Risk of colorectal cancer in patients with acute myocardial infarction and stroke: A nationwide cohort study

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Running title: Myocardial infarction and stroke and colorectal cancer risk

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Key words: Atherosclerosis; Colorectal neoplasm; myocardial infarction; stroke

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Number of figures: One
**Abstract**

**Background:** An association between colorectal cancer (CRC) and acute myocardial infarction (AMI) and stroke has been suggested, but evidence is conflicting.

**Method:** We conducted a population-based cohort study (1978-2010) of the association between AMI/stroke and CRC by linking nationwide Danish registries. We calculated standardized incidence ratios (SIRs) of CRC after AMI/stroke as the ratios of observed to expected incidence.

**Results:** 297,523 AMI patients (median age 69.4, 64% men) were followed for a median of 3.1 years (range 0-33 years) and 4,387 developed CRC (SIR=1.08, 95% CI: 1.05-1.11, p<0.001). In the first year of follow-up the SIR was 1.85 (95% CI: 1.73-1.98, p<0.001) while it was 0.98 (95% CI: 0.95-1.02, p=0.318) in the second and subsequent years. We followed 246,998 stroke patients (median age 72.4, 52% men) for a median of 2.9 years (range 0-33 years) and 3,035 developed CRC (SIR 1.04, 95% CI: 1.00-1.07, p=0.053). In the first year of follow-up the SIR was 1.42 (95% CI: 1.31-1.53, p<0.001) while it was 0.96 (95% CI: 0.93-1.00, p=0.072) thereafter. We found no difference between the SIRs for ischemic and hemorrhagic stroke. The increased one-year relative risks for AMI and stroke corresponded to a 0.3% absolute risk.

**Conclusion:** Our findings reflect detection of occult cancer at the time of the vascular event. The lack of increased risk after one year suggests that an association based on shared risk factors or chronic inflammation is unlikely.

**Impact:** In AMI/stroke patients the diagnostic workup including screening for CRC should follow that of the general population.
**Introduction**

In westernized countries the lifetime risk of acute myocardial infarction (AMI) and stroke is 30-40% and 15-20% (1,2), respectively, while the lifetime risk of colorectal cancer (CRC) is approximately 5% (3). The early development of all these diseases seems to involve chronic inflammation, which is known to be crucial in the atherosclerotic process, particularly in unstable plaques (4,5) and may also be important in CRC carcinogenesis (6-11). AMI, stroke, and CRC also share some risk factors such as smoking, obesity, metabolic syndrome, and diabetes, all of which have been associated with systemic inflammation (12-14). Evidence of an association between atherosclerosis and colorectal neoplasia was recently emphasized by a small cross sectional study from Hong Kong showing a higher prevalence of advanced neoplasia in patients with proven coronary artery disease (>50% stenosis in any one of the major coronary arteries) than among patients whose angiograms did not show coronary artery disease (18.4% vs. 8.7%) (15). Nonetheless, the nature of the association is not clear. Existing studies of the relation between coronary artery disease or AMI/stroke and CRC have been conflicting, with some confirming the association (6,7,15-19), and others not finding it (20-24). The presence of atherosclerosis (a chronic pathological condition) is conceptually different than the occurrence of AMI or stroke (acute clinical events) (6,7,15,22) characterized by unstable plaques prone to rupture (25). Therefore studies of atherosclerosis may not be generalizable to patients with AMI/stroke.

If an association between AMI/Stroke and CRC really exists, it may foster the understanding of the aetiology of these diseases and could also be relevant for screening and surveillance for patients with these common and lethal diseases. Therefore, we utilized the nationwide population-based Danish databases to conduct the largest cohort study of CRC risk in AMI and stroke patients to date.
**Materials and methods**

We conducted this cohort study in the setting of the entire Danish population, which, in the study period January 1, 1978 - December 31, 2010, included 8.0 million people. The Danish National Health Service provides tax-funded medical care for all Danish residents, and maintains clinical databases describing the care provided. All Danish residents are assigned a unique 10-digit civil registration number by the Civil Registration System at birth or immigration, an identifier routinely used to link patients across the various Danish medical databases (26).

**Data sources and cohort**

We identified patients with AMI and stroke (≥30 years of age) by extracting relevant inpatient diagnoses from the National Registry of Patients (NRP), which has tracked all non-psychiatric hospitalizations in Denmark since 1977 and outpatient hospital contacts since 1995. The NRP records the civil registration number, dates of admission and discharge, and up to 20 discharge diagnoses, coded by physicians according to the International Classification of Diseases (ICD) (8th revision until the end of 1993 and 10th revision thereafter). Patients were enrolled in the study cohort if they had ICD codes corresponding to AMI or stroke (see Supplementary table S1). From the NRP we also extracted information on comorbid diseases diagnosed before or at the time of AMI or stroke diagnosis: diabetes, chronic obstructive pulmonary disease, rheumatoid disease, venous thromboembolism, obesity, hyperlipidemia, hypertension, atrial fibrillation, and transient ischemic attack (see Supplementary table S1). Finally, we included information on colonoscopies conducted prior to or on the date of the AMI/stroke. Of note, there is no population CRC screening in Denmark.

Using the civil registration number, we linked all members of the study cohort to the nationwide Danish Cancer Registry (DCR). The DCR has recorded all incident malignant neoplasms in Denmark since 1943. Its data include month and year of cancer diagnosis, and tumour spread at diagnosis (localized, regional, metastasized, or unknown). Cancers are classified according to ICD-10 codes (see Supplementary table S1). Patients diagnosed with any cancer before date of AMI and stroke were excluded.
Statistical analyses

We calculated the proportion of AMI and stroke patients within categories of demographic characteristics. The follow-up period for cancer occurrence began at the date of AMI and stroke diagnosis and ended at the date of CRC diagnosis, emigration, death, or 31 December 2010, whichever came first. The number of CRC cases observed among the study subjects was compared to the number expected on the basis of cancer rates calculated from the DCR. The expected number was calculated by multiplying the number of person-years of observation for study subjects by the national CRC incidence rates for each sex in 1-year age groups. Standardized incidence ratios (SIRs) were calculated as the ratio of the observed to the expected number of CRC cases (27). The statistical methods assumed that the observed number of cases in any specific category followed a Poisson distribution. Confidence intervals (CIs) for the SIR were calculated based on Byar’s approximation; exact confidence limits were used if the observed number of cases was less than 10.

We calculated SIRs for AMI and stroke patients overall, and for ischemic and hemorrhagic stroke patients separately. SIRs were stratified by sex, age, year of AMI/stroke diagnosis, and follow-up interval (first year of follow-up and second and subsequent years). In a subanalysis, we further categorized follow-up into 0-<6 months, 6-<12 months, 12-<24 months, 2-<5 years, 5-<10 years, 10-<15 years, and 15+ years. We also calculated SIRs in AMI and stroke patients with prior colonoscopy and coexistence of each of the comorbid diseases listed above. As for the overall analysis, these analyses were standardized according to sex, age, and calendar period. In a sub-analysis we calculated SIRs for colon and rectal cancers separately. In addition, we estimated absolute risks of CRC one, five, and 10 years after AMI and stroke diagnosis, treating death as competing risk (28).

Finally, we evaluated whether CRCs were diagnosed at an earlier or later stage in AMI or stroke patients than among CRC patients without these diseases. We did this by matching each CRC patient with a history of AMI or stroke by age, gender, and year of diagnosis to five CRC patients from the general population.
without history of AMI/stroke. We calculated proportions ratios and associated 95% CIs by dividing the proportion of localized, regional, and metastatic CRCs in patients with an AMI and stroke history with the proportions in matched CRC patients with no history of these diseases.
Results

Acute Myocardial Infarction

We identified 297,523 AMI patients, of whom 64% were men (Table 1). They had a median age at diagnosis of 69.6 years and were followed for a median of 3.1 years (range 0-33 years). A total of 4,387 AMI patients were recorded with a CRC diagnosis during follow-up, corresponding to an overall SIR for CRC of 1.08 (95% CI: 1.05-1.11) (Table 2). Women and individuals older than 80 years at the time of AMI had the highest SIRs. Concomitant diabetes, chronic obstructive pulmonary disease, obesity, hypertension, or atrial fibrillation was associated with particularly increased risk of CRC. A total of 7,750 (2.6%) patients had a colonoscopy prior to CRC diagnosis and their SIR of CRC was similar to the overall result. The SIR for 1978-1983 was 1.35 (95% CI: 1.21-1.51) while it was close to 1.0 in the most recent periods.

The SIR for CRC was increased only in the first year after AMI diagnosis (1.85, 95% CI: 1.73-1.98) versus 0.98 (95% CI: 0.95-1.02) in the second and subsequent years) (Figure 1). The SIRs in the first year of follow-up were increased in both men (1.72, 95% CI: 1.57-1.87) and women (2.11, 95% CI: 1.89-2.35) throughout the study period (results by year not shown).

Even though the SIR was increased in the first year after AMI diagnosis, the absolute risk of CRC after AMI was only 0.3% (95% CI: 0.3%-0.3%). By five and 10 years after diagnosis, the absolute risk had increased only to 0.8% (95% CI: 0.7%-0.8%) and 1.2% (95% CI: 1.1%-1.3%).

Comparing the 840 CRC patients diagnosed within one year after AMI to 4,200 matched CRC patients without history of AMI, the proportion ratios were 46%/41% = 1.1 (95% CI: 1.0-1.2) for localized CRC, 26%/27% = 0.9 (95% CI: 0.8-1.1) for regional spread CRC, and 17%/20% = 0.8 (95% CI: 0.7-1.0) for metastatic CRC. For CRCs diagnosed more than one year after an AMI and their matched comparators, the corresponding proportion ratios were 43%/41% = 1.1 (95% CI: 1.0-1.1), 26%/26% =1.0 (95% CI: 0.9-1.1), and 19%/21% = 0.9 (95% CI: 0.8-1.0), respectively.
Stroke

A total of 243,998 stroke patients, with a median age at diagnosis of 72.8 years, were followed for a median of 2.9 years (range 0-33 years); 52% were men (Table 1). During follow-up, 3,035 patients had a CRC diagnosis, corresponding to an overall SIR of 1.04 (95% CI: 1.00-1.07) (Table 2). The SIRs were similar in men and women and over calendar periods, although the SIR decreased with increasing age. As expected, the coexistence of chronic obstructive pulmonary disease, obesity, or atrial fibrillation were associated with increased risk of CRC. Among the 10,716 (4.3%) patients with colonoscopy prior to stroke diagnosis, the SIR was similar to the overall result.

As for AMI patients, the SIR of CRC in stroke patients was increased in the first year after diagnosis (1.42, 95% CI: 1.31-1.53), but not in the second and subsequent years (0.96, 95% CI: 0.93-1.00) (Figure 1). The SIR of CRC within the first year of diagnosis was increased in both men (1.45, 95% CI: 1.31-1.60) and women (1.37, 95% CI: 1.22-1.54) throughout the study period (results by year not shown).

The sub-analysis for ischemic and haemorrhagic stroke patients is shown in the supplementary Table S2 and revealed no major differences in SIRs.

The absolute risk of CRC one year after a stroke diagnosis was 0.3% (95% CI: 0.3%-0.3%); the five and 10 year absolute risks were 0.8% (95% CI: 0.8%-0.9%) and 1.3% (95% CI: 1.2%-1.3%), respectively.

Finally, comparing the 663 CRC patients diagnosed within one year after stroke to 3,314 matched CRC patients without history of stroke, the proportion ratios were 40%/41% = 1.0 (95% CI: 0.9-1.1) for localized CRC, 26%/26% = 1.0 (95% CI: 0.9, 1.1) for regional spread CRC, and 18%/21% = 0.9 (95% CI: 0.7-1.0) for metastatic CRC. For CRCs diagnosed more than one year after a stroke, the corresponding proportion ratios were 39%/41% = 1.0 (95% CI: 0.9, 1.0), 23%/26% = 0.9 (95% CI: 0.8, 1.0), and 20%/21% = 1.0 (95% CI: 0.9, 1.1), respectively.
Discussion

In this Danish nationwide cohort study of 297,523 patients with AMI and 243,998 with stroke we found an increased risk of CRC in the first year of follow-up, but no increased risk thereafter. The increased relative risks for AMI and stroke corresponded to a one-year absolute risk of only 0.3%. As expected, the relative risk was highest in patients with known CRC risk factors such as diabetes and obesity coexisting with AMI/stroke. Cancer stage at diagnosis in AMI/stroke patient was virtually identical to CRC patients with the same gender, age -, and diagnosis year without AMI/stroke.

Our results are supported by other AMI/stroke studies finding no overall association with CRC, although these either excluded the first year of follow-up or did not evaluate first and subsequent years separately (20,21,23). In contrast, several previous studies have supported a relation between AMI/stroke and CRC (16-18). However these studies are inconsistent with regard to which gender shows the effect and whether colon or rectal cancer risk is involved. None of them examined risks over time since AMI/stroke diagnosis, and the modest relative risks observed are quite compatible with the pattern we found: an increase in the first year, and none thereafter. For example, a Swedish regional study (17), found that male patients were at increased colon cancer risk (SIR 1.13, 95 % CI: 1.01-1.26), but female patients were not. Similar results were found in a 2001 Israeli cohort study including only men (risk ratio of 1.18, 95% CI: 1.18-1.29) (18). In addition, a 2005 follow-up study of 110,972 Japanese, which used data on past history of AMI and stroke from baseline self-administered questionnaires, found an increased rectal cancer risk in female AMI patients (only 49 rectal cancer patients, hazard ratio 3.05, 95% CI: 1.28-7.28) but also a non-significant increased risk of rectal cancer in female stroke patients (hazard ratio 2.99, 95% CI: 0.72-12.45) (16).

Our data therefore clarify previous research on the AMI/stroke and CRC association by separating the first year of follow-up from the subsequent years, making clear that the relationship is likely not due to shared risk factors or common etiological pathways.
CRC risk has also been studied in stable atherosclerotic (stenosis) patients who have not experienced acute events such as AMI or stroke. At least two cross-sectional studies (7,15) and one case-control study (6) have reported an association, while a population-based case-control (20) and a cohort study (22) did not. However, the underlying pathology behind AMI and ischemic stroke may differ from that of stable atherosclerosis (25).

The overall relative risk of CRC particularly among AMI patients was highest in the early years of the study, whereas the relative risk in the first year of follow-up remained elevated throughout the study period. The increased CRC risk in the first year after AMI and stroke could have several explanations. First, occult bleeding from the tumour may cause anaemia, precipitating AMI or stroke. Second, AMI and stroke could be the clinical manifestation of a hypercoagulable paraneoplastic syndrome caused by the (occult) CRC (29,30). Finally, the increased risk may merely be the result of diagnostic bias, since AMI and stroke patients are hospitalized and then placed under close observation, increasing diagnostic testing. If this bias were profound, however, more early-stage cancers among AMI and stroke patients would be expected, a pattern which we did not clearly find. It is conceivable that the antithrombotic, thrombolytic, or aspirin treatment prescribed to AMI and ischemic stroke patients at diagnosis could cause an asymptomatic colorectal lesion to present as gastrointestinal bleeding. However, were this the case, hemorrhagic stroke patients, not treated with antithrombotics, thrombolytics, or aspirin, would have a lower SIR than those with thrombotic stroke, also a pattern we did not find.

The strengths of our study include the population-based design within a tax supported universal healthcare system with a complete hospital history. Our study includes the largest number of AMI and stroke patients to date among studies investigating this association; we had complete follow-up over a 30 year period and used standardized risk estimates. These features reduce the risk of selection bias and provide highly
generalizable results. We were also able to analyse the effect of time from the diagnosis of AMI and stroke to CRC providing important clinical evidence.

Our study also has potential limitations. The data in the NRP are primarily collected for administrative use and, thus, coding can be incorrect or missing. Fortunately, the validity of the diagnosis of AMI and stroke in the NRP has been found to be high and this is also the case for several of the comorbid diseases we considered (31-34). In contrast, some comorbid conditions such as obesity, hypertension, and hyperlipidemia are most likely underreported in the NRP and, moreover, probably represent the most severe cases. However, although underreported, the presence of the disease is most likely valid. In addition, we did not have information on other important CRC risk factors including polyp history, familial predisposition, and smoking status, although COPD history was included as proxy for the latter. Regarding data in the DCR, the completeness and positive predictive values are very high, estimated at 95%-98% for all cancers (35).

Another limitation of our study is the lack of information regarding use of aspirin and other nonsteroidal anti-inflammatory drugs, often prescribed to AMI and stroke patients. These drugs have protective effects on CRC risk, and could have caused underestimation of the association (36). Nonetheless, the similar results found for ischemic and hemorrhagic stroke patients indicate that aspirin may not have materially affected our findings.

In conclusion, we found that AMI and stroke patients were at 85% and 42% increased risk of being diagnosed with CRC, respectively, within the first year of diagnosis. However, we found no increased risk in the second and subsequent years. It is likely that the increased risk in the first year is caused by otherwise asymptomatic CRCs diagnosed during AMI or stroke treatment or follow-up. The lack of increased risk after one year suggests that an association based on shared risk factors and chronic inflammation is unlikely.
Grant support

The work was supported by the Karan Elise Jensen Foundation, Clinical Epidemiology Research Foundation, the Regional Clinical Epidemiological Monitoring Initiative, and by a grant from the Danish Cancer Society (grant no. R73-A4284-13-S17). The first author was supported by a scholarship from Aarhus University.
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Table 1: Characteristics of patients with acute myocardial infarction and stroke

<table>
<thead>
<tr>
<th></th>
<th>Acute Myocardial Infarction</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number</strong></td>
<td>297,523</td>
<td>246,998</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>189,878 (63.8%)</td>
<td>128,353 (52.0%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>107,645 (36.2%)</td>
<td>118,645 (48.0%)</td>
</tr>
<tr>
<td><strong>Median age at diagnosis</strong></td>
<td>69.4 years</td>
<td>72.4 years</td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1978-1983</td>
<td>68,396 (23.0%)</td>
<td>26,500 (10.7%)</td>
</tr>
<tr>
<td>1984-1988</td>
<td>52,649 (17.7%)</td>
<td>20,110 (8.1%)</td>
</tr>
<tr>
<td>1989-1993</td>
<td>46,539 (15.6%)</td>
<td>19,056 (7.7%)</td>
</tr>
<tr>
<td>1994-1998*</td>
<td>38,716 (13.0%)</td>
<td>51,760 (21.0%)*</td>
</tr>
<tr>
<td>1999-2004</td>
<td>48,404 (16.3%)</td>
<td>69,444 (28.1%)</td>
</tr>
<tr>
<td>2005-2010</td>
<td>42,819 (14.4%)</td>
<td>60,128 (24.3%)</td>
</tr>
<tr>
<td><strong>Subsequent colorectal cancer</strong></td>
<td>4,387</td>
<td>3,035</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>2,907 (66.3%)</td>
<td>2,078 (68.5%)</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1,480 (33.7%)</td>
<td>957 (31.5%)</td>
</tr>
</tbody>
</table>

* The abrupt increase in number of stroke patients between 1989-1993 and 1994-1998 was caused by a change in the International Classification of Disease codes in the Danish National Registry of Patients (8th revision until the end of 1993 and 10th revision thereafter).
Table 2: Standardized incidence ratios (SIR) of colorectal cancer in patients with acute myocardial infarction and stroke.

<table>
<thead>
<tr>
<th></th>
<th>Acute Myocardial Infarction</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>E</td>
</tr>
<tr>
<td>Total (colorectal cancer)</td>
<td>4387</td>
<td>4061</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>2848</td>
<td>2600</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>1464</td>
<td>1410</td>
</tr>
<tr>
<td>Men</td>
<td>3033</td>
<td>2817</td>
</tr>
<tr>
<td>Women</td>
<td>1354</td>
<td>1193</td>
</tr>
<tr>
<td>≤ 1 year follow-up</td>
<td>840</td>
<td>453</td>
</tr>
<tr>
<td>&gt; 1 year follow-up</td>
<td>3547</td>
<td>3607</td>
</tr>
<tr>
<td>Age at diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤49</td>
<td>210</td>
<td>190</td>
</tr>
<tr>
<td>50-59</td>
<td>755</td>
<td>743</td>
</tr>
<tr>
<td>60-69</td>
<td>1458</td>
<td>1382</td>
</tr>
<tr>
<td>70-79</td>
<td>1373</td>
<td>1277</td>
</tr>
<tr>
<td>80+</td>
<td>591</td>
<td>467</td>
</tr>
<tr>
<td>Year of diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1978-1983</td>
<td>308</td>
<td>228</td>
</tr>
<tr>
<td>1984-1988</td>
<td>518</td>
<td>445</td>
</tr>
<tr>
<td>1989-1993</td>
<td>634</td>
<td>583</td>
</tr>
<tr>
<td>1994-1998</td>
<td>705</td>
<td>688</td>
</tr>
<tr>
<td>1999-2004</td>
<td>1019</td>
<td>971</td>
</tr>
<tr>
<td>2005-2010</td>
<td>1203</td>
<td>1146</td>
</tr>
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</table>
Comorbid diseases:*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Observed</th>
<th>Expected</th>
<th>Incidence Ratio</th>
<th>95% CI Low</th>
<th>95% CI High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>210</td>
<td>167</td>
<td>1.26 (1.10 – 1.44)</td>
<td>199</td>
<td>193</td>
</tr>
<tr>
<td>COPD</td>
<td>159</td>
<td>125</td>
<td>1.27 (1.08 – 1.48)</td>
<td>150</td>
<td>117</td>
</tr>
<tr>
<td>Rheumatoid diseases</td>
<td>674</td>
<td>656</td>
<td>1.03 (0.95 – 1.11)</td>
<td>631</td>
<td>693</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>81</td>
<td>70</td>
<td>1.15 (0.91 – 1.43)</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td>Obesity</td>
<td>78</td>
<td>61</td>
<td>1.29 (1.02 – 1.60)</td>
<td>76</td>
<td>59</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>47</td>
<td>54</td>
<td>0.86 (0.63 – 1.15)</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>318</td>
<td>268</td>
<td>1.19 (1.06 – 1.32)</td>
<td>369</td>
<td>349</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>132</td>
<td>107</td>
<td>1.23 (1.03 – 1.46)</td>
<td>222</td>
<td>190</td>
</tr>
<tr>
<td>TIA</td>
<td>81</td>
<td>70</td>
<td>1.16 (0.92 – 1.44)</td>
<td>167</td>
<td>171</td>
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<tr>
<td>Prior colonoscopy:</td>
<td>83</td>
<td>73</td>
<td>1.14 (0.91 – 1.41)</td>
<td>87</td>
<td>97</td>
</tr>
</tbody>
</table>

Abbreviation:  COPD: Chronic Obstructive Pulmonary Disease; TIA: Transient Ischemic Attack

* Comorbid diseases were diagnosed before or at date of acute myocardial infarction or stroke diagnosis.

The observed incidence of colorectal cancer in patients with acute myocardial infarction/stoke and the relevant comorbid disease was compared to the expected age and gender specific incidence in the overall background population.
Figure 1: Risk of colorectal cancer in relation to length of the follow-up period among 297,523 patients with acute myocardial infarction (AMI) and 246,998 patients with stroke. The I bars represent 95% confidence intervals.
Figure 1

The graph shows the standardized incidence ratio for AMI (open circles) and stroke (filled circles) across different time periods following cancer diagnosis. The x-axis represents the time periods (0 to <6 mo, 6 to <12 mo, 12 to <24 mo, 2 to <5 yr, 5 to <10 yr, 10 to <15 yr, 15+ yr), and the y-axis represents the standardized incidence ratio, ranging from 0.8 to 3.0. The error bars indicate the variability in the data.
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