**Supplementary materials**

**Personal history of diabetes as important as family history of colorectal cancer for risk of colorectal cancer: A nationwide cohort study**

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**eMethods**

In this study, we reported standard incidence ratios (SIRs), which could be considered comparable to hazards ratios (HRs) from Cox regression because previous studies have shown that both methods result in similar estimates that are also similar to risk ratios (RRs) calculated by Poisson regression or even negative binomial regression. For example, regardless of the method of calculation, familial risk of colorectal cancer (CRC) was around 1.9-fold in the Swedish family-cancer datasets [HR=1.9 (1), SIR=1.9 (2), average RR for an affected parent or an affected sibling=1.9 by both Poisson regression and negative binomial regression (3)] and also in the Utah Population DataBase [HR=1.9 (4); SIR=1.9 (5)].

**eResults**

We observed that the lifetime cumulative risk (age 0-79 years) for those with a diabetes mellitus (DM) diagnosis at any age was higher (7.2%, 95% CI: 7.2%-7.2%) than for those without a DM diagnosis (3.8%, 95% CI: 3.8%-3.8%) and for those with only one FDR with CRC (6.3%, 95% CI: 6.3%-6.4%; **Table 2** in the main manuscript). The highest absolute risk was for those with a DM diagnosis at any age and at least two first-degree relatives (FDRs; 20%, 95% CI: 10.8%-28.3%). The lifetime CRC risk when one only had two or more FDRs with CRC and no DM diagnosis was 11% (95% CI: 9.9%-12.3%).

**eDiscussion**

A limitation of our study was lack of data on treatment of DM. However, our findings showed that patients with no family history of CRC who received a DM diagnosis in their 40s had a much higher risk of early-onset CRC diagnosed before age 50 (SIR=3.6, 95% CI: 2.8-4.5) than those with a DM diagnosis before age 30 (SIR=1.2, 95% CI: 0.8-1.6). Metformin is generally the first line of treatment for patients with DM type 2 (6), and despite the established protective effect of metformin against cancer, including CRC (7-9), we found elevated risk of CRC before age 50 in type 2 diabetic patients. Therefore, the true risk without metformin could have been even higher. Moreover, if insulin, which is the first line of treatment for type 1 DM and has association with increased risk of cancer (10), was the mediator of the association we found between DM and CRC, we would expect higher CRC risk in type 1 and lower risk in type 2 DM (due to metformin), which was not the case based on our large cohort study.

Information on insulin use or end-organ manifestations of DM was lacking in this study. However, in previous studies greater DM severity, established by hemoglobin A1C (HgbA1C) concentration, a measure of DM control, and administration of insulin therapy, has been associated with CRC risk. In a prospective cohort study, a 1.3-fold increase in CRC risk was reported with every 1% increase in HgbA1C concentrations (11). Other studies found that patients with HgbA1C ≥7.5% had developed CRC at younger ages and had increased adenomas (12, 13). Diabetic patients are also more prone to cardiovascular events (14) and aspirin is recommended to diabetic patients at high risk of coronary heart disease (15). Aspirin is also associated with reduced risk of CRC (16). It is thus unlikely that aspirin use had any confounding effect on the association we found between DM and early-onset CRC risk because it is used mostly after age 50 and it could have only diluted the association that we found, if any.

An additional potential limitation was that we did not have information on colonoscopy use within the cohort to check whether diabetic patients more frequently access health care and screening than those without the disease. It is important to note that in Sweden there is no nationwide CRC screening program in place apart from a pilot phase screening in Stockholm Gotland region (17). However, we have performed a sensitivity analysis by calendar period of diagnosis before and after CRC screening era in Sweden, which showed no substantial change in familial risk of CRC (18). Detection bias due to family history of CRC, regardless, does not affect the main finding of our study, which proposes DM personal history is a risk factor for early-onset CRC. In addition, the investigation into the association between DM and CRC (which is not in any CRC screening guideline) is fairly young in comparison to the established association between CRC and family history (which is already in CRC screening guidelines), making it unlikely that patients with DM being referred to colonoscopy more often than those with a family history. Moreover, there is no clear evidence that DM associates with colonoscopy. In fact, diabetic patients are known for being poor at adhering to their DM treatment regimen (19). Studies have observed that self-care in diabetes management is not up to standard in approximately 45% of patients with type 2 DM (20). This makes it unlikely that patients with type 2 DM would be motivated to be regular in CRC screening (let alone earlier screening than the general population) when they struggle to even adhere to treatment recommendations for their disease.

We also identified families that likely had patients with hereditary nonpolyposis colorectal cancer (HNPCC) based on Amsterdam II criteria. Removal of these individuals did not alter CRC familial risk estimates (18). Irrespective of this, the major findings of this study were involving sporadic CRC and familial cases with only one diagnosed FDR, making it highly unlikely that HNPCC cases affected the observed risk estimates since Amsterdam II criteria specifies that a person should have at least three relatives with CRC to qualify for HNPCC testing. We were also able to exclude patients with inflammatory bowel disease (IBD) in our sensitivity analysis and ensured that IBD as a CRC risk factor was not confounding the association observed between DM and CRC.

We also did not have data on lifestyle factors such as diet or physical activity, but we adjusted our results for sex, age, calendar period, socioeconomic status, and residential area to reconcile to some extent the effect of lifestyle factors on the association between DM and CRC risk and also the advantageous access to healthcare in large cities. In addition, we had information on hospitalization for chronic obstructive pulmonary diseases (COPD, as a surrogate to heavy smoking), alcoholism, and obesity; after further adjustment for these factors, our risk estimates did not change substantially.

One way to check whether the association between DM and CRC is due to increased access of diabetic patients to health care or not is to see if another chronic medical condition similar to DM like hypertension, which would not normally be associated with CRC but does associate with increased access to health care, has an association with increased CRC incidence (supporting a detection bias). We did not have data on hypertension, but a study involving several cohorts from Sweden and other Scandinavian countries showed a very weak or no association between hypertension and colon or anorectal cancer risk [in men (1.1-fold per 10 mm Hg increment in mid-blood pressure and in women (0.95 to1.03-fold)], suggesting that detection bias could not have a major role in our results (21). If the detection bias was the cause of the DM association with CRC risk, one would also expect a similar strong association with hypertension in both sexes, especially in women who seem to be more health conscious than men (22).

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**Supplementary Table S1: Risk of colorectal cancer (CRC) by type of diabetes mellitus (DM) in period 1997-2015**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Follow-up period** | **Relative with CRC** | **DM personal history by age at DM diagnosis (years)** | **DM** | **Age at CRC diagnosis (years)** | | | | | | | | | | | | | | |
| **All ages** | | | |  | **<50** | | | |  | **≥50** | | | | |
| **Obs** | **SIR** | **95% CI** | |  | **Obs** | **SIR** | **95% CI** | |  | **Obs** | **SIR** | **95% CI** | |
| **1997-2015** | **No** | **No** | **No** | 72,514 | Reference | | |  | 4,190 | Reference | | |  | 68,324 | Reference | | |
|  |  | **<50** | **Type 1** | 71 | 1.2 | 0.9 | 1.5 |  | 14 | **1.0** | 0.6 | 1.7 |  | 57 | **1.2** | 0.9 | 1.6 |
|  |  |  | **Type 2** | 94 | **1.5** | 1.2 | 1.8 |  | 26 | **3.5** | 2.3 | 5.1 |  | 68 | 1.2 | 0.9 | 1.5 |
|  | **1 FDR** |  | **Type 1** | 5 | 1.4 | 0.5 | 3.3 |  | 4 | **8.6** | 2.3 | 21.0 |  | 1 | **0.3** | 0.0 | 1.8 |
|  |  |  | **Type 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; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; FDR = First-degree relative; Bold values indicate significant risks.

**Supplementary Table S2: Standardized incidence ratio (SIR) of colorectal cancer by personal history of diabetes mellitus (DM), family history of CRC, and age at diagnosis of DM by CRC subsite**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **CRC subsite** | **Relative with CRC** | **DM personal history by age at DM diagnosis (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** | 2,307 | **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** | 1,699 | **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** | 2,027 | **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; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; Distal colon = Descending colon and sigmoid colon; FDR = First-degree relative; Bold values indicate significant risks.

**Supplementary Table S3: Risk of colorectal cancer (CRC) by type of diabetes mellitus (DM) in those without any inflammatory bowel disease (IBD)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **IBD status** | **Relative with CRC** | **DM personal history by age at DM diagnosis (years)** | **Age at CRC diagnosis (years)** | | | | | | | | | | | | | | | | | | | |
| **All ages** | | | | |  | | **<50** | | | | |  | | **≥50** | | | | | |
| **Obs** | **SIR** | **95% CI** | |  | | **Obs** | | **SIR** | **95% CI** | |  | | **Obs** | | **SIR** | **95% CI** | |
| **No** | **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 |

IBD = Inflammatory bowel disease; CRC = Colorectal cancer; DM = Diabetes mellitus; Obs = Observed number of colorectal cancer cases in each risk group; SIR = Standardized incidence ratio; FDR = First-degree relative; Bold values indicate significant risks.