FACULTY OF HEALTH SCIENCE, AARHUS UNIVERSITY

Lower Gastrointestinal Bleeding and Risk of Gastrointestinal Cancer

Research year report

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Preface

This research year report is based on a study conducted during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark, from February 1st 2014 to January 31st 2015. During the year, I have been introduced to the science of epidemiology and statistics.

I am deeply thankful to my main supervisor Henrik Toft Sørensen for giving me the opportunity to carry out the study and to share your extensive knowledge throughout the year. You have never let me wait for reply and I have gotten constructive feedback even with your fully packed schedule. Thank you.

I thank Kirstine Kobberøe Søgaard for reading, commenting and editing at any time, with a remarkable patience and engagement. From the very first premature draft, you have been vital for the project. Thank you for the endless daily supervision.

Thanks to all members of the study group for revising the manuscripts, and for improving my understanding of clinical research. Thanks to Dora K. Farkas for the statistical assistance with high quality analyses.

Finally, I will thank my lovely partner, Thea, for endless support. You are indispensable. And thanks to my wonderful daughter, Alva, for waking me up every morning; I would not do without your smile and fantastic energy during the early hours.

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Abbrevations

GI	Gastrointestinal
CRC	Colorectal cancer
DNPR	Danish National Patient Registry
DCR	Danish Cancer Registry
ICD-8	International Classification of Diseases, 8th revision
ICD-10	International Classification of Diseases, 10th revision
IBD	Inflammatory bowel disease
CCI	Charlson Comorbidity Index
SIR	Standardized incidence ratio
CI	Confidence intervals

Contents

Abstract

Background: Lower gastrointestinal (GI) bleeding is a well-known first symptom of colorectal cancer. However, it remains unclear whether a hospital diagnosis of incident bleeding is also a marker of other types of GI cancer.

Methods: This nationwide cohort study examined the risk of various types of GI cancer in patients with lower GI bleeding. We used Danish medical registries to identify all patients with a first-time hospital diagnosis of lower GI bleeding during 1995-2011 and followed them for 10 years, to detect subsequent GI cancer diagnoses. We first calculated absolute risks of cancer, treating death as a competing risk. We then calculated standardized incidence ratios (SIRs) by comparing observed cancer cases with cancer incidence rates in the general population of Denmark.

Results: Among 60,093 patients (49% men) with lower GI bleeding, we observed 2,845 GI cancers during complete 10-year follow-up, corresponding to a 10-year absolute risk of any GI cancer of 5.5%, and an overall SIR of 3.91 (95% confidence interval (CI): 3.77-4.06). During the first year of follow-up, the absolute GI cancer risk was 3.6%, and the SIR of any GI cancer was 16.1 (95% CI: 15.4-16.8). This was due mainly to an excess of colorectal cancers, but all GI cancers were diagnosed more frequently than expected. During 1-5 years of follow-up, the SIR of any GI cancer declined to 1.38 (95% CI: 1.26-1.51). Apart from rectal and gall bladder cancers, the risk of any individual GI cancers remained elevated during this period. Beyond 5 years of follow-up, the SIR of any GI cancer was close to unity. However, the risk of rectal cancer was reduced, while the risk of liver and pancreatic cancers persisted 5+ years after the lower GI bleeding episode.

Conclusions: Lower GI bleeding is a strong clinical marker of prevalent GI cancer, particularly colorectal cancer. It also predicts an increased risk of any GI cancer beyond 1 year of follow-up.

Dansk resumé

Baggrund: Blødning fra endetarmen er tidligere vist at være et tegn på tyk- og endetarmskræft, mens sammenhængen mellem blødning og andre typer mave-tarmkræft endnu ikke er belyst. Tidligere studier er primært baseret på patienter med blødning diagnosticeret hos den praktiserende læge og ikke i hospitalsregi. Endelig har ingen tidligere studier undersøgt langtidsrisikoen for kræft efter endetarmsblødning.

Metode: Vi undersøgte risikoen for forskellige typer kræft i mave-tarmkanalen i op til 10 år efter blødning fra endetarmen diagnosticeret i hospitalsregi. Vi identificerede patienter med blødningsdiagnosen i årene 1995-2011 i Landspatient registret, og med de unikke CPR-numre fulgte vi patienterne op til 10 år for en mave-tarmkræfts diagnose i Cancer registeret. Vi beregnede absolutte kræftrisici i perioden og tog hensyn til død som konkurrerende faktor. Dernæst udregnede vi relative risici for kræft for at sammenligne kræftrisikoen med baggrundsbefolkningens risiko for mave-tarm kræft.

Resultater: Vi fandt 2,845 mave-tarm kræfttilfælde iblandt 60,093 patienter med blødning fra nedre mavetarm-kanal i de ti års opfølgning. Dette svarer til en gennemsnitlig risiko på 5.5% for mavetarmkræft, og kræftrisikoen er derfor forhøjet ca. 3.9 gange (95% sikkerhedsinterval: 3.77-4.06). Risikoen var mest forhøjet det første år efter blødningsdiagnosen, hvor vi fandt en absolut kræftrisiko på 3.6%, hvilket betyder, at patienternes risiko for mavetarmkræft er forøget 16 gange (95% sikkerhedsinterval: 15.4-16.8) det første år. Den kraftigt forøgede kræft-risiko skyldes primært, at mange patienter fik konstateret tyk- eller endetarmskræft, men risikoen for alle typer mave-tarm kræft var forhøjet. I perioden 1-5 år efter blødningen fandt vi en 1.38 gange (95% sikkerhedsinterval: 1.26-1.51) forhøjet kræft-risiko. Efter mere end fem år var den totale mave-tarmkræft risiko tæt på baggrundsbefolkningens, dog fandt vi en stadigt forøget risiko for kræft i lever, og bugspytkirtel.

Konklusion: Blødning fra den nedre mave-tarm kanal er en stærk markør for prævalent mave-tarmkræft, særligt tyk- og endetarmskræft. Mere end et år efter blødningen forbliver mavetarm-kræftrisikoen let forøget, men efter mere end fem år er den generelle mave-tarmrisiko ikke større end baggrundsbefolkningens.

Extract

Introduction

Lower gastrointestinal (GI) bleeding is a well-known symptom of colorectal cancer (CRC) (1,2). It is defined as bleeding occurring distal to the ligament of Treitz. The annual incidence of adult hospitalization with the symptom is between 21 and 87 per 100,000 population (3-6). CRC is one of the most common cancer types, with an estimated 1.4 million new cases worldwide in 2012 (7).

Previous cross-sectional studies have estimated that CRC causes the bleeding in 4%-12% of patients hospitalized with lower GI bleeding (3,4,6,8).
Other GI cancer types also may be associated with lower GI bleeding.

To our knowledge, no previous cohort study has investigated the association between lower GI bleeding and subsequent CRC risk in a hospital setting. Moreover, no previous study has examined the association between a diagnosis of lower GI bleeding and other types of GI cancer, or the long-term risk of any GI cancer diagnosis after lower GI bleeding. GI cancers either could bleed directly into the intestinal lumen, or lead to systemic alterations in the coagulation system, increasing the tendency to bleed (9-12).

We therefore conducted a nationwide cohort study to examine if a first-time hospital-based diagnosis of lower GI bleeding is a marker of prevalent GI cancer and a predictor of prolonged elevated GI cancer risk after more than 1 year.

Methods

Data sources and study population

In our cohort study, Danish national medical databases were linked during the 1977-2011 period. All residents of Denmark have a unique civil registration number (13), which allows linkage between the Danish National Patient Registry (DNPR) and the Danish Cancer Registry (DCR). The DNPR contains 99% of all discharge diagnoses from Danish hospitals since 1977 and from emergency room and hospital outpatient visits since 1995. DNPR data include dates of admission and discharge, surgical procedures performed, and up to 20 discharge diagnoses coded according to the *International Classification of Diseases*, 8th revision (ICD-8) until the end of 1993 and 10th revision (ICD-10) thereafter. The classification of surgical procedure codes changed to ICD-10 in 1996. At discharge one diagnosis is coded as primary (the condition that prompted admission) and the others as secondary. (14)

The DNPR was used to identify all patients with a first-time hospital diagnosis of lower GI bleeding (specified in the Appendix) between 1995 and 2011. We included primary and secondary inpatient, outpatient, and emergency room diagnoses in the discharge record. We excluded patients with an earlier diagnosis of lower GI bleeding during 1977-1994, in order to focus on incident bleeding cases.

We obtained patients´ medical histories from the DNPR, including all types of endoscopic examination of the GI tract within 3 months prior to the bleeding, as well as inflammatory bowel disease (IBD), hemorrhoids, and adenomas diagnosed any time before the diagnosis of lower GI bleeding. In addition, to address a priori elevated cancer risk, we obtained data on conditions included in the Charlson Comorbidity Index (CCI). This data allowed us to calculate comorbidity scores (low = CCI score of 0, medium = CCI score of 1-2, and high = CCI score of ≥3), chronic liver disease, and alcoholism-related disease prior to the lower GI bleeding, (ICD codes are provided in the Appendix).

Cancer

We extracted information on cancer diagnoses from the DCR, which has recorded incident cancers in Denmark since 1943. The DCR classifies cancers according to ICD-10 and ICD-O, including information on cancer stage (15). All individuals who were identified from the DNPR as having lower GI bleeding were linked to the DCR. This allowed us to identify and exclude all patients with a previous cancer diagnosis (except for non-melanoma skin cancer) prior to the bleeding. All types of GI cancer (specified in the Appendix) were included in our analyses. Colon cancers were divided into those proximal and distal to the splenic flexure, as they have been found to differ in regard to etiology, epidemiology, and symptoms on presentation (16,17).

Statistical analysis

We followed each patient from the date of his/her first hospital contact for lower GI bleeding until the date of the first cancer diagnosis, death, emigration, or December 2011, whichever came first. We tabulated the covariates of interest (number and proportion) (Table 1) and median age at inclusion, and computed follow-up time.

We calculated the absolute risks (or cumulative incidence) of GI cancer in patients with lower GI bleeding during 1, 5, and 10 years of follow-up, considering death as a competing risk. To measure the relative risk of GI cancer among patients with lower GI bleeding compared to the risk in the general Danish population, we computed the observed/expected ratio or the standardized incidence ratio (SIR) of cancer. The expected numbers of cancers were estimated based on national general population cancer rates by age, sex, and calendar year. We calculated confidence intervals (CIs) for SIRs under the assumption that the observed number of cases in each category followed a Poisson distribution. Exact 95% CIs were used when the observed number was less than ten; otherwise Byar's approximation was applied (18).

The follow-up period was divided into three intervals: 0-<1 year (cancers detected during this period were considered prevalent cancers), 1-<5 years, and 5+ years (maximum of 10 years). We performed stratified analyses according to gender, age (categorized as ≤49, 50-69, and ≥70 years), presence of adenomas (diagnosed any time prior to the hospital contact for lower GI bleeding), and CCI score. Admission type (inpatient, outpatient, and emergency room), type of diagnosis (primary or secondary) and cancer risk in IBD patients were investigated in subanalyses.

Results

Patient characteristics

We identified a total of 60,093 patients with a first hospital contact for lower GI bleeding, of whom 49% were men. The median age at diagnosis was 60 years (interquartile range: 44-75 years), and median follow-up was 4.3 years (interquartile range: 1.5-8.2 years). The patients were diagnosed with GI bleeding during an inpatient hospital stay (44%) or hospital outpatient clinic visit (48%), with the remainder diagnosed in the emergency room (8%). Of the 28,616 patients diagnosed in an outpatient clinic, 2,018 (7%) were transferred directly to an inpatient department. Most patients had a low CCI score (64%), 27% had a medium score, and 9% had a high score. Among the patients, 6,776 (11%) had a previous diagnosis of colon or rectal adenomas, 1,500 (2.5%) had a previous diagnosis of IBD, and 5,217 (8.7 %) had recently (*i.e*. within 3 months) undergone an endoscopic examination. Within the 6 months following the bleeding event, 47,982 patients (80%) underwent a colonoscopic (44%), sigmoidoscopic (41%), or a rectoscopic (17%) examination (Table 1).In 53,854 (89.6%) patients, lower GI bleeding was coded as a primary diagnosis.

Overall risk of GI cancer

In total, we observed 2,845 GI cancers during complete follow-up of all study patients. The overall 10-year absolute risk of GI cancer was 5.5%, treating death as a competing risk. This corresponded to a 3.9-fold increased cancer risk during follow-up (Table 2). Men had a higher risk of cancer than women, and increasing age was associated with a greatly increased absolute risk of all GI cancers (Table 4). In all follow-up periods, patients younger than 50 years had a substantially higher relative GI cancer risk than older patients (Table 2). We found markedly increased absolute and relative risks of cancer among patients diagnosed with lower GI bleeding in the emergency room compared to hospital inpatient and outpatient settings (Table 2 and supplementary Table e-3).

GI cancer risk in the first year of follow-up

During the first year of follow-up, 2,115 patients (3.6%) were diagnosed with GI cancer, corresponding to a SIR of 16.1 (95% CI: 15.4-16.8). While all GI cancers occurred more frequently than expected during the first year of follow-up (Table 3), colon and rectal cancer accounted for most (91%) of the diagnosed GI cancers (Table 4). During the first year of follow-up, patients aged 0-49 years had an absolute risk of GI cancer of 0.4%, patients aged 50-69 years had an absolute risk of 4.0%, and patients aged 70 years or more had an absolute risk of 6.3% (Table 4).

GI cancer risk after one or more years of follow-up

The overall relative cancer risk decreased markedly throughout the follow-up period; during years 1-5 of follow-up, the overall SIR was 1.38 (95% CI: 1.26-1.51) and beyond 5 years the SIR was 0.97 (95% CI: 0.85-1.11). Still, we found increased risks of all types of GI cancer other than rectal and gallbladder cancer during years 1-5 of follow-up.

After 5 years of follow-up, the absolute risks of GI cancer were 0.6% in patients aged 0-49 years, 5.1% in patients aged 50-69 years, and 8.3% in patients aged 70 years or more (Table 4). The relative risks of rectal and distal colon cancer were lower than expected after 5 or more years of follow-up, while the risks of pancreatic, liver cancer, and anal cancer remained elevated (Table 3). For all other GI cancers, we found no or only weak associations with lower GI bleeding beyond 5 years of follow-up.

Colorectal cancer

We detected a higher absolute risk of distal colon and rectal cancer compared to proximal colon cancer during the first year of follow-up (data not shown). The relative risk of rectal cancer [SIR=30.1 (95% CI: 28.0-32.2)] was distinctly higher than that of distal colon cancer [SIR=25.5 (95% CI: 23.6-27.4)] and proximal colon cancer [SIR=14.4 (95% CI: 12.9-16.0)] in the first year of follow-up. Subsequently, the rectal cancer risk dropped below that of colon cancer.

Comorbidities

During the first year of follow-up, patients with low comorbidity had a higher relative risk of GI cancer than patients with medium or high comorbidity. Beyond one year of follow-up, a higher level of comorbidity was associated with a higher relative GI cancer risk (Table 2). We found that an elevated liver and pancreatic cancer risk after 5+ years was primarily found in patients with high levels of comorbidity, alcoholism-related disease, and severe liver disease (supplementary Tables e-1 and e-2). Patients with IBD had a markedly lower relative cancer risk during the first year of follow-up than patients without IBD, a difference that diminished in later follow-up periods (Table 2).

Discussion

We found that a hospital-based diagnosis of lower GI bleeding was associated with an increased risk of subsequent GI cancer. As expected, lower GI bleeding was a strong marker of prevalent colorectal cancer; however, the occurrence of any GI cancer was more frequent than in the background population during the first year of follow-up. While the increased risk of colon cancer persisted one year after the bleeding diagnosis, there was no excess rectal cancer beyond 1 year of follow-up, and even a reduced risk after 5 or more years. Of note, an increased risk of all GI cancers other than rectal and gallbladder cancers persisted beyond 1 year of follow-up, but only risks of pancreatic, liver, and anal cancers remained increased beyond 5 years of follow-up.

It is estimated that 4%-12% of lower GI bleeding events diagnosed in hospital are caused by CRC (3,4,6,8). However, studies to date did not exclude patients with known CRC or patients with more than one episode of lower GI bleeding. As well, previous studies of GI cancer risk after lower GI bleeding were not conducted in hospital settings. Three British studies [two cohort studies (19,20) including approximately 60,000 persons with rectal bleeding and one case-control study (21) including 5,477 CRC cases] compared CRC risk among persons presenting to their general practitioner with rectal bleeding to CRC risk in the general population. CRC risk was more than 70-fold increased during the first 6 months after the rectal bleeding (20), and remained 16-fold increased after one year (19), 20-fold increased after two years (21), and 17-fold increased after three years of follow-up (20).

We found slightly higher relative risks of CRC during the first year after the lower GI bleeding diagnosis in the hospital setting, compared to the studies restricted to primary care. The different study populations in hospital settings and primary care settings could explain this disparity.

Inclusion in our study of patients aged less than 40 years may have contributed to the higher overall relative risk of CRC.

No previous studies have investigated the risk of any other type of GI cancer in patients with lower GI bleeding, or provided separate risk estimates beyond 1 year after the bleeding episode. While the long-term association between lower GI bleeding and CRC risk has not been examined previously, long-term CRC risk after colonoscopic examination (screening, surveillance, or diagnostic) has been investigated. It has been found that after negative colonoscopic findings, patients have a decreased risk of CRC for up to 15 years (22,23). One study found a strong decrease in 1-10 year CRC risk [OR=0.28 (95%-CI: 0.20-0.40)] among patients whose indication for surveillance colonoscopy was rectal bleeding (23). In our study, not all patients underwent lower GI endoscopic examination of any kind, which might explain lower decrease in risk of colon and rectal cancer beyond 1 year of follow-up found in our study. Either removal of adenomas or negative lower endoscopic findings explain the decreased risk of distal colon and rectal cancer after 5 years of follow-up (22-24). We found a stronger association between lower GI bleeding and distal CRC than for proximal CRC, which is consistent with symptomatology and findings in previous studies (17,25). Some of the difference may be explained by easier examination of the rectum and distal colon than the proximal colon, or by underreporting of bleeding from proximal tumors, because of darker color and/or mixing with stool. The persistently increased risk of proximal colon cancer risk throughout the follow-up period could be due to aggressive cancers or insufficient examination of the proximal colon in patients with lower GI bleeding.

Our findings of increased risk of non-CRC GI cancers have several explanations. First, an invasive GI tumor may bleed into the intestinal lumen. Second, some cancers can cause systemic alterations

in the coagulation system (*e.g*., thrombocytopenia or decreased hepatic synthesis of coagulation factors), increasing the tendency to bleed (9-12). In 10%-15% of patients with hematochezia, the bleeding source is located above the ligament of Treitz (26). Diagnosis of lower GI bleeding can sometimes be difficult, and the recorded diagnoses we relied on may not have been enterily accurate. Such misclassification would tend to minimize the strength of the associations we recorded. Alcohol intake may both induce bleeding (27,28) and increase the risk of liver and pancreatic cancers (29-31).

Our study has several strengths. The Danish health care system provides free hospital treatment to all Danish residents, which permits the conduct of studies with nationwide participation and complete follow-up, minimizing risks of referral and selection biases. Both the Danish National Patient Registry (14) and the Danish Cancer Registry (15) are of high quality, as assessed by the validity of diagnoses and procedure codes and by completeness. Our study is the first to investigate long-term (up to 10 years) risk of all types of GI cancer following a hospital diagnosis of lower GI bleeding. Also, our study separately examined risks of proximal and distal CRC after lower GI bleeding.

Several potential study limitations should be kept in mind in interpreting our results. Due to the long follow-up period, we believe that we detected close to all patients with GI cancer in our cohort. Heightened diagnostic effort probably explains some of the associations in the short term. Our finding of increased risk of virtually all GI cancers at the time of the bleeding in the first year afterwards is consistent with this explanation. However, the increased risk was remarkably persistent years after the bleeding episode; diagnostic bias should not be prominent. Even in the

short term diagnostic bias seems unlikely. The period of increased cancer diagnosis would be followed by a compensatory deficit. We did not see such a pattern except for rectal cancer.

Our study also was limited by lack of some clinical detail. We did not have information about the severity of the lower GI bleeding, additional GI symptoms, or about lifestyle factors related to bleeding tendency and cancer. A previous study found that patients with dark rectal bleeding and with bleeding combined with other GI symptoms are more likely to be referred from primary care to hospital care than patients with mono-symptomatic fresh rectal bleeding (32). Hence our study probably over-represented patients with dark lower GI bleeding and patients with bleeding combined with other cancer-related symptoms (anemia, weight loss, change in bowel habits etc.).

Our study emphasizes the importance of considering prevalent GI cancer in patients with lower GI bleeding in the hospital setting. We found greatly increased short-term risks of all types of GI cancer in patients with lower GI bleeding, and a strong attenuation of long-term cancer risk beyond 1 year of follow-up. While the overall GI cancer risk remained increased 1-5 years after the lower GI bleeding diagnosis, lower GI bleeding did not predict elevated long-term overall risk of most GI cancers beyond 5 years of follow-up. Future studies are needed to elucidate the increased risk of almost all types of GI cancer beyond 1 year, and the weakly increased risk of several types of GI cancer beyond 5 years.

Supplementary information

Additional methods

In addition to the main analyses, we performed stratified analyses according to recent endoscopic evaluation (any GI endoscopy within 3 months prior to the bleeding).

Additional results

We found, that patients who had undergone endoscopic examination of the GI tract up to 3 months prior to the bleeding had a slightly higher GI cancer risk during the total follow-up, than patients with no recent history of endoscopic examination (Table e-4). However, when stratifying according to follow-up interval, we found no substantial difference in relative GI cancer risk in any of the follow-up intervals between the two groups.

Methodological considerations

Study design

We conducted the study as a historical cohort study using nationwide data. A cohort is a group of individuals, who share an experience or a condition, e.g. exposure to a job, a disease or a symptom. Individuals in a cohort study are in other words assembled by their exposure status, and a cohort may include more groups with different exposure status. The aim when conducting a cohort study is to estimate incidence of disease in the cohort, and usually to compare the incidence in groups of individuals with different exposure status (1). In our study, the exposed group included patients diagnosed with lower GI bleeding in hospital, and the unexposed reference group was the Danish population. Because of the nationwide health registries, the entire Danish population can act as an open cohort (2).

Individuals in our cohort (exposed) were continuously included during the study period. They left the cohort, when they were no longer exposed or at risk of the disease. Therefore our cohort could be characterized as an *open* or *dynamic cohort* (Figure 1). However, the data we used were nationwide data with minimal loss to follow-up, which allows us to treat the cohort as *closed*, with an imaginary collective date with start of follow-up (Figure 1). Our study took advantage of secondary data obtained from the Danish National Patient Registry, from which lower GI bleeding diagnoses and diagnoses of all covariates were retrieved, and the Danish Cancer Registry which includes information of any cancer diagnosis.

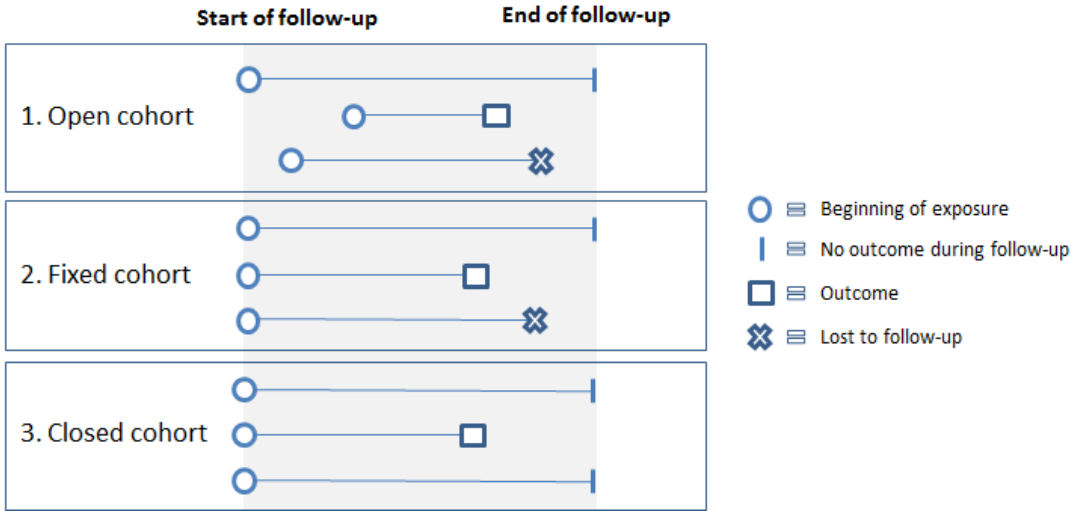

Figure 1.Follow-up in different types of cohort studies.

Exposure status is the key in the inclusion of participants in a cohort. The simplest way of identifying exposure is, when there are only two exposure levels (exposed vs. non-exposed), and the exposure is permanent. Our study exemplifies this, as we investigate the association between a symptom and subsequent disease; once an individual has experienced the symptom, the individual is exposed until the outcome occurs, end of follow-up, or loss to follow-up. As we did not graduate

the severity of lower GI bleeding, we are obviously not able to elucidate anything regarding dose-response between different exposure levels and cancer risks.

In our study, exposure of lower GI bleeding was defined by the diagnosis code "K62.5 Hemorrhage of anus and rectum". Other diagnosis codes describe GI tract bleeding. These unspecified GI bleeding codes were left out, mainly because they were believed to include patients with both upper and lower GI bleeding, and we wanted to examine only lower GI bleeding. Furthermore, unspecified diagnoses are used as work-up diagnosis, which can make them less valid.

Cohort studies can be characterized as *prospective*, when the study is planned before data are collected, or *retrospective* when the study is planned after the data are collected. In prospective cohort studies, it is possible to obtain data on all variables without the limitations of the usual data recording in medical records. This provides the possibility of a more complete control of confounding, than when using existing data. Furthermore, to minimize the risk of measurement error, prospective data collection allows information to be collected using standardized instructions (3). However, if the investigators who collect data are aware of the study hypothesis, then prospective data collection can result in inclusion of patients with different characteristics than the source population. This can lead to selection bias (see below). Also prospective studies tend to consume large amount of time and money, which makes alternative study designs attractive.

Retrospective studies are often far less time and money consuming than prospective ones. The recording of data can be performed after the follow-up period has ended, but alternatively retrospective studies can be conducted with prospectively collected data also known as secondary data (1). Retrospective data collection can lead to extensive systematic measurement errors and recall bias, which is probably the main reason why retrospective studies have a reputation of being less valid than prospective studies (4). Studies that use secondary data are sometimes referred to as

historical cohort studies, a term that is sometimes confusingly used for all retrospective cohort studies. A distinction between retrospective and historical is nevertheless appropriate, as the prospective data collection in a *historical cohort study* removes the risk of recall bias. In countries with high quality health registries, a historical cohort study can be an efficient way of investigating associations between exposure and diseases with long induction periods (e.g. development of cancer). We took advantage of the valuable source of the high quality secondary data in Danish health registries, and conducted a historical cohort study with complete follow-up.

Incidence proportion

In our study there was minimal loss to follow-up due to other causes than death, which allowed us to calculate incidence proportions to estimate average risk of GI cancer, and standardized incidence ratios to estimate the relative risk of GI cancer in the cohort (1).

The incidence proportion is a risk measure with the number of outcomes in the nominator, and the population at risk of the outcome in the denominator (Equation 1). The incidence proportion coheres to a certain period of time in which the proportion is calculated, and the average risk does not provide any information without a corresponding time indication (1). Incidence proportions in populations are easy to interpret as they correspond to absolute risks (or probabilities) of the outcome for individuals in the populations (i.e. 100 outcomes/10,000 persons at risk during the first year of follow-up is equal to 1% average risk of the outcome during the first year of follow-up for an individual in the population). Three basic criteria have to be fulfilled, before incidence proportions can be used as absolute risk measure. Firstly, the cohort must be closed (no loss to follow-up). Secondly, only new onset disease is counted. Thirdly, the time of follow-up must be specified for each incidence proportion.

$$Incidence\ proportion = \frac{\text{Number of outcomes}}{\text{Number at risk of outcome}} \qquad , Equation\ 1$$

A cumulative incidence proportion sums up the incidence proportions during one or more follow-up intervals, thereby estimating the probability that the outcome has occurred in a person at risk before a given time. As the cumulative incidence sums up the risk of disease in all previous intervals, the cumulative incidence proportion will never decrease from one follow-up interval to a subsequent interval. Cumulating the incidence proportion provides an easy interpretable risk of having had an outcome at a given time. We were allowed to use cumulative incidence to estimate absolute risk, as our cohort mimicked a closed cohort because of the small loss to follow-up.

Absolute risk measures explain the size of the health burdens that outcomes under study add to the population. However, absolute risk measures do not provide information about the extent to which an exposure is associated to an outcome. Relative risk estimates, on the other hand, describe to what extent a given exposure is related to a specific outcome.

Standardized incidence ratio

A standardized incidence ratio (SIR) is a relative risk measure. SIR is a ratio between incidence rate in the cohort and incidence rate in a standardized background population. In other words, it can be expressed as the ratio between observed outcomes in the study cohort and expected outcomes in the background population (with equal amounts of person-years) (Equation 2) (1). The standardization allows the investigator to compare the incidence of disease in the cohort with the incidence of disease in comparable individuals in the background population. Standardization can be made according to, e.g. age, gender, race and calendar year. In other words, the risk of outcomes in the study cohort is compared to the risk in the background population in individuals, who apart from the exposure theoretically have the same risk of the outcome.

$$SIR = \frac{incidence\ rate_{cohort}}{incidence\ rate_{population}} = \frac{\text{Observed cases}}{\text{Expected cases}} \quad , Equation\ 2$$

The SIR estimate will underestimate the relative risk when studying an exposure that is strongly related to the outcome, or when the study cohort accounts for a large part of the background population. This is because individuals in the cohort are also part of the entire population, to which the cohort is compared. Residual confounding can be a problem when using SIR as relative risk estimate. This is, if the study cohort and the background population differ in other ways than in exposure status, and these differences are related to the outcome. When studying the association between a symptom and a disease, such differences can also bias the association.

In our study the relative risk was estimated with SIRs. The exposure in our study (even though strongly related to the outcome) is not a necessity for the outcome, and furthermore hospitalized lower GI bleeding is not very common in the population, which diminishes risk of underestimating the relative risk. The risk of bias due to differences in the cohort and the background population is considered below.

Stratification

Our aim was to estimate overall values of GI cancer in patients with lower GI bleeding, and therefore we did not exclude certain groups of patients according to patient characteristics. Of note, when we present overall risk estimates for GI cancer, not all patients have the same a priori cancer risk. In other words, the cohort is heterogeneous. To explain these different risks in different groups of patients, we conducted stratified analyses. Stratification means that the cohort is split up to two or more groups according to different characteristics, and risk estimates can be calculated separately for each group (4).

However, stratification comes at a cost of decreased precision, and therefore it was not possible to fully explain long-term association between lower GI bleeding, and liver and pancreatic cancer. Further studies are needed to explain these associations.

Limitations

The aim in epidemiologic studies is to present estimations of the investigated associations. Estimations are not fully correct values, but they are approximations intended to be as close as possible to the true values. All studies have limitations, and in the following section I describe a selection of limitations that could have influenced our study. Of note, confounding by indication will not be dealt with in the following section, as we do not investigate a cause of cancer disease, but rather a marker of disease.

Selection bias (systematic error)

Selection bias is systematic error due to distortions in the selection of the study population or in factors influencing study participation. Selection bias can be introduced when the association between exposure and outcome is different in the study population and the background population (1). This occurs, when distortions in selection or participation results in unequal distribution of an outcome-related factor in the different exposure groups. Below, two main types of selection bias in historical cohort studies are described. Bias cannot be removed by statistical modeling, so these errors have to be dealt with when designing the study.

Medical surveillance bias may occur, when clinical contacts are associated to the exposure under study. Thereby, asymptomatic cases are more likely to be detected among the exposed individuals due to medical surveillance resulting in an overestimation of the relative risk of the outcome.

Admission with lower GI bleeding may have led to both GI endoscopic examination and other medical examinations such as CT-scans, ultrasound, blood tests, etc. If the lower GI bleeding was not caused by a GI cancer, then this might have resulted in detection of asymptomatic GI cancers, generating a medical surveillance bias. This bias would be present if the proportion of diagnosed asymptomatic GI cancers in the cohort exceeded that in the general population. This would lead to

and overestimation of the relative cancer risk during the first year of follow-up and a corresponding underestimation during the subsequent periods.

To ascertain that our results were not in risk of medical surveillance bias, we could have obtained information on medical examination in the cohort subsequent to the bleeding and compared it with the level of medical examination in the background population. Or we could have stratified by cancer stage to examine if GI cancers were diagnosed in an earlier stage in exposed than in non-exposed. However, these analyses would probably provide little if any at all information to our understanding, as most cancer-related symptoms are associated with earlier diagnosis. Of note, as our follow-up period was long and the outcome is a severe disease, then we expect the major part of the outcomes to be detected during follow-up both in the exposed group and in the background population.

Study participants were excluded from further follow-up when they had an outcome or if they had been diagnosed with cancer before 1995 or before a lower GI bleeding diagnosis. This was done to avoid selection bias, as former and current cancer patients have a higher a priori risk of developing cancer than non-cancer patients.

We did not conduct stratified analyses according to information that was recorded subsequent to the lower GI bleeding, as it would introduce immortal person-time bias to the analysis. Therefore, it was not possible to elucidate the risk of medical surveillance bias using variables that represent surveillance subsequent to the lower GI bleeding (e.g. endoscopic examination, CT scans, etc.). Instead, we performed stratified analyses according to medical surveillance of the GI tract prior to the lower GI bleeding. We did not find substantial differences between patients with and without recent hospital contact, when we stratified by endoscopic examination of the GI tract up to 3 months prior to the lower GI bleeding. We cannot reject any medical surveillance bias in the study,

but considering the factors discussed in the extract, we find it unlikely, that our study is heavily biased by selection bias.

Information bias (systematic error)

Information bias can affect results if errors in measuring exposure are related to the outcome. In our study, the exposure and outcome are both dichotomous variables and therefore any error in the measures is called misclassification. If the misclassification of a variable is dependent on the other variable, then the misclassification is called differential, and if not dependent it is called non-differential (1). Our study uses prospectively collected data, which reduces the risk of differential misclassification. At the time of recording exposure the doctors were unaware of the outcome. Unless doctors were prone to diagnose lower GI bleeding in patients who were suspected to have cancer and not in patients not suspected to have cancer, then differential misclassification is not a concern.

The false-positive probabilities in our study are believed to be low for both exposure and outcome. No validation studies have been made on the diagnosis code K62.5, but it is unlikely, that doctors would record a diagnosis code K62.5 in a patient if bleeding per rectum was not present. In contrast, the sensitivity might be lowered, because the diagnosis code is a symptom. If the underlying disease is detected, then the symptom code could be left out during a busy day at work. This type of misclassification is non-differential, and as the variables are dichotomous and independent of other errors, it will create bias toward null with a size depending on the extent of misclassification (1).

Random error

Random error is what most people interpret as chance. In small studies, estimates can be influenced by random error. A way to avoid substantial influence by random error is to increase the size of the cohort, and the nationwide registries we used allow us to include a large number of patients.

Justification of methods

The Danish health registries are a valuable source of secondary data in medical research. We aimed to examine both short- and long-term risk of cancer after lower GI bleeding, and using quality secondary data in a historical cohort study was an efficient, cheap and valid way of investigating the association. We estimated both absolute and relative risk estimates to elucidate the associations, as both types of measures are of high importance in describing the association. The risk measures we used to describe the association were appropriate for the study design. By performing stratified analyses, we explained important differences in strength of GI cancer risks in patients with different characteristics.

Considering factors discussed in the extract and elaborated in the supplement, we have no reason to believe that our results are heavily biased.

Additional perspectives

This study adds important knowledge to the association between lower GI bleeding and the risk of GI cancer. The association between lower GI bleeding and risk of liver and pancreatic cancer after more than 5 years of follow-up would be interesting to examine.

It would also be highly relevant to investigate the survival in GI cancer patients, who were diagnosed with lower GI bleeding prior to the cancer diagnosis compared to other GI cancer patients.

Moreover, as many cancer types can alter the coagulation, it would be interesting to investigate, whether lower GI bleeding is a marker of extra-gastrointestinal cancer types (eg. hematological cancer, kidney, prostate and others.)

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Tables

Table 1. Characteristics of 60,093 patients with a first-time hospital-based diagnosis of lower GI bleeding.

	Patients [no. (%)]
All	60,093 (100)
Sex	
Women	30,562 (50.9)
Men	29,531 (49.1)
Age at GI bleeding	
0 - 49 years	19,667 (32.7)
50 - 69 years	20,841 (34.7)
70+ years	19,585 (32.6)
Place of diagnosis	
Emergency Room	4,819 (8.0)
Inpatient unit	26,658 (44.4)
Outpatient clinic	28,616 (47.6)
Type of diagnosis	
Primary	53,854 (89.6)
Secondary	6,239 (10.4)
Adenomas	
No	53,317 (88.7)
Yes	6,776 (11.3)
Concurrent IBD	
No	58,593 (97.5)
Yes	1,500 (2.5)
Hemorrhoids	
No	52,850 (88.0)
Yes	7,243 (12.1)
Charlson score[a]	
0	38,339 (63.9)
1-2	16,404 (27.3)
3+	5,290 (8.8)
Alcoholism-related disease	
No	57,276 (95.3)
Yes	2,817 (4.7)
Chronic liver disease[a]	
No	58,686 (97.7)
Mild	936 (1.6)
Moderate-severe	471 (0.8)
Preceding endoscopy[b]	
No	54,876 (91.3)
Yes	5,217 (8.7)
Subsequent lower endoscopy[c]	
No	12,111 (20.2)
Yes	47,982 (79.8)

[a] According to Charlson Comorbidity Index

[b] Examination during the 3 months prior to bleeding

[c] Colonoscopic, sigmoidoscopic, or rectoscopic examination up to 6 months after bleeding

Table 2. Standardized Incidence Ratios (SIRs) for GI cancer after lower GI bleeding (n=60,093), by follow-up period and patient characteristics.

	Total		<1 year		1-<5 years		5+ years	
	O	SIR	O	SIR	O	SIR	O	SIR
All GI cancers	2,845	**3.91** [3.77-4.06]	2,115	**16.1** [15.4-16.8]	507	**1.38** [1.26-1.51]	223	**0.97** [0.85-1.11]
Sex								
Women	1,225	**3.62** [3.42-3.83]	881	**14.6** [13.6-15.6]	232	**1.36** [1.19-1.54]	112	**1.05** [0.86-1.26]
Men	1,620	**4.16** [3.96-4.37]	1,234	**17.4** [16.5-18.4]	275	**1.40** [1.24-1.58]	111	**0.91** [0.75-1.09]
Age								
0 - 49 years	134	**4.07** [3.41-4.82]	83	**26.5** [21.1-32.8]	28	**2.05** [1.36-2.96]	23	**1.43** [0.91-2.14]
50 - 69 years	1,099	**3.67** [3.54-3.99]	813	**20.9** [19.5-22.4]	173	**1.26** [1.08-1.46]	113	**0.97** [0.80-1.17]
70+ years	1,612	**4.00** [3.81-4.21]	1,219	**13.7** [12.9-14.4]	306	**1.41** [1.26-1.58]	87	**0.90** [0.72-1.11]
Year of bleeding diagnosis								
1995-2000	750	**2.90** [2.69-3.11]	473	**14.2** [12.9-15.5]	167	**1.51** [1.29-1.75]	110	**0.96** [0.79-1.16]
2001-2006	1,283	**3.57** [3.38-3.78]	920	**16.8** [15.7-17.9]	250	**1.32** [1.16-1.49]	113	**0.99** [0.82-1.19]
2007-2011	812	**7.39** [6.89-7.92]	722	**16.7** [15.5-18.0]	90	**1.35** [1.09-1.66]	-	-
Place of diagnosis								
Emergency room	309	**5.95** [5.30-6.65]	245	**24.7** [21.7-28.0]	44	**1.73** [1.26-2.32]	20	**1.21** [0.74-1.86]
Inpatient unit	1,470	**3.92** [3.72-4.12]	1,050	**14.3** [13.5-15.2]	307	**1.63** [1.45-1.82]	113	**1.00** [0.82-1.20]
Outpatient clinic	1,066	**3.55** [3.34-3.77]	820	**17.0** [15.9-18.2]	156	**1.02** [0.87-1.19]	90	**0.91** [0.73-1.12]
Type of diagnosis								
Primary	2,482	**3.79** [3.65-3.95]	1833	**15.7** [15.0-16.4]	446	**1.35** [1.23-1.48]	203	**0.98** [0.85-1.12]
Secondary	363	**4.94** [4.45-5.48]	282	**19.4** [17.2-21.8]	61	**1.64** [1.25-2.11]	20	**0.92** [0.56-1.42]
IBD								
No	2,806	**3.94** [3.79-4.08]	2098	**16.3** [15.6-17.0]	491	**1.36** [1.25-1.49]	217	**0.97** [0.84-1.10]
Yes	39	**2.66** [1.89-3.63]	17	**6.19** [3.60-9.91]	16	**2.14** [1.22-3.47]	6	**1.35** [0.50-2.94]
Adenomas								
No	2,365	**3.83** [3.67-3.98]	1768	**16.0** [15.3-16.8]	408	**1.32** [1.19-1.45]	189	**0.96** [0.83-1.10]
Yes	480	**4.37** [3.99-4.78]	347	**16.5** [14.8-18.3]	99	**1.73** [1.41-2.11]	34	**1.08** [0.75-1.51]
Charlson score[a]								
Low (0)	1,551	**3.68** [3.50-3.87]	1174	**18.6** [17.6-19.7]	243	**1.19** [1.04-1.34]	134	**0.87** [0.73-1.03]
Medium (1-2)	992	**4.04** [3.79-4.30]	711	**14.0** [13.0-15.0]	207	**1.60** [1.39-1.83]	74	**1.13** [0.89-1.42]
High (3+)	302	**5.00** [4.45-5.59]	230	**13.2** [11.5-15.0]	57	**1.72** [1.30-2.23]	15	**1.51** [0.85-2.50]
Alcoholism-related disease								
No	2,705	**3.83** [3.69-3.98]	2020	**15.9** [15.3-16.6]	475	**1.33** [1.22-1.46]	210	**0.94** [0.82-1.08]
Yes	140	**6.45** [5.42-7.61]	95	**20.6** [16.7-25.2]	32	**2.84** [1.94-4.01]	13	**2.22** [1.18-3.80]

GI: Gastrointestinal, SIR: Standardized Incidence Ratio, O: Observed number of patients with GI cancer

[a]including proximal and distal colon, multiple-sited colon cancer, colon cancer NOS, and cancer in recto-sigmoid junction.

[b]Including caecum, appendix, ascending, right flexure, transverse colon

[c]Including left flexure, descending, sigmoid colon, and recto-sigmoid junction.

[d]including biliary tract

Table 3. Standardized Incidence Ratios (SIRs) for GI cancer after lower GI bleeding (n=60,093), by follow-up period and cancer site.

	Total		<1 year		1-<5 years		5+ years	
	O	**SIR**	**O**	**SIR**	**O**	**SIR**	**O**	**SIR**
All GI cancers	2,845	**3.91** [3.77-4.06]	2,115	**16.1** [15.4-16.8]	507	**1.38** [1.26-1.51]	223	**0.97** [0.85-1.11]
Specific cancer site								
Esophagus	69	**1.57** [1.22-1.99]	13	**1.63** [0.87-2.79]	38	**1.71** [1.21-2.35]	18	**1.30** [0.77-2.06]
Stomach	78	**1.31** [1.04-1.64]	34	**3.07** [2.13-4.29]	33	**1.09** [0.75-1.54]	11	**0.61** [0.30-1.08]
Small intestine	37	**4.70** [3.31-6.48]	21	**15.2** [9.39-23.2]	15	**3.82** [2.14-6.31]	1	**0.39** [0.01-2.17]
Colon[a]	1,432	**4.65** [4.41-4.90]	1,107	**19.9** [18.7-21.1]	234	**1.50** [1.32-1.71]	91	**0.94** [0.76-1.16]
Proximal[b]	521	**3.77** [3.45-4.11]	355	**14.4** [12.9-16.0]	118	**1.70** [1.41-2.04]	48	**1.09** [0.80-1.44]
Distal[c]	796	**5.54** [5.16-5.94]	675	**25.5** [23.6-27.4]	86	**1.18** [0.94-1.45]	35	**0.79** [0.55-1.10]
Rectum	910	**6.08** [5.69-6.49]	808	**30.1** [28.0-32.2]	75	**0.99** [0.78-1.24]	27	**0.57** [0.38-0.83]
Anal canal	52	**5.33** [3.98-6.99]	36	**21.1** [14.8-29.2]	9	**1.84** [0.84-3.49]	7	**2.22** [0.89-4.58]
Liver	88	**2.81** [2.25-3.46]	37	**6.60** [4.65-9.10]	35	**2.22** [1.55-3.09]	16	**1.60** [0.92-2.61]
Gall bladder[d]	30	**1.38** [0.93-1.98]	12	**3.03** [1.56-5.29]	10	**0.91** [0.44-1.67]	8	**1.19** [0.51-2.34]
Pancreas	149	**1.55** [1.31-1.82]	47	**2.76** [2.03-3.67]	58	**1.20** [0.91-1.55]	44	**1.44** [1.04-1.93]

SIR: Standardized Incidence Ratio, O: Observed number of patients with GI cancer, GI: Gastrointestinal
[a] including proximal and distal colon, multiple-sited colon cancer, colon cancer NOS, and cancer in recto-sigmoid junction.
[b] Including caecum, appendix, ascending, right flexure, transverse colon
[c] Including left flexure, descending, sigmoid colon and recto-sigmoid junction
[d] including biliary tract

Table 4. Absolute risk (cumulative incidence in % with 95% confidence interval) of GI cancers after 1, 5 and 10 years by age group and cancer type.

	1 year	5 years	10 years
Overall GI cancer			
0-49 years	**0.43** [0.34-0.53]	**0.62** [0.51-0.74]	**0.90** [0.75-1.08]
50-69 years	**3.96** [3.70-4.23]	**5.06** [4.75-5.37]	**6.41** [6.02-6.82]
70+ years	**6.33** [5.99-6.68]	**8.33** [7.93-8.74]	**9.29** [8.85-9.75]
Colorectal Cancer[a]			
0-49 years	**0.37** [0.29-0.46]	**0.46** [0.37-0.57]	**0.58** [0.46-0.72]
50-69 years	**3.56** [3.32-3.82]	**4.15** [3.87-4.43]	**4.89** [4.55-5.23]
70+ years	**5.77** [5.45-6.11]	**7.11** [6.74-7.49]	**7.69** [7.29-8.10]
Other GI cancers combined[b]			
0-49 years	**0.06** [0.03-0.10]	**0.16** [0.10-0.23]	**0.33** [0.23-0.45]
50-69 years	**0.41** [0.33-0.51]	**0.95** [0.81-1.11]	**1.60** [1.38-1.85]
70+ years	**0.59** [0.49-0.71]	**1.32** [1.15-1.51]	**1.76** [1.54-2.00]

[a] including cancer in colon and rectum
[b] Including cancer in esophagus, stomach, small intestines, anal, liver, gall bladder and pancreas

Supplementary tables

Table e-1. Standardized Incidence Ratios (SIRs) of liver cancer after lower GI bleeding by follow-up period and comorbidities.

	Total		<1 year		1-<5 years		5+ years	
	O	**SIR**	**O**	**SIR**	**O**	**SIR**	**O**	**SIR**
Overall liver cancer	88	**2.81** [2.25-3.46]	37	**6.60** [4.65-9.10]	35	**2.22** [1.55-3.09]	16	**1.60** [0.92-2.61]
Charlson score[a]								
Low (0)	24	**1.31** [0.84-1.95]	8	**2.93** [1.26-5.77]	9	**1.01** [0.46-1.92]	7	**1.04** [0.42-2.14]
Medium (1-2)	35	**3.38** [2.35-4.69]	13	**6.10** [3.25-10.4]	16	**2.94** [1.68-4.78]	6	**2.14** [0.79-4.66]
High (3+)	29	**11.1** [7.44-16.0]	16	**21.5** [12.3-35.0]	10	**6.99** [3.35-12.9]	3	**6.89** [1.42-20.1]
Alcoholism-related disease								
No	59	**1.95** [1.49-2.52]	22	**4.10** [2.57-6.20]	26	**1.71** [1.12-2.51]	11	**1.14** [0.57-2.04]
Yes	29	**25.6** [17.1-36.8]	15	**64.4** [36.0-106]	9	**15.5** [7.09-29.4]	5	**15.7** [5.07-36.5]
Chronic liver disease [a]								
No	57	**1.85** [1.40-2.40]	22	**4.01** [2.51-6.07]	23	**1.48** [0.94-2.23]	12	**1.22** [0.63-2.13]
Mild	18	**49.6** [29.4-78.4]	9	**117** [53.5-222]	6	**32.0** [11.8-69.8]	3	**30.4** [6.27-88.9]
Moderate-severe	13	**89.7** [47.7-153]	6	**155** [57.0-339]	6	**78.4** [28.8-171]	1	**33.5** [0.85-187]

SIR: Standardized Incidence Ratio, O: Observed number of patients with liver cancer,

[a]Charlson Comorbidity Index (see diagnoses in Appendix)

Table e-2. Standardized Incidence Ratios (SIRs) of pancreatic cancer after lower GI bleeding by follow-up period and comorbidities.

	Total		<1 year		1-<5 years		5+ years	
	O	**SIR**	**O**	**SIR**	**O**	**SIR**	**O**	**SIR**
Overall pancreatic cancer	149	**1.55** [1.31-1.82]	47	**2.76** [2.03-3.67]	58	**1.20** [0.91-1.55]	44	**1.44** [1.04-1.93]
Charlson score[a]								
Low (0)	83	**1.48** [1.18-1.83]	24	**2.90** [1.86-4.31]	32	**1.17** [0.80-1.66]	27	**1.31** [0.86-1.90]
Medium (1-2)	51	**1.60** [1.19-2.10]	15	**2.30** [1.29-3.79]	22	**1.31** [0.82-1.99]	14	**1.63** [0.89-2.73]
High (3+)	15	**1.92** [1.07-3.16]	8	**3.58** [1.54-7.04]	4	**0.94** [0.26-2.40]	3	**2.28** [0.47-6.66]
Alcoholism-related disease								
No	140	**1.50** [1.27-1.77]	44	**2.67** [1.94-3.59]	56	**1.20** [0.90-1.55]	40	**1.34** [0.96-1.83]
Yes	9	**3.17** [1.45-6.03]	3	**5.01** [1.03-14.6]	2	**1.36** [0.17-4.92]	4	**5.19** [1.41-13.3]
Chronic liver disease [a]								
No	146	**1.55** [1.30-1.82]	45	**2.69** [1.96-3.60]	57	**1.20** [0.91-1.55]	44	**1.46** [1.06-1.95]
Mild	2	**1.88** [0.23-6.79]	1	**4.48** [0.11-25.0]	1	**1.80** [0.05-10.0]	0	-
Moderate-severe	1	**2.62** [0.07-14.6]	1	**9.42** [0.24-52.5]	0	-	0	-

SIR: Standardized Incidence Ratio, O: Observed number of patients with liver cancer

[a]Charlson Comorbidity Index (see diagnoses in Appendix)

Table e-3. Absolute risk (in % with 95% confidence interval) of GI cancer after 1 year of follow-up, by age-group and place of diagnosis.

	0-49 years	50-69 years	70+ years
All settings	**0.43** [0.34-0.53]	**3.96** [3.70-4.23]	**6.33** [5.99-6.68]
Emergency room	**0.80** [0.47-1.29]	**7.77** [6.36-9.35]	**8.10** [6.85-9.48]
Inpatient unit	**0.41** [0.27-0.60]	**4.84** [4.37-5.34]	**5.24** [4.86-5.64]
Outpatient clinic	**0.38** [0.28-0.50]	**2.99** [2.69-3.30]	**8.45** [7.71-9.24]

Table e-4. Standardized Incidence Ratios (SIRs) for GI cancer after lower GI bleeding (n=60,093), by follow-up period and recent endoscopic investigation.

	Total		**<1 year**		**1-<5 years**		**5+ years**	
	O	SIR	O	SIR	O	SIR	O	SIR
All GI cancers	2,845	**3.91** [3.77-4.06]	2,115	**16.1** [15.4-16.8]	507	**1.38** [1.26-1.51]	223	**0.97** [0.85-1.11]
Recent endoscopic examination[a]								
No	2,525	**3.82** [3.68-3.98]	1878	**15.9** [15.2-16.6]	449	**1.35** [1.23-1.48]	198	**0.95** [0.82-1.09]
Yes	320	**4.75** [4.24-5.30]	237	**17.9** [15.7-20.3]	58	**1.67** [1.27-2.16]	25	**1.28** [0.83-1.90]

[a]Endoscopic examination of the upper or lower GI tract during the 3 months prior to bleeding.

Appendix

Lower gastrointestinal bleeding

We included patients with following diagnosis codes for hemorrhage of anus and rectum to investigate lower GI bleeding. Before 1995 similar codes were used to exclude patients, as we only wanted to investigate first-time lower GI bleeding patients.

	ICD-8 1977-1993 (1995 for operations):	**ICD-10** 1994-2011 (from 1995 in outpatient visits):
Inclusion from 1st jan. 1995		K62.5
Exclusion criteria before 1995	569.15	K62.5

Gastrointestinal cancer

From 1995-2011 we counted following GI cancer types as positive outcomes in patients with lower GI bleeding: esophagus (C15), stomach (C16), small intestines (C17), large intestines (C18-19), rectum (C20), anus (C21), liver (C22), gall bladder and biliary tract (C23-24), pancreas (C25).

We excluded all patients with lower GI bleeding, who before 1995 or before the bleeding diagnosis had any cancer diagnosis (except non-melanoma skin cancer).
We excluded GI cancer diagnosis from the comorbidity score (see below)

	ICD-8 Before 1978	**ICD-10** 1978-2011
Outcome during follow-up 1995-2011		C15-C25
Exclusion criteria before 1995		C00-C96 (except C44)
Exclusion of GI cancer comorbidity from CCI score	150.00-159.99	C15-C25

Co-variates

We used following diagnoses to describe patient characteristics and to perform stratified analyses:

	ICD-8 1977-1993 (1995 for operations):	**ICD-10** 1994-2011 (from 1995 in outpatient visits):
Endoscopic investigation	91.000 ; 91.010 ; 91.020 ; 91.070; 91.080; 91.090; 91.100; 92.260; 92.280; 92.300; 92.340; 92.360	KUJC; KUJD; KUJF (02, 05, 32, 35, 42, 45, 82, 85, 92); KUJG; KUJH; KJFA15; KJGA05
IBD	563.01; 563.19; 569.04	K50; K51
Adenomas (benign tumor in colon/rectum)	211.31; 211.32; 211.33; 211.34; 211.35; 211.36; 211.38; 211.39;	D12; K62; K635

	211.49;	
Haemorrhoids	455	I84
Chronic liver disease (mild)	571; 573.01; 573.04	B18; K70.0–K70.3; K70.9; K71; K73; K74; K76.0
Chronic liver disease (moderate/severe)	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00–456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Alcoholism-related disorders	291.00-291.99 303.00-303.99 571.09 571.10 577.10	F10.2 – 10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, Z72.1; E244; E529A; K852; L278A; Z502; Z714

We used a modified Charlson Comorbidity Index (CCI) to stratify according to past history of comorbidity. Previous GI cancer diagnoses were excluded from the score (using ICD-10 codes from 1978 and ICD-8 from the DNPR before 1978).

Charlson Comorbidity Index category	**ICD-8**	**ICD-10**	**Charlson comorbidity index score**
Myocardial infarction	410	I21; I22; I23	1
Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
Cerebrovascular disease	430–438	I60–I69; G45; G46	1
Dementia	290.09–290.19; 293.09	F00–F03; F05.1; G30	1
Chronic pulmonary disease	490–493; 515–518	J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
Connective tissue disease		M09; M31; M36	1
Ulcer disease	530.91; 530.98; 531–534	K22.1; K25–K28	1
Mild liver disease	571; 573.01; 573.04	B18; K70.0–K70.3; K70.9; K71; K73; K74; K76.0	1
Diabetes type 2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9	
Hemiplegia	344	G81; G82	2
Moderate to severe renal disease	403; 404; 580–583; 584; 590.09; 593.19; 753.10–753.19; 792	I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61	2
Diabetes with end-organ damage, type 2	250.01–250.05; 250.08	E11.2–E11.8	2
Any cancer (except GI cancer)	140–149 160-194	C00-14 C26-C49, C51–C75	2
Leukemia	204–207	C91–C95	2
Lymphoma	200–203; 275.59	C81–C85; C88; C90; C96	2
Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00–456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
Metastatic solid tumor	195–198; 199	C76–C80	6
AIDS	079.83	B21–B24	6

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