The role of family history in colorectal cancer screening in East Asia

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Abstract

Background

Globally, colorectal cancer is one of the leading causes of cancer related death. Asia has had relatively low incidence rates of colorectal cancer when compared with western countries. Over the last decade, however, occurrences have increased in many Asian countries. In East Asia, colorectal cancer incidence has been increasing over last few decades; however, many countries are still lack of strategies on colorectal cancer screening. Colorectal cancer screening guidelines in many Western countries use family history information when assigning people into different risk categories to recommend for frequency and intensity of screening strategies. However, the relationship between family history and colorectal cancer and adenoma risk has not been well studied in Asian countries. Given that family structure and environmental exposures are likely to be different in Asian countries it is assumed, the association may also prove to be different.

Aims

This thesis aimed to investigate the role of family history of colorectal cancer in colorectal cancer screening in East Asian countries.

Method

This thesis includes the following five studies addressing the gaps in knowledge of role of family history in colorectal cancer screening strategies. The main database for this thesis is the prospective data of 175,000 men and women from three countries (Japan, Korea and China) who have been recruited into the Asia Cohort Consortium (ACC, https://www.asiacohort.org/).

1. A literature review of current colorectal cancer screening guidelines in Asian countries.

2. A systematic review of studies on the association between family history of colorectal cancer and the risk of colorectal cancer in Asian countries.
3. A pooled analysis of six prospective cohorts from Asia Cohort Consortium to investigate the association between family history of colorectal cancer and the incidence of colorectal cancer in Asian countries
4. A pooled analysis of six prospective cohorts from Asia Cohort Consortium to investigate the association between family history of colorectal cancer and the mortality of colorectal cancer in Asian countries
5. External validation of Asian-Pacific Colorectal Cancer Screening (APCS) Score using six prospective cohorts from Asia Cohort Consortium.

Results

Firstly, from the meta-analysis, the association of colorectal neoplasia with having at least one first-degree relative family history of colorectal cancer differed by Asian region: being 1.69 (1.46, 1.96) for East Asia; 3.44 (2.32, 5.10) for Western Asia and 5.14 (2.44, 10.8) for South-Eastern Asia. The strength of associations between family history of colorectal cancer and the risk of colorectal cancer and adenoma for East Asia was similar to that of Western populations, but higher for Western and South-Eastern Asia. This information will be useful to triage the populations in Asian countries for colorectal cancer screening by the strength of family history in different regions of Asia.

Secondly, with the pooled analysis of exist data from Asia cohort consortium, the family history of colorectal cancer associated with a higher risk of incidence of colorectal cancer in Asian countries.

Thirdly, the evidence from family history and mortality, this is no evidence for an association between family history of colorectal cancer and overall survival or colorectal cancer-specific mortality. However, specific mechanisms underlying family history may have prognostic impact and merit further study. Future studies need to collect data on possible

confounders of the effect, such as tumour stage at diagnosis, presence of multiple cancers, mode of presentation to hospital and surgical or clinical management in order to produce more conclusive results.

Last, the APCS scores were efficient to identify individuals with high risk of colorectal cancer in East Asia population.

Conclusions

This thesis has generated new knowledge about family history and risk of colorectal cancer in East Asia. The systematic review and meta-analysis demonstrate that there are large heterogenous in association of colorectal neoplasia with having at least one first-degree relative family history of colorectal cancer differed by Asian regions. Family history could be a useful tool for colorectal cancer screening program but might not be associated with the mortality of colorectal cancer. APCS scores can effectively identify individuals with high risk of colorectal cancer in East Asia. The feasibility and acceptability of the APCS score to the general population in Asia will need to be further examined.

Declaration

This is to certify that:

a) The thesis comprises only my original work towards the PhD except where indicated in the Preface;

b) Due acknowledgement has been made in the text to all other materials used; and

c) The thesis is fewer than 100,000 words in length, exclusive of tables, bibliographies and appendices.

Signed: Lin Zhang

Date: Dec 23 2019

Preface

My thesis is under the supervision of A/Prof Aung Ko Win (Principal Supervisor) and Prof Mark Jenkins (Co-supervisor) from Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne.

My thesis has used Asia Cohort Consortium (ACC) database with 6 prospective cohorts. Relevant data from participating cohorts were harmonized at the ACC coordinating centre at the University of Tokyo. The harmonization was discussed to ensure the included variables were accurately extracted and interpreted. Databases were investigated for inconsistency or missing values, and relevant queries were returned to ACC coordinating centre for confirmation. The distributions of variables were investigated and explored to identify errors or false or implausible values. For protection of individual confidentiality, the personal information including identifiers were removed, however study-specific identity numbers were retained to facilitate referral of questions back to the relevant individual cohort. My study was approved by the institutional review board of the ACC coordinating centre at the University of Tokyo and by the ethics committees of individual cohort.

My PhD was funded by the Melbourne International Research Scholarship and Melbourne International Fee Remission Scholarship. Also, I received the Population Health Investing in Research Student Training (PHIRST) and the Melbourne Abroad Travelling Scholarship (MATS) to support this project.

Research output

PhD pending publications

- Lin Zhang, S. Ghazaleh Dashti, Mark A. Jenkins, Aung Ko Win. Family history and the risk of colorectal cancer and adenoma in Asian countries: a meta-analysis and systematic review. (Under review).
- Lin Zhang, Mark A. Jenkins, Aung Ko Win. Association of family history with incidence of colorectal cancer-a pooled analysis of 6 prospective cohorts in the Asia Cohort Consortium. (In preparation)
- Lin Zhang, Mark A. Jenkins, Aung Ko Win. Association of family history with incidence of colorectal cancer-a pooled analysis of 6 prospective cohorts in the Asia Cohort Consortium. (In preparation)
- Lin Zhang, Mark A. Jenkins, Aung Ko Win. External Validity of Asia-pacific colorectal screening (APCS) score as a risk prediction score for colorectal cancer in Asian population – A study of 6 prospective cohorts of Asia cohort consortium. (In preparation)

Conference presentations

- Lin Zhang, S. Ghazaleh Dashti, Mark A. Jenkins, Aung Ko Win. Family History and the Risk of Colorectal Cancer and Adenoma in Asian Countries: A Meta-Analysis and Systematic Review. 2nd Singapore International Public Health Conference & 11th Singapore Public Health & Occupational Medicine Conference, Singapore, 29th to 30th September 2016 (See Appendix A: Abstract and Poster Presentation)
- Lin Zhang, S. Ghazaleh Dashti, Mark A. Jenkins, Aung Ko Win. Family History and the Risk of Colorectal Cancer and Adenoma in Asian Countries: A Meta-Analysis and Systematic Review. Cancer Therapeutics CRC Higher Degree

Research Symposium, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, Melbourne, Australia, 30th June 2017(See Appendix A: Abstract and Poster Presentation)

- Lin Zhang, S. Mark A. Jenkins, Aung Ko Win. Family history and risk of colorectal cancer in Asian population--Pooled analysis of Asia Cohort Consortium (ACC). Asian Cohort Consortium Annual Meeting, Nagoya, Japan. 4th to 5th September 2018 (See Appendix B: Oral Presentation1)
- Lin Zhang, S. Mark A. Jenkins, Aung Ko Win. Family history and risk of colorectal cancer in Asian population--Pooled analysis of Asia Cohort Consortium (ACC) with 170,000 population. U21 Health Sciences Group Doctoral Student Forum, Melbourne, Australia, 10th to 14th September 2018 (See Appendix C: Oral Presentation2)

Awards & Prizes

- 06/2018 Awarded the Melbourne Abroad Travelling Scholarship (MATS) by the University of Melbourne
- 07/2017 Awarded the University of Melbourne Fellow of The Australia-China Youth Dialogue (ACYD)
- 05/2016 Awarded the Population Health Investing in Research Student Training (PHIRST), The University of Melbourne
- 11/2015 Awarded the Melbourne International Research Scholarship, The University of Melbourne
- 11/2015 Awarded the Melbourne International Fee Remission Scholarship, The University of Melbourne

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- The Melbourne International Research Scholarship
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- The Melbourne Abroad Travelling Scholarship

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CHAPTER 1. Introduction

1.1 Problem Statement

Colorectal cancer is one of the leading causes of cancer-related mortality globally. The recent publication of global cancer statistics 2018 by GLOBOCAN with the data from the International Agency for Research on Cancer (IARC) reported that colorectal cancer is the third most commonly diagnosed cancer and second in terms of mortality, with over 1.8 million new cases and 881,000 deaths worldwide in 2018, accounting for about 1 in 10 cancer cases and deaths [1]. Assessing incidence and mortality trends globally, Arnold et al [2] identified 3 heterogenous global patterns linked to colorectal cancer incidence and mortality; in the first category, increases in both incidence and mortality in the most recent decade has been seen in Russia, China, and Brazil; in the second category, increasing incidence but decreasing mortality was in Canada, the United Kingdom, Denmark, and Singapore; in the third category, both decreasing incidence and decreasing mortality was in the United States, Japan, and France.

Though Asia has traditionally been considered having a relatively low incidence of colorectal cancer compared with Western countries, the incidence has been increasing over the last decade in many Asian countries. For example, In 2012, Japan (Miyagi Prefecture Cancer Registry) presented the highest colorectal cancer incidence in the world for men (62 per 100,000 person) and women (37 per 100,000 person) [3]. There are some reports of prevalence, incidence and mortality of colorectal cancer in Asian countries, but mainly focus on East Asian countries [4-7], the knowledge gap is that we did not have a whole picture of prevalence,

incidence and mortality of other parts of Asia, including Central Asia, West Asia and South-eastern Asia.

Screening for colorectal cancer is widespread in the Western population, and the goal of screening is to reduce mortality through a reduction in incidence of colorectal cancer through the detection and removal of polyps. This has been confirmed by randomized controlled trials (RCTs) that have shown that the screening significantly reduces the incidence and/or mortality of colorectal cancer [8-17]. Colorectal cancer screening guidelines in many Western countries recommend screening frequency/intensity and age at commencement based on the strength of family history [12, 14, 18]. While some countries in Asia have already implemented colorectal cancer screening [11], it is still lacking in many. The knowledge gap is that we did not know the correct screening guidelines for each Asian country and what criteria was best suited to the screening guidelines.

Several epidemiological studies from Western countries consistently reported that family history of colorectal cancer is a known strong risk factor for colorectal cancer [19-22]. The strength of this association differs with the number of relatives affected by colorectal cancer, the closeness of relatives with colorectal cancer, and the diagnosis age of the affected relative. For example, a study by Taylor et al [23] using a large family database linked to a cancer registry data in Utah, USA, has shown that colorectal cancer risk increases with an increased number of affected relatives, particular if the affected relatives are genetically closer, diagnosed at a younger age, and multiple relatives are affected. This is consistent with the

existence of risk factors for colorectal cancer that are shared by relatives including genetic factors but also lifestyle factors.

In comparison with Western countries, there have been relatively few understandings on family history as a risk factor for colorectal cancer in Asian countries. Given that family structure and lifestyle factors are likely to be different between Asian and Western countries, we hypothesized that the association with family history of colorectal cancer are also be different. The average size of families in Asian countries has been shrinking since 1980 [24], which can mask recognition of a genetic mutation as the cause of cancer in a family. Therefore, potentially altering the strength of family history as a risk factor. In addition, environmental or lifestyle exposures that might also be correlated within family members, such as diet, are likely to be different between Asian and Western countries. Additionally, the prevalence of family history of colorectal cancer in the population is different. It is estimated that up to 10% of US adults have a first-degree relative (FDR) who has been diagnosed with colorectal cancer, and approximately 30% have an affected FDR or second-degree relative (SDR). In the United Kingdom adults have similar prevalence of FDR and FDR or SDR with 9.4% and 28.8% respectively [25], and in Germany adults have 7.2% FDR family history [26]. The prevalence of the family history of colorectal cancer in each Asian country is under investigation. However, family history itself is not a good predictor of colorectal cancer, as the increased risk is applied to the very low average risk of colorectal cancer (lifetime risk approximately 5%), resulting in an absolute risk in those with a family history that is still low. resulting in a still low absolute risk of family history. However, family history can be used to

classify people without colorectal cancer diagnosis or symptoms into risk categories in which the number of colorectal cancer or adenomas is expected to be high enough to warrant further screening than the general population. In this situation, whether we should still include family history in the colorectal cancer screening practices in Asian countries is a question. This is indicative of the knowledge gaps of current research in Asian countries.

1.2 Rationale

Colorectal cancer incidence and mortality rates in some Asian countries continue to increase. Evidence shows that family history of colorectal cancer is an important risk factor for developing colorectal cancer in Western population. However, its association with the risk of colorectal cancer in the Asian population is not well understood. The association might be different because of the shrinking family sizes of Asian countries, especially the nuclear family in Japan, China and Korea. Additionally, environmental exposures are likely to be different in Asian countries compared with Western countries. Some countries in Asia have already implemented national colorectal cancer screening. However, screening is lacking in most of Asian countries [27, 28]. Optimal screening method in Asia countries remains unclear. This study tries to study the family history of colorectal cancer and risk of colorectal cancer in East Asia.

1.3 Aim of the research

This thesis aimed to investigate the role of family history of colorectal cancer in colorectal cancer screening in Asian countries.

The major aims of my thesis are to address these gaps in knowledge:

1. To understand the association of family history and risk of colorectal cancer in Asian countries with existing studies in Asian countries, I conducted a systematic review by examining published literature to test the hypothesis that having at least one first-degree relative with colorectal cancer increases the risk of colorectal cancer incidence in Asian countries, and I summarized these findings through a meta-analysis.
2. To understand the association of family history and risk of colorectal cancer incidence in Asian countries, I performed pooled analyses among six prospective cohorts included in Asia Cohort Consortium.
3. To understand the association of family history and risk of colorectal cancer mortality in Asian countries, I performed pooled analyses among six prospective cohorts included in Asia Cohort Consortium.
4. The Asia-Pacific Colorectal Screening (APCS) score has been widely recognised as a risk-stratification tool to predict the risk for advanced colorectal neoplasia in asymptomatic Asian population but has not yet been assessed for its validity of its use in multiple Asian countries with large participants, especially in Japanese. I investigated the external validity of Asian Pacific Colorectal Cancer Screening (APCS) score system in six large pooled data sets with multiple prospective cohorts from Japan, Korea and China.

1.4 Scope and settings

Although colorectal cancer is a global health issue, the incidence and mortality of colorectal cancer is still relatively low, comparing with cardiovascular diseases and diabetes, epidemiology study is an optimal method to investigate the rate outcome like colorectal cancer and rare exposure like family history of colorectal cancer. The observational research design, including case-control, cross-sectional and cohort research are good method to explore and investigate the association of family history and risk of colorectal cancer, though each of the study design has their own drawbacks. In this thesis, I conducted meta-analysis and cohort study to explore the association of family history and risk of colorectal cancer in Asian countries.

Resources: This thesis used Asia Cohort Consortium (ACC) database with six cohorts, which was acquired by A/Prof Aung Ko Win from the ACC committee. Relevant data from participating cohorts were harmonized at the ACC coordinating centre at the University of Tokyo. The harmonization was discussed to ensure the included variables were accurately extracted and interpreted. Databases were investigated for inconsistency or missing values, and relevant queries were returned to ACC coordinating centre for confirmation. The distributions of variables were investigated and explored to identify false or implausible values. For protection of individual confidentiality, the personal information including identifiers were removed, however study-specific identity numbers were retained to facilitate referral of queries back to the individual cohort. My study was approved by the institutional review board of the ACC coordinating centre at the University of Tokyo and by the ethics committees of each cohort.

1.5 Overview of this thesis

My thesis is under the supervision of A/Prof Aung Ko Win (Principal Supervisor) and Professor Mark Jenkins (Co-supervisor) from The University of Melbourne.

My contributions to each chapter:

Chapter 1 Introduction

- This chapter is mainly focused on the knowledge gap on the association of family history and colorectal cancer in Asian countries, the aims of this research project, and the score and setting of this thesis. Resources and method are included, as well as the overview of this thesis.
- My contribution to this chapter: I proposed the knowledge gap and conducted the study concept and design with supervisors; planed the research aims of this PhD project; drafted the manuscript for this chapter; approved of the final version of the manuscript.

Chapter 2 Background and literature review

- This chapter is focused on the background of the research project, including introduction of colorectal cancer in the context of a global epidemic; the risk factors of colorectal cancer; and screening methods of colorectal cancer in the global setting. I undertook a literature review on the current colorectal cancer screening guidelines in Asian countries, and the current research of family history and risk of colorectal cancer.
- My contribution to this chapter: I conducted the literature review of this chapter and drafted reviewed of the manuscript; approved of the final version of the manuscript.

Chapter 3 Methodology

- This chapter is focused on the introduction of Asia Cohort Consortium (ACC) and the six cohorts included in my thesis. Additionally, I briefly introduced the methods used in each chapter.
- My contribution to this chapter: I summarized the database and the methodology used in this PhD thesis.

Chapter 4 Family history and the risk of colorectal cancer and adenoma in Asian countries: A meta-analysis and systematic review

- In this systematic review, I examined published literature to test the hypothesis that having at least one first-degree relative with colorectal cancer increases the risk of colorectal cancer in Asian countries. I summarized these findings as a meta-analysis. This meta-analysis has shown that the strength of associations between family history and the risk of colorectal cancer and adenoma for East Asia is similar to that of Western populations, but higher for Western and South-Eastern Asia. This information will be useful to triage the populations in Asian countries for colorectal cancer screening by the strength of family history in different regions of Asia.
- My contribution to this chapter: I conducted the study concept and design with supervisors; search for the literature; abstracted the data; performed meta-analysis and interpreted the results; drafted and reviewed the manuscript for important intellectual content; approved of the final version of the manuscript.

Chapter 5 Association of family history and incidence of colorectal cancer: A pooled analysis of six prospective cohorts of the Asia Cohort Consortium

- This chapter focusses on the association of family history of colorectal cancer with the incidence of colorectal cancer in Asian countries. Family history of colorectal cancer was associated with a higher risk of colorectal cancer in the Western population, however the association with the risk of colorectal cancer in the Asian population is not well understood.
- My contribution to this chapter: I conducted the study concept and design with supervisors; performed Cox regression analysis and interpreted the results; drafted and reviewed the manuscript and approved of the final version of the manuscript.

Chapter 6 Association of family history and survival of colorectal cancer-a pooled

analysis of six prospective cohorts in the Asia Cohort Consortium

- In this chapter, I undertook a pooled analysis of 2,456 individuals diagnosed with colorectal cancer with self-reported family history of colorectal cancer, in six prospective cohorts included in the Asia Cohort Consortium.
- My contribution to this chapter: I conducted the study concept and design with supervisors; performed Cox regression analysis and interpreted the results; drafted and reviewed the manuscript and approved of the final version of the manuscript.

Chapter 7 Validation of Asia-pacific colorectal cancer screening score in Asian population: A pooled analysis of six prospective cohorts of the Asia Cohort Consortium

- This chapter is focussed on the external validity of the Asia-Pacific Colorectal Screening (APCS) score to predict colorectal cancer in a large pooled data with multiple prospective cohorts from Japan, Korea and China.
- My contribution to this chapter: I conducted the study concept and design with supervisors; performed analysis for the score system model and interpreted the results; drafted and reviewed the manuscript and approved of the final version of the manuscript.

CHAPTER 2. Literature Review

2.1 What is colorectal cancer?

Colorectal cancer refers to the tumour of rectum or large intestine (including appendix), which is caused by large intestine mucosa. Adenocarcinoma is the most common type of colorectal cancer (> 95%). Colorectal cancer usually develops from adenomatous polyps, which undergo atypical hyperplasia and become cervical cancer. Tumours can occur occasionally, but there are also some inherited colorectal cancer syndromes [29].

2.1.1 Carcinogenesis of colorectal cancer

Colorectal cancer progresses in a multistep process by which healthy epithelium develops into pre-cancerous polyps [30, 31]. A polyp is a benign, precursor of colorectal cancer, and it is the cornerstone of primary prevention of colorectal cancer. Most colorectal cancer (60-90%) develop from adenomas which is a type of polyp, through a series of genetic and epigenetic transformations, which are associated with a higher risk of colorectal cancer. Adenomatous polyps and adenocarcinoma are the largest epithelial tumours, which are the most common and clinically significant tumours in intestinal tumours. With age, polyps or adenomas are more likely to develop into cancer. Adenomas larger than 1 cm have extensive villous structures and an increased risk of developing cancer. Adenomas are common in adults over age 50 years, but the majority of polyps will not develop into adenoma. The time of malignant transformation from early adenoma to invasive cancer is estimated to last 5-15 years [32, 33], but these numbers are hampered by uncertainty, and the variation is probably even larger. The progression from colorectal polyp to colorectal cancer is demonstrated in **Figure 1.**

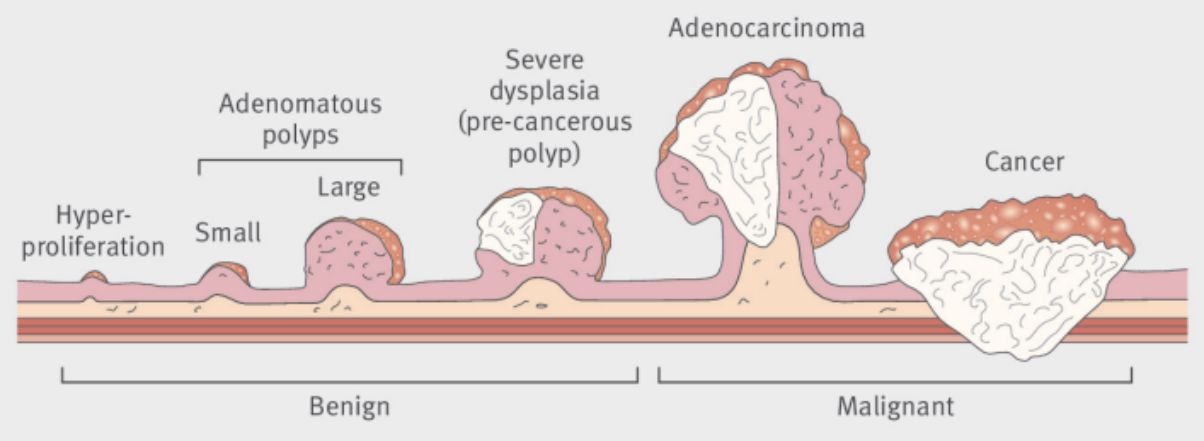

Figure 1. Progression from colorectal polyp to cancer[1]

2.1.2 Familial colorectal cancer

Family history of colorectal cancer is a major risk factor for the development of colorectal cancer to a large extent, because up to 20% of other family members of colorectal cancer patients are also affected by the disease. Patients with a family history of colorectal cancer are about twice as likely to be diagnosed with colorectal cancer as those without a family history [21]. The degree of personal risk depends on the number of affected relatives, the age of affected family members and the degree of intimacy of relatives [61, 62].

Many observational studies in Western countries have reported that the family history of colorectal cancer is a strong risk factor for colorectal cancer [19-22]. For example, a study by Taylor et al [23] using a large family database related to Utah cancer registration data, the risk of colorectal cancer increases with the number of affected relatives, especially if the affected relatives are more genetically similar, diagnosed at a younger age, and multiple relatives are affected. Four meta-analyses of the history of western developed countries have also

[1] Johns Hopkins Colon Cancer Centre. Polyps 101. https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/small_large_intestine/sporadic_nonhereditary_colorectal_cancer.pdf)

concluded that the risk of colorectal cancer is about twice as high for people with at least one affected first degree relative as for those without a family history of colorectal cancer, and the risk increases with the number of affected first degree relatives. [19-22]. The risk of colorectal cancer is more than 3-fold higher for persons with a first-degree relative is diagnosed under the age of 50 years, and 2- to 3-fold higher if a first-degree relative is diagnosed under the age of 60 years [23]. This is consistent with the existence of risk factors for colorectal neoplasia that are shared by relatives including genetic factors but also lifestyle factors. As a consequence, colorectal cancer screening guidelines in many Western countries recommend screening frequency and intensity and age at commencement based on the strength of family history [12, 14, 18]. In addition to family history of colorectal cancer, having a family history of adenomas is increasingly recognized as an important risk factor[63]. Given the new recommendations for more intense screening in patients with a family history of advanced adenomas, physicians become more aware of the presence of adenoma within family members. Patients frequently do not remember colonoscopy results, as shown in a study where only 8% of patients were able to accurately report the size, number, and pathology of polyps removed after colonoscopy. It is doubtful whether many patients would be able to accurately distinguish between a polyp and an advanced adenoma in a family member, creating a barrier to effective implementation of these new guidelines.

Most colorectal cancer cases with a familial component are referred for genetic evaluation because of the striking history of cancer affecting multiple family members, often at young ages. Although the clinical phenotypes of some of these families resemble those of known hereditary syndromes, such as Lynch syndrome or FAP, others appear to constitute distinct disease entities[43]. Families with a history of colorectal cancer that meet Amsterdam Criteria originally were referred to as hereditary nonpolyposis colorectal cancer to distinguish

them from those with polyposis phenotypes[44-46]. After the discovery of the role of MMR gene mutations in the pathogenesis of Lynch syndrome, hereditary nonpolyposis colorectal cancer families could be subdivided based on whether their colorectal cancer tumours had MMR-deficient or MMR-proficient phenotypes[45, 46]. Amsterdam Criteria families with MMR-proficient tumours have been found to differ from Lynch syndrome families in a number of ways, as follows: firstly, affected individuals tend to develop colorectal cancer at slightly older ages; second, risks for extracolonic tumours do not seem to be increased; third, risk for colorectal cancer among relatives is increased by only 2-fold[43]. The difficulty in identifying genes implicated in familial colorectal cancer has led some to suspect that it may not be a mono-genic condition but rather a multi-genic condition resulting from the interaction of several gene variants[47]. Another possibility is that epigenetic events that affect expression of oncogenes and tumoursuppressor genes, rather than specific gene mutations themselves, may have a role in carcinogenesis[48].

2.1.3 Hereditary colorectal cancer syndromes

Lynch syndrome is the most common of the hereditary colorectal cancer syndromes and has been implicated in 2% to 4% of colorectal cancer cases. It is characterized by a predisposition to develop colorectal, endometrial, and selected other cancers, which often arise at young ages[34]. Affected families frequently include multiple relatives with cancer and display an autosomal-dominant pattern of inheritance. More than 90% of Lynch-associated colorectal cancer tumours show phenotypes of high DNA microsatellite instability (MSIH) and loss of expression of DNA mismatch repair (MMR) proteins MLH1, MSH2, MSH6, or PMS2 by immunohistochemistry[35]. Familial adenomatous polyposis (FAP) is the second most common of the inherited colorectal cancer syndromes and accounts for approximately 1% of newly diagnosed colorectal cancer cases[36]. In 90% of classic FAP cases, germline mutations in the adenomatous polyposis coli (APC) gene can be detected through clinical genetic

testing. Although FAP is associated with autosomal-dominant inheritance, approximately 30% of affected individuals report no family history of the disease[37-39]. In cases of classic polyposis, the phenotype of hundreds to thousands of adenomatous polyps in the colon makes FAP easily recognizable[37]. Hamartomatous polyposis, defined as more than 3 to 5 hamartomatous polyps in the gastrointestinal tract, is implicated in less than 0.5% of all colorectal cancer cases[40]. Peutz–Jeghers syndrome (PJS) is characterized by multiple intestinal hamartomatous polyps. Mutations in the serine threonine kinase 11 (STK-11 also known as LKB-1) tumour-suppressor gene involved in the mammalian target of rapamycin pathway have been found in approximately 50% to 70% of PJS patients[41]. Juvenile polyposis syndrome (JPS) is characterized by multiple (3–5) juvenile polyps and increased risk for gastrointestinal cancers. Mutations in the *SMAD4* and *BMPR1A* genes are found in approximately 50% of individuals with a clinical diagnosis of JPS[42].

2.1.4 Risk factors of colorectal cancer

Most colorectal cancers cannot be attributed to any single risk factor, although age and male growth have been shown to be closely related to disease incidence in epidemiological studies [49]. Observational studies have identified several risk factors associated with an increased risk of colorectal cancer, including: lifestyle factors (obesity, physical inactivity, smoking, heavy alcohol use) and non-modifiable factors (aging, personal and family history of colorectal cancer or adenoma) [22]. The summary of risk factors of colorectal cancer was listed in the **Appendix 2.** recommended by American Cancer Society.

Age

The incidence of colorectal cancer increases from the age of 40, but is relatively low before the age of 50, and then accelerates rapidly. By the age of 80, the proportion seems to double every decade.

Sex

A meta-analysis of 17 studies involving 924,932 patients showed that the risk of advanced colorectal cancer was significantly higher in men than in women in all age groups (relative risk 1.83 (95% CI 1.69-1.97) [50].

Diet

Diet is one of the lifestyle factors that affects the risk of developing colorectal cancer in many ways. Many case-control studies show an association between lowered risk of colorectal cancer and a higher intake of vegetables, fibre and possibly also fruit. A pooled analysis of 13 such case-control studies found that high intake of fibre was associated with a 50% lower risk of colorectal cancer.

Similarly, a meta-analysis conducted between six case-control studies reported that high intake of vegetables or fibre was associated with a reduced risk of approximately 40%-50% for colorectal cancer. Large amounts of red meat consumption have also been found to increase colorectal cancer risk in many epidemiologic studies.[29]

A prospective study following a cohort of male health professionals in the United States found that men who ate red meat as a main dish more than five times a week had a 3-fold increase in risk of developing colorectal cancer compared to men who ate red meat less than once a month.[29]

Smoking

A meta-analysis of 28 prospective studies and 146,3796 subjects showed that regular smokers were 20% more at risk than non-smokers (95% CI 1.10-1.30) [51]. Another meta-analysis of 106 observational studies showed that the risk of colorectal cancer was 18% (95% CI 1.11-

1.25) higher in former smokers than in non-smokers; the risk of colorectal cancer was 7-11% higher in every 10 daily smokers [52].

Alcohol

Although the relationship between alcohol and cancer is slightly controversial, most evidence suggests that heavy drinking increases the risk of colorectal cancer [53]. A large prospective cohort study in the United States showed that heavy drinking increased the risk of colorectal adenomas [54].

Many studies have regularly shown that overweight is associated with an increased risk of colorectal cancer. A meta-analysis of 56 case-control and cohort studies included about 7 million people, including about 90,000 colorectal cancer patients. [55]. The results showed that as BMI categories increased for individuals, so did the risk of colorectal cancer [55].

Physical activity

The relationship between higher levels of physical activity and reduced colorectal cancer risk has been observed between studies [56, 57]. Although it could be reasoned that a lifestyle that is very physically active is usually associated with making other healthy lifestyle choices, many study characteristics show that high levels of physical activity directly prevent colorectal cancer[56, 57]. This is due to the association being reported consistently across many studies that vary in design, population, gender and use statistical methods to control for other lifestyle factors [58, 59]. According to a meta-analysis of 52 studies, people who were physically active had a 20 to 30 percent lower risk of colorectal cancer than those who were less active [60].

Personal history of colorectal cancer

People with a personal history of colorectal cancer are at higher risk. Individuals with a family history of colorectal cancer or adenoma, various hereditary polyposis and nonpolyposis syndromes, other cancers, and inflammatory bowel disease also have a higher risk of colorectal cancer. However, it should be noted that most patients do not have identifiable genetic risk factors.

2.2 Burden of colorectal cancer

2.2.1 Colorectal cancer in the world

Colorectal cancer is the third most common cancer in the world, with the second highest mortality rate. In 2018, there were more than 1.8 million new cases and 881,000 deaths worldwide, accounting for about one tenth of cancer cases and deaths [1]. The regions with the highest incidence of colon cancer are parts of Europe (such as Hungary, Slovenia, Slovakia, the Netherlands and Norway), Australia / New Zealand, North America and East Asia (Japan and the Republic of Korea, Singapore), with Hungary and Norway ranking first among men and women, respectively. There has also been an increase in the proportion of men to women in Uruguay. The incidence of rectal cancer has a similar regional distribution, although the Republic of Korea has the highest incidence among men and Macedonia has the highest incidence among women. In most parts of Africa and South Asia, the incidence of colon and rectal cancer is very low. (Detailed information can be shown in **Figure 2.**)

The incidence of colorectal cancer has changed a lot. The incidence of colorectal cancer and rectal cancer around the world are 8 times and 6 times, respectively. Assess the trend of incidence and mortality, Arnold et al [2] identified three different global patterns of colorectal cancer incidence and mortality associated with development levels: 1) increase in incidence and mortality in the last decade (including Baltic States, Russia, China and Brazil, which were previously low but are now high); 2) increase in incidence but decrease in mortality (Canada, UK, Denmark And Singapore); and 3) reduced morbidity and mortality (United States, Japan and France).

The increase in incidence may be due to intergenerational changes in risk factors such as diet patterns, obesity and lifestyle factors, while the decrease in incidence in the more developed

countries reflects the improvement in survival in the developed countries through the adoption of best practices in cancer treatment and management. Longer term screening and early detection programs, such as those implemented in the United States and Japan in the 1990s have also had an impact [64].

Because some risk factors for colorectal cancer, such as BMI and diet, may be more common in Western societies, the high incidence of colorectal cancer in these countries may reflect a westernized lifestyle.

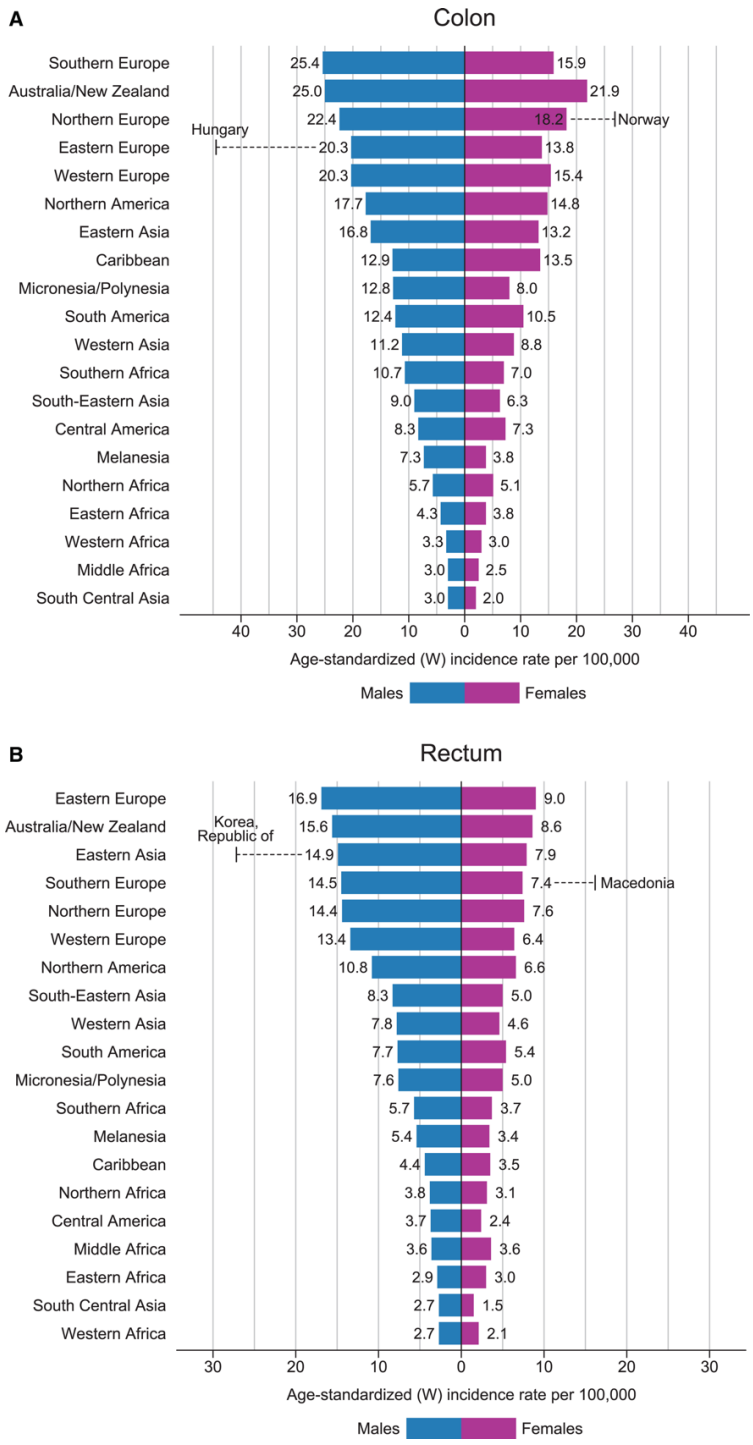

Figure 2. Region-Specific Incidence Age-Standardized Rates by Sex for Cancers of the (A) Colon and (B) Rectum in 2018.[2]

[2] Rates for colorectal cancer are shown in descending order of the world age-standardized rate. Source: GLOBOCAN 2018.

2.2.2 Colorectal cancer in Asian countries

In this thesis, Asia is defined according to the list of sovereign states and dependent territories in Asia by United Nation. Asia includes 48 countries and 6 states with limited international recognition. The population in Asia is 4.436 billion in 2016, accounting for 60% of world's population (7.480 billion). While most of Russia's area is in Asia, it is generalized as being in Europe since most of its population are in Europe. In the thesis, United Nations geoscheme for subregions of Asia was followed, including Central Asia, East Asia, Southern Asia, South-eastern Asia, and West Asia (Details of the subregion countries can be shown in **Appendix 1)**.

The incidence trend of colorectal cancer in the world is quite different. The incidence of colorectal cancer is historically low in some Asian countries, such as Japan, Israel, Singapore, China and Philippines are experiencing rising incidence rates [3]. Currently, the highest colorectal cancer incidence rates are observed in both men (62 per 100,000 person) and women (37 per 100,000 person) from Japan (Miyagi Prefecture Cancer Registry). In some developed countries, such as Singapore, Japan and South Korea, the burden of colorectal cancer has increased rapidly; in the past decades, the incidence of colorectal cancer has increased 2-4 times [65]. In 2012, the incidence of colorectal cancer per 100000 men in Japan and South Korea was 89.1 and 69.5 respectively, compared with 50.6 in Singapore [66]. In Taiwan and some parts of mainland China, the incidence of colorectal cancer is also increasing [67]. According to the National Cancer Database of China in 2003, colorectal cancer is one of the three most rapidly growing cancers in China in the past 20 years [68]. However, there is a lack of data on colorectal cancer incidence trends in India, Indonesia, the Philippines,

Vietnam and the Middle East (The colorectal cancer incidence annual change in Asian countries can be shown in **Figure 3.**). The increase in colorectal cancer incidence seems to be related to the westernized lifestyle and eating habits, which may be the result of high fat, high protein and low fiber diet intake.

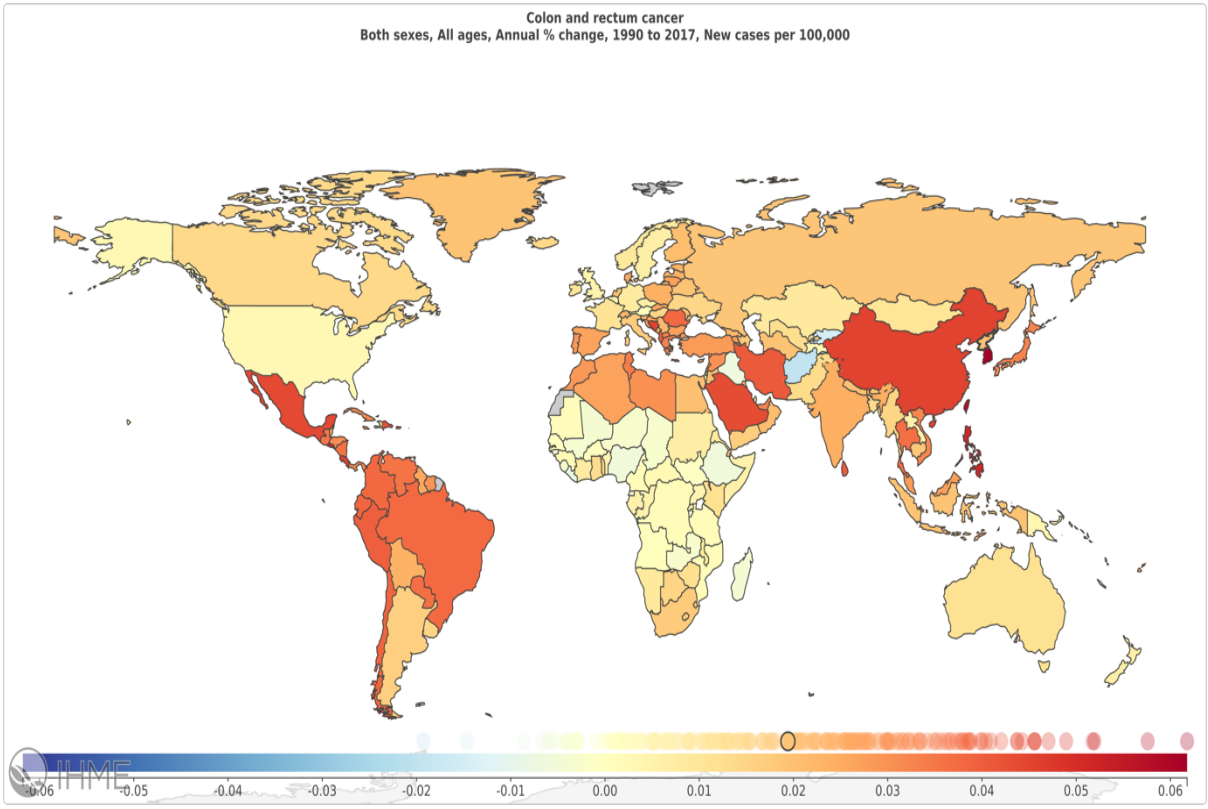

Figure 3. Colorectal cancer incidence annual percentage change, 1990-2017[3]

[3] Compiled from Institute for Health Metrics and Evaluation, GBD 2017, University of Washington. http://ihmeuw.org/4rvr

Although in the West, colorectal cancer mortality is declining (2.7% per year for men and 2.5% per year for women) [69], mortality continues to rise in Asia. According to the WHO mortality database, the mortality rate of colorectal cancer in Taiwan has doubled in the past 30 years [67], while the Korean National Cancer Center reported a 35% increase in colorectal cancer-related mortality in men and women [70]. Among urban and rural men in China, age-adjusted colorectal cancer mortality increased slightly [71]. However, there was no consistent time trend in colorectal cancer mortality observed in Japan and Hong Kong [72]. Some ethnic groups in Asia (such as Japanese, Korean and Chinese) are more likely to suffer from colorectal cancer. In multi-ethnic countries such as Malaysia and Singapore, the incidence of colorectal cancer in Chinese is significantly higher than that in Malays or Indians [73]. In addition, the Asia Pacific Working Group on colorectal cancer also found that people in Japan, South Korea and China have a higher risk of cancer [74, 75]. These observation present a comprehensive demonstraction of the important roles of genetic factors, ethinic culture and health resource availability in development of colorectal cancer.

The rising trend of incidence of colorectal cancer is observed in the Asia countries, however, there is a wide geographical variation in the country-specific incidence within the different Asia region. We can see a heterogeneous incidence pattern across different countries in Asia (Details of the heterogeneous incidence can be shown in **Figure 4.**). In Japan, Israel and Singapore, the incidence of colorectal cancer is much higher than that in Thailand and China and Philippine, reporting stable low incidences. The reasons for these heterogeneous incidence pattern in Asian countries are unknown.

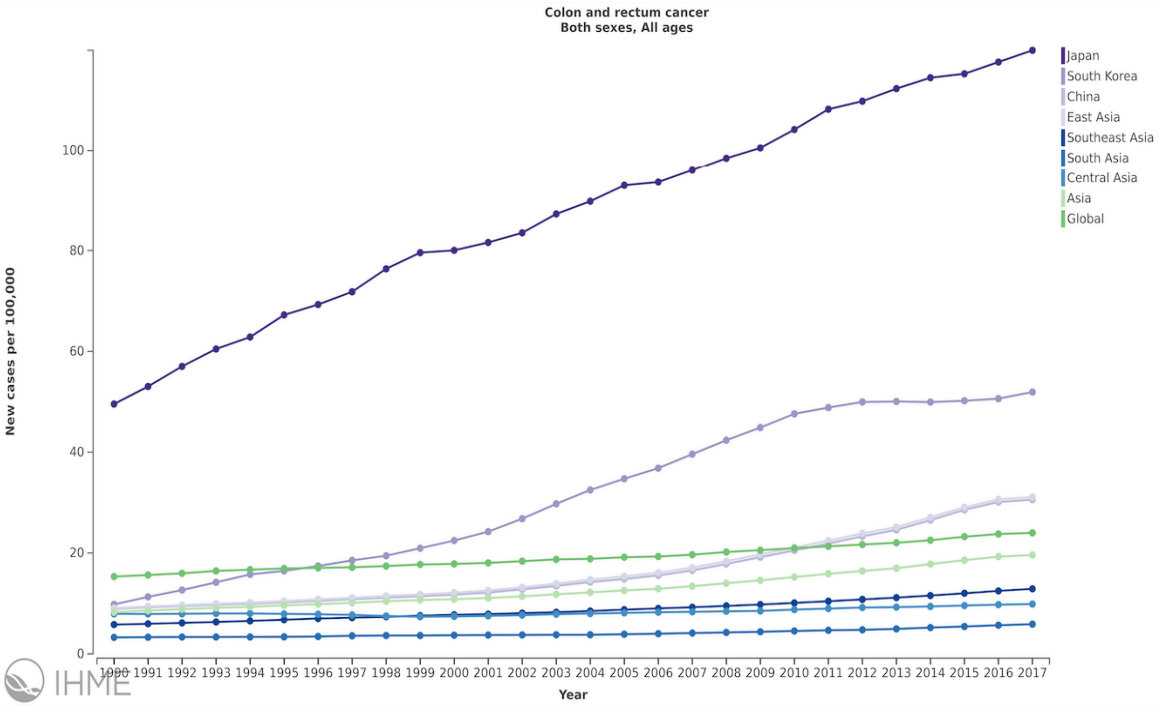

Figure 4. Colorectal cancer incidence trends, select countries, 1990-2017[4]

[4] Compiled from Institute for Health Metrics and Evaluation, GBD 2017, University of Washington. http://ihmeuw.org/4rvq

2.3 Family history of colorectal cancer

2.3.1 What is family history?

According to the definition of National Human Genome Research Institute: A family history is a record of medical information about an individual and their biological family.

Family history of colorectal cancer is a major risk factor for the development of colorectal cancer to a large extent, because up to 20% of other family members of colorectal cancer cases are affected by the disease. Those with a family history of colorectal cancer were twice as likely to be diagnosed as those without. The degree of personal risk depends on the number of affected relatives, the age of affected family members and the degree of intimacy of relatives.

2.3.2 What is familial aggregation?

Familial aggregation means that the relatives of persons with the trait are at increased risk of the trait. Many diseases and physical and health-related conditions have familial aggregation.

A measure of its strength, the familial risk ratio, is the risk for relatives of affected probands divided by the risk for relatives of unaffected probands. The familial risk ratio depends on a number of factors but, for first-degree relatives the risk is often in the range 1.5-2 for common diseases such as cancers, with higher values if the proband is affected at an early age, and sometimes higher values if the relative is a genetically identical twin

For familial aggregation to be manifest, there must be familial causes; that is, there must be at least some causes that are correlated between relatives, these can be due to shared genetics or shared environment. The effects of familial causes on familial aggregation depend on the complexity of the disease. For purely Mendelian conditions, the disease is present if and only if a specific genetic factor is present. The risk of disease depends on which relatives are affected and the mode of transmission (e.g. dominant and recessive), and there is usually no increased risk in the absence of any family history. For a complex disease, a genetic variant that greatly increases disease risk may contribute little to familial aggregation at the population level if that variant is rare. The same is true for common variants with moderate effects on risk; each variant explains only a small fraction of the disease and a small fraction of familial aggregation in the population.

2.3.3 Why is family history important?

Studying the risk of relatives with disease (affected proband) compared with relatives without disease (unaffected proband) can reveal important information about the possible causes of the disease. Without a strong potential family risk factor, even a moderate increase in the risk of relatives cannot exist. Studying the risk of relatives (including twins), as a function of the strength of genetic, environmental and cohabitation relationships with probands, can help to solve whether family risk factors may have genetic or environmental causes, the more so if specific genes and environmental exposures of one or more family members are measured.

Because only a small number of familial aggregations of colorectal cancer is explained by known genetic factors, there is a large space for us to expand our knowledge of disease aetiology by studying the information available through the risk of relatives.

2.3.4 How do we define first- and second-degree relative family history?

According to definition of National Human Genome Research Institute: A first-degree relative (FDR) is a family member who shares about 50 percent of their genes with a particular individual in a family. First degree relatives include parents, offspring, and siblings.

According to National Cancer Institute Dictionary of Genetics Terms: A second-degree relative (SDR) is someone who shares 25 percent of a person's genes. It includes uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings, and double cousins [76].

2.3.5 Why is first-degree family history of colorectal cancer important?

First degree relative family history has a reliable association with risk of colorectal cancer from Western countries [23]. Most family history is collated via self-report questionnaires, it is most reliable for a person to remember whether their parent, sibling, and children have colorectal cancer. There is a study by Taylor et al [23], using Utah population database, which assessed the risk of colorectal cancer based on various combinations of family history concluded that the number of first-degree relatives is the most important predictor of risk [23]. The study reported that for first degree relatives, the relative risk is of colorectal cancer increases about 2 fold; for two first degree relatives, the relative risk is increased about three fold; for three first degree relatives, the relative risk is increased about four fold; for four first

degree relatives, the relative risk is increased to around eight folds; for five and more first degree relatives, the relative risk is quite high at 20 fold.

2.3.6 Prevalence of family history of colorectal cancer in different populations

The lifetime risk of developing colorectal cancer in the general population is about 6%, but for people with a family history of colorectal cancer (FH), the risk is considered much higher. It is estimated that up to 10% of American adults have first degree relatives (FDR) who have been diagnosed with colorectal cancer, and about 30% have affected FDR or second-degree relatives (SDR).

2.3.7 Key points in measuring family history

- Family history is largely obtained based on a questionnaire or interview of people, in rare case, family linkage studies has been possible (e.g. Taylor study), but most other cases, are impossible.
- Accuracy of questionnaire-based family history depends on the closeness of relative, culture taboo (communication between relatives, health literacy of the people being asked the question, a doctor may not explicitly communicate with the diagnosis, is this particularly the case in Chinese families)
- These factors affect the accuracy of family history measures (the proportion of family history that is reported in the survey)

2.4 Screening of colorectal cancer

2.4.1 What is screening?

Screening for colorectal cancer is widespread in the Western world, and the aim of the screening is both to reduce colorectal cancer incidence and mortality. The screening may have a substantial impact on population health. Apart from screening, other possible explanations for the observed decline could be changes in lifestyle factors that are correlated with colorectal cancer, for example, alcohol drinking, smoking, obesity, diabetes, and a higher level of cancer awareness and advanced treatment.

In the current context, screening can be defined as exposing asymptomatic individuals to a test aimed at detecting a specific undiagnosed disease, or to detect individuals with a high probability of getting the disease. Screening for medical conditions can principally be organized in two ways: The first is opportunistic screening, where individuals on self-prompted request, or after consulting their primary care physician, are referred for testing. This is the most common approach for cancer screening in the US. The other approach is population-based screening, where people are systematically invited to testing in a screening program. Such screening program are usually publicly or nationally funded, the advantage is that all eligible individuals have equal access to the screening program.

Several high-quality randomized controlled trails (RCT) have shown that colorectal cancer screening significantly reduces the incidence and/or mortality of colorectal cancer [8-17].

The predominant tools used for colorectal cancer screening are fecal occult blood testing (FOBT), flexible sigmoidoscopy and colonoscopy.

However, screening is not a single test or examination; on the contrary, it involves the process of population participation, clinical diagnostic examination, treatment of tumour detection and regular monitoring. In addition, the screening of drugs with measurable indicators is indispensable to ensure their quality and maximize the effectiveness of the whole program.

Colorectal cancer screening is widely used in Western population. The purpose of cancer screening is to reduce the incidence of colorectal cancer and mortality by detecting and removing polyps. And some countries in Asia have already implemented colorectal cancer screening [11], most Asian countries lack screening. Therefore, the generality of these findings is still uncertain. This was confirmed by a randomized controlled trial (RCT), which laid the foundation for international guidelines for colorectal cancer screening and showed that screening can significantly reduce the incidence and/or mortality of colorectal cancer [8-17]. However, despite these recommendations, screening is currently only available to a small proportion of the target population. The predominant tools used for colorectal cancer screening are fecal occult blood testing (FOBT), flexible sigmoidoscopy and colonoscopy.

The question will become: if screening works as it detects and removes polyps, who should be screened?

Mutations in intestinal mucosal cells lead to development of adenomas, the most common colorectal cancer precursor. A series of further mutations lead to development of invasive

colorectal cancer in a small proportion of adenomas. Treatments that interact with the cancer development (such as removal of adenomas) may prevent cancer occurrence. For most cancers there is a time lag before giving rise to symptoms. This period of asymptomatic malignant disease is the potential window for early detection of cancers.

Endoscopy includes flexible sigmoidoscopy and combined nasal endoscopy. Both are basically the same test, except for the flexible sig examination, which only examined the rectum and distal part of the colon (sigmoid colon), while colonoscopy examined the rectum and the entire colon.

Endoscopic colorectal cancer screening may prevent cancer by removing precursor lesions (adenomas).Hence, colorectal cancer mortality can be reduced both by beneficial treatment options after early detection of cancers, and by a lower incidence of colorectal cancer due to adenoma removal. Both flexible sigmoidoscopy and colonoscopy use the same technical equipment, and both enable direct inspection of the intestinal mucosa, biopsy sampling, and adenoma removal in the same procedure. Compared to colonoscopy, flexible sigmoidoscopy is less resource demanding. Bowel preparation for flexible sigmoidoscopy can usually be done at the screening centre using an enema that cause little discomfort compared to the rigorous per-oral regimens that are needed prior to colonoscopy.

2.4.2 Organized vs. opportunistic screening

An organized screening program includes a systematic process of inviting the target population to participate in the screening and ensuring follow-up to the screening positive. An organized plan should measure and report on the quality of each step in the screening process.

The IARC outlines the following elements for organised screening programs:

- Clearly define the policy of age category, screening method and screening interval
- A defined target population
- A management team responsible for implementation
- A medical team responsible for determining, caring for and tracking patients undergoing positive screening tests
- A quality assurance structure for every step in the process
- A process for monitoring, evaluating and identifying cancer occurrence in the population.

In organized screening, a large amount of information technology infrastructure is needed to support the program, including invitation, recall, re care, tracking screening results, systems to ensure that clinical results such as cancer incidence, mortality and staging are tracked and tracked. In order to track the results of the screening, a set of universal measures and indicators for colorectal cancer screening has been established. 15 cancer registries are vital and can be linked to all other relevant databases, including laboratories and endoscopy centres.

In contrast, opportunistic screening is carried out outside the organized screening plan, usually through the reimbursement of doctors' service expenses. Because the organized screening focuses on quality assurance, it provides greater protection for the possible harm of screening, including over screening and under screening, low-quality screening, improper use of resources, complications caused by screening and poor follow-up for positive screening. In the United States, screening methods are basically opportunistic. The contribution and quality initiatives of many national institutions are critical, including the United States Preventive Services Task Force (USPSTF), an independent volunteer group of national experts in prevention and evidence-based medicine, which reviews evidence and makes recommendations to guide the selection of colorectal cancer screening trials. In addition, several professional associations emphasized the importance of colonoscopy quality in colorectal cancer screening.

2.4.3 Selection of Screening Modality

To choose the best screening method for organized screening, effectiveness and cost-effectiveness are equally important, because the allocation of public health resources is important.

Non-invasive stool tests

The premise for fecal occult blood testing (FOBT) to be effective is that invasive cancers in colon and rectum bleed, and that this blood can be detected by FOBT in the stool. Since tumours bleed intermittently, and the adenomas do not necessarily bleed, and because blood is degraded in the gastrointestinal tract, sensitivity of these tests, both with regard to colorectal cancer or adenoma, are less than perfect. To remedy the relatively low sensitivity, the tests need to be repeated, and annual and biennial testing is recommended. There are currently two screening methods in use to test for blood in the faeces: guaiac-based fecal occult blood tests (gFOBT) and immunochemical fecal occult blood test (iFOBT), the later also called fecal immunochemical test (FIT).

The ability of gFOBT-based screening to reduce incidence and mortality of colorectal cancer is extensively tested in long-term follow-up RCTs. A Cochrane meta-analysis for previous RCTs found that mortality from colorectal cancer was reduced by 16% after repeat testing, a 15% mortality for studies that used biennial screening, however, there was no effect on incidences of colorectal cancer. Fecal immunochemistry test (FIT) is perfomed in the same way as the gFOBT with less restrictions to drug or diet. FIT has better ability to detect early

colorectal cancer and late adenoma than gFOBT, and has also proved its effectiveness in reducing mortality of colorectal cancer in Taiwan colorectal cancer screening program [77].

In the Asian population screening project, FOBTs is non-invasive, cheap and easy to use. It is the most widely used colorectal cancer screening tool in the world. Positive FOBT needs to be followed up under colonoscopy for final diagnosis based on biopsy or adenomaectomy.

Invasive imaging techniques

Sigmoidoscopy: The effectiveness of sigmoidoscopy in reducing the incidence and mortality of colorectal cancer has been confirmed by previous randomized controlled trials, but due to the limitations of the scope of examination, its protective effect is limited to the distal colon and rectum [12].

Colonoscopy: The detection rate of colorectal cancer by colonoscopy is higher (invasive cancer > 95%, advanced adenoma > 90%), and it can remove non-invasive tumour. While randomized trials have shown flexible sigmoidoscopy to be less effective for reduction of proximal than distal CRC mortality[78-81], observational colonoscopy studies also suggest differences in effectiveness by location[82, 83].

Comparison of sigmoidoscopy and colonoscopy

Both colonoscopy and sigmoidoscopy can detect and remove polyps, potentially preventing malignant transformation and decreasing colorectal cancer incidence and mortality, and can also provide early detection of asymptomatic cancers, which might further decrease

mortality. Because colonoscopy can examine the entire colon, its effectiveness in reducing mortality is hypothesized to be superior to that of flexible sigmoidoscopy, which only directly examines the distal colon[84]. Although colonoscopy has a greater effect in reducing the mortality and morbidity of colorectal cancer, its high cost, strong invasion, low staffing and facilities requirements, low screening level and low public acceptance (especially the Asian population) limit its use as the main screening method in the region. [78-83]Some of the complications that can occur during bowel preparation of colonoscopy include perforation, bleeding, postpolypectomy syndrome, reaction to anesthetic, and infection[85]. Studies estimate the risk of complications for colonoscopy to be low, about 1.6%[86].

2.4.4 Colorectal cancer screening: the earlier the better?

The 2018 updated guideline for colorectal cancer screening by American Cancer Society (ACS) moved the starting age for screening from 50 years old to 45 for average-risk adults. The guideline recommended regular screening with FIT test or highly sensitive guaiac-based FOBT every year) or a structural examination (e.g. colonoscopy every 10 years, or CT colonography or flexible sigmoidoscopy every 5 years), according to the preference of patients and the effectiveness of the examination, patients with positive results of non colonoscopy should be examined in time.

The lower starting age of screening reflects people's understanding of the rising incidence of early colorectal cancer. Although the incidence and mortality of colorectal cancer in the U.S.

population over 50 years of age have declined over the past 20 years, the incidence of colorectal cancer in the population under 50 years of age has increased by 51% since 1994.

2.4.5 Why family history is important in the colorectal cancer screening?

A family history of colorectal cancer means that a person may be several times more likely to have colorectal cancer than a person without a family history. However, family history itself is not a good predictor of colorectal cancer, as the increased risk is applied to the very low average risk of colorectal cancer (about 5% of the risk for lifetime), resulting in a still low absolute risk of family history. However, family history can be used to classify people without colorectal cancer diagnosis or symptoms into risk categories in which the number of colorectal cancer or adenomas is expected to be high enough to require more in-depth screening than the general population. Based on this, the current practice in Australia and many other countries is to conduct more intensive or frequent screening for those with a strong family history. Most screening guidelines recommend a biennial fecal occult blood test (FOBT) or a 10-year minimum risk colonoscopy, a 5-year medium risk colonoscopy, and a yearly or biennial maximum risk colonoscopy, including patients with high-risk family syndrome. Most screening guidelines recommend starting at age 50 for all risk categories, or 10 years before the minimum age for colorectal cancer diagnosis in relative.

2.5 Current colorectal cancer screening in Asian countries

2.5.1 Definition of Asian countries

For this study, we defined Asia according to the "List of sovereign states and dependent territories in Asia" by the United Nation (https://unstats.un.org/unsd/methodology/m49/), in which Asia includes 48 countries and 6 states with limited international recognition. According to the United Nations geoscheme, Asia consists of five subregions: Central Asia, East Asia, Southern Asia, South-eastern Asia and West Asia (see **Appendix 1** for the counties included in each subregion). These subregions were used for this meta-analysis.

2.5.2 Why Asian countries?

Due to the differences in race, diet, lifestyle and economic development level, there are significant differences in the incidence and mortality of colorectal cancer in Asian countries. As the latest updated age standardized incidence of colorectal cancer is more than 30/100,000, the implementation of population screening is reasonable. In Asian countries with high incidence and mortality of colorectal cancer, including Japan, South Korea, Singapore and Taiwan, population-based screening programs have been launched to combat this devastating disease. The incidence of colorectal cancer is also rising in other parts of Asia, especially in economically developed urban areas, and the demand for screening is also increasing.

2.5.3 Colorectal cancer programs in Asian countries

In some countries in Asia, the incidence and mortality of colorectal cancer is increasing rapidly. However, screening guidelines are lacking and the best screening methods in Asia are still unclear. Public awareness of the screening and prevention of this new disease is low, and health authorities provide little support. In most Asian countries, colorectal cancer screening should be a national health priority. Research on screening barriers, public education and participation of family doctors are important strategies to promote colorectal cancer screening. With more healthcare support, increased public acceptance, and better access to the general population, colorectal cancer screening in Asia can effectively improve outcomes. The following table shows the screening program for colorectal cancer in Asia (**Table 1.**)

Table 1. The screening program of colorectal cancer in Asian regions.

Region/Country	ASRi	ASRm	Region(s)	Programme type	Type of screening test	Starting year	Age range (years)	Screening interval (months)
East Asia								
China	14.2	7.4						
			Hong Kong	Organised	gFOBT/Colonoscopy	2003	50+	
			Several including Shanghai and Hangzhou regions	Organised	gFOBT/DRE+Colonoscopy	2008	40–74	
Korea, South	45	12	All	Organised	FIT	2004	50+	12
Japan	32.2	11.9	All	Organised	iFOBT every 1 year from 40 years. National screening program	1992	40+	12
Mongolia								
Korea, North	21.8	10.7		Unknown				
Taiwan			All	Organised	FIT	2004	50–74	
South-Eastern Asia								
Singapore	33.7	11.8	All	Organised	FIT		50+	12
Thailand	12.4	7.3	Lampang Province	Organised	iFOBT every 1 year with APCS. National screening program (under consideration)	2011	50–65	
West Asia								
Israel	35.9	11.1	All	Organised	FIT	1990	50–74	12
Jordan	25.6	15.5		Opportunistic	gFOBT/FIT/Colonoscopy		50+	
Southern Asia								
Central Asia								

Abbreviation: ASRi, age-standarded rate-incidence; ASRm, age-standarded rate-mortality; gFOBT: guaiac faecal occult blood test; FIT: faecal immunochemical test.

2.5.4 Risk stratification in colorectal cancer screening

The current screening recommendations do not differ between age, gender and ethnic groups, but the results vary according to these characteristics. In Western and Asian Studies, the incidence of age adjusted colorectal cancer and advanced adenomas was higher in men than in women [87]. The prevalence of colorectal cancer increases with age. Colonoscopy in Asia showed a threefold increase in the risk of advanced cancer after age 50. Guidelines in most countries recommend starting screening at the age of 50. Other risk factors for colorectal cancer include family history, smoking, obesity, and metabolic syndrome. The risk of colorectal cancer in the first-degree relatives of patients with colorectal cancer was doubled [21]. Siblings of subjects with advanced tumours also had a fourfold increased risk of advanced tumours, suggesting that screening was important in these high-risk groups.

Smoking increases the risk of colorectal cancer. The relationship between smoking and colorectal cancer has been confirmed in Asian Studies [87]. The risk appears to be dose-related, with men and rectal cancer at greater risk [88].

Asia is a region of different populations. It is advisable to develop a risk stratification strategy based on age, gender, race and family history to identify the population with the highest risk priority in the screening program. In a prospective multicenter study of 11 Asian cities, risk scores based on age, gender, family history, and smoking (Asia Pacific colorectal screening score) were used to select asymptomatic Asian subjects for colorectal screening. The prevalence of advanced tumours in subjects in the moderate and high risk groups was 2.6 and 4.3 times higher than that in the average risk group [89]. The risk score is currently

undergoing large-scale validation and may prove to be an important tool to make full use of the limited resources of many Asian countries.

2.5.5 Challenges of colorectal cancer screening in East Asia

Despite the rise in the incidence of colorectal cancer, public awareness is low in many Asian countries. Only a small number of people at risk are screened for perceived health, exposure, and mental disorders [90]. In particular, men over the age of 50 do not know the symptoms of colorectal cancer and the benefits of screening, according to a population survey. Even primary care doctors have a low and insufficient understanding of the disease. New data show that knowledge and awareness bring greater screening intent. Doctors' screening recommendations have been shown to increase the likelihood of screening by a factor of 21 [90]. Resource and cultural interventions are recommended to improve the overall screening participation rate. It is necessary to carry out language and cultural education programs, involving doctors and the media, to improve colorectal cancer screening [91]. In the Hong Kong study, FOBT and colonoscopy were also superior to Chinese. Colonoscopy was the first choice among young patients with family history of colorectal cancer and poor self-reported health [92].

In addition, due to limited resources, the actual screening rate in many Asian countries is still very low. The national health system and medical insurance are only available to a few people. In many rural areas and communities with low socio-economic status, access to medical facilities is limited [65]. In addition, there is limited government support for colorectal cancer screening in Asian countries. Lack of financial support is considered a major obstacle to screening.

Taiwan provides free mass screening for colorectal cancer under the national health insurance program. The Korean government bears 50% of the cost of colorectal cancer screening, and 100% of them are low-income people. There are no formal screening programs in other Asian countries. In the United States, the United Kingdom and Canada, nurses are running flexible sigmoidoscopy procedures to speed up screening and reduce endoscopy. There are currently no such schemes in Asia, in part because of the lack of support from the medical and Nursing Committee, third-party reimbursement, accountability issues and lack of policies [87]. Under the circumstances of vigorous economic development, it is the mentality and current institutional arrangements as well as the lack of resources that are not conducive to the introduction of screening programs. The high rate of out of pocket medical expenses and the poor organization of primary health care make it difficult to organize population plans in the Asia Pacific region.

There are some countries in Asia that have already implemented colorectal cancer screening [11]. However, colorectal cancer screening guidelines are still lacking in most of Asian Countries, and the optimal screening method in Asia countries remains unclear.

2.6 Current research of family history and colorectal cancer

2.6.1 Family history and the risk of colorectal cancer in Western populations

About 85% of colorectal cancer cases occur in individuals considered to be at average risk, while 15% of colorectal cancer patients belong to known high-risk groups, such as patients

with a family history of colorectal cancer or rare genetic syndrome, such as FAP and Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer syndrome). Currently, there are several colorectal cancer screening guidelines of Western countries use family history information to define risk categories in the population and recommend specific screening intensity strategies for individuals at familial risk for colorectal cancer. Seven organizations from U.S. and one from Australia and Europe were identified for currently provided guidelines for colorectal cancer screening for persons with family history of colorectal cancer (**Table 2**).

Table 2. Summary of colorectal cancer screening guidelines currently used in some Western countries

Country	Organization	Family History	Recommendation
US	**ACS** [10]	1 FDR with CRC or adenoma at <60 y or ≥2 FDRs at any age	Start colonoscopy at 40 y or 10 y before earliest CRC (whichever is earlier); repeat every 5 y.
		1 FDR with CRC or adenoma at ≥60 y or ≥2 SDRs with CRC at any age	Start screening at 40 y (any modality); repeat as average risk.
	NCCN[8]	1 FDR with CRC at <60 y or ≥2 FDRs with CRC at any age	Start colonoscopy at 40 y or 10 y before earliest CRC (whichever is earlier); repeat every 5 y.
		1 FDR with CRC at ≥60 y	Start colonoscopy at 50 y or 10 y before earliest CRC; repeat every 5–10 y.
		1 SDR at <50 y	Start colonoscopy at 50 y; repeat every 5–10 y.
		1 FDR with advanced adenoma	Start colonoscopy at 50 y or at the age of adenoma (whichever is earlier); repeat every 5–10 y.
	USMSTF [15]	1 FDR with CRC or adenoma at <60 y or ≥2 FDRs at any age	Start colonoscopy at 40 y or 10 y before earliest CRC (whichever is earlier); repeat every 5 y.
	(including AGA, ACS, and ACR)	1 FDR with CRC or adenoma at ≥60 y or ≥2 SDRs with CRC at any age	Start screening at 40 y (any modality); repeat as average risk.
	ACG [14]	1 FDR with CRC or advanced adenoma at <60 y or ≥2 FDRs with CRC or advanced adenoma	Start colonoscopy at 40 y or 10 y before earliest CRC; repeat every 5 y.
		1 FDR with CRC or advanced adenoma at ≥60 y	Start colonoscopy at 50 y; repeat every 10 y.

	ASGE [16]	1 FDR with CRC or adenoma at <60 y	Start colonoscopy at 40 y or 10 y before earliest CRC; repeat every 3–5 y.
		1 FDR with CRC at ≥60 y	Start colonoscopy at 40 y; repeat every 10 y.
		1 FDR with adenoma at >60 y	Start colonoscopy (age of initiation individualized); repeat every 10 y.
	ACP [15]	1 FDR with CRC or adenoma at <60 y or ≥2 FDRs at any age	Start colonoscopy at 40 y or 10 y before earliest CRC in family; repeat every 5 y.
	ICSI [9]	1 FDR with CRC or adenoma at <60 y or ≥2 FDRs with CRC or adenoma at any age	Start colonoscopy at 40 y or 10 y before earliest case in family; repeat every 5 y.
		1 FDR with CRC or adenoma at ≥60 y or ≥2 SDRs with CRC	No specific recommendation is supported.
Australia	**NHMRC[93]**	1 FDR or SDR age ≥55 y at diagnosis	FOBT every 1-2 y and consider sigmoidoscopy (preferably flexible) every 5 y from age 50 y Routine colonoscopy is not recommended
		1 FDR age <55 y at diagnosis or 2 FDR or 1 FDR and 1 SDR on the same side of the family, any age at diagnosis	5 yearly colonoscopy from age 50 y or 10 y younger than the age of first diagnosis of CRC in the family, whichever comes first
		Known or suspected familial syndrome	Known FAP or Lynch Syndrome (i.e. HNPCC): Specialist referral, as per NHMRC Guidelines; Suspected Lynch Syndrome: Every 1 or 2 y from age 25 y or 5 y younger than the youngest affected family member (whichever comes first)
Europe	**European Colorectal Cancer Screening Guidelines Working Group**[94]	In the absence of hereditary syndromes person with a positive family history should not be excluded from CRC screening programs	European countries have their separate national guidelines

Abbreviations: ACG, American College of Gastroenterology; ACR, American College of Radiology; ACS, American Cancer Society; AGA, American Gastroenterological Association; ASGE, American Society for Gastrointestinal Endoscopy; ACP, American College of Physicians; ICSI, Institute for Clinical Systems Improvement; CRC, colorectal cancer; FDR, first-degree relative; NCCN, National Comprehensive Cancer Network; SDR, second-degree relative. USMSTF; US Multi-Society Task Force (including AGA, ACS, and ACR); NHMRC: National Health and Medical Research Council

Screening tests such as FOBT and colonoscopy are effective in reducing colorectal cancer mortality by 33% and 56%, respectively [83, 95]. U.S. Preventive Services Task Force (USPSTF) [96, 97] recommends colonoscopy for patients at increased risk of colorectal cancer (personal history of colorectal cancer or adenoma; personal history of inflammatory bowel disease, including ulcerative colitis or Crohn's disease; family history of colorectal cancer or adenoma; known family history of hereditary colorectal cancer syndrome, such as Lynch's syndrome or FAP) The average colorectal cancer risk individual (who has no known genetic disease family history and is prone to colorectal cancer) has a history of inflammatory bowel disease, adenoma or colorectal cancer. The history of colorectal cancer in first-degree relatives will recommend a person who begins screening at the age of 40 [11], For these people, colonoscopy is the preferred screening method. Some American associations recommend that if colorectal cancer or adenomas are diagnosed before the age of 60, a five-year colonoscopy should be performed as a start of screening in the family of the youngest affected individual by age 40 or 10 [97-99]. USA and European screening guidelines for colorectal cancer recommend screening to start at 50 years old [12, 14, 18], The age at which the screening stopped has not been set. The USPSTF guidelines recommend that individuals aged 76-85 be considered individually, and they do not recommend screening for people aged 85 or older [96, 97]. European guidelines recommend stopping flexible sigmoidoscopy and colonoscopy at age 75, but to continue FOBT until the age of 80 years [94].

Although young-onset colorectal cancer raises the possibility of a hereditary component, hereditary syndromes only explain a minority of young-onset cases. There is evidence to suggest that young-onset colorectal cancer have a different molecular profile than late-onset

colorectal cancer[100]. While the pathogenesis of young-onset is well characterized in individuals with an inherited colorectal cancer syndrome, knowledge regarding the molecular features of sporadic young-onset colorectal cancer is limited[101]. While the incidence of late-onset colorectal cancer has been decreasing, mainly attributed to an increase in colorectal cancer screening, the incidence of young-onset colorectal cancer is increasing[100, 102]. Differences in the molecular biology of these tumours and low suspicion of colorectal cancer in young symptomatic individuals, may be possible explanations[101]. Initiating screening at an earlier age based on cancer family history is one of the primary recommended strategies for the prevention and detection of early-onset colorectal cancer, but data supporting the effectiveness of this approach are limited[103]. Therefore, understanding the molecular mechanisms of young-onset colorectal cancer can help us tailor specific screening and management strategies[103, 104].

2.6.2 Family history and risk of colorectal cancer in Asian population

There is evidence of a link between a family history of colorectal cancer and colorectal cancer and an increased risk of colorectal cancer. Four meta-analyses to assess the risk of colorectal cancer in people with a family history of colorectal cancer [19-22]. Results from these studies consistently show that the risk of a family history of colorectal cancer in at least one affected first-degree relative is about twice as high as in people without a family history of colorectal cancer, and the risk increases with the number of affected first-degree relatives [23]. However, most studies on the relationship between colorectal cancer family history and colorectal cancer risk are conducted in Western populations.

Epidemiological studies show that the incidence of colorectal cancer continues to rise in Asia [3]; however, in different Asian regions, there are wide geographical differences in the specific incidence of countries. Asia is heterogeneous, with colorectal cancer rates higher in Japan, Israel, and Singapore than in Thailand, China, and the Philippines. However, there is no large prospective cohort study to investigate the impact of family history on colorectal cancer in Asia. Therefore, a large-scale prospective study on the relationship between family history and colorectal cancer in Asian population is neede

2.6.3 Limitation of narrative family history

The patient's age, family size (which, if small, can mask recognition of a genetic mutation as the cause of cancer in a family), as well as the possibility of uncertain paternity, should be taken into account when interpreting a narrative history or results from a prediction tool.

2.7 Addressing gaps in the current research

Unlike many parts of Europe and North America, colorectal cancer incidence and mortality continue to rise in Asia [3]. The incidence of colorectal cancer becomes closer and surpasses comparing with Western countries. Due to several reasons, the association of family history of colorectal cancer and risk of colorectal cancer and adenoma might be different. First, comparing with Western countries, there is family structure in Asian countries. For example, the most remarkable difference is the nuclear family in China due to the "One Child Policy", introduced from 1978 and began to be formally stopped in 2015, the largest birth control campaign in the world. In the most of Asian countries, the average family size declines, as shown on **Figure 5**. The average size of family for 25 countries in Asia is becoming smaller from year 1980 to 2011. Japan's average family size has declined from 3.2 in 1980 to 2.4 in 2010, China from 4.41 in 1982 to 3.1 in 2010, and India from 5.1 in 1983 to 4.7 in 2004 [105]. For these individuals who have no siblings, we do not know that whether the family history still a risk factor associated with colorectal cancer or adenoma. On the other hand, Environmental exposures are likely to be different in Asian countries compared with Western countries. Because family history both encompasses genetic and environment factors. In this situation, whether we could include family history of colorectal cancer in the colorectal cancer screening guideline in Asian countries is a question.

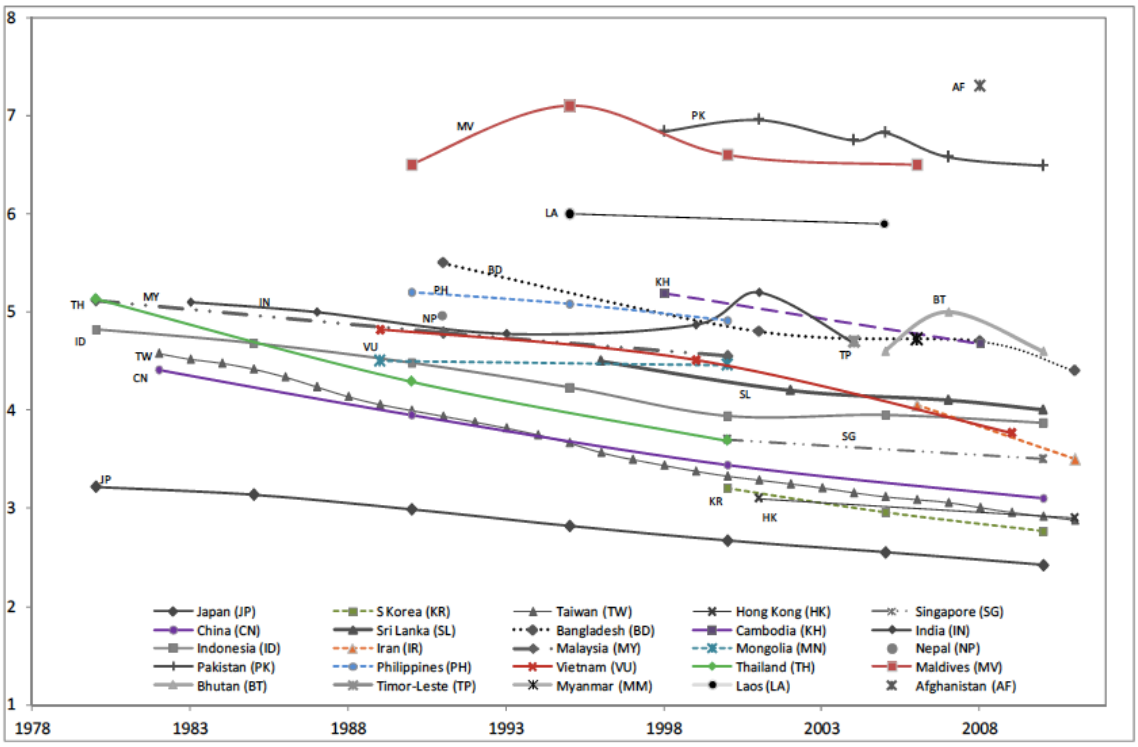

Figure 5. Average Family Size by Country, Asia 1980-2010[5]

[5] **Source:** Demographic Health Surveys and United Nations data.

2.8 Justification of research for this thesis

Family history is a known strong risk factor in Western studies, which encompasses both genetic and shared environmental risks. The increased risk of colorectal cancer for persons with a family history of colorectal cancer has been well investigated in Western countries, while there are not enough researches conducted for Asian countries. This thesis systematically collected the evidence of association of family history and risk of colorectal cancer in Asian countries and contributed to the academic area to strengthen the understanding of this association and provide the evidence to support for the colorectal cancer screening stretagy in Asian countries.

CHAPTER 3. Methodology

3.1 Introduction of Asia Cohort Consortium

3.1.1 The Asia Cohort Consortium

The Asia Cohort Consortium is led by co-chairs John Potter MD PhD, Member and Senior Advisor, Fred Hutchinson Cancer Research Centre, USA and Daehee Kang MD PhD, Chair, Department of Preventive Medicine, Seoul National University College of Medicine, Korea. The ACC focal point is located at the Fred Hutchinson Cancer Research Center and supports scientific cooperation, coordination and exchange, data operation and statistical advice.

Under the auspices of the ACC and on a biannual basis, investigators from China, India, Japan, Korea, Malaysia, Singapore, Taiwan, the United States, and other countries meet to report progress on colorectal cancer and screening programs. The group also shares insights and learnings relevant to the development of common protocol guidelines and actively explores opportunities for collaborative projects that will mutually benefit their common cause. The outcome of this review is commonly the formation of working groups to research common issues. The working group includes representatives from different Member States and has been established to closely review known colorectal cancer issues, including: diet; obesity and physical activity; occupation and environment; alcohol and tobacco; medical and reproductive history; family history; follow-up and endpoint determination; biological samples and sample collection; data collection and management; and previously established queues.

3.1.2 Rationale of establishment of Asia Cohort Consortium

The Asian Cohort Consortium (ACC) is trying to understand the relationship between genetics, environmental exposure and disease etiology by establishing a cohort or population laboratory, which is composed of at least 1 million healthy people around the world, who will be tracked to various disease endpoints, including colorectal cancer. What is needed is not

only to measure genetic variation, but also variation of environmental exposure. ACC solves the scientific needs of establishing complete disease susceptibility and disease resistance patterns, identifying diseases more precisely and determining which protein patterns provide signals for diseases. To achieve this goal, the ACC team is recruiting and tracking a large number of individuals from different environments, who have good genetic characteristics, whose behavior and environmental characteristics are well mapped, and whose disease patterns and mortality can be monitored. One of the things we've learned over the past five years is that many genetic variations associated with disease risk are only relevant if environmental variations exist.

3.1.2 Included cohorts in Asia Cohort Consortium

Table 3. Summary of the cohorts included in the Asia Cohort Consortium

Countries and Areas	Cohort Name
Bangladesh	Health Effects for Arsenic Longitudinal Study Bangladesh （HEALS）
China	China Hypertension Survey Epidemiology Follow-up Study (CHEFS)
	Linxian General Population Trial Cohort
	Shanghai Cohort Study (SCS)
	Shanghai Men's Health Study (SMHS)
	Shanghai Women's Health Study (SWHS)
India	Mumbai Cohort Study
Iran	Golestan Cohort Study
Japan	Japan Public Health Centre-based prospective Study (JPHC Study)
	Japan Collaborative Cohort Study (JACC)
	3 Prefecture Aichi
	Miyagi Cohort
	3 Prefecture Miyagi
	Ohsaki National Health Insurance Cohort Study
	Life Span Study Cohort
	Ibaraki Prefectural Health Study
	Takayama Study
Korea	Korean Multi-centre Cancer Cohort Study (KMCC)
	The Health Examinees' study
	Seoul Male Cancer Cohort
	Korean National Cancer Centre Cohort (KNCC)
Malaysia	Malaysian Cohort Study
	Cohort study on clustering of lifestyle risk factors and understanding its association with stress on health and wellbeing among schoolteachers in Malaysia (CLUSTer)
Mongolia	Nationwide cancer cohort study MON-COHORT
Singapore	Singapore Chinese Health Study
	Singapore Population Health Studies
Taiwan	Community-based Cancer Screening Project (CBCSP)
	Cardiovascular Diseases Risk Factor two-Township Study (CVDFACTS)
	Taiwan Biobank

At present, the members of the Federation are also the main researchers of the previously established cohort and are collaborating on a study focusing on body mass index and mortality in the Asian population. The scientific objective of the project is to assess the correlation between BMI and total and all-cause mortality, and to investigate the role of some confounding factors. As the first ACC pilot project, this cooperation is also intended to demonstrate the feasibility of data pools within ACC. ACC is

currently considering several additional pilot projects.The publication summary of the projects based on ACC collabration were listed in the **Apprendix 3.**

As part of the consortium, the new team has received funding and started operations in South Korea, Malaysia, Singapore and Taiwan [106]. Other countries are in the development stage. Instruments and protocols between consortium members are shared through password accessible websites, and discussions among working group members are conducted through occasional separate meetings and communications.

3.2 The process of collaboration with Asia Cohort Consortium

3.2.1 The application of the access to the ACC cohort database

My supervisor A/Prof Aung Ko Win applied for access to the database by submitting a proposal “Family history and risk of colorectal cancer” by following the "Guidance on using database, remote access and results circulation and publication in the Asia Cohort Consortium"(Details can be shown in **Appendix 4.**). I applied for access with the policy of ACC and signed an agreement to obtain the remote access to the ACC database (The Data Use Agreement was attached in the **Appendix 5.**).

3.2.2 The harmonization ACC cohort database and ethical approval

The data analysis was conducted by remote access to the ACC allocated computer with STATA software. Relevant data from participating cohorts were harmonized at the ACC coordinating centre at the University of Tokyo. The harmonization was discussed to ensure the included variables were correctly interpreted and extracted. Databases were investigated for inconsistency or missing values, and relevant queries were returned to ACC coordinating centre for confirmation. The distributions of variables were invesitgated and explored to identify errors or false or implausible values. For protection of individual confidentiality, the personal information including identifiers were removed, however study-specific identity numbers were retained to facilitate referral of questions back to the relevant individual cohort. My study was approved by the institutional review board of the ACC coordinating centre at the University of Tokyo and by the ethics committees of individual cohort.

3.3 Summary of six cohorts included in this PhD thesis

The study sample comprised the 6 ACC participating cohorts (Linxian General Population Trial Cohort, Miyagi Cohort Study, Ohsaki National Health Insurance Cohort Study, Three-Prefecture Cohort Study, Aichi, Korea Multi-Centre Cancer Cohort, Korean National Cancer Centre Cohort) from mainland China, Japan, Korea were included in this pooled analysis with a total of 175,807 individuals. Selected baseline characteristics of exposure and outcome of the six cohorts were summarized in **Table 4.**

Table 4. Descriptive information of each cohort in this thesis

Country	Cohort	ACC ID	No. of Partic-ipants	Enrol-ment Period	Mean No. of Years Fol-lowed (SD)	Mean Age at Study Entry, Years (SD)	Male (%)	Mean BMI at Study Entry (SD)	Ever Smok-ers at Study Entry (%)	Ever Alcohol User at Study Entry (%)	Diabetes at Study Entry (%)
China	Linxian General Popu-lation Trial Cohort	CN102	29459	1984–1987	18.5(7.4)	51.9(8.9)	44.6	22.0(2.5)	30.0	23.9	0.1
Japan	Miyagi Cohort Study	JP104	45523	1990	16.2(3.7)	52.0(7.5)	48.2	23.7(3.0)	42.3	52.2	4.2
	Ohsaki National Health Insurance Cohort Study	JP105	48043	1994	10.7(4.3)	60.2(10.3)	47.8	23.6(3.3)	41.0	49.7	6.5
	Three-Prefecture Co-hort Study, Aichi (3-Pref Aichi)	JP110	24557	1985	11.6(5.1)	55.4(10.9)	47.5	22.1(3.0)	47.2	61.4	3.1
Korea	Korea Multi-centre Cancer Cohort (KMCC)	KR101	20623	1993–2004	13.7(4.8)	54.1(14.3)	39.9	23.6(3.3)	33.0	41.0	4.3
	Korean National Cancer Centre Cohort (KNCC)	KR103	7670	2001	4.8(1.7)	52.7(8.4)	36.1	23.7(3.0)	39.4	58.3	5.7
Total			175875	1984-2004	13.7(6.0)	55.0(10.6)	45.9	23.1(3.1)	39.5	47	4.1

Abbreviation: ACC, Asia Cohort Consortium; ID, identification number; SD, standard deviation.

CHAPTER 4. Family history and the risk of colorectal cancer and adenoma in Asian countries: A meta-analysis and systematic review

4.1 Abstract

Objective: The role of family history of colorectal cancer on the risk of colorectal cancer and adenoma in Asian countries is not well understood although observational studies from Western countries consistently report that family history is a strong risk factor for the disease. This study is to investigate the estimates for association between a family history of colorectal cancer and the risk of colorectal cancer and adenoma for Asian countries.

Methods: We performed an electronic literature search using PubMed Medline and Embase to search all relevant articles published from 1980 to April 2016 using a combination of relevant medical subject heading terms and keywords. The search was extended by manually screening the reference lists of all included papers. Studies were included if they were observational studies that investigated the association between a family history of cancer specified to site and colorectal cancer or adenoma in Asian countries. Studies were excluded if they were review/editorial articles or not presented in English or did not well define a family history. We performed a random effects meta-analysis to obtain summary relative risk (RR) and corresponding confidence interval (CI) for association between a first-degree family history of colorectal cancer and the risk of colorectal neoplasia (cancer and adenoma combined) and separately for colorectal cancer and adenoma.

Results: Of a total of 1,066 studies from literature search, we included 25 studies containing 14 case-control, 3 cross-sectional and 8 cohort studies. The summary RRs (95% CIs) were 1.92 (1.61-2.28) for colorectal cancer, 2.63 (1.58-4.39) for colorectal adenoma, and 1.98 (1.72-2.26), respectively. The summary RRs for colorectal cancer were different between case-control and cohort studies (RR 2.35; 95% CI, 1.89-2.93 vs. RR 1.18; 95% CI, 1.03-1.34; $p = 0.003$). The association did not change substantially after adjusting for country of study ($p = 0.09$) or publication year ($p = 0.77$).

Conclusion: These summary estimates for associations between a family history of colorectal cancer and the risk of colorectal cancer or adenoma will useful to triage the populations in Asian countries for colorectal cancer screening

Key words: colorectal cancer, colorectal adenoma, family history, Asian countries, risk, meta-analysis

4.2 Introduction

Colorectal cancer is the third most commonly diagnosed cancer and second in terms of mortality, with over 1.8 million new cases and 881,000 deaths worldwide in 2018, accounting for about 1 in 10 cancer cases and deaths. [1] Some Asian countries where incidence of colorectal cancer was historically low, such as Japan, Israel, Singapore, China and Philippines, are experiencing rising incidence rates over the past decades. In 2012, Japan (Miyagi Prefecture Cancer Registry) presented the highest colorectal cancer incidence in the world for men (62 per 100,000 person) and women (37 per 100,000 person). [3] Observational studies have identified several risk factors associated with an increased risk of colorectal cancer including: lifestyle factors (obesity, physical inactivity, smoking, heavy alcohol use) and non-modifiable factors (aging, personal and family history of colorectal cancer or adenoma) [22]. Many observational studies conducted in Western countries have consistently reported that family history of colorectal cancer is a strong risk factor for colorectal cancer [19-22]. For example, a study by Taylor et al. [23] using a large family database linked to cancer registry data in Utah, USA, has shown that colorectal cancer risk increases with increasing number of affected relatives, particular if the affected relatives are genetically closer, diagnosed at a younger age, and multiple relatives are affected. Four meta-analyses of family history in Western countries also concluded that the risk of colorectal cancer is approximately 2-fold higher for persons with at least one affected first-degree relative than those without a family history of colorectal cancer, and that risk increases with the number of affected first-degree relatives [19-22]. The risk of colorectal cancer is more than 3-fold higher for persons with a first-degree relative diagnosed under the age of 50 years, and 2- to 3-fold higher if a first-degree relative is diagnosed under the age of 60 years [23]. This is consistent with the existence of risk factors for colorectal neoplasia that are shared by relatives including genetic and lifestyle factors. As a consequence, colorectal cancer screening guidelines in many Western

countries recommend screening frequency and intensity and age at commencement based on the strength of family history [12, 14, 18].

In comparison with Western countries, there have been relatively few studies in Asian countries on family history as a risk factor for colorectal cancer. Given that family structure and lifestyle factors are likely to be different between Asian and Western countries, we hypothesized that the association with family history of colorectal cancer are also be different. The average size of family in Asian countries has been shrinking since 1980. [24] For example, in China, the "One Child Policy", which was enforced from 1978 to 2015, has reduced the average family size (or average number of people per household) from 4.41 in 1982 to 3.1 in 2010. Similarly, in Japan the family size has reduced from 3.2 to 2.4, and in India from 5.1 to 4.0, therefore potentially altering the strength of family history as a risk factor. In addition, environmental or lifestyle exposures that might also be correlated within family members, such as diet, are likely to be differ between Asian and Western countries.

Despite the important role of family history on colorectal cancer risk, quantification of relative risk (RR) of colorectal cancer associated with family history has not been adequately determined in Asian countries. In this systematic review, we examined published literature to test the hypothesis that having at least one first-degree relative with colorectal cancer increases the risk of colorectal cancer and/or adenoma in Asian countries, and we summarized these findings through a meta-analysis.

4.3 Methods

We performed the systematic review according to a predetermined protocol and reported in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines[107]. We registered the research protocol with PROSPERO (registration number CRD42016045634). Two reviewers (L.Z. and S.G.D.) independently undertook the literature

search, assessment for eligibility, data extraction and qualitative assessment. Any inconsistencies between the two reviewers were reviewed by a third reviewer (A.K.W.) and resolved by consensus.

4.3.1 Definitions

For this study, we defined Asia according to the "List of sovereign states and dependent territories in Asia" by the United Nation (Details shown in **Appendix 1.**) in which Asia includes 48 countries and 6 states with limited international recognition. According to the United Nations geoscheme, Asia consists of five subregions: Central Asia, East Asia, Southern Asia, South-eastern Asia and West Asia. These subregions were used for this meta-analysis.

We defined three outcomes for this analysis: a diagnosis of colorectal cancer, a diagnosis of colorectal adenoma or a diagnosis of colorectal neoplasia (either colorectal cancer or adenoma). The primary exposure for this analysis was a family history of colorectal cancer, defined as having at least one first-degree relative (parents, siblings or children) diagnosed with colorectal cancer.

We defined ascertainment of the participants as two categories, including population-based and clinic-based. Participants from screening program, registry, health survey or routine health check-up examinations were defined as population-based ascertainment, while participants from hospital, out-patient clinics, primary care clinics or specialist clinics were defined as clinic-based ascertainment. Partially clinic-based ascertainment was defined for the studies participants partially from screening and partially from clinics in some multi-centre studies.

4.3.2 Literature search

We conducted an electronic literature search using PubMed and Embase to search all relevant articles that reported the association between family history of colorectal cancer and the risk of colorectal cancer and/or adenoma in Asian countries, published between January 1, 1980 and to April 22, 2016. The Medical Subject Heading (MeSH) terms were used in conjunction with the following key words to search for the studies: 'risk factor' / 'family history' / 'familial risk' / 'familial aggregation' / 'relatives' AND 'colorectal neoplasm' / 'colon neoplasm' / 'colorectal cancer' / 'colorectal neoplasm' / 'colon cancer' / 'colorectal neoplasms' AND 'Asian'. Full search strings were presented in **Appendix 6** & **7**. References from any relevant articles, editorials, conference abstracts, letters and reviews were also searched to identify any additional relevant studies. Full manuscripts of every article with a relevant title and abstract were then sought for assessment of eligibility.

4.3.3 Study selection

We include all studies that were: 1) case-control, cross-sectional or cohort studies that reported the association between family history of colorectal cancer and the risk of colorectal cancer and/or adenoma in Asian countries; 2) written in English language; and 3) peer-reviewed original research articles. Studies were excluded that: 1) were reviews, editorial, case report or guideline articles; 2) did not clearly define family history of colorectal cancer and/or adenoma; or 3) allowed for controls in case-control studies to have a previous diagnosis of a non-colorectal cancer (i.e. all controls must have no previous history of cancer). If data sources were duplicated in more than one study, only the original study was included in the meta-analysis, which was resolved by consensus by all three reviewers (L.Z., S.G.D. and A.K.W.).

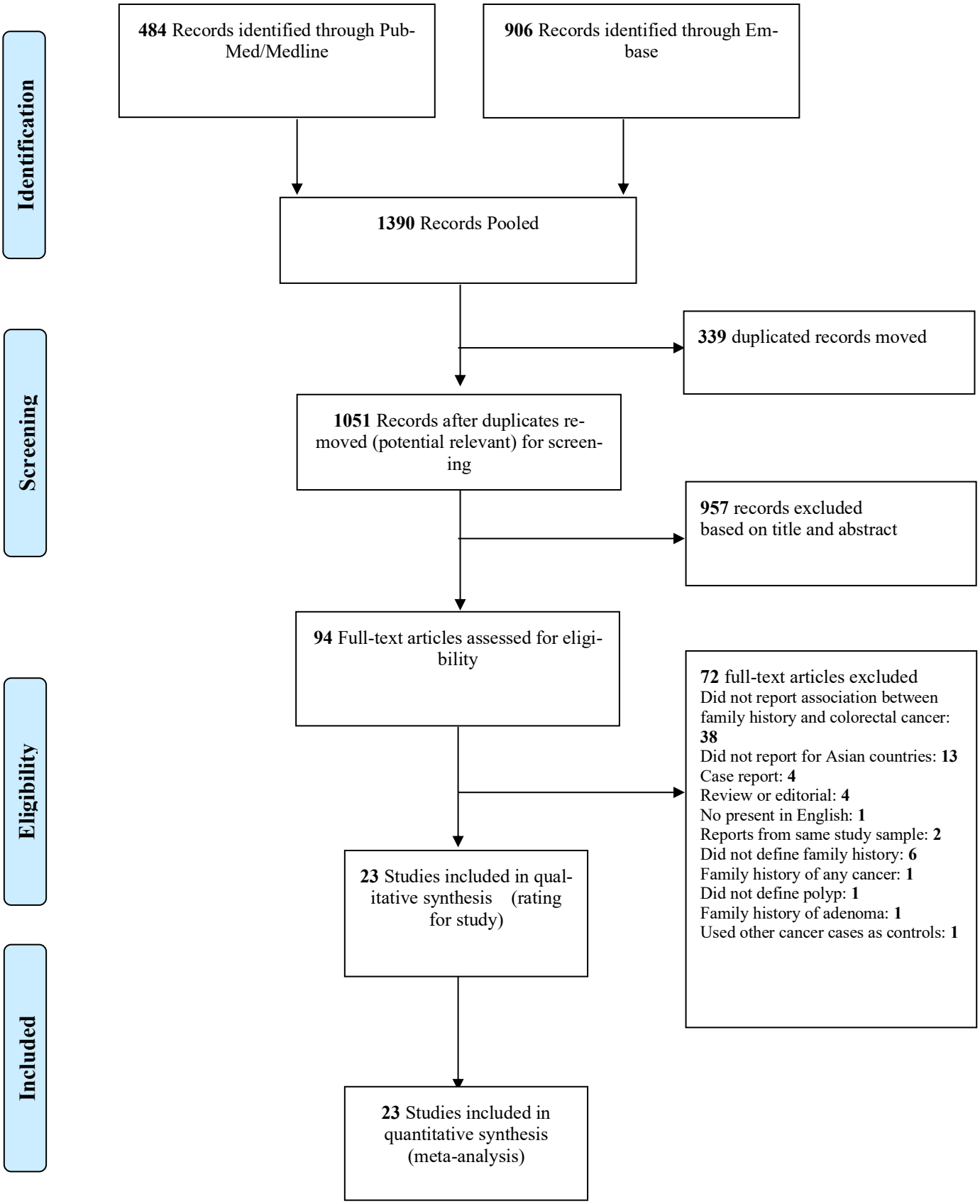

Figure 6. Flow diagram of study selection for meta-analysis

4.3.4 Data extraction

The following data was extracted from each study: name of journal, title, first author, year of publication, type of study, country where the study was conducted, selection criteria and the numbers of cases and controls (for case-control studies) and the numbers of total participants and incident cases (for cohort studies), definition of exposure, definition of outcome, results including odds ratio (OR) or relative risk (RR) and their corresponding 95% confidence intervals (CIs), and variables that were adjusted for (if any). Since OR and RR are usually comparable in magnitude when the disease studied is rare (e.g., in this meta-analysis, colorectal cancer), we used OR from the case control studies to calculate summary RR. For studies that reported both crude and adjusted estimates of the association between family history and colorectal cancer/adenoma/neoplasia, we used the adjusted estimates for the meta-analysis. For studies that reported several adjusted estimates of association, we used the estimates adjusted for the most variables.

4.3.5 Qualitative assessment

We applied the Newcastle-Ottawa Scale quality assessment [108] to evaluate the quality of the selected observational studies. This tool was used to measure the key aspects of the methodology in selected studies in regard to design quality and the risk of producing biased estimates based on three design criteria: 1) selection of study participants; 2) comparability of study groups; and 3) assessment of outcome and exposure with a star system (with a maximum of 9 stars). We judged studies that received a score of 7-9 stars to be at low risk of bias, studies that scored 4-6 stars to be at medium risk, and those that scored 3 or less to be at high risk of bias.

4.3.6 Statistical analysis

We used random-effects meta-analyses to generate summary RR and corresponding 95% CI for the association between a first-degree relative family history of colorectal cancer and the risk of colorectal cancer, colorectal adenoma and colorectal neoplasia separately. Subgroup analyses were performed by study design (case-control/cross-sectional vs. cohort), year of publication (before 2011 vs. 2011 and onwards), subregion (West Asia, East Asia, South-eastern Asia). Meta-regressions were conducted including study design, year of study and study subregion as covariates. To evaluate heterogeneity of the associations, I^2 statistic and τ^2 were calculated. Publication bias was evaluated by Begg's funnel plots and quantified by Egger's statistical test. Sensitivity analyses were conducted by omitting one study at a time and examining change in the overall RR to assess the influence of each individual study. All statistical analyses were performed using Stata 14.2 (StataCorp LP, College Station, TX).

4.3.7 Population attributable risk

The proportion of colorectal cancer or adenoma in the general population attributable (in statistical sense) to having a first-degree family history of colorectal cancer, i.e. population attributable risk, was calculated using the formula:

$$\mathrm{PAR} = \frac{\mathrm{P}\,(\mathrm{RR}-1)}{\mathrm{P}\,(\mathrm{RR}-1)+1}\; x\; 100$$

Where PAR is population attributable risk (%), P is the estimated proportion of the population with a first-degree relative family history of colorectal cancer (obtained from population-based cohort studies), and RR is the summary RR estimated from this meta-analysis.

4.4 Results

4.4.1 Search Results

The literature search yielded a total of 1,390 studies (906 from Embase and 484 from PubMed). We excluded 962 of these studies as not being relevant based on the titles and abstracts. Of the 96 studies which were assessed with full manuscripts, 23 were included in the final analyses (details shown in **Figure 6.**) comprising 11 case-control (summary can be shown in **Table 5.**), 7 cross-sectional (**Table 6.**) and 5 cohort studies (**Table 7.**). Of these, 5 ascertained subjects from population-based sources, [109-113] including cancer registries or national databases, while 18 studies ascertained subjects from clinic-based sources [114-131] by interviewing hospital outpatients and participants of clinical trials. Of the 23 studies, 14 studies were from East Asia, 2 were from South-eastern Asia, 5 were from West Asia, and 2 were from all Asia (studies conducted in different subregions of Asia). No studies were from Central Asia.

Table 5. Summary of 5 cohort studies included in the meta-analysis

Study	Year	Country	Case					Control			Family History		Adjusted Variables
			N	Age mean/SD or range	Sex(M/F)	Ascertainment of case	Confirmation	No. of participants	Age mean/SD or range	Sex(M/F)	1st Degree Relative Definition	Cancer Validation	
Byeon et al. [74]	2011	11 Asian cities #	168	NR	106/62	clinic-based	histological	860	54.4/11.6	471/389	FDR of CRC	self-reported	age, sex, ethnicity
Chang et al.[109]	2015	Taiwan	1383	NR	NR	population-based	colonoscopy	39384	55.9/11.6	23847/15537	FH of CRC	NR	age, sex, BMI, smoking, drinking, exercise frequency, education, diabetes, hypertension, irritable bowel syndrome
Hata et al.[117]	2013	Japan	83	40.5 (30-49)	49/34	clinic-based	histological	300	30-49	149/151	FH of CRC	self-reported	age, sex, family history of gastric cancer, FOBT
Kim et al.[120]	2015	South Korea	841	51.3/9.0	639/202	clinic-based	histological	3561	NR	2152/1409	FDR of CRC	self-reported	age, sex, BMI, smoking, drinking, diabetes
Murphy et al.[110]	2009	China	391	61/53-65	0/391	population-based	NR	73358	44-60	0/73358	FDR of CRC	self-reported	age, smoking, family income, education, BMI, physical activity, diabetes

Abbreviations: SD, Standard deviation; NR, Not reported; FH: Family History; CRC: Colorectal Cancer; FDR: First-degree Relative;
Bangkok, Guangzhou, Hong Kong, Jakarta, Kuala Lumpur, Manila, New Delhi, Seoul, Singapore, Taipei and Tokyo

Table 6. Summary of 11 case-control studies included in the meta-analysis

			Case					Control				Family History		
Study	**Year**	**Country**	**n**	**Age mean/SD or range**	**Sex (M/F)**	**Ascertainment of case**	**Confirmation**	**N**	**Age mean/SD or range**	**Sex (M/F)**	**Ascertainment of control**	**1st Degree Relative Definition**	**Cancer Validation**	**Adjusted Variables**
Arafa et al.[114]	2011	Jordan	220	M 56.3/12.3 F 53.7/6.8	118/102	clinic-based	histology	220	matched age	matched sex	clinic-based	FDR of CRC	self-reported	NR
Bener et al.[112]	2010	Qatar	146	54.1/12.4	93/53	clinic-based	national cancer disease registry	282	53.1/13.1	156/126	clinic-based	FH of CRC	self-reported	bakery products, BMI, smoking, soft drinks intake
Fatemi et al.[113]	2010	Iran	489	NR	NR	clinic-based	colonoscopy	249	NR	NR	clinic-based	FDR of CRC	self-reported	NR
Ghanadi et al.[116]	2014	Iran	112	52.2/15.3	60/52	clinic-based	histology	112	51.8/12.8	NR	clinic-based	FH of CRC	self-reported	NR
Huang et al.[118]	2004	Japan	1352	NR	819/533	clinic-based	NR	50,706	NR	14516/36190	partially clinic-based	FDR of CRC	self-reported	age, sex, smoking, drinking, BMI, physical exercise, consumption of raw vegetables
Kotake et al.[121]	1995	Japan	363	63.3/10.0	214/149	clinic-based	histology	363	59.4/10.3	214/149	clinic-based	FDR of CRC	NR	age and sex
Ng al.	2015	China	281	NR	NR	population-based	colonoscopy	4708	NR	NR	population-based	FH of CRC	self-reported	NR
Qin et al.[125]	2015	China	1106	Age group (# of people) ≤50: 286 50–59: 347 60–69: 294 ≥70: 166	673/421	clinic-based	histology	2212	Age group (# of people) ≤50: 967 50–59: 598 60–69: 465 ≥70: 173	1098/1102	clinic-based	FH of CRC	self-reported	age, sex, BMI, hospital, chronic disease, dietary factors
Safaee et al.[128]	2010	Iran	311	53.5/14.15	183/128	clinic-based	histology	393	44.2	152/154	population-based	FH of CRC	clinical record	age and sex
Seow et al.[129]	2002	Singapore	121	64.9/10.1	56/65	clinic-based	NR	222	56.9/12.2	88/134	population based	FDR of CRC	NR	age
Tung et al.[130]	2000	Taiwan	234	51.6/21.5	138/96	clinic-based	histology	468	53.3/20.7	276/192	clinic-based	FDR of CRC	self-reported	NR

Abbreviations: SD, Standard deviation; NR, Not reported; FH: Family History; CRC: Colorectal Cancer; FDR: First-degree Relative;

Table 7. Summary of 7 cross-sectional studies included in the meta-analysis

			Case					Control				Family History		
Study	**Year**	**Country**	**n**	**Age mean/SD or range**	**Sex (M/F)**	**Ascertainment of case**	**Confirmation**	**N**	**Age mean/ SD or range**	**Sex (M/F)**	**Ascertainment of control**	**1st-Degree Relative Definition**	**Cancer Validation**	**Adjusted Variables**
Chung et al.[115]	2010	South Korea	adenomas 1831 /cancer 12	Age group (age) 30-39yr 35.1/3.7 40-49yr 45.2/2.7 50-59yr 54.3/2.8	NR	clinic-based	histology	3859	NR	NR	clinic-based	FDR of CRC	NR	sex, BMI, abdominal obesity, smoking, drinking, aspirin or NSAIDs, education, income
Iwasaki et al.[119]	2006	Japan	1007	Age group (# of people) < 60 248 ≥60 553	1002/584	clinic-based	histology	579	NR	NR	clinic-based	FDR of CRC	self-reported	age and sex
Lee et al.[122]	2014	South Korea	154	57.2/9.3	92/62	clinic-based	colonoscopy	560	52.2 /8.1	213/347	clinic-based	FDR of CRC	NR	NR
Ng et al.[124]	2013	China	374	52.6/7.4	149/125	clinic-based	histology	374	52.7/7.4	149/125	clinic-based	FDR of CRC	registry	aspirin use
Rajendra et al.[126]	2005	Malaysia	36	NR	18/18	clinic-based	histology	275	NR	147/134	clinic-based	FH of CRC	NR	age, sex, race, NSAID use, smoking, drinking
Wong et al.[111]	2016	16 Asia-Pacific countries/regions *	4294	NR	5641/6156	partially clinic-based	histological	11797	40–70	5641/6156	partially clinic-based	FDR of CRC	self-reported	age, sex, smoking, drinking, BMI, diabetes
Yang et al. [131]	2014	South Korea	NR	NR	NR	population-based	colonoscopy	NR	NR	NR	population-based	FH of CRC	self-reported	NR

Abbreviations: SD, Standard deviation; NR, Not reported; FH: Family History; CRC: Colorectal Cancer; FDR: First-degree Relative;

* China (Hong Kong, Guangzhou, Xi'an), India (New Delhi), Indonesia (Jakarta), Japan (Tokyo), South Korea (Seoul), Malaysia (Kuala Lumpur, Kota Kinabalu), Pakistan (Karachi), Philippines (Manila), Singapore, Taiwan (Taipei, Kaohsiung), Thailand (Bangkok), and Australia (Sydney).

4.4.2 Qualitative assessment

The NOS tool was used to conduct a qualitative assessment of the selected studies to review quality of the studies and detect possible bias. Of the five cohort studies included in the systematic review, three studies were at low risk of bias[109, 110, 120] and two studies at medium risk[74, 117] (**Appendix 9.**). Of the 18 case-control and cross-sectional studies, five studies were at low risk of bias,[111, 115, 118, 124, 129] and 10 studies at medium risk,[112, 119, 121-123, 125, 126, 128, 130, 131] , the remaining three studies at high risk of bias [113, 114, 116] (**Appendix 10.**).

4.4.3 Meta-analysis

The summary RRs for the association between having at least one first-degree relative with colorectal cancer and the risk of colorectal cancer were 3.44 (2.32, 5.10) for West Asia, 1.69 (1.46, 1.96) for East Asia, and 5.14 (2.44, 10.82) for South-Eastern Asia (Forrest plots can be shown in **Figure 7.** and summary of meta-analysis results in geographic regions can be shown in **Figure 8.**).

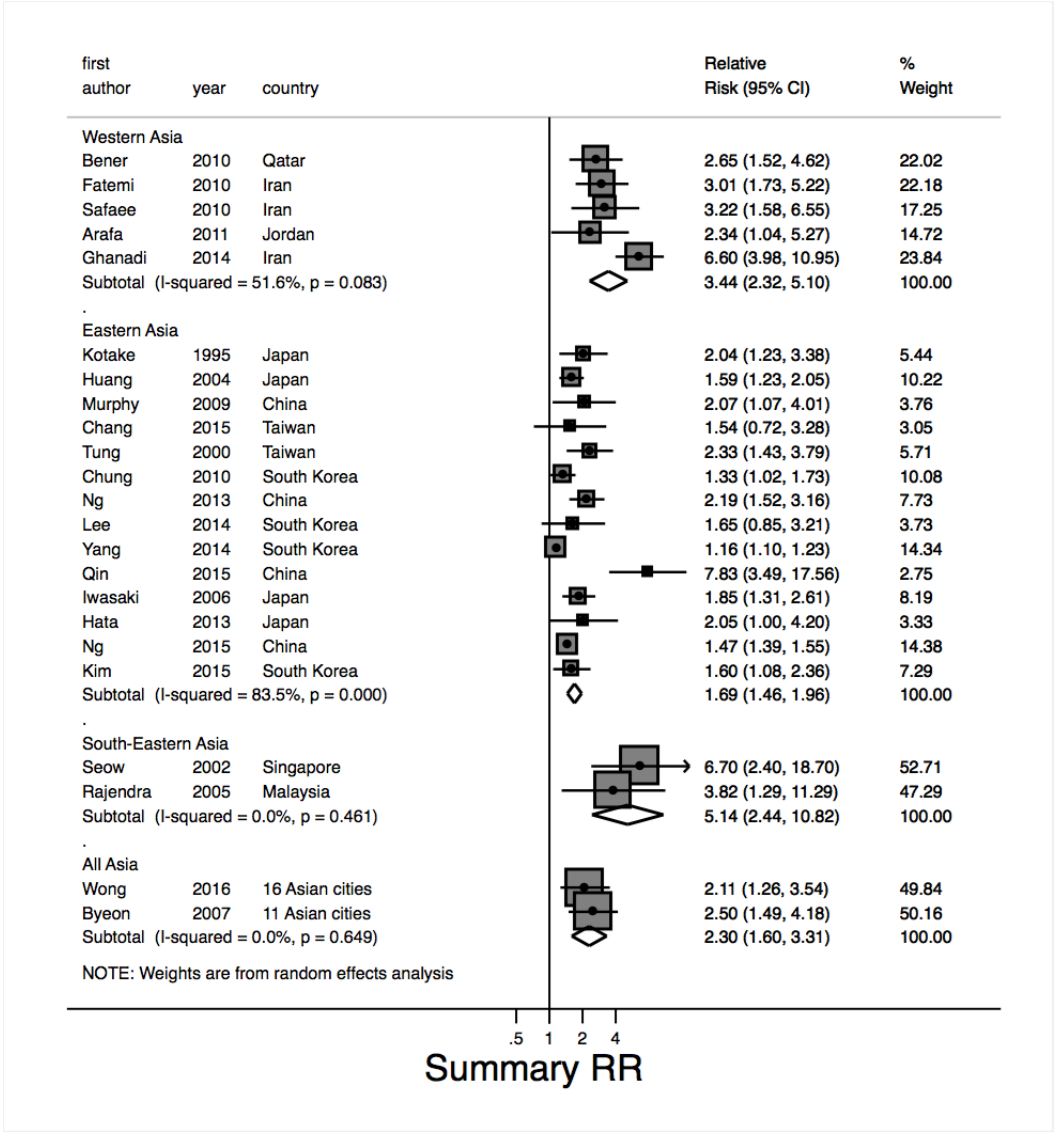

Figure 7. Meta-analysis of studies investigating the association between first-degree family history of colorectal cancer and the risk of colorectal cancer or adenoma by subregion of Asia (West Asia , East Asia, South-Eastern Asia and all Asia)

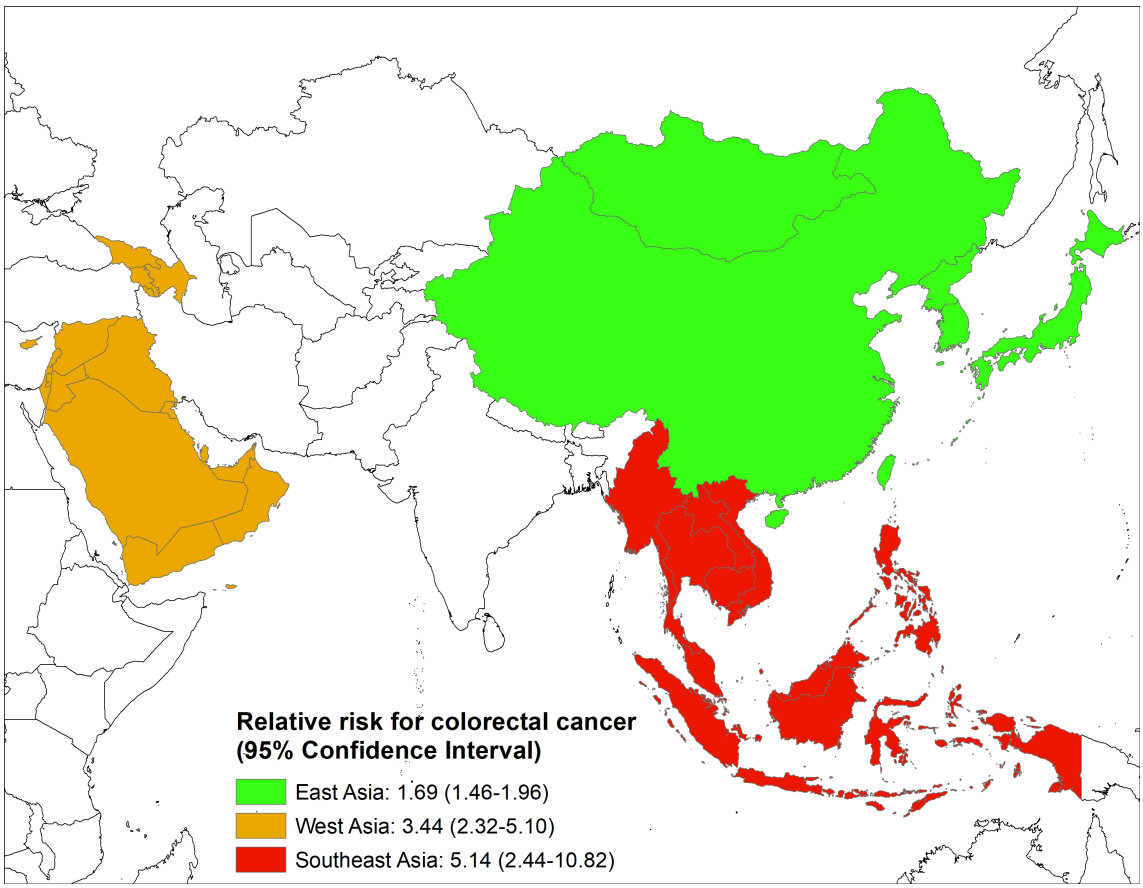

Figure 8. Summary of meta-analysis results of geographic regions (West Asia , East Asia, South-Eastern Asia) of association between first-degree family history of colorectal cancer and the risk of colorectal cancer or adenoma.

4.4.4 Subgroup and Sensitivity analysis

The strength of association differed by subregion of Asia, with the ratio of summary RR for West Asia vs. East Asia, being 1.41 (p = 0.006) and for South-eastern Asia vs. East Asia, being 2.96 (p = 0.034). There was no evidence of a difference in summary RRs by year of publication (p = 0.72) or study design (p = 0.51) (Details can be shown in **Table 8.)** The estimates of the summary RRs did not materially change when one study was omitted at a time.

Table 8. Summary of subgroup analysis for the associations between family history of colorectal cancer and the risk colorectal cancer and adenoma by year of publication, study type, and subregion of Asia.

	Number of studies	Random effect Summary RR (95% CI)	I^2 (%)	τ^2	Ratio of RRs (95% CI)	p-value
Year of publication						
Before 2011	12	2.10 (1.80-2.45)	84.1	0.16	1	
2011 onwards	11	1.99 (1.62-2.46)			0.93 (0.60-1.42)	0.72
Study type						
Cohort	5	1.89 (1.47-2.42)	86.1	0.16	1	
Case-control/Cross-sectional	18	2.15 (1.81-2.55)			1.19 (0.70-2.01)	0.51
Subregion						
East Asia	14	1.69 (1.46-1.96)	81.0	0.09	1	
West Asia	5	3.44 (2.32-5.10)			1.41(1.12,1.77	0.006
South-eastern Asia	2	5.14 (2.44-10.8)			2.96 (1.10,7.97)	0.034

Abbreviations: RR, Relative risk; I^2, Percent residual variation due to heterogeneity; τ^2, Residual maximum likelihood estimate of between-study variance; CI, Confidence interval

4.4.5 Publication bias

The Funnel plot and Egger's statistical test indicated moderate evidence of publication bias in the studies included in the meta-analysis for East Asia (p = 0.03), but no evidence of publication bias in the studies for West Asia (p = 0.31) (**Appendix 11.**).

4.4.6 Prevalence of first-degree family history in Asia

From the case-control and cross-sectional studies (**Appendix 12.**), for four population-based studies, [123, 128, 129, 131] 7.5% (95% CI 6.7-8.5%) of cases and 6.2% (5.8-6.5%) of controls were estimated to have at least one first-degree relative with colorectal cancer, while for 14 clinic-based studies, 14.9% (4.2-15.5%) of cases and 7.5% (7.3-7.7%) of controls were estimated to have at least one first-degree relative with colorectal cancer. [111-116, 118, 119, 121, 122, 124-126, 130] From 2 population-based cohort studies [109, 132] (**Appendix 13.**), 2.2% (95% CI 2.1-2.4%) of the population in Asian countries were estimated to have at least one first-degree relative with colorectal cancer, while from three clinic-based cohort studies, the prevalence of the first degree family history is 6.0% (5.3-6.7%).[74, 117, 120]

4.4.7 Population attributable risk

Based on the estimated prevalence of first-degree family history of colorectal cancer from population-based cohort studies, we estimated the population attributable risk to be 1.5% for East Asia, 5.1% for South-eastern Asia, and 8.3% for West Asia, which means 1.5%, 5.1% and 8.3% of colorectal cancer or adenoma cases were attributable

to first-degree family history of colorectal cancer in the corresponding Asian subregions.

4.5 Discussion

By conducting a meta-analysis of all published Asian studies, we found that the strength of associations between family history of colorectal cancer and the risk of colorectal cancer differed by Asian subregion, with the summary RR for East Asia being similar to that of Western populations, but higher for West and South-Eastern Asia. Despite being listed as countries of West Asia by the United Nation, we excluded one study from Israel [133], as the majority of their populations are of European and Jewish ethnicity.

The potential reasons of the heterogeneity in the strength of the association by Asian subregions may include many factors. Firstly, the type of food consumption varied according to the specific dietary habits and culture in each subregion of Asia. A systematic study on the relationship between dietary types, food or nutrients and colorectal cancer risk in Asian population was conducted. The results showed that there was a positive correlation between colorectal cancer risk and red meat, processed meat, pickled food, saturated / animal fat, cholesterol, high sugar food, spicy food, tuber or refined carbohydrate hydrate [134]. Secondly, as birth rates in Asian countries continue to decline over time [24], the effect of family size should be considered in heterogeneity of the strength of the association. One study conducted to estimate the effect of family size on the probability of diagnosing hereditary non-polyposis colorectal cancer suggested that family size is the unique discriminant factor, the probability of a positive diagnosis increases as the number of first-degree relatives increases [135]. Besides diet and family size, other personal and lifestyle factors (e.g., obesity,

smoking and drinking excessively) may alter the strength of the association and contributed to the heterogeneity of the association by Asian subregions.

These associations are consistent with the presence of inherited genetic risk factors for colorectal neoplasia aggregating within families but do not preclude a role of environmental factors that might also be aggregating within families, acting solely or in interaction with genetic factors; nor do they preclude recall bias where people with colorectal cancer are more likely to report colorectal cancer that has been diagnosed in their relatives than people without colorectal cancer.

Possible confounders for the association between colorectal neoplasia and family history of colorectal cancer include sex, age, smoking, alcohol drinking, body mass index and diabetes. Of the 23 studies included in this analysis, seven studies did not adjust any confounders [113, 114, 116, 122, 123, 130, 131], one study adjusted only for age of the cases and controls; [129] one study adjusted for aspirin use [124], three studies adjusted for age and sex [119, 121, 128], and eleven studies further adjusted for lifestyle factors and socioeconomic status including smoking, alcohol drinking, body mass index, diabetes, family income and education [74, 109-112, 115, 117, 118, 120, 125, 126]. Therefore, for these studies, the observed increased risk of colorectal neoplasia associated with a family history of colorectal cancer are less likely to be confounded by these known confounders.

Our analysis must be based on the limitations of existing data. Most studies in the meta-analysis did not confirm the diagnosis of colorectal cancer in first-degree relatives A study conducted by Mitchell et al [136] has quantified the inaccuracy of interview due to a family history of colorectal cancer, and concluded that report of family history under-reporting. Therefore, family history reported by cases and controls

without verification (as in the studies included in this analyses) should be interpreted with caution. Histologic confirmation of cancer diagnoses in relatives would be optimal validation, although this is difficult in retrospective designs due to challenges in obtaining medical records for events that may have occurred many years ago. In both case-control and retrospective cohort designs, people with colorectal cancer might be more likely to recall their family history of colorectal cancer than people without colorectal cancer (recall bias). We have attempted to reduce such recall bias by limiting our meta-analysis to studies that restricted family history to first-degree relatives, which should be more accurately recalled than for second-degree relatives or more distant genetic relationships.

Although the field of molecular epidemiology and genomics is rapidly expanding, including the discovery of new biomarkers, genome-wide association study (GWAS), epigenetics, and proteomics; Given that the utility of multifactorial biomarker-genetic risk stratification is still being investigated, family history is still one of the most valuable tools which can be used to identify people at increased risk of colorectal cancer. The utilisation of family history in colorectal cancer screening practices remains unclear, because many Asian countries do not have national colorectal cancer screening guidelines even though some countries have implemented nationwide colorectal cancer screening. For example, in Japan, a colorectal cancer screening program was incorporated into public health policy in 1992, while in both Taiwan and Korea, a national screening program was launched in 2004 [11, 28].

The differences in prevalence of family history may be due to research design. The cohort studies reported a lower prevalence of family history due to minimizing bias caused by selective volunteering of patients with positive family histories in the case-

control or cross-sectional studies. The clinic-based studies reported a higher prevalence of family history because people who have a family history are more likely to visit hospitals or clinics compared with population studies. By using the family history information from population-based cohort studies, the estimate of the prevalence of family history and risk of colorectal cancer may be the least biased for informing modelling of population-based screening program.

Prevalence of having a first-degree family history of colorectal cancer is 5.1% for the general Connecticut population (U.S) in the Family Health Study [137]. In the general Scottish population study, prevalence of first-degree relative family history affected by colorectal cancer is 9.4 % [25]. A recent Meta-analysis of seven Western population-based studies (six studies were from United States; one was from United Kingdom) reported the prevalence of having at least one first-degree relative with colorectal cancer was estimated between 3.1 and 10% [138]. Compared with the above Western population, the prevalence of having a first-degree family history of colorectal cancer in population-based cohort studies included in this meta-analysis is 2.2%, which was lower than the prevalence the Western populations. However, in our meta-analysis, two studies were the population-based cohorts [109, 110], but one study did not report the number of participants who had the family history [110]. Based on the low prevalence of first-degree family history of colorectal cancer in Asian countries, screening strategies targeted solely at people with family history will have limited impact on reducing mortality from colorectal cancer at the population level in Asian countries. In the future, risk based on multifactorial risk assessment may augment family history-based approaches.

The low prevalence of family history of colorectal cancer in Asian countries may due to following reasons. On one hand, the observed prevalence difference may reflect the methods used to ascertain case of the colorectal cancer and family history in the population. There was one cohort [117] and four case-control or cross-sectional studies [111, 112, 124, 130], which either checked the family history at screening centre [111], or retrieved the diagnosis and clinical data at the hospital, however, the remaining 18 studies were either self-reported or had no ascertainment information. To the extent that inaccurate recall might have occurred, it may lead to non-differential bias with underreporting which tends to result in an underestimation of the observed association. Whether or not using a systematic approach to the ascertainment of colorectal cancer history in family members may impact the resulting estimate of the prevalence of family history in the general population in Asian countries. Further, public awareness of colorectal cancer in Asian countries is low, which might have impacted the accuracy of self-reported family history of colorectal cancer. Therefore, accurate family history collection and reporting procedure should be promoted in Asian countries. Studies of family history also should report how family history was assessed, whether and how it was verified.

4.6 Conclusion

This meta-analysis provides valuable information for any future guideline development in Asian countries, on the use of family history, at least for first-degree relative, to guide the degree of colorectal cancer screening. Further studies may focus on evaluating more detailed family history such as how risk estimates change depending the degree of genetic relatedness and the number of relatives with colorectal cancer. A multinational, population-based studies in Asian countries may solve the issue of

heterogeneity in different subregions of Asia to generate detail information concerning colorectal cancer screening programs by using family history information in Asian countries.

CHAPTER 5. Association of family history and incidence of colorectal cancer: A pooled analysis of six prospective cohorts of the Asia Cohort Consortium

5.1 Abstract

Objective: Family history of colorectal cancer was associated with a higher risk of colorectal cancer in the Western population, but a correlating association with the risk of colorectal cancer in the Asian population is not well understood. This study is to determine the association of family history of colorectal cancer with the incidence of colorectal cancer in Asian countries.

Methods: We performed pooled analyses among East Asian individuals recruited in six prospective cohorts included in Asia Cohort Consortium with self-reported family history. We used Cox proportional hazards regression to estimate cohorts specific hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of family history of colorectal cancer with incidence colorectal cancer after adjusting for age, sex, BMI, smoking, and drinking.

Results: In a total of 175,807 participants with median age 55.0 (10.6) years and 45.9% male, 2,203 cancers were included with median 13.7(6.0) year's follow-up. We found that family history of colorectal cancer associated with an increased risk of colorectal cancer compared with no family history individuals (HR 1.84 95% CI 1.46, 2.32) in the univariable model, and after adjusting for age, sex, BMI, ever smoking, ever alcohol drinking, cohort with the multivariable model in the complete-case analysis (HR 2.14 95% CI 1.70, 2.70). There was substantial evidence of association between two first-degree relatives with colorectal cancer and the risk of colorectal cancer (HR 7.8 95% CI 2.52, 24.2) in the univariable model, and the association changed in the multivariable model analysis in both complete-case analysis (HR 5.1 95% CI 0.71, 36.2) and multiple imputations (HR 4.4 95% CI 0.62, 31.2). For no less than one first-degree relatives without the family history, the association also has the evidence (HR 1.7 95% CI 1.22, 2.36) in the multivariable model with complete-case. The similar associations were also shown in one first-degree relative with colorectal cancer,

family history from father and family history from the second-degree relative (HR 1.68 95% CI 1.21, 2.33; HR 2.34 95% CI 1.59, 3.46 and HR 1.87 95% CI 1.24, 2.83) in the multivariable model with complete-case. The association has no evidence for family history from mother and risk of colorectal cancer (HR 1.08 95% CI 0.61, 1.92) in the multivariable model with complete-case and the association did not change when multiple imputations were performed (HR 1.6 95% CI 1.01, 2.41).

Conclusion: Family history of colorectal cancer associated with a higher risk of colorectal cancer in Asian countries. Health care professionals providing counselling on risk and family history should emphasize that most of these associations were evident regardless of sex, age, BMI or smoking, and drinking history, supporting the broad generalizability of findings in Asian countries.

Keywords: colorectal cancer, family history, cohort, pooled analysis

5.2 Introduction

Globally, colorectal cancer is the third most common cancer in men and the second most common cancer in women, with 1.65 million new cases in 2015. The prevalence rate of male was significantly higher than that of female. The highest incidence of colorectal cancer is in Australia, New Zealand, Europe and North America. We can see that Africa and central and South Asia have the lowest incidence.These geographic differences appear to be attributable to differences in dietary and environmental exposures that are imposed upon a background of genetically determined susceptibility.

Family history is a known strong risk factor of colorectal cancer among colorectal cancer patients, which encompasses both genetic and shared environmental risks. Comparing with Western countries, there is a different family structure in Asian countries. For example, the

most remarkable difference is the nuclear family in China due to the "One Child Policy," introduced from 1978 and began to be formally stopped in 2015, the most significant birth control campaign in the world. For these individuals who have no siblings, whether the family history still a strong risk factor associated with colorectal cancer is a question. On the other hand, environmental exposures are likely to be different in Asian countries compared with Western countries. In this situation, whether family history of colorectal cancer and the risk of colorectal cancer is similar in Asian countries and Western countries is a question.

There is evidence of a link between family history of colorectal cancer and colorectal cancer and an increased risk of developing colorectal cancer. Four meta-analyses evaluated the risk of colorectal cancer associated with the person having a family history of colorectal cancer [19-22]. Results from these studies consistently showed that the risk of the family history of colorectal cancer is approximately 2-fold higher for persons with at least one affected first-degree relative than those without a family history of colorectal cancer, and that risk increases with the number of affected first-degree relatives [23]. However, most studies of the association between family history of colorectal cancer and colorectal cancer risk have been conducted in Western populations.

Epidemiological studies have documented consistent increases in the prevalence of colorectal cancer across Asia [3]; however, there is a wide geographical variation in the country-specific incidence within different Asia regions. Asia is heterogeneous, with higher colorectal cancer incidence in Japan, Israel, and Singapore than that in Thailand and China and Philippine. Currently, the highest colorectal cancer incidence rates are observed in both men (62 per 100,000 people) and women (37 per 100,000 people) in Japan (Miyagi Prefecture Cancer Registry) [3]. However, no large prospective cohort studies have investigated the influence of

family history on colorectal cancer in Asia. Large prospective studies on the association between family history and colorectal cancer in the Asian population are therefore needed.

Several prospective studies of family history and colorectal cancer have been conducted in individual cohorts in the Asian population. However, the majority of the studies included a small number of colorectal cancer patients with the family history or failed to control for important potential confounding variables such as BMI or obesity [117, 132, 139-141]. The only meta-analysis suggesting that risk of family history associated with colorectal cancer is similar in Asian as in Western countries.

5.3 Aim and objectives

In this study, we conducted a pooled analysis to evaluate the association between family history and risk of incidence from colorectal cancer in six prospective cohorts in Asia Cohort Consortium.

5.4 Methods

5.4.1 Exposure and outcome definitions

The family history of colorectal cancer which is the main risk factor of interest was defined as any family history of colorectal cancer regardless of the degree of relative information. One or two first-degree relatives (FDR) was defined as at least one first-degree relative relatives diagnosed with colorectal cancer. One FDR was defined as one first-degree relative diagnosed with colorectal cancer. Two FDR was defined as two first-degree relatives diagnosed with colorectal cancer. The information from Miyagi Cohort Study and Ohsaki National Health Insurance Cohort Study was extracted from the father or mother's colorectal cancer

history; second-degree relative (SDR) was defined as at least one second-degree relative diagnosed with colorectal cancer.

Potential confounders included baseline age, sex, baseline BMI, smoking status [never/ever], alcohol use [never/ever]). Age was defined as age at baseline; BMI was defined as BMI at baseline; smoking was defined as the status of ever (included current and former tobacco smokers)or never cigarette smoking at baseline; Alcohol drinking was defined as the status of ever (included current and former alcohol drinker) or never drinking at baseline. The variable was describe in details in previous publication of Asia Cohort Consortium[142, 143].

The outcome of interest was incidence of colorectal cancer, which was defined as diagnosis of colorectal cancer during the follow-up of the cohorts based on the ICD-9 Codes (http://www.icd9data.com/2015/Volume1/default.htm) including C18-Malignant neoplasm of colon, C19-malignant neoplasm of rectosigmoid junction, C20-malignant neoplasm of rectum or ICD-10 Codes (http://www.icd10data.com/ICD10CM/Codes) including 153-malignant neoplasm of colon and 154-malignant neoplasm of rectum rectosigmoid junction and anus. The number of diagnosis of colorectal cancer and the family history of colorectal cancer in each cohort is shown in **Table 10**.

5.4.2 Statistical analysis

To examine the association between family history and risk of colorectal cancer incidence, we estimated hazard ratios (HRs) and 95% confidence intervals (CIs) based on Cox proportional hazards regression models with age as the timescale. Time at risk started at risk from enrolment in the cohort and ended at diagnosis of colorectal cancer. We censored at the age of loss to follow-up or death, or end of follow-up, whichever occurred earliest.

The assumption of proportional hazards was examined by testing log survival function

within individual cohorts. The proportional hazards (PH) assumption was tested using the Schoenfeld and scaled Schoenfeld residuals. Univariable and multivariable models were fitted separately for each family history (family history regardless of the degree of relatives, one first-degree relative, two first-degree relatives, father, mother, second-degree relative).

The confounders were tested in the database for their correlation with family history and colorectal cancer. The variables that we considered as potential confounders are baseline age, sex, baseline BMI, smoking status [never/ever], alcohol use [never/ever] and cohort. Variables that did not meet the PH assumption were included in the model as time-dependent covariates (cohort). The change in the log-likelihood ratio assessed interactions after the addition of a cross-product term between the exposure and potential effect modifiers identified a priori (cohorts, geographic regions or year of entry). The effect of family history on the risk of colorectal cancer incidence was taken to be cohort-specific, assuming that log-HR associated with the family history had a fixed-effect in each cohort.

For multivariable models, we used complete case analysis(excluded 24,576 dataset) and multiple imputations to deal with the missing data. Numbers of missing values for all the variables were shown in **Table 9.** Missing data points were added using chained interactions, assuming that the absence was random. BMI, smoking status and alcohol drinking status were included in the imputation model; 20 imputed datasets were generated. The univariable HR and multivariable HR and corresponding 95% CI were presented in **Table 10**. All statistical tests were two-sided. All statistical analyses were conducted using Stata SE, version 14.2 (StataCorp LP, College Station, TX, USA).

5.5 Results

5.5.1 Descriptive analysis results

From the Asia cohort consortium, we identified six cohorts with a total of 191,818 individuals for this study. Of these individuals, we excluded 6,006 (3%) without the information of diagnosis of colorectal cancer, 9,937 (5%) without the information of the family history of colorectal cancer (regardless of the degree of relatives) and 68 without time under surveillance or less than zero. A total of 175,807 contributed to the analysis. In the six cohorts, the enrolment period was between 1984 to 2011, and the mean follow-up years were varied from 4.8 years to 18.5 years with total follow-up years 13.7 (SD 6.0). The baseline mean age of individuals in the six cohorts was 55.0 (SD 10.6) and 45.87% were male. A total of 2,203 individuals were reported to be diagnosed with colorectal cancer at baseline mean age of 60.2 (8.92) and 58.2% were males.

In the pooled data, 3,771 (2.14%) individuals had the family history of colorectal cancer (regardless of degree of relatives), in which 2,639 (1.5%) individuals had at least one first-degree relative with colorectal cancer, including 2,623 (1.49%) with one first-degree relative with colorectal cancer, and 27 individuals had two first-degree relatives with colorectal cancer. The data also demonstrated 831 and 792 individuals who had their father or mother with colorectal cancer, respectively, and 819 individuals had the second-degree relative family history of colorectal cancer (both of this information were available in the Miyagi Cohort Study and Ohsaki National Health Insurance Cohort Study).

The mean BMI of the pooled data was 23.1 (SD 3.1) with 8,114 individuals missing BMI information. The percentage of ever smoking and alcohol drinking in the individuals were 39.47% and 47.02%, respectively (The results shown in **Table 9.**).

Table 9. Summary of baseline characteristics of 6 included cohorts

	China (n=29449)		Japan (n=118114)		Korea (n=28244)		Total
Variables	Linxian General Population Trial Cohort (n=29,449, 16.75%)	Miyagi Cohort Study (n=45,522, 25.89%)	Ohsaki National Health Insurance Cohort Study (n=48,043, 27.33%)	Three-Prefecture Cohort Study, Aichi (3-Pref Aichi) (n=24,549, 13.96%)	Korea Multi-centre Cancer Cohort (KMCC) (n=20,574, 11.7%)	Korean National Cancer Centre Cohort (KNCC) (n=7,670, 4.36%)	175,807
Basic information of cohort							
Enrolment period	1984-1987	1990	1995	1985	1993-2004	2001	
Mean follow-up years (SD)	18.5(7.4)	16.2(3.7)	10.7(4.3)	11.6(5.1)	13.7(4.8)	4.8(1.7)	13.7(6.0)
Age, [by]							
Mean (SD)	51.9 (8.9)	52.0 (7.5)	60.2 (10.3)	55.4 (10.9)	54.1 (14.3)	52.7 (8.4)	55.0 (10.6)
Sex (n, %)							
Male	13121 (44.55)	21924 (48.16)	22971 (47.81)	11664 (47.51)	8197 (39.84)	2767 (36.08)	80644 (45.87)
Female	16328 (55.45)	23598 (51.84)	25072 (52.19)	12885 (52.49)	12377 (60.16)	4903 (63.92)	95163 (54.13)
Colorectal cancer							
No colorectal cancer	29386 (99.79)	44838 (98.50)	47262 (98.37)	24180 (98.50)	20283 (98.59)	7655 (99.8)	173604 (98.75)
Colorectal cancer	63 (0.21)	684 (1.50)	781 (1.63)	369 (1.50)	291 (1.41)	12 (0.2)	2203 (1.25)
Age, y	51.2 (7.3)	56.0 (6.2)	63.8 (8.3)	61.0 (10.1)	61.4 (9.3)	56.8 (8.7)	60.2 (8.9)
Male (%)	18 (28.6)	421 (61.6)	495 (63.38)	200 (54.2)	140 (48.1)	9 (60)	1283 (58.2)
Family history of colorectal cancer							
No family history	29392 (99.81)	44850 (98.52)	46327 (96.43)	23732 (96.67)	20386 (99.09)	7349 (95.81)	172036 (97.86)
Family history [d]	57 (0.19)	672 (1.48)	1716 (3.57)	817 (3.33)	188 (0.91)	321 (4.19)	3771 (2.14)
1 or 2 FDR	57(0.19)	505 (1.11)	1108 (2.3)	817 (3.33)	152 (0.73)	NR	2639 (1.5)
1 FDR	57 (0.19)	505 (1.11)	1108 (2.3)	801 (3.26)	152 (0.73)	NR	2623 (1.49)
father	NR	273 (0.6)	558 (1.16)	NR	NR	NR	831 (0.47)
mother	NR	234 (0.51)	558 (1.16)	NR	NR	NR	792 (0.45)
2 FDR	1 (0.003)	2(0.004)	8 (0.016)	16 (0.065)	NR	NR	27 (0.015)
SDR	NR	177 (0.39)	642 (1.33)	NR	NR	NR	819 (0.47)
BMI, kg/m^2 [c]							
Mean (SD)	22.0 (2.48)	23.7 (3.0)	23.6 (3.3)	22.1 (2.9)	23.6 (3.3)	23.7 (3.0)	23.1(3.1)
Missing data	6 (0.02)	2576 (5.7)	3261(6.8)	661 (2.7)	1610(7.8)	0	8114(4.6)
Smoking [e] (n, %)							
Never	20613 (70)	19298 (42.39)	21075 (43.87)	11786 (48.01)	12785 (62.14)	5117 (66.71)	90674 (51.58)
Ever	8836 (30)	19279 (42.35)	19708 (41.02)	11593 (47.22)	7445 (36.19)	2527 (32.95)	69388 (39.47)
Missing data	0	6945 (15.26)	7260 (15.11)	1170 (4.77)	344 (1.67)	26 (0.34)	15745 (8.96)
Alcohol drinking [f] (n, %)							
Never	22406 (76.08)	16523 (36.3)	18217 (37.92)	7788 (31.72)	11724 (56.98)	3185 (41.53)	79843 (45.42)
Ever	7043 (23.92)	23747 (52.17)	23885 (49.72)	15081 (61.43)	8431 (40.98)	4475 (58.34)	82662 (47.02)
Missing data	0	5252 (11.54)	5941 (12.37)	1680 (6.84)	419 (2.04)	10 (0.13)	13302 (7.57)

Abbreviation: FDR, first degree relative; SDR, second degree relative; BMI, body mass index; NA, not available

5.5.2 Main analysis results

Overall, we found that family history of colorectal cancer was associated with an increased risk of colorectal cancer compared with no family history individuals (HR 1.84 95% CI 1.46, 2.32) in the univariable model, and after adjusting for age, sex, BMI, ever smoking, ever alcohol drinking, cohort with the multivariable model in the complete-case analysis (HR 2.14 95% CI 1.70, 2.70). The results from multiple imputation analysis did not change the association (HR 1.58 95% CI 1.25, 1.99) (shown in **Table 10.**). There was no evidence of interactions between sex, age, BMI, ever smoking, ever alcohol drinking, but evidence of interactions of cohorts and countries. Subgroup analysis was performed for each cohort and country.

Table 10. Univariable and multivariable hazard ratios for the association between family history (regardless of the degree of relatives) and the risk of colorectal cancer

		Univariable Model						Multivariable Model ^								
Coun-try	Cohort							Complete-case analysis #						Multiple Imputation		
		No of CRC	No of obs	Person-years	HR	95%CI	P value	No of CRC	No of obs	Person-years	HR	95%CI	P value	HR	95%CI	P value
China	Linxian General Population Trial Cohort	63	29449	545671	NA	NA	NA	63	29449	545671	NA	NA	NA	NA	NA	NA
Japan		1818	118093	1529487	1.55	1.24, 1.97	<0.001	1521	95560	1237635	1.6	1.27, 2.03	<0.001	1.5	1.18,1.89	<0.001
	Miyagi Cohort Study	684	45522	731450	1.49	0.89, 2.49	0.12	567	36147	580796	1.62	0.97, 2.71	0.064	1.49	0.89, 2.49	0.126
	Ohsaki National Health Insurance Cohort Study	781	48040	515544	1.59	1.17, 2.14	0.003	632	37464	404730	1.82	1.34, 2.48	<0.001	1.63	1.21, 2.20	<0.001
	Three-Prefecture Cohort Study, Aichi (3-Pref Aichi)	353	24531	282492	1.23	0.72, 2.09	0.46	322	21949	252109	1.11	0.61, 2.03	0.73	1.24	0.73, 2.12	0.43
Korea		283	28221	319164	0.37	0.05, 2.63	0.32	264	26189	290925	0.41	0.06, 2.90	0.37	0.42	0.06, 2.97	0.38
	Korea Multi-centre Cancer Cohort (KMCC)	268	20551	282008	NA	NA	NA	249	18552	253983	NA	NA	NA	NA	NA	NA
	Korean National Cancer Centre Cohort (KNCC)	15	7670	37156	1.71	0.22, 13.1	0.6	15	7637	36941	1.71	0.22, 13.1	0.6	1.72	0.22, 13.2	0.6
Pooled		2164	175763	2394323	1.84	1.46, 2.32	<0.001	1848	151192	2074106	2.14	1.70, 2.70	<0.001	1.58	1.25,1.99	<0.001

^ Multivariable model adjusted for age (continuous), sex (binary), BMI (continuous), ever smoking (binary), ever alcohol use (binary), cohort (categorical). 2,4576 missing data elements were excluded from complete case analysis.

In the univariable model, the total observation was 175,807, with 16 event time missing and 28 observations end on or before entering. In the multivariable model, complete case analysis deleted 2,4576 missing data (either BMI, smoking or alcohol drinking), the total observation was 151,231, with 14 event times missing and 25 observations ending on or before entering.

Abbreviation: CRC, colorectal cancer; obs, observation; HR, hazard ratio; CI, confidence interval; NA, not available.

5.5.3 Subgroup analysis results

There was substantial evidence of association between two first-degree relatives with colorectal cancer and the risk of colorectal cancer (HR 7.8 95% CI 2.52, 24.2) in the univariable model, and the association changed in the multivariable model analysis in both complete-case analysis (HR 5.1 95% CI 0.71, 36.2) and multiple imputations (HR 4.4 95% CI 0.62, 31.2). For no less than one first-degree relatives with the family history of colorectal cancer, the association also has the evidence (HR 1.7 95% CI 1.22, 2.36) in the multivariable model with complete case. The similar associations were also shown in one first-degree relative with colorectal cancer, family history from father and family history from the second-degree relative (HR 1.68 95% CI 1.21, 2.33; HR 2.34 95% CI 1.59, 3.46 and HR 1.87 95% CI 1.24, 2.83) in the multivariable model with complete-case. The association has no evidence for family history from mother and risk of colorectal cancer (HR 1.08 95% CI 0.61, 1.92) in the multivariable model with complete-case and the association did not change when multiple imputations were performed (HR 1.6 95% CI 1.01, 2.41) (the results shown in **Table 11.**).

Table 11. Univariable and multivariable hazard ratios for the association between family history and the risk of colorectal cancer

	Univariable Model						Multivariable Model ^								
							Complete case analysis #						Multiple Imputation		
Family history	No of CRC	No of obs	Person-years	HR	95%CI	P value	No of CRC	No of obs	Person-year	HR	95%CI	P value	HR	95%CI	P value
2 FDR	1429	91976	1227294	7.8	2.51, 24.2	<0.001	1165	72260	968579	5.1	0.71, 36.2	0.1	4.4	0.62, 31.2	0.14
1 or 2 FDR	1479	94583	1259754	1.44	1.1, 1.9	0.009	1210	74527	997022	1.7	1.22, 2.36	0.002	1.58	1.15, 2.18	0.005
1 FDR	1540	123959	1804111	1.9	1.34, 2.51	<0.001	1271	103900	1541277	1.68	1.21, 2.33	0.002	1.57	1.14, 2.16	0.006
Father	1465	93562	1246994	2.18	1.48, 3.2	<0.001	1199	73611	985526	2.34	1.59, 3.46	<0.001	2.09	1.41, 3.08	<0.001
Mother	1465	93562	1246994	1.19	0.71, 2.02	0.51	1199	73611	985526	1.08	0.61, 1.92	0.78	1.12	0.66, 1.89	0.68
SDR	1465	93562	1246994	1.72	1.14, 2.60	0.01	1199	73611	985526	1.87	1.24, 2.83	0.003	1.6	1.01, 2.41	0.027

^Multivariable model adjusted for age(continuous), sex(binary), BMI (continuous), ever smoking(binary), ever alcohol use(binary), cohort(categorical).
24576 missing data were excluded for complete case analysis.
Abbreviation: CRC, colorectal cancer; FDR, first degree relative; SDR, second degree relative; obs, observation; HR, hazard ratio; CI, confidence interval; NA, not available

5.6 Discussion

Family history plays an essential role in the incidence of colorectal cancer. The association of family history of colorectal cancer (regardless of the degree of relative) and risk of colorectal cancer incidence is almost two folds in the pooled analysis according to different Asian countries in this study. For one or two first-degree relatives (FDRs) without the family history, the estimate (HR 1.7) also has the evidence of association with the risk of colorectal caner in the multivariable model. Given the higher risk of patients with one or two FDRs with colorectal cancer, more intense screening for colorectal cancer may be warranted in population of Asia with both frequency of the screening and early age stated for screening[144]. This study also found the consistent results of previous study about having a parent with colorectal cancer was associated with a doubling of risk[145]. However, there are few studies concerning the gender implication of the FDR being from the paternal or maternal side[145]. This study reveal a difference of association of family history from the paternal or maternal side with risk of colorectal cancer. Although gender disparity may play a role in the differenc,the exact mechanism of the association is unknown and needs to be explored in the future studies.

Family history comprises both genetic and environmental factors, which can help to interpret the association of the family history and risk colorectal cancer. The estimate of association among cohorts were different in our study, which might be interpreted due to sex and age distribution of the cohorts.

The included datasets were from China, Japan and Korea with almost 180,000 population, which can represent the study in East Asia due to the large population of 3 countries. Currently, the study of family history and colorectal cancer did not include the dataset from

other parts of Asian countries. Therefore, the database of other Asian countries is necessary to help us understand the whole picture of the association.

Major strengths of the present study included a large sample size of the diverse Asian population, allowing us to conduct several sensitivity analyses and stratified analyses by sex, age, smoking status, and alcohol use. Besides, we had detailed data at the individual level from all included cohorts for covariate adjustments and exploration of heterogeneity, avoiding some drawbacks of meta-analysis based on aggregate data from published results.

The limitation of our study is the use of self-reported family history and lack of closeness of family members, number and onset age of the affected relatives because the strength of association varies relying on factors such as closeness of family members, number and onset age of affected relatives. [146] This might have resulted in non-differential misclassification. Only cohorts of Miyagi Cohort Study and Ohsaki National Health Insurance Cohort Study provided the information of first or second-degree relative information. We did not estimate the subgroup of family history information and its association with colorectal cancer in other cohorts.

This study only estimated several confounding factors including sex, baseline age, baseline BMI, ever smoking or not and ever alcohol use or not. However, some possible confounders may alter the association of family history and risk of colorectal cancer, which includes social-economic factors such as income, marital status, education. Some disease status may alter the association, for instance, some studies about the status of diabetes of entry in the cohorts and incidence and mortality of colorectal cancer can assist to interpret some shared common factors of colorectal cancer[147, 148]. Given the increasing prevalence of diabetes and diabetes risk factors in Asian populations, it is essential to

understand the effect of diabetes on colorectal cancer in Asians. Hypertension and coronary heart diseases also may change the estimate of the association. The study of previously mentioned confounding factors can be conducted in future projects.

This study provided an estimate of association of family history of colorectal cancer and colorectal cancer incidence. However, the mortality is a critical estimate of the impact of disease on the population. In the future study, we will conduct a study about family history- related colorectal cancer prognosis. Both the study of family history and incidence and prognosis can provide more information on the association and its impact on the Asian population.

5.7 Conclusion

We observed that family history of colorectal cancer was related to an increased risk of incidence of colorectal cancer in East Asian countries. The finding indicated a potential need for appropriate cancer screening among individuals with family history of colorectal not only in Western population but also in Asians. We also found the estimate of association among cohorts are different. The reason requires future confirmation.

CHAPTER 6. Association of family history and mortality of colorectal cancer: A pooled analysis of six prospective cohorts of the Asia Cohort Consortium

6.1 Abstract

Objective: Family history of colorectal cancer is a recognized risk factor for developing colorectal cancer. However, effects of colorectal cancer family history on survival after a diagnosis of colorectal cancer are less well-defined.

Methods: We performed pooled analyses among diagnosed with colorectal cancer while participating in 6 prospective cohorts included in Asia Cohort Consortium with self-reported family history of colorectal cancer. We used Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for cancer-specific and overall mortality according to a family history of colorectal cancer, adjusting for age, sex, BMI and smoking, alcohol drinking and cohort.

Results: 2456 colorectal cancer cases were analysed, in which 796 were died because of colorectal cancer, and 212 were died because of reasons other than colorectal cancer. 2.9% of individuals dead due to colorectal cancer had family history of colorectal, and 1.6% had one first-degree relative family history. Individual with a family history of colorectal cancer experience an adjusted HR for overall survival of 0.81 (95% CI 0.51, 1.28) and colorectal cancer-specific survival of 0.75 (0.41, 1.38), and stratified with colon cancer-specific survival of 0.94 (0.37, 1.69) and rectum cancer-specific survival of 0.68 (0.24, 1.84). Family history of colorectal cancer was neither associated with increased overall survival nor colorectal cancer-specific survival.

Conclusion: This is no evidence for an association between family history of colorectal cancer and overall survival or colorectal cancer-specific mortality. However, specific mechanisms underlying family history may have prognostic impact and merit further study. Future studies need to collect data on possible confounders of the effect, such as tumour stage at

diagnosis, presence of multiple cancers, mode of presentation to hospital and surgical or clinical management in order to produce more conclusive results.

Keywords: colorectal cancer, family history, survival, mortality, pooled analysis

6.2 Introduction

Colorectal cancer is the third most commonly diagnosed cancer in men (746,000 new cases) and second in women (614,000 new cases) worldwide in 2012, accounting for 9.7% of the world's total cancer diagnoses, and 693,900 deaths [66]. Some Asian countries where incidence of colorectal cancer was historically low, such as Japan, Israel, Singapore, China and Philippines, are experiencing rising incidence rates over the past decades. In 2012, Japan (Miyagi Prefecture Cancer Registry) presented the highest colorectal cancer incidence in the world for men (62 per 100,000 person) and women (37 per 100,000 person) [3].

There is convincing evidence of a link between family history of colorectal cancer and colorectal cancer and an increased risk of developing colorectal cancer. Four meta-analyses evaluated the risk of colorectal cancer associated with person having a family history of colorectal cancer [19-22]. Several studies have reported on the association between family history and colorectal cancer survival, however whether a family history of colorectal cancer affects the survival of individuals with the colorectal cancer was controversial [136, 149-162].

It is important to understand how familial colorectal cancer risk influences the survival of those with the disease. The value of family history taking in individual with colorectal cancer is therefore not only to identify families with hereditary colorectal cancer, but also to add information to the prognosis of the patients. Prognostic family data would be very helpful in guiding therapy and genetic counselling for those with colorectal cancer and their relatives. Differing family histories of benign and malignant cancers would require distinct clinical approaches [160]. It would also facilitate selection processes in determining entry into screening programs and clinical trials of

chemotherapy. Overdiagnosis is a growing issue where cancer is detected through screening that would not have presented clinically in the individual in his or her lifetime. If familial cause-specific survival were able to be demonstrated, it could help alleviate this problem through more accurate predictions for cancer development and survival time [59].

6.3 Aim and objectives

In this study, we conducted a pooled analysis to evaluate the association between family history and mortality of colorectal cancer in 6 Asian prospective cohorts in Asia Cohort Consortium.

6.4 Methods

The Asia Cohort Consortium (ACC) is an international collaboration of cohort-based studies in Asia Pacific regions, with approximately 28 cohort studies from 9 countries, including China, Japan, Korea, Singapore, Malaysia, India, Bangladesh, Taiwan and Iran[163, 164]. The ACC was first proposed in 2004 with agreement on the demand to establish an international consortium of cohorts focusing on at least 1 million healthy individuals in Asia who followed until various disease endpoints, including cancer. Several studies of these cohorts have examined the association between body mass index, smoking, alcohol consumption or type 2 diabetes and cancer risk[142, 143, 165, 166]. Relevant data from participating cohorts were harmonised at the ACC coordinating centre at University of Tokyo. The harmonisation was discussed to ensure the included variables were correctly interpreted and extracted. Data were investigated for illogical or missing values, and queries were sent to ACC coordinating centre for clarification. The distributions of individual variables were explored to identify false or implausible values. The personal

identifiers were removed, but study-specific ID numbers were retained to facilitate referral of queries back to the individual cohort.

6.4.1 Study population

We conducted pooled analyses of 2456 incident colorectal cancer from six prospective cohorts which are members of ACC, including Linxian General Population Trial Cohort, Miyagi Cohort Study, Ohsaki National Health Insurance Cohort Study, Three-Prefecture Cohort Study, Aichi, Korea Multi-Centre Cancer Cohort, Korean National Cancer Centre Cohort from 3 Asian countries, China, Japan, Korea. We included patients with incident colorectal cancer who provided information regarding family history of colorectal cancer. Our study was approved by the institutional review board of the ACC coordinating centre at University of Tokyo and by the ethics committees of each individual cohort.

6.4.2 Data collection

Demographic and epidemiologic data were obtained at enrolment into the respective study. Family history of colorectal cancer was also collected as part of study questionnaire, defined as any relatives who diagnosed with colorectal. First-degree relative (FDR) family history was defined as either a parent, sibling, or child diagnosed with colorectal. Second-degree relative (SDR) family history was defined as at least one second-degree relative diagnosed with colorectal cancer. Incident colorectal cancer was identified through self-report with medical record review. Vital status was ascertained in all studies through follow-up. The outcome of interest was death of colorectal cancer, which was defined as diagnosis of colorectal cancer during the follow-up of the cohorts based on the ICD-9 Codes (http://www.icd9data.com/2015/Volume1/default.htm) including C18-Malignant

neoplasm of colon, C19-malignant neoplasm of rectosigmoid junction, C20-malignant neoplasm of rectum or ICD-10 Codes (http://www.icd10data.com/ICD10CM/Codes) including 153-malignant neoplasm of colon and 154-malignant neoplasm of rectum rectosigmoid junction and anus. The number of deaths of colorectal cancer and family history of colorectal cancer was shown in the **Table 12.**

6.4.3 Statistical analysis

Descriptive statistics were generated by mean with standard deviation for numerical variables and by number of individuals with percentage in the group for categorical variables. Time at risk started at risk from diagnosis of colorectal cancer in the cohort and ended at death due to colorectal cancer. Overall survival (OS) was defined as the time from diagnosis of colorectal cancer to the time of death from any cause. Colorectal cancer-specific survival was defined as the time from diagnosis of colorectal cancer to the time of death due to colorectal cancer. Cox proportional hazards (PH) regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between family history of colorectal cancer with overall survival and colorectal cancer-specific survival. PH assumption was verified using Schoenfeld residuals.

We fitted separate univariable and multivariable models for the the associations of family history of colorectal cancer (yes/no), FDR (yes/no), father (yes/no), mother (yes/no) and SDR (yes/no) with OS and colorectal cancer-specific survival. Missing data for smoking status, alcohol drinking status and body mass index (BMI) was accounted for by exclusion with complete data and multiple imputation. Multivariable analyses were adjusted for age at baseline, sex, BMI, smoking status,

alcohol drinking status(smoking was defined as the status of ever (included current and former tobacco smokers)or never cigarette smoking at baseline; Alcohol drinking was defined as the status of ever (included current and former alcohol drinker) or never drinking at baseline. The variable was describe in details in previous publication of Asia Cohort Consortium[142, 143].) and cohort. Additional analyses were adjusted for the covariates above and stratified by tumour location (colon or rectum). Tests of interactions between family history of colorectal cancer and potentially modifying covariates were assessed by entering the cross-product term for FDR and the covariate of interest in the multivariate models. Two-tailed P-value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata version14.2 (StataCorp LP, College Station, TX, USA).

6.5 Results

6.5.1 Descriptive analysis results

In the **Table 12.,** of the 2456 eligible participants, 88 (3.6%) individuals reported a family history of colorectal cancer in at the baseline interview, with 60 (2.4%) FDR family history. The median follow-up period was 12.1 years (SD=5.4) after colorectal cancer diagnosis. Among the 1008 total deaths, 796 (79%) deaths were attributed to colorectal cancer with death due to colon cancer (n=504) and rectum cancer (n=292). 23 (2.9%) of individuals dead due to colorectal cancer had family history of colorectal, and 13(1.6%) had one first-degree relative family history.

Table 12. Descriptive characteristics of the study population

	All Cause Death (n=1008)		Alive (n=1448)	Total (n=2456)
	Deaths due to CRC (n=796, 79%)	Deaths not due to CRC (212, 21%)		
Mean follow-up yrs. (SD)	8.6 (4.7)	9.5 (4.4)	14.4 (4.5)	12.1(5.4)
Age, Mean (SD) y [b]				
At baseline	61.0 (10.2)	62.7 (8.2)	58.8 (8.4)	59.8 (9.10)
Diagnosis of CRC	68.6 (10.2)	68.2 (8.1)	66.1 (8.4)	67.1 (9.1)
Sex (n, %)				
Male	426 (53.5)	145 (68.4)	826 (57.1)	1397 (56.9)
Family	370 (46.5)	67 (31.6)	622 (42.9)	1059 (43.1)
Family history of CRC (n, %) [c]				
No family history	773 (97.1)	204 (96.2)	1391 (96.1)	2368 (96.4)
Family history	23 (2.9)	8 (3.8)	57 (3.9)	88 (3.6)
1 FDR	13 (1.6)	3 (1.4)	44 (3.0)	60 (2.4)
father	5 (0.6)	2 (0.9)	20 (1.4)	27 (1.1)
mother	4 (0.5)	0	13 (0.9)	17 (0.7)
2 FDR	0	0	3 (0.2)	3 (0.2)
SDR	10 (1.3)	4 (1.9)	13 (0.9)	27 (1.1)
BMI, kg/m^2 [d]				
Mean (SD)	23.1(3.1)	23.0 (3.3)	23.6 (3.3)	23.4(3.2)
Missing data (n, %)	47 (5.8)	15 (7.1)	73 (5.0)	135 (5.5)
Smoking (n, %) [e]				
Never	324 (40.7)	72 (34.0)	609 (42.1)	1005 (40.9)
Ever	382 (48.0)	126 (56.4)	710 (49.0)	1218 (49.6)
Missing data	90 (11.3)	14 (6.6)	129 (8.9)	233 (9.5)
Alcohol drinking (n, %) [f]				
Never	291 (36.6)	65 (30.7)	495 (34.2)	851 (34.7)
Ever	435 (54.7)	134 (63.2)	842 (58.2)	1441 (57.4)
Missing data	70 (8.8)	13 (6.1)	111 (7.6)	194 (7.9)
Cohorts [g]				
Linxian	34 (4.3)	5 (2.4)	30 (2.1)	69 (2.8)
Miyagi	229 (28.8)	67 (31.6)	554 (38.4)	850 (34.6)
Ohsaki	285 (35.8)	92 (43.4)	484 (33.4)	861 (370)
3Pref-Aichi	166 (20.9)	19 (8.9)	185 (12.8)	370 (15.1)
KMCC	82 (10.3)	27 (12.7)	182 (12.6)	291 (11.9)
KNCC	0	2 (0.9)	13 (0.9)	15 (0.6)

[a] Colorectal cancer was defined as diagnosis of colorectal cancer during the follow-up of the cohorts.
[b] Age was defined as age at baseline.
[c] Family history of colorectal cancer was defined as any family history of colorectal cancer regardless of the degree of relative information; 1 FDR was defined as one first-degree relative diagnosed with colorectal cancer; 2 FDR was defined as two first-degree relatives diagnosed with colorectal cancer; SDR was defined as at least one second-degree relative diagnosed with colorectal cancer.
[d] BMI was defined as BMI at baseline.
[e] smoking was defined as the status of ever or never cigarette smoking at baseline.
[f] Alcohol drinking was defined as the status of ever or never drinking at base line.
[g] Linxian,Linxian General Population Trial Cohort; Miyagi, Miyagi Cohort Study; Ohsaki, Ohsaki National Health Insurance Cohort Study; 3pref-Aichi, Three-Prefecture Cohort Study, Aichi; KMCC, Korea Multi-Centre Cancer Cohort; KNCC, Korean National Cancer Centre Cohort.
Abbreviation: CRC, colorectal cancer; SD, standard deviation; FDR, first-degree relative; SDR, second-degree relative; yrs., years.

6.5.2 Main and subgroup analysis results

Overall, having a family history of colorectal cancer was not associated with OS (HR, 0.81; 95% CI, 0.51, 1.28) or colorectal cancer-specific survival (HR, 0.75; 95% CI, 0.41, 1.38) after adjusting for age at baseline, sex, BMI, smoking status, alcohol drinking status, and cohort. For first-degree relative family history of colorectal cancer, the association with OS (HR, 0.6; 95% CI, 0.28, 1.28) or colorectal cancer cancer-specific (HR, 0.64; 95% CI, 0.26, 1.57) survival was not significant as well (shown in **Table 13.**).

In subgroup analyses, there was no statistically significant association between family history of colorectal and colorectal cancer-survival among individuals with of colon cancer (HR 0.94; 95% CI 0.37, 1.69) or rectum cancer (HR 0.68; 95% CI 00.24, 1.84), respectly (shown in **Table 13.**).

Table 13. Univariable and multivariable hazard ratios for association between family history and survival (overall survival, colorectal cancer-specific survival, colon cancer-specific survival and rectum cancer-specific survival)

	Univariable Model						Multivariable Model *								
							Complete-case analysis						Multiple Imputation		
	No of death	No of obs	Person-years	HR	95%CI	P value	No of death	No of obs	Person-years	HR	95%CI	P value	HR	95%CI	P value
All cause (n=1008)															
Family history (yer or no)	570	1887	12147	0.84	0.53, 1.33	0.45	490	1619	10370	0.91	0.57, 1.45	0.7	0.81	0.51, 1.28	0.36
1 FDR	372	1348	9502	0.84	0.45, 1.57	0.58	305	1119	7917	0.71	0.33, 1.51	0.37	0.6	0.28, 1.28	0.19
father	336	1294	9316	1.22	0.54, 2.73	0.47	269	1068	7743	0.99	0.43, 2.25	0.98	0.94	0.42, 2.13	0.88
mother	336	1294	9316	0.24	0.03, 1.71	0.15	269	1068	7743	0.26	0.04, 1.83	0.18	0.18	0.03, 1.31	0.09
SDR	336	1294	9316	1.19	0.56, 2.53	0.65	269	1068	7743	0.97	0.45, 2.07	0.93	0.97	0.45, 2.06	0.93
Colorectal cancer (n=796)															
Family history (yer or no)	384	1701	11286	0.75	0.41, 1.37	0.36	332	1461	9641	0.89	0.48, 1.64	0.71	0.75	0.41, 1.38	0.36
1 FDR	229	1205	8840	0.95	0.45, 2.01	0.89	187	1001	7374	0.8	0.32, 1.96	0.62	0.64	0.26, 1.57	0.33
father	199	1157	8677	1.33	0.49, 3.60	0.6	157	956	7223	1.06	0.39, 2.92	0.91	0.96	0.35, 2.63	0.94
mother	199	1157	8677	0.4	0.06, 2.88	0.37	157	956	7223	0.39	0.05, 2.78	0.35	0.26	0.04, 1.88	0.18
SDR	199	1157	8677	1.19	0.44, 3.25	0.73	157	956	7223	0.93	0.35, 2.57	0.89	0.97	0.35, 2.66	0.96
Colon cancer (n=504)															
Family history (yer or no)	243	1560	10964	0.75	0.35, 1.6	0.46	211	1340	9367	0.97	0.45, 2.09	0.94	0.79	0.37, 1.69	0.54
1 FDR	143	1119	8623	1.07	0.43, 2.62	0.88	116	930	7201	1.21	0.44, 3.38	0.71	0.94	0.34, 2.59	0.9
father	114	1072	8462	2.32	0.85, 6.32	0.1	87	886	7051	2.15	0.75, 6.08	0.76	1.85	0.66, 5.14	0.24
SDR	114	1072	8462	1.11	0.27, 4.52	0.89	87	886	7051	0.74	0.18, 3.07	0.67	0.77	0.19, 3.16	0.72
Rectum cancer (n=292)															
Family history (yer or no)	141	1458	10869	0.75	0.28, 2.02	0.57	121	1250	9270	0.78	0.28, 2.12	0.62	0.68	0.24, 1.84	0.44
1 FDR	86	1062	8635	0.73	0.18, 2.98	0.66	71	885	7201	0.31	0.04, 2.28	0.25	0.26	0.04, 1.89	0.18
mother	85	1043	8525	0.89	0.12, 6.41	0.91	70	869	7103	0.79	0.11, 5.79	0.82	0.58	0.08, 4.22	0.59
SDR	85	1043	8525	1.33	0.32, 5.56	0.69	70	869	7103	1.17	0.27, 4.96	0.83	1.28	0.35, 5.34	0.74

* Multivariable model adjusted for age at baseline(continuous), sex(binary), BMI at baseline (continuous), ever smoking(binary), ever alcohol use(binary), cohort(categorical).
Abbreviation: obs, observation; HR, hazard ratio; CI, confidence interval; FDR, first-degree relative; SDR, second-degree relative

6.6 Discussion

In this large pooled analysis of 2456 colorectal cancer cases, having a family history of colorectal cancer was neither associated with increased overall survival nor colorectal cancer-specific survival in the overall population. There were also not significant association between FDR or SDR affected by colorectal cancer and colorectal cancer specific-survival.

Having a family history of colorectal cancer is a known risk factor for the development of colorectal cancer. However, the prognostic significance of family history of colorectal cancer remains uncertain. Our finding of no association between family history of colorectal cancer and survival in individuals with colorectal cancer is consistent with reports from 5 previous studies performed in population-based cohorts or within a clinical trial [150, 152, 154, 156, 157]. The most recent robust study was conducted within pooled analysis of eight epidemiologic studies with 5010 colorectal cancer participants which reported no association between family history of colorectal cancer and colorectal cancer-specific survival, after adjusting for age at diagnosis, sex, body mass index, smoking, regular use of aspirin or non-steroidal anti-inflammatory drugs, history of endoscopy screening, tumour location, stage at diagnosis, and study site. Another study was conducted within the Colon Cancer Family Registry Cohort which also reported no association between family history of colorectal cancer and colorectal cancer-specific survival after adjustment for microsatellite instability (MSI) status or tumour site [156].

Our results contradict several studies in which family history of colorectal cancer is associated with better survival after a diagnosis of colorectal cancer [158] and with favourable prognosis in stage III colon cancer [155], controversially, in two

studies, the family history of colorectal cancer was associated with a significant decrease in survival [149, 151]. Some of these studies have also been relatively limited in size and scope, leading to possibly imprecise estimates and contradictory results. One study reported a significant association of a family history of colorectal cancer in a first-degree relative with a poor survival [151]. Stratified estimates relating to tumour stage would also be important fator for survival in colorectal cancer. The TNM Classification of Malignant Tumours (TNM) serves as one of the most important pathological prognostic factors as it aids in describing the size and extension of the tumour, its lymphatic involvement and the existence of metastases to facilitate classification of the progression of cancer[167]. Stratified estimates relating to TNM stage would also have been useful to detect heterogeneity between the estimate of the association of risk of colorectal cancer and TNM stage as is one of the most important factors for survival in colorectal cancer[168-170]. In this study, due to data unavailability of TNM stage of diagnosis of the colorectal cancer, we did not include this important covariate for adjustment to eliminate the potential confounding.

Possible differences between those with family history of colorectal cancer and those without might also confound their association with survival. Those with a family history of colorectal cancer might be more aware of their risk for colorectal cancer through having earlier screenings or making lifestyle choices that help to increase chances of surviving due to prompting from relatives who have the disease. However, regarding earlier diagnosis through earlier screenings, a study on patients who were positive for family history of cancer indicated that they do not choose to seek help for their symptoms earlier than those with no family history [159].

Our study has several strengths. First, this analysis included a large study population of colorectal cancer (n=2,456) with detailed demographic and epidemiologic information from Asian population. Second, the included studies are prospective cohort studies from Asia, which minimized the possibility of recall bias attributed to differential reporting of family history of colorectal with varying cancer stages. Third, we had information on the FDR, father, mother and SDR with colorectal cancer in a subset of the population. This allowed us to explore the influence of FDR, father, mother and SDR of the affected colorectal cancer on survival.

There are several limitations in this study. First, family history information was obtained by self-report manner. This may lead to a potential for misclassification of family history. Second, we could not exclude cases with familial cancer syndromes (FAP and Lynch syndrome) from all cohorts as the cohorts did not elicit this information. Several studies have reported that those with defined genetic syndromes for colorectal cancer such as Lynch syndrome and FAP have a better chance of survival compared to those with sporadic colorectal cancer[171-173]. However, this is unlikely to alter our results significantly as familial colorectal cancer syndromes account for less than 5% of colorectal cases [161]. Third, we were unable to account for several potential confounders, including number of FDR, tumour stage at diagnosis, presence of multiple cancers, mode of presentation to hospital and surgical or clinical management. Last but not least, although we are unable to account for MSI and other mutation status due to lack of information, several studies suggested that adjustment for mismatch repair (MMR) and other mutation had minimal impact on the null associations [152, 156].

6.7 Conclusion

In conclusion, we found that having a family history of colorectal was generally not associated with overall survival and colorectal cancer-specific survival, after adjusting for other predictors of survival including age at baseline, sex, BMI, smoking and drinking status. Additional studies are necessary to be conducted to validate our finding and elucidate the potential pathways by which family history of colorectal cancer may affect survival.

CHAPTER 7. The validation of Asia-Pacific Colorectal Screening Score in the East Asia population: A study of six prospective cohorts of Asia Cohort Consortium

7.1 Abstract

Objective: The Asia-Pacific Colorectal Screening (APCS) score has been widely recognised as a risk-stratification tool that helps predict the risk for advanced colorectal neoplasia (ACN) in asymptomatic Asian population but has not yet been assessed for its validity of its use in multiple Asian countries with large participants, especially in Japanese. This study aimed to compare the external validity of the APCS to predict colorectal cancer in a large pooled data with multiple prospective cohorts from Japan, Korea and China.

Methods: 6 prospective cohorts were conducted in 3 countries across Japan, China and Korea. Cumulative scores were derived for each individual and categorized as average, moderate and high risk. The risk of colorectal cancer was assessed for each risk tier and the excess risk in moderate and high-risk tiers was compared with individuals with average risk. We evaluated the calibration, discriminatory capability of APCS scores by using receiver-operating characteristics (ROC curves) and accuracy at the individual level.

Results: A total of 175, 807 participants were included, where 45.8% were men. The average age of the participants was 55 years (SD 10.6 years); 39.47% were current or past smokers, and 47.02% were alcohol drinkers. 2639 patients (1.5%) had a family history of at least one first-degree relative with colorectal cancer. A total of 2203 (1.25%) cases of colorectal cancer were detected, in which the average age of the participants was 60.2 (SD 8.9 years), and 58.2% were men**.**

Based on the APCS score system (0-7), 25,793 participants (16.11%) were classified as belonging to the score 0, 8,251 (5.15%) to score 1, 63,216 (39.49%) to score 2, 18,935 (11.83%) to score 3, 37,976 (23.73%) to score 4, 51,83 (3.24%) to score 5,

635 (0.4%) to score 6 and 73 (0.05%) to score 7. The prevalence of colorectal cancer in score 0-7 respectively was 0.37%, 0.55%, 0.95%, 1.64%, 2.08%, 2.6%, 4.72%. 34,044 subjects (21.27%) were classified as belonging to the Avarage risk (AR) tier (score 0–1), 82,151 (51.32%) to the MR tier (score 2–3), and 43,867 (27.41%) participants to the HR tier (score 4–7). The prevalence of colorectal cancer in the AR, MR, and HR categories was 0.4%, 1.1%, and 2.18%, respectively. By logistic regression analysis, participants in the score 1, 2, 3, 4, 5, 6, 7 respectively were at a 1.5-fold, 2.6-fold, 4.6-fold, 5.7-fold, 7.2-fold, 13. 4-fold and 11.6-fold higher risk of colorectal cancer as compared with those in the score 0 in unadjusted analysis. while in adjusted analysis, participants in the score 1, 2, 3, 4, 5, 6, 7 respectively were at a 1.4-fold, 2.5-fold, 4.5-fold, 5.3-fold, 7.1-fold, 12.5-fold and 12.1-fold higher risk of colorectal cancer as compared with those in the score 0.APCS score=3 was identified as the optimal cut-off point.

34,044 subjects (21.27%) were classified as belonging to the AR tier (score 0–1), 82,151 (51.32%) to the MR tier (score 2–3), and 43,867 (27.41%) participants to the HR tier (score 4–7). The prevalence of colorectal cancer in the AR, MR, and HR categories was 0.4%, 1.1%, and 2.18%, respectively. By logistic regression analysis, participants in the MR and HR were at a 2.73-fold, 5.4-fold higher risk of colorectal cancer as compared with those in the score AR in unadjusted analysis, while in adjusted analysis(adjusted for BMI and alcohol drinking), participants in the MR and HR were at a 2.60-fold and 4.96-fold higher risk of colorectal cancer as compared with those in the AR.

Comparison of Area under ROC curve for both APCS scores and risk tiers system, the ROC curve demonstrated that 0.63 (0.62, 0.64) vs. 0.65 (0.64, 0.66) (P<0.001) in East Asia countries including Japan, Korea and China.

If APCS score as numerical variable, the OR was 1.49 (1.44-1.54, p<0.001) in an unadjusted model, and 1.48 (1.42-1.54, p<0.001) in adjusted model; If tiers were numerical variable, the OR was 2.15 (2.01-2.31, p<0.001) in an unadjusted model, and 2.08 (1.93-2.25, p<0.001) in adjusted model.

Conclusions: The APCS score can effectively identify a subset of asymptomatic Japanese and Korean population at high risk. The APCS scores were efficient to identify those subjects with high risk of colorectal cancer in East Asian population. Further studies are required to further validate West Asia, Central Asia and South-eastern Asia, and feasibility and acceptability of the APCS score to the general population in Asia will need to be further examined.

Keywords: APCS score, Asian population, colorectal cancer, risk tier

7.2 Introduction

Colorectal cancer is the third most commonly diagnosed cancer and second concerning mortality, with over 1.8 million new cases and 881,000 deaths worldwide in 2018, accounting for about 1 in 10 cancer cases and deaths [1]. Colorectal cancer has traditionally been one of the most prevalent cancers in the Western population, such as those in North America, Oceania, and Europe [3].However, there has been a rapid increase in the incidence of colorectal cancer and its associated mortality in Asia. Currently, the highest incidence rates of colorectal cancer in Asian countries are observed in both men (62 per 100,000 person) and women (37 per 100,000 person) from Japan (Miyagi Prefecture Cancer Registry) [3]. China has experienced a 2 to 4-fold increase in the incidence of colorectal cancer in the past a decade [65]. In Korea, the age-standardized incidence rate of colorectal cancer increased to 36.2/100,000 in 2010 from 30.8/100,000 in 2008 [174].

Colorectal cancer usually develops through an adenoma-carcinoma sequence, and adenomas with advanced features have been shown to exhibit higher risk. Screening for colorectal cancer, along with the removal of these premalignant lesions, is also widely accepted as an effective strategy to reduce colorectal cancer-related mortality and morbidity [175-177]. Therefore, early detection and removal of premalignant lesions by colorectal cancer screening have been advocated in many countries. However, limited resources have been an obstacle to expanding colorectal cancer screening [178]. In this regard, risk stratification models may help make colorectal cancer screening more effective.

Risk prediction models are essential tools for identifying individuals at differing risks of developing a disease, especially if they take into account disease in relatives, and

can be used to offer individually tailored prevention and clinical management. Independent validation of a risk model is essential to justify its implementation in early prevention and screening.

7.3 Background

Asia-pacific colorectal screening (APCS) score system

In 2011, the Asia-Pacific Working Group on colorectal cancer developed the Asia-Pacific Colorectal Screening (APCS) score, which is a validated risk-stratification tool that helps identify individuals at risk for advanced colorectal neoplasm amongst the asymptomatic population, which has been promulgated as an instrument to prioritize subjects for colorectal screening [89]. APCS was developed using segregation analyses based on 860 participants in the derivation set and 1892 participants in the validation set. The score is based on elementary clinical information such as age, sex, family history, and smoking status.

The APCS score was designed for a heterogeneous population comprising multiple races from many Asian countries. The validity of the APCS scoring system for predicting advanced colorectal neoplasia risk in asymptomatic Asian population has been demonstrated, into several Asian countries, including China, Korea, and Vietnam. Even one study assessed the external validation of APCS in Australia population. However, this scoring system does not assess its external validation in the Japanese population and with sizeable Asian population. The present study aimed to evaluate the efficacy of APCS scoring system for colorectal cancer screening in a large cohort of Asian population from Japan, Korea, and China.

7.4 Aims and objectives

The present study aimed to evaluate the efficacy of APCS scoring system for colorectal cancer screening in a large cohort of Asian population from Japan, Korea, and China.

7.5 Methods

7.5.1 Sample population

The Asia Cohort Consortium (ACC) is an international collaboration of cohort-based studies in Asia Pacific regions, with approximately 28 cohort studies from 9 countries, including China, Japan, Korea, Singapore, Malaysia, India, Bangladesh, Taiwan, and Iran. The ACC was first proposed in 2004 with agreement on the demand to establish an international consortium of cohorts focusing on at least 1 million healthy individuals in Asia who followed until various disease endpoints, including cancer. The study sample comprised the 6 ACC participating cohorts (Linxian General Population Trial Cohort, Miyagi Cohort Study, Ohsaki National Health Insurance Cohort Study, Three-Prefecture Cohort Study, Aichi, Korea Multi-Centre Cancer Cohort, Korean National Cancer Centre Cohort) from mainland China, Japan, Korea were included in this pooled analysis with a total of 175,807 individual data. Selected characteristics of the six cohorts were summarized in **Table 14**.

Table 14. Descriptive characteristics of the study population in each cohort

	Linxian General Population Trial Cohort (n=29,449, 16.75%)	Miyagi Cohort Study (n=45,522, 25.89%)	Ohsaki National Health Insurance Cohort Study (n=48,043, 27.33%)	Three-Prefecture Cohort Study, Aichi (3-Pref Aichi) (n=24,549, 13.96%)	Korea Multi-centre Cancer Cohort (KMCC) (n=20,574, 11.7%)	Korean National Cancer Centre Cohort (KNCC) (n=7,670, 4.36%)	Total (n=175,807)
Basic information of cohort							
Enrolment period	1984-1987	1990	1995	1985	1993-2004	2001	
Mean follow-up years (SD)	18.5(7.4)	16.2(3.7)	10.7(4.3)	11.6(5.1)	13.7(4.8)	4.8(1.7)	13.7(6.0)
Age, y[rs]							
Mean (SD)	51.9 (8.9)	52.0 (7.5)	60.2 (10.3)	55.4 (10.9)	54.1 (14.3)	52.7 (8.4)	55.0 (10.6)
Sex (n, %)							
Male	13,121 (44.55)	21,924 (48.16)	22,971 (47.81)	11,664 (47.51)	8,197 (39.84)	2,767 (36.08)	80,644 (45.87)
Family	16,328 (55.45)	23,598 (51.84)	25,072 (52.19)	12,885 (52.49)	12,377 (60.16)	4,903 (63.92)	95,163 (54.13)
Colorectal cancer[a]							
No colorectal cancer	29,386 (99.79)	44,838 (98.50)	47,262 (98.37)	24,180 (98.50)	20,283 (98.59)	7,655 (99.8)	173,604 (98.75)
Colorectal cancer	63 (0.21)	684 (1.50)	781 (1.63)	369 (1.50)	291 (1.41)	12 (0.2)	2,203 (1.25)
Age, y	51.2 (7.3)	56.0 (6.2)	63.8 (8.3)	61.0 (10.1)	61.4 (9.3)	56.8 (8.7)	60.2 (8.9)
Male (%)	18 (28.6)	421 (61.6)	495 (63.38)	200 (54.2)	140 (48.1)	9 (60)	1,283 (58.2)
Family history of colorectal cancer							
No family history	29,392 (99.81)	4,4850 (98.52)	4,6327 (96.43)	23,732 (96.67)	20,386 (99.09)	7,349 (95.81)	172,036 (97.86)
Family history[d]	57 (0.19)	672 (1.48)	1,716 (3.57)	817 (3.33)	188 (0.91)	321 (4.19)	3,771 (2.14)
1 or 2 FDR	57 (0.19)	505 (1.11)	1,108 (2.3)	817 (3.33)	152 (0.73)	NR	2,639 (1.5)
1 FDR	57 (0.19)	505 (1.11)	1,108 (2.3)	801 (3.26)	152 (0.73)	NR	2,623 (1.49)
father	NR	273 (0.6)	558 (1.16)	NR	NR	NR	831 (0.47)
mother	NR	234 (0.51)	558 (1.16)	NR	NR	NR	792 (0.45)
2 FDR	1 (0.003)	2(0.004)	8 (0.016)	16 (0.065)	NR	NR	27 (0.015)
SDR	NR	177 (0.39)	642 (1.33)	NR	NR	NR	819 (0.47)
BMI, kg/m^2[c]							
Mean (SD)	22.0 (2.48)	23.7 (3.0)	23.6 (3.3)	22.1 (2.9)	23.6 (3.3)	23.7 (3.0)	23.1(3.1)
Missing data	6 (0.02)	2,576 (5.7)	3,261(6.8)	661 (2.7)	1,610(7.8)	0	8,114(4.6)
Smoking[e] (n, %)							
Never	2,0613 (70)	1,9298 (42.39)	2,1075 (43.87)	1,1786 (48.01)	1,2785 (62.14)	5,117 (66.71)	9,0674 (51.58)
Ever	8,836 (30)	19,279 (42.35)	19,708 (41.02)	11,593 (47.22)	7,445 (36.19)	2,527 (32.95)	69,388 (39.47)
Missing data	0	6,945 (15.26)	7,260 (15.11)	1,170 (4.77)	344 (1.67)	26 (0.34)	1,5745 (8.96)
Alcohol drinking[f] (n, %)							
Never	2,2406 (76.08)	16,523 (36.3)	18,217 (37.92)	7,788 (31.72)	11,724 (56.98)	3,185 (41.53)	79,843 (45.42)
Ever	7,043 (23.92)	2,3747 (52.17)	23,885 (49.72)	15,081 (61.43)	8,431 (40.98)	4,475 (58.34)	82,662 (47.02)
Missing data	0	5,252 (11.54)	5,941 (12.37)	1,680 (6.84)	419 (2.04)	10 (0.13)	13,302 (7.57)

[a] Colorectal cancer was defined as a diagnosis of colorectal cancer during the follow-up of the cohorts.
[b] Age was defined as age at baseline.
[c] BMI was defined as BMI at baseline.
[d] Family history was defined as any family history of colorectal cancer regardless of the degree of relative information; 1 or 2 FDR was defined as at least one first-degree relative relatives diagnosed with colorectal cancer; 1 FDR was defined as one first-degree relative diagnosed with colorectal cancer; 2 FDR was defined as two first-degree relatives diagnosed with colorectal cancer; The information from Miyagi Cohort Study and Ohsaki National Health Insurance Cohort Study was extracted from the father or mother's colorectal cancer history; SDR was defined as at least one second-degree relative diagnosed with colorectal cancer.
[e] smoking was defined as the status of ever or never cigarette smoking at baseline; [f] Alcohol drinking was defined as the status of ever or never drinking at baseline.
Abbreviation: SD, standard deviation; FDR, first-degree relative; SDR, second-degree relative; NR, not reported.

Relevant data from participating cohorts were harmonized at the ACC coordinating centre at the University of Tokyo. The harmonization was discussed to ensure the included variables were correctly interpreted and extracted. Data were investigated for illogical or missing values, and queries were sent to ACC coordinating centre for clarification. The distributions of individual variables were explored to identify false or implausible values. The personal identifiers were removed, but study-specific ID numbers were retained to facilitate referral of queries back to the individual cohort. Our study was approved by the institutional review board of the ACC coordinating centre at the University of Tokyo and by the ethics committees of each cohort.

7.5.2 Statistical analysis

APCS scores (0-7) were calculated for each on the basis of their age, sex, family history, and smoking status (**Table 15.**). Age was defined as age at baseline; family history was defined as at least one first-degree relative diagnosed with colorectal cancer。

Table 15. Asia-Pacific Colorectal Screening (APCS) score system [89]

Risk factor	Criteria	Point
Age (yrs.)	<50	0
	50-69	2
	>=70	3
Sex	Female	0
	Male	1
Family history of colorectal cancer in the first-degree relative	Absent	0
	Present	2
Smoking	Absent	0
	Present	1

Smoking was defined as the status of ever (included current and former tobacco smokers)or never cigarette smoking at baseline; The variable was describe in details in previous publication of Asia Cohort Consortium[142, 143]. BMI was defined as BMI at baseline; Missing data for smoking status and BMI was accounted for by exclusion with complete data.

Our primary aim was to assess the validity of APCS score and risk tiers as a risk-prediction score for colorectal cancer in the pooled cohorts. Cochran-Armitage test for trend was used to assess the associations between the proportion of colorectal cancer in each APCS score. Logistic regression analysis was performed to assess the Odds Ratios (ORs) of colorectal cancer in APCS score 1-7 compared with Score 0 group. We fitted univariable models for the associations of APCS score and incidence of colorectal cancer, as well as a multivariable model with BMI and alcohol drinking status adjusted separately. Based on the APCS score, individuals were stratified into three groups (average risk [AR], score 0–1; moderate risk [MR], score 2–3; high risk [HR], score 4–7)

Cochran-Armitage test for trend was used to assess the associations between the proportion of colorectal cancer in each APCS risk tier. Logistic regression analysis was performed to assess the relative risk of colorectal cancer in the HR group and MR group compared with the AR group. All statistical tests were two-sided. All statistical analyses were conducted using Stata, version 14.2 (StataCorp LP, College Station, TX, USA).

Youden Index (J) is the main summary statistic of the ROC curve used in the interpretation and evaluation of an indicator, which defines the maximum potential effectiveness of a diagnostic test [179]. An optimum cut-off point can be determined by calculating Youden's index (J can be formally defined as J = maxc {Se (c) + Sp (c) − 1}) for each possible cut-off point. The cut-off point that achieves this maximum Youden's Index is referred to as the optimal cut-point (c*) because it is the cut-off point that optimizes the diagnostic test's differentiating ability when equal weight is given to sensitivity and specificity [179].

7.6 Results

7.6.1 Descriptive analysis results

A total of 175,807 participants were included, where 45.8% were men. The average age of the participants was 55 years (SD 10.6 years); 39.47% were current or past smokers, and 47.02% were alcohol drinkers. 2639 patients (1.5%) had a family history of at least one first-degree relative with colorectal cancer. A total of 2203 (1.25%) cases of colorectal c ancer were detected, in which the average age of the participants was 60.2 (SD 8.9 years), and 58.2% were men (**Table 14.**).

7.6.2 Risk stratification by APCS score

Based on the APCS score system (0-7), 25,793 participants (16.11%) were classified as belonging to the score 0, 8,251 (5.15%) to score 1, 63,216 (39.49%) to score 2, 18,935 (11.83)

to score 3, 37,976 (23.73) to score 4, 51,83 (3.24) to score 5, 635 (0.4) to score 6 and 73 (0.05) to score 7, and the prevalence of colorectal in score 0-7 respectively was 0.37%, 0.55%, 0.95%, 1.64%, 2.08%, 2.6%, 4.72%. (shown in **Table 16.** and **Figure 9.**). By logistic regression analysis, participants in the score 1, 2, 3, 4, 5, 6, 7 respectively were at a 1.5-fold (95% CI 1.04-2.12, P=0.03) , 2.6-fold (2.09-3.22, P<0.001), 4.6-fold (3.68-5.83, P<0.001), 5.7-fold (4.64-7.10, P<0.001), 7.2-fold (5.55-9.42, P<0.001), 13. 4-fold (8.83-20.38, P<0.001) and 11.6-fold (3.59-37.47, P<0.001) higher risk of colorectal cancer as compared with those in the score 0 in unadjusted analysis, while in adjusted analysis, participants in the score 1, 2, 3, 4, 5, 6, 7 respectively were at a 1.4-fold, 2.5-fold, 4.5-fold, 5.3-fold, 7.1-fold, 12.5-fold and 12.1-fold higher risk of colorectal cancer as compared with those in the score 0. (shown in **Table 16.**).

Table 16. The prevalence of colorectal cancer according to the APCS score (0-7)

Score	No. of participants (%)	Colorectal cancer (%)	Unadjusted (univariate analysis)		Adjusted (multivariate analysis) #	
Total	160,062 (100)	2,016 (1.26)	OR (95% CI)	*P*	OR (95% CI)	*P*
0	25,793 (16.11)	95 (0.37)	Ref.		Ref.	
1	8,251 (5.15)	45 (0.55)	1.48 (1.04, 2.12)	0.03	1.43 (1.0, 2.05)	0.05
2	63,216 (39.49)	600 (0.95)	2.59 (2.09, 3.22)	<0.001	2.48 (1.99, 3.10)	<0.001
3	18,935 (11.83)	319 (1.64)	4.64 (3.68 5.83)	<0.001	4.46 (3.44, 5.53)	<0.001
4	37,976 (23.73)	789 (2.08)	5.74 (4.64, 7.10)	<0.001	5.26 (4.21, 6.57)	<0.001
5	5,183 (3.24)	135 (2.6)	7.23 (5.55, 9.42)	<0.001	7.09 (5.38, 9.33)	<0.001
6	635 (0.4)	30 (4.72)	13. 41 (8.83, 20.38)	<0.001	12.52 (8.19, 19.14)	<0.001
7	73 (0.05)	3 (4.11)	11.59 (3.59, 37.47)	<0.001	12.14 (3.74, 39.46)	<0.001

*Consider the risk score as ordinal variable. # Adjusted for BMI and alcohol drinking
Abbreviation: CI, confidence interval; OR, odds ratio.

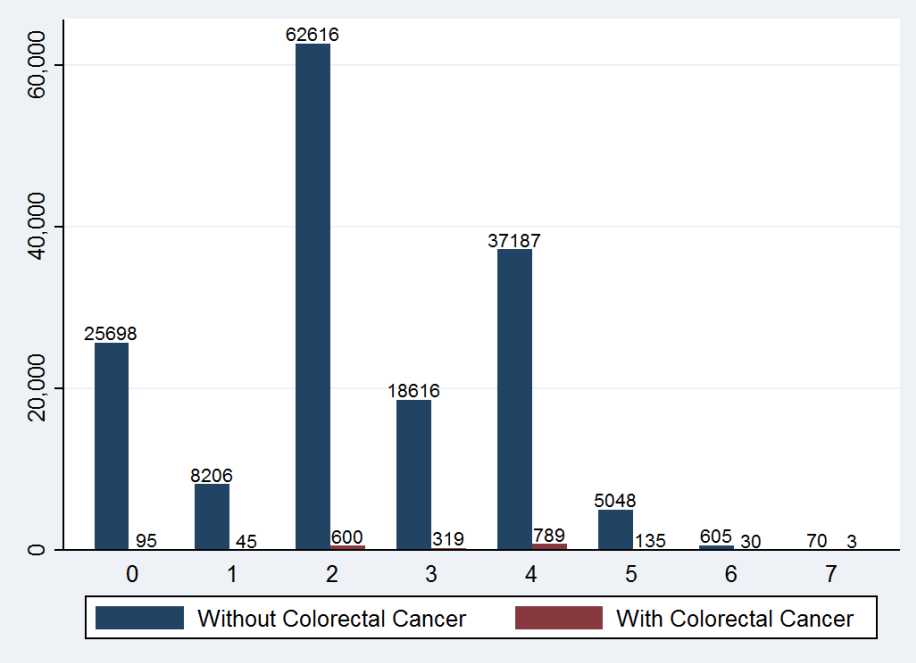

Figure 9. The number of participants with or without a diagnosis of colorectal cancer according to the APCS score (0-7)

The ROC curve demonstrated that Area under ROC curve was 0.65 with the APCS score system in the diagnosis of colorectal cancer in East Asia countries including Japan, Korea and China (shown in **Figure 10.**)

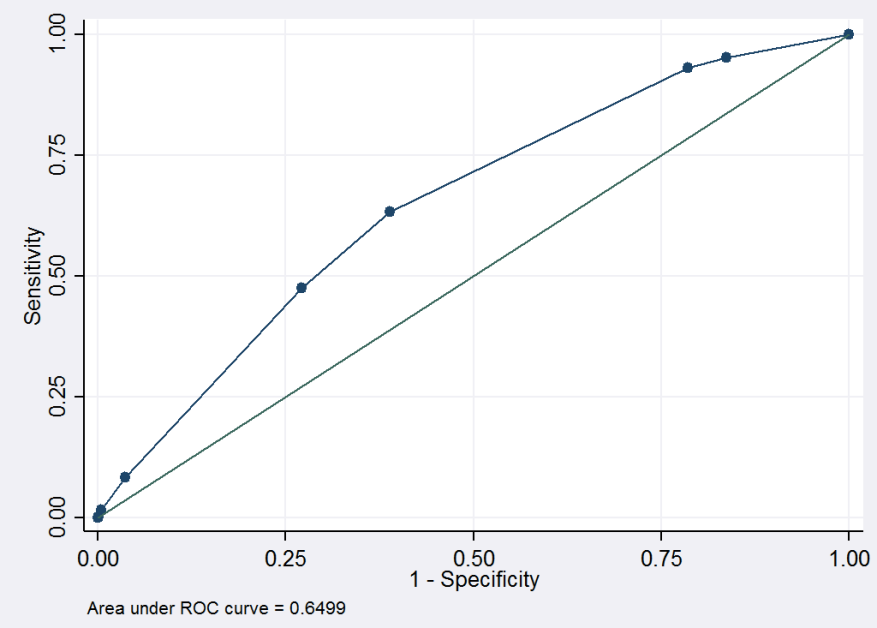

Figure 10. The Area under ROC curve of APCS score (0-7) in the diagnosis of colorectal cancer

7.6.3 The optimal cut-off point of APCS score

To investigate the optimal cut-off point of APCS score (0-7), Youden's index was calculated for each possible cut-off point (results shown in **Table 17.**). The cut-off point that achieves this maximum Youden's Index is referred to as the optimal cut-point (c*) because it is the cut-off point that optimizes the diagnostic test's differentiating ability when equal weight is given to sensitivity and specificity (details shown in **Table 18.**) APCS score=3 was identified as the optimal cut-off point, the sensitivity and specificity of the cut-off was 63.3% and 61.1%, respectively. The positive predictive value of the cut-off was 99.2% and negative predictive value was 2% (shown in **Table 19.**). The percentage of individuals with colorectal cancer when cut-offed by the APCS socre=3, was 0.76% (APCS score <3) and 2.03% (APCS score>=3) (show in **Table 20.**).

Table 17. The sensitivity and specificity of each cut-off point of APCS score (0-7) and its Youden's Index.

cut-off	sens	spec	sens+spec	Youden's index	correctly classified	LR+	LR-
>=0	100	0	100	0	1.26%	1	
1	95.29	16.26	111.55	0.1155	17.26%	1.1379	0.2898
2	93.06	21.45	114.51	0.1451	22.35%	1.1847	0.3237
3	63.29	61.07	124.36	0.2436 (c*)	61.10%	1.6259	0.601
4	47.47	72.85	120.32	0.2032	72.53%	1.7484	0.7211
5	8.33	96.38	104.71	0.0471	95.27%	2.3013	0.9511
6	1.64	99.57	101.21	0.0121	98.34%	3.8327	0.9978
7	0.15	99.96	100.11	0.0011	98.70%	3.36	0.999

c* stands for optimal cut-point of APCS score
Abbreviation: LR, likelihood ratio; sens, senstivity; spec, specificity

Table 18. Diagnostic accuracy parameters of the optimal cut-off point of APCS score (=3)

Variables	Estimate
Sample size =	160,062
Prevalence =	1.26%
Sensitivity =	63.3(95% CI 61.2, 65.4)
Specificity =	61.1(95% CI 60.8, 61.3)
PPV =	2%
NPV =	99.2%
LR + result*=	1.626
LR - result*=	0.601

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 19. Number of indivduals of colorectal cancer and non colorectal cancer with the cut-off point of APCS score

APCS score (cut-off point)	Without colorectal cancer	With colorectal cancer	Total
<3	96520 (99.24)	740 (0.76)	97260
>=3	61526 (97.97)	1276 (2.03)	62802
Total	158046 (98.74)	2016 (1.26)	160062

7.6.4 Subgroup analysi of Area under ROC curve for APCS score in cohort and country.

Subgroup analysis of the Area under ROC curve in each cohort demonstrated similar Area under ROC curve (0.62-0.65) except Chinese cohort (Linxian General Population Trial Cohort) and the similar results shown in each country (0.62-0.63) (results shown in **Table 20.** and **Table 21.**).

Table 20. Subgroup analysis of the Area under ROC curve in each cohort.

Cohorts	No. of Observations	ROC Area	95%CI
Linxian General Population Trial Cohort	29,449	0.43	0.37-0.49
Miyagi Cohort Study	45,522	0.65	0.63-0.67
Ohsaki National Health Insurance Cohort Study	48,043	0.64	0.62-0.66
Three-Prefecture Cohort Study, Aichi (3-Pref Aichi)	24,549	0.62	0.60-0.65
Korea Multi-centre Cancer Cohort (KMCC)	20,574	0.63	0.60-0.66
Korean National Cancer Centre Cohort (KNCC)	7,670	0.64	0.49-0.79

Table 21. Subgroup analysis for the Area under ROC curve in each country.

Country	No. of Observations	Under ROC Area	95%CI
China	29,449	0.45	0.38-0.51
Japan	102,739	0.62	0.61-0.63
Korea	27,874	0.63	0.60-0.65

7.6.5 The Risk stratification by APCS risk tiers

34,044 subjects (21.27%) were classified as belonging to the AR tier (score 0–1), 82,151 (51.32%) to the MR tier (score 2–3), and 43,867 (27.41%) participants to the HR tier (score 4–7). The prevalence of colorectal cancer in the AR, MR, and HR categories was 0.4%, 1.1%, and 2.18%, respectively (shown in **Table 22.** and **Figure 11.**).

By logistic regression analysis, participants in the MR and HR were at a 2.73-fold (95% CI 2.29-3.27, P<0.001) , 5.4-fold (4.52-6.45 P<0.001) higher risk of colorectal cancer as compared with those in the score AR in unadjusted analysis, while in adjusted analysis(adjusted for BMI and alcohol drinking), participants in the MR and HR were at a 2.60-fold (2.18-3.13, P<0.001) and 4.96-fold (4.13-5.97, P<0.001) higher risk of colorectal cancer as compared with those in the AR (shown in **Table 25.**).

Table 22. The prevalence of colorectal cancer and according to the APCS tiers (AR, MR, and HR)

Risk tier * (APCS score)	**No. of participants (%)**	**Colorectal cancer (%)**	**Unadjusted (univariate analysis)**		**Adjusted (multivariate analysis) #**	
Total	160,062 (100)	2016 (1.26)	OR (95% CI)	*P*	OR (95% CI)	*P*
AR: Average Risk (0-1)	34,044 (21.27)	140 (0.4)	Ref.		Ref.	
MR: Moderate Risk (2-3)	82,151 (51.32)	919 (1.1)	2.73 (2.29-3.27)	<0.001	2.60 (2.18-3.13)	<0.001
HR: High Risk (4-7)	43,867 (27.41)	957 (2.18)	5.40 (4.52-6.45)	<0.001	4.96 (4.13-5.97)	<0.001

*Consider the risk tier as ordinal variable. # Adjusted for BMI and alcohol drinking.
Abbreviation: CI, confidence interval; OR, odds ratio.

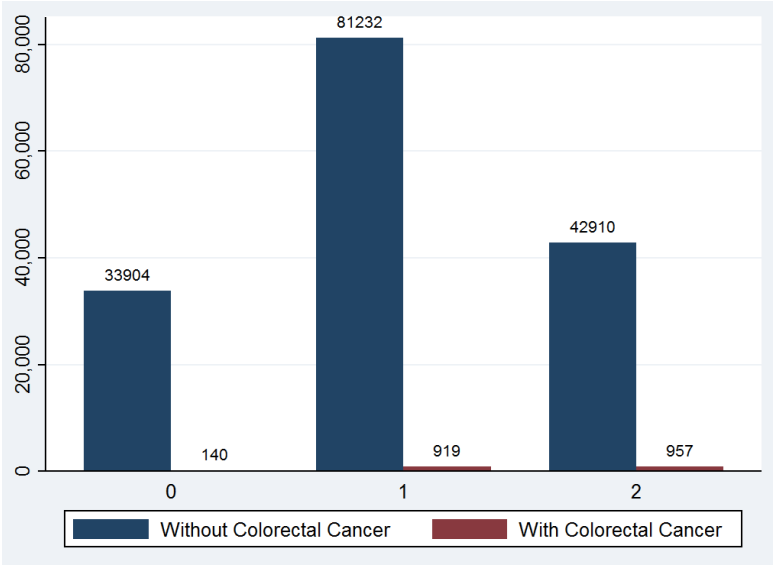

Figure 11. The number of participants with or without a diagnosis of colorectal cancer according to the APCS risk tiers (0=AR, 1=MR, 2=HR).

The ROC curve demonstrated that Area under ROC curve was 0.63 with the APCS risk tier system (AR, MR and HR) in the diagnosis of colorectal cancer in East Asia countries including Japan, Korea and China (shown in **Figure 12.**).

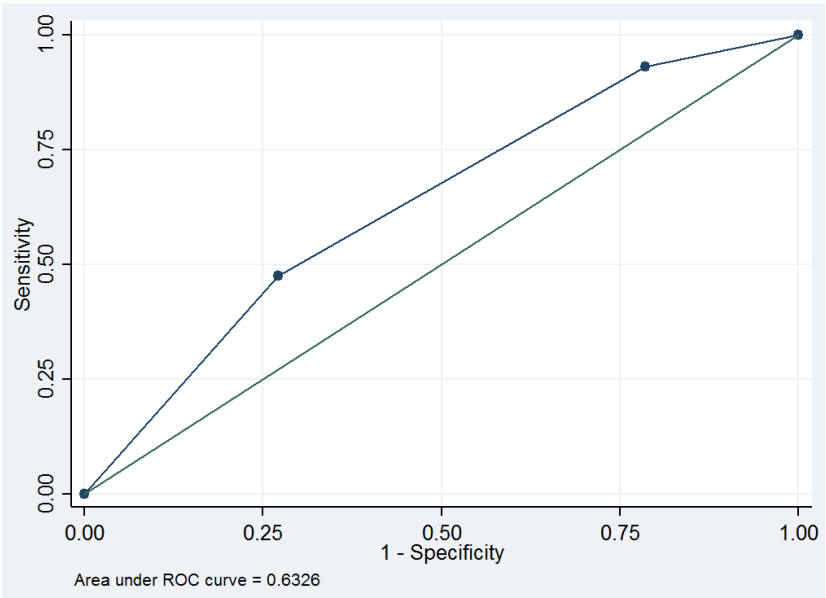

Figure 12. The Area under ROC curve of APCS risk tiers (AR, MR, and HR) in the diagnosis of colorectal cancer.

Comparison of Area under ROC curve for both APCS scores and risk tiers system, the ROC curve demonstrated that 0.63 (0.62, 0.64) vs. 0.65 (0.64, 0.66) (P<0.001, show in **Table 23.**).

Table 23. Area under ROC curve of both APCS score and risk tiers

		No. of Observations	**ROC Area**	**95% CI**	**p-value**
APCS	Score (0-7)	160,062	0.65	0.64-0.66	<0.001
	Risk tier (AR, MR, HR)	160,062	0.63	0.62-0.64	

7.6.6 Subgroup analysis of Under ROC Area for APCS risk tiers in each country.

Subgroup analysis of the Area under ROC curve for APCS risk tiers in Japan and Korea demonstrated similar ROC area (0.64) except Chinese cohort (Linxian General Population Trial Cohort) (results shown in **Table 24.**).

Table 24. subgroup analysis for APCS risk tiers for countries

Country	**No. of Observations**	**ROC Area**	**95%CI**
China	29,449	0.43	0.37-0.49
Japan	10,2739	0.64	0.63-0.65
Korea	27,874	0.64	0.62-0.67

7.6.7 Sensitivity analysis

If setting APCS score as numerical variable, the OR was 1.49 (1.44-1.54, p<0.001) in unadjusted model, and 1.48 (1.42-1.54, p<0.001) in adjusted model; If setting category risk tiers were numerical variable, the OR was 2.15 (2.01-2.31, p<0.001) in unadjusted model, and 2.08 (1.93-2.25, p<0.001) in adjusted model.

7.7 Discussion

The APCS score can effectively identify a subset of asymptomatic Japanese and Korean population at high risk for colorectal cancer, and for non-diabetic population, the APCS score is more useful to identify the high risk for colorectal cancer in the Asian population. Further studies are required to identify other risk factors, and the acceptability of the score to the general population will need to be further examined.

The APCS scoring system can be used in individual screening for sporadic colorectal cancer in Chinese population [180].The combination of APCS scores and obesity significantly improves the efficacy of screening.

The Korean Colorectal Screening (KCS) score was developed by optimizing and adjusting the Asia-Pacific Colorectal Screening (APCS) score to predict advanced neoplasia in an asymptomatic Korean population, which includes age, sex, body mass index, smoking and family history of colorectal cancer with good discriminative power (ROC=0.681) and higher sensitivity compared with APCS score for the high-risk tier [141].

A study of 1,157 Chinese individuals with suspected coronary artery disease found that even in the absence of family history of colorectal cancer, CAD patients at a high risk of developing advanced colorectal neoplasms classified by the APCS score still showed a remarkably high prevalence of colorectal adenomas [181]. APCS was validated in 645 Australian people from Sydney, to a great extent than in the Asian population, independent to symptoms [182].Li and his colleagues validated APCS score in 1,010 asymptomatic individuals who underwent colonoscopy screening in Beijing and found that APCS score can effectively identify a subset of the asymptomatic Chinese individuals at high risk for advanced colorectal neoplasm [183].

Another study recruited 5,899 Chinese individuals in a colonoscopy screening program [184] and implemented six scoring tools, from the U.S, Spain, Germany, Poland; and the Korean colorectal screening (KCS) score, including the modified Asia pacific colorectal screening (APCS) scores{Sung, 2018 #6142}, which include additional BMI as the predictor in the model. The modified APCS scoring system had the highest c-statistics (0.65, 95% C.I. 0.58–0.72).

A study from Vietnam, evaluated the APCS score in 404 patients with irritable bowel syndrome (IBS), and found that APCS useful to identify IBS patients with high risk of advanced colorectal neoplasms for colonoscopy priority [185].Sung's team validated a modified risk algorithm based on the APCS score incorporating BMI with 5,744 individuals recruited prospectively for a colonoscopy in Hong Kong, which can improve risk prediction of advanced neoplasia and reduce colonoscopy resources [186].

The APCS score can effectively identify a subset of asymptomatic Japanese and Korean population at high risk. The APCS scores were efficient to identify those subjects with high risk of colorectal cancer in East Asian population. Further studies are required to further validate West Asia, Central Asia and South-eastern Asia, and feasibility and acceptability of the APCS score to the general population in Asia will need to be further examined. The external validation of the score demonstrates heterogeneity of the population under review which poses serious challenges and has been identified as a future research direction. The modified APCS score can also be investigated in the Asian population in the future studies.

CHATPER 8. Synthesis and Discussion

8.1 Summary of research contributions and results

Chapter 4: The inconsistent report of association of family history and risk of colorectal cancer in Asian countries, the evidence of the association of family history and colorectal cancer in Asian countries from current literature is lacking. I conduct a systematic review and meta-analysis on association between at least one first-degree relative family history and the risk of the colorectal cancer in Asian countries. I found that the association of colorectal cancer with having at least one first-degree relative family history of colorectal cancer differed by Asian region: 1.69 (1.46, 1.96) for East Asia; 3.44 (2.32, 5.10) for West Asia; 5.14 (2.44, 10.8) for South-Eastern Asia. The association is heterogenous in Asian countries. This information may be useful to triage the populations in Asian countries for colorectal cancer screening by the strength of family history in different regions of Asia.

Chapter 5: After conducting the systematic review and meta-analysis on the association of family history and risk of colorectal cancer, I found that most of the studies performed in Asian countries are case-control and cross-sectional studies. The studies in Asian countries have relatively small sample size and the definition of family history is not clear. I conducted a pooled analysis of 6 prospective cohorts from Asia Cohort Consortium with existing data to assess the association between family history and incidence of colorectal cancer in East Asian countries. I found that the prevalence of the family history is quite low (2.14%), especially in China (0.19%), which support evidence that family history of colorectal cancer is associated with incidence of colorectal cancer in East Asia.

Chapter 6: After I studied the association of family history and incidence of colorectal cancer, I was thinking that whether family history associated with the mortality of the colorectal cancer in Asian countries. Not many studies in Asian countries conducted for the association of family history and mortality of colorectal cancer in Asian countries. I conducted a pooled analysis with the same 6 prospective cohorts from Asia Cohort Consortium to investigate the the association between family history and mortality of colorectal cancer in East Asia. I found that there was no evidence that family history of colorectal cancer is associated with of colorectal cancer, neither colon cancer nor rectum cancer. However, survival is a complicated process, and it depends on stage of the colorectal cancer, the treatment method, the condition of the patient.

Chapter 7: The Asia-Pacific Colorectal Screening (APCS, 2011) score has been recognised as a risk-stratification tool for colorectal cancer in Asian population. However, APCS was designed with clinical-based model and internal validation, and then have external validation in China, Korea and Vietnam, as well as Australia. APCS did not assess its external validation in the Japanese population and with sizeable Asian cohorts. I conducted an external validity of the APCS to predict colorectal cancer in pooled large prospective cohorts from Japan, Korea and China, and found that APCS is a fairly good risk-stratification tool for the average risk population in East Asian countries.

8.2 Strengths and limitations of this thesis

Strengths

- Because of the current study with limitation of sample size and countries to provide a robust evidence for association of family history and colorectal cancer in Asian countries, my thesis used a large pooled database from Japan, China and Korea to investigate the association of family history and colorectal cancer, including the association with incidence and mortality of the colorectal cancer.
- Conducted systematic literature review of the current research of family history and colorectal cancer in Asian countries
- Understand the association of family history and colorectal cancer incidence and mortality in East Asia countries by using 6 East Asian cohorts
- External validated the APCS score system in by using 6 East Asian cohorts.

Limitations

- Since ACC has 31 Participating Cohorts (2019) which covers majority of Asian countries. However, the information of family history did not contain in most of the cohorts in ACC, therefore in my thesis, I only investigate the family history and risk of colorectal cancer in East Asia including Japan, Korea and China.
- Family history information may underestimate according the its prevalence.
- Since the data availability, the inability to exclude known hereditary colorectal cancer syndromes is a limitation of this research, which may lead to bias of the results.

8.3 Knowledges translation framework

This thesis suggested that family history is a risk factor for incidence of colorectal cancer, bur may not a predictor for prognosis of colorectal cancer. The APCS score include family history may be a as a score system for colorectal cancer screening in Asia countries, however, we may conduct an expanded study and include more predictors (modified APCS score) to estimate its effectiveness. This thesis provides a clear picture of family history and its association with colorectal cancer in Japan and Korea and provide some clue of the association for the Chinese population, however it may not a robust result since the data shows some inconsistence and bias. Furthermore, we do not know much about other Asian countries.

8.4 Implications for future research

- Whether family history-based screening strategy is a potential goal for Asian countries?
- Will the family history of adenoma be also recognized as an important risk factor in family history-based screening strategy in Asia , represent another future research direction?
- What would be the target population for the screening program in Asian countries (Average risk, Elevated risk or High risk) ?
- What method and when to screen in Asian countries?
    - IFOBT vs. colonoscopy?
    - Begin at 50 years, earlier for high risk and later for low risk?
- How will be predicted efficacy of family history-based screening in Asian countries?
    - Sensitivity for advanced adenoma and colorectal cancer?

- Number of adenomas and colorectal cancer identified?
- Number of adenomas and colorectal cancer not screened for?

8.5 Implications for practice

- May suggest that Asia cohort consortium add family history information for the survey in the countries which did not cover yet for further investigation of the association with colorectal cancer.
- Cost-effective analysis to estimate whether family history can be applied to the family history-based screening program to provide the evidence in Asian countries.
- May suggest that the policy makers to implement the family history in the screening program in Asian countries.
- The collection of accurate family history information is also a barrier for implementing a family history-based screening program. Currently, the electronic-based family history tools are available and can support with this collection. (The available tools for family history collection with or without colorectal cancer risk assessment in Supplementary 11)

8.6 Implications for screening policy

The decision to start a family history-based risk strategy for colorectal cancer screening or not in Asian countries, and to choose the optimal screening strategy for the local setting, are not one easy choice. The practice and experience from other types of cancer screening strategies which have been implemented for a longer time, including prostate-specific antigen (PSA) for prostate cancer screening and mammography for breast cancer screening, demonstrate that the efficacy of screening when implemented in the general population in the

realworld scenario might be different from the effect that was observed in the randomized controlled trials that lead to wide-spread screening. Furthermore, the negative consequences of screening (including false positive tests, overdiagnosis, and overtreatment) have not been thoroughly investigated before screening was implemented. We should very be cautious to suggest the family history to be included in the colorectal cancer screening strategy, since family history is rare, if the risk assessment is based entirely on family history then it may miss a lot of the individual risk factors for colorectal cancer screening.

CHATPER 9. Conclusion

In East Asia, colorectal cancer incidence has been increasing over last few decades; however, many countries are still lack of strategies on colorectal cancer screening. This thesis investigated the prevalence of family history of colorectal cancer in the population, family history association with colorectal cancer incidence and mortality, and its role in disease risk prediction in East Asia, using prospective data of 175,000 people from 3 countries.

- The association of first-degree relative family history and risk of colorectal cancer is heterogenous in Asian countries.
- The prevalence of the family history is quite low-2.14%
- Family history of colorectal cancer is associated with incidence of colorectal cancer in East Asian countries.
- No evidence of family history of colorectal cancer is associated with mortality of colorectal cancer (neither colon cancer nor rectum cancer).
- APCS is a fairly good risk-stratification tool for colorectal cancer in East Asia.

The thesis contributes to the academic understanding of family history and risk of colorectal cancer in Asian countries, especially in East Asia. The findings are useful to guide colorectal cancer screening strategies in East Asia.

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Appendices

Appendix A. Abstract and Poster Presentation

Family History and the Risk of Colorectal Cancer or Adenoma for Asian Countries: A Meta-Analysis and Systematic Review

Lin Zhang, [1] Ghazaleh Dashti, [1] Mark A. Jenkins, [1] Aung Ko Win[1]

[1] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia.

Purpose: To investigate the estimates for association between a family history of colorectal cancer and the risk of colorectal cancer and adenoma for Asian countries.

Methods: We performed an electronic literature search using PubMed Medline and Embase to search all relevant articles published from 1980 to April 2016 using a combination of relevant medical subject heading terms and keywords. The search was extended by manually screening the reference lists of all included papers. Studies were included if they were observational studies that investigated the association between a family history of cancer specified to site and colorectal cancer or adenoma in Asian countries. Studies were excluded if they were review/editorial articles or not presented in English or did not well define a family history. We performed a random effects meta-analysis to obtain summary relative risk (RR) and corresponding confidence interval (CI) for association between a first-degree family history of colorectal cancer and the risk of colorectal neoplasia (cancer and adenoma combined) and separately for colorectal cancer and adenoma.

Results: Of a total of 1,066 studies from literature search, we included 25 studies containing 14 case-control, 3 cross-sectional and 8 cohort studies. The summary RRs (95% CIs) were 1.92 (1.61-2.28) for colorectal cancer, 2.63 (1.58-4.39) for colorectal adenoma, and 1.98 (1.72-2.26), respectively. The summary RRs for colorectal cancer were different between case-control and cohort studies (RR 2.35; 95% CI, 1.89-2.93 vs. RR 1.18; 95% CI, 1.03-1.34; $p = 0.003$). The association did not change substantially after adjusting for country of study ($p = 0.09$) or publication year ($p = 0.77$).

Conclusion: These summary estimates for associations between a family history of colorectal cancer and the risk of colorectal cancer or adenoma will be useful for targeted colorectal cancer screening depending on the strength of family history in Asian countries.

Family History and the Risk of Colorectal Cancer or Adenoma for Asian Countries: A Meta-Analysis and Systematic Review

Lin Zhang, Ghazaleh Dashti, Mark A. Jenkins, Aung Ko Win

Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia.

Background

- Colorectal cancer (CRC) is the third most commonly diagnosed malignancy for men and second for women worldwide, with 1.36 million newly diagnosed cases in 2012 globally.
- The incidence of CRC substantially varies geographically across worldwide. Some Asian countries where incidence of CRC was historically low, such as Japan, Singapore, China, Philippines and Israel are experiencing rising incidences. However, reasons for this increase are unknown.
- Family history of CRC is a strong risk factor for CRC but the degree at risk varies depending on the closeness of family members, and number and age at diagnosis of affected relatives.
- Currently, CRC screening guidelines used in many countries are based on family history information to define risk categories in the population, and recommend more intensive screening strategies for individuals with a strong family history of CRC.
- The size of families in some Asian countries (for example, due to One Chile Policy in China) seems to be different from Western countries. Therefore, the prevalence of family history, and the association between family history and the risk of colorectal cancer are important to investigate for Asian countries. These information are important for recommending relevant colorectal cancer screening based on family history.

Aims

- To conduct a systematic review and meta-analysis of existing literature to investigate the association between family history of colorectal cancer and the risk of colorectal cancer or adenoma for Asian countries.
- To estimate the prevalence of family history of colorectal cancer in the Asian countries

Methods

- The systematic review protocol was submitted to the international database of prospectively registered systematic reviews (PROSPERO registration number CRD42016045634).

Search strategy

- An electronic literature search was performed using PubMed Medline and Embase to search all relevant articles that reported association between family history of colorectal cancer and the risk of colorectal cancer or adenoma for Asian countries published from 1980 up to April 22, 2016.
- The Medical Subject Heading (MeSH) terms were used in conjunction with the following key words to search for the studies: 'risk factor' ⅄ 'family history' ⅄ 'familial risk' ⅄ 'familial aggregation' ⅄ 'relatives' AND 'colorectal neoplasm' ⅄ 'colon neoplasm' ⅄ 'colorectal cancer' ⅄ 'colorectal neoplasm' ⅄ 'colon cancer' ⅄ 'colorectal neoplasms' AND 'Asian'.

Eligibility criteria

- Studies were eligible for inclusion if they were: 1) case-control, cross-sectional or cohort studies that investigated the association between family history of CRC and the risk of CRC or adenoma for Asian countries; 2) written in English language; and 3) peer-reviewed original research articles.
- Studies were excluded if they: 1) were reviews, editorial, case report or guideline articles; 2) did not clearly define family history. 3) studied biological mechanism.
- If data source were duplicated in more than one study, only the most recent study was included in the meta-analysis.

Data extraction

- The following data were extracted from each study: name of journal, title, first author, year of publication, type of study, studied population in terms of country, selection criteria and numbers of cases and controls (for case-control studies), selection criteria and numbers of participants and cases (for cohort studies), definition of exposure, definition of outcome, result (odds ratio (OR), relative risk (RR)[,] and corresponding 95% confidence interval (95% CI), and adjusted variables.

Statistical Analysis

Meta-analysis

- Random-effects and fixed-effect meta-analyses were performed to generate summary RR and corresponding 95% CI for association between a first-degree family history of CRC and the risk of colorectal neoplasia (cancer and adenoma combined), and separately for colorectal cancer and adenoma.
- Heterogeneity of effects across studies was assessed by using the I^2 statistic.

Subgroup analysis & Meta-regression

- Subgroup analyses were performed by study design (case-control/cross-sectional and cohort), year of publication (before 2011 and 2011 onwards) and region (West Asia, East Asia, Southeast Asia, and all Asia). Meta-regression models were conducted including these variables in the models.

Publication bias

- Publication bias were evaluated by Begg's funnel plots and quantified by Egger's statistical test.
- All statistical analyses were performed by using Stata 13.0 (StataCorp LP, College Station, TX).

Population attributable risk

The proportion of CRCs attributable to family history in the general population, i.e. population attributable risk was calculated using the formula

$$\mathrm{PAR} = \frac{P\,(\mathrm{RR}-1)}{P\,(\mathrm{RR}-1)+1}$$

where PAR is population attributable risk, P is the estimated proportion of participants with a first-degree family history (from population-based cohort studies), and RR is the pooled RR estimated from this meta-analysis.

Results

Figure 1. Flow diagram of the selection of studies.

Figure 2. Meta-analysis of association between family history of CRC and the risk of CRC or adenoma

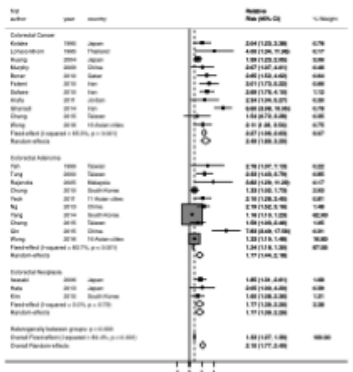
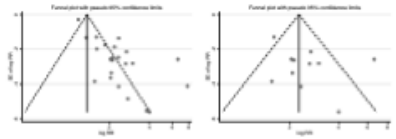


Table 1. Summary of subgroup analyses

	Number of studies	Fixed-effect Summary RR (95% CI)	I^2 (%)	T^2	Ratio of RRs (95% CI)	p-value
Overall meta-analysis						
Before 2011	10	2.34 (1.86-3.02)	81.6	0.14	1.00	
2011 onwards	13	2.71 (1.77-2.98)			1.02 (0.68-1.53)	0.90
Study type						
Case-control/ Cross-sectional	16	2.47 (1.84-3.19)	86.3	0.14	1.00	
Cohort	7	1.91 (1.84-2.34)			1.19 (0.76-1.87)	0.42
Region						
West Asia	5	3.27 (2.24-4.79)			1.00	
East Asia	14	1.82 (1.63-2.40)				
Southeast Asia	2	3.81 (1.81-8.44)	83.7	0.88	1.19 (0.86-1.37)	0.83
All Asia	2	2.10 (1.47-3.81)				

Abbreviations: RR, Relative risk; I^2, Percent residual variance due to heterogeneity; T^2, Residual maximum likelihood estimate of between-study variance; CI, Confidence interval

Figure 3. Funnel plot for (A) all studies included in the meta-analysis and (B) studies of association between family history and the risk of colorectal cancer



Egger's statistical test P <0.001 | Egger's statistical test P = 0.19

Population attributable risk

Prevalence of a first-degree family history of CRC = **5.6% (95% CI 5.4% to 5.8%)**

Population Attributable Risk = **5.8% (95% CI 4.1% to 7.7%)**

Conclusion

These summary estimates for associations between a family history of CRC and the risk of CRC or adenoma will be useful for targeted colorectal cancer screening depending on the strength of family history in Asian countries.

Prevalence of a first-degree family history of CRC in the Asian countries, esp. East Asia, appeared to be lower than the Western countries.

Funding

National Health and Medical Research Council, Australia
- Program grant (MJ)
- Fellowships (AKW, MAJ)

The University of Melbourne, Australia
- Melbourne International Fee Remission Scholarship (LZ)
- Melbourne International Research Scholarship (LZ)
- Public Health Investing in Research Students' Training (LZ)

Peking Union Medical College Hospital, China
- One Hundred Elite Scholarship (LZ)

Appendix B: Oral Presentation1

Family history and risk of colorectal cancer in Asian population--Pooled analysis of Asia Cohort Consortium (ACC)

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University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre

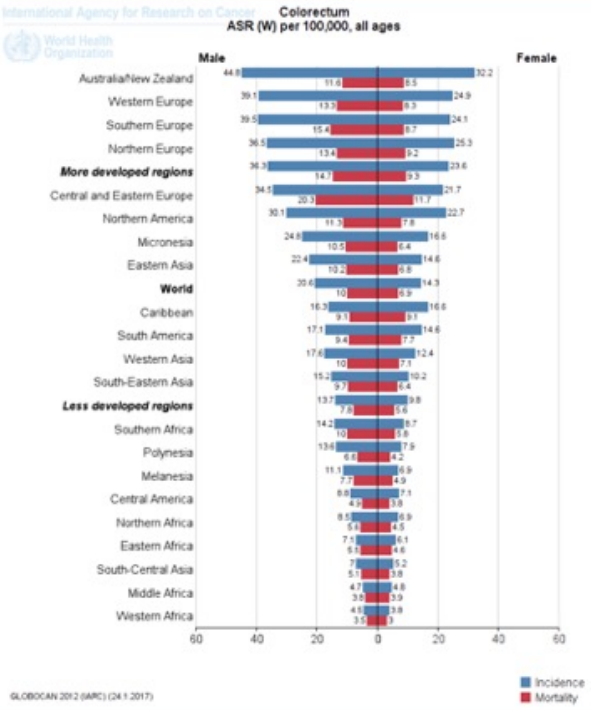
04/09/2018

Background

Colorectal Cancer (CRC)

is **third** leading causes of cancer globally. (*Ferlay et al. 2015*)

- **1.36 million** newly diagnosed cases in 2012.
- The **third** most commonly diagnosed cancer in **men** and **second** in **women.**



Ferlay, J., et al. Int J Cancer, 2015.

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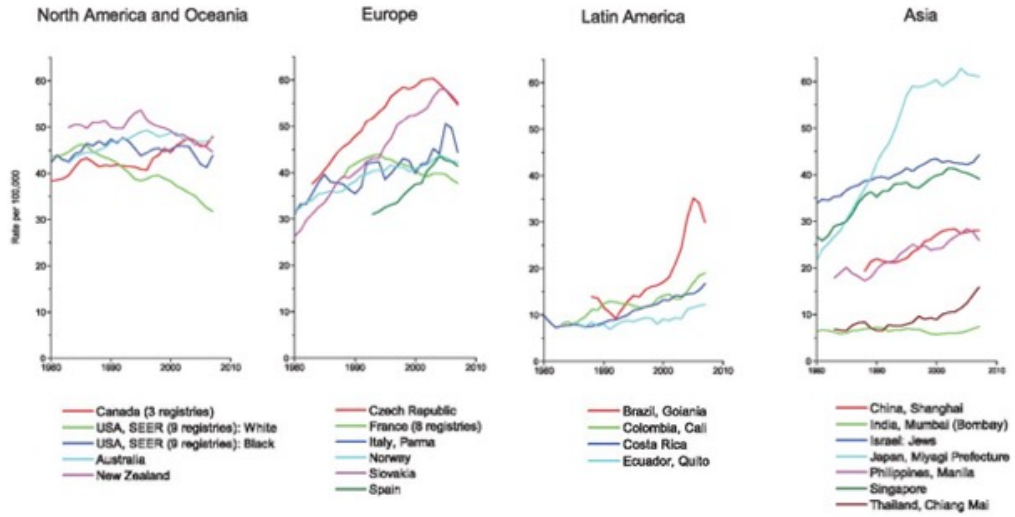
Background

Colorectal Cancer incidence trends for *Male*, select countries, 1980-2007



Well studied

Under studied

Data source: Cancer Incidence in Five Continents (CI5plus), International Agency for Research on Cancer (IARC)

Torre, L.A., et al., Cancer Epidemiol Biomarkers Prev, 2016

3

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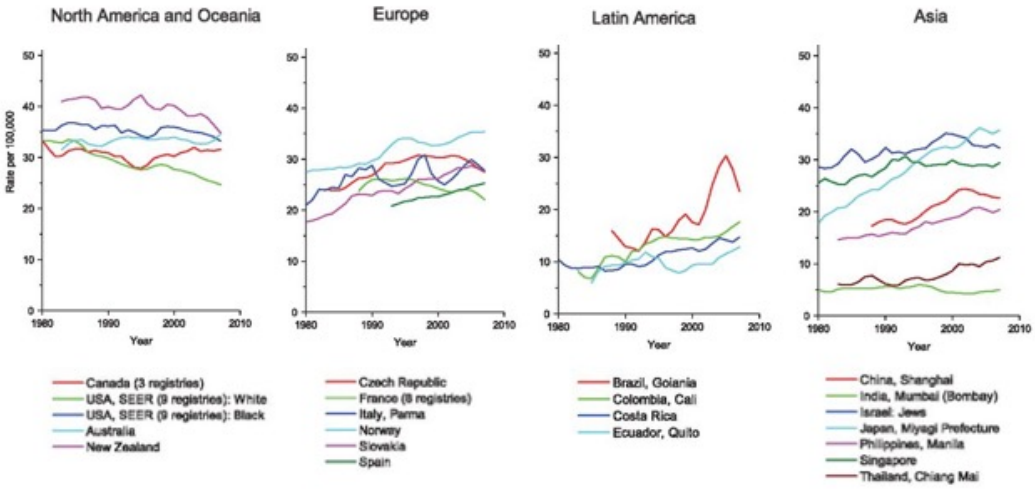
Background

Colorectal Cancer incidence trends for *Female*, select countries, 1980-2007



Well studied

Under studied

Data source: Cancer Incidence in Five Continents (CI5plus), International Agency for Research on Cancer (IARC)

Torre, L.A., et al., Cancer Epidemiol Biomarkers Prev, 2016

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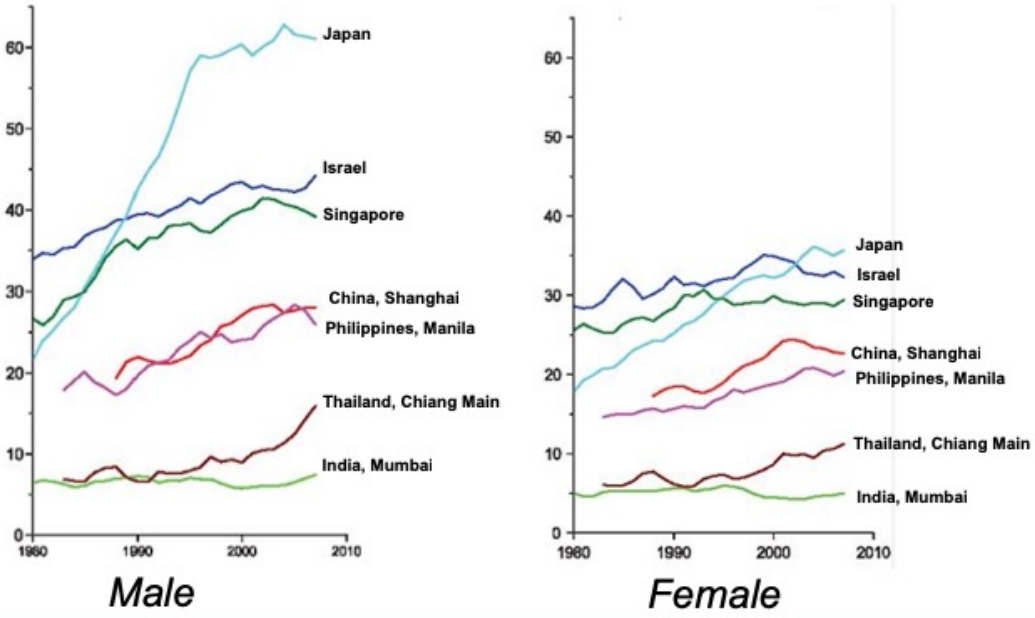
Background

Colorectal Cancer incidence trends for *Male and Female* in Asian Countries, 1980-2007



Torre, L.A., et al., Cancer Epidemiol Biomarkers Prev, 2016

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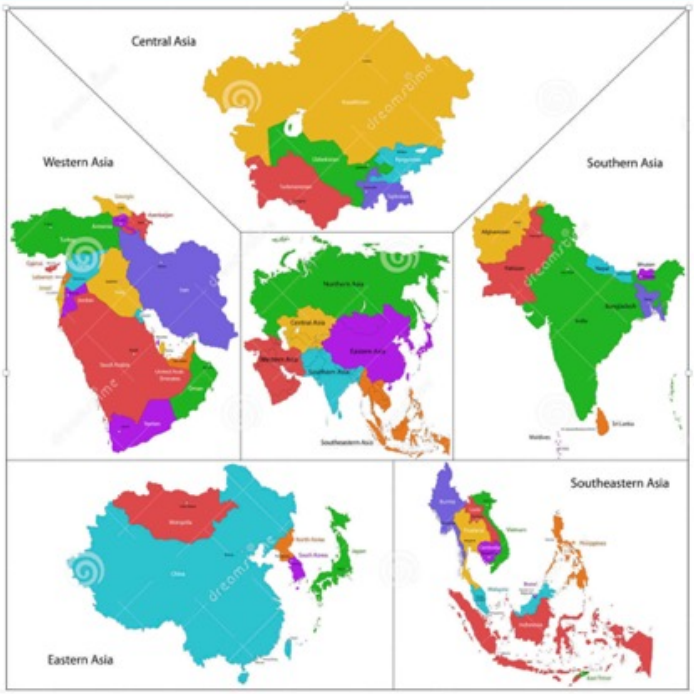
Background



Asia is world largest and most populous continent, including **5 subregions**.

According to United Nation definition, Asia has **48 countries** and **6 states** with limited international recognition.

Population: **4.436 billion** (2016), accounts for **60%** of world's population.

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Incidence and mortality of colorectal cancer in Asia

- Traditionally, highest incidence in western countries
- Currently, the incidence of CRC in Asia is increasingly high
- The highest CRC incidence rates in both males (620/100,000) and females (37/100,000) currently are observed in (**Miyagi Prefecture Cancer Registry**) .
- Heterogeneous pattern across different countries in Asia
- Increasing incidence in Asian countries are unknown
  - more westernized lifestyle
  - dietary habits change.

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Risk factors of colorectal cancer

Risk ↑

- aging
- overweight
- diabetes
- processed and red meat
- alcohol
- smoking
- family history of CRC
- personal history CRC
- personal history of inflammatory bowel disease(IBD)
- Inherited syndromes

- physical activity
- nonsteroidal anti-inflammatory drugs (NASIDs)
- vegetables, fruits, and whole grains
- foods rich in calcium, vitamin D, folate, and dietary fiber

↓ Risk

Source: American Cancer Society

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Project 1

To conduct a **systematic review and meta-analysis** of studies on association between a family history of CRC and the risk of CRC and adenoma in Asian countries.

Family history and the risk of colorectal cancer and adenoma in Asian countries:
A meta-analysis and systematic review

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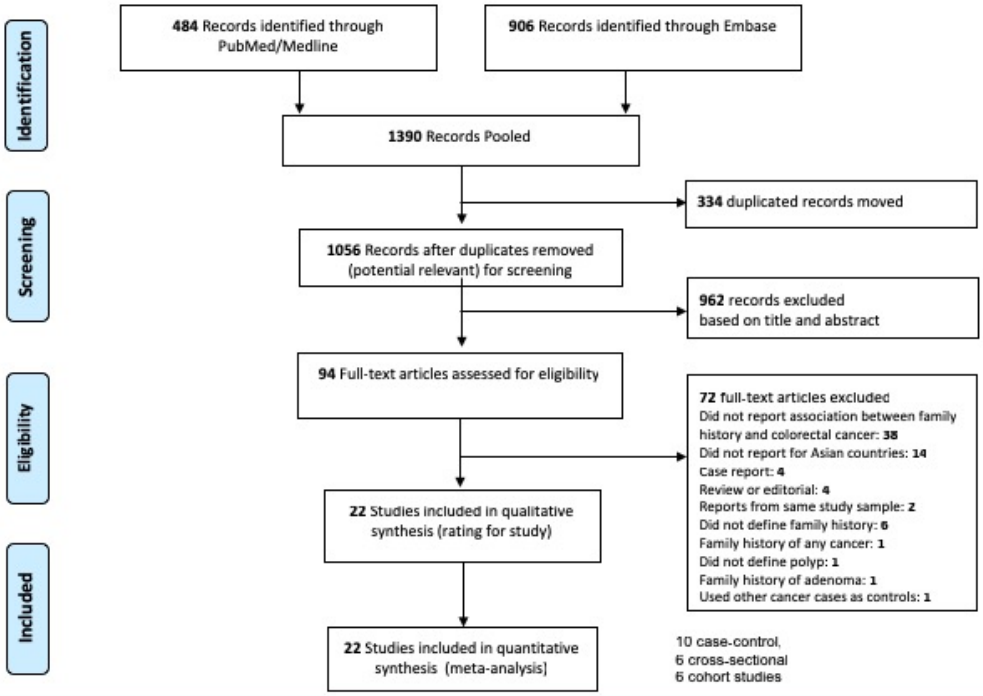
Meta analysis-flow diagram



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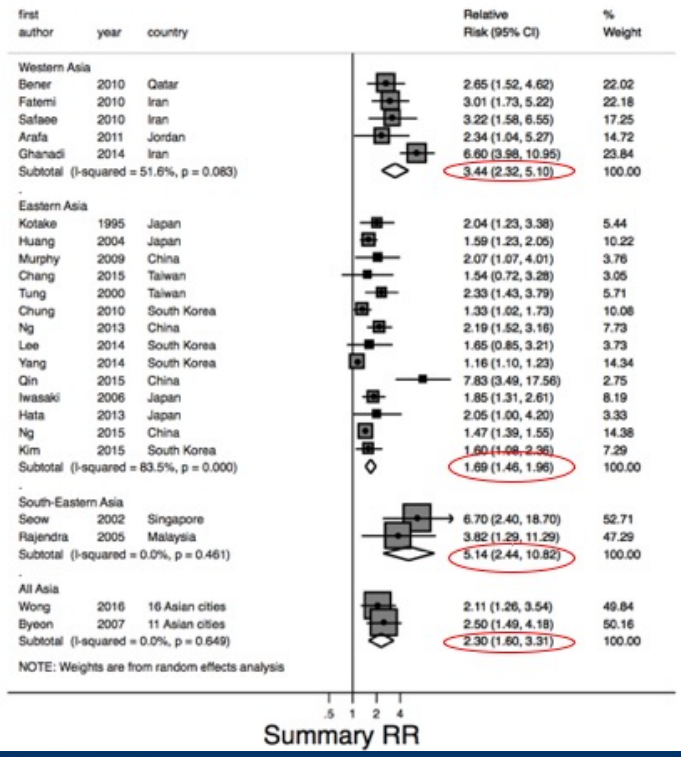
Meta analysis-results



Summary of subgroup analyses

	Number of studies	Random effect Summary RR (95% CI)	I^2 (%)	τ^2	Ratio of RRs (95% CI)	p-value
Year of publication						
Before 2011	12	2.10 (1.80-2.45)	84.1	0.16	1	
2011 onwards	11	1.99 (1.62-2.46)			0.93 (0.60-1.42)	0.72
Study type						
Cohort	5	1.89 (1.47-2.42)	86.1	0.16	1	
Case-control/Cross-sectional	18	2.15 (1.81-2.55)			1.19 (0.70-2.01)	0.51
Subregion						
Eastern Asia	14	1.69 (1.46-1.96)	81.0	0.09	1	
Western Asia	5	3.44 (2.32-5.10)			1.41(1.12,1.77	0.006
South-eastern Asia	2	5.14 (2.44-10.8)			2.96 (1.10,7.97)	0.034

Abbreviations: RR, Relative risk; I^2, Percent residual variation due to heterogeneity; τ^2, Residual maximum likelihood estimate of between-study variance; CI, Confidence interval

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Project 2

To conduct large prospective cohorts analysis of existing data on the association between **family history of CRC and the risk of incidence of CRC** in Asian countries.

Association of family history with the risk of incidence from colorectal cancer-a pooled analyses of 6 prospective cohorts in the Asia Cohort Consortium

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Statistical Analysis

- **Exposure:** Family history of CRC
  - Types of relatives affected by CRC:
    - First degree relatives(FDR)
    - Second degree relatives (SDR)
  - Number of FDR: 1 or 2 FDR
  - Father or mother
- **Outcome**: Diagnosis of CRC
- **Potential Confounders**: age, sex, smoking, alcohol drinking, body mass index (*Wong, et al 2014*)
- **Subgroup analysis**: countries and cohorts
- **Statistical Analysis** : Univariable and multivariable analysis with Cox regression analyses after adjusting for potential confounders

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Descriptive analysis

	China (n=29449)		Japan (n=118114)		Korea (n=28244)		Total
	Linxian General Population Trial Cohort	Miyagi Cohort Study	Ohsaki National Health Insurance Cohort Study	Three-Prefecture Cohort Study, Aichi (3-Pref Aichi)	Korea Multi-Centre Cancer Cohort (KMCC)	Korean National Cancer Centre Cohort (KNCC)	175807
	(n=29449, 16.75%)	(n=45522, 25.89%)	(n=48043, 27.33%)	(n=24549, 13.96%)	(n=20574, 11.7%)	(n=7670, 4.36%)	
No colorectal cancer	29386 (99.79)	44838 (98.50)	47262 (98.37)	24180 (98.50)	20283 (98.59)	7655 (99.8)	173604 (98.75)
Colorectal cancer	63 (0.21)	684 (1.50)	781 (1.63)	369 (1.50)	291 (1.41)	12 (0.2)	2203 (1.25)
No family history	29392 (99.81)	44850 (98.52)	46327 (96.43)	23732 (96.67)	20386 (99.09)	7349 (95.81)	172036 (97.86)
Family history	57 (0.19)	672 (1.48)	1716 (3.57)	817 (3.33)	188 (0.91)	321 (4.19)	3771(2.14)
1 or 2 FDR	57(0.19)	505 (1.11)	1108 (2.3)	817 (3.33)	152 (0.73)	NR	2639 (1.5)
1 FDR	57 (0.19)	505 (1.11)	1108 (2.3)	801 (3.26)	152 (0.73)	NR	2623 (1.49)
Father	NR	273 (0.6)	558 (1.16)	NR	NR	NR	831 (0.47)
Mother	NR	234 (0.51)	558 (1.16)	NR	NR	NR	792 (0.45)
2 FDR	1 (0.003)	2(0.004)	8 (0.016)	16 (0.065)	NR	NR	27 (0.015)
SDR	NR	177 (0.39)	642 (1.33)	NR	NR	NR	819 (0.47)

Family history was defined as any family history of colorectal cancer regardless of the degree of relative information; 1 or 2 FDR was defined as at least one first-degree relative relatives diagnosed with colorectal cancer; 1 FDR was defined as one first-degree relative diagnosed with colorectal cancer; 2 FDR was defined as two first-degree relatives diagnosed with colorectal cancer;

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Descriptive analysis

	Linxian General Population Trial Cohort	Miyagi Cohort Study	Ohsaki National Health Insurance Cohort Study	Three-Prefecture Cohort Study, Aichi (3-Pref Aichi)	Korea Multi-Centre Cancer Cohort (KMCC)	Korean National Cancer Centre Cohort (KNCC)	175807
	(n=29449, 16.75%)	(n=45522, 25.89%)	(n=48043, 27.33%)	(n=24549, 13.96%)	(n=20574, 11.7%)	(n=7670, 4.36%)	
Enrolment period	1984-1987	1990	1995	1985	1993-2004	2001	
Mean follow-up years (SD)	18.5(7.4)	16.2(3.7)	10.7(4.3)	11.6(5.1)	13.7(4.8)	4.8(1.7)	13.7(6.0)
Age, y							
Mean (SD)	51.9 (8.9)	52.0 (7.5)	60.2 (10.3)	55.4 (10.9)	54.1 (14.3)	52.7 (8.4)	55.0 (10.6)
Sex (n, %)							
Male	13121 (44.55)	21924 (48.16)	22971 (47.81)	11664 (47.51)	8197 (39.84)	2767 (36.08)	80644 (45.87)
Female	16328 (55.45)	23598 (51.84)	25072 (52.19)	12885 (52.49)	12377 (60.16)	4903 (63.92)	95163 (54.13)
BMI, kg/m^2							
Mean (SD)	22.0 (2.48)	23.7 (3.0)	23.6 (3.3)	22.1 (2.9)	23.6 (3.3)	23.7 (3.0)	23.1(3.1)
Missing data	6 (0.02)	2576 (5.7)	3261(6.8)	661 (2.7)	1610(7.8)	0	8114(4.6)
Smoking (n, %)							
Never	20613 (70)	19298 (42.39)	21075 (43.87)	11786 (48.01)	12785 (62.14)	5117 (66.71)	90674 (51.58)
Ever	8836 (30)	19279 (42.35)	19708 (41.02)	11593 (47.22)	7445 (36.19)	2527 (32.95)	69388 (39.47)
Missing data	0	6945 (15.26)	7260 (15.11)	1170 (4.77)	344 (1.67)	26 (0.34)	15745 (8.96)
Drinking (n, %)							
Never	22406 (76.08)	16523 (36.3)	18217 (37.92)	7788 (31.72)	11724 (56.98)	3185 (41.53)	79843 (45.42)
Ever	7043 (23.92)	23747 (52.17)	23885 (49.72)	15081 (61.43)	8431 (40.98)	4475 (58.34)	82662 (47.02)
Missing data	0	5252 (11.54)	5941 (12.37)	1680 (6.84)	419 (2.04)	10 (0.13)	13302 (7.57)

Age was defined as age at baseline; BMI was defined as BMI at baseline. Smoking was defined as the status of ever or never cigarette smoking at baseline; Alcohol drinking was defined as the status of ever or never drinking at base line.

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Results

	Univariable Model			Multivariable Model					
				Complete case analysis			Multiple Imputation		
Family history	HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
2 FDR	7.8	2.51, 24.2	<0.001	5.1	0.71, 36.2	0.1	4.4	0.62, 31.2	0.14
1 or 2 FDR	1.44	1.1, 1.9	0.009	1.7	1.22, 2.36	0.002	1.58	1.15, 2.18	0.005
1 FDR	1.9	1.34, 2.51	<0.001	1.68	1.21, 2.33	0.002	1.57	1.14, 2.16	0.006
Father	2.18	1.48, 3.2	<0.001	2.34	1.59, 3.46	<0.001	2.09	1.41, 3.08	<0.001
Mother	1.19	0.71, 2.02	0.51	1.08	0.61, 1.92	0.78	1.12	0.66, 1.89	0.68
SDR	1.72	1.14, 2.60	0.01	1.87	1.24, 2.83	0.003	1.6	1.01, 2.41	0.027

Multivariable model adjusted for age(continuous), sex(binary), BMI(continuous), ever smoking(binary), ever alcohol use(binary), cohort(categorical). Age was defined as age at baseline; BMI was defined as BMI at baseline. Smoking was defined as the status of ever or never cigarette smoking at baseline; Alcohol drinking was defined as the status of ever or never drinking at base line.

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Results

Subgroup analysis for association between family history (regardless of degree of relatives) and the risk of colorectal cancer

		Univariable Model			Multivariable Model					
Country	**Cohort**				Complete-case analysis			Multiple Imputation		
		HR	95%CI	P value	HR	95%CI	P value	HR	95%CI	P value
China	Linxian General Population Trial Cohort	NA	NA	NA	NA	NA	NA	NA	NA	NA
Japan		1.55	1.24, 1.97	<0.001	1.6	1.27, 2.03	<0.001	1.5	1.18,1.89	<0.001
	Miyagi Cohort Study	1.49	0.89, 2.49	0.12	1.62	0.97, 2.71	0.064	1.49	0.89, 2.49	0.126
	Ohsaki National Health Insurance Cohort Study	1.59	1.17, 2.14	0.003	1.82	1.34, 2.48	<0.001	1.63	1.21, 2.20	<0.001
	Three-Prefecture Cohort Study, Aichi (3-Pref Aichi)	1.23	0.72, 2.09	0.46	1.11	0.61, 2.03	0.73	1.24	0.73, 2.12	0.43
Korea		0.37	0.05, 2.63	0.32	0.41	0.06, 2.90	0.37	0.42	0.06, 2.97	0.38
	Korea Multi-Centre Cancer Cohort (KMCC)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Korean National Cancer Centre Cohort (KNCC)	1.71	0.22, 13.1	0.6	1.71	0.22, 13.1	0.6	1.72	0.22, 13.2	0.6
Pooled		1.84	1.46, 2.32	<0.001	2.14	1.70, 2.70	<0.001	1.58	1.25,1.99	<0.001

Multivariable model adjusted for age(continuous), sex(binary), BMI(continuous), ever smoking(binary), ever alcohol use(binary), cohort(categorical). Age was defined as age at baseline; BMI was defined as BMI at baseline. Smoking was defined as the status of ever or never cigarette smoking at baseline; Alcohol drinking was defined as the status of ever or never drinking at base line.

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Project 3

To conduct large prospective cohorts analysis of existing data on the association between **family history of CRC and the risk of mortality of CRC** in Asian countries.

Association of family history and survival of colorectal cancer-a pooled analyses of 6 prospective cohorts in the Asia Cohort Consortium

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Statistical Analysis

- **Exposure:** Family history of CRC
  - Types of relatives affected by CRC:
    - First degree relatives(FDR)
    - Second degree relatives (SDR)
  - Number of FDR: 1 or 2 FDR
  - Father or mother
- **Outcome**: death of CRC
- **Potential Confounders**: age, sex, smoking, alcohol drinking, body mass index
- **Subgroup analysis**: colorectal cancer (colon cancer/rectum cancer)
- **Statistical Analysis** : Univariable and multivariable analysis with Cox regression analyses after adjusting for potential confounders

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Descriptive analysis

	All Cause Death (n=1008)		Alive (n=1448)	Total (n=2456)
	Deaths due to CRC (n=796, 79%)	Deaths not due to CRC (212, 21%)		
Mean follow-up yrs (SD)	8.6 (4.7)	9.5 (4.4)	14.4 (4.5)	12.1(5.4)
Age, Mean (SD) y [b]				
At baseline	61.0 (10.2)	62.7 (8.2)	58.8 (8.4)	59.8 (9.10)
Diagnosis of CRC	68.6 (10.2)	68.2 (8.1)	66.1 (8.4)	67.1 (9.1)
Sex (n, %)				
Male	426 (53.5)	145 (68.4)	826 (57.1)	1397 (56.9)
Famle	370 (46.5)	67 (31.6)	622 (42.9)	1059 (43.1)
Famly history of CRC (n, %) [c]				
No family history	773 (97.1)	204 (96.2)	1391 (96.1)	2368 (96.4)
Famil history	23 (2.9)	8 (3.8)	57 (3.9)	88 (3.6)
1 FDR	13 (1.6)	3 (1.4)	44 (3.0)	60 (2.4)
father	5 (0.6)	2 (0.9)	20 (1.4)	27 (1.1)
mother	4 (0.5)	0	13 (0.9)	17 (0.7)
2 FDR	0	0	3 (0.2)	3 (0.2)
SDR	10 (1.3)	4 (1.9)	13 (0.9)	27 (1.1)
BMI, kg/m^2 [d]				
Mean (SD)	23.1(3.1)	23.0 (3.3)	23.6 (3.3)	23.4(3.2)
Missing data (n, %)	47 (5.8)	15 (7.1)	73 (5.0)	135 (5.5)
Smoking (n, %) [e]				
Never	324 (40.7)	72 (34.0)	609 (42.1)	1005 (40.9)
Ever	382 (48.0)	126 (56.4)	710 (49.0)	1218 (49.6)
Missing data	90 (11.3)	14 (6.6)	129 (8.9)	233 (9.5)
Alcohol drinking (n, %) [f]				
Never	291 (36.6)	65 (30.7)	495 (34.2)	851 (34.7)
Ever	435 (54.7)	134 (63.2)	842 (58.2)	1441 (57.4)
Missing data	70 (8.8)	13 (6.1)	111 (7.6)	194 (7.9)
Cohorts [g]				
Linxian	34 (4.3)	5 (2.4)	30 (2.1)	69 (2.8)
Miyagi	229 (28.8)	67 (31.6)	554 (38.4)	850 (34.6)
Ohsaki	285 (35.8)	92 (43.4)	484 (33.4)	861 (370)
3pref-Aichi	166 (20.9)	19 (8.9)	185 (12.8)	370 (15.1)
KMCC	82 (10.3)	27 (12.7)	182 (12.6)	291 (11.9)
KNCC	0	2 (0.9)	13 (0.9)	15 (0.6)

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Results

Univariable and multivariable hazard ratios for association between family history with All cause, colorectal cancer, colon cancer, rectum cancer)

	Univariable Model						Multivariable Model *								
							Complete-case analysis						Multiple Imputation		
	No of death	No of obs	Person-years	HR	95%CI	P value	No of death	No of obs	Person-years	HR	95%CI	P value	HR	95%CI	P value
All cause (n=1008)															
Family history (yer or no)	570	1887	12147	0.84	0.53, 1.33	0.45	490	1619	10370	0.91	0.57, 1.45	0.7	0.81	0.51, 1.28	0.36
1 FDR	372	1348	9502	0.84	0.45, 1.57	0.58	305	1119	7917	0.71	0.33, 1.51	0.37	0.6	0.28, 1.28	0.19
father	336	1294	9316	1.22	0.54, 2.73	0.47	269	1068	7743	0.99	0.43, 2.25	0.98	0.94	0.42, 2.13	0.88
mother	336	1294	9316	0.24	0.03, 1.71	0.15	269	1068	7743	0.26	0.04, 1.83	0.18	0.18	0.03, 1.31	0.09
SDR	336	1294	9316	1.19	0.56, 2.53	0.65	269	1068	7743	0.97	0.45, 2.07	0.93	0.97	0.45, 2.06	0.93
Colorectal cancer (n=796)															
Family history (yer or no)	384	1701	11286	0.75	0.41, 1.37	0.36	332	1461	9641	0.89	0.48, 1.64	0.71	0.75	0.41, 1.38	0.36
1 FDR	229	1205	8840	0.95	0.45, 2.01	0.89	187	1001	7374	0.8	0.32, 1.96	0.62	0.64	0.26, 1.57	0.33
father	199	1157	8677	1.33	0.49, 3.60	0.6	157	956	7223	1.06	0.39, 2.92	0.91	0.96	0.35, 2.63	0.94
mother	199	1157	8677	0.4	0.06, 2.88	0.37	157	956	7223	0.39	0.05, 2.78	0.35	0.26	0.04, 1.88	0.18
SDR	199	1157	8677	1.19	0.44, 3.25	0.73	157	956	7223	0.93	0.35, 2.57	0.89	0.97	0.35, 2.66	0.96
Colon cancer (n=504)															
Family history (yer or no)	243	1560	10964	0.75	0.35, 1.6	0.46	211	1340	9367	0.97	0.45, 2.09	0.94	0.79	0.37, 1.69	0.54
1 FDR	143	1119	8623	1.07	0.43, 2.62	0.88	116	930	7201	1.21	0.44, 3.38	0.71	0.94	0.34, 2.59	0.9
father	114	1072	8462	2.32	0.85, 6.32	0.1	87	886	7051	2.15	0.75, 6.08	0.76	1.85	0.66, 5.14	0.24
SDR	114	1072	8462	1.11	0.27, 4.52	0.89	87	886	7051	0.74	0.18, 3.07	0.67	0.77	0.19, 3.16	0.72
Rectum cancer (n=292)															
Family history (yer or no)	141	1458	10869	0.75	0.28, 2.02	0.57	121	1250	9270	0.78	0.28, 2.12	0.62	0.68	0.24, 1.84	0.44
1 FDR	86	1062	8635	0.73	0.18, 2.98	0.66	71	885	7201	0.31	0.04, 2.28	0.25	0.26	0.04, 1.89	0.18
mother	85	1043	8525	0.89	0.12, 6.41	0.91	70	869	7103	0.79	0.11, 5.79	0.82	0.58	0.08, 4.22	0.59
SDR	85	1043	8525	1.33	0.32, 5.56	0.69	70	869	7103	1.17	0.27, 4.96	0.83	1.28	0.35, 5.34	0.74

* Multivariable model adjusted for age at baseline(continueous), sex(binary), BMI at baseline (continueous), ever smoking(binary), ever alcohol use(binary), cohort(categorical).
Abbreviation: obs, observation; HR, hazard ratiol; CI, confidence interval; FDR, first-degree relative; SDR, second-degree relative

Conclusion

1. The association of first degree relative family history and risk of colorectal cancer is heterogenous in Asian countries.
2. Family history of colorectal cancer is significantly associated with incidence risk of colorectal cancer, especially in subgroup of 2 first degree relatives and father with colorectal cancer.
3. Family history of colorectal cancer is not significantly associated with mortality of colorectal cancer.

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Acknowledgements

- Dr. Aung Ko Win (PI of family history and colorectal cancer)
- Prof. Mark Jenkins
- All contributing cohorts

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Appendix C: Oral Presentation2

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Family history and risk of colorectal cancer in Asian population--Pooled analysis of Asia Cohort Consortium (ACC) with 170,000 population

Lin Zhang, MBBS, PhD Candidate

Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health

University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre

U21 Health Sciences

10/09/2018

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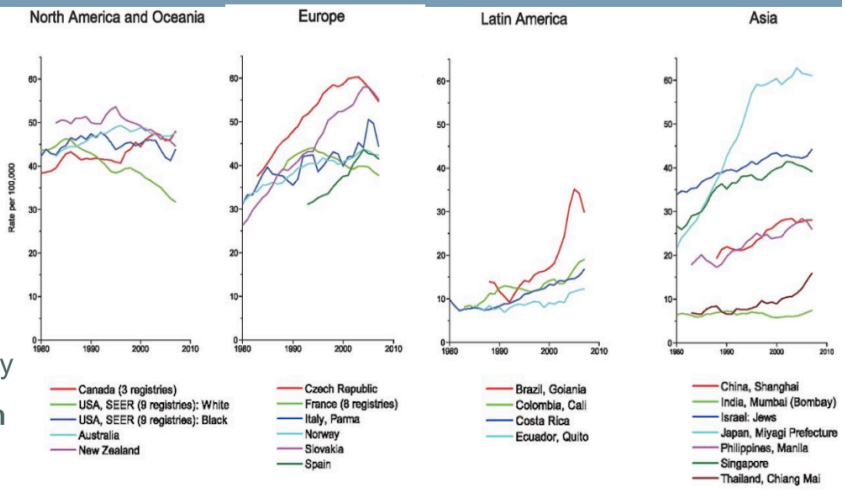
Background

Colorectal cancer is **third** leading causes of cancer globally.

- **1.36 million** newly diagnosed cases in 2012 globally.
- The **third** most commonly diagnosed cancer in **men** and **second** in **women.**



Well studied

Under studied

- Traditionally, highest incidence in western countries
- Currently, the incidence in Asia is increasingly high
- The highest incidence rates in both males and females currently are observed in Japan.
- Heterogeneous pattern across different countries in Asia
- Increasing incidence in Asian countries are unknown

2

Data source: Cancer Incidence in Five Continents (CI5plus), International Agency for Research on Cancer (IARC)

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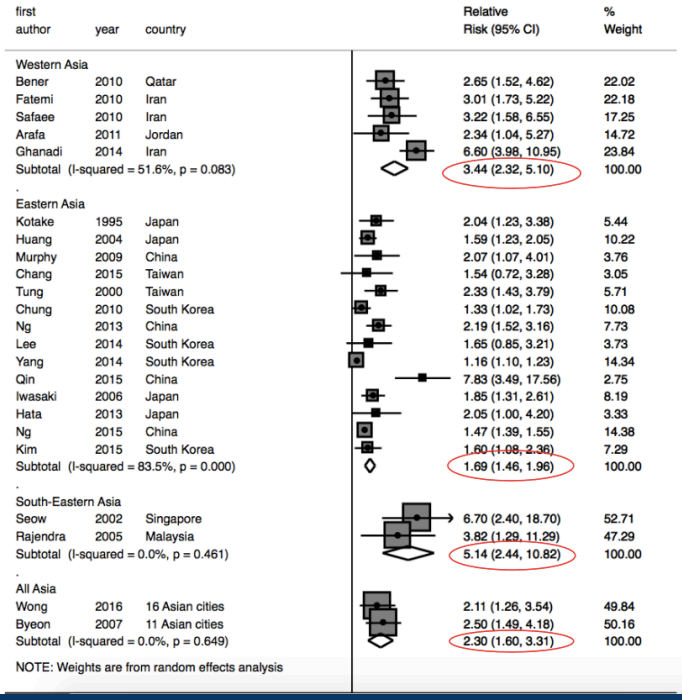
Meta analysis



The association of first degree relative family history and risk of colorectal cancer is heterogenous in Asian countries.

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	Univariable Model			Multivariable Model		
Family history	HR	95%CI	P value	HR	95%CI	P value
2 FDR	7.8	2.51, 24.2	<0.001	5.1	0.71, 36.2	0.1
1 or 2 FDR	1.44	1.1, 1.9	0.009	1.7	1.22, 2.36	0.002
1 FDR	1.9	1.34, 2.51	<0.001	1.68	1.21, 2.33	0.002
Father	2.18	1.48, 3.2	<0.001	2.34	1.59, 3.46	<0.001
Mother	1.19	0.71, 2.02	0.51	1.08	0.61, 1.92	0.78
SDR	1.72	1.14, 2.60	0.01	1.87	1.24, 2.83	0.003

HR, hazard ratio;
CI, confidence interval;
FDR, first-degree relative;
SDR, second-degree relative

* Multivariable model adjusted for age at baseline(continuous), sex(binary), BMI at baseline (continuous), ever smoking(binary), ever alcohol use(binary).

Colorectal cancer Incidence

Family history of colorectal cancer is significantly associated with incidence risk of colorectal cancer, especially in subgroup of 2*first degree relatives and father with colorectal cancer.

Acknowledgements

- Dr. Aung Ko Win
- Prof. Mark Jenkins
- All contributing cohorts

Outlook

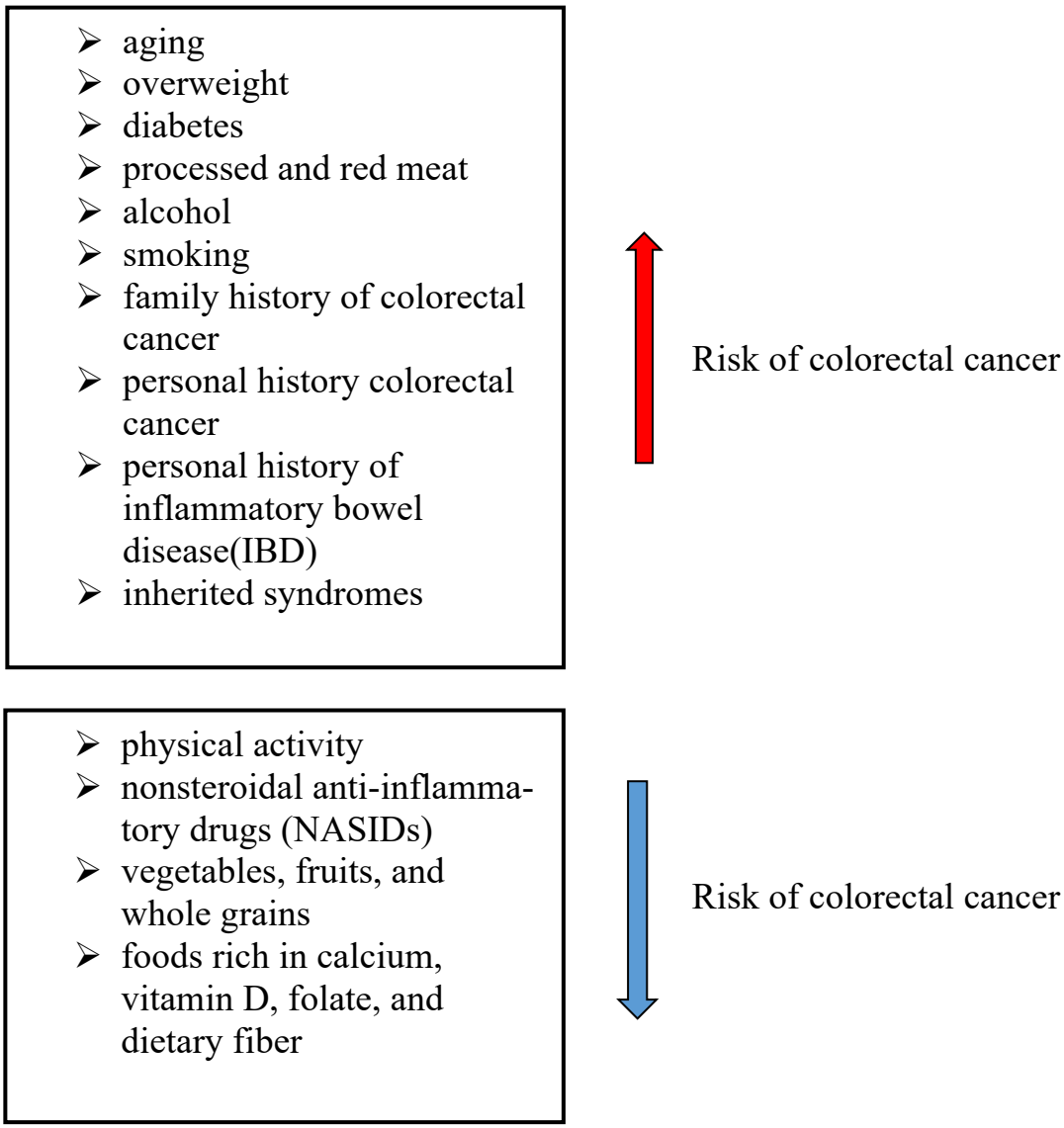
"From negative to active,

From intervention to prevention"

Appendix 1. List of countries in subregions of Asia defined by the United Nation.

Central Asia	***East Asia***	***South Asia***	***South-Eastern Asia***	***West Asia***
Kazakhstan	China	Afghanistan	Brunei	Armenia
Kyrgyzstan	China, Hong Kong	Bangladesh	Cambodia	Azerbaijan
Tajikistan	China, Macao	Bhutan	Indonesia	Bahrain
Turkmenistan	South Korea	India	Lao	Cyprus
Uzbekistan	Japan	Maldives	Malaysia	Georgia
	Mongolia	Nepal	Myanmar	Iran
	North Korea	Pakistan	Philippines	Iraq
	Taiwan	Sri Lanka	Singapore	Israel
			Thailand	Jordan
			Timor-Leste	Kuwait
			Vietnam	Lebanon
				Oman
				Qatar
				Saudi Arabia
				Palestine
				Syria
				Turkey
				United Arab Emirates
				Yemen

Appendix 2. Risk factors of colorectal cancer from American Cancer Society



Source: American Cancer Society

Appendix 3. Summary of publication of these ACC cohorts have examined the association between body mass index, smoking, alcohol consumption or type 2 diabetes and cancer risk[142, 143, 165, 166].

Research paper based on ACC					
First Author	**Title**	**Journal**	**Year**	**Exposure**	**Outcome**
Boffetta P[187]	Body mass index and diabetes in Asia: a cross-sectional pooled analysis of 900,000 individuals in the Asia cohort consortium. 2011;6(6):e19930. doi: 10.1371/journal.pone.0019930. PubMed PMID: 21731609; PubMed Central PMCID: PMCPMC3120751.	PLoS One.	2011	BMI	diabetes
Zheng W[188]	Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians.	New England Journal of Medicine.	2011	BMI	death
Boffetta P[142]	Body mass, tobacco smoking, alcohol drinking and risk of cancer of the small intestine--a pooled analysis of over 500,000 subjects in the Asia Cohort Consortium.	Ann Oncol.	2012	BMI, tobacco smoking, alcohol drinking	cancer of the small intestine
Chen Y[189]	Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium.	BMJ	2013	BMI	cardiovascular disease mortality
Lee JE[190]	Meat intake and cause-specific mortality: a pooled analysis of Asian prospective cohort studies.	The American journal of clinical nutrition	2013	Meat intake	cause-specific mortality
Lin Y[165]	Association of body mass index and risk of death from pancreas cancer in Asians: findings from the Asia Cohort Consortium.	Eur J Cancer Prev.	2013	BMI	death from pancreas cancer
Zhang B[191]	Genome-wide association study identifies a new SMAD7 risk variant associated with colorectal cancer risk in East Asians.	Int J Cancer.	2014	SMAD7 variant	colorectal cancer
Zheng W[192]	Burden of Total and Cause-Specific Mortality Related to Tobacco Smoking among Adults Aged ≥45 Years in Asia: A Pooled Analysis of 21 Cohorts.	PLOS Medicine.	2014	Tobacco Smoking	total and cause-specific mortality
Fowke JH[143]	Associations of body mass index, smoking, and alcohol consumption with prostate cancer mortality in the Asia Cohort Consortium.	Am J Epidemiol.	2015	BMI, Smoking, alcohol consumption	prostate cancer mortality
Chen Y[166]	Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium.	Diabetologia.	2017	type 2 diabetes	cancer mortality
Liu Y[193]	Association of leisure-time physical activity with total and cause-specific mortality: a pooled analysis of nearly a half million adults in the Asia Cohort Consortium.	International Journal of Epidemiology.	2018	leisure-time physical activity	total and cause-specific mortality
Yang JJ[194]	Tobacco Smoking and Mortality in Asia: A Pooled Meta-analysis.	JAMA Netw Open.	2019	Tobacco Smoking	mortality
Introduction paper of ACC					
First Author	**Title**	**Journal**	Year		
Rolland B[163]	Coordinating centres in cancer epidemiology research: the Asia Cohort Consortium coordinating centre.	Cancer Epidemiol Biomarkers Prev	2011		
Song M [164]	Asia Cohort Consortium: challenges for collaborative research.	J Epidemiol.	2012		

Appendix 4. Guidance on using database, remote access and results circulation and publication in the Asia Cohort Consortium

Guidance on how to use the ACC data

- The ACC Coordinating Center will invite Cohorts to join in the project
- The Project PI will propose a variable list for additional data collection (if the CC does not have the data)
- Once the data is collected (and cleaned), we will consult with the PI if the team is ready for starting the analysis.
- Step-by-step guidance for remote access is available on the ACC member-only website

Guidance on Remote Access

- Datasets are saved as CSV and Stata(.dta)
- Datasets are updated as and when we receive new data
- Maintenance of PC once a week: Monday morning Japan time
- During maintenance time, please log off from both VPN and Windows account
- SAS, Stata and R are available for use
- Please write your program codes legibly with comments: the ACC Coordinating Center keeps all program codes for verification

Guidance on results ready

- Please contact the ACC CC to circulate the tables with cohort PIs. This will ensure that the cohort PIs agree with your analysis results before proceeding to manuscript preparation.
- Send the draft manuscript to the ACC CC – we will circulate among co-authors. Allow plenty of time for this step.
- Please ensure that all co-authors approved the final version of the manuscript before submitting to a journal.
- You will need to submit a revised proposal to the ACC CC and obtain an approval from the Executive Committee if you'd like to conduct further analyses beyond the original proposal.

Appendix 5. Data Use Agreement of the ACC database

DATA USE AGREEMENT

FOR THE REMOTE ACCESS TO

THE ASIA COHORT CONSORTIUM DATA CENTER

Investigator: Lin Zhang (PI: Aung Ko Win)

Institution: University of Melbourne

Project Name: Family History and Colorectal Cancer

As an investigator of the above-mentioned project name, I agree with the terms and conditions for the use of the pooled data via the remote access to the Asia Cohort Consortium (ACC) Data Center, located at the National Cancer Center, Japan, for research purposes as defined below.

1. I agree to use the ACC pooled data for non-profit research purposes only and will not use the data for any purposes other than the above-mentioned project, or for any commercial purposes.
2. I agree to:
   - i. Install the latest antivirus software in the designated PC where the remote access will be conducted;
   - ii. Store the ID and passwords for the remote access in a secured place located at the investigator's institution;
   - iii. Save all the working files and outputs in the host PC located at the ACC Data Center, and no data and outputs shall be directly downloaded to the local PC in the home country;
   - iv. Make no changes in the settings of the host PC at the ACC Data Center, and all changes shall be made by the ACC Data Manager at the ACC Data Center;
   - v. Follow the schedules for the remote access as agreed in the Project, and when not in use, log off from the network;
   - vi. Make no use of screen shots or cameras to take pictures of the PC screen;
   - vii. Receive the output files saved in the host PC by password-protected e-mails or the equivalent upon completion of the analyses;
   - viii. Commit no misconduct regarding the data use other than the above-mentioned conditions.
3. I shall be liable for any loss, claim, damage, or liability that is incurred as a result of my activities under this agreement.

(Signature of Investigator) LIN ZHANG 林骕

(DATE) 2016. 7. 21

Page 1 of 1

Appendix 6. Search Strategy for PubMed database

	Medline Search	Results
1	(family history or familial risk or familial aggregation or relatives or risk factor).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	233,633
2	(colorectal cancer* or colorectal neoplasm* or colon cancer* or colon neoplasm*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	122,559
3	exp Colorectal Neoplasms/	166,417
4	2 or 3	192,261
5	(Prognosis or mortality or survival).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1,732,079
6	(asian* or Afghanistan or Armenia or Azerbaijan or Bahrain or Bangladesh or Bhutan or Brunei or Cambodia or China or Cyprus or Georgia or India or Indonesia or Iran or Iraq or Israel or Japan or Jordan or Kazakhstan or Kuwait or Kyrgyzstan or Laos or Lebanon or Malaysia or Maldives or Mongolia or Myanmar or Burma or Nepal or North Korea or Oman or Pakistan or Palestine or Philippines or Qatar or Russia or Saudi Arabia or Singapore or South Korea or Sri Lanka or Syria or Taiwan or Tajikistan or Thailand or Timor-Leste or Turkey or Turkmenistan or United Arab Emirates or Uzbekistan or Vietnam or Yemen).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	823,283
7	1 and 4 and 6	525
8	1 and 4 and 5 and 6	138
9	7 or 8	525
10	limit 9 to (english language and yr="1980 -Current")	484

Appendix 7. Search Strategy for Embase database

	Embase Search	Search
1	(family history or familial risk or familial aggregation or relatives or risk factor).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	963,107
2	(colorectal cancer* or colorectal neoplasm* or colon cancer* or colon neoplasm*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	196,017
3	exp Colorectal Neoplasms/	18,527
4	2 or 3	202,567
5	(Prognosis or mortality or survival).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2,527,596
6	(asian* or Afghanistan or Armenia or Azerbaijan or Bahrain or Bangladesh or Bhutan or Brunei or Cambodia or China or Cyprus or Georgia or India or Indonesia or Iran or Iraq or Israel or Japan or Jordan or Kazakhstan or Kuwait or Kyrgyzstan or Laos or Lebanon or Malaysia or Maldives or Mongolia or Myanmar or Burma or Nepal or North Korea or Oman or Pakistan or Palestine or Philippines or Qatar or Russia or Saudi Arabia or Singapore or South Korea or Sri Lanka or Syria or Taiwan or Tajikistan or Thailand or Timor-Leste or Turkey or Turkmenistan or United Arab Emirates or Uzbekistan or Vietnam or Yemen).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1,196,289
7	1 and 4 and 6	1,461
8	1 and 4 and 5 and 6	460
9	7 or 8	1,461
10	limit 9 to (english language and yr="1980 -Current" and article)	906

Appendix 8. List and details of the excluded studies from the meta-analysis

Reason for exclusion	Author	Year	Title	Journal
Did not report association between family history and colorectal cancer (n=38)	Adakan Y, et al.	2014	Implementation of screening colonoscopy amongst first- degree relatives of patients with colorectal cancer in Turkey: a cross-sectional questionnaire based survey	Asian Pacific journal of cancer prevention
	Al Ahwal MS, et al.	2006	Distribution of risk factors in patients with colorectal cancer in Saudi Arabia	Qatar Medical Journal
	Atzmon I, et al.	2012	Cancer risks in the Druze Isifya Village: Reasons and RF/MW antennas	Pathophysiology
	Aykan NF, et al.	2015	Epidemiology of colorectal cancer in Turkey: A cross-sectional disease registry study (a Turkish oncology group trial)	Turkish Journal of Gastroenterology
	Azadeh S, et al.	2008	Colorectal cancer in Iran: An epidemiological study	Asian Pacific Journal of Cancer Prevention
	Bafandeh Y, et al.	2008	Clinical predictors of colorectal polyps and carcinoma in a low prevalence region: Results of a colonoscopy based study	World Journal of Gastroenterology
	Bastani R, et al.	2015	Randomized trial to increase colorectal cancer screening in an ethnically diverse sample of first-degree relatives	Cancer
	Dalpatadu KU, et al.	2011	Uses of a familial adenomatous polyposis registry	The Ceylon medical journal
	Fakheri H, et al.	2011	Familial aspects of colorectal cancers in Southern Littoral of Caspian Sea	Archives of Iranian Medicine
	Gulten M, et al.	1999	Epidemiological features of the young cases with colorectal carcinoma in Bursa	Medecine Biologie Environnement
	Han Y.	2005	Comparative analysis of patients with clinically diagnosed colorectal cancer and those detected by mass screening	Chinese Journal of Digestive Diseases
	Hilmi I, et al.	2010	Negative perception in those at highest risk - Potential challenges in colorectal cancer screening in an urban Asian population	Asian Pacific Journal of Cancer Prevention
	Ishii N, et al.	2011	Factors affecting encouragement of relatives among families with Lynch syndrome to seek medical assessment	Familial Cancer
	Kashfi SMH, et al.	2015	Evaluation of the left-to-right shift of colon tumours in Iran: Is the trend changing?	Journal of Research in Medical Sciences
	Kilickap S, et al.	2012	Screening colonoscopy participation in Turkish colorectal cancer patients and their first degree relatives	Asian Pacific Journal of Cancer Prevention
	Lee SC, et al.	2005	Clinical and molecular characteristics of hereditary non-polyposis colorectal cancer families in Southeast Asia	Clinical Genetics

	Lin JT, et al.	2005	Outcome of colorectal carcinoma in patients under 40 years of age	Journal of Gastroenterology & Hepatology
	Mahdavinia M, et al.	2005	Family history of colorectal cancer in Iran	BMC Cancer
	Meng W, et al.	2009	Performance value of high risk factors in colorectal cancer screening in China	World Journal of Gastroenterology
	Moghimi Dehkordi B, et al.	2010	Prevalence of positive family history of colorectal cancer in the Iranian general population	Iranian Journal of Cancer Prevention
	Nemati A, et al.	2012	Hereditary nonpolyposis colorectal cancer and familial colorectal cancer in Central part of Iran, Isfahan	Journal of Research in Medical Sciences
	Okada T, et al.	2016	International collaboration between Japan and Chile to improve detection rates in colorectal cancer screening	Cancer
	Otani T, et al.	2003	Alcohol Consumption, Smoking, and Subsequent Risk of Colorectal Cancer in Middle-Aged and Elderly Japanese Men and Women: Japan Public Health Centre-based Prospective Study	Cancer Epidemiology Biomarkers and Prevention
	Raman R, et al.	2014	A positive family history of cancer or lifestyle factors may not explain the high incidence of early-onset colorectal cancer in India	Colorectal Cancer
	Ramzi NH, et al.	2014	Role of genetic & environment risk factors in the aetiology of colorectal cancer in Malaysia	The Indian journal of medical research
	Registry committee, Japnese Research Society for Cancer of the Colon and Rectum	1993	Clinical and pathological analyses of patients with a family history of colorectal cancer. Registry Committee, Japanese Research Society for Cancer of the Colon and Rectum	Japanese journal of clinical oncology
	Rozen P, et al.	2003	A Prospective Study of the Clinical, Genetic, Screening, and Pathologic Features of a Family With Hereditary Mixed Polyposis Syndrome	American Journal of Gastroenterology
	Rozen P, et al.	1981	Selective screening for colorectal tumours in the Tel-Aviv area: Relevance of epidemiology and family history	Cancer
	Siraj AK, et al.	2015	Prevalence of Lynch syndrome in a Middle Eastern population with colorectal cancer	Cancer
	Tabata S, et al.	2006	Genetic polymorphism of cholesterol 7alpha-hydroxylase (CYP7A1) and colorectal adenomas: Self Defense Forces Health Study	Cancer Science
	Vasen HF, et al.	1993	Surveillance in hereditary nonpolyposis colorectal cancer: an international cooperative study of 165 families. The International Collaborative Group on HNPCC	Diseases of the Colon & Rectum
	Wang VW, et al.	2012	Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary nonpolyposis colorectal cancer in Singapore	Familial Cancer

	Wang XL, et al.	2006	Clinical and genetic characteristics of Chinese hereditary nonpolyposis colorectal cancer families	World Journal of Gastroenterology
	Wee LE, et al.	2012	Socioeconomic factors affecting colorectal, breast and cervical cancer screening in an Asian urban low-income setting at baseline and post-intervention	Preventive Medicine
	Wong MCS, et al.	2014	Predictors of advanced colorectal neoplasia for colorectal cancer screening	American Journal of Preventive Medicine
	Yeh CC, et al.	2003	Risk factors for colorectal cancer in Taiwan: A hospital-based case-control study	Journal of the Formosan Medical Association
	Zeinalian M, et al.	2015	Epidemioclinical Feature of Early-Onset Colorectal Cancer at-Risk for Lynch Syndrome in Central Iran	Asian Pacific Journal of Cancer Prevention
	Zubaidi AM, et al.	2015	Public awareness of colorectal cancer in Saudi Arabia: A survey of 1070 participants in Riyadh	Saudi Journal of Gastroenterology
Did not report for Asian countries (n=13)	Anderson JC, et al.	2010	Increased frequency of serrated aberrant crypt foci among smokers	American Journal of Gastroenterology
	Glenn BA, et al.	2011	Changes in Risk Perceptions in Relation to Self-Reported Colorectal Cancer Screening Among First-Degree Relatives of Colorectal Cancer Cases Enrolled in a Randomized Trial	Health Psychology
	Le Marchand L, et al.	1996	Family history and risk of colorectal cancer in the multiethnic population of Hawaii	American Journal of Epidemiology
	Le Marchand L, et al.	1999	Independent and joint effects of family history and lifestyle on colorectal cancer risk: implications for prevention	Cancer Epidemiology, Biomarkers & Prevention
	Perencevich M, et al.	2013	Racial and ethnic variations in the effects of family history of colorectal cancer on screening compliance	Gastroenterology
	Pinsky PF, et al.	2003	Reported family history of cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	American Journal of Epidemiology
	Ponce NA, et al.	2012	Disparities in cancer screening in individuals with a family history of breast or colorectal cancer	Cancer
	Ponce NA, et al.	2005	Do HMO market level factors lead to racial/ethnic disparities in colorectal cancer screening? A comparison between high-risk Asian and Pacific Islander Americans and high-risk whites	Medical Care
	Rozen P, et al.	1987	Family history of colorectal cancer as a marker of potential malignancy within a screening program	Cancer
	Scheuner MT, et al.	2010	Population prevalence of familial cancer and common hereditary cancer syndromes. The 2005 California Health Interview Survey	Genetics in Medicine

	Stein B, et al.	2010	Body mass index as a predictor of colorectal neoplasia in ethnically diverse screening population	Digestive Diseases & Sciences
	Talaat N.	2015	Adherence and barriers to colorectal cancer screening varies among Arab Americans from different countries of origin	Arab Journal of Gastroenterology
	Zhivotovskiy AS, et al.	2012	Colorectal cancer risk factors among the population of south-east siberia: A case-control study	Asian Pacific Journal of Cancer Prevention
Case report (n=4)	Rashid MU, et al.	2011	Identification of the deleterious 2080insA BRCA1 mutation in a male renal cell carcinoma patient from a family with multiple cancer diagnoses from Pakistan	Familial Cancer
	Taki K, et al.	2014	A case of a child with an APC pathogenic mutation, aberrant expression of splice variants and positive family history of FAP	Japanese Journal of Clinical Oncology
	Wanitsuwan W, et al.	2011	Benefits from genetic test in descendants of familial adenomatous polyposis syndrome: Report of a family in southern Thailand	Asian Biomedicine
	Yeh CC, et al.	2013	Synchronous triple carcinoma of the colon and rectum	World Journal of Surgical Oncology
Review or editorial (n=4)	Ng SC, et al.	2013	Colorectal cancer screening in Asia	British Medical Bulletin
	Rasool S, et al.	2013	A comparative overview of general risk factors associated with the incidence of colorectal cancer	Tumour Biology
	Sung JJ, et al.	2015	An updated Asia Pacific Consensus Recommendations on colorectal cancer screening	Gut
	Sung JJ, et al.	2008	Asia Pacific consensus recommendations for colorectal cancer screening	Gut
Reports from same study sample (n=2)	Byeon JS, et al.	2007	Colorectal neoplasm in asymptomatic Asians: a prospective multinational multicentre colonoscopy survey	Gastrointestinal Endoscopy
	Shin A, et al.	2011	Site-specific risk factors for colorectal cancer in a korean population	PLoS ONE
Did not define family history (n=6)	Poomphakwaen K, et al.	2015	Risk Factors for Colorectal Cancer in Thailand	Asian Pacific Journal of Cancer Prevention: Apjcp
	Poomphakwaen K, et al.	2014	XRCC1 gene polymorphism, diet and risk of colorectal cancer in Thailand	Asian Pacific journal of cancer prevention : APJCP
	Promthet SS, et al.	2010	Risk factors for colon cancer in Northeastern Thailand: interaction of MTHFR codon 677 and 1298 genotypes with environmental factors	Journal of epidemiology / Japan Epidemiological Association
	Shin A, et al.	2014	Risk prediction model for colorectal cancer: National Health Insurance Corporation study, Korea	PloS one

	Sriamporn S, et al.	2007	Risk factors for colorectal cancer in northeast Thailand: lifestyle related	Asian Pacific journal of cancer prevention : APJCP
	Wei YS, et al.	2009	Risk factors for sporadic colorectal cancer in southern Chinese	World Journal of Gastroenterology
Family history of any cancer (n=1)	Huang Y, et al.	2015	Genetic polymorphisms in XRCC1 genes and colorectal cancer susceptibility.	World Journal of Surgical Oncology.
Did not define polyp (n=1)	Barzin G, et al.	2014	Screening colonoscopy in first-degree relatives of patients with colorectal cancer.	Archives of Iranian Medicine.
Family history of adenoma (n=1)	Ng SC, et al.	2016	Risk of Advanced Adenomas in Siblings of Individuals With Advanced Adenomas: A Cross-Sectional Study.	Gastroenterology.
Used other cancer cases as controls (n=1)	Kato I, et al.	1990	A case-control study of male colorectal cancer in Aichi Prefecture, Japan: With special reference to occupational activity level, drinking habits and family history.	Japanese Journal of Cancer Research.
Not in English (n=1)	Asghari Jafarabadi M, et al.	2010	Comparison the role of BMI, pathologic stage and hereditary related factors on survival between colon and rectal cancers: Frailty competing risks model.	Iranian Journal of Epidemiology.

Appendix 9. Newcastle-Ottawa Scale review for cohort studies from systematic review

			Selection				Comparability		Outcome			
Study	**Country**	**Region**	S1	S2	S3	S4	C1	C2	O1	O2	O3	**Total**
Byeon et al.[139]	11 Asian cities	All Asia	★	★		★	★		★		★	6
Chang et al.[140]	Taiwan	East Asia	★	★		★	★	★	★	★	★	8
Hata et al.[117]	Japan	East Asia		★	★	★	★	★	★			6
Kim et al.[141]	South Korea	East Asia	★	★	★	★	★	★	★	★	★	9
Murphy et al.[132]	China	East Asia	★	★	★	★	★	★	★	★	★	9

Guidelines for review

Selection:

S1, Representativeness of the exposed cohort; ★a) representative of the community (e.g. community-based colorectal cancer-screening programme or registry) or (single hospital or clinic); b) selected group of people (e.g. nurses, volunteers); d) no description of the derivation of the cohort

S2, Selection of the non-exposed cohort: ★a) drawn from the same community as the exposed cohort; b) drawn from a different source; c) no description of the derivation of the non-exposed cohort

S3, Ascertainment of exposure: ★ a) secure record (e.g. medical records); ★b) structured interview; c) written self-report; d) no description

S4, Demonstration that outcome of interest was not present at start of study: ★ a) yes; b) no

Comparability:

C1, ★ Study controls for age/sex (the most important factors);

C2, ★ Study controls for any additional factors (1> additional factors, e.g. BMI, drinking or smoking)

Outcome:

O1, Assessment of outcome: ★a) independent blind assessment; ★b) record linkage; c) self -report; d) no description

O2, Follow-up was long enough for outcomes to occur (>1 year): ★a) yes; b) no

O3, Adequacy of follow-up of cohorts: a) complete follow up - all subjects accounted for; b) subjects lost to follow up unlikely to introduce bias - small number lost > 10 %; c) follow up rate < 90% and no description of those lost; d) no statement

Appendix 10. Newcastle-Ottawa Scale review for case-control and cross-sectional studies from systematic review

			Selection				Comparability		Exposure			
Study	**Country**	**Region**	S1	S2	S3	S4	C1	C2	E1	E2	E3	**Total**
Wong et al.[195]	16 Asian cities	All Asia	★	★	★	★	★	★	★	★		8
Chung et al.[196]	South Korea	EastAsia	★	★	★	★	★	★	★	★		8
Huang et al.[197]	China	EastAsia	★	★	★	★	★	★	★	★	★	9
Iwasaki et al.[198]	Japan	EastAsia	★	★		★	★		★	★		6
Kotake et al.[121]	Japan	EastAsia	★	★			★		★	★		5
Lee et al.[199]	South Korea	EastAsia	★	★	★				★	★		5
Ng et al. (2015)[200]	China	EastAsia	★	★	★	★				★		5
Ng et al. (2013)[124]	China	EastAsia	★	★	★	★	★		★	★	★	8
Qin et al.[201]	China	EastAsia	★			★	★	★	★	★		6
Tung et al.[130]	Taiwan	EastAsia	★			★			★	★		5
Yang et al.[202]	South Korea	EastAsia	★	★	★	★				★		5
Rajendra et al.[203]	Malaysia	South-eastern Asia	★	★		★	★	★				5
Seow et al.[129]	Singapore	South-eastern Asia	★	★	★	★	★		★	★	★	8
Arafa et al.[204]	Jordan	West Asia	★			★			★	★		4
Bener et al.[112]	Qatar	WestAsia	★		★	★	★		★	★		6
Fatemi et al.[205]	Iran	West Asia	★		★	★				★		4
Ghanadi et al.[206]	Iran	West Asia	★	★		★				★		4
Safaee et al.[207]	Iran	West Asia	★		★	★	★		★	★		6

Guidelines for review

Selection:

S1, Case definition adequacy: ★a) requires independent validation (>1 person/record/time/process to extract information, or reference to primary record source such as colonoscopy or medical/hospital records); b) record linkage or self-report with no reference to primary record; c) no description

S2, Representativeness of the cases: ★a) consecutive or obviously representative series of cases; b) potential for selection biases or not stated

S3, Selection of controls: ★a) community controls; b) hospital controls, within same community as cases; c) no description

S4, Definition of controls: ★a) no history of colorectal cancer or adenoma; b) no description of source

Comparability:

C1, ★ Study controls for age/sex (the most important factors);

C2, ★ Study controls for any additional factors (1> additional factors, e.g. BMI, drinking or smoking)

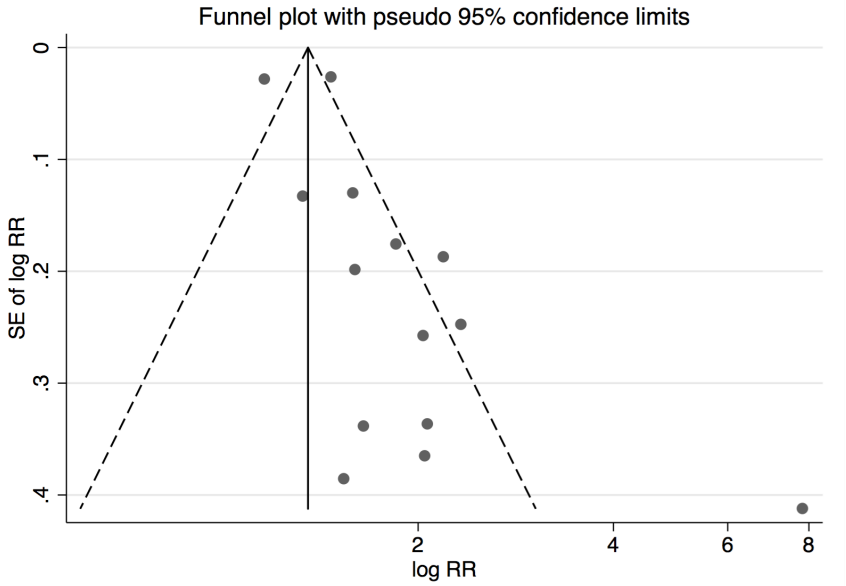
Exposure:

O1, Ascertainment of exposure: ★a) secure record (e.g. medical records); ★b) structured interview where blind to case/control status; c) interview not blinded to case/control status; d) written self report or medical record only; e) no description

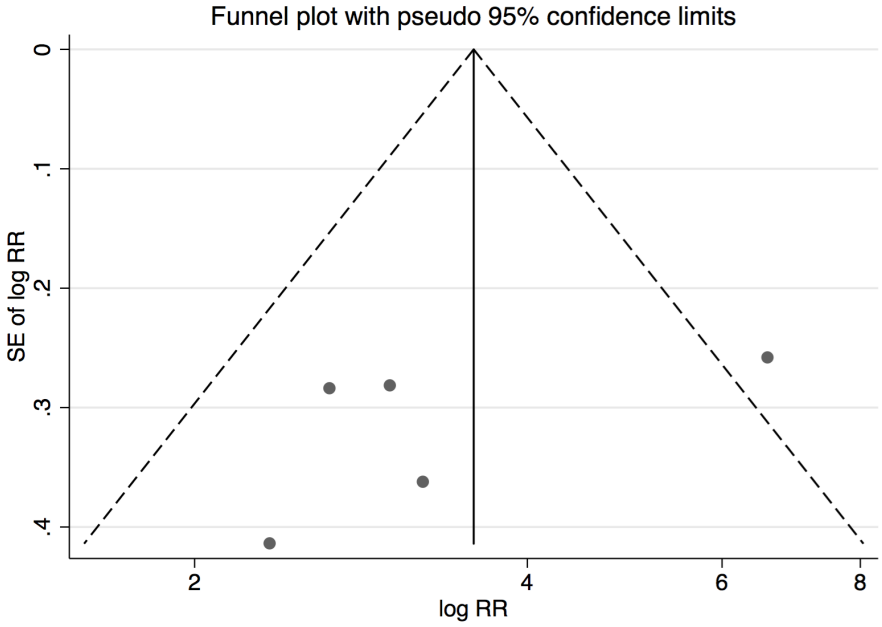
O2, Same method of ascertainment for cases and controls: ★a) yes; b) no

O3, Non-response rate: ★a) same rate for both groups; b) non respondents described; c) rate different and no designation

Appendix 11. Funnel plot for publication bias of the studies included in the meta-analysis for (A) East Asia and (B) West Asia



(A) Egger's statistical test p = 0.03



(B) Egger's statistical test p = 0.31

Appendix 12. Summary of case-control and cross-sectional studies providing number of cases and controls with first-degree family history of colorectal cancer

First author	Year	Country	Study type	Ascertainment of case	Ascertainment of controls	Case			Control		
						Total Case	Case with family history	Prevalence of family history in case	Total Control	Control with family history	Prevalence of family history in control
Ng	2015	China	case-control	population based	population based	281	54	19.2%	4708	656	13.9%
Safaee	2010	Iran	case-control	clinic-based	population based	393	61	15.5%	393	9	2.3%
Seow	2002	Singapore	case-control	clinic-based	population based	121	12	9.9%	222	5	2.3%
Yang	2014	South Korea	cross-sectional	population based	population based	2456	118	4.8%	16916	699	4.1%
Total						**3251**	**245**	**7.5% (6.7-8.5%)**	**22239**	**1369**	**6.2% (5.8-6.5%)**
Arafa	2011	Jordan	case-control	clinic-based	clinic-based	220	20	9.1%	220	9	4.1%
Bener	2010	Qatar	case-control	clinic-based	clinic-based	146	33	22.6%	282	39	13.8%
Chung	2010	South Korea	cross-sectional	clinic-based	clinic-based	1,383	115	8.3%	3,871	233	6.0%
Fatemi	2010	Iran	case-control	clinic-based	clinic-based	489	153	31.3%	249	24	9.6%
Ghanadi	2014	Iran	cross-sectional	clinic-based	clinic-based	112	22	19.6%	112	4	3.6%
Huang	2004	Japan	case-control	clinic-based	clinic-based	1,352	124	9.2%	50,706	2,456	4.8%

Iwa-saki	2006	Japan	cross-sec-tional	clinic-based	clinic-based	1,639	209	12.8%	579	44	7.6%
Ko-take	1995	Japan	case-control	clinic-based	partially clinic-based	363	47	12.9%	363	25	6.9%
Lee	2014	South Korea	cross-sec-tional	clinic-based	clinic-based	154	11	7.1%	560	63	11.3%
Qin	2015	China	case-control	clinic-based	clinic-based	1,106	69	6.2%	2,212	18	0.8%
Rajen-dra	2005	Malaysia	cross-sec-tional	clinic-based	clinic-based	36	6	16.7%	275	13	4.7%
Tung	2000	Taiwan	case-control	clinic-based	clinic-based	234	28	12.0%	468	30	6.4%
Wong	2016	16 Asian cities	cross-sec-tional	partially clinic-based	partially clinic-based	4,294	788	18.4%	7,503	1,909	25.4%
Ng	2013	China	cross-sec-tional	clinic-based	clinic-based	184	116	63%	561	255	45.5%
Total						**11,712**	**1,741**	**14.9% (14.2-15.5%)**	**67,961**	**5,122**	**7.5 % (7.3-7.7%)**

Abbreviations: NR, Not reported; NA, Not available.

Appendix 13. Summary of 3 cohort studies providing total number of cohort participants and the number of participants with first-degree family history of colorectal cancer, and prevalence of family history

First author	Year	Country	Ascertainment of case	Total number of participants	Number of participants with family history	Prevalence of family history in control
Chang	2015	Taiwan	population-based	39,384	877	2.23%
Murphy	2009	China	population-based	73,358	NR	NA
Total				**38,284**	**877**	**2.2% (2.1-2.4%)**
Byeon	2011	11 Asian cities	clinic-based	860	109	12.6%
Hata	2013	Japan	clinic-based	300	45	15.0%
Kim	2015	South Korea	clinic-based	3,561	127	3.6%
Total				**4,721**	**281**	**6.0% (5.3-6.7%)**

Abbreviations: NR, Not reported; NA, Not availabl

Appendix 14. Tools for family history collection with or without colorectal cancer risk assessment

Tool Name	Creators	Family history is entered by	Family history is entered as	Risk assessment for familial CRC risk	Results returned to
CancerGene	David Euhus, MD	Clinician	Structured data	Electronic	Clinician
CancerGene Connect	Previously UTSW, now commercial company (TX, USA)	Patient	Structured data	Electronic	Patient and clinician
CancerIQ	Commercial company (IL, USA)	Patient	Structured data	Manual	Patient and clinician
Cyrillic	Commercial company (Reading, UK)	Patient, clinician, and/or other record	Both structured and free text	Manual	Clinician
Genial (Shire)	Commercial company (Chester, UK)	Clinician	Both structured and free text	Manual	Clinician
Health Heritage	NorthShore Health (Illinois, USA)	Patient, clinician, and/or other record	Structured data	Electronic	Patient
Hughes RiskApps	Previously Harvard Partners, now commercial company (USA)	Patient	Structured data	Electronic	Clinician
Invitae Family History Tool	Commercial company (CA, USA)	Patient, clinician, and/or other record	Both structured and free text	Both electronic and manual	Patient and clinician
MeTree	Genomedical Connection/Duke University (NC,USA)	Patient	Both structured and free text	Both electronic and manual	Patient and clinician
MyFamily	Cleveland Clinic (OH, USA)	Patient	Structured data	Electronic	Clinician
Myriad FamilyHistory Tool	Commercial company (UT, USA)	Patient	Structured data	Electronic	Patient
Our Family Health	Intermountain Health Care (UT, USA)	Patient	Both structured and free text	Manual	Patient
Power Lineage	Commercial company (MA, USA)	Patient, clinician, and/or other record	Both structured and free text	Both electronic and manual	Clinician
Progeny	Commercial company (FL, USA)	Patient, clinician, and/or other record	Both structured and free text	Manual	Clinician
Trakgene (Kintrack)	Commercial company (South Australia)	Clinician	Both structured and free text	Manual	Clinician