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Brief Report: Family cancer history affecting risk of colorectal cancer in a prospective cohort of Chinese women

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Abstract

An elevated risk of colorectal cancer has been associated with sporadic colorectal cancer in first degree relatives, mostly in Western populations. Limited data exists from traditionally low-risk areas, such as Asia, where the prevalence of risk factors may differ. We examined the association of family history of cancer and subsequent colorectal cancer risk in a cohort of traditionally low-risk Chinese women.

We followed 73,358 women in the Shanghai Women's Health Study for cancer incidence until December 2005. After an average of 7 years of follow-up, 391 women were diagnosed with colorectal cancer. We calculated hazard ratios and 95% confidence intervals using Cox proportional hazards models adjusted for age, smoking, family income, education, body mass index, physical activity and history of diabetes.

We observed a significant association between colorectal cancer risk and history of a parent being diagnosed with colorectal cancer (hazard ratio: 3.34; 95% confidence interval: 1.58, 7.06). No association was observed for colorectal cancer diagnosed among siblings. Colorectal cancer risk was not influenced by a positive family history of cancer generally or any of the other cancers investigated (lung, breast, prostate, gastric, esophageal, endometrial, ovarian, urinary tract, central nervous system, small bowel).

Our cohort results suggest that, consistent with findings from Western populations, having a family history of colorectal cancer may influence colorectal cancer risk to a similar extent in a low-risk population.

Keywords

colorectal cancer; cohort studies; family history

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Introduction

Colorectal cancer (CRC) is the third most common form of cancer and the second leading cause of cancer-related death in the Western world, causing 655,000 deaths worldwide per year (1). Traditionally a region of low CRC incidence, rates in China have been increasing rapidly in recent years. Age-standardized incidence rates in Shanghai, China between 1998 and 2002 were estimated at 27.2 per 100,000 for men and 23.2 per 100,000 for women (2) relative to 14 and 12.3 per 100,000 for men and women, respectively, between 1972 and 1977 (3).

Familial clustering of colorectal cancer is generally recognized to occur even outside the context of familial syndromes such as familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer. Sporadic CRC in one or more first degree relatives has been associated with a risk approximately twofold that of individuals without a family history (4–6). These estimates of increased risk are mostly based on studies of Western populations, reports from Asian populations are rare and generally arise from case-control studies (7). Given the potential differences in the prevalence of risk factors in high-risk versus low-risk regions and the potential recall and survival biases in case-control studies, we sought to determine whether CRC risk is increased in individuals with a family history of cancer in a large prospective study of women from Shanghai, China, a traditionally low-risk area for CRC.

Methods

The Shanghai Women's Health Study is a population-based prospective study of women aged 40–70 years at recruitment and living in seven urban communities of Shanghai, China. Details of the study methodology have been previously described (8). A total of 74, 942 women were interviewed between March 1997 and May 2000 (baseline), yielding a response rate of 93%. Participants who had a prevalent cancer at baseline (n=1576) or who did not accrue any follow-up time (n=8) were excluded, resulting in a cohort of 73, 358 women for the current analysis.

The cohort was followed for occurrence of cancer and other chronic diseases by biennial home visits and linkage to the population-based Shanghai Cancer Registry records. Medical charts were reviewed and the pathological characteristics of the tumor were recorded. The death certificate data from the Shanghai Vital Statistics Office was used to update the vital status of cohort members and identify causes of death. Incident colorectal cancers (ICD-9: 153–154.2) occurred in 391 participants through December 31, 2005. The study was approved by all relevant institutional review boards in the Peoples Republic of China and in the United States.

A two-part standardized questionnaire administered at baseline has been previously described in detail (8). Information on family history of cancer in a first-degree relative was collected as part of the baseline questionnaire. Subjects were asked whether their parents, children or siblings had ever been diagnosed with cancer. Those reporting a positive family history were then asked about the type of cancer and the age at which the family member was diagnosed. In addition, information on age at interview, educational attainment, household income, disease and surgery history, dietary practices, physical activity, occupational history, and smoking and alcohol drinking habits were also recorded.

Analyses were performed with STATA version 9.2 (StataCorp, College Station, TX). An alpha level of less than 0.05 was considered statistically significant and all tests were two-sided. Cox proportional hazards regression (9) was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) and the STATA "stphtest" command was used to test agreement with Cox proportional hazards assumptions (10). Models were adjusted for age, education, family income, adult body mass index, tea drinking, total physical activity, history of diabetes and smoking. Further adjustment for alcohol drinking, use of aspirin-based medicines, and history

of diabetes, familial polyposis or ulcerative colitis did not meaningfully alter the risk and were therefore not included in the models.

Results

Of the 73,358 participants included in the analysis, 391 were diagnosed with CRC over 541,143 person-years of follow-up. CRC cases were generally older, heavier, had less education and lower income, and drank less tea compared to the cohort overall (Table 1). CRC cases were more likely to be diabetic than women in the cohort overall.

Compared to women with no family history of cancer, those who reported having a first degree relative diagnosed with colorectal cancer had an increased risk of CRC themselves (HR: 2.07; 95% CI: 1.07, 4.01). The excess risk was confined to individuals reporting a history of CRC in either of their parents (HR: 3.37; 95% CI: 1.59, 7.12), but not in their siblings (Table 2). CRC risk was not associated with a family history of cancer overall (HR: 1.11; 95% CI: 0.89, 1.39). We further investigated family history of cancer at a number of sites including lung, esophageal, breast, prostate and found no association with risk of CRC. Tumors associated with hereditary nonpolyposis colorectal cancer (endometrial, gastric, ovarian, urinary tract, central nervous system, small bowel) were also investigated (individually and combined) and were not associated with CRC risk. Results were similar for colon (n=234) and rectal cancer (n= 157) cases. A history of CRC from either parent was significantly associated with an elevated risk of colon (HR: 2.09; 95% CI: 1.02, 4.27) and rectal cancer (HR: 3.63; 95% CI: 1.22, 10.79).

Discussion

Consistent with previous reports from the U.S. and other Western countries (4,6), having had a first-degree relative diagnosed with CRC was associated with a threefold increased risk of CRC in our study population of Chinese women. This risk was greater for individuals reporting a parent, rather than a sibling, with CRC.

Though our findings, and those of others (5,7), are generally interpreted to reflect a genetic susceptibility to developing colon cancer, no specific mechanisms are apparent for sporadic colorectal cancer. The observed familial clustering is likely a complex interaction between polygenic inheritance, shared family environment, environment/gene interactions and/or partial penetrance of an autosomal dominant susceptibility gene(11,12). Tomlinson *et al.* (13) conducted a genome-wide association study of 550,000 tag single nucleotide polymorphism (SNPs) in 930 familial colorectal tumor cases and 960 controls. The strongest association they report was between a SNP in the 8q24.21 region, where a variety of SNPs have also been associated with breast and prostate cancers (14,15), underscoring the hypothesis that a variety of common, low-penetrance susceptibility alleles likely predispose to colorectal and other neoplasia. We found no excess risk of CRC among those reported having a sibling also diagnosed with CRC, but the result was based on only two cases with such a family history. Further investigations are needed to clarify whether factors inherited from parents outweigh those of a shared early environment among siblings.

The proportion of subjects in our study reported a family history of cancer (2.6%) is lower than those in similar studies in the U.S. where estimates range between 10% (16) and 14% (17). The low CRC risk in China and the relatively young age of our study participants (average 52 years old at cohort entry) may explain, in part, the relative low frequency of a family CRC history being reported. However, underreporting of a family member with CRC among our study participants is also possible, as cancer diagnosis might not have been as openly discussed in China compared with the West in the late 1990s. If such underreporting existed it should be

non-differential between cases and controls as the information was obtained prior to case diagnosis.

Contrary to some previous reports (18), our study does not support an association of CRC risk with a family history of other cancer types, although our ability to detect a weak association was limited by the small number of cases reporting a family history of any specific cancer. It is unlikely that our finding of an association with a parental history of colorectal cancer was due to selective recall, since the information was obtained at baseline prior to disease onset and exclusion of cases during the first two years of follow-up did not materially alter the risk estimates. Information on family history of cancer was collected from subjects recall alone, no efforts were made to contact relatives to verify the diagnosis. To the extent that inaccurate recall might have occurred, it may lead to non-differential bias which tends to result in an under-estimation of the observed association. Other potential sources of bias, such as selection and survival bias, are minimized by the prospective design of our study, the high participation rate and virtually complete follow-up of cohort participants.

In conclusion, our results showed that CRC risk is increased among a population of Chinese women who reported having a parent also diagnosed with CRC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BMI	body mass index
CI	confidence interval
CRC	colorectal cancer
HR	hazard ratio

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Table 1

Selected baseline characteristics of 73,358 participants in the Shanghai Women's Health Study

	Cohort n=73,358		CRC cases n=391		*P value*
Characteristics	**Median**	**IQR**	**Median**	**IQR**	
Age	50	44–60	61	53–65	< 0.001
Body mass index (kg/m^2)	23.7	21.6–26.1	24.5	22.3–26.5	< 0.001
Waist-to-hip ratio	0.81	0.77–0.84	0.82	0.79–0.86	< 0.001
[1] MET hrs/wk/yr (mean; SE)	100.4	74.5–131.6	104.3	81.2–134.5	0.04
Education	**N**	**%**	**N**	**%**	
Elementary/less	15,688	21.3	162	41.4	
Middle school	27,267	37.2	108	27.6	
High school	20,488	28.0	81	20.7	
College or higher	9,902	13.5	40	10.2	< 0.001
Income (yuan/yr)					
<10,000	11,811	16.1	90	23.0	
10,000–20,000	28,059	38.2	160	40.9	
20,000–30,000	20,599	28.1	88	22.5	
>30,000	12,873	17.6	53	13.6	< 0.001
[2] Ever drank tea	21,925	29.9	82	21.0	< 0.001
[3] Consumed alcohol	1,654	2.3	10	2.6	0.69
[4] Ever smoked	2,044	2.8	9	2.3	0.56
Taken hormone replacement therapy	2,595	3.5	15	3.8	0.10
Taken aspirin based meds in past year	1,469	2	12	3	0.14
Diabetes	3,137	4.3	33	8.4	< 0.001
Ulcerative colitis	455	0.6	3	0.8	0.72
Familial adenomatous polyposis	82	0.1	0	0	0.51

Median and inter-quartile range or number and % quoted with p values from Wilcoxon rank-sum and Pearson's χ^2 statistical testing, as appropriate.

[1] MET, total metabolic equivalents;

[2] Ever drank tea 3 or more times/wk for 6 months or longer;

[3]Ever consumed alcohol 3 or more times/wk for 6 months or longer;

[4]Ever smoked 1 or more cigarette/day for 6 months or longer

Table 2

Adjusted hazard ratios and 95% confidence intervals for colorectal cancer by family history of cancer

Family History	Cases	Multivariate HR*	
		HR	95% CI
First degree relative with cancer	115	1.11	0.89, 1.39
Parents	78	1.09	0.84, 1.42
Siblings	37	1.16	0.81, 1.64
Colorectal cancer	10	**2.07**	**1.07, 4.01**
Parents	8	**3.37**	**1.59, 7.12**
Siblings	2	0.80	0.20, 3.29
Lung cancer	16	1.23	0.73, 2.09
Parents	12	1.14	0.63, 2.09
Siblings	4	1.46	0.53, 4.00
Stomach cancer	24	1.06	0.70, 1.62
Parents	18	1.03	0.63, 1.68
Siblings	6	1.16	0.51, 2.65
Oesophageal cancer	13	1.30	0.74, 2.29
Parents	11	1.44	0.78, 2.66
Siblings	2	0.87	0.21, 3.56

Women who reported no family history of cancer were used as the referent group. Analyses are adjusted for age, smoking, family income, education, body mass index, physical activity and diabetes. Estimates for first degree relatives with breast or prostate cancer were excluded due to small numbers (n=1 and n=2, respectively).