Introduction

In westernized countries, the lifetime risk of acute myocardial infarction (AMI) and stroke is 30% to 40% and 15% to 20% (1, 2), respectively, whereas the lifetime risk of colorectal cancer is approximately 5% (3). The early aetiology of all of 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 colorectal cancer carcinogenesis (6-11). AMI, stroke, and colorectal cancer 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 colorectal cancer 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 pathologic condition) is conceptually different than the occurrence of AMI or stroke (acute clinical events; refs. 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 colorectal cancer 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 used the nationwide population-based Danish databases to conduct the largest cohort study of colorectal cancer risk in patients with AMI and stroke to date.

Abstract

Background: An association between colorectal cancer 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 colorectal cancer by linking nationwide Danish registries. We calculated standardized incidence ratios (SIR) of colorectal cancer after AMI/stroke as the ratios of observed to expected incidence.

Results: A total of 297,523 patients with AMI (median age, 69.4 years; 64% men) were followed for a median of 3.1 years (range, 0-33 years) and 4,387 developed colorectal cancer (SIR, 1.08; 95% confidence interval (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), whereas it was 0.98 (95% CI, 0.95-1.02; P = 0.318) in the second and subsequent years. We followed 246,998 patients with stroke (median age, 72.4 years; 52% men) for a median of 2.9 years (range, 0-33 years) and 3,035 developed colorectal cancer (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), whereas 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.

Conclusions: 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 patients with AMI/stroke, the diagnostic workup including screening for colorectal cancer should follow that of the general population. Cancer Epidemiol Biomarkers Prev; 22(11); 1994-9. ©2013 AACR.
Materials and Methods

We conducted this cohort study in the setting of the entire Danish population, which, in the study period January 1, 1978 to 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 nonpsychiatric 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 before or on the date of the AMI/stroke. Of note, there is no population colorectal cancer 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 tumor 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 patients with AMI and stroke 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 colorectal cancer diagnosis, emigration, death, or December 31, 2010, whichever came first. The number of colorectal cancer cases observed among the study subjects was compared with 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 colorectal cancer incidence rates for each sex in 1-year age groups. Standardized incidence ratios (SIR) were calculated as the ratio of the observed to the expected number of colorectal cancer cases (27). The statistical methods assumed that the observed number of cases in any specific category followed a Poisson distribution. Confidence intervals (CI) for the SIR were calculated on the basis of Byar’s approximation; exact confidence limits were used if the observed number of cases was less than 10.

We calculated SIRs for patients with AMI and stroke overall and for patients with ischemic and hemorrhagic stroke 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 patients with AMI and stroke with prior colonoscopy and coexistence of each of the comorbid diseases listed earlier. As for the overall analysis, these analyses were standardized according to sex, age, and calendar period. In a subanalysis, we calculated SIRs for colon and rectal cancers separately. In addition, we estimated absolute risks of colorectal cancer 1, 5, and 10 years after AMI and stroke diagnosis, treating death as competing risk (28).

Finally, we evaluated whether colorectal cancers were diagnosed at an earlier or later stage in patients with AMI or stroke than among patients with colorectal cancer without these diseases. We did this by matching each patient with colorectal cancer with a history of AMI or stroke by age, gender, and year of diagnosis to 5 patients with colorectal cancer 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 colorectal cancers in patients with an AMI and stroke history with the proportions in matched colorectal cancer patients with no history of these diseases.

Results

AMI

We identified 297,523 patients with AMI, 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 patients with AMI were recorded with a colorectal cancer diagnosis during follow-up, corresponding to an overall SIR for colorectal cancer of 1.08 (95% CI, 1.05–1.11; Table 2). Women and individuals more than 80 years of age 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 colorectal cancer. A total of 7,750 (2.6%) patients had a colonoscopy before AMI diagnosis and their SIR of colorectal cancer was similar to the overall result. The SIR for 1978 to 1983 was 1.35 (95% CI, 1.21–1.51), whereas it was close to 1.0 in the most recent periods.

The SIR for colorectal cancer was increased only in the first year after AMI diagnosis (1.85; 95% CI, 1.73–1.98 vs. 1.08 (95% CI, 1.05–1.11; Table 2). Women and individuals more than 80 years of age 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 colorectal cancer. A total of 7,750 (2.6%) patients had a colonoscopy before AMI diagnosis and their SIR of colorectal cancer was similar to the overall result. The SIR for 1978 to 1983 was 1.35 (95% CI, 1.21–1.51), whereas it was close to 1.0 in the most recent periods.

The SIR for colorectal cancer was increased only in the first year after AMI diagnosis (1.85; 95% CI, 1.73–1.98 vs.
0.98; 95% CI, 0.95–1.02) as compared with the second and subsequent years (Fig. 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 colorectal cancer after AMI was only 0.3% (95% CI, 0.3%–0.3%). By 5 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%), respectively.

Comparing the 840 patients with colorectal cancer diagnosed within 1 year after AMI with 4,200 matched colorectal cancer patients without history of AMI, the proportion ratios were 46%/41% = 1.1 (95% CI, 1.0–1.2) for localized colorectal cancer, 26%/27% = 0.9 (95% CI, 0.8–1.1) for regional spread colorectal cancer, and 17%/20% = 0.8 (95% CI, 0.7–1.0) for metastatic colorectal cancer. For colorectal cancers diagnosed more than 1 year after an AMI and their matched comparators, the corresponding proportion ratios were 43%/41% = 1.1 (95% CI, 1.0–1.2), 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 patients with stroke, 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 colorectal cancer diagnosis, corresponding to an overall SIR of 1.42 (95% CI, 1.31–1.53), but not in the second and subsequent years (0.96; 95% CI, 0.93–1.00; Fig. 1). The SIR of colorectal cancer 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 subanalysis for patients with ischemic and hemorrhagic stroke is shown in the Supplementary Table S2 and revealed no major differences in SIRs.

The absolute risk of colorectal cancer after 1 year of a stroke diagnosis was 0.3% (95% CI, 0.3%–0.3%); the 5- 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 patients with colorectal cancer diagnosed within 1 year after stroke with 3,314 matched colorectal cancer patients without history of stroke, the proportion ratios were 40%/41% = 1.0 (95% CI, 0.9–1.1) for localized colorectal cancer, 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 stroke, we found an increased risk of colorectal cancer in the first year of follow-up, but no increased risk thereafter. The increased

### Table 1. Characteristics of patients with AMI and stroke

<table>
<thead>
<tr>
<th></th>
<th>AMI</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>297,523</td>
<td>246,998</td>
</tr>
<tr>
<td>Male</td>
<td>189,878 (63.8%)</td>
<td>128,353 (52.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>107,645 (36.2%)</td>
<td>118,645 (48.0%)</td>
</tr>
<tr>
<td>Median age at diagnosis, y</td>
<td>69.4</td>
<td>72.4</td>
</tr>
<tr>
<td>Year of diagnosis</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>Subsequent colorectal cancer</td>
<td></td>
<td></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>

NOTE: The abrupt increase in number of patients with stroke between 1989 to 1993 and 1994 to 1998 was caused by a change in the ICD codes in the Danish NRP (8th revision until the end of 1993 and 10th revision thereafter).
Our results are supported by other AMI/stroke studies finding no overall association with colorectal cancer, although these either excluded the first year of follow-up or did not evaluate first and subsequent years separately. In contrast, several previous studies have supported a relation between AMI/stroke and colorectal cancer (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 of 110,972 Japanese, which used data on past history questionnaires, found an increased rectal cancer risk in female patients with AMI (only 49 patients with rectal cancer, HR, 1.37; 95% CI, 1.18–1.51) (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, 1.10–1.27) (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 patients with AMI (only 49 patients with rectal cancer, HR,

Table 2. SIR of colorectal cancer in patients with AMI and stroke

<table>
<thead>
<tr>
<th>Year of diagnosis</th>
<th>O</th>
<th>E</th>
<th>SIR (95% CI)</th>
<th>O</th>
<th>E</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978–1983</td>
<td>308</td>
<td>228</td>
<td>1.35 (1.21–1.51)</td>
<td>110</td>
<td>80</td>
<td>1.37 (1.13–1.66)</td>
</tr>
<tr>
<td>1984–1988</td>
<td>518</td>
<td>445</td>
<td>1.16 (1.06–1.27)</td>
<td>176</td>
<td>187</td>
<td>0.94 (0.81–1.09)</td>
</tr>
<tr>
<td>1989–1993</td>
<td>634</td>
<td>583</td>
<td>1.09 (1.00–1.18)</td>
<td>228</td>
<td>224</td>
<td>1.02 (0.89–1.16)</td>
</tr>
<tr>
<td>1994–1998</td>
<td>705</td>
<td>688</td>
<td>1.02 (0.96–1.10)</td>
<td>408</td>
<td>404</td>
<td>1.01 (0.91–1.11)</td>
</tr>
<tr>
<td>1999–2004</td>
<td>1,019</td>
<td>971</td>
<td>1.05 (0.99–1.12)</td>
<td>906</td>
<td>860</td>
<td>1.05 (0.99–1.12)</td>
</tr>
<tr>
<td>2005–2010</td>
<td>1,203</td>
<td>1,146</td>
<td>1.05 (0.99–1.11)</td>
<td>1,198</td>
<td>1,152</td>
<td>1.04 (0.98–1.10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbid diseases</th>
<th>O</th>
<th>E</th>
<th>SIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>210</td>
<td>167</td>
<td>1.26 (1.10–1.44)</td>
</tr>
<tr>
<td>COPD</td>
<td>159</td>
<td>125</td>
<td>1.27 (1.08–1.48)</td>
</tr>
<tr>
<td>Rheumatoid diseases</td>
<td>674</td>
<td>656</td>
<td>1.03 (0.95–1.11)</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>81</td>
<td>70</td>
<td>1.15 (0.91–1.43)</td>
</tr>
<tr>
<td>Obesity</td>
<td>78</td>
<td>61</td>
<td>1.29 (1.02–1.60)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>47</td>
<td>54</td>
<td>0.86 (0.63–1.15)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>318</td>
<td>268</td>
<td>1.19 (1.06–1.32)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>132</td>
<td>107</td>
<td>1.23 (1.03–1.46)</td>
</tr>
<tr>
<td>TIA</td>
<td>81</td>
<td>70</td>
<td>1.16 (0.92–1.44)</td>
</tr>
</tbody>
</table>

Abbreviations: TIA, transient ischemic attack; O, observed; E, expected.

*Comorbid diseases were diagnosed before or at date of AMI or stroke diagnosis. The observed incidence of colorectal cancer in patients with AMI/stroke and the relevant comorbid disease was compared with the expected age- and gender-specific incidence in the overall background population.
with hemorrhagic stroke, not treated with antithrombotics, gastrointestinal bleeding. However, were this the case, patients might present as gastrointestinal (GI) bleed in the absence of other symptoms. The increased colorectal cancer risk in the first year after MI/stroke is a pattern which we did not find. It is conceivable that the antithrombotic, thrombolytic, or aspirin treatment prescribed to patients with AMI and ischemic stroke at diagnosis could cause an asymptomatic colorectal lesion to present as gastrointestinal bleeding. However, were this the case, patients with hemorrhagic stroke, 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. To date, among the studies investigating this association, our study includes the largest number of patients with AMI and stroke; we had a 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 analyze the effect of time from the diagnosis of AMI and stroke to colorectal cancer 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 colorectal cancer risk factors including polyp history, familial predisposition, and smoking status, although chronic obstructive pulmonary disease (COPD) history was included as proxy for the latter. Regarding data in the DCR, the completeness and validity of the diagnosis of AMI and stroke are high, estimated at 95% for all cancers (35).

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

In conclusion, we found that patients with AMI and stroke were at 85% and 42% increased risk of being diagnosed with colorectal cancer, 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 colorectal cancers diagnosed during AMI or stroke treatment or follow-up. The lack of increased risk after 1 year suggests that an association based on shared risk factors and chronic inflammation is unlikely.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: R. Erichsen, H.T. Sørensen
Development of methodology: R. Erichsen, C. Sværke
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Sværke, H.T. Sørensen

Figure 1. Risk of colorectal cancer in relation to length of the follow-up period among 297,523 patients with AMI and 246,998 patients with stroke. The I bars represent 95% CIs.

The overall relative risk of colorectal cancer particularly among patients with AMI was highest in the early years of the study, whereas the relative risk in the first year of hospitalization remained elevated throughout the study period. The increased colorectal cancer risk in the first year after AMI and stroke could have several explanations. First, occult bleeding from the tumor may cause anemia, precipitating AMI, or stroke. Second, AMI and stroke could be the clinical manifestation of a hypercoagulable paraneoplastic syndrome caused by the (occult) colorectal cancer (29, 30). Finally, the increased risk may merely be the result of diagnostic bias, as patients with AMI and stroke are hospitalized and then placed under close observation, increasing diagnostic testing. If this bias were profound, however, more early-stage cancers among patients with AMI and stroke would be expected, a pattern which we did not clearly find. It is conceivable that the antithrombotic, thrombolytic, or aspirin treatment prescribed to patients with AMI and ischemic stroke at diagnosis could cause an asymptomatic colorectal lesion to present as gastrointestinal bleeding. However, were this the case, patients with hemorrhagic stroke, not treated with antithrombotics,
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Erichsen, C. Sverker, R.S. Sandler, J.A. Baron

Writing, review, and/or revision of the manuscript: R. Erichsen, H.T. Sørensen, R.S. Sandler, J.A. Baron

Study supervision: H.T. Sørensen

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Risk of Colorectal Cancer in Patients with Acute Myocardial Infarction and Stroke: A Nationwide Cohort Study

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