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Risk of second primary malignancies and causes of death in patients with adenocarcinoma and carcinoid of the small intestine

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ABSTRACT

We studied risk of second malignancies and causes of death in 1829 cases of adenocarcinoma and 3055 cases of carcinoid tumours in the small bowel reported to the Swedish Cancer Registry from 1960 through to 2000. Data on causes of death were analysed as from 1966 whereas data on second tumours was available during the whole registry-period. Follow-up was available until 2001.

Standard mortality ratio (SMR) and standard incidence ratio (SIR) were calculated.

Female patients with adenocarcinoma had increased risk of acquiring cancer in the female genital organs (SIR 3.2; 95% confidence intervals (CI) 1.9–5.0) and breasts (SIR 2.7; 95% CI 1.1–5.4). Both sexes combined had increased risk of second tumours in the gastrointestinal tract (SIR 1.5; 95% CI 1.1–2.1) and skin (SIR 4.6; 95% CI 1.2–12). Men with carcinoid tumour had increased risk of prostate cancer (SIR 2.8; 95% CI 1.6–4.6). Increased risk was seen for both sexes with carcinoid for malignant melanoma (SIR 6.3; 95% CI 2.7–12), malignant skin tumours (SIR 3.6; 95% CI 1.7–6.7) and malignancies of endocrine organs (SIR 2.3 95% CI 1.3–3.8). Patients with adenocarcinoma had increased risk of dying from malignant diseases other than the primary cancer (SMR 9.5; 95% CI 8.6–10) and gastrointestinal disease (SMR 2.6 95% CI 1.6–4.2). The cohort with carcinoid had higher than expected risk of dying from malignant disease (SMR 4.3; 95% CI 4.0–4.6), gastrointestinal disease (SMR 2.8; 95% CI 2.1–3.6) and cardiovascular disease (SMR 1.1; 95% CI 1.0–1.3).

The increased risk of second malignant tumours is an indication of common aetiology, or possibly, a general vulnerability to malignant disease for these patients. A detailed analysis of causes of death in a population-based cohort of small intestinal malignancies has not been presented before in the literature.

1. Introduction

Second malignant neoplasms associated with tumours of the small intestine have been recognised in autopsy studies[1] and numerous relatively small case series.[2–7] Few population-based studies have investigated the incidence of second primary cancers in patients with small intestinal malignancies. Analyses of cases from the Danish Cancer Registry revealed

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statistically significant excess risks of cancer of the liver and biliary tract and statistically non-significant excess risks of colorectal and pancreatic cancers.[8] A similar analysis of the Connecticut tumour registry cases found statistically significantly increased risks of acquiring cancers of the digestive system and the prostate gland.[9] These studies were not stratified for histolopathologic subtype of the small bowel neoplasms. In a recent report of data from the SEER database it was noted that 29% of patients with small intestinal carcinoid had associated malignancies.[10] Earlier analyses of data from the same registry have described increased risk of colorectal cancer following small intestinal adenocarcinoma and increased risk of prostate cancer following carcinoid tumour in the small intestine.[11] A recent population-based study including cases from 13 national cancer registries showed increased incidence of cancers of the oropharynx, colon, rectum, ampulla of Vater, pancreas, corpus uteri, ovary, prostate, kidney, thyroid gland, skin and soft tissue sarcomas after primary diagnosis of small intestinal malignancies.[12]

Increased incidence of a second primary tumour could indicate shared etiologic factors between the index cancer and the second malignancy or that agents used in the treatment are oncogenic. Furthermore, the demonstration of reciprocally excessive occurrences supports the plausibility of a common pathogenesis.[13] Excess risk of small intestinal malignancies has been reported following colorectal cancer .[11,14,15] Increased incidence rates of small intestinal carcinoid have been reported following prostate cancer[16] and after thyroid and other endocrine gland tumours.[17]

Knowledge of causes of death of patients with small intestinal carcinoid mainly comes from small series from specialist centres. Heart-valve disease with heart failure is often stated as a common cause of death in these patients whereas other causes of death not directly related to the malignancy are described as uncommon.[18] There are no population-based descriptions of causes of death of patients with small intestinal adenocarcinoma in the literature although prognosis is described as poor and most patients die of their malignancy.[19]

The aim of this study was to estimate the excess risk of second primary malignancies and causes of death following adenocarcinoma or carcinoid tumours in the small intestine using data from the Swedish Cancer Registry.

2. Patients and methods

2.1. The National Causes of Death Registry and Cancer Registry

Data on causes of deaths in Sweden have been systematically collected and classified according to the International classification of Diseases (ICD) in the National Causes of Death Registry since 1951. Obligatory death certificates, including the date and cause of death, are issued by the physician who has examined the dead body (clinical examination, autopsy or forensic necropsy).[20]

The Swedish Cancer Registry was established in 1958. Physicians, pathologists and cytologists must report all cases of diagnosed malignant tumours to the registry, whereby most cases are reported twice. The information from death certificates is supplied from the causes of death registry and merged into the files of the Cancer Registry supplying date, underlying and contributory causes of death.[21]

2.2. Patients

We have studied all cases of primary adenocarcinoma and carcinoid in the small intestine (histological type 096 and 084, ICD-7 152.0–152.9, WHO/HS/CANC/24.1 Histology Code), diagnosed during 1960–2000 and reported to the Swedish Cancer Registry. A total number of 1982 cases of adenocarcinoma and 3741 cases of carcinoid were recruited from the registry. Cases where date of death was the same as date of diagnosis of the primary small intestinal tumour were excluded (Table 1). Tumours of the ampulla of Vater (ICD 155.3) were disregarded. The definitive cohorts included 1829 patients with adenocarcinoma and 3055 patients with carcinoid.

The main second primary tumour-groups of interest were as follows (ICD-7): the gastrointestinal system (140–151,153–158), the female genital tract and breasts (170–176), the respiratory system (160–164), the prostate gland (177), urinary tract (180–181), brain (193), skin (190–191), and endocrine organs (1940–1959). We only included tumours occurring after diagnosis of the small bowel malignancy. The correctness of the diagnoses in individuals reported to suffer from multiple malignancies in the Swedish Cancer Registry has been analysed earlier; in conclusion, the registry data are reliable enough to be used for adequate analyses aiming at studying the epidemiology of multiple malignant tumours in a large unselected population.[22]

Causes of death according to the Swedish Causes of Death Registry were pooled into subgroups. Corresponding ICD-codes in relation to different time-periods are shown in Table 2. In the analysis of causes of death, cases who succumbed 30 days or less after diagnosis of the primary malignancy were excluded leaving 1586 patients with adenocarcinoma and 2531 patients with carcinoid.

2.3. Statistical method

Computation of person-years (pyr) at risk started at the date of diagnosis of small intestinal adenocarcinoma or carcinoid, and ended at the diagnosis of the second primary cancer, the date of death, or the end of the follow-up period. The expected number of second tumours was calculated by multiplication of pyr at risk by the corresponding age-, sex- and period-specific incidence rates. Incidence rates for all cancer sites for the Swedish population were obtained from the Swedish Cancer Registry, as was information on the observed incidence of second tumours in the cohort. The standard inci-

Table 1 – Cases recruited from the Swedish Cancer Registry and exclusions due to lack of diagnosis in vivo

	Adenocarcinoma	Carcinoid
Total number reported	1982	3741
Date of diagnosis same as date of death	153	686
Included	1829	3055