interesting given that several lifestyle and dietary factors have been differentially associated with colon and rectal cancer.[23,33]

While a small number of genetic variants has a substantial effect on colorectal cancer, a considerable portion of its heritability is thought to result from multiple low-risk variants.[8,34,35] Over 50 have been identified as credibly associated with colorectal cancer risk (summarized in ref. 5), but they account for a small proportion of heritability.[6] All common variants genome-wide only account for 8% of heritability.[4] It is likely that rare variants, other genetic variation, gene-gene interactions, and/or epigenetics contribute to the total heritability of colorectal cancer.

For all of the cancer sites we evaluated, heritability was larger among females than males. Chance could have played a role given the limited sample sizes of stratified analyses, but the results could also be attributable to an increased prevalence of lifestyle risk factors for colorectal cancer among men relative to women. For example, men in Nordic countries smoke tobacco[36] and drink alcohol[37] more than women. These behaviors tend to aggregate within families,[38,39] so it is perhaps unsurprising that we see higher estimates for common environmental effects on liability to colorectal cancer among males than females. That the unique environmental components of disease liability were consistently higher for males than females could also have reduced the heritability components. If, however,

environmental risk factors were to interact with genetic factors, then heritability could be either greater or lesser among men than women.

Our study included all cancers at the relevant sites, regardless of histology. We were also unable to exclude cancers attributable to hereditary syndromes; while these cases were likely rare, our estimates for sporadic cancer could be slightly skewed. We had limited power to distinguish heritable genetic from environmental effects, particularly in stratified analyses. For some models, we detected minor violations of the equal thresholds assumption, but forced equality of the marginal risks for MZ and DZ twins. However, heritability estimates without the assumption were comparable, and observed differences in cumulative risk between MZ and DZ pairs were small. Our study also lacked information regarding colorectal cancer screening. Our analyses assumed that the probability of screening among co-twins is independent of zygosity. If, however, an MZ co-twin were more likely to be screened than a DZ co-twin of a diagnosed twin, then the genetic component of our analyses could have been biased. It seems unlikely that this would have been a sizable issue given that the study countries did not have national endoscopy screening programs during the study time frame, and that any consequential sporadic screening likely would not have started until well into the study period (i.e., the 1980s).

In summary, colorectal cancer has a substantial heritable component and it may be more heritable in women than men. Given that the risk variants that have been discovered in GWAS thus far do not come close to accounting for the disease's heritability, there remain many genetic risk variants that have yet to be uncovered. Much research remains to be done to explain the 40% of variation in colorectal cancer liability that we determined to be attributable to heritability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CIN	chromosomal instability
CIMP	CpG island methylator phenotype

DZ	dizygotic
FRR	familial risk ratio
MSI	microsatellite instability
MZ	monozygotic
NorTwinCan	Nordic Twin Study of Cancer

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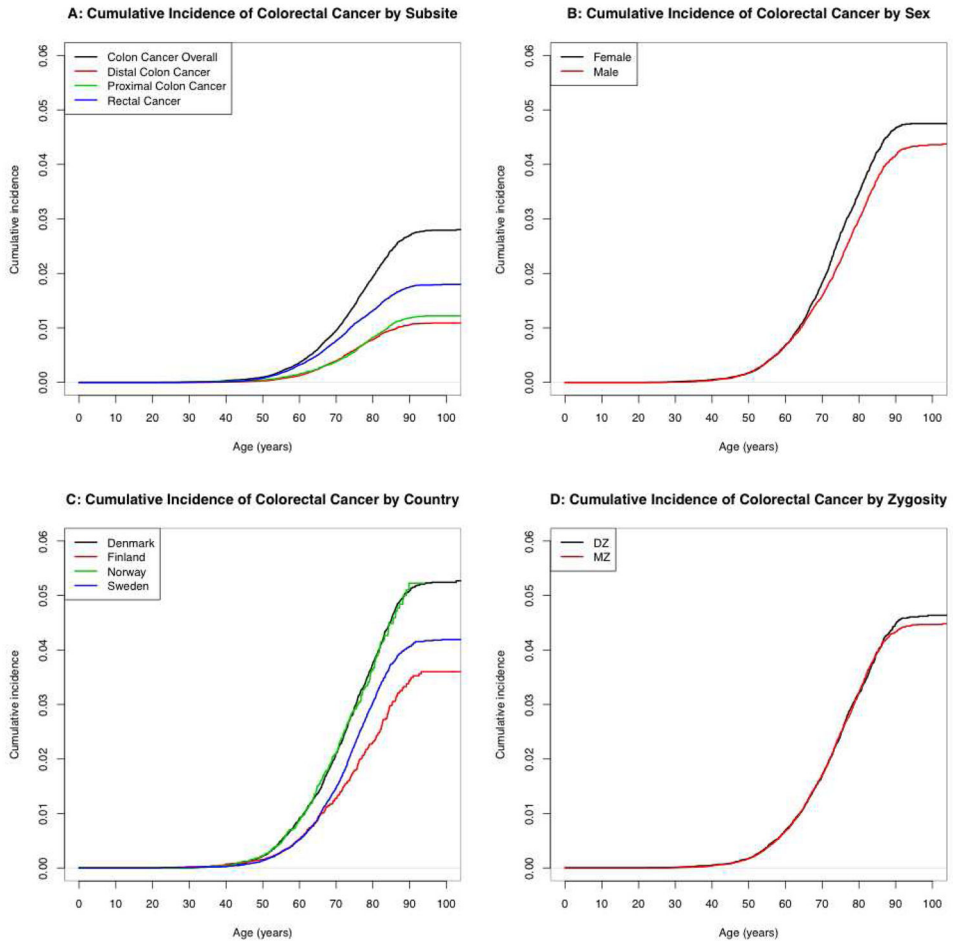


Figure 1.

Cumulative incidence of colorectal cancer by (A) subsite, (B) sex, and (C) country, and (D) zygosity in NorTwinCan adjusted for left- and right-censoring and competing risk of death

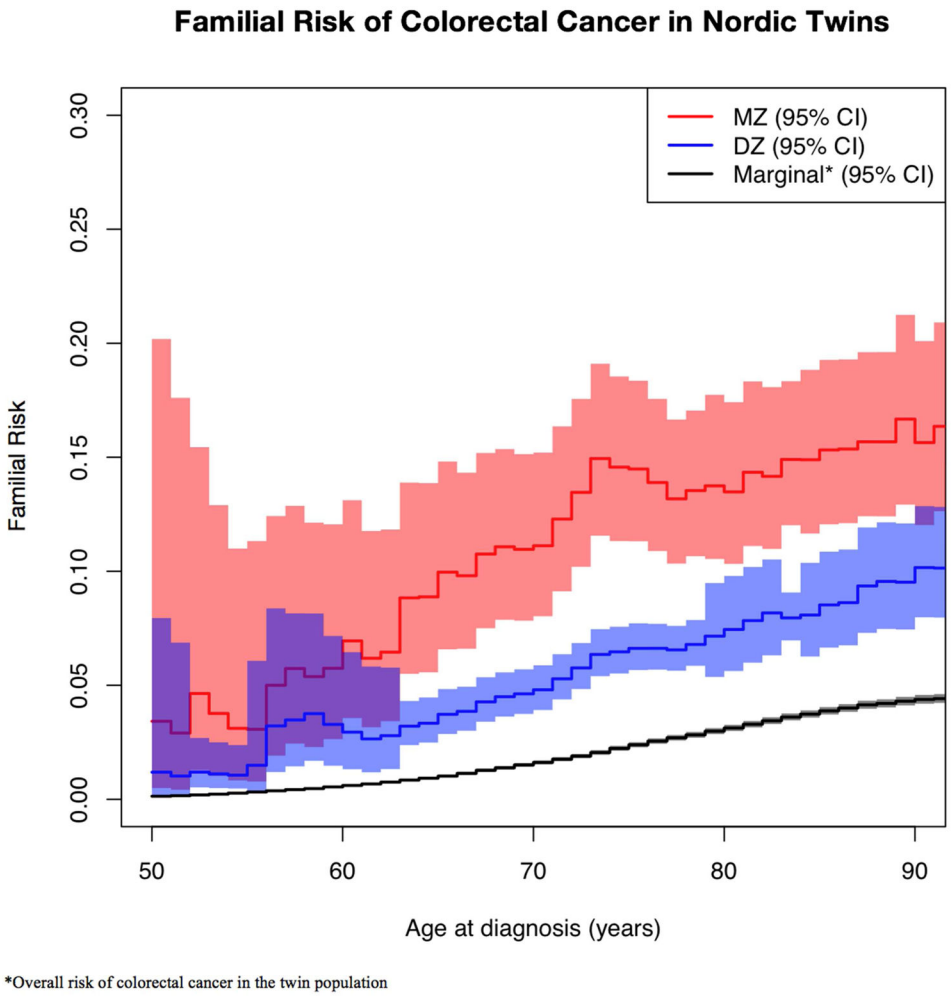


Figure 2.

Familial risk for colorectal cancer by age adjusted for left- and right-censoring and competing risk of death

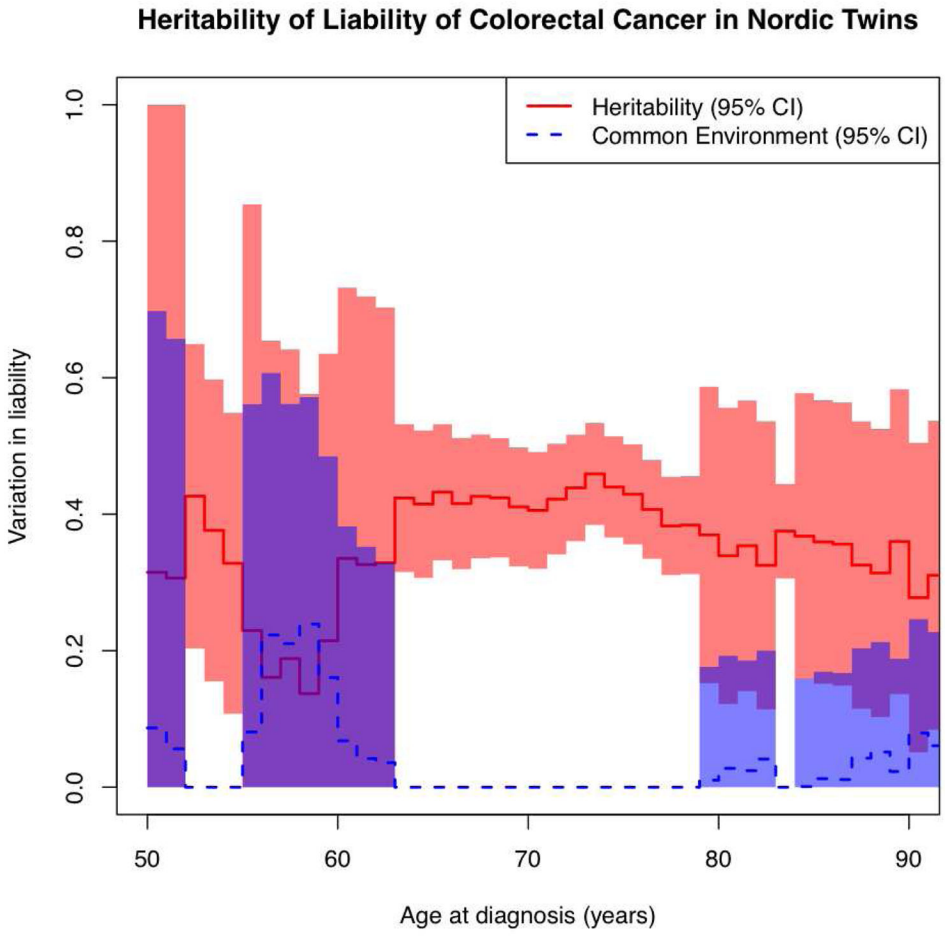
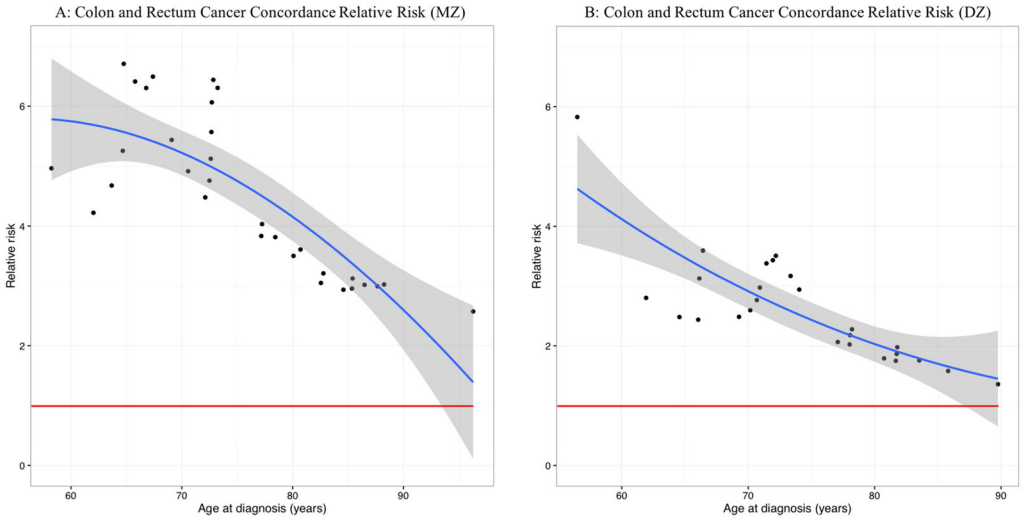


Figure 3.

Cumulative heritability in liability to colorectal cancer by five-year intervals of age at diagnosis, modeling heritability and common and unique environmental components of liability to disease, adjusted for censoring using inverse probability weighting



At each age at which a twin was diagnosed with colon cancer whose co-twin had already been diagnosed with rectal cancer, or vice versa, we calculated the concordance risk of such a twin pair divided by the marginal cumulative incidence of colon and rectal cancer. Each dot corresponds to the age at diagnosis of the second twin diagnosed with cancer in a pair in which one twin was diagnosed with colon cancer and the other was diagnosed with rectal cancer. The blue lines (and gray shading) are smoothed curves (and 95% confidence bands) that best fit the dots.

Figure 4.

Concordance relative risk of colon and rectal cancer for (A) MZ twins and (B) DZ twins

Table 1

Description of same-sex twins from NorTwinCan

	Denmark	Finland	Norway	Sweden	Total
Birth Cohorts	1870–2004	1875–1957	1915–1979	1886–2000	N/A
Initiation of Cancer Registration	1943	1953	1953	1958	N/A
Initiation of Follow-up	1943	1974	1964	1961	N/A
End of Follow-up	12/31/2009	12/31/2010	12/31/2008	12/31/2009	N/A
Median Follow-up (years)	41.4	34.7	27.9	24.7	31.9
Median Age at Start of Follow-up (years)	12.3	32.1	29.8	32.2	26.4
Number of Twins[a]	68,319	24,661	23,683	87,027	203,690
MZ /DZ Male Pairs[b]	6,148 /11,310	1,792 /4,222	2,389 / 3,022	8,540 / 11,884	18,869 / 30,438
MZ / DZ Female Pairs[b]	6,235 / 10,430	2,026 / 4,179	2,936 / 3,439	9,924 / 12,957	21,121 / 31,005
Number of Incident Colorectal Cancers	1,153	357	316	1,268	3,094
Number of Incident Colon Cancers[c]	668	210	199	784	1,861
Proximal Colon Cancer[d]	228	113	95	359	795
Distal Colon Cancer[d]	260	78	89	310	737
Number of Incident Rectal Cancers[c]	492	149	123	504	1,268

[a] Includes individuals from broken twin pairs in addition to complete pairs (i.e. individuals with a deceased twin at the start of follow-up); excludes twins with unknown zygosity and from opposite-sex pairs

[b] Number of pairs for which both twins were alive at the start of follow-up

[c] Includes 35 individuals with both colon and rectal cancer who count only once as colorectal cancer cases

[d] The number of proximal + distal colon cancers do not sum to the total number of colon cancers on account of cancers diagnosed in multiple or unspecified parts of the colon

Table 2

Cumulative risk, familial risk and heritability of cancers, modeling heritability and common and unique environmental components of liability to disease, adjusted for left- and right-censoring and competing risk of death

		Number of Twin Pairs Concordant / Discordant[a]		Familial Risk (%)(95% CI)		Estimates from Twin Modeling (%)(95% CI)		
	Cumulative Risk (%)	MZ	DZ	MZ	DZ	Heritability	Common Envt.	Unique Envt.
Colorectal Cancer	4.6	73 / 528	70 / 1,137	18.1 (14.7, 22.1)	9.9 (8.7, 11.2)	40.2 (32.8, 47.5)	0.0 (N/A)[c]	59.8 (52.5, 67.2)
Male Pairs	4.8	33 / 285	38 / 579	15.7 (10.5, 22.7)	10.2 (7.4, 14.0)	27.8 (0.0, 60.7)	6.5 (0.0, 29.7)	65.8 (52.3, 79.2)
Female Pairs	4.4	40 / 243	32 / 558	20.3 (15.5, 26.1)	10.4 (8.8, 12.3)	45.0 (35.3, 54.7)	0.0 (N/A)[c]	55.0 (45.3, 64.7)
Colon Cancer	2.7	30 / 323	31 / 713	10.6 (7.2, 15.3)	7.8 (5.3, 11.3)	16.4 (0.0, 45.6)	15.3 (0.0, 37.5)	68.3 (57.4, 79.2)
Male Pairs	2.6	10 / 161	16 / 327	7.7 (5.2, 11.3)	7.7 (5.2, 11.3)	0.0 (N/A)[b]	23.9 (13.7, 34.1)	76.1 (65.9, 86.3)
Female Pairs	2.8	20 / 162	15 / 386	14.4 (9.0, 22.3)	7.1 (4.0, 12.3)	40.2 (0.0, 80.5)	0.2 (0.0, 31.9)	59.6 (45.2, 74.0)
Proximal	1.0	11 / 136	9 / 308	10.9 (6.0, 19.1)	4.8 (2.4, 9.3)	37.9 (0.0, 78.6)	7.2 (0.0, 38.9)	54.8 (40.1, 69.5)
Distal	0.69	5 / 131	3 / 267	6.6 (3.0, 14.0)	2.5 (1.5, 4.0)	37.9 (21.1, 54.6)	0.0 (N/A)[c]	62.1 (45.4, 78.9)
Rectal Cancer	1.8	14 / 254	13 / 482	6.4 (3.6, 11.0)	4.6 (2.6, 8.0)	14.5 (0.0, 50.1)	10.9 (0.0, 38.2)	74.6 (61.4, 87.9)
Male Pairs	2.2	8 / 148	8 / 285	5.9 (2.7, 12.1)	4.9 (2.3, 9.8)	8.4 (0.0, 55.8)	11.9 (0.0, 48.2)	79.7 (62.1, 97.3)
Female Pairs	1.4	6 / 106	5 / 197	7.3 (3.1, 16.2)	4.2 (1.8, 9.8)	24.2 (0.0, 77.7)	7.6 (0.0, 48.3)	68.2 (48.3, 88.1)

[a] Among pairs with complete follow-up (i.e., those for which both twins were diagnosed with cancer or died); discordant twin pairs with censoring are not counted because it is unknown whether they would have become concordant

[b] Because there is no difference in concordance between MZ and DZ pairs, there is no indication of heritability and the model sets the additive genetic component to zero.

[c] Based on the concordances in MZ and DZ pairs (and potentially lack of power), there is no indication of common environment and the model sets the common environmental component to zero.