**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.

We imputed missing age using age information of other family member and their familial relationship. If the age of parents is missing, the age of father was imputed to be 27 years older than the oldest off-sprint and the age of mother was imputed to be 3 years younger than the father. Similarly, missing age of off-spring was calculated. If the age of sibling is missing, it was imputed to be 3 years older than younger sibling.

***Pedigree trimming***

To reduce the 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. In 2015, the age-standardized prevalence of CRC was reported as 0.248% in Korea (9) and the threshold was 2.81 accordingly. 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 age and the sex as covariates. The age was coded as 1 if the subject is older than 50 and otherwise 0. The sex was coded as 1 for female and 0 for male. All covariates were standardized to be mean of 0 and variance of 1.

***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 (10).

***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 (11). 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***

The narrow-sense heritability of CRC was estimated at 40.21% (P-value = 3.5110-12) on the liability scale. The coefficient estimates of the age and the sex were 0.259 and -0.047, respectively. It means that the threshold decreases in 0.259 for person older than 50 and increases in 0.047 for female. Change in the threshold value directly affect to the risk of CRC. If we assume that we don’t have information about family of the disease, male over 50, female under 50 and female over 50 had 1.4, 7.8, 10.36 times higher risks than male under 50 (Table 2).

A risk of CRC is also affected by the number of affected relatives. We considered a nuclear family consisting of parents and two offsprings to calculate risks of being affected to the CRC for the first offspring in the following cases: 1) Parents and the other offspring are unaffected, 2) Only father is affected, 3) Parents are affected and the other offspring is unaffected, and 4) Parents and the other offspring are affected. All family members were assumed to be younger than 50 years old. Figure 1 illustrates that the relative risk of the probability of being affected to the CRC to the baseline risk is monotonically increasing as the number of affected FDRs increases for various prevalences. For all prevalences, the relative risks of the subjects with no affected FDRs were less than 1. The relative risk depends on the prevalence and the smaller the prevalence, the great the increase in the relative risk.

To investigate the effect of the unaffected relatives on the risk of CRC, we considered five virtual probands which have from two to six female FDRs with age under 50 respectively and all probands were assumed to have two affected FDRs. Figure 2 shows that the relative risk of the probability of being affected to the proband with no unaffected FDR decreases as the number of unaffected FDRs increases. That is, even though the numbers of affected relatives are same, the risk probability can be different by the number of unaffected relatives. However, the decrease in relative risk with increasing unaffected relative was not significantly greater than the increase in relative risk with increasing affected relative.

***Risk assessment by family history***

We performed the Cox proportional hazard model for the age of CRC onset of probands including the age, the sex and the family history as risk factors. A positive family history in the FDR (no family history or at least one affected FDR) was significantly associated with the risk of CRC with a hazard ratio (HR) of 1.20 and 95% confidence interval (CI) of [1.03 - 1.40] (Table 3). There is about 20% increase in the expected hazard for the proband with a positive family history relative to the proband with no family history.

We further categorized probands into three groups which are no family history, 1 affected FDR, more than 2 affected FDRs. Table 3 shows that probands having one affected FDR have about 25% increase in the expected hazard relative to probands with no family history (HR=1.25, 95% CI = [1.07 – 1.48]). However, probands with ≥2 affected FDRs did not have an increased HR over proband with no family history and did not reach statistical significance (HR=0.95, 95% CI = [0.91 – 1.09]).

To account for the number of unaffected FDRs in estimating increase in hazard, 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 3. 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 (Figure 4). Each representative cohort was labeled as low FH, moderate FH, and high FH. Compared to the reference (low FH) there showed to be a higher risk with increasing proportion of members affected (Table 3).

**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 (12).

**CONCLUSION**

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**TABLE LEGENDS**

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