Risk and prognosis of primary liver, gallbladder, bile duct, and pancreatic cancer after a negative CT scan of the abdomen:

A Danish population-based cohort study

Research year report

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ABBREVIATIONS

CCI	Charlson Comorbidity Index
CI	Confidence interval
CPP	Cancer patient pathway
CRC	Colorectal cancer
CRN	Civil registration number
CRS	The Danish Civil Registration System
CT	Computed tomography
CT-TAP	Computed tomography, thorax-abdomen-pelvis
DCR	The Danish Cancer Registry
DNPR	The Danish National Patient Registry
DPR	The Danish Pathology Registry
ICD	International Classification of Diseases
IQR	Interquartile range
LGBP	Primary liver, gallbladder, bile duct, and pancreas
LGGB	Lever, galdeblære, galdegange og bugspytkirtelkræft
MRR	Mortality rate ratio
NOMESCO	Nordic Medico-Statistical Committee
PPV	Positive predictive value
PR	Prevalence ratio
SIR	Standardized incidence ratio
SNOMED	Systematized Nomenclature of Medicine

ABSTRACT

Background: Computed tomography (CT) plays a key role in ruling out and detecting primary liver, gallbladder, bile duct, and pancreatic (LGBP) cancers, however, the risk and prognosis of a LGBP cancer diagnosed after a negative CT scan remains unknown. We therefore conducted this study to investigate the risk of LGBP cancers diagnosed after a negative CT scan of the abdomen (post-CT LGBP cancer) and to examine the prognosis for patients with a post-CT LGBP cancer relative to patients whose LGBP cancer was diagnosed at first-time CT scan (detected LGBP cancer).

Methods: We conducted a population-based cohort study during 2002-2013 based on data obtained from Danish nationwide health registries. We included all patients with a first-time contrast-enhanced CT scan of the abdomen. We defined detected LGBP cancers as diagnosed within three months after the CT scan and post-CT LGBP cancers as diagnosed more than three months after the scan. We computed the absolute risk of post-CT LGBP cancers among patients with a negative contrast-enhanced CT scan of the abdomen. As a relative risk measure, we calculated age-, sex-, and calendar-period standardized incidence ratios (SIRs) of post-CT LGBP cancers in patients with a negative CT scan compared with the risk of these cancers in the background population. Prevalence ratios (PRs) were calculated to compare the distribution of cancer stages in patients with post-CT and detected LGBP cancers. Survival was evaluated through calculation of survival probabilities and mortality rate ratios (MRRs) comparing post-CT LGBP cancer patients with detected LGBP cancer patients.

Results: We observed 687 post-CT LGBP cancers among 136,628 patients recorded as having a negative contrast-enhanced CT scan of the abdomen. The absolute risk of post-CT LGBP cancer was 0.12% (95% confidence interval (CI): 0.10-0.14) during 6 months, 0.22% (95% CI: 0.19-0.24) during 12 months, 0.42% (95% CI: 0.38-0.46) during 3 years, and 0.55% (95% CI: 0.51-0.60) during 5 years after the index CT scan, respectively. The SIR was 9.46 (95% CI: 8.05-11.04) during 3-6 months, 4.00 (95% CI: 3.33-4.76) during 6-12 months, 2.21 (95% CI: 1.93-2.52) during 1-3 years, and 1.52 (95% CI: 1.23-1.86) during 3-5 years after the

index CT scan. The adjusted PRs were 1.19 (95% CI: 1.05-1.35) for non-metastatic, 0.76 (95% CI: 0.68-0.86) for metastatic, and 1.19 (95% CI: 1.05-1.35) for unknown cancer stages. Five-year survival was 9.5% (95% CI: 6.8-12.7) for post-CT LGBP cancers and 6.4% (95% CI: 5.2-7.8) for detected LGBP cancers. The adjusted MRR was 0.88 (95% CI: 0.80-0.97).

Conclusion: Although the absolute risk was low, patients with a negative CT scan had an increased relative risk of a post-CT LGBP cancer. Prognosis after LGBP cancer was poor regardless of diagnosis timing.

DANSK RESUMÉ

Baggrund: CT-scanninger spiller en væsentlig diagnostisk rolle ved mistanke om primær lever-, galdeblære-, galdegangs- og bugspytkirtelkræft (LGGB). Risikoen og prognosen for LGGB diagnosticeret efter en negativ CT-scanning er endnu ubeskrevet. Vi udførte derfor dette studie for at undersøge risikoen for LGGB blandt patienter med en CT-scanning, som ikke viste tegn på kræft sammenlignet med risikoen for disse kræfttyper i baggrundsbefolkningen. Derudover for at undersøge prognosen for LGGB hos patienter diagnosticeret efter en negativ CT-scanning (post-CT LGGB) sammenlignet med patienter diagnosticeret med LGGB ved deres førstegangs-CT-scanning (detekteret LGGB).

Metode: Vi anvendte data fra danske sundhedsregistre til dette kohortestudie. Vi inkluderede alle patienter med en CT scanning af maven udført med kontrast. Detekteret LGGB blev defineret som kræft diagnosticeret mindre end tre måneder efter CT scanningen, mens vi definerede post-CT LGGB som kræft diagnosticeret mere end tre måneder efter CT scanningen. Vi udregnede den absolutte risiko for post-CT LGGB blandt patienter med en negativ CT-scanning. Dernæst anvendte vi standardiserede incidensratioer som et mål for den relative risiko for post-CT LGGB. I den prognostiske del af studiet sammenlignede vi prævalensen af non-metastatisk, metastatisk og ukendte cancerstadier hos patienter med post-CT LGGB og patienter med detekteret LGGB. Derefter udregnede vi overlevelsessandsynligheder og mortalitetsrate ratioer (MMR), hvor vi sammenlignede patienter med post-CT LGGB med patienter med detekteret LGGB.

Resultater: Vi observerede 687 tilfælde af post-CT LGGB blandt 136.628 patienter med en negativ abdominal CT-scanning foretaget med kontrast. Den absolutte risiko var 0.12 % (95 % konfidensinterval (CI): 0.10-0.14) gennem 6 måneder, 0.22 % (95 % CI: 0.19-0.24) gennem 12 måneder, 0.42 % (95 % CI: 0.38-0.46) gennem 3 år og 0.55 % (95 % CI: 0.51-0.60) gennem 5 år efter index CT-scanningen. Den relative risiko var 9.46 (95 % CI: 8.05-11.04) gennem 3-6 måneder, 4.00 (95 % CI: 3.33-4.76) gennem 6-12 måneder, 2.21 (95 % CI: 1.93-2.52) gennem 1-3 år og 1.52 (95 % CI: 1.23-1.86) gennem 3-5 år efter index CT-scanningen. Den justerede prævalensratio var henholdsvis 1.19 (95 % CI: 1.05-1.35) for non-metastatisk, 0.76 (95 % CI:

0.68-0.86) for metastatisk og 1.19 (95 % CI: 1.05-1.35) for ukendt cancerstadie. 5-års overlevelsen var 9.5 % (95 % CI: 6.8-12.7) blandt patienter med post-CT LGGB og 6.4 % (95 % CI: 5.2-7.8) hos patienter med detekteret LGGB. Den justerede MMR var 0.88 (95 % CI: 0.80-0.97).

Konklusion: Selvom den absolutte risiko var lav, havde patienter med en negativ CT-scanning en øget relativ risiko for LGGB sammenlignet med baggrundsbefolkningen. Prognosen for LGGB var dårlig uanset diagnosetidspunkt.

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MANUSCRIPT

1. INTRODUCTION

Computed tomography (CT) plays a key role in ruling out and detecting primary liver, gallbladder, bile duct, and pancreatic (LGBP) cancers. More than 1,700 incident cases of LGBP cancers were diagnosed in Denmark in 2017 (1). LGBP cancers are estimated to account for more than 14% of all cancer deaths worldwide (2). Low five-year survival rates are reported for all these cancers (2-5). The sensitivity for CT scans to detect LGBP cancers has been estimated at 60%-100% (6-9), however the risk of LGBP cancers diagnosed more than three months after a CT scan in which no cancer was found remains unknown.

CT scans are included as either the primary diagnostic test or as a supplement to endoscopy, biopsy, or other diagnostic imaging in the Danish national Cancer Patient Pathways (CPPs) for all gastrointestinal cancers (10-16). The CPPs were introduced nationally in 2007 to prevent delays in the diagnostic process for patients with symptoms indicating a certain type of cancer. In addition to their important role in cancer diagnosis, CT scans are also widely used for detection of multiple infectious abdominal diseases and post-surgical conditions. Hence, CT scans are some of the most common diagnostic tests performed, accounting for around a million scans in 2017 in Denmark (17). Among different CT modalities, contrast-enhanced scans are preferred for detection of LGBP cancers in symptomatic patients due to an increased visualization of the blood perfusion in potential tumors (18). These scans are also broadly able to reveal malignant pathology even though originally performed for other diagnostic purposes. Contrast-enhanced CT scans should therefore always be evaluated for prevalent malignant disease regardless of the indication for the scan.

Knowledge on risk of a LGBP cancer after a negative CT scan (referred to as post-CT LGBP cancers) can help patient guidance and the planning of potential surveillance strategies for symptomatic patients with a negative CT scan. Evidence on prognosis after a post-CT LGBP cancer can help evaluating whether these cancers tend to have an aggressive biology or represented missed cancers. For colorectal cancers (CRCs),

knowledge on risk and prognosis of CRCs detected after a negative colonoscopy has fostered quality improvements in the national CRC screening program through the determination of key quality indicators for colonoscopies (19). In addition, this knowledge has helped clinical decision-making and patient guidance (20-26). However, analogue evidence for post-CT LGBP cancer is missing. This lack of evidence is striking given the key role of CT scans in the CPPs and in cancer diagnosis in general. We therefore conducted this cohort study to investigate the risk of LGBP cancers after a negative CT scan of the abdomen compared with the risk of these cancers in the background population. We further examined the prognosis among patients with a post-CT LGBP cancer compared with patients who had LGBP cancer diagnosed during their first-time CT scan.

2. METHODS

2.1 Setting and data sources

We conducted this population-based cohort study within the entire Danish population (approximately six million people) for the period 1 January 2002 through 31 December 2013. We obtained individual-level, prospectively collected data from the Danish National Patient Registry (DNPR), the Danish Cancer Registry (DCR), and the Danish Pathology Registry (DPR). The data were linked using the unique 10-digit civil registration number (CRN) issued by the Danish Civil Registration System (CRS) (27). The CRS assigns this personal and permanent identifier to each Danish resident at the time of birth or immigration and also monitors the occurrence of death or emigration from the country (28). All Danish residents are covered by the tax-funded medical care system provided by the National Health Service.

The DNPR contains records on all inhospital stays since 1977 (29). Since 1995, the registry also includes hospital outpatient visits and contacts to emergency rooms. Data include CRN, dates of hospital admission and discharge, surgical procedures (including endoscopies), selected diagnostic procedures (including CT scans), 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. Surgical procedures are coded since 1996 using a Danish version of the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical procedures. Since 2002, the reporting of all CT scans to the DNPR has been mandatory. All radiological procedures are coded according to the Danish Classification of Radiological Procedures (see Supplementary Table 3 for codes). The DCR holds records on all incident malignant neoplasms diagnosed in Denmark since 1943 (30). The registry contains data on CRN, diagnosis date, tumor location and tumor stage at diagnosis. Cancers are coded according to the ICD-10 (recoded from ICD-7 before 2004). The DCR receives data from the DPR regarding primary tumor histology coded according to the Systematized Nomenclature of Medicine (SNOMED) coding system. The DPR contains records on all pathology specimens examined in Denmark since 1997 (31).

This study was approved by the Danish Data Protection Agency (record number 2016-051-000001). According to Danish legislation, no approval from an ethics committee or informed consent from patients is required for register-based studies (32).

2.2 Study cohort

We identified all patients who received a first-time radiological procedure code for an abdominal CT scan in the DNPR during the study period (see Supplementary Table 3 for codes). Only contrast-enhanced CT-abdomen and CT thorax-abdomen-pelvis (CT-TAP) scans performed during inhospital stays, outpatient visits, or acute admissions were included. Patients who received a diagnosis of any cancer recorded in the DCR before the date of their first-time CT scan were excluded. We defined the first-time CT scan recorded in the DNPR during the study period as the "index CT". CT scans without a corresponding diagnosis of LGBP cancer recorded in the DCR within three months after the scan were considered as negative CT scans.

From the DNPR, we additionally obtained data on gastrointestinal diagnostic procedures performed within three months of the index CT. These were categorized as follows: lower endoscopies (colonoscopies,

sigmoidoscopies, protoscopies, and anoscopies), upper endoscopies (gastroscopies), and endoscopic retrograde cholangiopancreatographies (see Supplementary Table 3 for codes).

2.3 LGBP cancers

All incident cases of LGBP cancer recorded at or after the index CT were identified from the DCR. These cancers were categorized as either “detected” or “post-CT” (according to the terminology used for post-colonoscopy CRCs (33)). We defined cancers diagnosed within three months after the index CT scan as detected. Cancers were defined as post-CT if the index CT scan was performed more than three months prior to the diagnosis. All incident cases of LGBP cancers observed during the study period were further subcategorized according to cancer site as follows: primary liver cancer, gallbladder and biliary tract cancer, and pancreatic cancer. The LGBP cancers were further categorized according to their primary histological subtype: hepatocellular carcinomas, neuroendocrine tumors, other, and unknown for primary liver cancers; cholangiocarcinomas, adenocarcinomas, other, and unknown for gallbladder and biliary tract cancers; and adenocarcinomas, neuroendocrine tumors, other, and unknown for pancreatic cancers. Finally, all LGBP cancers were categorized according to the TNM stage (34) at diagnosis into non-metastatic (T0-4,x; N0-3; M0, T0-2; N0; Mx, T0-1; Nx; M0,x), metastatic (T0-4,x; N1-3; M1,x, T0-4,x; N0;M1, T0-4,x, Nx; M1), and unknown stage (T2-4,x; Nx; M0,x; T3-3,x; N0; Mx) (see Supplementary Table 3 for codes).

2.4 Mortality

Data on date of death were obtained from the CRS to evaluate the survival after a detected LGBP cancer and after a post-CT LGBP cancer.

2.5 Comorbidity

Data on comorbid diseases recorded before the index CT were obtained from the DNPR. The Charlson Comorbidity Index (CCI) was used as a measure of the burden of comorbidity (35). The CCI is a scoring system that assigns from one to six points to a range of diseases as the components of a summed, aggregate score (see Supplementary Table 4 for codes). Patients were categorized into three subgroups according to their calculated CCI score: low (no comorbidities) = CCI score of 0, medium = CCI score of 1-2, or high = CCI score of 3 or more. As recommended in previous literature, we included all available information on conditions included in the CCI before the index CT (36, 37). Of note, we applied a modified CCI excluding any prior tumors from counting in the index.

To account for conditions not included in the CCI, we additionally obtained data on the presence/absence of the following conditions recorded at any time before the index CT scan in the DNPR: alcoholism-related disorders, hepatitis, inflammatory bowel diseases, primary sclerosing cholangitis, acute and chronic pancreatitis, cholecystitis, and cholangitis.

2.6 Statistical analyses

2.6.1 Absolute and relative risks

Patients with a negative CT scan were followed from three months after their index CT scan until first occurrence of post-CT LGBP cancer, death, emigration, or 31 December 2013 (Figure 1). Patients who were diagnosed with LGBP cancer (detected LGBP cancers), died, emigrated, or experienced administrative study end within three months after their index CT were disregarded from this analysis. We calculated the absolute risk as the cumulative incidence proportion of post-CT LGBP cancers during 6 months, 12 months, 3 years, and 5 years after the CT scan treating death as a competing risk. As a measure of relative risk, we computed standardized incidence ratios (SIRs) of post-CT LGBP cancers as the ratio of the observed number

of post-CT LGBP cancers during the study period to the expected number of LGBP cancers based on national cancer rates calculated from the DCR. The expected number of LGBP cancers was calculated by multiplying the number of person-years of observation for patients with a post-CT LGBP cancer by the national LGBP cancer incidence rates for each sex, calendar periods, and age in one-year-intervals. The SIRs were computed by time period elapsed since the index CT scan (3-6 months, 6-12 months, 1-3 years, 3-5 years, and more than 5 years). We stratified cumulative incidence proportions and SIRs by age, sex, modified CCI score, presence/absence of gastrointestinal endoscopy within three months of the CT scan, and cancer site. Confidence intervals (CIs) were computed under the assumption that the observed number of LGBP cancer followed a Poisson distribution. Exact 95% CIs were used when the observed number was less than ten, otherwise, Byar's approximation was applied.

2.6.2 Cancer stage and primary histological subtype

The distribution of LGBP cancer stages and primary histological subtypes among patients with a post-CT LGBP cancer was compared with the corresponding distribution in patients with a detected LGBP cancer. For each cancer stage and histological subtype, we used the robust Poisson method to calculate crude and adjusted prevalence ratios (PRs) and associated CIs. The adjusted model included age, gender, and CCI score at the LGBP cancer diagnosis.

2.6.3 Mortality

We evaluated mortality among all patients with a diagnosis of LGBP cancer (either detected or post-CT) recorded during the study period. Patients were followed from the date of their LGBP cancer diagnosis until death, emigration, or end of study (Figure 2). Survival probabilities after one and five years of follow-up were estimated using the Kaplan Meier technique. We used Cox proportional-hazards regression analysis to

compute hazard ratios as an estimate of the mortality rate ratio (MRR), comparing patients who had a post-CT LGBP cancer with patients who had a detected LGBP cancer. The adjusted model included age, sex, CCI score at the LGBP diagnosis, and calendar year of the CT scan.

2.6.4 Sensitivity analyses

We conducted two sensitivity analyses. The first assessed potential differences among two types of CT scans by restricting the analyses to study participants with 1) contrast-enhanced CT scans of the abdomen, and 2) contrast-enhanced CT-TAP scans. The second sensitivity analysis evaluated the impact of our definition of a negative CT scan by defining a negative CT scan as a scan without a LGBP cancer diagnosis within four months (rather than three months) after the scan.

The data management and statistical analyses were performed using the Stata statistical software package version 15.1 (StataCorp, Texas, USA) and the SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina).

3. RESULTS

3.1 Patients with a negative CT scan

We identified a total of 154,405 patients recorded as having a first-time contrast-enhanced CT scan of the abdomen during 2002-2013. In total, 2,167 patients were diagnosed with detected LGBP cancer at index CT while 15,610 died or experienced administrative study end (31 December 2013) within three months after the index CT scan. Thereby, 17,777 patients were disregarded from this part of our study while 136,628 had a negative CT scan and were included in the follow-up (Figure 3). The baseline characteristics (number and proportions) are shown in Table 1. Of patients with a negative CT scan, 48% were female. Median age at the CT scan was 57 years (interquartile range (IQR): 42-70).

Of all patients with a negative CT scan, 687 patients developed a post-CT LGBP cancer while 135,941 patients were free of LGBP cancer at the administrative end of study (i.e. had a true negative index CT scan). Patients with a post-CT cancer were older (median age at index CT: 57 years (IQR: 42-70)) and were more likely to be male, to be recorded as having an endoscopy within three months of the CT scan, to have a higher CCI score, and to be diagnosed with alcoholism-related disorders, hepatitis, primary sclerosing cholangitis, pancreatitis, cholecystitis, and cholangitis before the index CT scan than patients with a true negative CT scan (Table 1).

3.2 Absolute risks

A total of 687 patients developed a post-CT LGBP cancer during the follow-up period. The corresponding absolute risk was 0.99% (95% CI: 0.85-1.15). The absolute risk of post-CT LGBP cancer was 0.12% (95% CI: 0.10-0.14) during 6 months, 0.22% (95% CI: 0.19-0.24) during 12 months, 0.42% (95% CI: 0.38-0.46) during 3 years, and 0.55% (95% CI: 0.51-0.60) during 5 years after the index CT scan, respectively (Figure 4). Of all post-CT cancers, 194 (28%) were primary liver cancers, 120 (18%) were gallbladder and bile duct cancers, and 373 (54%) were pancreatic cancers. The absolute risk was 0.11% (95% CI: 0.09-0.13) for primary liver cancer, 0.08% (95% CI: 0.07-0.10) for gallbladder and bile duct cancers, and 0.23% (95% CI: 0.20-0.26) for pancreatic cancers 3 years after the index CT scan, respectively (Figure 4). Increasing age, a high CCI score, and presence of endoscopy within three months of the CT scan were associated with a particularly high risk of a post-CT LGBP cancer (Table 2).

3.3 Relative risks

Patients with a negative CT scan were at increased risk of LGBP cancer compared with the background population during the follow-up with an 50% increased risk (SIR = 1.50 (95% CI: 1.20-1.84)) of being

diagnosed with a LGBP cancer more than five years after a negative CT scan (Figure 5). The SIR was 9.46 (95% CI: 8.05-11.04) during 3-6 months, 4.00 (95% CI: 3.33-4.76) during 6-12 months, 2.21 (95% CI: 1.93-2.52) during 1-3 years, and 1.52 (95% CI: 1.23-1.86) during 3-5 years after the index CT scan, respectively. Stratification by cancer sites yielded same patterns with the greatest relative risk increase observed during the first three to six months after the CT scan and a decreasing relative risk with time elapsed since the index CT scan (Figure 5).

The relative risk of LGBP cancer were elevated for all age groups compared with the background population, however, the youngest individuals yielded the highest relative risk estimates. A high CCI score was associated with a substantially increased relative risk (Table 3).

3.4 Patients with LGBP cancer

Table 4 outlines the characteristics of all patients diagnosed with LGBP cancer during the study period (categorized as either post-CT or detected). Of 687 post-CT LGBP cancers, the majority (50%) were diagnosed between 6 and 36 months after the index CT scan. One hundred sixty-one (23.4%) were diagnosed between 3-6 months while 184 (26.6%) were diagnosed more than 36 months after the index CT, respectively. The distribution of post-CT cancers (according to cancer site) are reported above. Of 2,167 detected LGBP cancers, 412 (19%) were primary liver cancers, 384 (18%) were gallbladder and bile duct cancers, and 1,371 (63%) were pancreatic cancers. Of patients with a detected LGBP cancer, 42% were female. Median age at the index CT scan was 68 years (IQR: 61-75). Of patients with a post-CT cancer, 41% were female. Median age at the index CT scan was 67 years (IQR: 58-73). Patients diagnosed with post-CT cancers were more likely to have a medium or high CCI score and in general more likely to be recorded with specific comorbidities (alcoholism-related disorders, hepatitis, inflammatory bowel diseases, pancreatitis, cholecystitis, and cholangitis) before the index CT scan than patients who had a detected LGBP cancer.

3.5 Cancer stage and primary histological subtype

Comparing post-CT LGBP cancer patients with detected LGBP cancer patients, 33% versus 27% had a non-metastatic cancer, 33% versus 44% had a metastatic cancer, and 33% versus 28% had an unknown stage cancer. The corresponding adjusted PRs were 1.19 (95% CI: 1.05-1.35), 0.76 (95% CI: 0.68-0.86), and 1.19 (95% CI: 1.05-1.35) (Table 5). The slightly increased prevalence of non-metastatic cancers and the lower prevalence of metastatic cancers among patients with a post-CT LGBP cancer were also observed when we stratified our analysis by cancer site. After stratification by primary histological subtype, we observed a lower prevalence of cholangiocarcinomas among patients with a post-CT LGBP cancer (PR = 0.61 (95% CI: 0.33-1.12)) and a lower prevalence of adenocarcinomas located in the pancreas (PR = 0.72 (95% CI: 0.63-0.81)). Overall, no subtypes were substantially increased among patients with a post-CT cancer.

3.6 Mortality

During follow-up, 2,403 patients died of whom 560 had a post-CT LGBP cancer and 1,843 had a detected LGBP cancer. The survival for all LGBP cancers diagnosed during the entire study period were generally poor. The overall five-year survival probability was 9.5% (95% CI: 6.8-12.7) among patients with a post-CT LGBP cancer, while the corresponding probability among patients with a detected LGBP cancer was 6.4% (95% CI: 5.2-7.8) (Table 6 and Figure 6). The five-year survival probability among patients with a post-CT cancer was 7.5% (95% CI: 2.7-15.6) for patients with a primary liver cancer, 11.6% (95% CI: 5.6-20.1) for patients with a gallbladder or biliary tract cancer, and 8.9% (95% CI: 5.7-12.9) for patients with a pancreas cancer. Overall, patients with a post-CT cancer had a slightly decreased mortality compared with patients whose cancer was detected at index CT (MRR = 0.88 (95% CI: 0.80-0.97)). After stratification by cancer site, the corresponding MRRs were 0.88 (95% CI: 0.72-1.08) for primary liver cancers, 1.00 (95% CI: 0.79-1.26) for gallbladder and biliary tract cancers, and 0.86 (95% CI: 0.76-0.98) for pancreatic cancers (Table 6).

3.7 Sensitivity analyses

No substantial differences were observed when restricting our analyses to CT-abdomen, and CT-TAP scans (data not shown). Low absolute risk estimates and increased relative risks of a LGBP cancer after a negative CT scan were observed for all cancer sites when considering CT scans without a corresponding cancer diagnosis within four months after the scan (rather than three months) as negative scans (Supplementary table 1 and 2). Thereby the observed patterns were identical with the main analysis, however the relative risk estimates were generally lower during the first follow-up periods in the sensitivity analysis.

4. DISCUSSION

Although the absolute risk was low, our study showed that patients with a negative contrast-enhanced CT-scan of the abdomen had an increased relative risk of developing a LGBP cancer. The relative risk remained increased during more than five years after the scan was performed. Non-metastatic cancer stage was more prevalent among patients with a post-CT LGBP cancer compared with patients whose cancer was detected. Prognosis was poor for all cancers observed during the study period regardless of diagnosis time.

The strengths of our study include its population-based design in a setting with free access to healthcare in combination with high quality and continuously updated data on medical procedures, comorbidities, and cancer diagnoses (30, 35, 38-40). However, our study has certain limitations. The DNPR lacks data on indications for the CT scans and we were thereby unable to distinguish CT scans performed for detection of suspected cancers from scans performed for examination of non-malignant conditions. It is, however, challenging to determine how this impacted the direction of our risk estimates. Patients with cancer symptoms might be more likely to have a LGBP cancer diagnosed at the index CT scan, thereby decreasing the proportion of post-CT cancers during the follow-up. In contrast, patients with cancer symptoms may have a higher probability of being diagnosed with a post-CT LGBP cancer than patients scanned for other purposes. Therefore, it is plausible, that an analysis restricted to CT scans performed for cancer suspicion

might have yielded higher risk estimates. Overall, readers should keep in mind that our results are applicable for all patients with a negative CT scan regardless of the indication for the scan.

We restricted our study cohort to patients with a contrast-enhanced CT, however, we lacked data on several other important factors in relation to the scans. Of these, type of CT scan (multislice CT or multidetector CT), phases of enhancement (early arterial, late arterial, hepatic or late portal phase etc.), and type, total amount, and injection rate of contrast are pivotal (41-43). We are thereby not able to rule out the possibility that the increased relative risk might reflect a suboptimal choice of scan modality nor to evaluate the risk of post-CT LGBP cancers after a specific type of CT scan.

Varying completeness and validity of individual variables obtained from the DNPR should be considered. No prior study has evaluated the accuracy of the abdominal radiological codes in the DNPR. We are therefore unable to rule out misclassification of our exposure, however, we find a potential misclassification unlikely to be dependent of the LGBP cancer risk. Thereby, a possible misclassification will be non-differential and could only have biased our risk estimates towards the null. As the DNPR lacks nationwide data on CT scans performed before 2002 (29), we could not exclude patients with a CT scan performed before the study period. LGBP cancers categorized as detected cancers may therefore be misclassified which possibly could have introduced a conservative misclassification bias.

Finally, the possibility of detection bias is important for this study and should be considered. Detection bias is a differential misclassification of the outcome (44). Since all patients who undergo a CT scan have an indication for the scan (including symptoms of cancer), they might have a higher probability of being diagnosed with a LGBP cancer compared to the background population during the follow-up. This type of bias would potentially lead to an overestimation of the relative risk of LGBP cancers among patients with a negative CT scan.

To the best of our knowledge, this is the first study to evaluate risk and prognosis of LGBP cancers after a negative CT scan of the abdomen. The post-CT cancers may represent either rapidly progressive tumors or

cancers that were missed at the index CT scan. For multiple reasons, our findings did not suggest an aggressive tumor biology. First, in case of a particularly aggressive tumor biology we would have expected an increased prevalence of metastatic cancers in patients with post-CT cancers compared with patients whose LGBP cancer was detected. However, we observed a lower prevalence of metastatic cancers among patients with post-CT LGBP cancers. Second, we would have expected the survival to be worse than for patients who had a detected LGBP cancer. We observed a poor prognosis regardless of diagnosis time. Of note, we observed a slightly lower mortality among patients with a post-CT LGBP cancer compared with patients whose cancer was detected. Third, the prevalence of primary histological subtypes suggested a generally heterogeneous diagnostic frequency of subtypes among post-CT cancers. In case of an aggressive tumor biology, we would have expected to observe a substantially increased risk of few and specific histological subtypes. However, small numbers of post-CT cancers and lack of data on molecular characteristics of the tumors compromised this analysis. Last, we observed the greatest relative risk increase within the first three to six months after the index CT scan. As cancers generally are thought to develop within years (45), our findings suggest that the majority of the post-CT cancers represented cancers that were missed at the index scan. However, several limitations (discussed above and in the following) highlight the need for additional and conclusive research.

Absolute and relative risk estimates were substantially elevated for patients with a high CCI score. Additionally, prevalent pancreatitis and hepatitis diagnosed before the CT scan were more frequent among patients with post-CT LGBP cancers than among patients who had a detected LGBP cancer and among patients with a true negative CT scan. As both conditions are known risk factors for development of a subsequent LGBP cancer (46-48), these patients may benefit from targeted cancer surveillance. Of note, our incidence and prognostic estimates were not stratified by specific comorbidities due to small numbers of these patients.

As mentioned, our study suggests that post-CT cancers might represent overlooked cancers. However, in this register-based study, we lacked important information regarding the planning of potential subsequent CT scans. Suspicious findings which at the time of a CT scan cannot be diagnosed as frank malignancies, are generally followed up by an additional scan within a certain period of time. In case that a LGBP cancer is diagnosed at a follow-up scan performed more than three months after the index CT scan, this cancer will be categorized as a post-CT cancer in our study. As malignant pathology was suspected at the index scan, this cancer should, however, not be classified as a missed cancer. We might therefore overestimate the risk of post-CT LGBP cancers. We changed our definition of a negative CT scan in our second sensitivity analysis to evaluate the potential for this type of misclassification. This analysis yielded slightly decreased risk estimates during the first follow-up periods compared with our results from the main analysis, however, the risk of post-CT LGBP cancers was still increased during all follow-up periods. This finding suggests that late follow-up scans did not independently explain the increased relative risk of a LGBP cancer after a negative CT scan.

In conclusion, the absolute risk of a post-CT LGBP cancer was low, however the relative risk of LGBP cancers after a negative abdominal contrast-enhanced CT scan was substantially increased. Our findings did not suggest that post-CT cancers represent rapidly growing malignancies, but rather missed cancers. Several methodological issues such as the possibility for detection bias, and lack of data on the indication for the scan and planning of potential follow-up examinations need to be taken into account before applying these findings in a clinical setting.

SUPPLEMENTARY

1. METHODOLOGICAL CONSIDERATIONS

We used individual-level, prospectively collected, and validated registry data with life-long follow up on virtually all study participants. The data were obtained within the entire Danish population in a setting with a universal, tax-funded, and income-independent healthcare system. Our approach secured the optimal conditions for answering our research question. However, errors, insufficient study design, and/or statistical approaches may disturb the accurate estimates of the effect of an exposure on a given outcome and should be taken into account when interpreting estimates from every scientific study. The following section addresses the possible sources of errors in our study concerning study design, statistical analyses, selection and information bias, and confounding. Finally, the external validity is discussed.

2. Study design

Multiple observational study designs are available. We chose to design a cohort study using prospectively collected registry data in order to answer our research question. A cohort study measures the occurrence of an event within a cohort during a given period of time, usually by comparing the occurrence of the event of interest in an exposed and an unexposed cohort (49). Thereby, the study participants are identified by their exposure status while the event(s) is/are measured during the follow-up time. Several limitations such as the cost and time-consuming nature and the requirements of large study cohorts without a great loss of follow-up need to be taken into consideration before conducting a cohort study. On the other hand, prospective cohort studies have several strengths such as the ability to measure multiple outcomes in one study, to establish absolute risk estimates, and to eliminate the possibility of recall bias. Another common design for observational studies is the case-control design. In a case-control study, the cases are identified by their outcome status. A control group consisting of participants without the outcome is then sampled

from the entire source population that gave rise to the cases. The distribution of exposure is then evaluated within the group of cases and controls. Case-control studies can provide information that mirrors the findings from a cohort study but are usually thought to be more efficient and less expensive. However, case-control studies usually provide only ratio measures (relative risk measure) of a given association which is one of the main drawbacks of conducting a case-control study. The relative risk indicates to which extent a given exposure is associated with occurrence of disease, while the absolute risk provides information on the size of disease burden, which is added to a population during a given period of time. As demonstrated in the present study, the relative risk may be substantially increased but with little public health consequence (49). Like the cohort design, the case-control design is susceptible for confounding. Several design and statistical approaches are available to eliminate or minimize the effect of confounding (as discussed under Random and systematic errors). Randomization is one of these and has the advantage of potentially preventing confounding by both known and unknown confounders (50). Therefore, randomized controlled trials are traditionally considered the gold standard regarding study design. However, such studies are often by far the most expensive and time consuming and can only be used when investigating the effect of an intervention on the occurrence of an outcome. Since we aimed to investigate different outcomes at varying follow-up periods, we chose to design a cohort study instead of other observational designs like a case control study. Additionally, we found it important to be able to report both absolute and relative risk estimates. Finally, we were not able to assign patients a negative CT scan, which eliminates the possibility of conducting a randomized trial.

3. Exposures and outcomes

The present study includes an incidence and a prognostic part. We evaluated the incidence (risk) of LGBP cancer after a negative CT scan of the abdomen in the first part, and the prognosis after a post-CT LGBP cancer in the second part. The definitions of exposures and outcomes are described below.

3.1 Incidence of LGBP cancer

All patients with a contrast-enhanced CT scan of the abdomen recorded in the DNPR during 2002-2013, without a prior diagnosis of any cancer recorded in the DCR and without a diagnosis of LGBP cancer within three months after the index CT scan, were considered as exposed study participants. To obtain relative risk estimates, the risk of a LGBP cancer among the exposed cohort was compared with the risk of these cancers in the background population. Thereby, the background population acts as an unexposed comparison cohort.

The primary outcome for this part of the study was defined as the occurrence of a LGBP cancer recorded in the DCR more than three months after the date of the index CT scan. All incident LGBP cancers recorded after a negative CT scan during the study period were categorized according to cancer site. Secondary outcomes were death, emigration (both recorded in the CRS), or administrative end of study.

3.2 Mortality

For the prognostic part of the study, we defined the exposure as time of diagnosis of LGBP cancer recorded in the DCR. Time of diagnosis were categorized as either after a negative CT scan (post-CT cancers) or diagnosed at the index CT scan (detected cancers).

The primary outcome was death recorded in the CRS. Secondary outcomes were emigration recorded in the CRS or administrative end of study.

4. Time to event analysis: statistical considerations

We used the principles of the time-to-event analysis, including Kaplan-Meier method, Cox proportional hazards analysis, and Poisson regression. We observed whether the study participants experienced the

event before the end of the follow-up period or not. Study participants who did not experience the event during the follow-up period were considered as event free. For the incidence analysis, the study participants were followed from three months after a negative CT scan until first occurrence of a LGBP cancer, death, emigration, or end of study. For the prognostic part, study participants who received a LGBP cancer diagnosis during the study period were followed from the date of their cancer diagnosis until first occurrence of death, emigration, or study end. The time-to-event analysis requires that the right-censoring is independent of the risk of the event (51). We thereby assume that study participants being censored at a time *t* are representative for the remaining individuals in the study cohort at time *t*.

4.1 Cumulative incidence proportions

As an absolute risk measure, we calculated the cumulative incidence proportion of LGBP cancers after a negative CT scan of the abdomen. The risk equals the number of individuals with incident LGBP cancers during a given follow-up period divided by the number of individuals who were initially cancer free during the same follow-up period (49).

$$Risk = \frac{Number\ of\ subjects\ developing\ a\ post-CT\ LGBP\ cancer\ during\ a\ time\ period}{Number\ of\ subjects\ with\ a\ negative\ CT\ scan\ for\ the\ time\ period}$$

The risk increases with the time of follow-up due to a prolonged time for the event to occur. Individuals who died without having a cancer diagnosis were no longer at risk for developing cancer. We therefore considered death as a competing risk by taking into account that individuals who died will not develop a cancer later on. Using cumulative incidence proportion as an absolute risk measure requires 1) a minimal loss of follow-up due to other causes than the event(s), 2) that only incident disease is counted, and 3) that the time of follow-up is specified for each incidence proportion (49). Minimal loss of follow-up due to other

causes than occurrence of LGBP cancer, death, emigration, or study end, and specified dates on exposure and outcome from the Danish registries allowed us to calculate cumulative incidence proportions as absolute risk measures in this study. The absolute risks estimated the size of disease burden, which was added to the population during the study period, however, they did not provide knowledge on the risk of cancer among patients with a negative CT scan relative to the cancer risk among non-exposed individuals.

4.2 Standardized incidence ratios

We used SIRs as a relative risk measure to evaluate the risk of LGBP cancers after a negative CT scan compared with the risk of these cancers in the background population. SIRs equal the observed number of post-CT LGBP cancers among patients with a negative CT scan divided by the expected number of LGBP cancers in the background population. The expected number was calculated on the basis of national cancer incidence rates obtained from the DCR according to sex, age, and calendar time distribution of person-years in one-year intervals multiplied by the number of person-years of observation for patients with a post-CT LGBP cancer. Multiplying the number of person-years by the incidence rates will yield the number of LGBP cancer cases that would be expected if patients with a negative CT scan have the same risk of cancer as the background population. We thereby used the principles of indirect standardization (52).

$$SIR = \frac{Observed\ number\ of\ post-CT\ LGBP\ cancer}{Expected\ number\ of\ LGBP\ cancers} = \frac{Number\ of\ post-CT\ LGBP\ cancers\ among\ patients\ with\ a\ negative\ CT\ scan\ within\ each\ group\ of\ sex, age, and\ calendar\ time}{(National\ incidence\ rates\ of\ LGBP\ cancers\ within\ each\ group\ of\ sex, age, and\ calendar\ time) * (number\ of\ person-years\ of\ observation\ for\ patients\ with\ a\ post-CT\ LGBP\ cancer)}$$

By using incidence ratios, we addressed potential competing risks as an individual who experienced the disease ceased to contribute with follow up time after the event occurred (49).

An incidence rate (obtained from the DCR) equals the number of participants developing disease divided by the total time experienced by the population being followed. The timescale is often expressed by person-years-at-risk (53).

$$Incidence\ rate = \frac{Number\ of\ patients\ developing\ a\ LGBP\ cancer}{Total\ time\ experienced\ for\ all\ subjects\ being\ followed}$$

The standardization process enabled us to compare the incidence of cancer among patients with a negative CT scan with the incidence of cancer in a comparable (on age, sex, and calendar period) cohort. As discussed below, standardization is one of the statistical tools whereby confounding can be taken into account in observational studies. SIRs should not be used in situations where the study cohort accounts for a large proportion of the background population as individuals from the study cohort are also a part of the background population. In this case, the risk estimates will tend to underestimate the association between exposure and outcome. Our study population consisted of 136,628 exposed individuals, who we did not consider as a large proportion of the background population.

Of note, we stratified our SIR estimates by age, sex, modified CCI, and presence/absence of endoscopy within three months of the CT scan. When stratifying by other variables than age, sex, and calendar period, the cancer incidence rates within the relevant strata among patients with a negative CT scan will be compared with the cancer incidence rates from the overall background population. In other words, we did not take into account whether or not persons from the background population were recorded with comorbidities or endoscopies.

4.3 The Kaplan-Meier method

To evaluate survival, we categorized all LGBP cancers diagnosed during the study period as either 1) post-CT LGBP cancer, or 2) detected LGBP cancer. We used Kaplan-Meier estimates to plot survival curves showing the proportion of individuals surviving in a given length of time. This method should be used with caution in situations with other outcomes than overall survival as every individual who is censored due to death is assumed to be at risk of the outcome after the censoring. This could possibly overestimate the risk of the investigated outcome (54). We chose the Kaplan-Meier method since our outcome was defined as overall survival. In other words, any death that occurred represented an outcome accounting in the numerator of the risk measure.

Multiple assumptions need to be fulfilled when using the Kaplan-Meier method. First, the probability of being censored should not be related to the risk of the event occurring (55). In this study, we censored individuals who emigrated during follow-up or were alive at the administrative end of follow-up. Individuals who were alive at the study end or emigrated during the study period will die in the future, but we do not know when. However, their probability of being censored is unlikely to be related to the risk of dying. Second, the time of the event has to be observed exactly (55). We obtained information on exact date of death through the CRS. Finally, all studied individuals should have the same risk of dying at time zero (55). We assumed that the risk of dying was the same for study participants recruited early and late in the study period.

4.4 Cox proportional hazard analysis

We used cox proportional-hazards regression models to compute hazard ratios as an estimate of the MRR, comparing patients who had a post-CT LGBP cancer with patients who had a detected LGBP cancer. This regression model is by far the most common used for time-to-event data. The central assumption for using this model is that the ratio of the hazards comparing different exposure groups (in this case post-CT LGBP

cancers and detected LGBP cancers) remains constant over time. We evaluated this assumption by plotting the log-minus-log of the two survival curves. The curves were visually deemed to be parallel and we considered the proportional hazard assumption as fulfilled.

4.5 Prevalence ratios

The distribution of LGBP cancer stage and primary histological subtype among patients with a post-CT LGBP cancer was compared with the corresponding distribution in patients with a detected LGBP cancer. For each cancer stage and histological subtype, we used the robust Poisson method to calculate PRs and associated CIs.

$$PR = \frac{\frac{Number\ of post-CT\ LGBP cancers\ within\ the\ different\ groups\ of\ cancer\ stages\ and\ primary\ histological\ subtypes}{Total\ number\ of\ post-CT\ cancers}}{\frac{Number\ of\ detected\ LGBP\ cancers\ within\ the\ different\ groups\ of\ cancer\ stages\ and\ primary\ histological\ subtypes}{Total\ number\ of\ detected\ LGBP\ cancers}}$$

Poisson regression is used to estimate rate ratios comparing different exposure groups in the same way that logistic regression models are used to estimate odds ratios (52).

5. Random and systematic errors

Potential errors can affect the precision and validity of the effect measures in every study. It is not possible to determine to which extent errors affect the estimates as the true association is often unknown (49). However, multiple steps can be taken to minimize the effect of potential errors through design and statistical approaches. Two types of errors should be assessed: random error and systematic error. Random error relates to the statistical precision. We quantified the precision of our estimates by evaluating the

width of the 95% CIs rather than using p-values (49, 56). In the present study, we yielded statistically precise estimates with narrow confidence intervals suggesting that possible random errors played a minimal role. This might reflect the large number of study participants, as the risk of random error decreases with increasing study size. On the contrary, the potential for systematic errors is unaffected by the study size (49). The main sources of possible systematic errors are selection bias, information bias, and confounding. Potential systematic errors can affect the internal and thereby the external validity.

5.1 Selection bias

Selection bias arise when participants included in the study are not representative for the target population due to the procedure used to select the participants. Thereby, the association between exposure and outcome differs among study participants and non-participants (57). Selection bias may also occur if continued participation in a cohort study depends on the exposure or outcome (referred to as differential loss to follow-up or competing risk). As the association between exposure and outcome among non-participants is unknown, the presence of selection bias usually needs to be inferred, rather than observed (49). We identified our study cohort through the DNPR. Due to the universal healthcare system in Denmark and the mandatory reporting to the DNPR, virtually all CT scans performed at public hospitals in Denmark are captured in the DNPR since 2002 (29). A small number of CT scans are performed at private hospitals, however registration to the DNPR for CT scans performed at private hospitals has been mandatory since 2003 (39). Our approach secured an almost complete inclusion of patients who underwent a CT scan of the abdomen in Denmark during the study period, which virtually eliminates the possibility for selection bias. An almost complete follow-up of all included patients minimized the potential for differential loss of follow-up.

5.2 Information bias

Information bias arise in case of mismeasurement of study variables, mainly regarding exposure and outcome. Information bias are referred to as misclassification if the error leads to a study subject being placed in an incorrect category (49). For the present study, information about exposure and outcome was considered in categories. Therefore, potential information error will lead to misclassification. The direction of the subsequent bias in our estimates depends on whether the potential misclassification is differential or non-differential. For both exposure and outcome, differential misclassification is a misclassification that differs according to the value of its counterpart. This error can either exaggerate or underestimate the association (49). In contrast, non-differential misclassification of exposure and outcome is unrelated to its counterpart. Non-differential misclassification of dichotomous variables biases the association towards the null, which will underestimate an effect.

Overall, data on exposure were collected prospectively without any knowledge about various outcomes. Hence, non-differential misclassification is most likely in the present study.

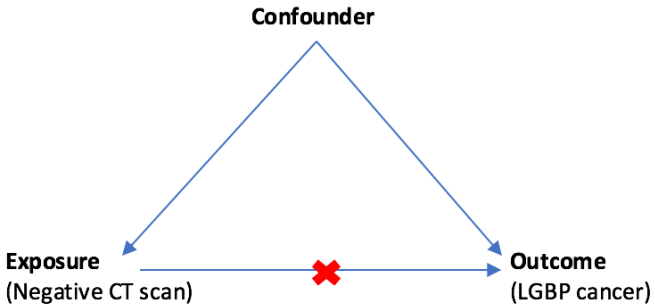
Exposure misclassification could have arisen from incorrect coding of the CT scans in the DNPR. An extensive previous validation study reported high positive predictive values (PPVs) for many diagnoses coded in the DNPR (29). The high PPV (i.e. validity) of diagnoses means that the proportion of patients recorded in the DNPR with a disease, who actually have the given disease, is high. Of note, no prior evaluation of the PPV for abdominal CT scans has been performed. However, in case that a CT scan is coded but not performed we would expect the misclassification to be non-differential. Another issue that needs to be addressed regards the coding of contrast enhancement as only patients with a contrast-enhanced scan were included in our study. Contrast enhancement is coded as a supplementary code in relation to the primary radiological procedure code. The completeness of supplementary codes in the DNPR is known to be lower than for the primary codes (29). Thereby, we could have missed a substantial proportion of individuals who actually met the criteria for “enrollment” in our study. We evaluated whether locally

coding practices within the five regions of Denmark could have introduced a substantial loss of patients and found that our study cohort included the expected number of patients from each region. We cannot rule out potential misclassification due to incorrect coding of CT scans, however, we assume that the chance of being misclassified is independent of the risk of being diagnosed with cancer. A potential misclassification will therefore bias our results towards the null.

With respect to outcome misclassification in the incidence part of our study, the completeness and validity of diagnoses in the DCR have been found to be high (30). However, as mentioned in the discussion part, we cannot rule out some misclassification in relation to our definition of post-CT LGBP cancers due to lack of data on planning of subsequent CT scans. For the prognostic part of the study, death is coded essentially without errors in the CRS, why information bias from this source are negligible (40).

5.3 Confounding

Confounding can be thought of as a confusion of effects (49). Confounding occurs when a predictor of the outcome is unequally distributed between the exposed and unexposed groups. A variable must fulfill the following requirements to be considered as a confounder: 1) be associated with the outcome (either as a cause or as a proxy for a cause), 2) be associated with the exposure, and 3) not be included on the causal pathway between the exposure and outcome.



Confounding can be controlled through design by randomization, restriction or matching and through statistical approaches by standardization, stratification, or adjustment. As mentioned above, randomization can prevent potential confounding by unknown confounders, whereas other approaches only deal with confounding from known confounders (49, 50).

We dealt with potential confounding caused by age, sex, and calendar time distribution of person-years by indirect standardization in our relative risk estimates. We additionally stratified our cumulative incidence and SIR analyses by age, sex, CCI score, and presence of endoscopy within three months of the CT scan. Of note, adjustment for CCI score might be insufficient as the registration and diagnostic work-up for some of the conditions included in the CCI most likely improved over time (misclassification of covariates). To account for conditions not included in the CCI, we collected information on presence of several diseases known to be associated with the risk of a LGBP cancer. However, small numbers of events within these groups did not allow useful stratification.

For the prognostic part of our study, we controlled for potential confounding by adjusting for age, sex, CCI score, and year of CT scan. Finally, we restricted our study cohort to only include patients with: 1) CT abdomen, and 2) CT-TAP in a sensitivity analysis. The latter did not change our estimates substantially. Although we dealt with confounding by multiple approaches, our results may still be influenced by residual confounding. Most importantly, we had no information on the indication for the CT scan, smoking, and use of medication.

6. Generalizability

Selection bias, information bias, and confounding are all related to the internal validity of a study. The internal validity explains to what degree the interpretation of the data is correct (57). A high internal validity is a prerequisite for a scientific study with a high external validity or generalizability (57). The concept of generalizability refers to either the statistical generalization or the scientific generalization of a

study. The statistical generalization exist in the field of survey sampling were researchers draw samples from a population. In this case, generalizing to the source population will be the main concern. However, scientific generalization (which exist in epidemiology and in biological research of animals) refers to the process of constructing a correct statement about the way the nature works (58). Thus, we preferred to study a homogeneous cohort that only differed in respect to the exposure status rather than studying a heterogeneous population in respect to genes, environment, and race. Since the Danish population has a relatively stable and homogeneous demography in relation to race, socioeconomic factors and health-care behavior (29), we thereby limited the variability of confounding by these factors. This approach is opposed to seeking representativeness in survey sampling. Assuming that systematic error is negligible, our study conducted in Denmark showing that patients with a negative CT scan of the abdomen had an increased relative risk of LGBP cancers does not need to be repeated in Norway to determine whether Norwegian patients with a negative CT scan also have an increased risk of LGBP cancers (49). Still, potential differences in diagnostic work-up, quality, and interpretation of CT scans might impact the risk of post-CT LGBP cancers and should be assessed in a potential extrapolation of our results.

7. CLINICAL IMPLICATIONS AND PERSPECTIVES

We demonstrated that patients with a negative CT scan of the abdomen had an increased relative risk of being diagnosed with a LGBP cancer during more than five years after their first-time scan. Physicians and patients should be aware of this risk. The low absolute risk, the poor prognosis regardless of diagnosis time, and the lowered proportion of metastatic cancers among patients with a post-CT cancer should be considered and included in the patient information to secure optimal patient guidance.

We showed that patients with a high burden of comorbidity were at substantially increased risk of post-CT LGBP cancers. These results highlight the need for a low threshold for further examination or even cancer

surveillance in multimorbid patients with a negative CT scan. This finding is of major health importance in a rapidly aging global population with an increasing number of patients with multimorbidity (59).

Several study limitations need to be addressed in future research. Most importantly, future studies performed among patients referred for a CPP are needed. Additionally, the completeness and validity of the coding of radiological procedures in the DNPR as well as the exact planning of follow-up scans should be evaluated – probably through medical chart reviews.

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TABLES AND FIGURES

Figure 1: Definition of the follow-up period for patients with a negative contrast-enhanced CT scan.

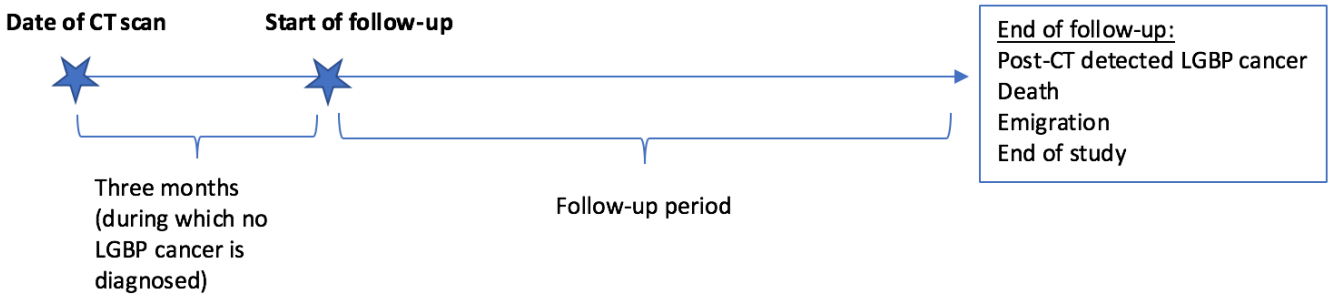


Figure 2: Definition of the follow-up period for patients with a LGBP cancer (either detected or post-CT).

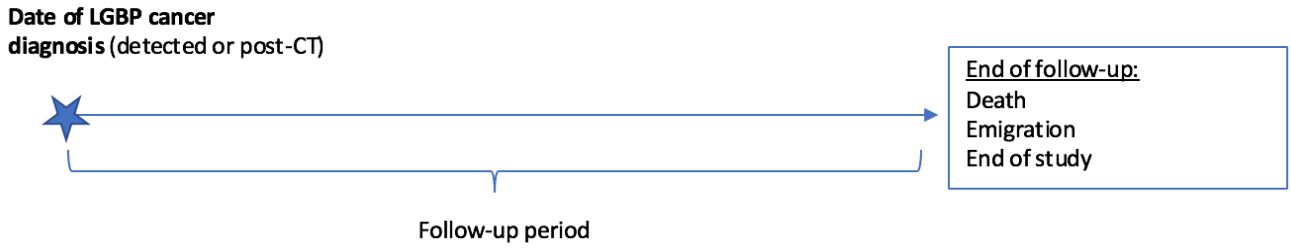


Figure 3: Study flow diagram

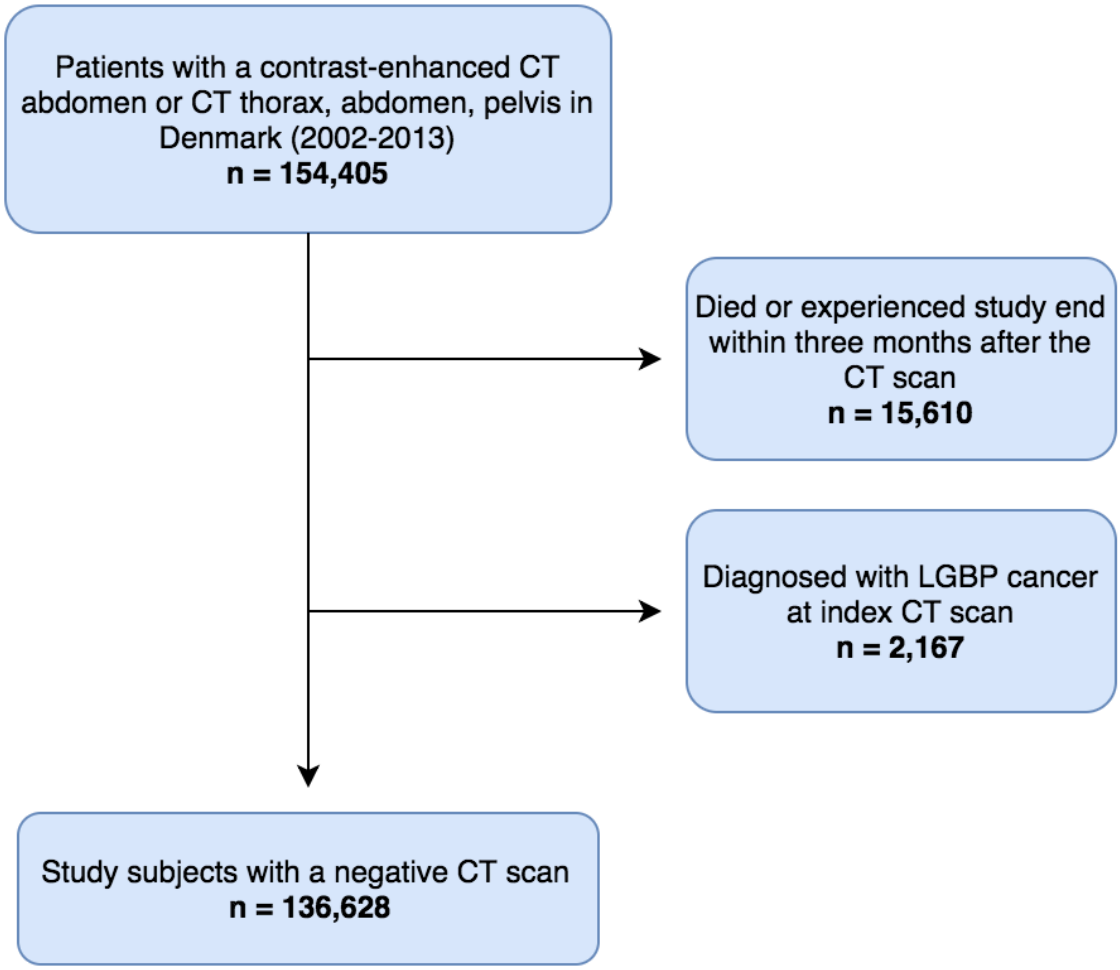
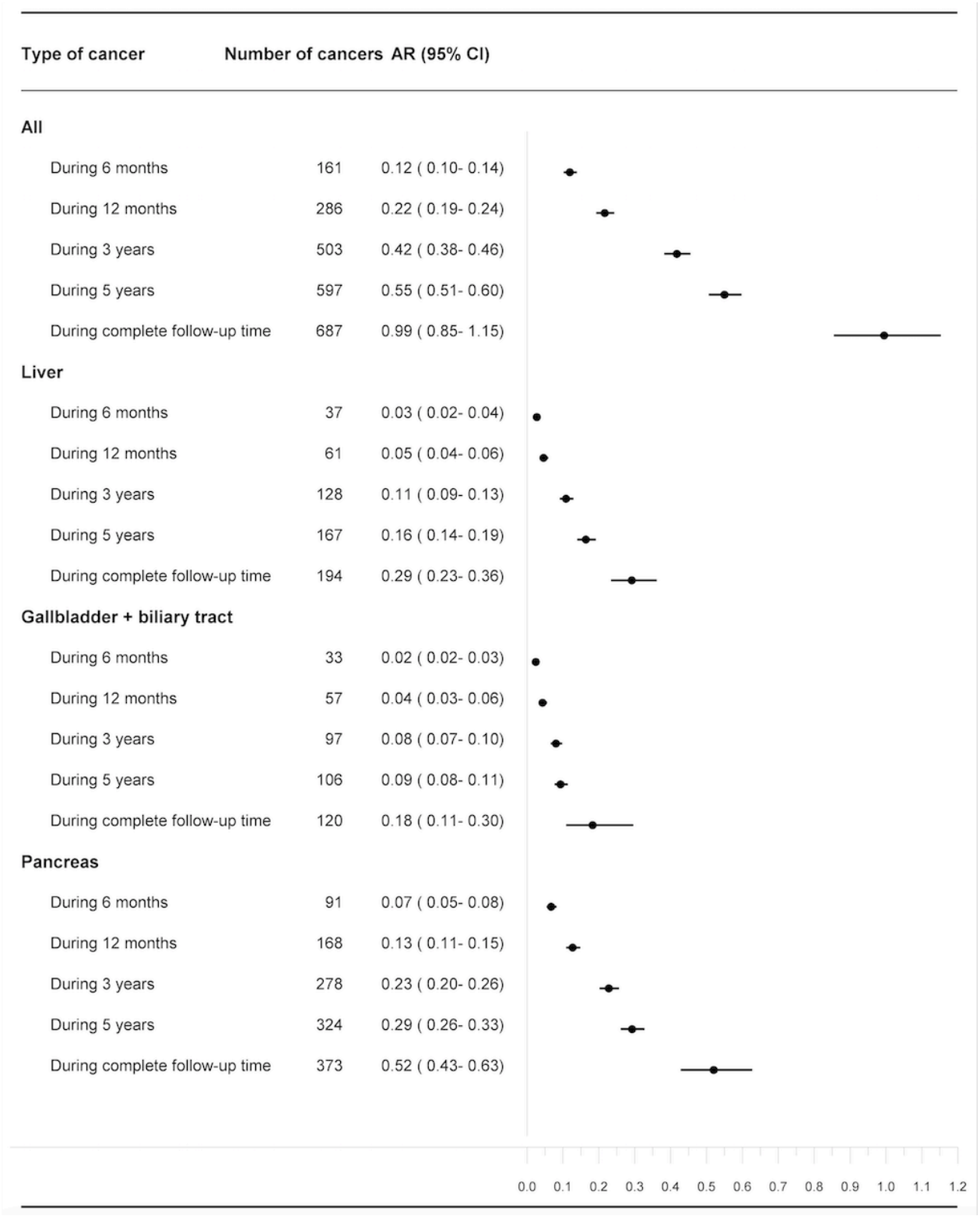


Table 1: Characteristics of patients with a contrast-enhanced CT-abdomen or CT-Thorax-Abdomen-Pelvis (CT-TAP) scan. Denmark 2002-2013.

Characteristic	All patients N (%)	Patients with a negative CT scan [a] N (%)	Patients with a true negative CT scan [b] N (%)	Patients with a post-CT LGBP cancer [c] N (%)
All	154,405 (100)	136,628 (100)	135,941 (100)	687 (100)
Type of scan				
CT-Abdomen	73,486 (47.6)	65,612 (48.0)	65,239 (48.0)	373 (54.3)
CT-TAP	80,919 (52.4)	71,016 (52.0)	70,702 (52.0)	314 (45.7)
Age				
0-49	53,046 (34.4)	50,592 (37.0)	50,529 (37.2)	63 (9.2)
50-69	59,320 (38.4)	53,001 (38.8)	52,647 (38.7)	354 (51.5)
70+	42,039 (27.2)	33,035 (24.2)	32,765 (24.1)	270 (39.3)
Sex				
Female	74,403 (48.2)	66,056 (48.3)	65,774 (48.4)	282 (41.1)
Male	80,002 (51.8)	70,572 (51.7)	70,167 (51.6)	405 (58.9)
Calendar year of scan				
2002-2004	16,836 (10.9)	15,306 (11.2)	15,154 (11.1)	152 (22.1)
2005-2007	30,727 (19.9)	27,836 (20.4)	27,650 (20.3)	186 (27.1)
2008-2010	49,984 (32.4)	45,637 (33.4)	45,390 (33.4)	247 (35.9)
2011-2013	56,858 (36.8)	47,849 (35.0)	47,747 (35.1)	102 (14.8)
Type of hospital admission				
Inpatient unit	72,630 (47.0)	61,589 (45.1)	61,260 (45.1)	329 (47.9)
Outpatient clinic	68,871 (44.6)	62,853 (46.0)	62,509 (46.0)	344 (50.1)
ER department	12,904 (8.4)	12,186 (8.9)	12,172 (9.0)	14 (2.0)
Concurrent gastrointestinal endoscopy				
No	137,501 (89.1)	121,778 (89.1)	121,214 (89.2)	564 (82.1)
Yes	16,904 (10.9)	14,850 (10.9)	14,727 (10.8)	123 (17.9)
Type of endoscopy [d]				
Lower endoscopy	8,361 (49.5)	7,567 (51.0)	7,524 (51.8)	43 (34.9)
Upper endoscopy	7,897 (46.7)	6,830 (46.0)	6,779 (46.0)	51 (41.5)
ERCP	646 (3.8)	453 (3.0)	424 (2.9)	29 (23.6)
Modified Charlson Comorbidity Index Score [e]				
0	132,593 (85.9)	119,568 (87.5)	119,024 (87.6)	544 (79.2)
1-2	19,528 (12.6)	15,602 (11.4)	15,485 (11.4)	117 (17.0)
3+	2,284 (1.5)	1,458 (1.1)	1,432 (1.05)	26 (3.8)
Alcoholism-related disorders	33,915 (22.0)	28,234 (20.7)	28,002 (20.6)	232 (33.8)
Hepatitis	1,388 (0.9)	1,162 (0.8)	1,119 (0.8)	43 (6.3)
Inflammatory Bowel diseases	5,414 (3.5)	4,967 (3.6)	4,950 (3.6)	17 (2.5)
Pancreatitis	6,036 (3.9)	5,299 (3.9)	5,205 (3.8)	94 (13.7)
Cholecystitis	2,723 (1.8)	2,310 (1.7)	2,283 (1.7)	27 (3.9)
Cholangitis	663 (0.4)	531 (0.4)	516 (0.4)	15 (2.2)

a: Patients with a contrast-enhanced CT scan of the abdomen without a corresponding diagnosis of primary liver, gallbladder, bile-duct, or pancreatic (LGBP) cancer within three months after the scan, b: patients with a negative CT scan who were cancer free at end of follow-up, c: LGBP cancers detected more than three months after the index CT scan, d: lower endoscopy (colonoscopy, sigmoidoscopy, proctoscopy, anoscopy), upper endoscopy (gastroscopy), ERCP (Endoscopic retrograde cholangiopancreaticography), e: Any type of cancer excluded.

Figure 4: Cumulative incidence proportions (ARs) in percentage and 95% confidence intervals (CIs) of primary liver, gallbladder, bile duct and pancreatic cancer after a negative contrast-enhanced CT scan of the abdomen [a], treating death as a competing risk, by cancer site and time period since index CT scan [b]. Denmark 2002-2013.



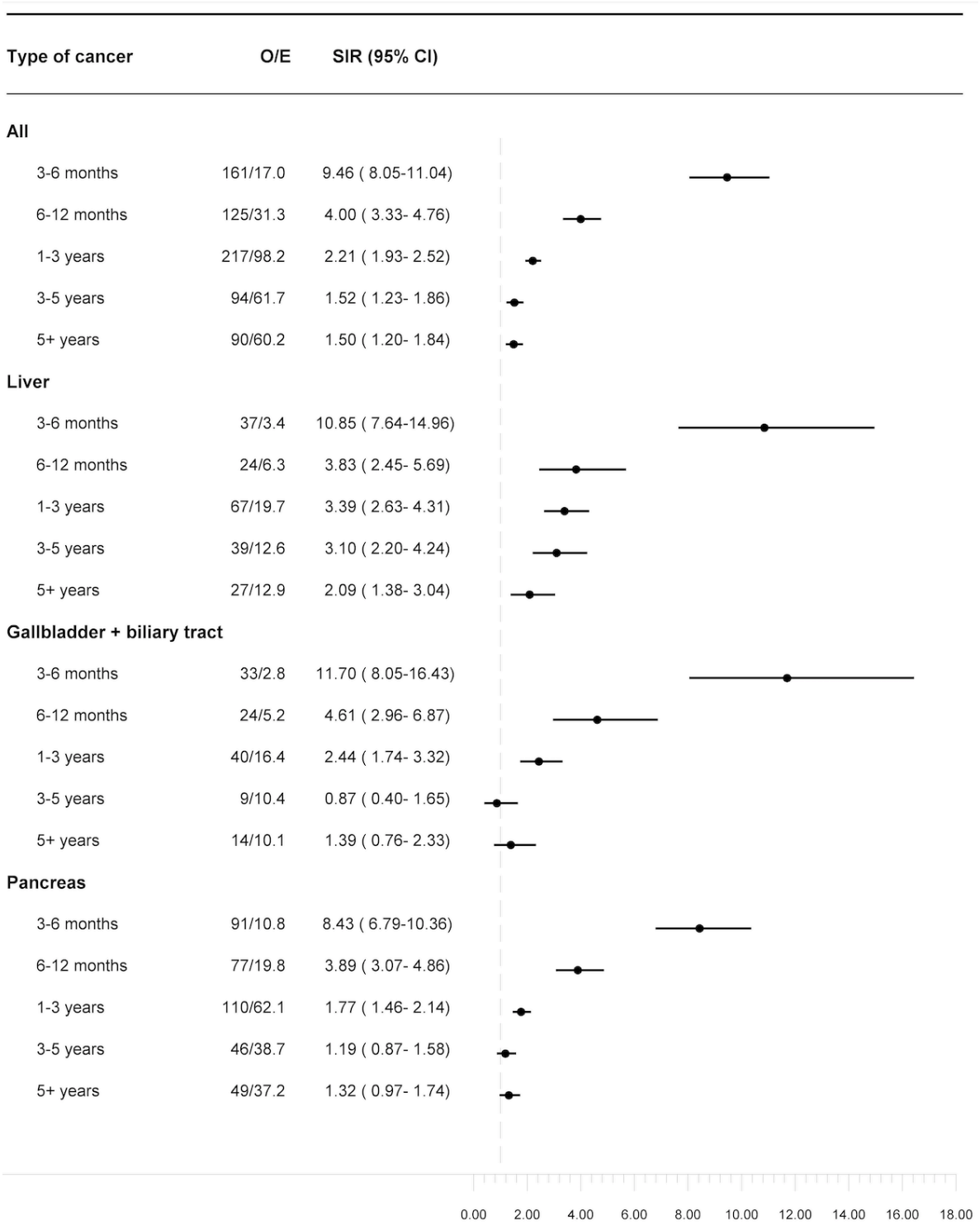
a: A CT scan without a corresponding diagnosis of primary liver, gallbladder, bile duct or pancreatic cancer recorded within three months after index CT, b: Patients were followed from three months after index CT.

Table 2: Cumulative incidence proportions (ARs) in percentage and 95% confidence intervals (CIs) of primary liver, gallbladder, bile duct and pancreatic cancer after a negative contrast-enhanced CT scan of the abdomen[a], treating death as a competing risk, by baseline characteristics and time period since index CT scan [b]. Denmark 2002-2013.

	AR (95% CI)	AR (95% CI)	AR (95% CI)	AR (95% CI)	N	
	6 months	**1 year**	**3 years**	**5 years**		**Complete follow-up**
All	0.12 (0.10-0.14)	0.22 (0.19-0.24)	0.42 (0.38-0.46)	0.55 (0.51-0.60)		0.99 (0.85-1.15)
Age						
0-29	0.01 (0.00-0.03)	0.01 (0.00-0.03)	0.01 (0.00-0.03)	0.01 (0.00-0.05)	N/A	0.10 (0.01-0.47)
30-49	0.04 (0.02-0.07)	0.07 (0.04-0.10)	0.14 (0.10-0.19)	0.18 (0.14-0.24)	N/A	0.42 (0.28-0.61)
50-69	0.14 (0.11-0.17)	0.25 (0.21-0.29)	0.51 (0.45-0.58)	0.74 (0.66-0.83)	354	1.55 (1.20-1.96)
70+	0.23 (0.18-0.29)	0.43 (0.37-0.51)	0.78 (0.68-0.88)	0.92 (0.81-1.05)	270	1.33 (1.09-1.62)
Sex						
Female	0.10 (0.08-0.13)	0.19 (0.16-0.23)	0.36 (0.31-0.41)	0.46 (0.40-0.52)	282	1.02 (0.75-1.37)
Male	0.14 (0.11-0.17)	0.24 (0.20-0.28)	0.47 (0.42-0.53)	0.63 (0.57-0.70)	405	1.00 (0.86-1.14)
Modified Charlson Comorbidity Index Score [c]						
0	0.11 (0.09-0.13)	0.20 (0.17-0.22)	0.37 (0.34-0.41)	0.49 (0.44-0.53)	544	0.93 (0.78-1.10)
1-2	0.19 (0.13-0.28)	0.33 (0.25-0.43)	0.66 (0.53-0.80)	0.89 (0.73-1.08)	117	1.20 (0.90-1.56)
3+	0.35 (0.13-0.78)	0.71 (0.37-1.26)	1.40 (0.86-2.17)	2.05 (1.31-3.05)	26	4.15 (1.98-7.58)
Endoscopy within three months of the CT scan						
No	0.10 (0.09-0.12)	0.20 (0.18-0.23)	0.38 (0.34-0.41)	0.51 (0.46-0.56)	564	0.95 (0.80-1.13)
Yes	0.25 (0.18-0.34)	0.35 (0.27-0.46)	0.76 (0.62-0.92)	0.90 (0.74-1.09)	123	1.33 (1.05-1.66)

a: A CT scan without a corresponding diagnosis of primary liver, gallbladder, bile duct or pancreatic cancer recorded within three months after the scan.
b: Patients were followed from three months since index CT.
c: Any type of cancer excluded.

Figure 5: Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of primary liver, gallbladder, bile duct and pancreatic cancer comparing patients with a negative contrast-enhanced CT-abdomen or CT- Thorax-abdomen-pelvis (CT-TAP) [a] with the background population, by cancer site and time period since index CT scan [b]. Denmark 2002-2013.



a: A CT scan without a corresponding diagnosis of primary liver, gallbladder, bile duct or pancreatic cancer recorded within three months after the scan. b: Patients were followed from three months since the index CT.

Table 3: Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of primary liver, gallbladder, bile duct, and pancreatic cancers comparing patients with a negative contrast-enhanced CT-abdomen or CT- Thorax-abdomen-pelvis (CT-TAP) [a] with the background population, by baseline characteristics and time period since index scan [b]. Denmark 2002-2013.

	3-6 months		6-12 months		1-3 years		3-5 years		5+ years		Complete follow-up	
	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)
All	161	9.5 (8.0-11.0)	125	4.0 (3.3-4.8)	217	2.2 (1.9-2.5)	94	1.5 (1.2-1.9)	90	1.50 (1.2-1.8)	687	2.6 (2.4-2.8)
Age												
0-29	N/A	89.5 (2.3-498.6)	0	0.0 (.-.)	0	0.0 (.-.)	N/A	13.5 (0.3-75.2)	N/A	6.6 (0.2-36.8)	N/A	8.9 (1.8-26.0)
30-49	N/A	33.6 (17.9-57.5)	8	10.5 (4.5-20.7)	19	6.4 (3.9-10.1)	N/A	2.7 (1.1-5.6)	N/A	3.0 (1.6-5.2)	N/A	5.5 (4.2-7.1)
50-69	72	10.8 (8.5-13.6)	54	4.3 (3.2-5.6)	111	2.6 (2.1-3.1)	62	2.0 (1.5-2.5)	55	1.5 (1.2-2.0)	354	2.7 (2.5-3.0)
70+	75	7.5 (5.9-9.4)	63	3.5 (2.7-4.5)	87	1.7 (1.4-2.1)	24	0.9 (0.6-1.3)	21	1.1 (0.7-1.6)	270	2.1 (1.9-2.4)
Sex												
Female	66	8.8 (6.8-11.2)	57	4.2 (3.1-5.4)	85	2.0 (1.6-2.4)	33	1.2 (0.9-1.7)	41	1.7 (1.2-2.3)	282	2.4 (2.2-2.8)
Male	95	10.0 (8.1-12.2)	68	3.9 (3.0-4.9)	132	2.4 (2.0-2.8)	61	1.7 (1.3-2.2)	49	1.4 (1.0-1.8)	405	2.6 (2.4-2.9)
Modified Charlson Comorbidity Index Score [c]												
0	126	9.1 (7.6-10.8)	100	3.9 (3.2-4.8)	169	2.1 (1.8-2.4)	70	1.4 (1.1-1.7)	79	1.5 (1.2-1.9)	544	2.4 (2.2-2.7)
1-2	30	10.2 (6.9-14.5)	20	3.7 (2.3-5.8)	40	2.5 (1.8-3.4)	19	2.0 (1.2-3.2)	N/A	1.0 (0.4-1.9)	117	2.8 (2.3-3.3)
3+	N/A	22.9 (7.4-53.5)	5	13.3 (4.3-31.0)	8	7.7 (3.3-15.1)	5	9.4 (3.0-21.9)	N/A	7.3 (1.5-21.2)	26	10.1 (6.6-14.8)
Endoscopy within three months of the CT scan												
No	125	8.5 (7.1-10.1)	110	4.1 (3.4-4.9)	168	2.0 (1.7-2.3)	84	1.6 (1.3-2.0)	77	1.4 (1.1-1.8)	564	2.4 (2.2-2.6)
Yes	36	15.5 (10.9-21.4)	15	3.5 (2.0-5.8)	49	3.6 (2.7-4.8)	10	1.2 (0.6-2.2)	13	1.9 (1.0-3.2)	123	3.5 (2.9-4.1)

a: Patients with a contrast-enhanced CT scan of the abdomen without a corresponding diagnosis of primary liver, gallbladder, bile duct, and pancreatic cancer diagnosed within three months after their index CT scan.
b: Patients were followed from three months after the index scan.
c: Any type of cancer excluded.

Table 4: Characteristics of patients diagnosed with post-CT [b] or detected LGBP cancer [a]. Denmark 2002-2013.

Characteristic	Patients with a detected LGBP cancer [a] N (%)	Patients with a post-CT LGBP cancer [b] N (%)
All	2,167 (100)	687 (100)
Type of scan		
CT-Abdomen	1,073 (49.5)	373 (54.3)
CT-TAP	1,094 (50.5)	314 (45.7)
Age		
0-49	124 (5.7)	63 (9.2)
50-69	1,113 (51.4)	354 (51.5)
70+	930 (42.9)	270 (39.3)
Sex		
Female	917 (42.3)	282 (41.1)
Male	1,250 (57.7)	405 (58.9)
Calendar year of scan		
2002-2004	164 (7.6)	152 (22.1)
2005-2007	468 (21.6)	186 (27.1)
2008-2010	749 (34.6)	247 (35.9)
2011-2013	786 (36.3)	102 (14.8)
Type of hospital admission		
Inpatient unit	1,078 (49.7)	329 (47.9)
Outpatient clinic	1,088 (50.2)	344 (50.1)
Concurrent gastrointestinal endoscopy		
No		
Yes	1,802 (83.2)	564 (82.1)
	365 (16.8)	123 (17.9)
Type of endoscopy [c]		
Lower endoscopy	84 (23.0)	43 (34.9)
Upper endoscopy	151 (41.4)	51 (41.5)
ERCP	130 (35.6)	29 (23.6)
Modified Charlson Comorbidity Index Score [d]		
0	1,842 (85.0)	544 (79.2)
1-2	282 (13.0)	117 (17.0)
3+	43 (2.0)	26 (3.8)
Alcoholism-related disorders	592 (27.3)	232 (33.8)
Hepatitis	62 (2.9)	43 (6.3)
Inflammatory Bowel diseases	35 (1.6)	17 (2.5)
Pancreatitis	80 (3.7)	94 (13.7)
Cholecystitis	53 (2.4)	27 (3.9)
Cholangitis	40 (1.8)	15 (2.2)
Time of diagnosis (only post-CT LGBP cancers)		
3-<6 months after CT	N/A	161 (23.4)
6-36 months after CT	N/A	342 (49.9)
> 36 months after CT	N/A	184 (26.6)

a: LBGP cancers detected within three months after the index CT scan, b: LGBP cancers detected more than three months after the index CT scan, c: lower endoscopy (colonoscopy, sigmoidoscopy, proctoscopy, anoscopy), upper endoscopy (gastroscopy), ERCP (Endoscopic retrograde cholangiopancreaticography), d: Any type of cancer excluded.

Table 5: Crude and adjusted prevalence ratios (PRs) and 95% confidence intervals (CIs) comparing cancer stage at diagnosis and primary histological subtype among patients with Post-CT LGBP cancers [a] and patients with detected LGBP cancers [b]. Denmark 2002-2013.

	N (%) Post-CT LGBP cancers	N (%) Detected LGBP cancers	Crude PR (95% CI)	Adjusted PR [c] (95% CI)
Total	687 (100)	2,167 (100)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
All				
Non-metastatic	230 (33.5)	594 (27.4)	1.22 (1.08-1.38)	1.19 (1.05-1.35)
Metastatic	232 (33.8)	965 (44.5)	0.76 (0.68-0.85)	0.76 (0.68-0.86)
Unknown	225 (33.7)	608 (28.1)	1.17 (1.03-1.32)	1.19 (1.05-1.35)
Primary liver cancer				
Cancer stage				
Non-metastatic	92 (13.4)	140 (6.5)	2.07 (1.62-2.66)	1.85 (1.44-2.37)
Metastatic	30 (4.4)	101 (4.7)	0.94 (0.63-1.40)	0.88 (0.60-1.29)
Unknown	72 (10.5)	171 (7.9)	1.33 (1.02-1.73)	1.23 (0.94-1.61)
Primary histological subtype				
Hepatocellular carcinoma	82 (11.3)	211 (9.7)	1.23 (1.00-1.56)	1.11 (0.87-1.40)
Neuroendocrine tumor	0 (0.0)	N/A	-	-
Other	83 (12.1)	N/A	2.24 (1.71-2.93)	2.05 (1.57-2.68)
Unknown	29 (4.2)	80 (3.7)	1.14 (0.75-1.73)	1.09 (0.72-1.65)
Gallbladder and biliary tract cancer				
Cancer stage				
Non-metastatic	34 (4.9)	94 (4.3)	1.14 (0.78-1.67)	1.13 (0.77-1.65)
Metastatic	35 (5.1)	148 (6.8)	0.75 (0.52-1.07)	0.78 (0.54-1.11)
Unknown	51 (7.4)	142 (6.5)	1.13 (0.83-1.54)	1.20 (0.89-1.62)
Primary histological subtype				
Cholangiocarcinomas	11 (1.6)	54 (2.5)	0.64 (0.34-1.22)	0.61 (0.33-1.12)
Adenocarcinomas	64 (9.3)	206 (9.5)	0.98 (0.75-1.28)	1.00 (0.77-1.31)
Other	11 (1.6)	55 (2.5)	0.63 (0.33-1.20)	0.69 (0.37-1.29)
Unknown	34 (4.9)	69 (3.2)	1.55 (1.04-2.32)	1.70 (1.14-2.52)
Pancreas cancer				
Cancer stage				
Non-metastatic	104 (15.1)	360 (16.6)	0.91 (0.75-1.11)	0.93 (0.76-1.13)
Metastatic	167 (24.3)	716 (33.0)	0.74 (0.64-0.85)	0.74 (0.64-0.86)
Unknown	102 (14.8)	295 (13.6)	1.09 (0.89-1.34)	1.14 (0.93-1.40)
Primary histological subtype				
Adenocarcinomas	208 (30.3)	923 (42.6)	0.71 (0.63-0.80)	0.72 (0.63-0.81)
Neuroendocrine tumors	11 (1.6)	31 (1.4)	1.12 (0.57-2.21)	1.12 (0.57-2.21)
Other	56 (8.1)	149 (6.9)	1.19 (0.88-1.59)	1.30 (0.97-1.72)
Unknown	98 (14.2)	268 (12.4)	1.15 (0.93-1.43)	1.17 (0.94-1.45)

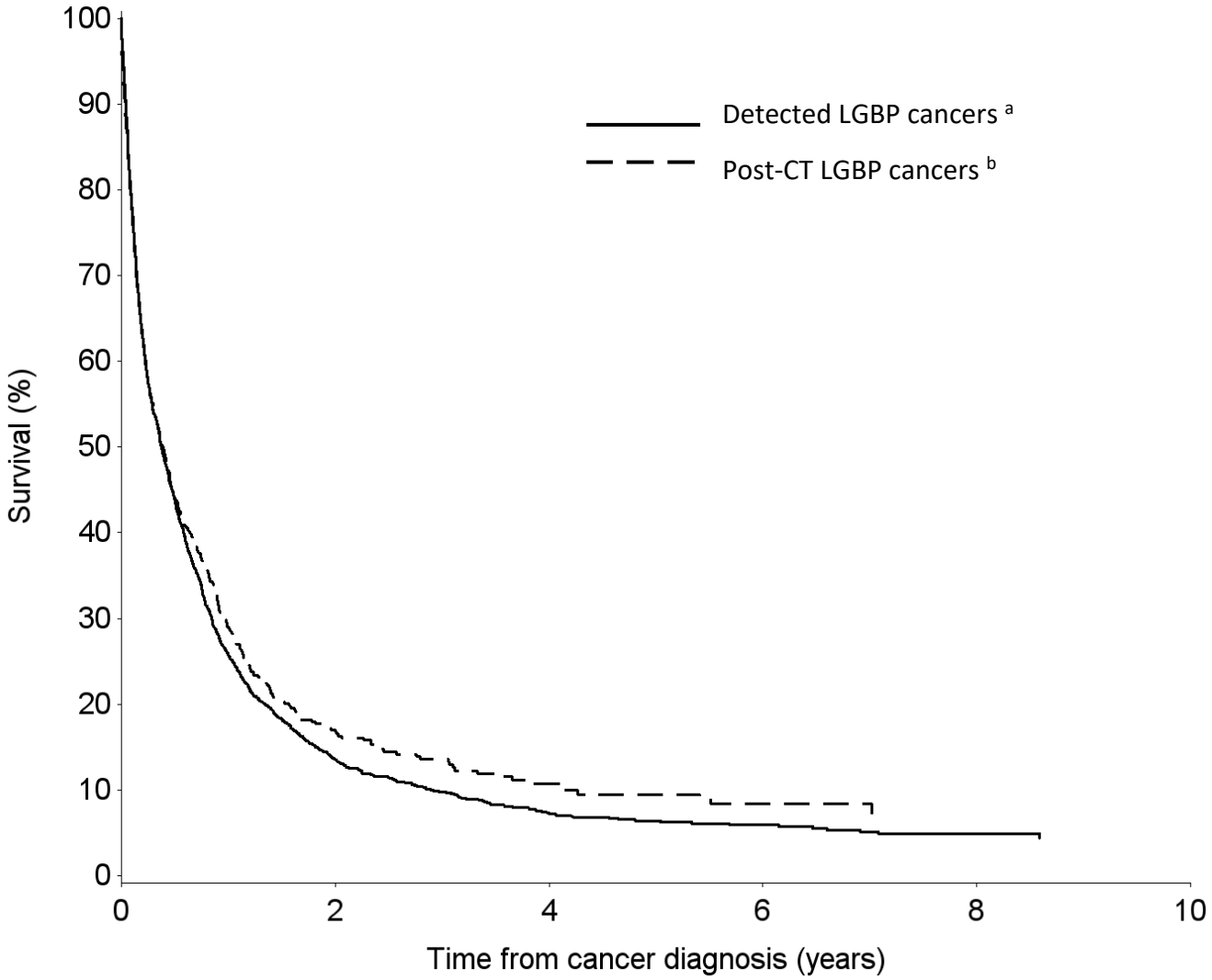
a: Diagnosed more than three months after the index CT scan.
b: Diagnosed within three months after the index CT scan.
c: Adjusted for age, gender and CCI score.

Table 6: Survival probabilities and 95% confidence intervals (CIs) and crude and adjusted mortality rate ratios (MMRs) and CIs comparing patients with post-CT LGBP cancer [a] with patients who had detected LGBP [b]. Denmark 2002-2013.

	1-year survival probabilities in patients with post-CT LGBP [a]	1-year survival probabilities in patients with detected LGBP [b]	5-year survival probabilities in patients with post-CT LGBP [a]	5-year survival probabilities in patients with detected LGBP [b]	Crude MRR	Adjusted MRR [c]
All	29.0 (25.5-32.5)	25.7 (23.8-27.7)	9.5 (6.8-12.7)	6.4 (5.2-7.8)	0.93 (0.84-1.02)	0.88 (0.80-0.97)
Liver	30.3 (23.8-37.1)	25.0 (20.7-29.5)	7.5 (2.7-15.6)	8.6 (5.4-12.5)	0.90 (0.74-1.09)	0.88 (0.72-1.08)
Gallbladder + biliary tract	35.8 (27.1-44.6)	35.6 (30.6-40.5)	11.6 (5.6-20.1)	9.4 (6.2-13.5)	1.05 (0.84-1.33)	1.00 (0.79-1.26)
Pancreas	26.0 (21.5-30.8)	23.3 (21.0-25.6)	8.9 (5.7-12.9)	4.8 (3.5-6.5)	0.93 (0.82-1.05)	0.86 (0.76-0.98)

a: LGBPs detected more than three months after the index CT scan
b: LBGPs detected within three months after the index CT scan
c: Adjusted for age, sex, Charlson Comorbidity Index, year of index CT scan

Figure 6: Kaplan Meier curves of overall survival according to time at diagnosis of primary liver, gallbladder, bile duct and pancreatic cancer. Denmark 2002-2013.



a: LGBP cancers detected within three months after the index CT scan.

b: LBGP cancers detected more than three months after the index CT scan.

SUPPLEMENTARY TABLES

Supplementary table 1: Cumulative incidence proportions (ARs) in percentages and 95% confidence intervals (CIs) of primary liver, gallbladder, bile duct or pancreas cancer, after a negative contrast-enhanced CT-abdomen or CT- Thorax-abdomen-pelvis (CT-TAP) [a], treating death as a competing risk. By cancer site and time since index CT [b].

	N	AR (95%)	N	AR (95%)	N	AR (95%)	N	AR (95%)	N	AR (95%)
		6 months		1 year		3 years		5 years		Complete follow-up
Cancer site										
Liver	20	0.02 (0.01-0.02)	44	0.03 (0.02-0.05)	111	0.10 (0.08-0.12)	150	0.15 (0.13-0.18)	177	0.28 (0.22-0.35)
Gallbladder and biliary tract	21	0.02 (0.01-0.02)	45	0.03 (0.03-0.05)	85	0.07 (0.06-0.09)	94	0.09 (0.07-0.10)	108	0.18 (0.10-0.29)
Pancreas	38	0.03 (0.02-0.04)	95	0.09 (0.07-0.11)	225	0.19 (0.17-0.22)	271	0.26 (0.23-0.29)	320	0.49 (0.39-0.59)

a: Patients with a contrast-enhanced CT scan of the abdomen without a corresponding diagnosis of liver, pancreas or gallbladder + bile-duct cancer within four months after the CT scan.
b: Patients were followed from three months after the index CT scan.

Supplementary table 2: Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) of primary liver, gallbladder, bile duct or pancreas cancer comparing patients with a negative contrast-enhanced CT-abdomen or CT- Thorax-abdomen-pelvis (CT-TAP)[a] with the background population, by cancer site and time since index CT [b].

	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)	N	SIR (95% CI)
		4-6 months		6-12 months		1-3 years		3-5 years		5+ years		Complete follow-up
Cancer site												
Liver	20	8.9 (5.4-13.7)	24	3.8 (2.5-5.7)	67	3.4 (2.6-4.3)	39	3.1 (2.2-4.2)	27	2.1 (1.4-3.0)	177	3.3 (2.8-3.8)
Gallbladder and biliary tract	21	11.3 (7.0-17.3)	24	4.6 (3.0-6.9)	40	2.4 (1.7-3.3)	9	0.9 (0.4-1.7)	14	1.4 (0.8-2.3)	108	2.5 (2.0-3.0)
Pancreas	38	5.3 (3.8-7.3)	77	3.9 (3.1-4.9)	110	1.8 (1.5-2.1)	46	1.2 (0.9-1.6)	49	1.3 (1.0-1.7)	320	1.9 (1.7-2.2)

a: Patients with a contrast-enhanced CT scan of the abdomen without a corresponding diagnosis of liver, pancreas or gallbladder + bile-duct cancer within four months after the CT scan.
b: Patients were followed from three months after the index CT scan.

Supplementary table 3: Registry data used in the analyses.

Registry	Code
Danish National Patient Registry (DNPR): Diagnosis	
ICD-8 [a] (1977-1993)	
Alcoholism-related disorders	291.00-291.99, 303.00-303.99, 571.09, 571.10, 577.10, 070.01, 070.02, 070.03, 070.05, 070.06,
Hepatitis	070.07, 070.08, 070.09, 570.00, 570.01, 570.08, 570.09, 571.93
Inflammatory bowel diseases	563.03, 563.19, 569.04
Primary sclerosing cholangitis	-
Pancreatitis	577.00, 577.01, 577.19
Cholecystitis	575.00, 575.01
Cholangitis	575.04
ICD-10 [a] (since 1994)	
Alcoholism-related disorders	F10.2-10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, Z72.1, E24.4, E52.9A, K85.2, L27.8A, Z50.2, Z71.4, BRHE2 (treatment code)
Hepatitis	B15, B17, B18.2, B17.1
Inflammatory bowel diseases	K50, K51
Primary sclerosing cholangitis	K83.0F
Pancreatitis	K85, K86
Cholecystitis	K81
Cholangitis	K83.0
Danish National Patient Registry (DNPR): Procedures	
NOMESCO [a]	
Lower endoscopies	KUJF32, KUJF35, KUJF42, KUJF45, KUJG05, KUJG02, KUJH02
Upper endoscopies	KUJD02, KUJD05, KUJC05, KUJC12, KUJC15, KUJF82, KUJF85
ERCP	KUJK02, KUJK05
DANISH CLASSIFICATION OF RADIOLOGOCAL PROCEDURES	
CT-abdomen	UXCD00
CT-Thorax-abdomen-pelvis	UXCC00 + UXCD00 + UXCD15
Contrast enhancement	UXZ10
Danish Cancer Registry (DCR)	
ICD-10 [a]	
Primary liver cancer	DC220, DC222, DC223, DC224, DC227, DC229
Biliary tract + gallbladder cancer	DC221, DC239, DC240, DC241, DC248, DC249
Pancreas cancer	DC25

TNM [a]	
Non-metastatic	T0-4,x; N0-3; M0, T0-2; N0; Mx, T0-1; Nx; M0, x
Metastatic	T0-4,x; N1-3; M1,x, T0-4,x; N0; M1, T0-4, x; Nx; M1
Unknown	T2-4,x; Nx; M0, x, T3-4, x; N0; Mx
Danish Pathology Registry	
SNOMED [a]	
Liver	
Hepatocellular carcinoma	"81703", "81713", "81723", "81733", "81743", "81753", "81803"
Neuroendocrine tumor	"82461", "82401", "82403", "82463", "82469"
Unknown	"99903"
Biliary tract + gallbladder	
Cholangiocarcinoma	"81603", "81609", "81800" "81803"
Adenocarcinoma	"81403", "84803"
Unknown	"99903"
Pancreas	
Adenocarcinoma	"81403", "84803"
Neuroendocrine tumor	"82461", "82401", "82403", "82463", "82469"
Unknown	"99903"

a: Abbreviations: ICD = *International Classification of Diseases*, NOMESCO = *Nordic Medico-Statistical Committee*, ATC = Anatomical Therapeutic Chemical Classification System, SNOMED = *Systematized Nomenclature of Medicine,* TNM = *TNM Classification system (T: describes the primary tumor size, N: describes regional lymph node involvement, M: describes the presence of distant metastases).*

Supplementary Table 4: Conditions included in the Charlson Comorbidity Index (any tumors excluded).

Covariate	ICD-8 codes	ICD-10 codes	CCI 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	712, 716, 734, 446, 135.99	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86	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 1 and 2	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9	1
Hemiplegia	344	G81, G82	2
Moderate to severe renal disease	403, 404, 580–583, 584, 590.09, 593.19, 753.10–753.19, 792	12, I13, N00–N05, N07, N11, N14, N17–N19, Q61	2
Diabetes with end-organ damage	249.01–249.05, 249.08, 250.01–250.05, 250.08	E10.2–E10.8, E11.2–E11.8	2
Leukemia	204–207	C91–C95	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
AIDS	079.83	B21–B24	6

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