**Original Article**

**The relevance of family history to increased risk of colorectal cancer in Korea**

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**ABSTRACT**

**BACKGROUND:** A family history of colorectal cancer (CRC) has been regarded as a risk factor for colorectal cancer. We aimed to estimate relative risk (RR) associated with family history of CRC in the Korea population.

**METHODS**: We used a prospective cohort of CRC patients-based pedigree including 2.027 pedigrees with 38,581 individuals excluding families already proven to be of hereditary trait (Lynch syndrome, familial polyposis syndrome). We examined the relative-risk based on the absolute number of affected first-degree relatives (FDR; FDR=0,1, ≥2) and the proportion of affected FDRs (low, moderate, high), putting into account the difference of the sizes of families and FDRs.

**RESULTS:**

**CONCLUSION:**

**INTRODUCTION**

It has been estimated that as many as a quarter of colorectal cancers (CRC) have a hereditary trait (1). These include cancers that are linked to a more profound genetic condition such as familial adenomatous polyposis, or Lynch syndrome. However, despite the progress of genetic tools and software to better provide a tailored approach to cancer patients, many mutations are still of unknown significance in its relationship to the pathogenesis of CRC. The most simple and relevant way to identify patients with increased risk of CRC is through a detailed family history (2). A family history of colorectal cancer (CRC) is known to be related to have and increased risk of developing CRC with variable risks based on the number, proximity (first-degree, second-degree, etc.), or onset of the affected family members (3).

Various guidelines acknowledge the importance of family history of CRC and incorporate it into their guidelines of screening (4, 5). By beginning screening at an earlier age potentially increases the chance of cure and survival by detection and removal of precursor lesions or cancer at an earlier stage. We conducted this study to estimate the increased risk of CRC in those with a positive family history in the Korean population based on pedigree analysis. This was to provide a basis for future policy decisions regarding CRC screening and diagnosis for individuals with a family history of CRC.

**PATIENTS AND METHODS**

***Study families and Pedigree Acquisition***

This was a cross-sectional study of a prospective database registry of family pedigrees from two tertiary centers. The probands were CRC patients who underwent surgery from 2003 to 2016 at Seoul National University Hospital and Seoul National University Bundang Hospital. Pedigrees were excluded from analysis if proven to be familial adenomatosis polyposis (FAP) or Lynch syndrome.

Following pathologic confirmation of CRC and before surgery, each patient was interviewed about his/her family history for 30–60 minutes at the bedside by a well-trained physician assistant or research assistant. All included patients provided informed consent for family history taking. Patients were asked for their date of birth, personal cancer history, type of cancer, and the age/year of diagnosis. Respondents were then asked to list all biological relatives and to provide information on their status (living or dead), year of birth, age (if living), age of death (if deceased), age at onset of colonic polyps, history of cancer, and if obtainable, cancer type, site, and age/year of diagnosis.

***Pedigree trimming***

To reduce the chance of recall bias and increase the integrity of the findings we included only first-degree relatives (FDR) in the analysis. This is due to previous reports where there was a significant difference in the accuracy of the memory according to the distance of the relative (6, 7). We also excluded pedigrees if the age onset was over 80 years due to belief that more influence of lifestyle and environmental factors were at hand for these probands (8).

***Estimating narrow-sense heritability of CRC in Korea population***

Narrow-sense heritability of CRC was estimated using the liability threshold model. Under the liability threshold model, disease status is determined by both the unobserved continuous liability score and the threshold underlying the disease. The threshold can be calculated as where is the cumulative distribution function of standard normal and is the prevalence of the disease. Individuals whose liability score is larger than the threshold are affected by the disease, otherwise they are not affected by the disease. The liability scores are presumed to be followed the multivariate normal distribution with a variance-covariance matrix of where is a heritability, is a kinship coefficient matrix multiplied by two and is an identity matrix. If we denote the covariates as , then the mean of the liability scores will be . In this study, we included the standardized age (mean=0, variance=1) as a covariate.

***Cox proportional hazard model***

We used the Cox proportional hazard model to calculate the increased risk of CRC based on affected FDRs. We first calculated the hazard ratio based on the absolute number of affected FDRs which was categorized into three groups; FDR=0, 1 and ≥2 respectively. Second, we calculated the hazard ratio based on the proportion of affected FDRs for the those with a positive family history (FH). This was to investigate the increased risk of CRC with increasing family members, standardizing for the family size. We used the proportion of affected FDR, defined as the number of affected FDRs divided by the total FDRs in each pedigree. Optimizing of this normalized value using two cutoff values categorized the subjects into three groups, low FH, moderate FH and high FH. Using low FH as the reference, we calculated the hazard ratio of each group in comparison. Proportional hazard assumption was assessed for all covariates using graphical and statistical analysis. Statistical analysis was done using the R survival package (9).

***Optimization of cut-off values***

We performed a grid search based on all of the observed proportions of affected FDRs to optimize the cut-off values. For each cut-off, we fitted Cox proportional hazard model and calculated Akaike information criterion (AIC) which is a statistics widely used for model selection (10). AIC is usually defined as where is the number of parameters in the model and   is the maximum value of the likelihood function. Here the partial likelihood function was used instead of the likelihood function since the baseline hazard is not estimated for the Cox proportional hazard model.

Optimization of cut-off values were conducted by two steps. First, we divided the subjects into two groups based on each observed proportion except the largest value and fitted the Cox proportional hazard models. For the proportion with the minimum AIC was selected as the first cut-off value. Second, we divided the subjects into three groups based on the first cut-off value and each remaining proportion. Then, the Cox proportional hazard model for each cut-off value was fitted. Finally, we determined the proportion which has the smallest AIC to the second cut-off value.

**RESULTS**

***Data collection***

We collected a total of 2,027 pedigrees, of which 96.3% (n=1,952) had an onset before age 80. These probands had 38,581 relatives in total, and 16,270 FDRs. The number of FDRs ranged from 2 to 17 and most of probands have no affected FDR (90.5%). A positive family history in the FDR was found in 9.5% (186/1,952) of the pedigrees. The basic characteristics of probands and their FDRs are shown in Table 1.

***Heritability of Colorectal cancer in Korean population***

In 2015, the age-standardized prevalence of CRC was reported as 0.248% in Korea and the threshold was 2.81 accordingly (11). Estimated hertiabiltiy of CRC was 40.21% (P-value = ). The coefficient estimate

LTMH was used to examine the family-based samples derived from the T2D dataset, and heritability of T2D was estimated. Estimated heritability of T2D was 29.44%, and it was statistically significant under the significance level of 0.05 (P-value = 1.2010-5). This finding is slightly overestimated in comparison to other determinations of heritability estimates for T2D (26%) using the ACE model based on twin data (12). This difference may be attributable to racial differences. The coefficient estimate for non-standardized age was 0.051 (0.8 for standardized age), which means that the threshold for disease is reduced by 0.051 at the liability scale if age increases by 1. The function of age is well described in Figure 3A, which illustrates the probability of being affected by T2D as a function of age. Results demonstrate that the risk increases monotonically by age, reflecting the reduction effect on disease threshold. Individuals with a higher number of T2D affected relatives exhibit greater risk. In comparison to random samples, the influence of family history is greater at a young age, and determining familial risk for early-onset T2D is highly important (Figure 3B).

In Table 2, a positive family history in the FDR was significantly associated with the risk of CRC (HR = 1.20; 95% CI = [1.03-1.40]). However, probands with ≥2 affected FDRs did not have an increased HR over those with 1 affected FDR and did not reach statistical significance. In a subgroup analysis grouped by onset of the proband, the proportion of affected FDR in the age≤50 group was more than that of the age>50 group (Table 3). Subgroup analysis stratified for age showed in increased HR for… (table 3결과 설명)

Since the number of FDRs and size of the families varied, we normalized the number of affected FDR by the number of affected FDRs in each pedigree with a positive FH. This resulting ‘proportion’ ranged from 0.05-0.40 and is shown in Figure 1. To find the increased risk of CRC according to increasing number of affected FDRs, several cutoffs in the proportions were investigated to further divide the cohort into significant groups. We found cut-off values of 0.125 and 0.300 to best explain the increased HR according to increased proportion of affected FDRs in our cohort (Table 4). Each representative cohort was labeled low FH, moderate FH, and high FH. Compared to the reference (low FH) there showed to be an higher risk with increasing proportion of members affected (Table 4).

**DISCUSSION**

This study evaluates the increased risk of CRC based on the largest cohort for family pedigrees of CRCs in Korea. It is also the first to report the proportion of affected FDRs, rather than the absolute number of affected FDRs translate into increased risk of CRC. In concordance with previous studies, we found an increased risk for CRC for those with a family history of CRC. We additionally found that higher proportion of affected FDRs was associated with a greater risk of CRC.

Increased risk of CRC based on affected FDRs has been investigated in various populations around the world. A recent meta-analysis pooling 9.3 million individuals from 63 studies showed an increased relative risk (RR=1.76) of CRC for those with a family history in FDR (8).

Since 2004, Korea has adapted a national screening program for CRC screening starting at the age of 50. However, this does not put into account the increased risk of cancer for individuals with a family history of cancer, and the recommendation of family members to receive colonoscopy is done on a case-by-case basis. However even with the knowledge of increased incidence with family history there are significant barriers for these individuals to take action (13).

Statistical method(analysis)와 관련하여 다른 연구와 비교

우리의 finding – FDR 0.3이상일 경우 1.33배 위험도 증가

이것에 대한 다른 연구와의 비교, 우리 통계 method의 특징/차이점

한계

정리

**CONCLUSION**

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**TABLE LEGENDS**

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