Aus dem Deutschen Krebsforschungszentrum, Heidelberg
Wissenschaftlicher Vorstand: Prof. Dr. med. Michael Baumann
Abteilung Präventive Onkologie
Leiter: Prof. Dr. med. Hermann Brenner

Colorectal cancer risk prediction and risk-adapted colorectal cancer screening in patients with diabetes mellitus

Inauguraldissertation
zur Erlangung des Doctor scientiarum humanarum (Dr. sc. hum.)
an der
Medizinischen Fakultät Heidelberg
der
Ruprecht-Karls-Universität

vorgelegt von
Uzair Ali Khan
aus Toronto, Canada
2020

Dekan: Prof. Dr. med. Hans-Georg Kräusslich

Doktorvater: Prof. Dr. med. Hermann Brenner

DEDICATION

This dissertation is dedicated to my direct supervisors, Dr. Mahdi Fallah, leader of the Risk Adapted Prevention (RAD) Group, and Dr. Elham Kharazmi, co-leader of the RAD Group, for their guidance, patience and insight during the course of my project.

Also to my parents, Arif Ali Khan and Nazima Abdul Gani, who gave me the confidence to pursue this challenge.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

1.1 Epidemiology of colorectal cancer

Colorectal cancer is a neoplasm caused by adenomatous polyps emerging from the innermost layer of the large intestine (Amersi et al. 2005). When epithelial cells of the intestinal mucosa cumulate mutations, the cells develop into adenomas, which over time may morph into carcinomas (Bogaert and Prenen 2014; Leslie et al. 2002). As of 2018, colorectal cancer was the third most diagnosed and the second leading cause in cancer-related deaths with an estimated 1.8 million new cases and 861,000 deaths worldwide (Bray et al. 2018). In Europe alone, almost 500,000 novel cases occurred with approximately half as many colorectal cancer-related deaths, highlighting the global impact of the disease. Nonetheless, Europe contains 9% of the global population but a significant 25% of new annual colorectal cancer cases, suggesting a disproportionate burden of this cancer worldwide (Ferlay et al. 2018).

The highest incidence rates of colorectal cancer are observed in Australia and regions of Europe and North America, whereas the lowest are recorded in South Asia and Africa (**Figure 1**). It is believed that disparity in incidence between these regions are owed largely to differences in genetic susceptibility and environmental factors, namely diet (Global Burden of Disease Cancer Collaboration 2017). Colorectal cancer incidence is also three to four-fold more likely in economically more developed nations as opposed to lesser developed nations, reflecting an effect of socioeconomic status and human development index (Bray et al. 2018). Sex differences are also present in colorectal cancer distribution with men consistently having higher incidence and colorectal cancer-related mortality (**Figure 2**).

Despite the rising new cases and deaths worldwide, there are a few countries with a high human development index that have observed an overall reduction of incidence and mortality rates in recent years, such as Australia, the US and certain European nations (Center et al. 2009; Schreuders et al. 2015). The main reasons for these trends are not fully understood; however, they are at least in part due to the emergence of cancer screening programs and improvements in radiotherapy and chemotherapy (Center et al. 2009). On the other hand, there are also nations with rapid economic growth that are observing increases in both incidence and mortality probably due to the changes in diet and lifestyle associated with improved human development (Arnold et al. 2017). In Japan, between the 1950s and 1970s (a significant period of economic growth) 'westernization' of diet is believed to have led to the surge of colorectal cancer incidence and mortality observed until the 1990s (Kono 2004). While number of new colorectal cancer cases continues to rise globally and disease incidence and mortality are projected to increase 60% by 2030, controlling the disease remains an important public health issue (Ferlay et al. 2015).

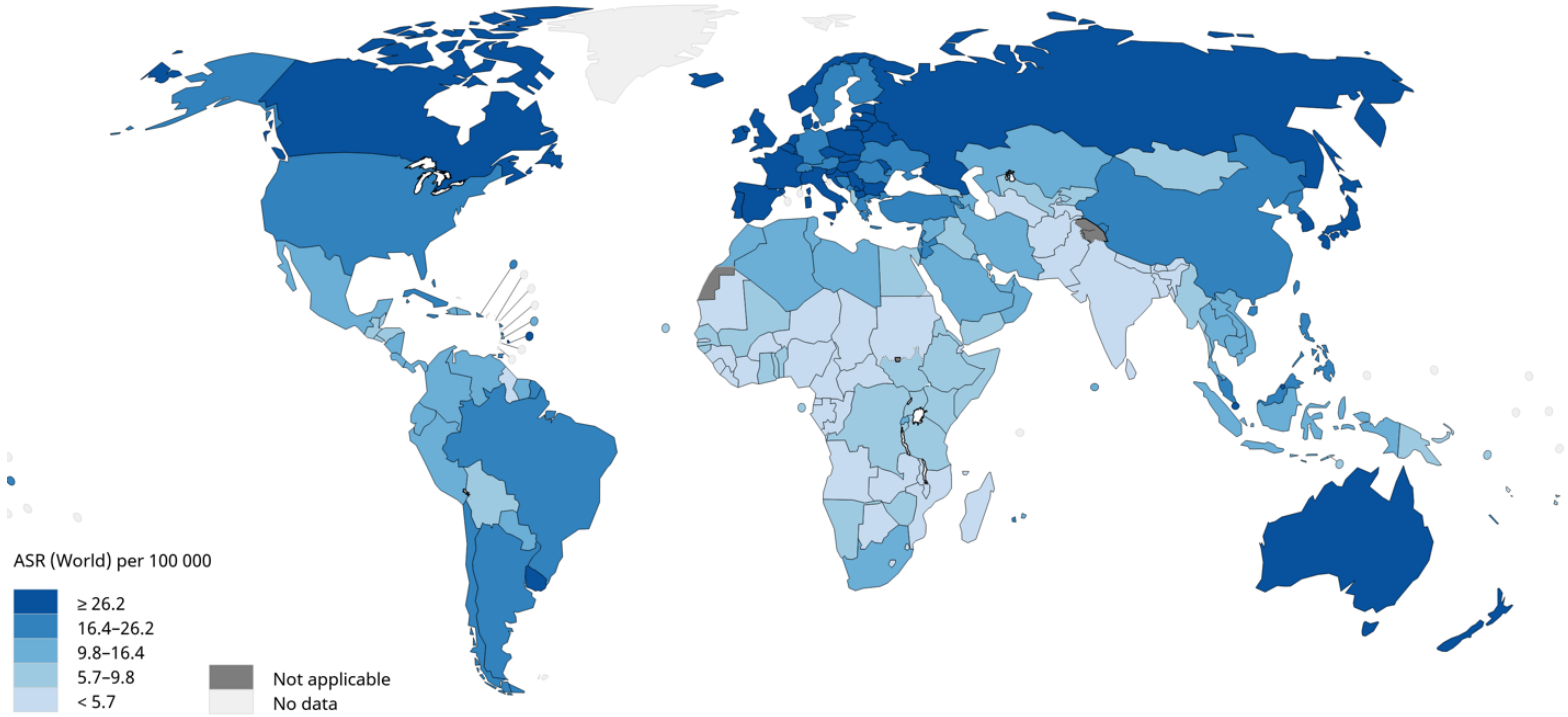


Figure 1. Colorectal cancer age-standardized incidence rates in 2018
Available from https://gco.iarc.fr/; Accessed on 01/19/2020.

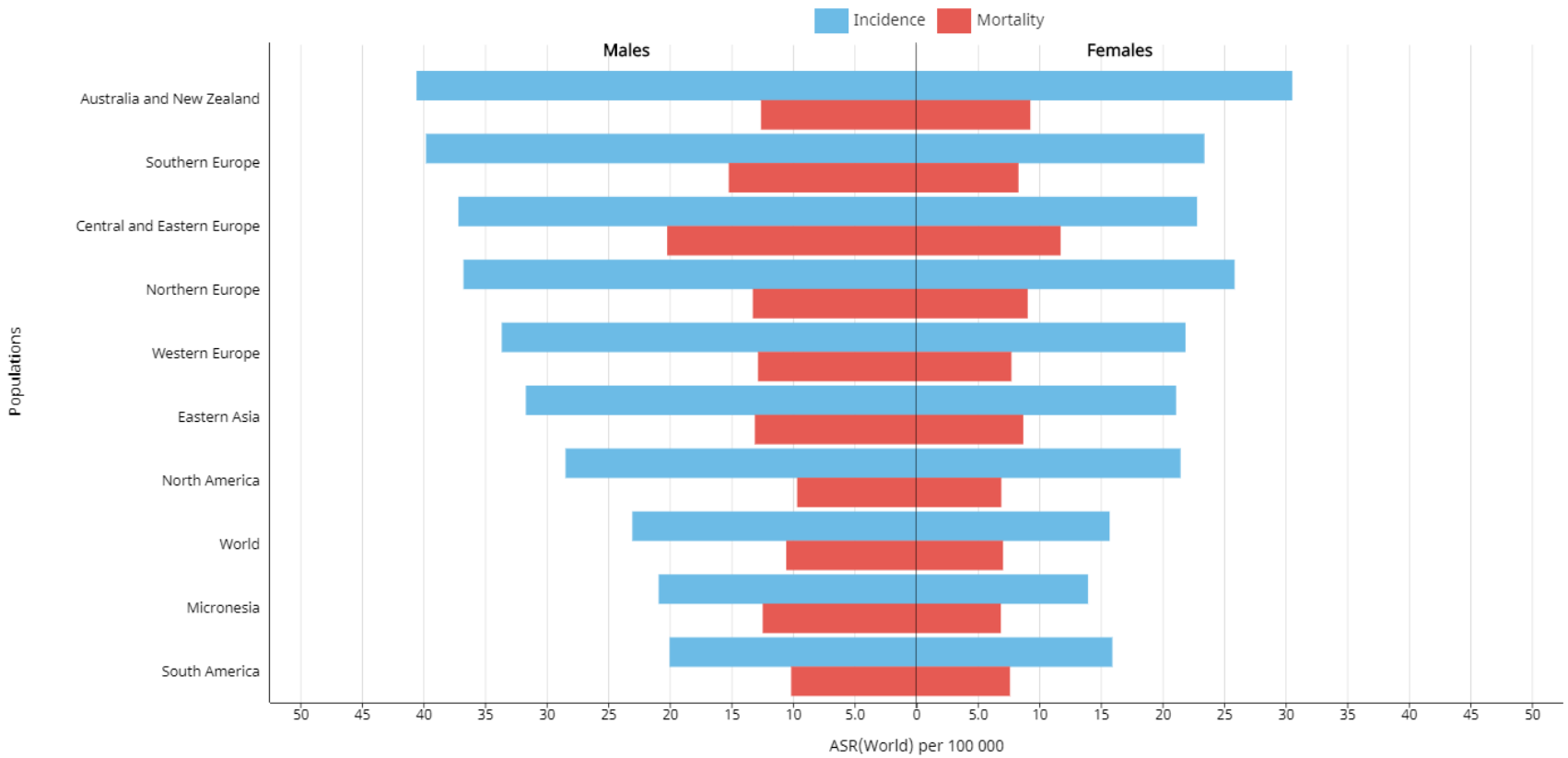


Figure 2. Colorectal cancer age-standardized incidence and mortality rates by sex in 2018

Available from https://gco.iarc.fr/; Accessed on 01/19/2020.

1.2 Risk factors of colorectal cancer

It is widely understood that both genetic and environmental factors contribute to the development of colorectal cancer. Environmental risk factors, such as diet (high in red/processed meats, low in vegetables), low physical activity, obesity, smoking and alcohol, have all been associated with increased risk of colorectal cancer (Bagnardi et al. 2015; Botteri et al. 2008; Robsahm et al. 2013; Zhao et al. 2017). These modifiable factors, namely diet and physical activity, have been suggested to explain the elevated burden of colorectal cancer in transitioning and developing regions around the world (Bishehsari et al. 2014). Furthermore, regulation of such dietary and lifestyle factors has been associated with reduction in as much as 50% of colorectal cancer risk (Colditz et al. 1996).

Of the non-modifiable genetic risk factors, advanced age, male sex, family history, and inherited genetic syndromes are the most notable (Rawla et al. 2019). Male sex (across regions and all ages) has been associated with increased risk of colorectal cancer (Bray et al. 2018). Genetic syndromes, such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), contribute 5% to 10% of colorectal cancer cases (Toma et al. 2012). These risk factors, although associated with an extremely high lifetime risk of colorectal cancer, are far less common than familial cases of colorectal cancer, which account for about 20-30% of all cases and involve a combination of both genetic and environmental factors (De Rosa et al. 2015; Rawla et al. 2019). Family history is a well-established risk factor with risk increasing with cumulative numbers of first-degree and second-degree relatives with colorectal cancer (Johns and Houlston 2001; Tian et al. 2019).

Personal history of certain diseases has also been associated with elevated colorectal cancer risk. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are major risk factors and are associated with roughly 3-fold risk of colorectal cancer (Johnson et al. 2013). Personal history of an inflammatory bowel disease is also associated with increased colorectal cancer-related mortality (Amersi et al. 2005). Studies have suggested that long-term presence of inflammatory bowel diseases, as well as the extent of the bowel affected, both contribute to increase in the risk of colorectal cancer, with an estimated 7% to 14% of cases developing colorectal cancer within 25 years of the disease diagnosis (Gillen et al. 1994; Gyde et al. 1988). Due to their robust association with colorectal cancer, inflammatory bowel diseases are also among a few colorectal risk factors that have been indicated in many colorectal cancer screening guidelines around the world.

1.3 Screening for colorectal cancer

Colorectal cancer screening has been determined to be more cost-effective (or even cost-saving) in the long run than not screening (Lansdorp-Vogelaar et al. 2009; Patel and Kilgore 2015). There are two main categories of colorectal cancer screening, invasive and non-invasive (Schreuders et al. 2015). The best established non-invasive tests are tests for the presence of blood in stool. The two most common such tests are the Guaiac fecal occult blood test (gFOBT), as well as the fecal immunochemical test (FIT) (Bevan and Rutter 2018). The gFOBT, though limited by low sensitivity, has been the most widely used non-invasive test since the emergence of colorectal cancer screening programs due to its low cost, ease of use, and evidence of effectiveness from randomized controlled trials (RCTs) (Rabeneck et al. 2012). The FIT has

replaced the gFOBT in several programs since it is unaffected by false positive results from food, only requires one sample, and multiple studies and meta-analyses have shown that it is more accurate than the gFOBT (Brenner and Tao 2013; Lee et al. 2014; Steele et al. 2013). When stool samples yield a positive result, patients are recommended to undergo an invasive test, such as colonoscopy. Colonoscopy is deemed to be the gold standard of all forms of colorectal cancer screening and serves the purpose of colorectal cancer detection as well as a secondary purpose of adenoma removal. Since physicians can remove precancerous lesions such as adenomas during colonoscopy, this procedure has a major advantage not afforded by other cancer screening modes (Bevan and Rutter 2018).

There are a wide variety of screening programs globally. Despite their differences, studies evaluating the long-term effectiveness of individual screening programs have yielded a reduction in colorectal cancer incidence and mortality (Brenner et al. 2015a; Greuter et al. 2016; Lew et al. 2017). Screening programs vary not only in the age of first screening, frequency of screening, and screening modality, but also in the management of high-risk cases. Currently, most screening programs recommend earlier screening for high-risk groups, such as those with a first-degree relative (FDR) diagnosed with colorectal cancer, genetic syndromes like FAP or HNPCC, prior history of adenomas, and inflammatory bowel diseases (Wilkins et al. 2018). Apart from family history of colorectal cancer, these high-risk groups contribute to a minority of colorectal cancer cases.

Overall, it has been found that colorectal cancer screening is effective in reducing incidence and mortality of colorectal cancer. A 2015 study tracking incidence in the US found that since 1975

there has been a 0.92% decrease per year in age-adjusted incidence in those over the age of 49 years. It is believed that colonoscopy screening, specifically targeted for those aged 50 or older is largely responsible for the reduction in incidence over time (Bailey et al. 2015; Edwards et al. 2010). The idea that screening is responsible for colorectal cancer incidence reductions is supported by the fact that countries such as US and Germany have observed a much larger reduction in colorectal cancer incidence and mortality than countries such as Sweden and the Netherlands, with similar high level of development, but without or with only recently installed organized screening programs (Ait Ouakrim et al. 2015). In spite of the success in reducing incidence, the 2015 US study established that an increase in incidence was observed among young people below the age of 50 who are not being targeted by screening. Similar trends are observed across Europe with colorectal cancer cases rapidly rising among young adults in an analysis of 20 European countries (Vuik et al. 2019). As a result, some countries have lowered the ages of first screening such as from 50 to 45 in the US, and a proposed change from 60 to 50 in the UK (Cairns et al. 2010; Wolf et al. 2018). Although this is one method of reducing cancer incidence in young people, there are several limitations, such as the cost of screening an additional large portion of the population, as well as the risks associated with colonoscopy such as perforation which may be unnecessary in a young individual who is otherwise at low risk for colorectal cancer (Megna and Shaukat 2019).

It has been suggested that a personalized screening, rather than a one-size-fits-all approach, would allow those with high risk to be targeted while simultaneously reducing the burden of screening on those with low risk who are unlikely to develop colorectal cancer in their lives (Kuipers and Spaander 2018). Though currently the ability to distinguish those at high and low

risk is weak, identifying additional risk factors, such as personal history of diseases that may pose a threat to young individuals, is becoming increasingly important as it may help to provide the basis of a risk-adapted (personalized) screening.

1.4 Epidemiology of diabetes mellitus

Diabetes mellitus is a metabolic disease characterized by long-term hyperglycemia due to deficits in insulin function. There are two most common forms of diabetes, type 1 and type 2. Type 1 diabetes represents between 5% and 10% cases and is an autoimmune disease most commonly affecting children and adolescents, in which beta cells of the pancreas, which produce insulin, are destroyed (Kharroubi and Darwish 2015). Type 2 diabetes, characterized by insulin resistance or deficiency, is the most common form of diabetes representing roughly 90% of diabetes cases with hundreds of millions of people affected worldwide. The global burden of diabetes is significant with an estimated prevalence of 9% (463 million) worldwide and a predicted prevalence of 10% (578 million) by 2030. Although the causes of type 1 diabetes are not well understood, type 2 diabetes has genetic and lifestyles components and is well known to be preventable (Wu et al. 2014). Furthermore, like colorectal cancer, variation in type 2 diabetes prevalence is observed across geographic location. The lowest prevalence is often in rural areas of developing countries, whereas the highest is observed in developed countries and in societies that have adopted a western lifestyle (Forouhi and Wareham 2014).

Apart from similarity in geographic distribution, type 2 diabetes and colorectal cancer share important risk factors. The main risk factors of type 2 diabetes are obesity, physical inactivity, family history, diets high in sugar and processed or red meats (InterAct Consortium 2013a;

InterAct Consortium 2013b; Wu et al. 2014). With the similarities in risk factors, it is not surprising that diabetes has been associated with colorectal cancer. Meta-analyses have shown that personal history of diabetes is associated with about 30% increased risk of colorectal cancer (Kramer et al. 2012; Larsson et al. 2005). However, it is noteworthy that overlapping risk factors between diabetes and colorectal cancer alone may not explain the association since type 1 diabetes (which does not share risk factors with colorectal cancer) has also been implicated with colorectal cancer, albeit with a modest association (Carstensen et al. 2016). Diabetes incidence has also been rapidly increasing among young adults. A UK study demonstrated that the age-standardized rate of new diabetes cases in people aged 40 or below rose significantly from 217 per 100,000 in 1996-2000 to 598 per 100,000 in 2006-2010 (Lascar et al. 2018). Hence, shared risk factors, similar geographic distribution, and rising incidence in young people make diabetes an ideal candidate to be explored as a colorectal cancer risk factor.

1.5 Gaps in the literature

As mentioned before, diabetes has been associated with moderately increased risk of colorectal cancer in several studies in recent decades (Larsson et al. 2005). Despite this, there are still several gaps in the literature. For instance, to date no study has evaluated the risk of colorectal cancer in young diabetic patients by age at diagnosis and family history of colorectal cancer. A large study with accurate information on personal history of diabetes and family history of colorectal cancer demonstrating the association between diabetes and colorectal cancer could provide the robust evidence needed to establish diabetes as a colorectal cancer risk factor.

Since the emergence of colorectal cancer screening only a handful of risk factors have been indicated in screening guidelines. However, these risk factors are unlikely to explain the surge in colorectal cancer cases in young adults. Researchers hypothesize that this trend may be a reflection of a more sedentary lifestyle in recent decades (Edwards et al. 2010). Since diabetes is directly associated with such a lifestyle as well, introduction of diabetic patients as a new high-risk group into colorectal cancer screening guidelines could be an important gap to fill. Furthermore, if 'lifestyle' practices are indeed leading to higher rates of colorectal cancer in young adults, it becomes increasingly important to identify associated risk factors to be used as basis of an earlier risk-adapted colorectal cancer screening.

1.6 Aims

The main aims of this study are to determine the risk of colorectal cancer in diabetic patients with and without a family history of colorectal cancer and to provide the basis for risk-adapted first screening in diabetic patients, using the world's largest nationwide family-cancer datasets from Sweden.

1.6.1 Assessing risk of colorectal cancer in diabetic patients

- To evaluate whether diabetic patients are at increased risk of colorectal cancer and what effect age at diabetes diagnosis has on colorectal cancer risk
- To evaluate the risk of early-onset and late-onset colorectal cancer in diabetic patients by sex and family history of colorectal cancer.

1.6.2 Determining risk-adapted starting ages of colorectal cancer screening for diabetic patients using 10-year cumulative risk curves

- To determine the age-specific 10-year cumulative risk of colorectal cancer in diabetic patients by sex and family history of colorectal cancer
- To provide risk-adapted starting ages of screening for diabetic patients.

1.6.3 Comparison of risk of colorectal cancer between dynamic and static variable definitions

- To compare the absolute and relative risk of colorectal cancer in diabetic patients by the dynamic and static definitions of diabetes history and family history of colorectal cancer.
- To compare risk-adapted first screening ages by dynamic and static definitions of diabetes history and family history of colorectal cancer.

2 METHODS

2.1 Database description

In this study, the Swedish family-cancer datasets were utilized. These datasets were initially produced during the 1990s by connecting data from the Multi-generation Register, national censuses, Swedish Cancer Registry, and death register using unique lifetime national registration numbers (Hemminki et al. 2001). These culminate to produce the world's largest family-cancer dataset to date with data on all Swedish residents (irrespective of country of birth) born from 1932 onwards (offspring generation) and their parents (parental generation). Data on ancestry and familial relationship were obtained using the Multi-generation register. This was linked with the Swedish Cancer registry, which was established in 1958, and contains detailed information on cancer diagnosis. Four-digit diagnostic codes based on the seventh revision of the International Classification of Diseases (ICD-7) were used to classify cancer types. Linkage between these two registers is the foundation of the database with updates every two years. The most recent edition of the database (with data until end of 2015) culminates to a total of 16.1 million individuals, with roughly 2 million primary invasive cancer cases recorded from 1958 to 2015. Further linkage with the Death Registry and the National Census bolsters the database with cause and date of death data, residential area, occupation, socioeconomic status, immigration, and emigration records among others.

2.2 Study population

In order to form the study population, the aforementioned Swedish family-cancer datasets were linked to the Swedish National Inpatient and Outpatient Registers. The Inpatient Register

contains patient records from 1964 to 2015, while the outpatient records contain records from 2001 to 2015. In total, there were approximately 37 million hospital visit records for a list of over 60 cancer-related diseases. After removing all individuals without known first-degree relatives, the study population composed of roughly 12.6 million individuals (**Figure 3**). The population datasets were pseudonymized, therefore, contact with and identification of participants was not possible. As a result, participants were not involved in development of the present study, or in the writing or interpretation of the results. Lastly, there is no intention of disseminating the results directly to any participants. Approval of the study protocol was granted by the Lund regional ethic committee (2012/795).

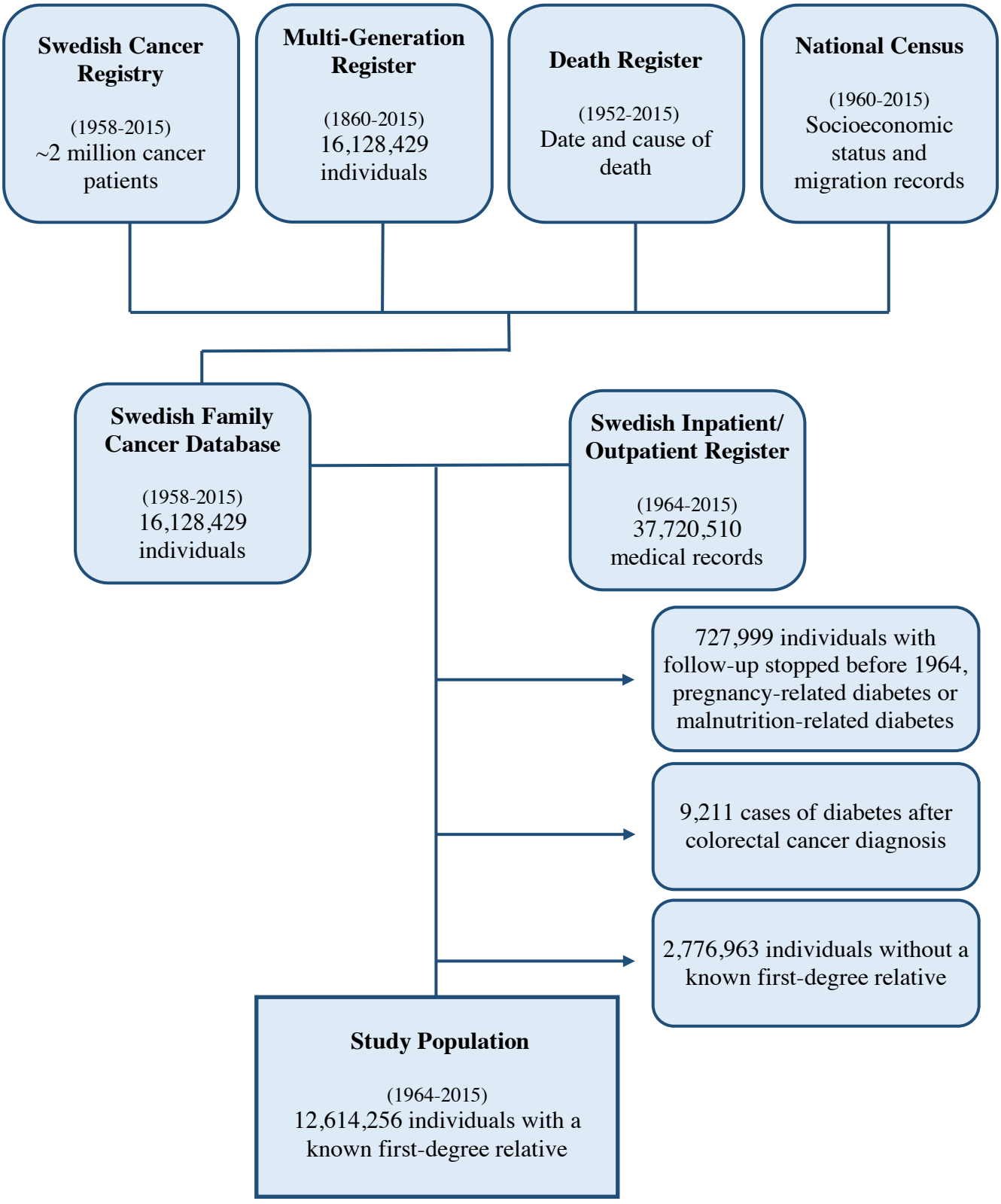


Figure 3. Flowchart of study population

2.3 Follow-up

Start of follow-up for each individual was established as the most recent of birth year, immigration year, or 1964 (the first year in which hospital records were available). Follow-up ended in year of death, colorectal cancer diagnosis, emigration, or at the end of 2015, whichever happened earlier. The maximum length of follow-up was 51 years from the start of 1964 until the end of 2015.

2.4 Dynamic disease and family history definitions

Disease history was established in our study using the National Inpatient/Outpatient Registers, while family history was available through the linkage between the Swedish Cancer Registry and the Multi-generation Register. Family history was established in first-degree relatives (anyone with whom a participant shared 50% of their genetic information), i.e. parents, siblings and children. Individuals with colorectal cancer and one or more first-degree relatives were referred to as familial cases, while those without any diagnosed first-degree relatives were known as sporadic (non-familial) cases. In this study, personal history of diabetes and family history of colorectal cancer were handled using two methods; the 'static' and 'dynamic' methods (**Figure 4**). In this study, all disease (personal or family) histories, unless otherwise expressed, were allocated according to the dynamic method, while the static method was used in some analyses as a comparison method in risk estimation. All participants were recorded as cases or non-cases of diabetes, and as without family history or with family history of colorectal cancer, with subcategorization of family history based on the number of affected first-degree relatives.

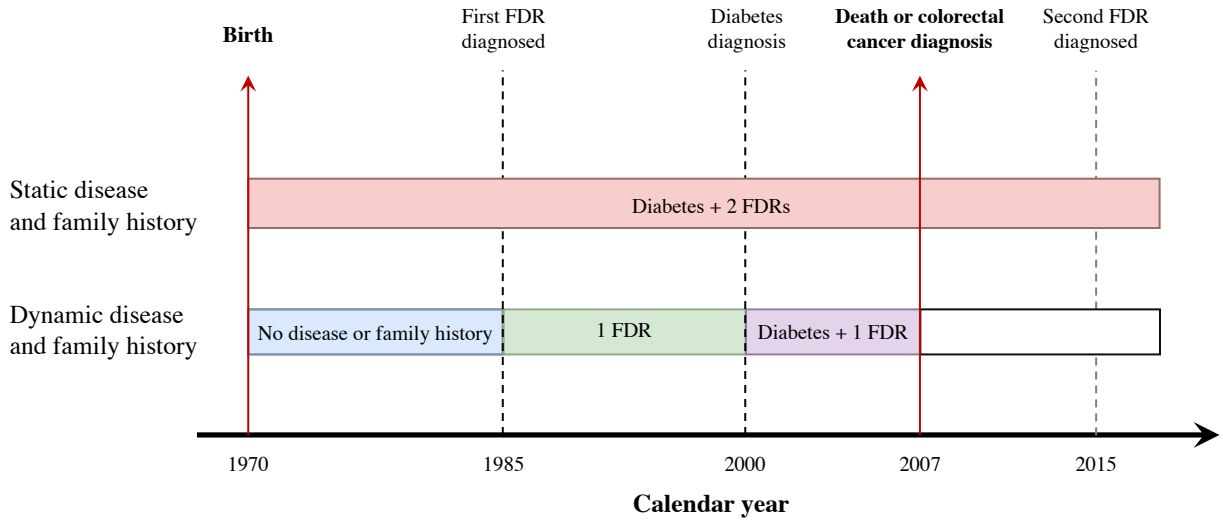


Figure 4. Illustration depicting static and dynamic definitions of personal history of diabetes and family history of colorectal cancer in a hypothetical case

(FDR = first-degree relative)

Example: According to the static definition of family history, the index person in Figure 4 has a personal history of diabetes and two first-degree relatives with colorectal cancer for their entire follow-up period. Based on the dynamic definition, his life can be divided into three phases: for the period 1970-1985 he would be categorized as a non-diabetic person without family history of colorectal cancer; for the period 1985-2000 he would be categorized as a non-diabetic person with a family history of colorectal cancer in one first-degree relative; and from 2000 to 2007 he would be categorized as a diabetic patient with a family history of colorectal cancer in one first-degree relative.

Static disease and family history: The static approach is based on the information available in the most recent data release (2015, end of study follow-up). Due to record linkage between the Swedish Cancer Registry and the Multi-generation Register, all individuals' personal and family history whether occurring prior to or after the end of follow-up for the index person, was known. In cases where additional family history was registered before birth or even after end of the follow-up for the index person, it was considered during risk-estimation. In other words, disease and family history were independent of the index person's follow-up and person-years in risk estimation were allocated to a single risk category. The static approach might also be called time-independent or register-based method (Brandt et al. 2010).

Dynamic disease and family history: In the dynamic approach, participant's family history and personal disease history is fully dependent on the chronological timeline of events occurring during follow-up, with the notable exception of family history prior to birth which was also registered since it was 'in effect' at the commencement of follow-up of the index person. In this method, a participant's life can be divided into phases in which his personal and family history status is unique and in risk calculation, person-years are allocated accordingly. Since these histories are time dependent, a person was only allocated in a certain group based on the time of diagnosis. In short, a person was only registered as being diabetic from the age at which they were diagnosed with diabetes, and prior to that were registered as non-diabetic cases. Similarly, if a person's first-degree relative was diagnosed with colorectal cancer, he was only registered as having a family history from that point onwards and prior to that was registered as not having a family history of cancer. If a first-degree relative of the index person was diagnosed with colorectal cancer or diabetes after the conclusion of individual's follow-up, it was not considered as 'with history'. This approach is also considered as time-dependent or time-varying.

2.5 Colorectal cancer and diabetes diagnosis

Data on colorectal cancer diagnosis was available through the Swedish Cancer Registry. Diagnoses of primary invasive cancer were registered according to the International Classification of Diseases, seventh revision for the entire study period. The following codes were used to define colorectal cancer: 153, 153.0, 153.1, 153.2, 153.3, 153.4, 153.8, 153.9, 154, 154.0, and 154.8. All colorectal cancers included in this study, whether personal or family history, were primary invasive cancers and did not precede a diabetes diagnosis. All cases of diabetes were extracted from the Swedish Inpatient (hospital records) Register and Outpatient Register

(specialized day clinic records) and were defined according to the following International Classification of Diseases (ICD) codes and calendar periods of diagnosis: ICD-7 from year 1964 to 1968: 260; ICD-8 from 1969 to 1986 250; ICD-9 from 1987 to 1996 250; and ICD-10 from 1997 to 2015: E10, E11, E13, and E14. Cases with diabetes due to malnutrition or pregnancy-related diabetes were excluded. Diabetes diagnosis date was registered as the first visit in which a diabetes code was recorded. Furthermore, cases with a colorectal cancer diagnosis preceding a diabetes diagnosis were also excluded to avoid the bias due to reverse-causation. Diabetes subtype was only registered from 1997 onwards, since the Swedish Inpatient/Outpatient Registers did not recognize a distinction between Type 1 and Type 2 diabetes until the tenth revision of the ICD (Liu et al. 2015).

2.6 Statistical analysis

All analyses were performed using SAS v9.4 (by SAS Institute Inc., Cary, NC, USA).

2.6.1 Relative risk

In this study standardized incidence ratios (SIRs) were used to estimate relative risk. The exposures of interest were primarily diabetes personal history, age at diabetes diagnosis, and family history of colorectal cancer. The main outcome of interest was colorectal cancer diagnosis. SIRs were calculated as a ratio between the observed and expected number of cases. The expected number was a product of strata-specific person-years in those with the exposures of interest (personal and family history) and strata-specific incidence rates in those without the exposures of interest.

SIRs were adjusted for 5-year age group, calendar period (1964-1969, 1970-1974,…, 2005-2009, 2010-2015), socioeconomic status (white collar worker, blue collar worker, private, farmer,

professional, unspecified/other), residential area (small cities in North Sweden, small cities in South Sweden, and large cities) and sex. The 95% confidence intervals for SIRs were calculated based on a Poisson distribution.

In this study, SIRs were reported, which are comparable to other relative risk estimators such as hazards ratios (HRs) from Cox proportional hazard regression. Prior studies have shown that both methods produce similar estimates, which are also similar to risk ratios (RRs) calculated by Poisson regression and even negative binomial regression. For example, it has been established that regardless of the method of relative risk estimation, risk of familial colorectal cancer is roughly 1.9-fold in the Swedish family-cancer database [HR=1.9 (Kharazmi et al. 2012), SIR=1.9 (Frank et al. 2014), average RR of an affected parent or affected sibling=1.9 by Poisson regression and negative binomial regression (Frank 2015)], similar results have also been observed in the Utah Population DataBase [HR=1.9 (Samadder et al. 2015); SIR=1.9 (Taylor et al. 2010)].

As an additional analysis, SIRs were adjusted for hospitalization due to alcoholism, obesity and chronic obstructive pulmonary disorder (which was used as a surrogate for heavy smoking). An additional sensitivity analysis was conducted which excluded patients with inflammatory bowel diseases to ensure that they did not confound any associations since they are established colorectal cancer risk factors. Furthermore, risk of colorectal cancer by subsite was evaluated to determine if certain regions of the bowel are differentially affected. Finally, sensitivity analysis by subtype of diabetes (type 1 and type 2) was conducted for cases diagnosed from 1997 onwards to detect any difference in risk between the two exposures, however those with both subtypes recorded were excluded from this analysis.

2.6.2 Absolute risk

In this study, cumulative risk was used to establish absolute risk. Cumulative risk since birth was calculated at 10-year increments (0-9, 0-19, 0-29, …, and 0-79). Lifetime cumulative risk (LCR) was defined as the cumulative risk up to age 79 because the average life expectancy in Europe in 2015 was 80 years. LCR was calculated using the following equations:

- Age-specific yearly incidence rate = Total cases at each 1-year age divided by the total person-years at that age
- Lifetime cumulative rate = Sum of all age-specific incidence rates by age 79
- Lifetime cumulative risk = $1 - e^{(\text{-lifetime cumulative rate})}$

Conventional aggregated data was not used for the calculation of cumulative incidence, rather, exact values from individual participant's age-specific yearly data were used. The 95% confidence intervals for the lifetime cumulative rates were calculated based on Poisson distribution.

2.6.3 10-year cumulative risk

To determine risk-adapted starting ages of screening, age-specific 10-year cumulative risk curves were used. 10-year cumulative risk represents the risk of developing an outcome within the next 10 years and is calculated based on the following equations:

- Age-specific yearly incidence rate = Total cases at each 1-year age divided by the total person-years at that age
- 10-year cumulative rate for age X = Sum of ten consecutive yearly age-specific incidence rates from age X to age X+9
- 10-year cumulative risk = $1 - e^{(- \text{10-year cumulative rate})}$.

Exact values from individual participant's age-specific yearly data (not the conventional aggregated data) were used. Risk-adapted screening ages were determined by comparing 10-year cumulative risk curves of each risk group with 10-year cumulative risk curve for the general population. A moving average technique was employed to curves to reduce the effects of random variation in incidence rates. For example, for 10-year cumulative risk at age 40, the risks at age 39, 40, and 41 were averaged, while for age 41, the risks at age 40, 41 and 42 were averaged and so on to smoothen the curves and be able to accurately infer risk-adapted first screening ages (**Figure 5**). This method of calculating risk-adapted starting age of cancer has also been utilized for other conditions (Mukama et al. 2020a; Mukama et al. 2020c; Tian et al. 2020). The risk-adapted screening ages were provided for different benchmark ages of first screening mentioned in screening programs (i.e. 45, 50, 55, and 60).

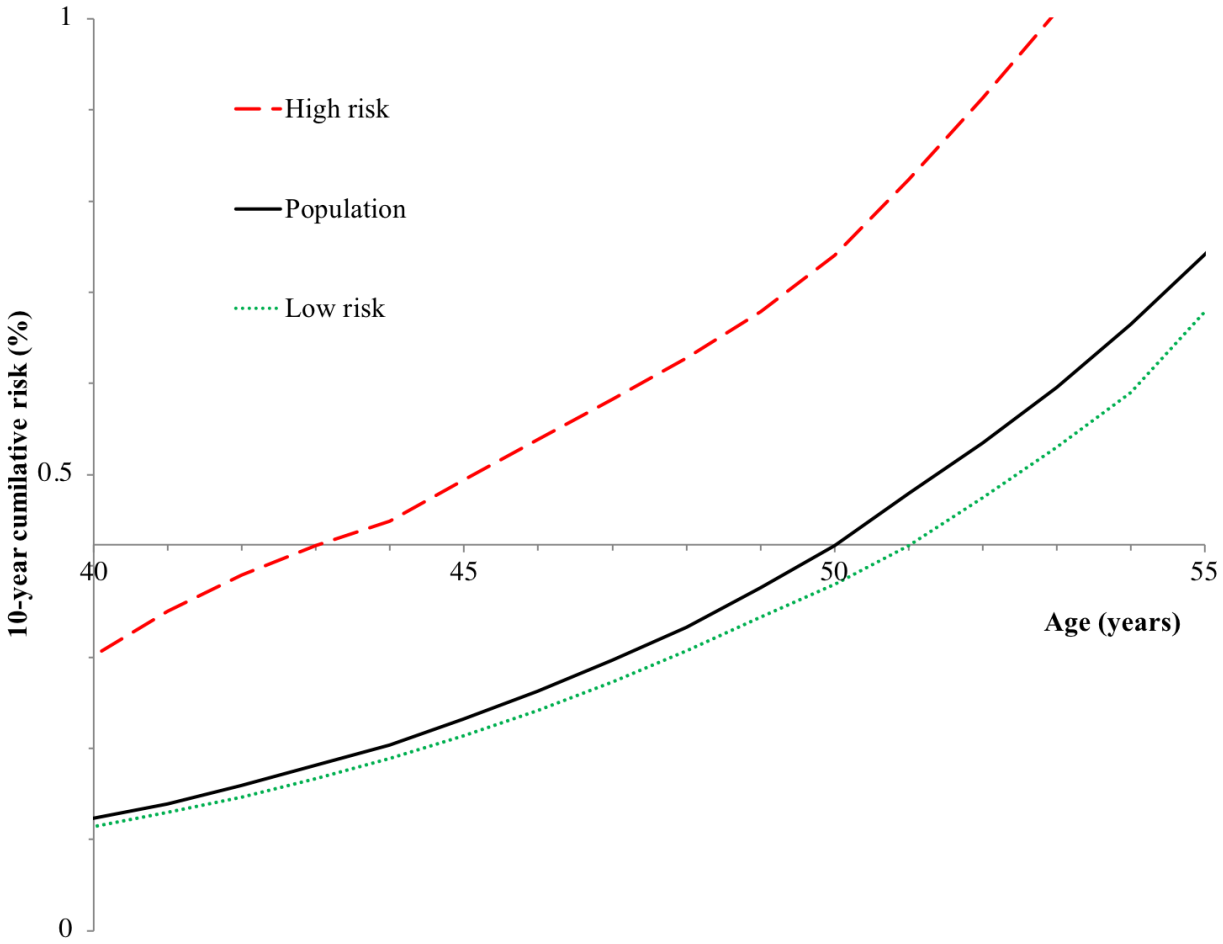


Figure 5. Sample 10-year cumulative risk plot used to infer risk-adapted starting age of first screening

The horizontal line represents the 10-year cumulative risk of colorectal cancer for 50-year-old individuals in the general population.

Example: The population (black line) 10-year cumulative risk shows that at age 50, the most common age of first screening, the 10-year cumulative risk of developing an outcome is 0.4%. The high-risk (red dashed line) group reaches this population level of risk seven years earlier (at age 43), suggesting that they could be screened at that age. Similarly, low-risk individuals (green dotted line) reach the same population level of risk one year later, suggesting that screening can be accordingly delayed for them.

3 RESULTS

3.1 Population demographics

The study population consists of a total of 12,614,256 individuals with at least one known first-degree relative who have been residing in Sweden some time during 1964 to 2015. The maximum possible follow-up was 52 years (January 1964 to December 2015) and the median length of follow-up was 33 years. In the study population, a total of 559,375 (4.4%) were diabetic patients, of which 101,135 (18%) were diagnosed with diabetes before the age of 50 (**Table 1**). Of all diabetic patients, 288,348 (51.5%) were men and the median age of diabetes diagnosis was 64 for men, four years younger than that for women. The period with most diabetes cases diagnosed per year was 2010-2015, with over 16,000 cases per year, whereas from 2000-2010 nearly 15,000 cases were diagnosed per year.

Within the study population 162,226 cases of colorectal cancer were identified (**Table 2**). In total, 155,247 of all colorectal cancer cases were without a family history (95.6%), with an approximately equal distribution between men and women (52.5% men). Compared with familial colorectal cancer cases, sporadic (without a family history) colorectal cancer was diagnosed five years later (mean diagnosis age 69.3, median 71). Of all colorectal cancer cases 17,969 cases were not distinguishable by location of tumor. The most common was colorectal cancer of the proximal colon (40.4%), followed by the rectum (34.7%) and the distal colon (24.8%), all of which had similar mean age of onset. Approximately 6.5% of sporadic colorectal cancer and 9% of familial colorectal cancer cases occurred before the age of 50.

Table 1. Characteristics of diabetic patients in study population

	Diabetic patients					
	All		Without CRC		With CRC	
	N	%	N	%	N	%
Total	559,375	100.0	547,839	97.9	11,536	2.1
Sex						
Men	288,348	51.5	281,609	51.4	6,739	58.4
Women	271,027	48.5	265,230	48.4	4,797	41.6
Age at DM diagnosis						
<20	28,639	5.1	28,601	5.22	38	0.3
20-29	15,196	2.7	15,121	2.76	75	0.7
30-39	20,373	3.6	20,198	3.69	175	1.5
40-49	37,066	6.6	36,549	6.67	517	4.5
50-59	76,678	13.7	75,107	13.7	1571	13.6
60-69	130,909	23.4	127,239	23.2	3670	31.8
70-79	153,043	27.4	148,863	27.2	4180	36.2
80-84	97,471	17.4	96,161	17.6	1310	11.4
Period of diagnosis						
1964-1969	5,466	1.0	5,406	1.0	60	0.5
1970-1979	57,752	10.3	56,646	10.3	1106	9.6
1980-1989	114,024	20.4	111,702	20.4	2322	20.1
1990-1999	137,054	24.5	133,876	24.4	3178	27.5
2000-2009	147,111	26.3	143,800	26.2	3311	28.7
2010-2015	97,968	17.5	96,409	17.6	1559	13.5
Disease history						
IBD	19,232	3.4	18,848	3.4	384	3.3
HNPCC	82	0.0	74	0.0	8	0.1
Obesity*	19,019	3.4	18,705	3.4	314	2.7
Alcoholism*	20,074	3.6	19,733	3.6	341	3.0
COPD*	52,096	9.3	50,970	9.3	1126	9.8

* Hospitalization for these conditions

Abbreviations: CRC = Colorectal cancer, DM = Diabetes mellitus, IBD = Inflammatory bowel disease, HNPCC = Hereditary nonpolyposis colorectal cancer, N = Number of people; % = Percentage of diabetic patients with the specified characteristic out of total number of diabetic patients

Table 2. Characteristics of colorectal cancer patients in study population

	Patients with colorectal cancer					
	All		Non-familial CRC		Familial CRC	
	N	%	N	%	N	%
Total	162,226	100.0	155,247	95.7	6,979	4.3
Sex						
Men	85,212	52.5	81,245	52.3	3,808	54.6
Women	77,014	47.5	74,002	47.7	3,171	45.4
Age at diagnosis						
<20	428	0.3	427	0.3	1	0.0
20-29	920	0.6	897	0.6	23	0.3
30-39	2,347	1.4	2,221	1.4	126	1.8
40-49	7,160	4.4	6,676	4.3	484	6.9
50-59	20,238	12.5	18,840	12.1	1398	20.0
60-69	42,534	26.2	40,019	25.8	2515	36.0
70-79	53,577	33.0	51,646	33.3	1931	27.7
≥80	35,022	21.6	34,521	22.2	501	7.2
Period of diagnosis						
1964-1969	5,400	3.3	5,398	3.5	2	0.0
1970-1979	15,901	9.8	15,880	10.2	21	0.3
1980-1989	26,141	16.1	25,686	16.5	455	6.5
1990-1999	36,236	22.3	35,617	22.9	619	8.9
2000-2009	45,586	28.1	42,942	27.7	2,644	37.9
2010-2015	32,962	20.3	29,724	19.1	3,238	46.4
Age at diabetes diagnosis						
<50	805	0.5	738	0.5	67	1.0
≥50	10,731	6.6	10,252	6.6	479	6.9
All ages	11,536	7.1	10,990	7.1	546	7.8
Disease history						
IBD	6,198	3.8	5,662	3.6	536	7.7
HNPCC	103	0.1	0	0.0	103	1.5
Obesity*	2,918	1.8	2,747	1.8	171	2.5
Alcoholism*	4,660	2.9	4,456	2.9	204	2.9
COPD*	13,324	8.2	12,618	8.1	706	10.0

***** Hospitalization for these conditions

Abbreviations: CRC = Colorectal cancer, DM = Diabetes mellitus, IBD = Inflammatory bowel disease, HNPCC = Hereditary nonpolyposis colorectal cancer, N = Number of people; % = Percentage of patients with specified characteristic out of total number of patients with colorectal cancer

3.2 Relative risk of colorectal cancer in diabetic patients

3.2.1 SIR by age at diabetes diagnosis

3.2.1.1 Sporadic (non-familial) colorectal cancer

3.2.1.1.1 Both sexes

In the combined analysis for sporadic colorectal cancer in both sexes, diabetic patients had 1.6-fold risk of colorectal cancer (95% CI: 1.6-1.7; **Table 3**) compared to those without history of diabetes. The median age of colorectal cancer diagnosis for diabetic patients of any age was 74 years. Overall, for diabetic patients diagnosed before age 50, relative risk of colorectal cancer before age 50 was higher (SIR 1.9, 95% CI: 1.6-2.3) than for colorectal cancer at/after age 50 (SIR 1.3, 95% CI: 1.2-1.4). The highest relative risk of colorectal cancer before age 50 was observed for patients diagnosed with diabetes between ages 40 and 49 who had 3.6-fold risk (95% CI: 2.8-4.5). In patients with diabetes diagnosed between ages 30 and 39, the SIR was 1.6 (95% CI: 1.1-2.2) and the association was not statistically significant for diabetic patients diagnosed before age 30 (SIR 1.2, 95% CI: 0.8-1.6). The median age of colorectal cancer for diabetes before age 50 was 12 years lower (age 59) than for patients without diabetes (age 71).

Table 3. Relative risk of sporadic colorectal cancer by age at diabetes diagnosis in both sexes combined

DM personal history by Dx age (years)	Age at CRC diagnosis (years)												Median age at CRC diagnosis (years)
	All ages				<50				≥50				
	Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI		
No	144,257	Reference			10,080	Reference			134,177	Reference			71
Yes (Any age)	10,990	**1.6**	1.6	1.7	141	**1.9**	1.6	2.3	10,849	**1.6**	1.6	1.7	74
<50	738	**1.4**	1.3	1.5	141	**1.9**	1.6	2.3	597	**1.3**	1.2	1.4	59
<30	102	**1.2**	1.0	1.5	38	1.2	0.8	1.6	64	1.3	1.0	1.6	51
<20	35	**1.5**	1.0	2.0	19	1.2	0.7	1.9	16	**2.0**	1.1	3.2	44
20-29	67	1.1	0.9	1.5	19	1.2	0.7	1.8	48	1.1	0.8	1.5	53.5
30-39	161	**1.2**	1.1	1.4	33	**1.6**	1.1	2.2	128	1.2	1.0	1.4	58
40-49	475	**1.5**	1.4	1.6	70	**3.6***	2.8	4.5	405	**1.4**	1.2	1.5	61
≥50	10,252	**1.7**	1.6	1.7	NA	NA	-	-	10,252	**1.7**	1.6	1.7	75

CRC = Colorectal cancer; DM = Diabetes mellitus; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; NA = Not applicable; Bold values indicate significant risks.

*Example: Individuals with a personal history of diabetes mellitus diagnosed at age 40-49 without a family history of colorectal cancer had 3.6-fold risk of colorectal cancer before age 50 compared to individuals without history of diabetes and without a family history of colorectal cancer.

3.2.1.1.2 Men

In the analysis for sporadic colorectal cancer in men, diabetic patients were at elevated risk of colorectal cancer at all ages (SIR 1.7, 95% CI: 1.6-1.7; **Table 4**). The relative risk of colorectal cancer before age 50 among diabetic men diagnosed before age 50 was higher (SIR 2.5, 95% CI: 2.1-3.1) than for colorectal cancer at/after age 50 (SIR 1.4, 95% CI: 1.2-1.5). The median age of colorectal cancer diagnosis among men with diabetes before age 50 was 59 years, with roughly 20% of all colorectal cancer diagnoses occurring before age 50. Diabetic men diagnosed before age 20 had 1.7-fold (95% CI: 1.1-2.7) risk of colorectal cancer at all ages, but this effect was not significant for colorectal cancer before age 50 (SIR 1.3, 95% CI: 0.6-2.4). The relative risk of colorectal cancer before age 50 increased with increasing age of diabetes diagnosis; SIR 2.0 (95% CI: 1.1-3.2) for diabetes diagnosed between ages 20 and 29, SIR 2.2 (95% CI: 1.4-3.2) for diabetes diagnosed between ages 30 to 39, and SIR 4.0 (95% CI: 3.0-5.2) for diabetes diagnosed between ages 40 to 49.

Table 4. Relative risk of sporadic colorectal cancer by age at diabetes diagnosis in men

DM personal history by Dx age (years)	Age at CRC diagnosis (years)												Median age at CRC diagnosis (years)
	All ages				<50				≥50				
	Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI		
No	75,120	Reference			4,781	Reference			70,399	Reference			70
Yes (Any age)	6,388	**1.7**	1.6	1.7	101	**2.5**	2.1	3.1	6,287	**1.7**	1.6	1.7	73
<50	479	**1.5**	1.4	1.7	101	**2.5**	2.1	3.1	378	**1.4**	1.2	1.5	59
<30	58	**1.5**	1.2	2.0	25	1.6	1.0	2.4	33	1.5	1.0	2.1	51
<20	20	**1.7**	1.1	2.7	10	1.3	0.6	2.4	10	**2.6**	1.2	4.8	47
20-29	38	1.4	1.0	2.0	15	**2.0**	1.1	3.2	23	1.2	0.7	1.8	54
30-39	91	**1.3**	1.0	1.6	26	**2.2**	1.4	3.2	65	1.1	0.8	1.4	56
40-49	330	**1.6**	1.5	1.8	50	**4.0***	3.0	5.2	280	**1.5**	1.3	1.6	61
≥50	5,909	**1.7**	1.6	1.7	NA	NA	-	-	5,909	**1.7**	1.6	1.7	74

CRC = Colorectal cancer; DM = Diabetes mellitus; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; NA = Not applicable; Bold values indicate significant risks.

*Example: Men with a personal history of diabetes mellitus diagnosed at age 40-49 without a family history of colorectal cancer had 4.0-fold risk of colorectal cancer before age 50 compared to men without a history of diabetes and without a family history of colorectal cancer.

3.2.1.1.3 Women

In women, risk of colorectal cancer at all ages among diabetic patients was 1.6-fold (SIR 1.6, 95% CI: 1.6-1.6; **Table 5**) compared to that in women without diabetes. No statistically significant association was detected in women between diabetes and colorectal cancer before age 50, though the median age of colorectal cancer diagnosis in woman with diabetes was 11 years younger (age 60) than in women without diabetes (age 71). Risk of colorectal cancer before age 50 in women was not significantly associated with diabetes, except in women diagnosed with diabetes between age 40 and 49 who had a nearly 3-fold risk (SIR 2.9, 95% CI: 1.7-4.4). Diabetic women diagnosed at/after age 50 had the highest relative risk of colorectal cancer at all ages (SIR 1.6, 95% CI: 1.6-1.7).

Table 5. Relative risk of sporadic colorectal cancer by age at diabetes diagnosis in women

DM personal history by Dx age (years)	Age at CRC diagnosis (years)												Median age at CRC diagnosis (years)
	All ages				<50				≥50				
	Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI		
No	69,137	Reference			5,299	Reference			63,838	Reference			71
Yes (Any age)	4,602	**1.6**	1.6	1.6	40	1.2	0.9	1.7	4,562	**1.6**	1.6	1.6	76
<50	259	**1.2**	1.1	1.4	40	1.2	0.9	1.7	219	**1.2**	1.0	1.4	60
<30	44	1.0	0.7	1.3	13	0.8	0.4	1.3	31	1.1	0.8	1.6	52
<20	15	1.2	0.7	2.0	9	1.1	0.5	2.1	6	1.4	0.5	3.1	40
20-29	29	0.9	0.6	1.3	4	0.5	0.1	1.2	25	1.1	0.7	1.6	53
30-39	70	1.2	0.9	1.5	7	0.8	0.3	1.6	63	1.3	1.0	1.6	61
40-49	145	**1.3**	1.1	1.5	20	**2.9***	1.7	4.4	125	1.2	1.0	1.4	61
≥50	4,343	**1.6**	1.6	1.7	NA	NA	-	-	4,343	**1.6**	1.6	1.7	76

CRC = Colorectal cancer; DM = Diabetes mellitus; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; NA = Not applicable; Bold values indicate significant risks.

*Example: Women with a personal history of diabetes mellitus diagnosed at age 40-49 without a family history of colorectal cancer had 2.9-fold risk of colorectal cancer before age 50 compared to women without a history of diabetes and without a family history of colorectal cancer.

3.2.1.2 Familial colorectal cancer

3.2.1.2.1 Both sexes

In the analysis of familial colorectal cancer among men and women combined those without a diabetes diagnosis but just one first-degree relative with colorectal cancer had 1.6-fold risk of colorectal cancer at all ages (95% CI: 1.6-1.7; **Table 6**). The SIR of colorectal cancer before age 50 was 2.4 (95% CI: 2.2-2.6), whereas for colorectal cancer at/after age 50 it was 1.6 (95% CI: 1.5-1.6). When an additional personal history of diabetes was present, irrespective of age at diagnosis, risk of colorectal cancer at all ages was 3.2-fold (95% CI: 3.0-3.5) compared to that in those without a first-degree relative and without a personal history of diabetes. For those with a personal history of diabetes diagnosed before age 50 and a first-degree relative with colorectal cancer, risk of colorectal cancer at all ages was 2.3-fold (SIR 2.3, 95% CI: 1.7-2.9). whereas nearly 7-fold risk was observed in this risk group for colorectal cancer before age 50 (SIR 6.9, 95% CI: 3.8-11). The median age of colorectal cancer diagnosis for those with diabetes and one first-degree relative with colorectal cancer was 71. It was six years lower for those without diabetes and one first-degree relative with colorectal cancer (age 65) and 12 years lower for those without both, diabetes and family history of colorectal cancer (age 59). Highest relative risk of colorectal cancer before age 50 in those with an affected first-degree relative was observed in those with diabetes diagnosed between ages 40 and 49 (SIR 12, 95% CI: 4.7-24). In those with at least two first-degree relatives with colorectal cancer, diabetic patients had nearly 5-fold (SIR 4.7, 95% CI: 3.2-6.7) risk of colorectal cancer at all ages, whereas those with just a family history of colorectal cancer had approximately 3-fold (SIR 2.8, 95% CI: 2.5-3.1) risk of colorectal cancer at all ages.

Table 6. Relative risk of familial colorectal cancer by age at diabetes diagnosis in men and women combined

Relative with CRC	DM personal history by Dx age (years)	Age at CRC diagnosis (years)												Median age at CRC diagnosis (years)
		All ages				<50				≥50				
		Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI		
1 FDR	**No**	6,033	**1.6**	1.6	1.7	589	**2.4**	2.2	2.6	5,444	**1.6**	1.5	1.6	65
	Yes (Any age)	516	**3.2**	3.0	3.5	15	**6.9**	3.8	11	501	**3.2**	2.9	3.5	69
	<50	63	**2.3**	1.7	2.9	15	**6.9***	3.8	11	48	**1.9**	1.4	2.5	59
	<30	11	**2.3**	1.2	4.2	6	**6.5**	2.4	14	5	1.3	0.4	3.1	49.5
	<20	3	3.0	0.6	8.7	3	**7.2**	1.5	21	0	-	-	-	47
	20-29	8	2.2	0.9	4.3	3	**5.8**	1.2	17	5	1.6	0.5	3.9	53
	30-39	14	**1.6**	0.9	2.7	2	3.0	0.4	11	12	1.5	0.8	2.6	62
	40-49	38	**2.6**	1.8	3.6	7	**12**	4.7	24	31	**2.2**	1.5	3.2	61
	≥50	453	**3.4**	3.1	3.8	NA	NA	-	-	453	**3.4**	3.1	3.8	70
≥2 FDRs	**No**	400	**2.8**	2.5	3.1	29	**7.6**	5.1	11	371	**2.6**	2.4	2.9	67
	Yes (Any age)	30	**4.7**	3.2	6.7	1	29	0.7	159	29	**4.6**	3.1	6.5	69
	<50	4	**4.8**	1.3	12	1	29	0.7	159	3	3.7	0.8	11	53.5
	≥50	26	**4.7**	3.1	6.9	NA	NA	-	-	26	**4.7**	3.1	6.9	71

CRC = Colorectal cancer; DM = Diabetes mellitus; FDR = First-degree relative; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; NA = Not applicable; Bold values indicate significant risks.

*Example: Individuals with a personal history of diabetes diagnosed before age 50 with a history of colorectal cancer in one first-degree relative had 6.9-fold risk of colorectal cancer before age 50 compared to those without a history of diabetes and without a family history of colorectal cancer.

3.2.1.2.2 Men

Diabetic men with history of colorectal cancer in a first-degree relative had 3.4-fold (95% CI: 3.0-3.7) risk of colorectal cancer at all ages compared to men without diabetes and a family history of colorectal cancer, whereas the risk in those with a first-degree relative with colorectal cancer without personal history of diabetes was 1.7-fold (95% CI: 1.6-1.7) (**Table 7**). Of the 516 cases of familial colorectal cancer in diabetic patients with one affected first-degree relative, 330 (64%) occurred in men. Nine of these cases occurred in patients before the age of 50, with over 7-fold (SIR 7.5, 95% CI: 3.4-14) risk of colorectal cancer compared to sporadic colorectal cancer in men without diabetes. Relative risk of colorectal cancer at all ages in patients with one first-degree relative was highest for men diagnosed with diabetes at/after age 50 (SIR 3.6, 95% CI: 3.2-4.0). Among men with at least two first-degree relatives with colorectal cancer and an additional diabetes diagnosis, risk of colorectal cancer at all ages was 5-fold (SIR 5.1, 95% CI: 3.2-7.8), whereas it was 3-fold for such men without diabetes (SIR 2.9, 95% CI: 2.6-3.3). There was only one case of colorectal cancer before age 50 among diabetic patients with at least two first-degree relatives with colorectal cancer.

Table 7. Relative risk of familial colorectal cancer by age at diabetes diagnosis in men

Relative with CRC	DM personal history by Dx age (years)	Age at CRC diagnosis (years)												Median age at CRC diagnosis (years)
		All ages				<50				≥50				
		Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI		
1 FDR	**No**	3,232	**1.7**	1.6	1.7	310	**2.6**	2.3	2.9	2,922	**1.6**	1.6	1.7	65
	Yes (Any age)	330	**3.4**	3.0	3.7	9	**7.5**	3.4	14	321	**3.3**	2.9	3.7	69
	<50	38	**2.3**	1.6	3.1	9	**7.5***	3.4	14	29	**1.9**	1.2	2.7	58
	<30	6	**2.9**	1.1	6.3	3	**6.7**	1.4	20	3	1.8	0.4	5.3	50
	<20	1	2.0	0.1	11.0	1	**4.9**	0.1	27	0	0.0	0.0	0.0	47
	20-29	5	3.2	1.0	7.4	2	**8.2**	1.0	30	3	2.2	0.5	6.5	52
	30-39	8	**1.7**	0.7	3.3	1	2.9	0.1	16	7	1.6	0.6	3.3	62
	40-49	24	**2.4**	1.5	3.6	5	**12**	4.0	28	19	**2.0**	1.2	3.1	60
	≥50	292	**3.6**	3.2	4.0	0	0	0.0	0.0	292	**3.6**	3.2	4.0	70
≥2 FDRs	**No**	225	**2.9**	2.6	3.3	17	**9.1**	5.3	14	208	**2.8**	2.4	3.2	66
	Yes (Any age)	21	**5.1**	**3.2**	**7.8**	1	47	1.2	261	20	**4.9**	3.0	7.6	68
	<50	3	**6.6**	1.4	19	1	47	1.2	261	2	4.6	0.6	17	54
	≥50	18	**4.9**	2.9	7.8	0	0	0.0	0.0	18	**4.9**	2.9	7.7	68

CRC = Colorectal cancer; DM = Diabetes mellitus; FDR = First-degree relative; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; NA = Not applicable; Bold values indicate significant risks.

*Example: Men with a personal history of diabetes diagnosed before age 50 with a history of colorectal cancer in one first-degree relative had 7.5-fold risk of colorectal cancer before age 50 compared to men without a history of diabetes and without a family history of colorectal cancer.

3.2.1.2.3 Women

In women with familial colorectal cancer, a similar trend as in men was observed. Having diabetes and a first-degree relative with colorectal cancer was associated with 3.1-fold (95% CI: 2.6-3.5) risk of colorectal cancer at all ages, whereas those without diabetes had a 1.6-fold risk of familial colorectal cancer at all ages (95% CI: 1.6-1.7). Relative risk of colorectal cancer before age 50 in diabetic women with one first-degree relative with colorectal cancer (SIR 6.2, 95% CI: 2.3-13) was similar to that in women without a diabetes diagnosis but at least two first-degree relatives with colorectal cancer (SIR 6.2, 95% CI: 3.2-11). The highest relative risk of colorectal cancer at all ages in women was observed in those with both a diabetes diagnosis and a diagnosis of colorectal cancer in two first-degree relatives (SIR 3.9, 95% CI: 1.8-7.4).

Table 8. Relative risk of familial colorectal cancer by age at diabetes diagnosis in women

Relative with CRC	DM personal history by Dx age (years)	Age at CRC diagnosis (years)												Median age at CRC diagnosis (years)
		All ages				<50				≥50				
		Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI		
1 FDR	**No**	2,801	**1.6**	1.6	1.7	279	**2.3**	2.0	2.6	2,522	**1.5**	1.5	1.6	66
	Yes (Any age)	186	**3.1**	2.6	3.5	6	**6.2**	2.3	13	180	**3.0**	2.6	3.5	70
	<50	25	**2.3**	1.5	3.3	6	**6.2***	2.3	13	19	**1.9**	1.1	2.9	61
	<30	5	**1.9**	0.6	4.5	3	**6.3**	1.3	18	2	1.0	0.1	3.4	49
	<20	2	4.0	0.5	14	2	**9.5**	1.1	34	0	0.0	0.0	0.0	36
	20-29	3	1.4	0.3	4.2	1	3.8	0.1	20	2	1.1	0.1	4.0	53
	30-39	6	1.5	0.6	3.3	1	3.2	0.1	18	5	1.4	0.4	3.2	62
	40-49	14	**3.1**	1.7	5.2	2	**11**	1.3	40	12	**2.8**	1.4	4.8	62
	≥50	161	**3.2**	2.8	3.8	0	0	0.0	0.0	161	**3.2**	2.8	3.8	71.5
≥2 FDRs	**No**	175	**2.6**	2.2	3.0	12	**6.2**	3.2	11	163	**2.5**	2.1	2.9	68
	Yes (Any age)	9	**3.9**	1.8	7.4	0	0	0.0	0	9	**3.9**	1.8	7.4	71
	<50	1	**2.6**	0.06	15	0	0	0.0	0	1	2.7	0.1	15	53
	≥50	8	**4.1**	1.8	8.2	0	0	0.0	0.0	8	**4.1**	1.8	8.2	71.5

CRC = Colorectal cancer; DM = Diabetes mellitus; FDR = First-degree relative; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; NA = Not applicable; Bold values indicate significant risks.

*Example: Women with a personal history of diabetes diagnosed before age 50 with a history of colorectal cancer in one first-degree relative had 6.2-fold risk of colorectal cancer before age 50 compared to women without a history of diabetes and without a family history of colorectal cancer.

3.2.2 Absolute (cumulative) risk by age at diabetes diagnosis

3.2.2.1 Sporadic colorectal cancer

3.2.2.1.1 Both sexes

Lifetime (0-79 years) risk of colorectal cancer in the study population was 4.0% (95% CI: 4.0%-4.0%) for men and women combined, whereas risk of colorectal cancer before age 50 was 0.2% (95% CI: 0.2%-0.2%; **Table 9**). Those with no diabetes and no family history of colorectal cancer had a 3.8% (95% CI: 3.8%-3.8%) lifetime risk of colorectal cancer, and a 0.2% (95% CI: 0.2-0.2) risk of colorectal cancer before age 50. Among diabetic patients diagnosed before age 50, lifetime risk of colorectal cancer was 5.0% (95% CI: 4.4%-5.6%) and colorectal cancer risk before age 50 was 0.4% (95% CI: 0.3%-0.4%), double that of people without diabetes. Among diabetic patients, those diagnosed between ages 40 and 49 had the highest lifetime risk (LCR 5.5%, 95% CI: 4.7%-6.4%); 463 (63.7%) diabetes cases diagnosed before age 50 were diagnosed between ages 40 and 49. The lifetime risk of colorectal cancer increased with increasing age at diagnosis of diabetes; LCR 2.0% (95% CI 0.6%-3.3%) for diabetes diagnosed before age 20, 2.6% (1.2%-3.9%) for diagnosis between ages 20 and 29, 3.9% (2.6%-5.2%) for diagnosis between ages 30 and 39, and 5.5% (4.7%-6.4%) for diabetes between ages 40 and 49. The highest lifetime risk of sporadic colorectal cancer was for those diagnosed with diabetes at/after age 50 with almost 8% lifetime risk (LCR: 7.7%, 95% CI: 7.7%-7.7%), twice that of those without diabetes. Out of all diabetic patients who developed colorectal cancer, 7,333 (90.9%) developed diabetes at/after age 50.

Table 9. Lifetime and age-specific cumulative risk of sporadic colorectal cancer by age at diagnosis of diabetes in men and women combined

Sex	DM personal history by Dx age (years)	Cumulative risk (CR%) of colorectal cancer by age group (years)																
		0-29			0-39			0-49			0-59			0-69			0-79			
		CR	95% CI		CR	95% CI		CR	95% CI		CR	95% CI		CR	95% CI		CR	95% CI		Obs
Any	**No**	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.6	0.6	0.6	1.6	1.6	1.6	3.8	3.8	3.8	113,220
	Yes (Any age)	0.0	0.0	0.0	0.1	0.1	0.1	0.3	0.3	0.3	1.3	1.3	1.3	3.5	3.5	3.5	7.2	7.2	7.2	8,059
	<50	0.0	0.0	0.0	0.1	0.1	0.1	0.4	0.3	0.3	1.0	1.0	1.0	2.3	2.1	2.5	5.0*	4.4	5.6	726
	<30	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.8	0.6	1.0	1.6	1.2	2.0	2.6	1.3	4.0	102
	<20	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	1.2	0.6	1.8	2.0	0.6	3.3	2.0	0.6	3.3	35
	20-29	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.7	0.5	0.9	1.5	1.0	2.0	2.6	1.2	3.9	67
	30-49	0.0	0.0	0.0	0.1	0.1	0.1	0.4	0.4	0.4	1.0	1.0	1.0	2.4	2.2	2.6	5.1	4.5	5.7	624
	30-39	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.8	0.6	1.0	2.0	1.7	2.4	3.9	2.6	5.2	161
	40-49	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.3	0.7	1.1	0.9	1.3	2.6	2.3	3.0	5.5	4.7	6.4	463
	≥50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5	1.4	1.4	4.0	3.7	4.2	7.7	7.7	7.7	7,333
Population	**NA**	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.6	0.6	0.6	1.7	1.6	1.7	4.0	4.0	4.0	127,765

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; CR = Cumulative risk; Obs = Observed number of colorectal cancer cases in each risk group for age group 0-79 years; CI = Confidence interval

*Example: Individuals with a personal history of diabetes diagnosed before age 50 had a 5.0% lifetime risk of colorectal cancer.

3.2.2.1.2 By sex

Overall, lifetime risk of colorectal cancer was consistently higher for diabetic men than for diabetic women in all risk groups (**Table 10**). For instance, the lifetime risk of sporadic colorectal cancer among diabetic patients diagnosed at any age was 8.2% (95% CI: 8.2%-8.2%) among men and 6.0% (95% CI: 6.0%-6.1%) among women. Cumulative risk of developing colorectal cancer before age 50 was 0.2% for both men and women. The highest risk of lifetime cumulative risk among diabetic patients for both men (LCR 8.6%, 95% CI: 8.6%-8.6%) and women (LCR 6.4%, 95% CI: 6.4%-6.4%) was for those with diabetes diagnosed at/after age 50. Among diabetic patients diagnosed before age 50, men had 6.0% (95% CI: 5.0%-7.1%) risk of developing colorectal cancer, whereas such a risk was 3.8% in women (95% CI: 3.0%-4.6%). Men also constituted 65.4% (n=475) of all colorectal cancer cases among diabetic patients diagnosed before age 50. Men with diabetes before age 20 had a 2.2% (95% CI: 0.6%-3.8%) lifetime risk of colorectal cancer, whereas in women the risk was 1.8% (95% CI: 0.0%-3.8%).

Table 10. Lifetime and age-specific cumulative risk of sporadic colorectal cancer by age at diagnosis of diabetes and sex

Sex	DM personal history by Dx age (years)	Cumulative risk (CR%) of colorectal cancer by age group (years)								
		0-29	0-39	0-49	0-59	0-69	0-79			
		CR	CR	CR	CR	CR	CR	95% CI		Obs
Men	**No**	0.0	0.1	0.2	0.6	1.8	4.4	4.4	4.4	60,304
	Yes (Any age)	0.0	0.1	0.4	1.6	4.1	8.2	8.2	8.2	4,952
	<50	0.0	0.1	0.4	1.1	2.7	6.0*	5.0	7.1	475
	<30	0.0	0.1	0.3	1.0	2.2	3.1	1.0	5.2	58
	<20	0.0	0.1	0.2	1.6	2.2	2.2	0.6	3.8	20
	20-29	0.0	0.1	0.3	0.8	2.1	3.0	0.9	5.1	38
	30-49	0.0	0.1	0.5	1.2	2.7	6.1	5.1	7.1	417
	30-39	0.0	0.1	0.3	0.9	2.1	3.8	2.0	5.6	91
	40-49	0.0	0.0	0.6	1.3	3.0	6.8	5.6	7.9	326
	≥50	0.0	0.0	0.0	1.7	4.4	8.6	8.6	8.6	4,477
Men population	**NA**	0.0	0.1	0.2	0.6	1.9	4.6	4.6	4.6	68,855
Women	**No**	0.0	0.1	0.2	0.6	1.5	3.4	3.4	3.4	52,916
	Yes (Any age)	0.1	0.1	0.2	1.0	2.8	6.0	6.1	6.1	3,107
	<50	0.1	0.1	0.2	0.8	1.9	3.8	3.0	4.6	251
	<30	0.1	0.1	0.1	0.7	1.2	2.3	0.5	4.0	44
	<20	0.0	0.1	0.2	0.8	1.8	1.8	0.0	3.8	15
	20-29	0.1	0.1	0.1	0.7	1.1	2.2	0.4	3.9	29
	30-49	0.0	0.0	0.2	0.8	2.0	3.9	3.0	4.7	207
	30-39	0.0	0.0	0.1	0.7	1.9	4.0	2.2	5.7	70
	40-49	0.0	0.0	0.4	0.9	2.1	3.9	3.1	4.8	137
	≥50	0.0	0.0	0.0	1.2	3.2	6.4	6.4	6.4	2,856
Women population	**NA**	0.0	0.1	0.2	0.6	1.6	3.5	3.5	3.5	58,910

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; CR = Cumulative risk; Obs = Observed number of colorectal cancer cases in each risk group for age group 0-79 years; CI = Confidence interval

*Example: Men with a personal history of diabetes diagnosed before age 50 had a 6.0% lifetime risk of colorectal cancer.

3.2.2.2 Familial colorectal cancer

3.2.2.2.1 Both sexes

Lifetime cumulative risk of colorectal cancer among people with just a first-degree relative with colorectal cancer was 6.3% (95% CI: 6.3%-6.4%; **Table 11**). Those with a first-degree relative with colorectal cancer and an additional diabetes diagnosis had a 14% (95% CI: 12%-15%) lifetime risk, over 3-fold the lifetime risk of colorectal cancer in the general population (LCR 4.0%, 95% CI: 4.0%-4.0%). The lifetime risk of colorectal cancer in those with a diabetes diagnosis before age 50 (LCR 7.0%, 95% CI: 4.5%-9.4%) was half that of those with diabetes diagnosed at or after age 50 (LCR 14%, 95% CI: 13%-16%). Of those diagnosed with diabetes before age 50 and one first-degree relative with colorectal cancer, patients who were diagnosed with diabetes between ages 40 and 49 had the highest lifetime risk of familial colorectal cancer (LCR 10%, 95% CI: 5.5%-15%). The lifetime risk of familial colorectal cancer increased with increasing age at diagnosis of diabetes; LCR 1.8% (95% CI 0.0%-3.9%) for diabetes diagnosed before age 20, 3.0% (0.7%-5.2%) for diagnosis between ages 20 and 29, 4.8% (1.1%-8.3%) for diagnosis between ages 30 and 39. Those with at least two first-degree relatives without diabetes had an 11% (95% CI: 9.9%-12%) lifetime risk of colorectal cancer. People with an additional diabetes diagnosis had the highest risk out of all risk groups, with 20% (95% CI: 11%-28%) risk of developing colorectal cancer in their lifetime.

Table 11. Lifetime and age-specific cumulative risk of familial colorectal cancer by diabetes age at diagnosis in men and women combined

Sex	Relative with CRC	DM personal history by Dx age (years)	Cumulative risk (CR%) of colorectal cancer by age group (years)																						
			0-29			0-39			0-49			0-59			0-69			0-79							
			CR	95% CI		CR	95% CI		CR	95% CI		CR	95% CI		CR	95% CI		CR	95% CI		Obs				
Any	**1 FDR**	**No**	0.1	0.1	0.1	0.2	0.2	0.2	0.5	0.5	0.5	1.2	1.2	1.2	2.9	2.9	2.9	6.3	6.3	6.4	5,595				
		Yes (Any age)	0.7	0.0	2.0	0.8	0.0	2.1	1.7	0.3	3.1	3.0	1.6	4.5	7.4	5.8	8.9	14*	12	15	472				
		<50	0.7	0.0	2.0	0.8	0.0	2.1	1.7	0.3	3.1	2.5	1.0	3.9	4.7	3.1	6.4	7.0	4.5	9.4	63				
		<30	0.7	0.0	2.0	0.9	0.0	2.2	1.6	0.0	3.1	2.2	0.5	3.8	3.3	1.0	5.5	3.3	1.0	5.5	11				
		<20	0.8	0.0	2.4	0.8	0.0	2.4	1.8	0.0	3.9	1.8	0.0	3.9	1.8	0.0	3.9	1.8	0.0	3.9	3				
		20-29	0.0	0.0	0.0	0.4	0.0	1.1	1.0	0.0	2.0	1.8	1.1	3.2	3.0	0.7	5.2	3.0	0.7	5.2	8				
		30-49	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.4	2.0	2.1	0.1	3.0	4.5	3.1	5.8	6.8	4.5	9.1	52				
		30-39	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	1.0	1.0	1.0	1.8	3.1	1.4	4.8	4.8	1.1	8.3	14				
		40-49	0.0	0.0	0.0	0.0	0.0	0.0	4.1	0.0	8.0	5.1	1.4	9.0	7.6	3.4	12	10	5.5	15	38				
		≥50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.4	2.5	3.5	7.4	6.1	8.7	14	13	16	409				
	≥2 FDRs	**No**	0.0	0.0	0.0	0.8	0.1	1.5	1.6	0.8	2.4	3.3	2.1	4.2	6.0	5.0	7.0	11	9.9	12	391				
		Yes (Any age)	0.0	0.0	0.0	0.0	0.0	0.0	4.1	0.0	12	6.8	0.0	14.8	13	4.2	21	20	11	28	28				
		<50	0.0	0.0	0.0	0.0	0.0	0.0	4.1	0.0	12	7.9	0.0	16.6	11	0.0	21	11	0.0	21	4				
		≥50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8.0	3.5	12	16	9.7	21	24				
Population	**NA**	**NA**	0.0	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2	0.6	0.6	0.6	1.7	1.6	1.7	4.0	4.0	4.0	127,765				

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; CR = Cumulative risk; Obs = Observed number of colorectal cancer cases in each risk group for age group 0-79 years; CI = Confidence interval

*Example: Individuals with a personal history of diabetes had a 14% lifetime risk of colorectal cancer.

3.2.2.2.2 By sex

When stratifying the study population by sex, men consistently had a higher lifetime cumulative risk of familial colorectal cancer (**Table 12**). Among those with diabetes and a first-degree relative with colorectal cancer, men had 15% (95% CI: 13%-17%), whereas women had 12% (95% CI: 9.0%-15%) lifetime risk of colorectal cancer. This risk was also higher than that of men (LCR 12%, 95% CI: 11%-14%) and women (LCR 9.8%, 95% CI: 8.0%-12%) without diabetes but with at least two first-degree relatives with colorectal cancer. Men with diabetes and two first-degree relatives also had the highest lifetime risk, with 22% (95% CI: 9.0%-33%), followed by women of the same category who had a 15% (95% CI: 4.8%-25%) lifetime risk.

Table 12. Lifetime and age-specific cumulative risk of familial colorectal cancer by diabetes age at diagnosis in men

Sex	Relative with CRC	DM personal history by Dx age (years)	Cumulative risk (CR%) of colorectal cancer by age group (years)								
			0-29	0-39	0-49	0-59	0-69	0-79			
			CR	CR	CR	CR	CR	CR	95% CI		Obs
Men	**1 FDR**	**No**	0.1	0.2	0.5	1.2	3.3	7.1	7.1	7.1	3,042
		Yes (Any age)	0.0	0.0	1.3	2.9	7.5	15*	13	17	316
		<50	0.0	0.0	1.3	2.3	4.3	7.5	4.0	11	38
		<30	0.0	0.0	1.1	2.1	3.4	3.4	0.2	6.6	6
		<20	0.0	0.0	1.0	1.0	1.0	1.0	0.0	3.1	1
		20-29	0.0	0.0	1.2	2.6	4.1	4.1	0.2	7.9	5
		30-49	0.0	0.0	1.6	2.6	4.7	8.0	4.3	12	32
		30-39	0.0	0.0	0.4	1.1	3.4	6.4	0.0	13	8
		40-49	0.0	0.0	5.7	6.8	8.8	12	5.0	19	24
		≥50	0.0	0.0	0.0	2.5	7.8	16	14	17	278
	≥2 FDRs	**No**	0.0	1.0	1.8	3.8	7.1	12	11	14	222
		Yes (Any age)	0.0	0.0	6.1	7.9	17	22	9.0	33	19
		<50	0.0	0.0	6.1	9.0	15	15	0.0	30	3
		≥50	0.0	0.0	0.0	0.0	10	16	8.7	24	16
Men Population	**NA**	**NA**	0.0	0.1	0.2	0.6	1.9	4.6	4.6	4.6	68,855
Women	**1 FDR**	**No**	0.1	0.2	0.5	1.1	2.6	5.7	5.7	5.7	2,553
		Yes (Any age)	1.4	1.6	2.1	3.1	6.9	12	9.0	15	156
		<50	1.4	1.6	3.1	2.7	5.2	6.2	2.8	9.5	25
		<30	1.4	1.8	2.1	2.4	3.4	3.4	0.0	6.8	5
		<20	1.7	1.7	2.6	2.6	2.6	2.6	0.0	6.2	2
		20-29	0.0	0.8	0.8	1.2	2.3	2.3	0.0	4.9	3
		30-49	0.0	0.0	0.7	1.4	4.2	5.4	2.8	7.9	20
		30-39	0.0	0.0	0.4	0.8	2.9	2.9	0.5	5.3	6
		40-49	0.0	0.0	0.9	1.9	5.3	7.2	3.1	11.1	14
		≥50	0.0	0.0	0.0	2.4	6.8	12	9.4	15	131
	≥2 FDRs	**No**	0.0	0.7	1.4	2.8	5.0	9.8	8.0	12	169
		Yes (Any age)	0.0	0.0	0.0	3.8	6.3	15	4.8	25	9
		<50	0.0	0.0	0.0	4.7	4.7	4.7	0.0	13	1
		≥50	0.0	0.0	0.0	0.0	3.2	13	4.2	21	8
Women Population	**NA**	**NA**	0.0	0.1	0.2	0.6	1.6	3.5	3.5	3.5	58,910

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; CR = Cumulative risk; Obs = Observed number of colorectal cancer cases in each risk group for age group 0-79 years; CI = Confidence interval

*Example: Men with a personal history of diabetes had a 15% lifetime risk of colorectal cancer.

3.2.3 Sensitivity analyses

3.2.3.1 By type of diabetes

As a sensitivity analysis, the study period was limited to 1997 to 2015 (with available information on type of diabetes) to stratify the analysis by confirmed cases of type 1 and type 2 diabetes. After excluding patients who were defined as both type 1 and type 2, a total of 165 (56.9% type 2) cases of sporadic colorectal cancer, and 16 (68.8% type 2) cases of familial colorectal cancer were identified (**Table 13**). Those with type 2 diabetes has a 3.5-fold risk of sporadic colorectal cancer before age 50 (95% CI: 2.3-5.1), whereas those with type 1 diabetes did not show any significant association with sporadic colorectal cancer before age 50 (SIR 1.0, 95% CI 0.6-1.7). Both types of diabetes, similarly, did not show any statistically significant association with risk of colorectal cancer diagnosed at/after age 50. Among those with a family history of colorectal cancer, patients with type 1 diabetes had an 8.6-fold (95% CI 2.3-21, n=4) risk of colorectal cancer before age 50, whereas those with type 2 diabetes had an 18-fold risk of colorectal cancer before age 50 (95% CI 5.9-42, n=5).

3.2.3.2 Diabetic patients without inflammatory bowel diseases (IBD)

After excluding patients with IBD from the analysis, no substantial changes to SIRs were observed (**Table 14**).

Table 13. Relative risk of colorectal cancer by type of diabetes in period 1997-2015

Relative with CRC	DM personal history by Dx age (years)	DM type	Age at CRC diagnosis (years)											
			All ages				<50				≥50			
			Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI	
No	**No**	**NA**	72,514	Reference			4,190	Reference			68,324	Reference		
	<50	**1**	71	1.2	0.9	1.5	14	1.0	0.6	1.7	57	1.2	0.9	1.6
	<50	**2**	94	**1.5**	1.2	1.8	26	**3.5***	2.3	5.1	68	1.2	0.9	1.5
Yes	**<50**	**1**	5	1.4	0.5	3.3	4	**8.6**	2.3	21	1	0.3	0.0	1.8
	<50	**2**	11	**3.0**	1.5	5.4	5	**18**	5.9	42	6	1.8	0.7	3.9

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; Bold values indicate significant risks.
*Example: Risk of non-familial colorectal cancer before age 50 was 3.5-fold for those with type 2 diabetes diagnosed before age 50 compared to those without a history of diabetes and without a family history of colorectal cancer.

Table 14. Relative risk of colorectal cancer in those without any inflammatory bowel disease (IBD)

Relative with CRC	DM personal history by Dx age (years)	Age at CRC diagnosis (years)											
		All ages				<50				≥50			
		Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI	
No	**No**	138,975	Reference			9,512	Reference			129,463	Reference		
	<50	700	**1.4**	1.3	1.5	128	**1.9***	1.6	2.2	572	**1.3**	1.2	1.4
	<30	93	1.2	1.0	1.5	35	1.2	0.8	1.6	58	1.3	1.0	1.6
	30-39	151	**1.2**	1.1	1.5	30	**1.5**	1.0	2.2	121	1.2	1.0	1.4
	40-49	456	**1.5**	1.4	1.7	63	**3.4**	2.6	4.4	393	**1.4**	1.3	1.5
1 FDR	**No**	5,783	**1.6**	1.6	1.7	569	**2.5**	2.3	2.7	5,214	**1.6**	1.5	1.6
	<50	60	**2.3**	1.8	3.0	13	**6.4**	3.4	11	47	**2.0**	1.4	2.6

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; Bold values indicate significant risks.
*Example: Risk of non-familial colorectal cancer before 50 was 1.9-fold for those with diabetes diagnosed before age 50 compared to those without a history of diabetes and without a family history of colorectal cancer

3.2.3.3 By colorectal cancer subsite

After excluding cases with unspecified subsites, relative risk of colorectal cancer by subsite was analyzed. In general, those with a family history of colorectal cancer and without diabetes diagnosis had a 2.4-fold risk of colorectal cancer before age 50 compared to those without diabetes and without a family history of colorectal cancer (**Table 6**). The subsites were divided into the proximal colon, distal colon and the rectum, however statistically significant differences in relative risk of colorectal cancer among those without diabetes and with one first-degree relative between the three subsites were not observed (overlap of 95% CIs; **Table 15**). Highest relative risk of sporadic colorectal cancer before age 50 among diabetic patients diagnosed before age 50 was observed for the distal colon (SIR 2.3, 95% CI: 1.7–3.2), followed by the proximal colon (SIR 1.8, 95% CI: 1.4–2.4) and the rectum (SIR 1.8, 95% CI: 1.3–2.0). In all three subsites, relative risk of colorectal cancer before age 50 in diabetic patients was higher than the relative risk of colorectal cancer at/after age 50, except for those with diabetes diagnosed before age 30.

Table 15. Standardized incidence ratio of colorectal cancer by personal history of diabetes, family history of colorectal cancer, age at diagnosis of diabetes, and colorectal cancer subsite

CRC subsite	Relative with CRC	DM personal history by Dx age (years)	Age at CRC diagnosis (years)											
			All ages				<50				≥50			
			Obs	SIR	95% CI		Obs	SIR	95% CI		Obs	SIR	95% CI	
Proximal colon	**No**	**No**	58,333	Reference			4,735	Reference			53,598	Reference		
		<50	283	**1.5**	1.3	1.7	58	**1.9**	1.4	2.4	225	**1.4**	1.2	1.6
		<30	47	**1.5**	1.1	2.0	22	1.4	0.9	2.1	25	**1.5**	1.0	2.2
		30-39	63	**1.3**	1.0	1.7	15	1.8	1.0	2.9	48	1.3	0.9	1.7
		40-49	173	**1.5**	1.3	1.8	21	**2.9**	1.8	4.4	152	**1.4**	1.2	1.7
	1 FDR	**No**	2307	**1.7**	1.6	1.7	235	**2.4**	2.1	2.7	2,072	**1.6**	1.5	1.7
		<50	26	**2.7**	1.8	3.9	7	**8.2**	3.3	17	19	**2.1**	1.3	3.4
Distal colon	**No**	**No**	35,852	Reference			2,216	Reference			33,636	Reference		
		<50	207	**1.5**	1.3	1.7	39	**2.3**	1.7	3.2	168	**1.4**	1.2	1.6
		<30	25	1.2	0.8	1.8	8	1.2	0.5	2.3	17	1.2	0.7	2.0
		30-39	47	1.4	1.0	1.8	10	2.0	1.0	3.7	37	1.3	0.9	1.7
		40-49	135	**1.6**	1.4	1.9	21	**4.4**	2.7	6.7	114	**1.5**	1.2	1.8
	1 FDR	**No**	1699	**1.7**	1.7	1.8	164	**2.8**	2.4	3.3	1,535	**1.7**	1.6	1.8
		<50	19	**2.5**	1.5	3.9	6	**11**	4.1	25	13	**1.9**	1.0	3.2
Rectum	**No**	**No**	50,072	Reference			3,129	Reference			46,943	Reference		
		<50	248	**1.2***	1.1	1.4	44	**1.8**	1.3	2.4	204	**1.2**	1.0	1.3
		<30	30	1.0	0.7	1.4	8	0.8	0.4	1.6	22	**1.1**	0.7	1.7
		30-39	51	1.0	0.8	1.4	8	1.1	0.5	2.1	43	**1.0**	0.8	1.4
		40-49	167	**1.4**	1.2	1.6	28	**3.8**	2.5	5.4	139	**1.2**	1.0	1.5
	1 FDR	**No**	2027	**1.5**	1.5	1.6	190	**2.3**	1.9	2.6	1,837	**1.5**	1.4	1.5
		<50	18	**1.7**	1.0	2.6	2	2.5	0.3	9.1	16	1.6	0.9	2.6

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; Bold values indicate significant risks.

*Example: Risk of non-familial rectal cancer was 1.2-fold for those with diabetes diagnosed before age 50 compared to those without a history of diabetes and without a family history of colorectal cancer.

3.3 Risk-adapted starting age of colorectal cancer screening in diabetic patients

3.3.1 First screening in the general population at benchmark age 50

Using age-specific 10-year cumulative risk curves, risk-adapted ages of colorectal cancer screening were generated for diabetic patients with and without family history of colorectal cancer. Among men, the 10-year cumulative risk of colorectal cancer in the general population at age 50 was 0.44% (**Figure 6**). The risk in men without a family history of colorectal cancer but with a diabetes diagnosis before age 50, reached the same 0.44% 10-year cumulative risk approximately five years earlier, at age 45. Men with both a family history of colorectal cancer and a diabetes diagnosis reached the 0.44% 10-year cumulative risk at age 32 (18 years earlier than men in the general population). Men with no diabetes and no family history of colorectal cancer reached the 0.44% population level of risk, roughly one year later, at age 51.

In women, the 10-year cumulative risk of colorectal cancer at age 50 was 0.41% (**Figure 7**). Women without family history of colorectal cancer but with a diabetes diagnosis reached the population level of risk four years earlier, at age 46. The risk in women with both a diabetes diagnosis and family history of colorectal cancer reached the 0.41% population level of risk in 50-year-old women, 12 years earlier, at age 38. The 10-year cumulative risk of women with no diabetes and no family history of colorectal cancer was not substantially different from women in the general population at age 50.

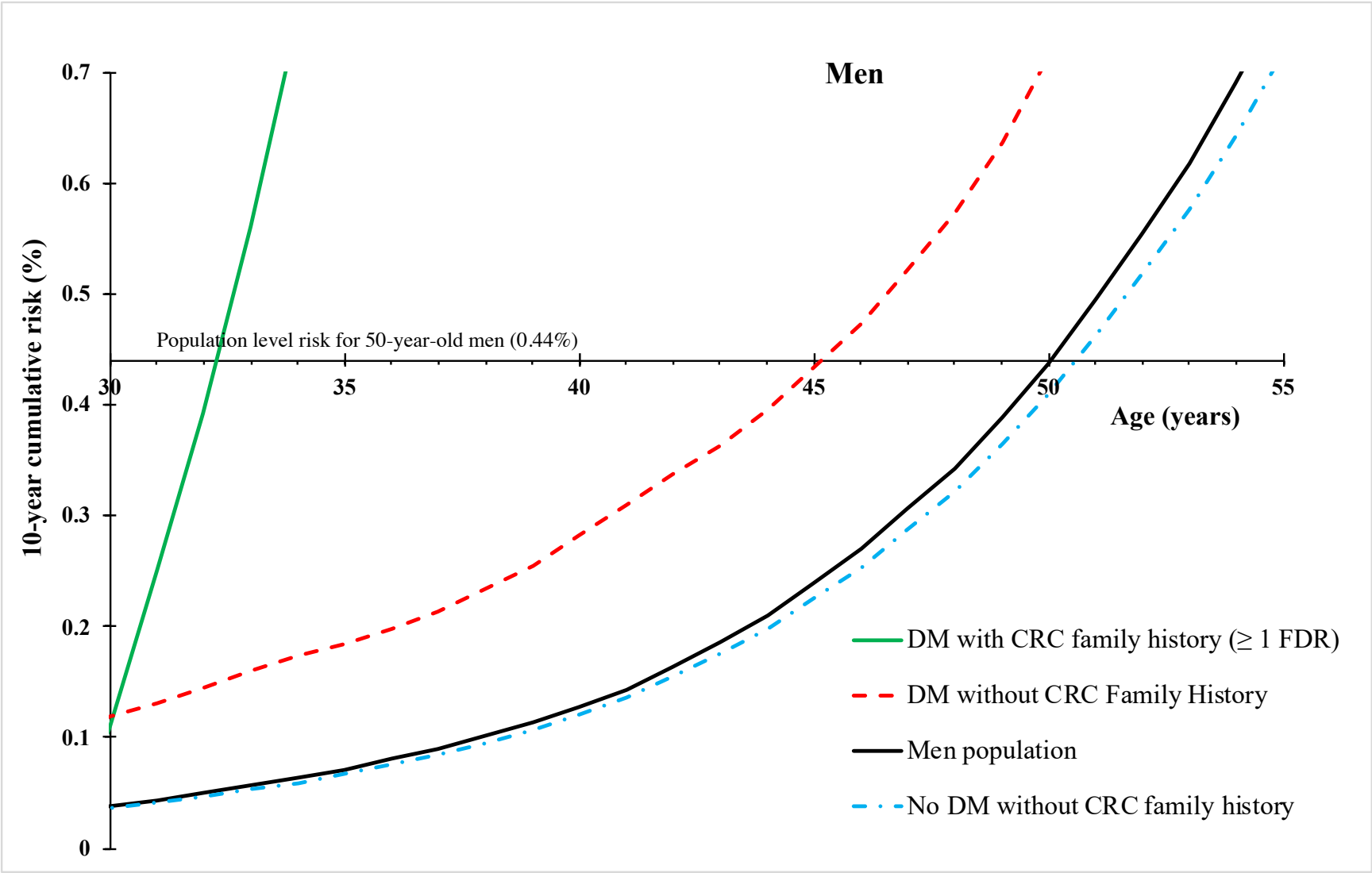


Figure 6. Age-specific 10-year cumulative risk of colorectal cancer by personal history of diabetes before age 50 and family history of colorectal cancer in first-degree relatives among men

DM = Diabetes mellitus; CRC = Colorectal cancer; FDR = First-degree relative

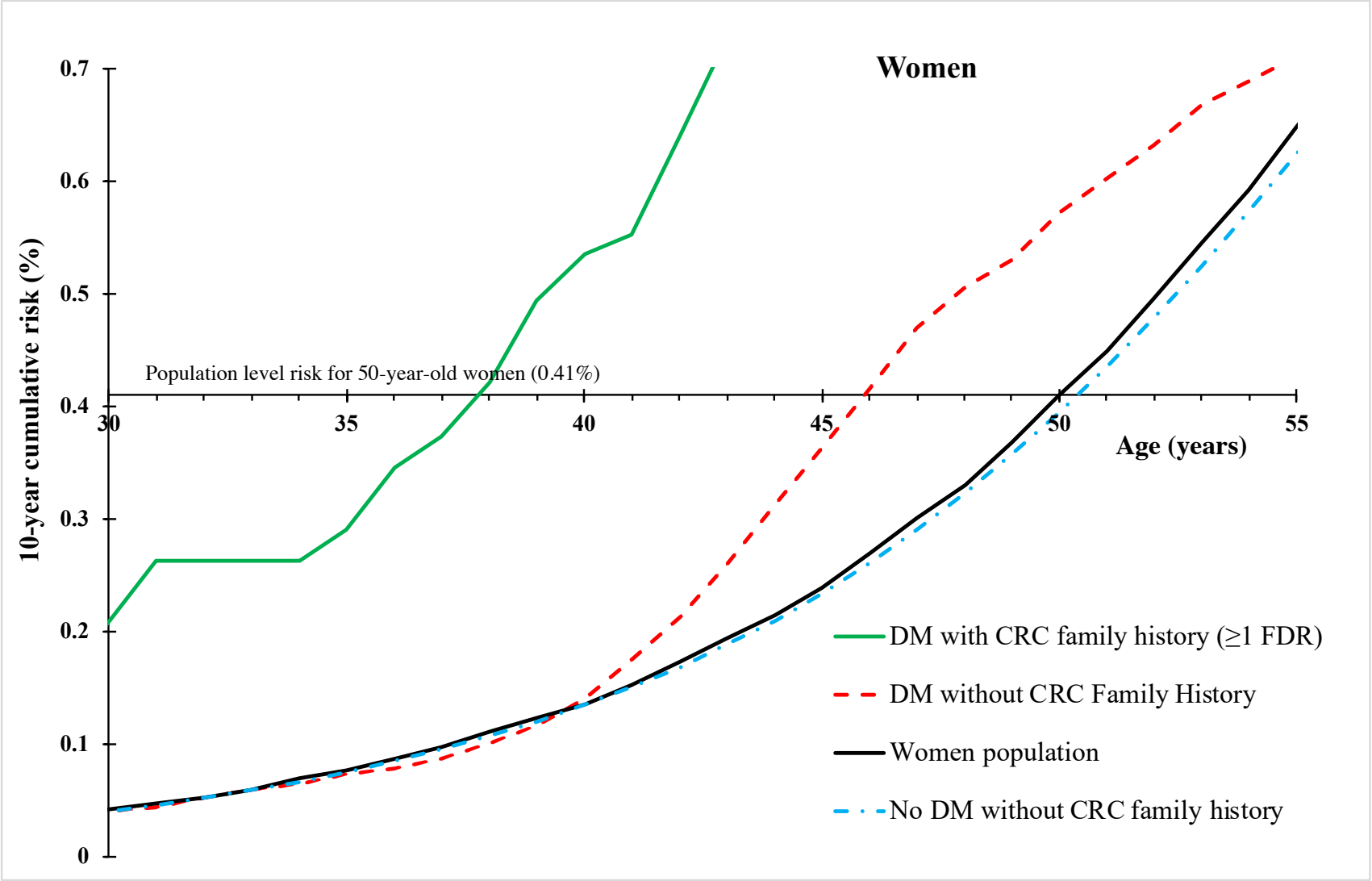


Figure 7. Age-specific 10-year cumulative risk of colorectal cancer by personal history of diabetes before age 50 and family history of colorectal cancer in first-degree relatives among <u>women</u>

DM = Diabetes mellitus; CRC = Colorectal cancer; FDR = First-degree relative

3.3.2 Ten-year cumulative risk by risk groups in men and women

Age-specific 10-year cumulative risk data was used to generate risk-adapted starting ages of screening for diabetic patients (**Table 16**). In men, between the ages of 45 and 49, the average 10-year cumulative risk of developing colorectal cancer was 0.31% (95% CI: 0.30%-0.31%) in the general population, 0.29% (95% CI: 0.28%-0.29%) in those without diabetes and without a family history of colorectal cancer, 0.53% (95%CI: 0.44%-62%) for diabetic patients with no family history of colorectal cancer, 0.61% (95% CI: 0.16%-1.06%) for diabetic patients with a family history of colorectal cancer. In women, 10-year cumulative risks in all risk groups were consistently lower than their corresponding values in men. Between the ages of 45 and 49, the average 10-year cumulative risk of developing colorectal cancer was 0.30% (95% CI: 0.29%-0.31%) in the general population of women, 0.29% (95% CI: 0.28%-0.30%) in women without diabetes and without a family history of colorectal cancer, 0.42% (95%CI: 0.33%-0.52%) for diabetic women with no family history of colorectal cancer, 0.92% (95% CI: 0.28%-1.55%) for diabetic women with a family history of colorectal cancer.

Table 16. Sex and age-specific 10-year cumulative risk of colorectal cancer in population and different risk groups by personal history of diabetes (diagnosed before age 50) and family history of colorectal cancer

		10-year cumulative risk (CR) of colorectal cancer											
		Population			No DM, No FH			DM Dx age <50, No FH			DM Dx age <50, FH		
Sex	Age group, y	N	%	95% CI	N	%	95% CI	N	%	95% CI	N	%	95% CI
Men	**0-9**	46	0.00	0.00–0.00	46	0.00	0.00–0.00	0	0.00	-	0	0.00	-
	10-14	191	0.01	0.01–0.01	189	0.01	0.01–0.01	0	0.00	-	0	0.00	-
	15-19	317	0.01	0.01–0.01	309	0.01	0.01–0.01	1	0.01	0.00–0.02	0	0.00	-
	20-24	483	0.02	0.01–0.02	461	0.01	0.01–0.02	5	0.04	0.01–0.08	0	0.00	-
	25-29	830	0.03	0.03–0.03	775	0.03	0.02–0.03	12	0.08	0.03–0.12	0	0.00	-
	30-34	1,487	0.05	0.05–0.05	1,360	0.05	0.05–0.05	28	0.15	0.10–0.21	2	0.54	0.00–1.16
	35-39	2,581	0.09	0.09–0.09	2,342	0.08	0.08–0.09	48	0.20	0.14–0.26	8	1.06	0.26–1.86
	40-44	4,451	0.16	0.16–0.17	4,013	0.15	0.15–0.16	94	0.34	0.28–0.41	9	0.89	0.26–1.51
	45-49	7,722	0.31	0.30–0.31	6,867	0.29	0.28–0.29	133	0.53	0.44–0.62	8	0.61	0.16–1.06
	50-54	12,780	0.56	0.55–0.56	11,228	0.52	0.51–0.53	165	0.92*	0.77–1.06	13	1.24	0.56–1.91
	55-59	19,409	0.95	0.94–0.97	16,897	0.89	0.88–0.90	176	1.33	1.13–1.53	17	2.16	1.14–3.17
	60-64	25,926	1.53	1.51–1.55	22,520	1.43	1.42–1.45	135	1.81	1.48–2.14	14	2.74	1.22–4.23
	65-69	29,544	2.28	2.26–2.31	25,732	2.16	2.13–2.18	90	2.49	1.91–3.08	8	4.05	0.82–7.19
	70-74	28,155	3.09	3.06–3.13	24,632	2.96	2.92–3.00	50	3.32	2.23–4.41	3	2.52	0.00–5.45
	75-79	21,205	3.68	3.62–3.73	18,684	3.56	3.51–3.61	19	3.03	1.23–4.80	0	0.00	-
	80-84	11,477	3.70	3.63–3.78	10,182	3.62	3.54–3.70	2	1.09	0.00–2.60	0	0.00	-
	85-89	3,968	2.95	2.86–3.11	3,534	2.92	2.82–3.09	0	0.00	-	0	0.00	-
Women	**0-9**	105	0.00	0.00–0.00	104	0.00	0.00–0.00	0	0.00	-	0	0.00	-
	10-14	314	0.01	0.01–0.01	310	0.01	0.01–0.01	1	0.01	0.00–0.03	0	0.00	-
	15-19	451	0.02	0.01–0.02	439	0.02	0.01–0.02	4	0.03	0.00–0.07	1	1.36	0.00–3.97
	20-24	587	0.02	0.02–0.02	561	0.02	0.02–0.02	5	0.04	0.01–0.08	1	1.36	0.00–3.97
	25-29	867	0.03	0.03–0.03	818	0.03	0.03–0.03	4	0.03	0.00–0.06	0	0.00	0.00–0.00
	30-34	1,549	0.05	0.05–0.06	1,444	0.05	0.05–0.05	8	0.05	0.02–0.09	1	0.26	0.00–0.77
	35-39	2,755	0.10	0.09–0.10	2,548	0.09	0.09–0.10	17	0.10	0.05–0.14	2	0.40	0.00–0.99
	40-44	4,646	0.17	0.17–0.18	4,253	0.17	0.16–0.17	42	0.21	0.15–0.28	5	0.62	0.07–1.16
	45-49	7,564	0.30	0.29–0.31	6,880	0.29	0.28–0.30	78	0.42	0.33–0.52	8	0.92	0.28–1.55
	50-54	11,613	0.50	0.49–0.50	10,545	0.47	0.47–0.48	92	0.67	0.54–0.81	7	0.99	0.30–1.67
	55-59	16,219	0.77	0.76–0.78	14,665	0.74	0.72–0.75	83	0.83	0.65–1.01	10	1.65	0.61–2.67
	60-64	20,686	1.14	1.13–1.16	18,530	1.09	1.07–1.11	76	1.27	0.97–1.58	11	2.42	0.85–3.96
	65-69	23,805	1.64	1.62–1.66	21,068	1.55	1.53–1.57	57	1.71	1.22–2.19	5	1.96	0.15–3.73
	70-74	24,060	2.19	2.16–2.21	21,182	2.08	2.05–2.11	29	2.35	1.34–3.35	1	0.64	0.00–1.89
	75-79	20,525	2.65	2.62–2.69	18,131	2.57	2.53–2.60	14	2.60	1.03–4.15	0	0.00	-
	80-84	12,889	2.61	2.56–2.65	11,422	2.55	2.50–2.60	4	7.94	0.00–20.0	0	0.00	-
	85-89	5,037	1.97	1.91–2.04	4,462	1.93	1.87–2.01	1	6.89	0.00–19.1	0	0.00	-

Abbreviations: CR = Cumulative risk; CI = Confidence interval; DM = Diabetes mellitus; FH = Family history; Dx age = Diagnosis age.

*Example: 10-year cumulative risk of developing non-familial colorectal cancer between ages 50 and 54 in men with diabetes diagnosed before age 50 was 0.92%.

3.3.3 Other benchmark ages for initial mass screening

Since screening programs globally have different benchmark initial screening ages, other than the most common first screening age 50, 10-year cumulative risk and risk-adapted screening ages for diabetic patients based on other benchmark mass screening ages were also provided (45, 55, and 60; **Table 17**). For benchmark age 45, men and women in the general population had a 10-year cumulative risk of 0.24% at that age. Men with diabetes and no family history of colorectal cancer reached the 10-year cumulative risk of 0.24% at age 40, five years earlier, whereas women with diabetes reached this level of 10-year cumulative risk at age 42, 3 years earlier. Both men and women with diabetes and a family history of colorectal cancer reached the population level of risk 14 years earlier at age 31.

For benchmark screening ages 55 and 60, population levels of 10-year cumulative risk for men were 0.77% and 1.28%, respectively, whereas for women the population level of 10-year cumulative risk was 0.65% and 0.98%, respectively. Men and women with no diabetes and no family history of colorectal cancer reached the population level of risk one year later, at age 56 and 61, respectively. Conversely, those with both diabetes and family history of colorectal cancer reached the general population risk 21 years earlier (men) and between 14 and 15 years earlier (women). Finally, men with diabetes but no family history of colorectal cancer reached the population level of risk at ages 5 year earlier, for benchmark screening ages 55 and 60, respectively. Women with diabetes reached the population level of risk at age 51 and 55 for benchmark screening ages 55 and 60, respectively.

Table 17. Risk-adapted starting ages of colorectal cancer screening by sex, personal history of diabetes and family history of colorectal cancer tailored to different benchmark stating age of mass screening in the population

Sex	Diabetes personal history†	CRC family history	Patients (Obs)	Risk-adapted starting age of screening (years)			
Population*	**Any**	**Any**	**162,226**	**45**	**50**	**55**	**60**
Men	**No**	**No**	75,120	45	51	56	61
	Yes	**No**	6,388	40	45‡	50	55
	Yes	**≥1 FDR**	351	31	32	34	39
Women	**No**	**No**	69,137	45	50	56	61
	Yes	**No**	4,602	42	46	51	55
	Yes	**≥1 FDR**	195	31	38	41	45

CRC = Colorectal cancer; FDR = First-degree relative; Obs: Number of observations with colorectal cancer; bold ages indicate benchmark starting ages of colorectal cancer screening in the general population.

*Ten-year cumulative risks of colorectal cancer in the general population at ages 45, 50, 55, and 60 were 0.24%, 0.44%, 0.77%, and 1.28% in men, and 0.24%, 0.41%, 0.65%, and 0.98% in women, respectively.

†Diabetes was diagnosed before CRC diagnosis and benchmark starting age of mass screening in the population i.e. diabetes diagnosis age <45 for benchmark screening age 45, diabetes diagnosis age <50 for benchmark screening age 50, etc.

‡Example: 45-year-old men with a personal history of diabetes without family history of colorectal cancer reached the same 10-year cumulative risk of colorectal cancer as 50-year-old men in the general population who were subject to colorectal cancer screening in their society, i.e. with a benchmark starting age of mass screening in the general population at age 50 years, the risk-adapted starting age for those with only personal history of diabetes was 45 years, thus those with a personal history of diabetes without family history of colorectal cancer could be screened at age 45 years, five years earlier than the general population.

3.3.4 Comparison with existing guidelines

Although diabetes has yet to be included as a risk factor in any colorectal cancer screening guidelines, a comparison between the findings regarding diabetic patients with a family history of colorectal cancer and existing screening guidelines for those with a first-degree relative diagnosed with colorectal cancer was made (**Table 18**). Specifically, recommended screening ages in the US (benchmark first screening age 45), Canada (benchmark first screening age 50), and part of the United Kingdom (benchmark first screening age 60), for a specific sample age, were compared with the risk-adapted screening ages in this study and the difference between them, in years, was provided. In most cases, it was found that the evidence-based findings yielded earlier screening ages. The comparison revealed wide-ranging differences between the risk-adapted starting ages of screening and those in the current guidelines (between -5 and 21 years). However, the differences for other sample ages could be even more. Nonetheless, a direct comparison was not possible since an investigation of risk-adapted screening for diabetic patients is a novel one.

Table 18. Comparison between recommended risk-adapted starting ages of screening in the US, Canada, and UK Guidelines and our evidence-based ones

			Recommended starting age of colorectal cancer in population								
			45			50			60		
Sex	FDR Dx Age,[a] y	Example age[b], y	United States[c]	Evidence[d]	Diff[e]	Canada[c]	Evidence[d]	Diff[e]	Part of United Kingdom[c]	Evidence[d]	Diff[e]
Men	**<45**	**43**	33	31	2	33	32	1	55	39	16
	45-49	**47**	37	31	6	37	32	5	55	39	16
	≥50	**60**	40	31*	9	45	32	13	60	39	21
Women	**<45**	**43**	33	31	2	33	38	-5	55	45	10
	45-49	**47**	37	31	6	37	38	-1	55	45	10
	≥50	**60**	40	31	9	45	38	7	60	45	15

FDR = first-degree relative; Dx Age = age at diagnosis in affected first-degree relative

[a]Age at diagnosis of colorectal cancer in the affected first-degree relative(s)

[b]Example youngest diagnosis age of each category was given to allow a head-to-head comparison between our starting ages and those in the guidelines.

[c]Recommended age of screening based on nation specific guidelines for individuals with one first-degree relative with colorectal cancer only (since diabetes has not been mentioned in any screening guidelines)

[d]The recommended evidence-based risk-adapted starting age of screening from our study in individuals with at least one affected first-degree relative and a personal history of diabetes (actually only 4 cases had >1 affected first-degree relatives + diabetes before age 50, so it can be considered as 1 affected first-degree relative + diabetes).

[e]Difference between the recommended starting age by guideline and our evidence-based value.
(years).

*Example: In a country with a benchmark initial screening age at 45 years, our study recommended men with one affected first-degree relative with colorectal cancer diagnosed at age 60 and a personal history of diabetes could start screening at age 31 years, whereas the US Multi-Society Task Force on Colorectal Cancer recommends that at age 40 years, nine years later.

3.4 Comparison of dynamic and static risk of colorectal cancer

This study compared the risk estimates of standardized incidence ratios between the static and dynamic definitions of disease history and found significant differences (**Table 19**). In general, there were many more cases of familial colorectal cancer by the static method, whereas for sporadic colorectal cancer cases there were more cases when using the dynamic method. For sporadic colorectal cancer at all ages, relative risk in diabetic patients diagnosed before age 50 was higher by the dynamic method (SIR 1.4, 95% CI: 1.3-1.5) compared to the static method (SIR 1.2, 95% CI: 1.1-1.3). For colorectal cancer before age 50 in the same group, with the dynamic method nearly 2-fold (SIR 1.9, 95% CI: 1.6-2.3) risk was observed, whereas with the static method a statistically significant effect was not observed (SIR 1.2, 95% CI: 0.96-1.37). For diabetes before age 20, relative risk of sporadic colorectal cancer at all ages was the same using both methods (SIR 1.5, 95% CI: 1.0-2.0), even for colorectal cancer before age 50 (SIR 1.2, 95% CI: 0.7-1.9) even though the relationship was not statistically significant. The relative risk of colorectal cancer at all ages was also higher by the dynamic method for those with diabetes diagnosed between ages 40 and 49 (SIR 1.5, 95% CI: 1.4-1.6) than by the static method (SIR 1.3, 95% CI: 1.1-1.4). This difference was more pronounced for colorectal cancer before age 50 where 3.6-fold risk (SIR 3.6, 95% CI: 2.8-4.5) was observed, but the association was not significant by the static method (SIR 1.2, 95% CI: 0.9-1.5).

A similar pattern was also observed in familial cases of colorectal cancer. Relative risk of colorectal cancer was nearly identical by the dynamic (SIR 1.6, 95% CI: 1.6-1.7) and static methods (SIR 1.6, 95% CI: 1.6-1.6) for those with a first-degree relative with colorectal cancer but without a diabetes diagnosis. However, for colorectal cancer before age 50, the dynamic

method yielded a higher relative risk (SIR 2.4, 95% CI: 2.2-2.6) compared to the static method (SIR 1.9, 95% CI: 1.8-2.0). For those with an additional diabetes diagnosis before age 50, relative risk of familial colorectal cancer at all ages was again higher by the dynamic method (SIR 2.3, 95% CI: 1.7-1.9) than the static method (SIR 2.0, 95% CI: 1.6-2.5).

Table 19. Standardized incidence ratios (SIR) of colorectal cancer in diabetic patients with and without a family history of colorectal cancer by dynamic and static methods of disease history and family history allocations

Method of disease history	CRC status	CRC affected relative	DM by Dx age (years)	Age at CRC diagnosis (years)											
				All ages				<50				≥50			
				N	SIR	95% CI		N	SIR	95% CI		N	SIR	95% CI	
Dynamic	**Sporadic**	**No**	**No**	144,257	Reference			10,080	Reference			134,177	Reference		
			<50	738	**1.4**	1.3	1.5	141	**1.9***	1.6	2.3	597	**1.3**	1.2	1.4
			<20	35	**1.5**	1.0	2.0	19	1.2	0.7	1.9	16	**2.0**	1.1	3.2
			20-29	67	1.1	0.9	1.5	19	1.2	0.7	1.8	48	1.1	0.8	1.5
			30-39	161	**1.2**	1.1	1.4	33	**1.6**	1.1	2.2	128	1.2	1.0	1.4
			40-49	475	**1.5**	1.4	1.6	70	**3.6**	2.8	4.5	405	**1.4**	1.2	1.5
	Familial	**1 FDR**	**No**	6,033	**1.6**	1.6	1.7	589	**2.4**	2.2	2.6	5,444	**1.6**	1.5	1.6
			<50	63	**2.3**	1.7	2.9	15	**6.9**	3.8	11	48	**1.9**	1.4	2.5
			<20	3	3.0	0.6	8.7	3	**7.2**	1.5	21	0			
			20-29	8	2.2	0.9	4.3	3	**5.8**	1.2	17	5	1.6	0.5	3.9
			30-39	14	**1.6**	0.9	2.7	2	3.0	0.4	11	12	1.5	0.8	2.6
			40-49	38	**2.6**	1.8	3.6	7	**12**	4.7	24	31	**2.2**	1.5	3.2
		≥2 FDRs	**No**	400	**2.8**	2.5	3.1	29	**7.6**	5.1	11	371	**2.6**	2.4	2.9
			<50	4	**4.8**	1.3	12	1	29	0.7	159	3	3.7	0.8	11
Static	**Sporadic**	**No**	**No**	137,958	Reference			9,436	Reference			128,522	Reference		
			<50	709	**1.2**	1.1	1.3	131	1.2	1.0	1.4	578	**1.2**	1.1	1.4
			<20	35	**1.5**	1.0	2.0	19	1.2	0.7	1.9	16	**2.0**	1.1	3.2
			20-29	65	1.1	0.8	1.4	18	1.0	0.6	1.6	47	1.1	0.8	1.5
			30-39	167	1.2	1.0	1.4	31	1.2	0.8	1.7	126	1.2	1.0	1.4
			40-49	452	**1.3**	1.1	1.4	63	1.2	0.9	1.5	389	**1.3**	1.2	1.4
	Familial	**1 FDR**	**No**	11,751	**1.6**	1.6	1.6	1,203	**1.9**	1.8	2.0	10,548	**1.6**	1.5	1.6
			<50	86	**2.0**	1.6	2.5	23	**3.0**	1.9	4.5	63	**1.8**	1.4	2.3
			<20	3	1.9	0.4	5.5	3	3.5	0.7	10.4	0			
			20-29	9	1.7	0.8	3.2	3	2.3	0.5	6.6	6	1.5	0.6	3.3
			30-39	18	1.4	0.8	2.2	4	2.0	0.5	5.1	14	1.3	0.7	2.2
			40-49	56	**2.4**	1.8	3.1	13	**3.7**	2.0	6.3	43	**2.2**	1.6	2.9
		≥2 FDRs	**No**	978	**2.7**	2.6	2.9	138	**4.8**	4.0	5.6	840	**2.5**	2.4	2.7
			<50	9	**4.3**	2.0	8.1	3	**8.7**	1.8	25.5	6	**3.4**	1.3	7.5

CRC = Colorectal cancer; DM = Diabetes mellitus; Dx age = Age at diagnosis of diabetes; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; CI = Confidence interval; Bold values indicate significant risks.

*Example: Using the dynamic method, risk of non-familial colorectal cancer before age 50 was 1.9-fold in diabetic patients diagnosed before age 50 compared to those without a history of diabetes and without a family history of colorectal cancer..

3.5 Comparison of dynamic and static age at first screening

The dynamic and static methods of determining the age of first screening for diabetic patients using 10-year cumulative risk for benchmark screening at age 50 were also compared (**Figure 8** and **Figure 9**). There were minor differences in risk-adapted screening ages for men with diabetes but no family history of colorectal cancer. The dynamic and static method yielded a risk-adapted screening age of 45 and 46, respectively, with a 1-year difference. For men with diabetes and family history of colorectal cancer, the dynamic method yielded a risk-adapted screening age of 32, as opposed to 38 estimated by the static method. Men with no diabetes and no family history did not reach the population level of risk one year later by the static method, as was observed by the dynamic method. Among women, a similar pattern was observed where the dynamic method yielded earlier risk-adapted screening ages among diabetic patients. For those with diabetes and a family history of colorectal cancer, the dynamic method yielded a risk-adapted screening age of 38, whereas with the static method it was at age 40. Similarly, for patients with diabetes but no family history the dynamic method yielded a screening age one year earlier than the static method, at age 46.

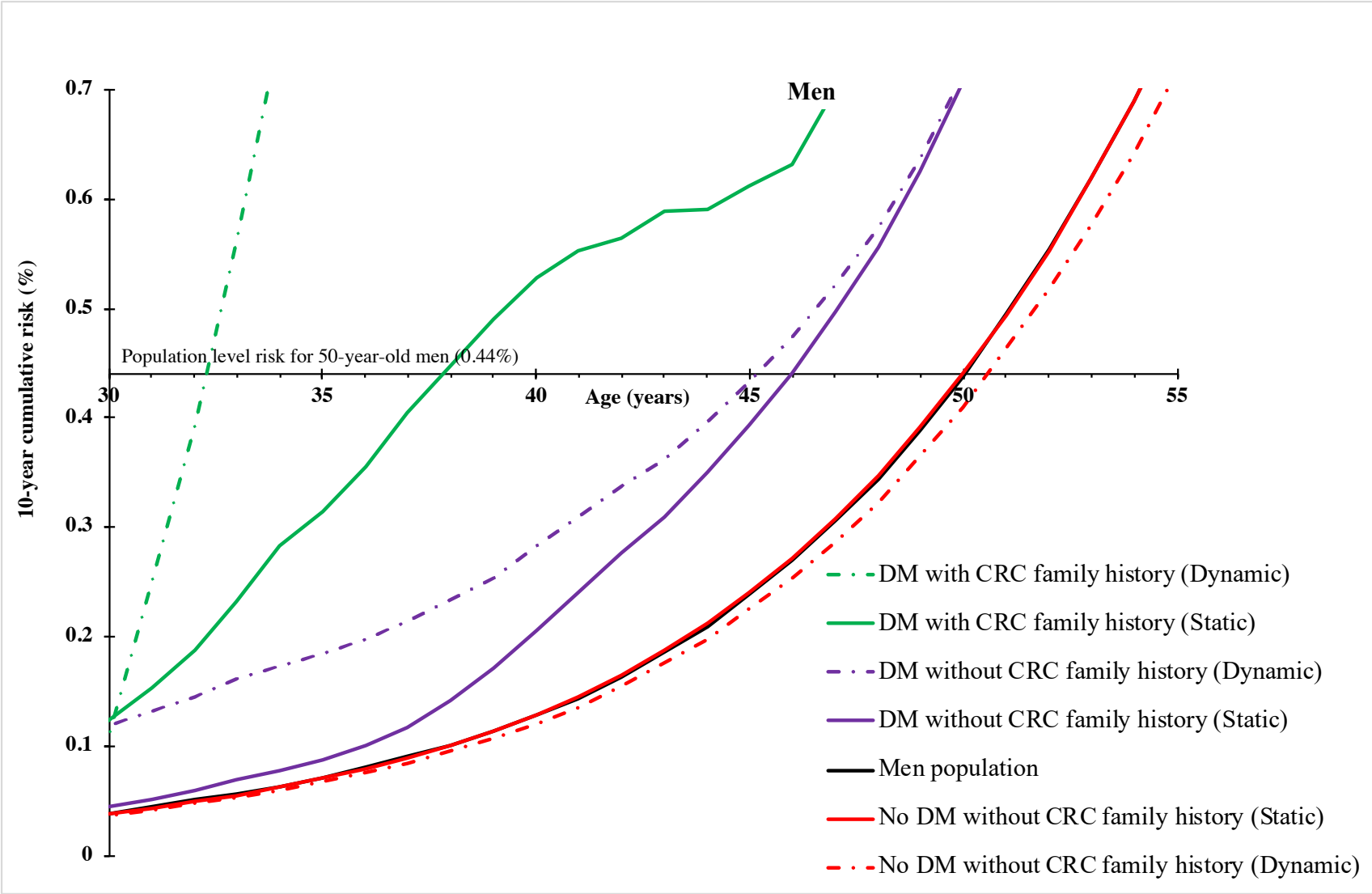


Figure 8. Comparison of dynamic and static methods of age-specific 10-year cumulative risk of colorectal cancer by personal history of diabetes before age 50 and family history of colorectal cancer in first-degree relatives among men

CRC = Colorectal cancer; DM = Diabetes mellitus

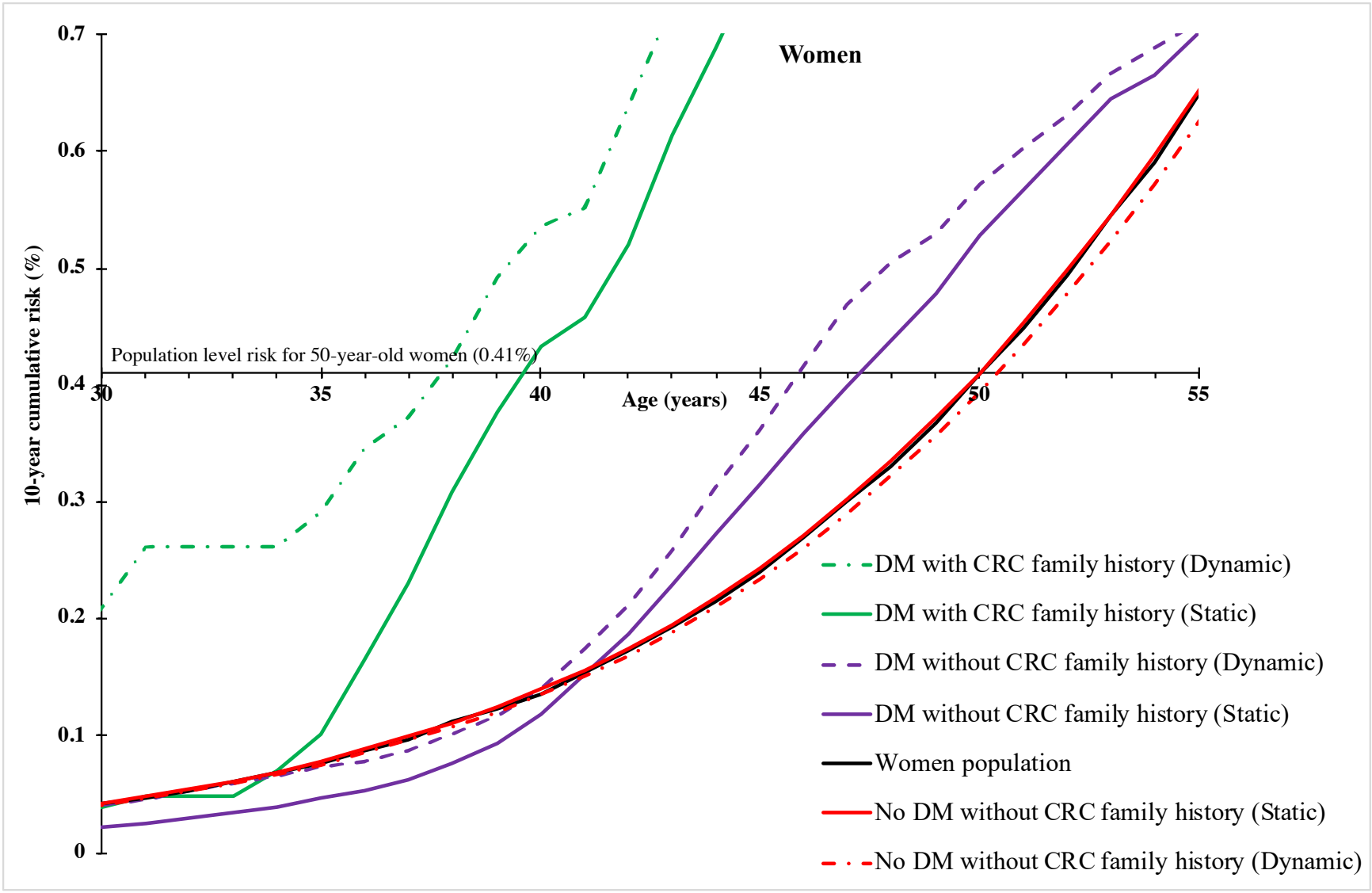


Figure 9. Comparison of dynamic and static methods of age-specific 10-year cumulative risk of colorectal cancer by personal history of diabetes before age 50 and family history of colorectal cancer in first-degree relatives among women

CRC = Colorectal cancer; DM = Diabetes mellitus

4 DISCUSSION

4.1 Risk by age at diagnosis and family history of colorectal cancer

4.1.1 Principal findings

This study presented novel evidence regarding the associations between family history of colorectal cancer, personal history of diabetes, and increased risk of colorectal cancer. It was established that having diabetes was associated with elevated risk of colorectal cancer in a similar magnitude to having a first-degree relative with colorectal cancer. It was further found that these relationships were most prominent in young adults, as opposed to the elderly, and in concordant age groups. More specifically, having a diabetes diagnosis between ages 40 and 49 was associated with 3.6-fold risk of early-onset colorectal cancer compared to those without diabetes, much higher than in those without diabetes and just a first-degree relative with colorectal cancer. Furthermore, it was observed that having both diabetes and a family history of colorectal cancer was associated with a nearly 7-fold risk of early-onset colorectal cancer in comparison to those without such disease histories. This marked increase in risk of colorectal cancer in the presence of diabetes and family history of colorectal cancer suggests an interaction between the two factors, warranting additional exploration.

4.1.2 Comparison with other studies

Apart from family history of colorectal cancer, few other indicators such as male sex, rare genetic syndromes like HNPCC or gastroenterology-related diseases like IBD have been associated with early-onset colorectal cancer (Ballester et al. 2016; Gausman et al. 2019; Mauri et al. 2019; Triantafillidis et al. 2009). These aforementioned factors have been mentioned as colorectal cancer risk factors, while diabetes has not. A meta-analysis of colorectal cancer risk

among diabetic patients established a positive association between diabetes history and colorectal cancer risk [SIR 1.21, 95% CI: 1.02-1.42 (Guraya 2015)]. Nonetheless, the meta-analysis showed a wide disparity in the risk estimates provided by the studies incorporated. Estimates of risk ratios observed were as high as 2.05 (95% CI: 1.69-2.48) and others as low as 1.05 (95% CI: 0.94-1.18). Meanwhile the relative risk estimate in this study was in between with 1.6-fold risk of colorectal cancer at all ages in diabetic patients. The disparity observed in risk estimates is likely due to variance in study design, cohort or sample sizes, age at diagnosis of diabetes and colorectal cancer, use of any diabetic medication, and management of family history of colorectal cancer. Prior studies have also implicated prediabetes, a precursor to type 2 diabetes, with increased risk of later colorectal cancer, implying that glycemic imbalances and lifestyle factors associated with type 2 diabetes may have a mediating effect on the associations between diabetes and colorectal cancer (Zhou et al. 2010). An association between family history of colorectal cancer and risk of colorectal cancer has been thoroughly documented in the literature with risk estimated for having first-degree relatives with 1.87-fold (95%CI: 1.68-2.09) risk as estimated by a meta-analysis. Additionally, those with just one first-degree relative with colorectal cancer had an estimated increase in risk of colorectal cancer by a factor of 1.76 (Mehraban Far et al. 2019).

4.1.3 Novel contributions to the literature

Although studies have found that diabetes is associated with increased risk of colorectal cancer, to date, no study has investigated the association between risk of colorectal cancer and different combinations of personal history of diabetes at different ages and family history of colorectal cancer. Our finding regarding elevated risk of early-onset colorectal cancer in diabetic patients

could be even more important considering that early-onset colorectal cancer might be a unique subset of colorectal cancer in which the association with diabetes has not been explored (Silla et al. 2014). Furthermore, our record linkage to produce the world's largest nationwide family-cancer cohort of its kind enabled us to investigate this association and provide clinically-relevant risk estimates using real-world data.

4.1.4 Implications of findings

Due to the emerging trend of elevated colorectal cancer incidence among young adults below the age of screening, studies have explored if the starting age of colorectal screening for the average-risk population should be reduced (Brenner et al. 2017; Peterse et al. 2018), and resultantly, many countries have shifted their screening recommendation towards a younger first screening age (McFerran et al. 2019; Walter et al. 2018). There are prospective issues with such an approach, such as greater expenses associated with screening resources since many more individuals in the population become eligible, and yet there still may be high-risk individuals in the population who do not meet age requirements for subsidized screening who are being overlooked (Liang 2018). It was found that individuals with diabetes before age 50 were diagnosed with colorectal cancer at younger ages (median age 59) than the general population (age 71) and even those who did not have diabetes but had a family history of colorectal cancer (age 65). When also considering that the mean time for an adenomatous polyp to progress into colorectal cancer is more than 10 years (Atkin and Saunders 2002), screening of diabetic patients before age 50 (most commonly recommended starting age of screening) ought to be considered. Nonetheless, further studies are warranted to elucidate the underlying mechanism of our findings

and to determine whether the underlying risk factors of diabetes are involved, some of which are also known to predispose individuals to colorectal cancer.

Risk factors such as advanced body mass index (BMI) and sedentary lifestyle, involved in both diabetes and colorectal cancer, appear to play significant roles in this association. It has been further suggested that the atypically high levels of insulin and glucose may produce an environment in the bowel that promotes the development of colorectal cancer (Atkinson et al. 2014; Khaw et al. 2004; Siddiqui et al. 2008; Vu et al. 2014). The prevalence of diabetes in Sweden is lower than in most developed nations, roughly 4.5% compared to a prevalence of 9% in the US (Bullard et al. 2018). Further, mean BMI in Sweden was 25.8 as of 2014, whereas it was 28.8 in the US (Mendis et al. 2015a). Since diabetes is more common in the US and accompanied with other colorectal cancer risk factors such as advanced BMI, colorectal cancer screening for diabetic patients may be even more necessary in the US given our finding that diabetes, namely type 2, is associated with a prominent risk of early-onset colorectal cancer.

4.1.5 Strengths of the study

The primary strength of this study was utilization of the world's largest nationwide register-based family-disease datasets with up to 52 years of follow-up. The nature of these linked datasets reduces the effects of recall and selection biases that are common in most cohort and case-control studies. As an example, the family history data used in this study, which was produced by linking the cancer registry and Multi-generation database, ensured accurate information; avoiding the biases involved in self-reported family history and information bias. Additional details regarding disease diagnosis such as age at diabetes diagnosis allowed us to

minimize the risk of a reverse association between diabetes and colorectal cancer. Furthermore, it enabled us to allocate person-years precisely based on the dynamic nature of such histories.

The method of analyses in this study for the purpose of risk estimation is also superior to that utilized in most register-based cohort studies that conventionally allocate disease history independently to the age or time of diagnosis (Goldgar et al. 1994; Schoen et al. 2015). The findings are according to the dynamic method of disease history assessment, and resultantly produce risk estimates that are more valid for real-world scenarios and can be implemented in clinical risk assessment and counselling. Another advantage of this study was the employment of absolute (cumulative) risk as a tangible risk estimator in addition to relative risk estimates. It provides more practical insight into risk of colorectal cancer in the population as opposed to only the use of conventional relative risk measures, such as hazard ratios or SIRs (Guraya 2015; Larsson 2005).

Utilization of the dynamic method of family history of colorectal cancer and diabetes personal history ascertainment is another novel aspect and key benefit of this study. Large registry-based cohort studies typically do not employ this method of disease history ascertainment (Guraya 2015; Johnson et al. 2013). Typically, whatever is known regarding an individual's histories at the commencement of study follow-up is attributed to them lifelong. However, this does not reflect the time-dependent nature of disease onset. This study ensured that individuals were considered as cases from the time of diagnosis to ensure the estimates reflect the real-time risks.

4.1.6 Potential limitations and sensitivity analysis

A limitation of the study was that details regarding the type of diabetes diagnoses for individuals diagnosed before 1997 were not available. As a result, a sensitivity analysis was conducted limiting the follow-up period from 1997 to 2015 to determine the association between type of diabetes and risk of colorectal cancer in a subset of the study population. A positive association was found between diagnosis of type 2 diabetes and risk of early-onset colorectal cancer, but not type 1 diabetes in patients without a family history of colorectal cancer. Since type 1 diabetes occurs primarily in adolescents, patients with type 1 diabetes diagnosed from 1997 onward would not have reached the age of colorectal cancer by the end of the study in 2015. Alternatively, if diabetes diagnosed before age 30 was classified as type 1 [a valid criterion with proven predictive value in other studies utilizing the same database (Mollazadegan et al. 2013)], type 1 diabetic patients had 1.2-fold risk of early-onset colorectal cancer (95% CI 1.0-1.5). An additional analysis by subsite of colorectal cancer demonstrated that, irrespective of the subsite, diabetes personal history was associated with an elevated risk of cancer in all regions of the bowel, which internally validated the association between diabetes and colorectal cancer.

An additional limitation of the study was that there was no information on any treatments used to manage diabetes in diabetic patients. Nonetheless, the study findings revealed that those without a family history of colorectal cancer but diagnosed with diabetes between age 40 and 49 had a significantly elevated relative risk of early-onset colorectal cancer (SIR=3.6, 95% CI: 2.8-4.5) compared to those patients diagnosed with diabetes before age 30, which was not statistically significant (SIR=1.2, 95% CI: 0.8-1.6). Since metformin is the primary treatment of type 2 diabetes (Rojas and Gomes 2013), and in spite of the well-known protective influence of

metformin on cancer, including colorectal cancer (Dulskas et al. 2020; Higurashi and Nakajima 2018; Saraei et al. 2019), increased risk of early-onset colorectal cancer in type 2 diabetic patients was observed. Consequently, the true risk in the absence of metformin could have been even higher. Moreover, the first line of treatment for type 1 diabetes is insulin, and has been found to increase cancer risk (Atkinson et al. 2014). If insulin mediated the association, higher increase in risk of colorectal cancer in type 1 patients, as opposed to type 2, would have been expected, which was not observed in this study.

Based on Amsterdam II criteria families with patients with high likelihood of having HNPCC were found. Excluding these individuals did not affect risk estimates for familial colorectal cancer. Thus making it unlikely that HNPCC patients confounded any findings since Amsterdam II criteria stipulates that an individual should have three family members with colorectal cancer and/or other related cancers to be tested for HNPCC (Vasen et al. 1999). In a sensitivity analysis, IBD patients were also excluded and little to no changes in risk estimates were observed.

Lastly, there was no access to data on lifestyle factors such as physical activity or diet, though data on socioeconomic status, residential area, hospitalization for COPD, obesity, and alcoholism was available. After adjusting for these hospitalization factors, no significant changes in relative risk estimates were observed. The SIRs in this study were also adjusted for sex, age, socioeconomic status, residential area, and calendar period to partially consider lifestyle factors and differences in healthcare access between different regions.

4.1.7 Conclusion

This study provides evidence that diabetic patients have an elevated risk of colorectal cancer, namely early-onset colorectal cancer. It was determined that young diabetic patients, regardless of an existing family history of colorectal cancer, are at increased risk of colorectal cancer in a comparable manner to individuals with a family history of colorectal cancer. The present findings warrant an exploration into potentially screening diabetic patients earlier, and an investigation into the practicality, benefits and limitations of screening in young diabetic patients earlier than the average-risk population, particularly in those with type 2 diabetes.

4.2 Risk-adapted colorectal cancer screening in diabetic patients

4.2.1 Principal findings

Using the world's largest family-cancer database, this study showed that patients with diabetes reach the same level of colorectal cancer risk as 50-year-olds in the general population four to five years earlier, depending on sex. It was also found that diabetic patients, with a family history of colorectal cancer, reach this level of risk 12 years earlier in women, and 18 years earlier in men in comparison to those in the general population. Repeating the analysis for several benchmark ages of screening (45, 55 and 60) showed that patients with diabetes and a family history of colorectal cancer reached the population level of risk 12-21 years earlier, depending on sex and the benchmark age. For those diabetic patients without a family history of colorectal cancer the risk advancement was three to five years earlier, again depending on sex and the benchmark age.

4.2.2 Novel contributions to the literature and implications of findings

The relationship between diabetes, family history of colorectal cancer, and colorectal cancer risk has been described in the literature (Guraya 2015; Larsson 2005; Peeters et al. 2015). Nonetheless, to date, studies have not evaluated the clinical relevance of such associations and how they can be used to counsel diabetic patients in clinic or offer risk-adapted starting ages of screening to them. This study fills this gap in the literature by providing clinically useful information regarding colorectal cancer screening for diabetic patients. Not only are diabetic patients not given particular attention as a high risk group in any colorectal cancer screening guidelines, but colorectal cancer first screening recommendations in individuals at high-risk are also largely based on expert opinions and/or low-quality evidence (Canadian Task Force on Preventive Health Care 2016; Gupta et al. 2019; Lichtenstein et al. 2018; Rubin et al. 2019). In contrast, this study provides strong evidence based on high-quality data. Furthermore, 10-year cumulative risk was utilized and tracked colorectal cancer incidence by age to provide risk-adapted screening ages, a method never used before to evaluate colorectal cancer risk in diabetic patients (Larsson 2005).

In this study 10-year cumulative risk was employed to evaluate colorectal cancer risk in different risk strata, which were dependent on various combinations of age, diabetes status, family history of colorectal cancer, and different benchmark ages of initial colorectal cancer screening. This study demonstrated the use of 10-year cumulative risk with a benchmark initial screening age of 50 years since this is the most commonly recommended age of first colorectal cancer screening in the majority of programs globally (Navarro et al. 2017). This study established that diabetic patients reach the population level of colorectal cancer risk a few years earlier than the general

population, however when considering that diabetic patients have higher risk of early-onset colorectal cancer than late-onset (Ali Khan et al. 2020), screening prior to age 40 may even be warranted in patients with an additional family history of colorectal cancer. Even though screening at young ages is uncommon, colorectal cancer incidence is rapidly rising in young people and since colonoscopy screening allows the removal of precancerous polyps (Atkin and Saunders 2002), it could be justified. Even though randomized trial results for colonoscopy are not yet available, increased rates in young adults have spiked and need to be addressed (Brenner et al. 2015b; Doubeni et al. 2018; Larsen et al. 2018). Furthermore, it has been deduced that screening for colorectal cancer is cost-effective and a risk-adapted approach to screening is ideal (Patel and Kilgore 2015; Reeves et al. 2019).

In this study, the proportion of patients with colorectal cancer who at the time of their diagnosis had a history of such a cancer in their first-degree relatives (4.3%) was consistent with that in another study on risk of colorectal cancer by family history constellations (4.4%) (Tian et al. 2020). Another Swedish study utilizing the family-cancer datasets demonstrated that risk of colorectal cancer in first-degree relatives (i.e. parents, siblings) did not show significant differences by the type of relationship (Tian et al. 2019). Additionally, this study on diabetic patients observed common patterns in the 10-year cumulative risk of colorectal cancer in diabetic men and women, which establishes internal validity of the results. Nevertheless, it is important to note that evaluations of the cost-effectiveness of advanced screening in diabetic patients are required and warrant exploration.

Due to global differences in the initial age of colorectal cancer screening such as the UK (age 55/60, depending on location), in the Netherlands (age 55) and in the US (recent change to age 45) (Dyer 2018; Navarro et al. 2017), risk-adapted screening ages for various benchmark ages were provided. It was observed that, irrespective of benchmark age of first screening, diabetic patients with an additional family history of colorectal cancer reach the population level of risk much earlier than diabetic patients without a family history, which suggests that both conditions provide unique contributions to colorectal cancer risk. The findings could be informative for use in risk calculators and potentially could be combined with additional risk factors of colorectal cancer or polygenic risk scores (Driver et al. 2007; Freedman et al. 2009; Tao et al. 2014) to produce further stratified personalized screening ages for colorectal cancer in the future. The process of implementing such findings into risk predictors with other factors have been mentioned in another study (Mukama et al. 2020c). At the very least, indicating diabetes as modifiable risk factor mentioned in colorectal cancer guidelines would increase its importance as a risk factor and patients at risk for diabetes could be wary and encouraged to have better lifestyle habits. Furthermore, the findings of this analysis were compared with those of another study, which demonstrated first screening in first-degree relative with colorectal cancer to be roughly five years earlier (Tian et al. 2020), which is the same as the risk advancement that was observed for diabetic patients. This suggests that, regarding colorectal cancer screening, diabetic patients could be treated similarly to those with a family history of colorectal cancer.

4.2.3 Strengths of this study

Elevated risk of colorectal cancer has been previously reported in diabetic patients. However, relative risk estimates (such as SIRs, hazard ratios), as opposed to an absolute risk measures such as 10-year cumulative risk may not be as practical in reference to determining screening ages

(Taylor et al. 2011). Quantification and use of 10-year cumulative risk in this study, namely the real-world risk of developing colorectal cancer in the next 10 years, is particularly appropriate for colorectal cancer screening since the mean time for precancerous polyps to progress into colorectal cancer is roughly 10 years (Atkin and Saunders 2002). Further, since 10-year cumulative risk tracks incidence in the next 10 years at each age, it allows us to consider how absolute risk changes dynamically with age, making it more suited than standard absolute risk measures (i.e. from birth to a certain age) for risk-adapted screening. The method employed in this study has the added benefit that it can be applied to fit different populations with different favored benchmark ages of first screening.

This study also benefitted from using the world's largest nationwide family-cancer dataset of its kind. The large size of the database results in sample sizes large enough to make conclusions regarding risk groups defined by several criteria such as sex, diabetes status and family history of colorectal cancer. Furthermore, use of such a nationwide database is advantageous for risk-adapted screening since it captures the holistic characteristics of a real population, which is exactly what risk-adapted screening is meant for. The study population also benefits from long-term stability of colorectal cancer incidence rates in Sweden. Since Sweden is one of the few countries with high Human Development Index (HDI) without widespread colorectal cancer screening, colorectal cancer incidence has not markedly changed in the time-frame of the study as demonstrated by NORDCAN data (**Supplementary Figure 1**). Resultantly, any potential effects of a cohort-effect are minimized (Drackert B 2019). Hence making Sweden an ideal population for investigation into risk-adapted colorectal cancer screening. The present study also allows for the clinical application of risk estimates of colorectal cancer in diabetic patients and

can be viewed as building on the idea of "risk advancement periods" which has been proposed to quantify exposure effect on diseases such as colorectal cancer, where incidence increases with age (Brenner et al. 1993).

4.2.4 Potential limitations

Despite the value of utilizing such a large nationwide database with accurate family history information, there are potential limitations to be wary of. Firstly, although the findings show that diabetic patients have an advanced risk of colorectal cancer, these findings may only be generalizable to similar populations with similar disease incidence rates. Nonetheless, the method of generating risk-adapted screening ages may be used to produce similar risk-adapted screening ages tailored to a specific population with different demographic characteristics.

It is important to discuss that information on colonoscopy uptake within the cohort, to determine whether diabetic patients would be more likely to seek out colonoscopy or other forms of screening, was not available. In Sweden, as of 2015, a nationwide screening program did not exist apart from in the Gotland region, where pilot phase screening has commenced (Blom et al. 2014). In a previous study, an analysis by calendar period of colorectal cancer diagnosis before and after screening program initiation demonstrated no considerable change in familial colorectal cancer risk (Tian et al. 2019). Irrespective of this, detection bias due to elevated screening uptake in those with a family history of cancer does not impact the primary focus of the study, which is colorectal cancer risk in diabetic patients. Furthermore, the association with diabetes is not well established compared to the association with family history of colorectal cancer, making it unlikely that diabetic patients would be recommended to be screened earlier. Rather, diabetic

patients are notorious for poorly adhering to treatment regimens, and studies have suggested nearly half of all type 2 patients do not meet self-care standards. (Kurtz 1990; Polonsky and Henry 2016). This makes it unlikely that they would undergo screening for a new potential disease while they struggle to adhere to recommendations for a preexisting disease. A study comparing adenoma detection rates in two cohorts of patients aged 40 to 49 years with diabetes and without diabetes demonstrated three times the risk in diabetic patients (Vu et al. 2014). This supports a real association rather than a detection bias in diabetic patients.

Additional data on diabetes treatment and end-organ manifestations was also lacking. Studies have demonstrated that high hemoglobin A1C (HgbA1C) levels and insulin administration, which represent advanced diabetes, were associated with increased risk of colorectal cancer (Khaw et al. 2004; Siddiqui et al. 2008; Vu et al. 2014). However, metformin is commonly the first line of treatment for type 2 diabetes and has a protective effect on risk of colorectal cancer. A related study on the same study population showed that the majority of diabetic cases with colorectal cancer before age 50 have type 2 diabetes (Ali Khan et al. 2020). This implies that any confounding affect from diabetes treatment in the findings is likely to dilute (rather than over-estimate) 10-year cumulative risk estimates.

Even though further exploration into the practicality of earlier screening of diabetic patients is warranted, prevalence of several shared diabetes and colorectal cancer risk factors indicate that risk estimates in the Swedish population may in fact be conservative and that risk-adapted screening in diabetic patients may be more critical in other nations. The prevalence of diabetes in Sweden is 4.5%, nearly half of that in the US (Bullard et al. 2018). As of 2014, the mean adult

BMI in Sweden was also markedly lower (25.8) in comparison to the US (28.8), where obesity rates are also much higher (Mendis et al. 2015b). In terms of tobacco consumption, Sweden has one of the lowest age-standardized rates of smoking in Europe (18.9%), which is also lower than in the US (21.9%). In addition, approximately 23% of the Swedish adult population is considered to undergo insufficient physical activity. The prevalence in the US is nearly twice as high (40%) (World Health Organization 2019). Although the aforementioned risk factors are potential confounders in the association between diabetes and colorectal cancer, if shared risk factors such as BMI, smoking, and physical inactivity are mediating the relationship, the findings would suggest that risk of colorectal cancer in diabetic patients is likely greater in other populations. Resultantly, earlier screening of diabetic patients may be more important in countries such as the US, where these risk factors are more prominent. It is noteworthy that the utility of diabetes as a risk factor would appear to be contingent on the availability/intensity of diabetes screening or diagnosis in the population. Studies have found that roughly 20% of patients with type 2 diabetes remain undiagnosed, nonetheless, due the presence of opportunistic screening for diabetes in Sweden since the 1980s, a significantly smaller percentage of undiagnosed diabetics are anticipated in comparison to other countries (Andersson et al. 1991; Midthjell et al. 1995; Thunander et al. 2008).

4.2.5 Conclusion

To conclude, this study provides novel evidence-based data for risk-adapted personalized starting ages of colorectal cancer screening in diabetic patients. The rising colorectal cancer rates in young individuals calls for a change in screening practices. This, in combination with the accrual of evidence that diabetic patients are at increased risk of colorectal cancer, especially early-onset

warrants the targeting of diabetic patients in an attempt to curb the increasing colorectal cancer incidence in the population below screening age. The findings demonstrate that diabetic patients reach the population level of colorectal cancer risk four to five years earlier in those without a family history of colorectal cancer, and 12 to 21 years earlier in those with family history. These findings warrant an exploration into the practicality, benefits and limitation of risk-adapted screening of diabetic patients.

4.3 Comparison between dynamic and static definitions

4.3.1 Principal findings

When comparing the dynamic and static methods of evaluating disease history some marked differences in relative risk of colorectal cancer among diabetic patients were detected. It was found that in diabetic patients diagnosed before age 50, risk of colorectal cancer at all ages was 1.4-fold by the dynamic method, but 1.2-fold by the static method. For early-onset colorectal cancer, the risk was 1.9-fold by the dynamic method, and was 1.2-fold by the static method, but was not statistically significant. In patients diagnosed with diabetes before age 20, the dynamic and static methods yielded similar results, with 1.5-fold colorectal cancer risk in both methods. In terms of relative risk of familial colorectal cancer, risk estimates of diabetic patients were consistently higher using the dynamic method, particularly for early-onset colorectal cancer. However, familial colorectal cancer risk estimates for those without a diabetes diagnosis were similar by both methods. In regard to risk-adapted screening ages, both methods yielded dissimilar results with diabetic patients reaching the population level of risk consistently earlier by the dynamic method in comparison to the static method.

4.3.2 Comparison between methods

Overall, for both risk prediction and risk-adapted screening ages, the dynamic and static methods yielded different results for risk of colorectal cancer among diabetic patients. The important difference in these two methods is that the dynamic method allocates disease history only from the time of diagnosis, whether it is a diabetes diagnosis or a family member diagnosed with colorectal cancer. As a result, the person-years allocated in risk calculations will be different by both methods. For example, when evaluating the risk of early-onset colorectal cancer in diabetic patients diagnosed before age 50, if a person is diagnosed with diabetes at age 40 and colorectal cancer at age 45, by the static method the full 45 years of this individual's person-years will be allocated to the group with diabetes. By the dynamic method, only 5 years from age 40 to 45 will be allocated to the diabetes risk calculation, while 40 person-years will be allocated to the 'non-diabetic' group. Since over 60% of diabetes cases before age 50 occurred after age 40, by the dynamic method a large portion of person-years of diabetic patients were allocated to the non-diabetic group, which resulted in the large differences observed in SIRs by the dynamic and static methods, especially for risk of early-onset colorectal cancer.

By the same token, differences by both methods were not observed in diabetic patients diagnosed before age 20, since only a small portion of person-years were being allocated to the 'non-diabetic' group by the dynamic method. For example, if a person is diagnosed with diabetes at age 5 and develops colorectal cancer at age 45, by the dynamic method 40 years are allocated to the 'diabetic' group while 45 years are allocated to the same group using the static method, a much smaller difference between the two. A comparison of the risk estimates using the static method (SIR 1.2, 95% CI 1.1-1.3) with those of other studies employing the static method

showed very similar results for risk of colorectal cancer in diabetic patients with roughly 20% increased risk (Guraya 2015).

In a recent study comparing the dynamic and static definitions for family history of breast cancer, the dynamic method consistently yielded elevated relative risk and absolute risk estimates (Mukama et al. 2020b). The study demonstrated that both methods of disease history can be applied to estimate the disease risk, however the best option depends on the desired implication of the study. The dynamic method is understood to be the most appropriate for studies involving risk prediction and risk stratification since it provides real-time risk estimates for individuals that can be applied in clinical settings. For example, if individuals want to know the risk of developing colorectal cancer at the present time, only known histories can be taken account. Meanwhile, the static method is possible in register-based studies where an individual's entire prior personal or family histories are known at the conclusion of study follow-up. As a result, the static method captures disease history completely and would be most valid for estimating the overall effect (burden or attributable fraction) of a risk factor on an outcome. In this study, the dynamic (time-dependent) method was employed since the primary aim of the study was risk prediction and risk stratification of colorectal cancer in diabetic patients that could be used for real-time counselling. In brief, the dynamic method reflects the time-dependent nature of family and personal disease histories making it better suited for the purposes of this study.

4.4 Overall conclusions

The present study using the world's largest nationwide family-cancer datasets with the use of a time-dependent method of ascertaining disease history provides evidence-based information on the risk of colorectal cancer in diabetic patients with clinical utility. It was found that individuals with diabetes before age 50 are at increased risk of colorectal cancer at all ages, especially early-onset colorectal cancer and in concordant age groups. It was demonstrated that individuals with diabetes are at elevated risk for early-onset colorectal cancer in a magnitude similar to having a family history of colorectal cancer suggesting that diabetes could be considered an established risk factor of colorectal cancer. Furthermore, individuals with personal history of diabetes and family history of colorectal cancer had nearly 7 times the risk of early-onset colorectal cancer, higher than the multiplicative product of their individual relative risks by these histories, which implies an interaction between the two criteria. These results may be helpful for evidence-based counselling of diabetic and prediabetic patients to make them aware of the elevated risk of colorectal cancer. This may in the long run help alleviate the burden of early-onset colorectal cancer by earlier screening and/or informing diabetic patients to take precautions via improved lifestyle practices, which are common modifying factors for both diseases.

For the first-time, risk-adapted starting ages of colorectal cancer screening were also provided for diabetic patients taking into account sex, family history of colorectal cancer, suggesting an adjustment to existing colorectal cancer screening practices. The rising incidence of colorectal cancer in young adults has increased pressure on countries to adjust their screening programs to improve incidence and outlook of colorectal cancer in individuals below screening age. The results follow recent studies that suggest a risk-adapted approach to colorectal cancer screening

and promote allocation of screening resources to individuals who are at high-risk in the population. The risk-adapted screening ages derived in this study may help guide clinicians to recommend diabetic patients to the best course of action for prevention of colorectal cancer in a timely manner.

5 SUMMARY

Colorectal cancer is currently the third most common and the second most deadly of all cancers. Despite the success of global colorectal cancer screening programs in reduction of both incidence and mortality, in recent decades the incidence in young individuals, particularly before the age of 50, has risen in several countries. Resultantly, there is a call for colorectal cancer screening programs to alter screening recommendation and identify risk factors that make young people susceptible. Diabetes is a disease that has also been rising in young people in recent decades. Additionally, diabetes shares several risk factors with colorectal cancer and has been associated with colorectal cancer in some studies. Hence, it becomes increasingly important to determine if diabetic patients are at increased risk and if they should be directed for an earlier screening than the general population.

This study aimed to investigate the associations between diabetes and early-onset and late-onset colorectal cancer and determine what effect age of diabetes diagnosis, family history of colorectal cancer, and sex have on these associations. In addition, if diabetic patients are at increased risk of colorectal cancer, it aimed to provide evidence-based risk-adapted screening ages in diabetic patients with and without a family history of colorectal cancer, given that diabetes has yet to be mentioned in global screening guidelines.

The analysis was conducted using the Swedish family-cancer datasets, the world's largest of their kinds with record linkage to the Swedish Inpatient and Outpatient Registers. The study population consisted of 12,614,256 individuals with valid genealogical information (at least one first-degree relatives) and up to 52 years of follow-up spanning from 1964 to 2015. Among the

12.6 million individuals, 559,375 cases of diabetes and 162,226 cases of colorectal cancer were identified. Standardized incidence ratios, lifetime cumulative risk (age 0 to 79), and 10-year cumulative risk of colorectal cancer in diabetic patients with and without a family history of colorectal cancer were calculated. Both family and personal disease histories were ascertained using a dynamic (time-dependent) method, in which individuals were treated as cases only from their age at diagnosis onwards.

It was observed that diabetic patients are at an increased risk of colorectal cancer, particularly early-onset colorectal cancer and that the magnitude of this association was similar to that of having a first-degree relative with colorectal cancer. This risk was further elevated in diabetic patients with an additional family history of colorectal cancer with nearly 7 times the risk of colorectal cancer compared to those in the general population with no diabetes and no family history of colorectal cancer. Building on these findings, the study provided risk-adapted ages of initial colorectal cancer screening for diabetic patients with and without a family history of colorectal cancer. It was found that diabetic patients reached the population level of risk several years earlier irrespective of the benchmark age of screening in the population (age 45, 50, 55 or 60).

The results regarding risk of colorectal cancer in diabetic patients provide clinically-relevant and evidence-based data designed for real-time counselling of diabetic patients who are at an increased risk for early-onset colorectal cancer. The findings could help physicians provide personalized screening recommendation for diabetic patients and at the very least make patients wary of their increased risk so they can make lifestyle changes accordingly. Overall, irrespective

of the specific application, the findings carry strong potential in impacting the management of diabetes, especially in young patients who are not targeted by colorectal cancer screening.

5 ZUSAMMENFASSUNG

Darmkrebs ist derzeit die dritthäufigste Krebserkrankung und die zweithäufigste Krebstodesursache weltweit. Trotz des Erfolgs globaler Darmkrebsvorsorge-Programme in Hinblick auf Häufigkeit und Mortalität ist in den letzten Jahrzehnten die Häufigkeit bei jungen Menschen, insbesondere vor dem 50. Lebensjahr drastisch gestiegen. Daraus ergibt sich die Forderung an Darmkrebs-Früherkennungsprogramme, die Früherkennungsempfehlungen zu ändern und Risikofaktoren zu identifizieren, welche junge Menschen anfällig machen. Eine weitere Krankheit, die bei jungen Menschen in den letzten Jahrzehnten deutlich zugenommen hat, ist Diabetes. Darüber hinaus teilt sie mehrere Risikofaktoren mit dem Kolorektalkarzinom und wurde in jüngsten Studien mit dem Kolorektalkarzinom in Verbindung gebracht. Daher wird es immer wichtiger festzustellen, ob Diabetes-Patienten ein erhöhtes Risiko haben und ob sie für eine frühere Vorsorgeuntersuchung vorgesehen werden sollten.

Ziel dieser Studie war es, die Zusammenhänge zwischen Diabetes und Darmkrebs zu untersuchen und festzustellen, welchen Einfluss das Alter bei der Diabetes-Diagnose, die Familiengeschichte in Bezug auf Darmkrebs und das Geschlecht auf diese Zusammenhänge haben. Im Falle, dass Diabetes-Patienten ein erhöhtes Risiko für Darmkrebs haben, zielte sie zudem darauf ab, ein evidenzbasiertes, risikoadaptiertes Früherkennungsalter bei Diabetes-Patienten mit und ohne Darmkrebs-Familiengeschichte zu ermitteln, da Diabetes bisher in keiner globalen Früherkennungsrichtlinie spezielle Berücksichtigung fand.

Die Analyse wurde mit Hilfe der Krebsdatensätze schwedischer Familien durchgeführt, dem weltweit größten landesweiten Familien-Krebsregister mit “record linkage”. Die

Studienpopulation bestand aus 12.614.256 Personen mit gültigen genealogischen Informationen (mindestens ein Verwandter ersten Grades) und einer 52-jährigen Nachbeobachtung, die sich von 1964 bis 2015 erstreckte. Unter den 12,6 Millionen Personen wurden 559.375 Fälle von Diabetes und 162.226 Fälle von Kolorektalkrebs festgestellt. Es wurden standardisierte Inzidenzverhältnisse, das kumulative Lebenszeitrisiko (Alter 0 bis 79 Jahre) und das kumulative Zehn-Jahres-Risiko für Darmkrebs bei Diabetikern mit und ohne familiäre Vorgeschichte von Darmkrebs berechnet. Sowohl die familiäre als auch die persönliche Krankheitsgeschichte wurden mit einer dynamischen (zeitabhängigen) Methode ermittelt, bei der Personen, ab dem Alter bei der Diagnose, als Fälle behandelt wurden.

Es wurde beobachtet, dass Diabetes-Patienten ein erhöhtes Risiko haben, an Darmkrebs, insbesondere an Darmkrebs in relativ jungem Lebensalter, zu erkranken und dass das Ausmaß dieser Assoziation ähnlich groß ist wie bei einem Verwandten ersten Grades mit Darmkrebs. Dieses Risiko war bei Patienten mit einer zusätzlichen Familiengeschichte von Darmkrebs weiter erhöht, wobei das Risiko für Darmkrebs fast siebenmal höher war als in der Allgemeinbevölkerung ohne Diabetes und ohne Familiengeschichte von Darmkrebs. Aufbauend auf diesen Ergebnissen lieferte die Studie risikoadaptierte Altersangaben für die Darmkrebs-Erstvorsorge für Patienten mit Diabetes, mit und ohne familiärer Darmkrebsvorgeschichte. Es stellte sich heraus, dass Diabetiker das Risikoniveau der Bevölkerung einige Jahre früher erreichten, unabhängig vom Referenzalter der Früherkennung in der Bevölkerung (Alter 45, 50, 55 oder 60 Jahre).

Die Ergebnisse bezüglich des Darmkrebsrisikos bei Diabetikern liefern klinisch relevante Daten, die für die Echtzeit-Beratung von Diabetikern mit erhöhtem Risiko für Darmkrebs im Frühstadium relevant sind. Die Ergebnisse könnten Ärzten helfen, personalisierte Empfehlungen für die Vorsorgeuntersuchung von Diabetes-Patienten auszusprechen und die Patienten zumindest vor ihrem erhöhten Risiko zu warnen, damit sie ihre Lebensweise entsprechend ändern können. Unabhängig von der spezifischen Anwendung bergen die Ergebnisse ein großes Potenzial für die Verbesserung der Krebsvorsorge von Diabetikern, insbesondere bei jungen Patienten, die nicht ins Visier der Darmkrebs-Früherkennung fallen.

6 REFERENCES

Ait Ouakrim, D., Pizot, C., Boniol, M., Malvezzi, M., Boniol, M., Negri, E., Bota, M., Jenkins, M. A., Bleiberg, H. and Autier, P. (2015). **Trends in colorectal cancer mortality in Europe: retrospective analysis of the WHO mortality database**. BMJ *351*, h4970, doi: 10.1136/bmj.h4970.

Ali Khan, U., Fallah, M., Tian, Y., Sundquist, K., Sundquist, J., Brenner, H. and Kharazmi, E. (2020). **Personal History of Diabetes as Important as Family History of Colorectal Cancer for Risk of Colorectal Cancer: A Nationwide Cohort Study**. Am J Gastroenterol *115*, 1103-1109, doi: 10.14309/ajg.0000000000000669.

Amersi, F., Agustin, M. and Ko, C. Y. (2005). **Colorectal cancer: epidemiology, risk factors, and health services**. Clin Colon Rectal Surg *18*, 133-140, doi: 10.1055/s-2005-916274.

Andersson, D. K., Svardsudd, K. and Tibblin, G. (1991). **Prevalence and incidence of diabetes in a Swedish community 1972-1987**. Diabet Med *8*, 428-434, doi: 10.1111/j.1464-5491.1991.tb01626.x.

Arnold, M., Sierra, M. S., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2017). **Global patterns and trends in colorectal cancer incidence and mortality**. Gut *66*, 683-691, doi: 10.1136/gutjnl-2015-310912.

Atkin, W. S. and Saunders, B. P. (2002). **Surveillance guidelines after removal of colorectal adenomatous polyps**. Gut *51*, v6-v9, doi: 10.1136/gut.51.suppl_5.v6.

Atkinson, M. A., Eisenbarth, G. S. and Michels, A. W. (2014). **Type 1 diabetes**. Lancet *383*, 69-82, doi: 10.1016/S0140-6736(13)60591-7.

Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., Scotti, L., Jenab, M., Turati, F., Pasquali, E., Pelucchi, C., Galeone, C., Bellocco, R., Negri, E., Corrao, G.,

Boffetta, P. and La Vecchia, C. (2015). **Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis**. Br J Cancer *112*, 580-593, doi: 10.1038/bjc.2014.579.

Bailey, C. E., Hu, C. Y., You, Y. N., Bednarski, B. K., Rodriguez-Bigas, M. A., Skibber, J. M., Cantor, S. B. and Chang, G. J. (2015). **Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010**. JAMA Surg *150*, 17-22, doi: 10.1001/jamasurg.2014.1756.

Ballester, V., Rashtak, S. and Boardman, L. (2016). **Clinical and molecular features of young-onset colorectal cancer**. World J Gastroenterol *22*, 1736-1744, doi: 10.3748/wjg.v22.i5.1736.

Bevan, R. and Rutter, M. D. (2018). **Colorectal Cancer Screening-Who, How, and When?** Clin Endosc *51*, 37-49, doi: 10.5946/ce.2017.141.

Bishehsari, F., Mahdavinia, M., Vacca, M., Malekzadeh, R. and Mariani-Costantini, R. (2014). **Epidemiological transition of colorectal cancer in developing countries: environmental factors, molecular pathways, and opportunities for prevention**. World J Gastroenterol *20*, 6055-6072, doi: 10.3748/wjg.v20.i20.6055.

Blom, J., Kilpelainen, S., Hultcrantz, R. and Tornberg, S. (2014). **Five-year experience of organized colorectal cancer screening in a Swedish population - increased compliance with age, female gender, and subsequent screening round**. J Med Screen *21*, 144-150, doi: 10.1177/0969141314545555.

Bogaert, J. and Prenen, H. (2014). **Molecular genetics of colorectal cancer**. Ann Gastroenterol *27*, 9-14.

Botteri, E., Iodice, S., Bagnardi, V., Raimondi, S., Lowenfels, A. B. and Maisonneuve, P. (2008). **Smoking and colorectal cancer: a meta-analysis**. JAMA *300*, 2765-2778, doi: 10.1001/jama.2008.839.

Brandt, A., Bermejo, J. L., Sundquist, J. and Hemminki, K. (2010). **Familial risks of breast and prostate cancers: does the definition of the at risk period matter?** Eur J Cancer *46*, 752-757, doi: 10.1016/j.ejca.2009.11.016.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A. and Jemal, A. (2018). **Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries**. CA Cancer J Clin *68*, 394-424, doi: 10.3322/caac.21492.

Brenner, H., Altenhofen, L., Stock, C. and Hoffmeister, M. (2015a). **Expected long-term impact of the German screening colonoscopy programme on colorectal cancer prevention: analyses based on 4,407,971 screening colonoscopies**. Eur J Cancer *51*, 1346-1353, doi: 10.1016/j.ejca.2015.03.020.

Brenner, H., Gefeller, O. and Greenland, S. (1993). **Risk and rate advancement periods as measures of exposure impact on the occurrence of chronic diseases**. Epidemiology *4*, 229-236, doi: 10.1097/00001648-199305000-00006.

Brenner, H., Stock, C. and Hoffmeister, M. (2015b). **Colorectal cancer screening: the time to act is now**. BMC Med *13*, 262, doi: 10.1186/s12916-015-0498-x.

Brenner, H. and Tao, S. (2013). **Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy**. Eur J Cancer *49*, 3049-3054, doi: 10.1016/j.ejca.2013.04.023.

Brenner, H., Zwink, N., Ludwig, L. and Hoffmeister, M. (2017). **Should screening colonoscopy be offered from age 50? Results from a statewide pilot project, and from a randomized intervention study**. Dtsch Arztebl Int *114*, 94-100, doi: 10.3238/arztebl.2017.0094.

Bullard, K. M., Cowie, C. C., Lessem, S. E., Saydah, S. H., Menke, A., Geiss, L. S., Orchard, T. J., Rolka, D. B. and Imperatore, G. (2018). **Prevalence of Diagnosed Diabetes in Adults by Diabetes Type - United States, 2016**. MMWR Morb Mortal Wkly Rep *67*, 359-361, doi: 10.15585/mmwr.mm6712a2.

Cairns, S. R., Scholefield, J. H., Steele, R. J., Dunlop, M. G., Thomas, H. J., Evans, G. D., Eaden, J. A., Rutter, M. D., Atkin, W. P., Saunders, B. P., Lucassen, A., Jenkins, P., Fairclough, P. D., Woodhouse, C. R., British Society of, G., Association of Coloproctology for Great, B. and Ireland (2010). **Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002)**. Gut *59*, 666-689, doi: 10.1136/gut.2009.179804.

Canadian Task Force on Preventive Health Care (2016). **Recommendations on screening for colorectal cancer in primary care**. CMAJ *188*, 340-348, doi: 10.1503/cmaj.151125.

Carstensen, B., Read, S. H., Friis, S., Sund, R., Keskimaki, I., Svensson, A. M., Ljung, R., Wild, S. H., Kerssens, J. J., Harding, J. L., Magliano, D. J., Gudbjornsdottir, S., Diabetes and Cancer Research, C. (2016). **Cancer incidence in persons with type 1 diabetes: a five-country study of 9,000 cancers in type 1 diabetic individuals**. Diabetologia *59*, 980-988, doi: 10.1007/s00125-016-3884-9.

Center, M. M., Jemal, A., Smith, R. A. and Ward, E. (2009). **Worldwide variations in colorectal cancer**. CA Cancer J Clin *59*, 366-378, doi: 10.3322/caac.20038.

Colditz, G. A., DeJong, W., Willett, W. C., Trichopoulos, D. and Hunter, D. J. (1996). **Harvard report on cancer prevention**. Cancer Causes Control *7*, (suppl):1-59, doi: 10.1023/a:1008984432272.

De Rosa, M., Pace, U., Rega, D., Costabile, V., Duraturo, F., Izzo, P. and Delrio, P. (2015). **Genetics, diagnosis and management of colorectal cancer (Review)**. Oncol Rep *34*, 1087-1096, doi: 10.3892/or.2015.4108.

Doubeni, C. A., Corley, D. A., Quinn, V. P., Jensen, C. D., Zauber, A. G., Goodman, M., Johnson, J. R., Mehta, S. J., Becerra, T. A., Zhao, W. K., Schottinger, J., Doria-Rose, V. P., Levin, T. R., Weiss, N. S. and Fletcher, R. H. (2018). **Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study**. Gut *67*, 291-298, doi: 10.1136/gutjnl-2016-312712.

Drackert B, F. J., Engholm G, Hansen HL, Johannesen TB, Khan S, Køtlum JE, Ólafsdóttir E, Schmidt LKH, Virtanen A, Storm HH (2019). **NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 8.2 (26.03.2019).** (Danish Cancer Society. Accessed on 23/08/2020.

Driver, J. A., Gaziano, J. M., Gelber, R. P., Lee, I. M., Buring, J. E. and Kurth, T. (2007). **Development of a Risk Score for Colorectal Cancer in Men**. Am J Med *120*, 257-263, doi: 10.1016/j.amjmed.2006.05.055.

Dulskas, A., Patasius, A., Linkeviciute-Ulinskiene, D., Zabuliene, L., Urbonas, V. and Smailyte, G. (2020). **Positive effect of metformin treatment in colorectal cancer patients with type 2 diabetes: national cohort study**. Eur J Cancer Prev *29*, 289-293, doi: 10.1097/CEJ.0000000000000547.

Dyer, O. (2018). **Colorectal cancer: US guidelines urge screening from age 45 as incidence soars in younger adults.** BMJ (Clinical research ed.) *361*, k2452, doi: 10.1136/BMJ.K2452.

Edwards, B. K., Ward, E., Kohler, B. A., Eheman, C., Zauber, A. G., Anderson, R. N., Jemal, A., Schymura, M. J., Lansdorp-Vogelaar, I., Seeff, L. C., van Ballegooijen, M., Goede, S. L. and Ries, L. A. (2010). **Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates**. Cancer *116*, 544-573, doi: 10.1002/cncr.24760.

Ferlay, J., Colombet, M., Soerjomataram, I., Dyba, T., Randi, G., Bettio, M., Gavin, A., Visser, O. and Bray, F. (2018). **Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018**. Eur J Cancer *103*, 356-387, doi: 10.1016/j.ejca.2018.07.005.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D. and Bray, F. (2015). **Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012**. Int J Cancer *136*, E359-386, doi: 10.1002/ijc.29210.

Forouhi, N. G. and Wareham, N. J. (2014). **Epidemiology of diabetes**. Medicine (Abingdon) *42*, 698-702, doi: 10.1016/j.mpmed.2014.09.007.

Frank, C. (2015) **Population landscape of familial cancer**. Thesis, Heidelberg University.

Frank, C., Fallah, M., Ji, J., Sundquist, J. and Hemminki, K. (2014). **The population impact of familial cancer, a major cause of cancer**. Int J Cancer *134*, 1899-1906, doi: 10.1002/ijc.28510.

Freedman, A. N., Slattery, M. L., Ballard-Barbash, R., Willis, G., Cann, B. J., Pee, D., Gail, M. H. and Pfeiffer, R. M. (2009). **Colorectal cancer risk prediction tool for white men and women without known susceptibility**. J Clin Oncol *27*, 686-693, doi: 10.1200/JCO.2008.17.4797.

Gausman, V., Dornblaser, D., Anand, S., Hayes, R. B., O'Connell, K., Du, M. and Liang, P. S. (2019). **Risk Factors Associated With Early-Onset Colorectal Cancer**. Clin Gastroenterol Hepatol, doi: 10.1016/j.cgh.2019.10.009.

Gillen, C. D., Andrews, H. A., Prior, P. and Allan, R. N. (1994). **Crohn's disease and colorectal cancer**. Gut *35*, 651-655, doi: 10.1136/gut.35.5.651.

Global Burden of Disease Cancer Collaboration (2017). **Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study**. JAMA Oncol *3*, 524-548, doi: 10.1001/jamaoncol.2016.5688.

Goldgar, D. E., Easton, D. F., Cannon-Albright, L. A. and Skolnick, M. H. (1994). **Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands**. J Natl Cancer Inst *86*, 1600-1608, doi: 10.1093/jnci/86.21.1600.

Greuter, M. J., Demirel, E., Lew, J. B., Berkhof, J., Xu, X. M., Canfell, K., Dekker, E., Meijer, G. A. and Coupe, V. M. (2016). **Long-Term Impact of the Dutch Colorectal Cancer Screening Program on Cancer Incidence and Mortality-Model-Based Exploration of the Serrated Pathway**. Cancer Epidemiol Biomarkers Prev *25*, 135-144, doi: 10.1158/1055-9965.EPI-15-0592.

Gupta, N., Kupfer, S. S. and Davis, A. M. (2019). **Colorectal Cancer Screening**. JAMA *321*, 2022-2023, doi: 10.1001/jama.2019.4842.

Guraya, S. Y. (2015). **Association of type 2 diabetes mellitus and the risk of colorectal cancer: A meta-analysis and systematic review**. World J Gastroenterol *21*, 6026-6031, doi: 10.3748/wjg.v21.i19.6026.

Gyde, S. N., Prior, P., Allan, R. N., Stevens, A., Jewell, D. P., Truelove, S. C., Lofberg, R., Brostrom, O. and Hellers, G. (1988). **Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres**. Gut *29*, 206-217, doi: 10.1136/gut.29.2.206.

Hemminki, K., Li, X., Plna, K., Granstrom, C. and Vaittinen, P. (2001). **The nation-wide Swedish family-cancer database--updated structure and familial rates**. Acta Oncol *40*, 772-777.

Higurashi, T. and Nakajima, A. (2018). **Metformin and Colorectal Cancer**. Frontiers in endocrinology *9*, 622-622, doi: 10.3389/fendo.2018.00622.

InterAct Consortium (2013a). **Association between dietary meat consumption and incident type 2 diabetes: the EPIC-InterAct study**. Diabetologia *56*, 47-59, doi: 10.1007/s00125-012-2718-7.

InterAct Consortium (2013b). **Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct**. Diabetologia *56*, 1520-1530, doi: 10.1007/s00125-013-2899-8.

Johns, L. E. and Houlston, R. S. (2001). **A systematic review and meta-analysis of familial colorectal cancer risk**. Am J Gastroenterol *96*, 2992-3003, doi: 10.1111/j.1572-0241.2001.04677.x.

Johnson, C. M., Wei, C., Ensor, J. E., Smolenski, D. J., Amos, C. I., Levin, B. and Berry, D. A. (2013). **Meta-analyses of colorectal cancer risk factors**. Cancer Causes Control *24*, 1207-1222, doi: 10.1007/s10552-013-0201-5.

Kharazmi, E., Fallah, M., Sundquist, K. and Hemminki, K. (2012). **Familial risk of early and late onset cancer: nationwide prospective cohort study**. Bmj *345*, e8076, doi: 10.1136/bmj.e8076.

Kharroubi, A. T. and Darwish, H. M. (2015). **Diabetes mellitus: The epidemic of the century**. World J Diabetes *6*, 850-867, doi: 10.4239/wjd.v6.i6.850.

Khaw, K. T., Wareham, N., Bingham, S., Luben, R., Welch, A. and Day, N. (2004). **Preliminary communication: glycated hemoglobin, diabetes, and incident colorectal cancer in men and women: a prospective analysis from the European prospective investigation into cancer-Norfolk study**. Cancer Epidemiol Biomarkers Prev *13*, 915-919.

Kono, S. (2004). **Secular trend of colon cancer incidence and mortality in relation to fat and meat intake in Japan**. Eur J Cancer Prev *13*, 127-132, doi: 10.1097/00008469-200404000-00006.

Kramer, H. U., Schottker, B., Raum, E. and Brenner, H. (2012). **Type 2 diabetes mellitus and colorectal cancer: meta-analysis on sex-specific differences**. Eur J Cancer *48*, 1269-1282, doi: 10.1016/j.ejca.2011.07.010.

Kuipers, E. J. and Spaander, M. C. (2018). **Personalized screening for colorectal cancer**. Nat Rev Gastroenterol Hepatol *15*, 391-392, doi: 10.1038/s41575-018-0015-8.

Kurtz, S. M. (1990). **Adherence to diabetes regimens: empirical status and clinical applications**. Diabetes Educ *16*, 50-59, doi: 10.1177/014572179001600112.

Lansdorp-Vogelaar, I., van Ballegooijen, M., Zauber, A. G., Habbema, J. D. and Kuipers, E. J. (2009). **Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening**. J Natl Cancer Inst *101*, 1412-1422, doi: 10.1093/jnci/djp319.

Larsen, M. B., Njor, S., Ingeholm, P. and Andersen, B. (2018). **Effectiveness of Colorectal Cancer Screening in Detecting Earlier-Stage Disease-A Nationwide Cohort Study in Denmark**. Gastroenterology *155*, 99-106, doi: 10.1053/j.gastro.2018.03.062.

Larsson, S., Orsini Nicola, Wolk, Alicja (2005). **Diabetes Mellitus and Risk of Colorectal Cancer: A Meta-Analysis**. J Natl Cancer Inst *97*, 1679-1687.

Larsson, S. C., Orsini, N. and Wolk, A. (2005). **Diabetes mellitus and risk of colorectal cancer: a meta-analysis**. J Natl Cancer Inst *97*, 1679-1687, doi: 10.1093/jnci/dji375.

Lascar, N., Brown, J., Pattison, H., Barnett, A. H., Bailey, C. J. and Bellary, S. (2018). **Type 2 diabetes in adolescents and young adults**. Lancet Diabetes Endocrinol *6*, 69-80, doi: 10.1016/S2213-8587(17)30186-9.

Lee, J. K., Liles, E. G., Bent, S., Levin, T. R. and Corley, D. A. (2014). **Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis**. Ann Intern Med *160*, 171, doi: 10.7326/M13-1484.

Leslie, A., Carey, F. A., Pratt, N. R. and Steele, R. J. (2002). **The colorectal adenoma-carcinoma sequence**. Br J Surg *89*, 845-860, doi: 10.1046/j.1365-2168.2002.02120.x.

Lew, J. B., St John, D. J. B., Xu, X. M., Greuter, M. J. E., Caruana, M., Cenin, D. R., He, E., Saville, M., Grogan, P., Coupe, V. M. H. and Canfell, K. (2017). **Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study**. Lancet Public Health *2*, e331-e340, doi: 10.1016/S2468-2667(17)30105-6.

Liang, P. S. A., JamesLadabaum, UriMartinez, Maria ElenaMurphy, Caitlin C.Schoen, Robert E.Shaukat, AasmaTinmouth, JillGupta, Samir et al. (2018). **Potential Intended and Unintended Consequences of Recommending Initiation of Colorectal Cancer Screening at Age 45 Years**. Gastroenterology *155*, 950-954.

Lichtenstein, G. R., Loftus, E. V., Isaacs, K. L., Regueiro, M. D., Gerson, L. B. and Sands, B. E. (2018). **ACG Clinical Guideline: Management of Crohn's Disease in Adults**. Am J Gastroenterol *113*, 481-517, doi: 10.1038/ajg.2018.27.

Liu, X., Hemminki, K., Forsti, A., Sundquist, K., Sundquist, J. and Ji, J. (2015). **Cancer risk in patients with type 2 diabetes mellitus and their relatives**. Int J Cancer *137*, 903-910, doi: 10.1002/ijc.29440.

Mauri, G., Sartore-Bianchi, A., Russo, A. G., Marsoni, S., Bardelli, A. and Siena, S. (2019). **Early-onset colorectal cancer in young individuals**. Mol Oncol *13*, 109-131, doi: 10.1002/1878-0261.12417.

McFerran, E., Kee, F. and Coleman, H. G. (2019). **Colorectal cancer screening: surely FIT for us too**. Frontline Gastroenterol, flgastro-2018-101125, doi: 10.1136/flgastro-2018-101125.

Megna, B. and Shaukat, A. (2019). **Is 45 the new 50? Controversies in lowering the screening age for colorectal cancer**. Expert Rev Gastroenterol Hepatol *13*, 915-917, doi: 10.1080/17474124.2019.1681973.

Mehraban Far, P., Alshahrani, A. and Yaghoobi, M. (2019). **Quantitative risk of positive family history in developing colorectal cancer: A meta-analysis**. World J Gastroenterol *25*, 4278-4291, doi: 10.3748/wjg.v25.i30.4278.

Mendis, S., Davis, S. and Norrving, B. (2015a). **Organizational Update The World Health Organization Global Status Report on Noncommunicable Diseases 2014; One More Landmark Step in the Combat Against Stroke and Vascular Disease**. Stroke *46*, E121-E122, doi: 10.1161/Strokeaha.115.008097.

Mendis, S., Davis, S. and Norrving, B. (2015b). **Organizational update: the world health organization global status report on noncommunicable diseases 2014; one more**

landmark step in the combat against stroke and vascular disease. Stroke *46*, e121-122, doi: 10.1161/STROKEAHA.115.008097.

Midthjell, K., Bjorndal, A., Holmen, J., Kruger, O. and Bjartveit, K. (1995). **Prevalence of known and previously unknown diabetes mellitus and impaired glucose tolerance in an adult Norwegian population. Indications of an increasing diabetes prevalence. The Nord-Trondelag Diabetes Study**. Scand J Prim Health Care *13*, 229-235, doi: 10.3109/02813439508996766.

Mollazadegan, K., Kugelberg, M., Montgomery, S. M., Sanders, D. S., Ludvigsson, J. and Ludvigsson, J. F. (2013). **A population-based study of the risk of diabetic retinopathy in patients with type 1 diabetes and celiac disease**. Diabetes Care *36*, 316-321, doi: 10.2337/dc12-0766.

Mukama, T., Fallah, M., Tian, Y., Sundquist, K., Sundquist, J., Brenner, H. and Kharazmi, E. (2020a). **Risk-tailored starting age of breast cancer screening based on women's reproductive profile: A nationwide cohort study**. Eur J Cancer *124*, 207-213, doi: 10.1016/j.ejca.2019.10.011.

Mukama, T., Kharazmi, E., Sundquist, K., Sundquist, J., Brenner, H. and Fallah, M. (2020b). **Familial risk of breast cancer by dynamic, accumulative, and static definitions of family history**. Cancer *126*, 2837-2848, doi: 10.1002/cncr.32815.

Mukama, T., Kharazmi, E., Xu, X., Sundquist, K., Sundquist, J., Brenner, H. and Fallah, M. (2020c). **Risk-Adapted Starting Age of Screening for Relatives of Patients With Breast Cancer**. JAMA Oncol *6*, 68-74, doi: 10.1001/jamaoncol.2019.3876.

Navarro, M., Nicolas, A., Ferrandez, A. and Lanas, A. (2017). **Colorectal cancer population screening programs worldwide in 2016: An update**. World Journal of Gastroenterology *23*, 3632-3642, doi: 10.3748/wjg.v23.i20.3632.

Patel, S. S. and Kilgore, M. L. (2015). **Cost Effectiveness of Colorectal Cancer Screening Strategies**. Cancer Control *22*, 248-258, doi: 10.1177/107327481502200219.

Peeters, P. J. H. L., Bazelier, M. T., Leufkens, H. G. M., De Vries, F. and De Bruin, M. L. (2015). **The risk of colorectal cancer in patients with type 2 Diabetes: Associations with treatment stage and obesity**. Diabetes Care *38*, 495-502, doi: 10.2337/dc14-1175.

Peterse, E. F. P., Meester, R. G. S., Siegel, R. L., Chen, J. C., Dwyer, A., Ahnen, D. J., Smith, R. A., Zauber, A. G. and Lansdorp-Vogelaar, I. (2018). **The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline**. Cancer *124*, 2964-2973, doi: 10.1002/cncr.31543.

Polonsky, W. H. and Henry, R. R. (2016). **Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors**. Patient Prefer Adherence *10*, 1299-1307, doi: 10.2147/PPA.S106821.

Rabeneck, L., Rumble, R. B., Thompson, F., Mills, M., Oleschuk, C., Whibley, A., Messersmith, H. and Lewis, N. (2012). **Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening**. Can J Gastroenterol *26*, 131-147, doi: 10.1155/2012/486328.

Rawla, P., Sunkara, T. and Barsouk, A. (2019). **Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors**. Prz Gastroenterol *14*, 89-103, doi: 10.5114/pg.2018.81072.

Reeves, P., Doran, C., Carey, M., Cameron, E., Sanson-Fisher, R., Macrae, F. and Hill, D. (2019). **Costs and Cost-Effectiveness of Targeted, Personalized Risk Information to Increase Appropriate Screening by First-Degree Relatives of People With Colorectal Cancer**. Health Educ Behav, 1090198119835294, doi: 10.1177/1090198119835294.

Robsahm, T. E., Aagnes, B., Hjartaker, A., Langseth, H., Bray, F. I. and Larsen, I. K. (2013). **Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies**. Eur J Cancer Prev *22*, 492-505, doi: 10.1097/CEJ.0b013e328360f434.

Rojas, L. B. and Gomes, M. B. (2013). **Metformin: an old but still the best treatment for type 2 diabetes**. Diabetol Metab Syndr *5*, 6, doi: 10.1186/1758-5996-5-6.

Rubin, D. T., Ananthakrishnan, A. N., Siegel, C. A., Sauer, B. G. and Long, M. D. (2019). **ACG Clinical Guideline: Ulcerative Colitis in Adults**. Am J Gastroenterol *114*, 384-413, doi: 10.14309/ajg.0000000000000152.

Samadder, N. J., Smith, K. R., Hanson, H., Pimentel, R., Wong, J., Boucher, K., Ahnen, D., Singh, H., Ulrich, C. M., Burt, R. W. and Curtin, K. (2015). **Increased Risk of Colorectal Cancer Among Family Members of All Ages, Regardless of Age of Index Case at Diagnosis**. Clinical Gastroenterology and Hepatology *13*, 2305-2311.e2302, doi: https://doi.org/10.1016/j.cgh.2015.06.040.

Saraei, P., Asadi, I., Kakar, M. A. and Moradi-Kor, N. (2019). **The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances**. Cancer Manag Res *11*, 3295-3313, doi: 10.2147/CMAR.S200059.

Schoen, R. E., Razzak, A., Yu, K. J., Berndt, S. I., Firl, K., Riley, T. L. and Pinsky, P. F. (2015). **Incidence and mortality of colorectal cancer in individuals with a family history of colorectal cancer**. Gastroenterology *149*, 1438-1445 e1431, doi: 10.1053/j.gastro.2015.07.055.

Schreuders, E. H., Ruco, A., Rabeneck, L., Schoen, R. E., Sung, J. J., Young, G. P. and Kuipers, E. J. (2015). **Colorectal cancer screening: a global overview of existing programmes**. Gut *64*, 1637-1649, doi: 10.1136/gutjnl-2014-309086.

Siddiqui, A. A., Maddur, H., Naik, S. and Cryer, B. (2008). **The association of elevated HbA1c on the behavior of adenomatous polyps in patients with type-II diabetes mellitus**. Dig Dis Sci *53*, 1042-1047, doi: 10.1007/s10620-007-9970-6.

Silla, I. O., Rueda, D., Rodriguez, Y., Garcia, J. L., de la Cruz Vigo, F. and Perea, J. (2014). **Early-onset colorectal cancer: a separate subset of colorectal cancer**. World J Gastroenterol *20*, 17288-17296, doi: 10.3748/wjg.v20.i46.17288.

Steele, R. J., McDonald, P. J., Digby, J., Brownlee, L., Strachan, J. A., Libby, G., McClements, P. L., Birrell, J., Carey, F. A., Diament, R. H., Balsitis, M. and Fraser, C. G. (2013). **Clinical outcomes using a faecal immunochemical test for haemoglobin as a first-line test in a national programme constrained by colonoscopy capacity**. United European Gastroenterol J *1*, 198-205, doi: 10.1177/2050640613489281.

Tao, S., Hoffmeister, M. and Brenner, H. (2014). **Development and validation of a scoring system to identify individuals at high risk for advanced colorectal neoplasms who should undergo colonoscopy screening**. Clin Gastroenterol Hepatol *12*, 478-485, doi: 10.1016/j.cgh.2013.08.042.

Taylor, D. P., Burt, R. W., Williams, M. S., Haug, P. J. and Cannon–Albright, L. A. (2010). **Population-Based Family History–Specific Risks for Colorectal Cancer: A Constellation Approach**. Gastroenterology *138*, 877-885, doi: https://doi.org/10.1053/j.gastro.2009.11.044.

Taylor, D. P., Stoddard, G. J., Burt, R. W., Williams, M. S., Mitchell, J. A., Haug, P. J. and Cannon-Albright, L. A. (2011). **How well does family history predict who will get colorectal cancer? Implications for cancer screening and counseling**. Genet Med *13*, 385-391, doi: 10.1097/GIM.0b013e3182064384.

Thunander, M., Petersson, C., Jonzon, K., Fornander, J., Ossiansson, B., Torn, C., Edvardsson, S. and Landin-Olsson, M. (2008). **Incidence of type 1 and type 2 diabetes in adults and children in Kronoberg, Sweden**. Diabetes Res Clin Pract *82*, 247-255, doi: 10.1016/j.diabres.2008.07.022.

Tian, Y., Kharazmi, E., Brenner, H., Xu, X., Sundquist, K., Sundquist, J. and Fallah, M. (2020). **Calculating the Starting Age for Screening in Relatives of Patients With Colorectal Cancer Based on Data From Large Nationwide Data Sets**. Gastroenterology *159*, 159-168 e153, doi: 10.1053/j.gastro.2020.03.063.

Tian, Y., Kharazmi, E., Sundquist, K., Sundquist, J., Brenner, H. and Fallah, M. (2019). **Familial colorectal cancer risk in half siblings and siblings: nationwide cohort study**. BMJ *364*, l803, doi: 10.1136/bmj.l803.

Toma, M., Belusica, L., Stavarachi, M., Apostol, P., Spandole, S., Radu, I. and Cimponeriu, D. (2012). **Rating the environmental and genetic risk factors for colorectal cancer**. J Med Life *5*, 152-159.

Triantafillidis, J. K., Nasioulas, G. and Kosmidis, P. A. (2009). **Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies**. Anticancer Res *29*, 2727-2737.

Vasen, H. F., Watson, P., Mecklin, J. P. and Lynch, H. T. (1999). **New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC**. Gastroenterology *116*, 1453-1456, doi: 10.1016/s0016-5085(99)70510-x.

Vu, H. T., Ufere, N., Yan, Y., Wang, J. S., Early, D. S. and Elwing, J. E. (2014). **Diabetes mellitus increases risk for colorectal adenomas in younger patients**. World J Gastroenterol *20*, 6946-6952, doi: 10.3748/wjg.v20.i22.6946.

Vuik, F. E., Nieuwenburg, S. A., Bardou, M., Lansdorp-Vogelaar, I., Dinis-Ribeiro, M., Bento, M. J., Zadnik, V., Pellise, M., Esteban, L., Kaminski, M. F., Suchanek, S., Ngo, O., Majek, O., Leja, M., Kuipers, E. J. and Spaander, M. C. (2019). **Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years**. Gut *68*, 1820-1826, doi: 10.1136/gutjnl-2018-317592.

Walter, L. C., Wender, R. C., Church, T. R., Brooks, D., Fontham, E. T. H., Manassaram-Baptiste, D., Wolf, A. M. D., Andrews, K. S., Siegel, R. L., Flowers, C. R., Oeffinger, K. C., LaMonte, S. J., McKenna, M. T., Etzioni, R., Smith, R. A., Brawley, O. W., Shih, Y.-C. T., Guerra, C. E. and Fedewa, S. A. (2018). **Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society**. CA Cancer J Clin *68*, 250-281, doi: 10.3322/caac.21457.

Wilkins, T., McMechan, D., Talukder, A. and Herline, A. (2018). **Colorectal Cancer Screening and Surveillance in Individuals at Increased Risk**. Am Fam Physician *97*, 111-116.

Wolf, A. M. D., Fontham, E. T. H., Church, T. R., Flowers, C. R., Guerra, C. E., LaMonte, S. J., Etzioni, R., McKenna, M. T., Oeffinger, K. C., Shih, Y. T., Walter, L. C., Andrews, K. S., Brawley, O. W., Brooks, D., Fedewa, S. A., Manassaram-Baptiste, D., Siegel, R. L., Wender, R. C. and Smith, R. A. (2018). **Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society**. CA Cancer J Clin *68*, 250-281, doi: 10.3322/caac.21457.

World Health Organization (2019). **World health statistics overview 2019: monitoring health for the SDGs, sustainable development goals**, World Health Organization.

Wu, Y., Ding, Y., Tanaka, Y. and Zhang, W. (2014). **Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention**. Int J Med Sci *11*, 1185-1200, doi: 10.7150/ijms.10001.

Zhao, Z., Feng, Q., Yin, Z., Shuang, J., Bai, B., Yu, P., Guo, M. and Zhao, Q. (2017). **Red and processed meat consumption and colorectal cancer risk: a systematic review and meta-analysis**. Oncotarget *8*, 83306-83314, doi: 10.18632/oncotarget.20667.

Zhou, X. H., Qiao, Q., Zethelius, B., Pyorala, K., Soderberg, S., Pajak, A., Stehouwer, C. D., Heine, R. J., Jousilahti, P., Ruotolo, G., Nilsson, P. M., Calori, G., Tuomilehto, J. and Group, D. S. (2010). **Diabetes, prediabetes and cancer mortality**. Diabetologia *53*, 1867-1876, doi: 10.1007/s00125-010-1796-7.

7 PUBLICATIONS

Ali Khan U, Fallah M, Tian Y, Sundquist K, Sundquist J, Brenner H, Kharazmi E. Personal History of Diabetes as Important as Family History of Colorectal Cancer for Risk of Colorectal Cancer: A Nationwide Cohort Study. ***Am J Gastroenterol*** 2020 ;115(7):1103-1109, doi: 10.14309/ajg.0000000000000669.

8 CURRICULUM VITAE

PERSONAL INFORMATION

First name: Uzair

Last name: Ali Khan

Year of birth: 1994

Nationality: Canadian

Address: National Center for Tumor Diseases (NCT), German Cancer Research Center (DKFZ), Im Neuenheimer Feld 581, 69120, Heidelberg, Germany

E-mail: uzair.alikhan@nct-heidelberg.de; alikhanuzair1@gmail.com

EDUCATION

Oct. 2017-present — **PhD Student – Risk Adapted Prevention Group, Division of Preventive Oncology, National Center for Tumor Diseases (NCT), German Cancer Research Center (DKFZ), Heidelberg, Germany**

Field: Cancer epidemiology, risk-adapted cancer prevention,

Sep. 2016 - Aug. 2017 — **MSc– Social, Genetic and Developmental Psychiatry (SGDP) Center, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), Kings College London, London, UK**

Field: Genetics, Environmental and Development of Psychiatric disorders

Sep. 2012 - Jun. 2016 — **HBSc – University of Toronto Mississauga, Mississauga, Canada**

Field: Biology for health sciences, psychology, genetics

PUBLICATIONS

Ali Khan U, Fallah M, Tian Y, Sundquist K, Sundquist J, Brenner H, Kharazmi E. Personal History of Diabetes as Important as Family History of Colorectal Cancer for Risk of Colorectal Cancer: A Nationwide Cohort Study. ***Am J Gastroenterol*** 2020 ;115(7):1103-1109 (impact factor 10).

MANUSCRIPTS SUBMITTED

Ali Khan U, Fallah M, Sundquist K, Sundquist J, Brenner H, Kharazmi E. Risk-adapted colorectal cancer screening in patients with diabetes mellitus: A Nationwide Cohort Study. 2020.

CONFERENCE ABSTRACTS

1. **Ali Khan U,** Fallah M, Sundquist K, Sundquist J, Brenner H, Kharazmi E. Elevated colorectal cancer risk and personalized colorectal cancer screening for patients with diabetes mellitus. *The 2020 National Center of Tumor Diseases (NCT) Retreat*, March 2020, Dresden, Germany. Poster presentation.

2. **Ali Khan U,** Tian Y, Sundquist K, Sundquist J, Brenner H, Fallah M, Kharazmi E. Diabetes mellitus patients as strong candidates for earlier risk-adapted colorectal cancer screening. *PhD Poster Presentation,* November 2019, Heidelberg, Germany. Poster presentation.

3. **Ali Khan U,** Tian Y, Sundquist K, Sundquist J, Brenner H, Fallah M, Kharazmi E. Risk-adapted colorectal cancer screening in patients with diabetes mellitus. *12th International PhD Student Cancer Conference,* June 2019, Amsterdam, Netherlands. Poster presentation.

4. **Ali Khan U,** Tian Y, Sundquist K, Sundquist J, Brenner H, Fallah M, Kharazmi E. Risk-adapted colorectal cancer screening in patients with diabetes mellitus. *1st German Cancer Research Conference,* February 2019, Heidelberg, Germany. Poster presentation.

HONORS AND AWARDS

2017	Helmholtz International Graduate School Stipend
2013	Secondary School Research Experience Program (SSREP) Winner, Qatar National Research Fund (QNRF)

PRESS RELEASES

2020	Reuters/Medscape https://www.medscape.com/viewarticle/932247
	National Center for Tumor Diseases (NCT), Heidelberg, Germany https://www.nct-heidelberg.de/en/the-nct/newsroom/news/details/diabetes-mellitus-a-risk-factor-for-early-colorectal-cancer.html

RESEARCH PRESENTATIONS

2017 - 2019	Weekly, Risk Adapted Prevention (RAD) group meeting, Heidelberg
2017 - 2020	Yearly, Division of Preventive Oncology Meeting, Heidelberg
2017 - 2020	Yearly, Thesis Advisory Committee Meeting, Heidelberg

SKILLS AND LANGUAGES

Skills	Data analysis, colorectal cancer epidemiology, colorectal cancer screening, genetics, psychiatry, statistics
Language	English (*native*), Urdu (*fluent*), Hindi (*fluent*), German (*beginner*), Spanish (*beginner*)
Statistical programming	SAS (*proficient*), SPSS, Plink, R

MEMBERSHIP

2018 - present	American Society of Clinical Oncology (ASCO)
2018 - present	European Association for Cancer Research (EACR)

9 ACKNOWLEDGMENTS

Throughout my PhD I have received support and guidance from many different sources. I would like to thank Prof. Hermann Brenner for offering me the opportunity to conduct research at such a reputable institution. His comments and experience were motivational and instrumental during my PhD. I would like to sincerely thank my direct supervisor, Dr. Mahdi Fallah, for seeing potential in me and allowing me the opportunity to work in his Risk Adapted Prevention Group on such a clinically significant topic for someone young in his scientific career. He continually motivated me and supported my research goals with valuable guidance to help shape me into a better scientist. His attention, knowledge, and tips for success were invaluable during the last three years and will continue to be throughout my career. I would also like to thank our group coleader Dr. Elham Kharazmi, who guided me and worked closely with me during the preparation of my first publications, which will remain especially memorable for me. Their comments and advice were essential for the development of my confidence and persistence as a young scientist.

I would like to give a special thanks to Dr. Yu Tian, Trasias Mukama and Xing Xu. Their selflessness and companionship during our PhD journey were enriching socially and scientifically. Our successes motivated each other and I was fortunate to learn from such bright minds.

Finally, I would like to thank my family, namely my parents Arif and Nazima, who always encouraged my educational pursuits and believed in me. My PhD would not have been possible without their love and support.

10 EIDESSTATTLICHE VERSICHERUNG

1. Bei der eingereichten Dissertation zu dem Thema

Colorectal cancer risk prediction and risk-adapted colorectal cancer screening in patients with diabetes mellitus

handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

3. Die Arbeit oder Teile davon habe ich bislang nicht an einer Hochschule des In- oder Auslands als Bestandteil einer Prüfungs- oder Qualifikationsleistung vorgelegt.

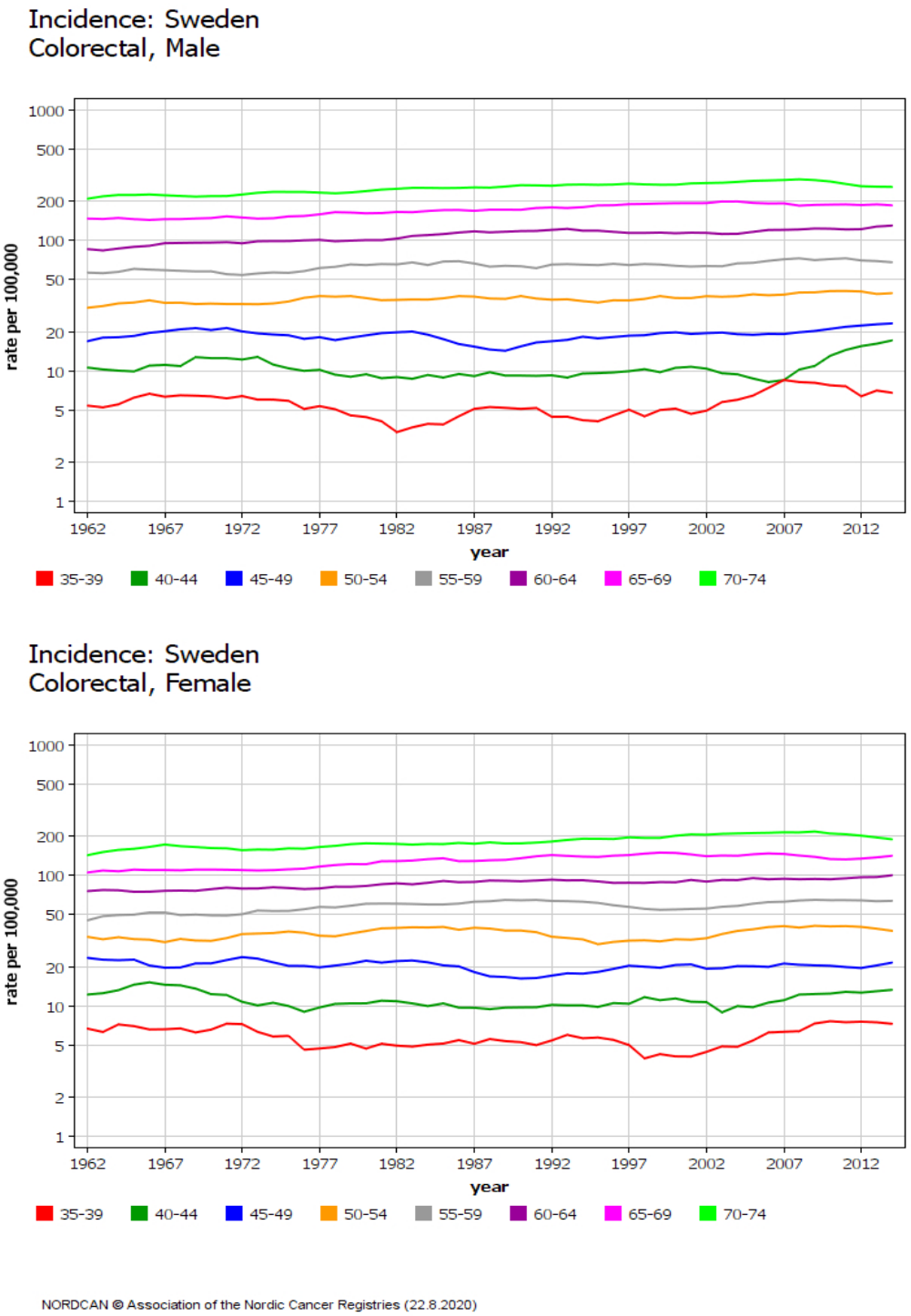
4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

5. Die Bedeutung der eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Versicherung sind mir bekannt. Ich versichere an Eides statt, dass ich nach bestem Wissen die reine Wahrheit erklärt und nichts verschwiegen habe.

Ort und Datum Unterschrift

11 APPENDIX

11.1 Supplementary Figure



Supplementary Figure 1. Age-specific incidence of colorectal cancer in Sweden over time (1962-2015) by sex