Epidemiological Studies of Small Intestinal Tumours

NIKLAS ZAR
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Abstract
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Malignant tumours of the small intestine are rare. Age-standardised incidence in Europe is
between 0.5-1.5 per 100 000. As the small intestine represents more than 90 % of
the gastrointestinal mucosal surface, it is surprising that it gives rise to less than 2 % of
gastrointestinal malignancies. The dominating histological subtypes are carcinoids and
adenocarcinomas.

We used three population-based registries in Sweden to study survival, second malignant
tumours, causes of death, and Crohn’s disease as a risk factor for small intestinal
adenocarcinoma and carcinoid.

We evaluated tumour site, sex, age, and year of diagnosis as prognostic factors. For
adenocarcinomas there was no difference in survival between duodenal and jejunal/ileal
tumours. Women with jejunal/ileal adenocarcinomas showed higher probabilities of survival
than men, while no such relation was found for duodenal tumours. Old age correlated with
poor survival for duodenal tumours, and prognosis has improved in later years. For
carcinoids, duodenal tumours had a more favourable prognosis than jejunal/ileal tumours.
There was no difference in survival between sexes. Old age correlated with poor survival, and
survival has improved in recent years.

Female patients with adenocarcinoma had increased risk of acquiring cancer in the genital
organs and breasts, and both sexes had increased risks of second tumours in the
gastrointestinal tract and skin. Men with carcinoid tumours had increased risk of prostate
cancer. Both sexes had increased risk of malignant melanoma and malignancies of endocrine
organs.

Patients with adenocarcinoma had increased risk of dying from malignant diseases other
than the primary small intestinal cancer and from gastrointestinal disease. The cohort with
carcinoid had higher than expected risk of dying from malignant disease, gastrointestinal
disease, and cardiovascular disease.

Patients with Crohn’s disease had increased risk of small intestinal adenocarcinoma and
carcinoid, and the risk has increased for patients diagnosed in recent years.

Keywords: small intestine, adenocarcinoma, carcinoid, epidemiology, survival, second
malignancies, causes of death, Crohn's disease

Niklas Zar, Department of Surgical Sciences, Akademiska sjukhuset, Uppsala University,
SE-75185 Uppsala, Sweden

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List of papers

This thesis is based on the following papers, which are referred to in the text by their roman numerals.


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### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>5-HIAA</td>
<td>5-hydroxyindoleacetic acid</td>
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<td>5-HT</td>
<td>5-hydroxytryptamine</td>
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<td>CD</td>
<td>Crohn’s disease</td>
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<td>CgA</td>
<td>Chromogranin A</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<td>CTGF</td>
<td>Connective tissue growth factor</td>
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<td>FAP</td>
<td>Familial adenomatous polyposis</td>
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<td>FCDS</td>
<td>Florida Cancer Data System</td>
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<td>FDG</td>
<td>Fluorodeoxyglucose</td>
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<td>GEP-NET</td>
<td>Gastroenteropancreatic neuroendocrine tumours</td>
</tr>
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<td>HNPCC</td>
<td>Hereditary non-polyposis colorectal cancer</td>
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<tr>
<td>ICD</td>
<td>International classification of diseases</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
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<tr>
<td>PJS</td>
<td>Peutz-Jeghers syndrome</td>
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<tr>
<td>PYR</td>
<td>Person-years</td>
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<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results</td>
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<tr>
<td>SIR</td>
<td>Standardised incidence ratio</td>
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<tr>
<td>SMR</td>
<td>Standardised mortality ratio</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
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<tr>
<td>TGF-β</td>
<td>Transforming growth factor beta</td>
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<td>TNM</td>
<td>Tumour, node, metastasis</td>
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Introduction

Malignant tumours of the small intestine are relatively rare. Although located between the stomach and the large bowel, sites commonly affected by cancer, the small bowel seldom develops a malignancy. As the small intestine represents more than 90% of the mucosal surface of the gastrointestinal tract, it is surprising that it gives rise to less than 2% of gastrointestinal malignancies (Mittal et al. 1980; Lanzafame et al. 1982; O'Riordan et al. 1996; Neugut et al. 1998). The reason for the low incidence of small intestinal neoplasms is virtually unknown. Numerous explanations have been presented in the literature:

- The contents of the small intestine are fluid in nature which may cause less mucosal irritation, and reduce the intensity of exposure of the small bowel to oral carcinogens (Lowenfels 1973; Gill et al. 2001).
- Rapid transit of intestinal contents through the small bowel may reduce contact of its mucosa to carcinogens (Lowenfels 1973; Gill et al. 2001).
- The low bacterial count in the small intestine may result in decreased conversion of bile-acids into carcinogens (Lewis et al. 1972; Ross et al. 1991).
- The known carcinogen benzpyrene is converted to less toxic metabolites by benzpyrenehydroxylase, which is present in high concentrations in the small intestine (Wattenberg 1971).
- Lymphoid accumulations within the small bowel wall may be protective (Lowenfels 1973).

Small intestinal tumours are a heterogeneous group with diverse clinical characteristics depending on histological subtype as well as location. Adenocarcinoma and carcinoid are the most common tumours in the Western world (Gabos et al. 1993; Chow et al. 1996; Lepage et al. 2006; Shack et al. 2006) but patients may present with other primary malignant tumours such as lymphoma, leiomyosarcoma, and gastrointestinal stromacell tumours. In a series from India, lymphoma was the most frequent type (Gupta et al. 1982). In a Japanese series, the most common tumour type was adenocarcinoma whereas carcinoids were infrequent (Kusumoto et al. 1992).

The first article on carcinoma of the jejunum was written by Sorlin in 1824 (Sorlin 1824), who described a 49-year-old man who died of intense vomiting, presumably on the basis of small intestinal obstruction. Oberndorfer became the first to 100 years ago adequately characterize carcinoid tu-
mours, and referred to them as ‘benign carcinomas’ (Oberndorfer 1907). Oberndorfer’s first case described a 48-year-old woman who had been presumed to die from tuberculosis. Autopsy found four pea-sized tumours in the ileum; the first three of these tumours were separated by approximately 20 cm along the intestine, and the fourth was only 1 cm distal to the third (Modlin et al. 2004).

Small bowel adenocarcinomas are epithelial tumours that, histologically, resemble their more common counterparts in the colon, but with a higher proportion of poorly differentiated tumours (Hamilton et al. 2000). Grading is identical to that used for colorectal cancer; well-, moderately, and poorly differentiated. Staging is by the tumour-node metastasis (TNM) classification (Sobin et al. 2002).

Small intestinal carcinoids are derived from neuroendocrine cells that are dispersed in the intestinal mucosa (Feyrter 1938; Falkmer 1993; Modlin et al. 2004). A characteristic feature of neuroendocrine tumours is the uptake and decarboxylation of various amine precursors as 5-hydroxytryptophan and dihydroxyphenylalanine (Pearse 1980). Historically, carcinoid tumours have been classified according to embryonic origin into foregut, midgut, and hindgut tumours (Williams et al. 1963). The classification of gastrointestinal endocrine tumours has recently been revised (Solcia et al. 2000). Although still in clinical use, the term ‘carcinoid’ is not considered adequate to cover the diversity of tumours emerging from the disseminated neuroendocrine system (Oberg et al. 2004a), and the description of primary tumour site by embryonic origin is of questionable clinical value. Instead, the term ‘gastro-enteropancreatic neuroendocrine tumours’ (GEP NETs), and an anatomical description of tumour site is recommended. Malignant potential of GEP-NETs is now described using a combination of the classical growth and microscopic structural criteria, and the value of the Ki-67 proliferation index (Parrado et al. 1996). Recently, the usefulness of this classification in predicting malignant behaviour has been questioned (Alexiev et al. 2007). Most neuroendocrine tumours of the distal jejunum and ileum are histopathologically well-differentiated neuroendocrine carcinomas with a Ki-67 proliferation index of around 2% (Oberg et al. 2004b). A TNM classification for GEP-NETs has recently been proposed (Rindi et al. 2006; Rindi et al. 2007).

The text in the present thesis will concentrate mainly on small intestinal adenocarcinoma and carcinoid.

Incidence

Reports from cancer registries over the world reveal major differences in the incidence rates of small intestinal tumours (Parkin et al. 2003). African and Asian countries are mostly low incidence populations with reported age-
adjusted incidence rates between 0.1 and 1.0 per 100 000. In Europe the highest incidence rates are seen in Iceland (1.5 per 100 000 for men, and 1.8 per 100 000 for women), and in North America high rates are generally seen in the black population. Most registries, with few exceptions, report higher incidence rates in men than in women (Parkin et al. 2003). A majority of population based series report adenocarcinoma as the most common type, comprising 35 to 47 % of all small intestinal malignancies (Vuori 1971; Gabos et al. 1993; Chow et al. 1996; Howe et al. 1999; Haselkorn et al. 2005; Lepage et al. 2006; Shack et al. 2006). Others claim carcinoid to be the dominating type (Barclay et al. 1983; DiSario et al. 1994; Severson et al. 1996). The relative distribution of histological subtypes seems to have changed over time. The most recent analysis of Surveillance, Epidemiology, and End Results (SEER) data from the United States indicates an increasing proportion of carcinoids (Modlin et al. 2007). Adenocarcinomas are most frequent in the duodenum although the reported relative frequency regarding site varies between 26 to 61% (Vuori 1971; Gabos et al. 1993; DiSario et al. 1994; Chow et al. 1996; Severson et al. 1996; Howe et al. 1999; Haselkorn et al. 2005; Shack et al. 2006; Verma et al. 2006). Carcinoids, on the other hand, dominate in the ileum; again, reported percentages vary remarkably between authors (Vuori 1971; Barclay et al. 1983; Weiss et al. 1987; DiSario et al. 1994; Severson et al. 1996; Haselkorn et al. 2005; Shack et al. 2006; Modlin et al. 2007). Notably, Berge and Linell have presented an autopsy series where carcinoids constituted 95% of small intestinal malignancies, indicating that most small intestinal carcinoids remain undetected in vivo (Berge et al. 1976).

There are few reports on incidence trends over time for small intestinal tumours. An analysis of cases reported to a Canadian cancer registry 1979-1989 showed a linear increase in rates for adenocarcinoma in men but decreasing rates for women (Gabos et al. 1993). Carcinoid rates did not change over time. Data from approximately the same period from the SEER program demonstrated increasing incidence rates for both adenocarcinomas and carcinoids (Chow et al. 1996). A more recent analysis of cancer registry data from England, Wales and Scotland showed significant increases in the incidence of adenocarcinomas and carcinoids with an increasing proportion of adenocarcinomas during the study period (1977-2002) (Shack et al. 2006). The latest update of data from the SEER program indicates a 460% increase of small intestinal carcinoids over 30 years (Modlin et al. 2007).

Clinical presentation

Small bowel tumours often present with vague and non-specific complaints. Early and accurate diagnosis of small bowel tumours is seldom achieved
because of the rarity of this disease, its insidious nature, the symptomatic 
similarity to other abdominal conditions, and difficulty of demonstrating the 
underlying pathologic condition radiologically (Pagtalunan et al. 1964; Mag-
linte et al. 1982). In some series it has even been stated that a substantial 
percentage of patients are investigated with negative findings, and labelled 
as neurotic (Hancock 1970). Because of the divergence in biological behav-
our, and their predilection to different sites in the small bowel, adenocarci-
nomas and carcinoids differ somewhat in clinical presentation.

Adenocarcinoma

Abdominal pain, obstruction, and bleeding are the dominating symptoms for 
patients with adenocarcinoma of the small intestine (Dabaja et al. 2004; 
Agrawal et al. 2007). Obstruction is more common in distally located tu-
mours, otherwise symptoms are similar regardless of site (Dabaja et al. 
2004). Twenty to 70% of patients present with either lymph node or liver 
metastases (Bauer et al. 1994; Frost et al. 1994; Cunningham et al. 1997; 
Talamonti et al. 2002; Dabaja et al. 2004; Halfdanarson et al. 2006; Lepage 
et al. 2006; Wu et al. 2006). A substantial number of tumours, especially 
those located in the distal small bowel, are recognized at emergency surgery 
for bowel obstruction.

Carcinoid

As for adenocarcinomas, abdominal pain and intermittent bowel obstruction 
are the most frequent symptoms in small intestinal carcinoid, whereas occult 
and overt bleeding is quite uncommon (Moertel et al. 1961; Modlin et al. 
2003). Multiple tumours occur in about 30% in both clinical and autopsy 
series (Berge et al. 1976; Modlin et al. 2007). Recent data suggest that these 
multiple tumours may represent metastases as well as independent neoplastic 
growths (Katona et al. 2006). The primary tumour is often small and infre-
quently causes intestinal obstruction by itself. Mesenteric metastases occur 
in approximately 40% and they tend to be substantially larger than the pri-
mary tumour (Moertel et al. 1961; Modlin et al. 2007). These metastases are 
typically surrounded by fibrosis, causing indirect obstruction of the intestine 
(Akerstrom et al. 2005). Recent data indicates that the fibrosis seen in small 
intestinal carcinoids is a consequence of the secretory activity of carcinoid 
tumour cells invading the mesentery mediated by connective tissue growth 
factor (CTGF) production and transforming growth factor beta (TGF-β) act-
ing on intestinal myofibroblastic cells (Kidd et al. 2007). Twenty-five to 30 
% of small intestinal carcinoids present with liver metastases (Moertel et al. 
1961; Talamonti et al. 2002; Modlin et al. 2007).

A unique feature of carcinoid tumours is the carcinoid syndrome consist-
ing of flush, diarrhoea, right-sided heart fibrosis and sometimes bronchial
constriction (Grahame-Smith 1968). Although proposed by Sholte in 1931, the first series describing this syndrome was by Thorson and co-workers (Scholte 1931; Thorson et al. 1954). It is caused by a variety of peptides and amines released by the carcinoid tumour (Feldman 1989). The frequency of the carcinoid syndrome varies in the literature but probably do not exceed 20% for patients with liver metastases or extensive lymphatic spread (Akerstrom et al. 2007).

Etiology and risk factors

Association with colorectal cancer

The etiology of small bowel malignancies is largely unknown. It has been proposed that these tumours share risk factors with colorectal cancer, as there is a geographical correlation between the two tumour sites (Lowenfels 1973; Haselkorn et al. 2005). Countries with a high incidence of colorectal cancer have relatively high rates of small intestinal cancer. Interestingly, there is no such association between stomach cancer and small bowel cancer (Haselkorn et al. 2005). In these analyses, there was no stratification for histological subtypes.

Further evidence for an association between small and large bowel cancers, at least for adenocarcinomas, comes from the fact that adenomas seem to be pre-cancerous in the small intestine. The adenoma-carcinoma sequence has been recognized since many years in the large bowel (Morson 1974). Through a large literature review Sellner investigated the adenoma-carcinoma sequence in the small intestine and found it as valid as for colorectal cancer (Sellner 1990). The mean and median patient ages for the solitary, symptomatic benign small-bowel adenomas were less than those of adenoma-with-carcinoma or carcinoma. The ratio by sex of these three types of solitary small bowel neoplasms was the same. The spatial distribution over the small bowel of benign and malignant epithelial neoplasms was similar.

Moreover, increased risk of small bowel cancer in patients with colorectal cancer has been noted in a number of studies (Enblad et al. 1990; Chen et al. 1994; Scélo et al. 2006). Consequently, as the risk of subsequent colorectal cancer after diagnosis of small bowel cancer seems to be elevated, similar risk factors for the two tumour sites has been proposed (Chen et al. 1994; Scélo et al. 2006).

Hereditary non-polyposis colorectal cancer

Another shared feature with colorectal cancer is the increased risk in hereditary non-polyposis colorectal cancer (HNPCC). The development of pre-
dominantly right-sided colon carcinomas at an early age and an excess risk of metachronous and synchronous colonic cancers as well as extracolonic cancer is characteristic of HNPCC (Lynch et al. 1993). Four mismatch repair genes responsible for hereditary nonpolyposis colorectal cancer have been identified and high relative risks of cancer of the small bowel has been observed in carriers of either gene (Vasen et al. 1996). The life-time risk of developing small bowel cancer is still relatively low for these patients; 4.2 % (ten Kate et al. 2007).

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal-dominant disorder characterized by mucocutaneous pigmentation and gastrointestinal hamartomous polyposis (Tomlinson et al. 1997; Keller et al. 2001). Germ-line mutations in the serine/threonine kinase gene on chromosome 19p13.3 cause PJS (Hemminki et al. 1998). Patients with PJS are at increased risk of developing various gastrointestinal cancers including colorectal cancer and small bowel cancer, as well as malignancies in other non-gastrointestinal sites as the breast, uterus ovaries and lungs (Giardiello et al. 1987; Hearle et al. 2006). The cumulative risk of acquiring any cancer at age 60 for patients with PJS has been estimated to 63 %, compared with 8.5 % in the general population at the same age (Lim et al. 2004). In a recent meta-analysis, the relative risk of small intestinal cancer for patients with PJS compared with the general population was 520, and the cumulative risk from age 15 to 64 13% (Giardiello et al. 2000).

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant condition caused by mutations of the FAP gene on the long arm of chromosome 5 (Groden et al. 1991; Kinzler et al. 1991). FAP is characterized by the development of hundreds of colorectal adenomas, which if left untreated, inevitably will lead to colorectal cancer at young age (Lockhart-Mummery 1925; Lockhart-Mummery 1934). In addition, FAP includes various extracolonic hyperproliferative disorders of which desmoids and duodenal and ileal adenomas receive most clinical attention (Tulchinsky et al. 2005). Classification of duodenal polyposis is made on a 5-grade scale (stages 0-IV), based on polyp number, size, histology, and severity of dysplasia (Spigelman et al. 1989). Patients with stage IV disease are at greatest risk of malignant change and require close surveillance, or even prophylactic surgery. The relative risk of duodenal carcinoma for patients with FAP has been estimated to 330 whereas no statistically significantly increased risk of malignancy in jejunum or ileum has been noted (Offerhaus et al. 1992). The major causes of death
for patients with FAP who has undergone prophylactic proctocolectomy are desmoid tumour and duodenal carcinoma (Arvanitis et al. 1990).

Diet
Dietary risk factors for small bowel malignancies have been investigated in a handful case-control studies. In a study from the United States including 430 cases and 921 controls, Chow and co-workers found that consumption of red meat at least once a week and frequent intake of salt-cured/smoked foods was associated with increased risk of small intestinal malignancies, although there was no evidence of a linear dose-response relationship (Chow et al. 1993). The analyses were not stratified for different histological subtypes. Wu and co-workers analysed 36 cases with adenocarcinoma and 998 population controls. In this study, risk of small intestinal adenocarcinoma was increased in relation to frequent intake of barbecued or smoked meat, but only for males (Wu et al. 1997). Furthermore, high daily intake of sugar was a strong risk factor for both sexes in this study, with a linear trend of increasing risk with increasing intake. Negri and co-workers derived data from two Italian case-control studies including 23 patients with adenocarcinoma and 230 controls. Increased risk was related to consumption of bread/pasta/rice, sugar and beef/veal and inversely related to intake of coffee, fish, vegetables and fruit (Negri et al. 1999).

Smoking and alcohol
Data regarding the association of smoking and alcohol with small intestinal malignancies are conflicting. Some authors describe no increased risks for users of tobacco and alcohol (Chow et al. 1993; Negri et al. 1999), whereas others report opposite results (Chen et al. 1994; Wu et al. 1997). These studies do not distinguish between histological subtypes. A recent multi-centre case-control study involving 10 European countries including 97 cases of small intestinal adenocarcinoma and 2070 matched controls examined how smoking and drinking habits influenced the risk of this histological subtype exclusively (Kaerlev et al. 2000b). High intake of beer and sprits was associated with increased risk of small intestinal adenocarcinoma, whereas wine drinking and tobacco smoking was not. Adjusting for educational level did not alter the results. Smoking and alcohol intake as risk factors for small bowel carcinoid have been analysed in a later study including data from the above mentioned case-control study (Kaerlev et al. 2002a). Smokers had increased risk of small bowel carcinoid and the relative risk remained high in former smokers. Total alcohol intake was not associated with increased relative risk.
Occupation

Several uncommon tumours are associated with particular occupations and these cancers are sometimes called signal cancers, as they should alert physicians to the possibility of an occupational aetiology (Veys 1996). Increased occurrence of small bowel adenocarcinoma has been seen in dry cleaners, textile workers, general farm labourers, dockers or freight handlers and welders (Kaerlev et al. 2000a). Proposed high-risk occupations for small bowel carcinoid are shoemakers, structural metal preparers, construction painters and other construction workers, bookkeepers, machine fitters, and welders (Kaerlev et al. 2002b). For both histological subtypes, the excess occurrences were small, and the causal factors, if any, probably only affected a limited subset of workers.

Crohn’s disease

Gastrointestinal malignancy in coexistence with Crohn’s disease (CD) was earlier considered as purely coincidental (Hoffman et al. 1977). Over time, case reports and small series have been presented, suggesting an association between CD and small intestinal cancer as well as colorectal cancer (Fielding et al. 1972; Nesbit et al. 1976; Hawker et al. 1982; Collier et al. 1985; Senay et al. 1989).

Risk estimates regarding small intestinal malignancies associated with CD vary widely in the literature. Ekbom and co-workers found no increased risk (Ekbom et al. 1991a) whereas analyses of a population-based cohort in Denmark suggested the risk to be increased more than 60-fold (Jess et al. 2004). In a meta-analysis including five population based studies (Ekbom et al. 1991a; Persson et al. 1994; Bernstein et al. 2001; Jess et al. 2004; Jess et al. 2006) the overall pooled standardised incidence ratio (SIR) was 27 (Jess et al. 2005). A more recent meta-analysis estimated the relative risk of small bowel malignancy in CD compared with the baseline population to 28 (von Roon et al. 2007). For comparison, the relative risk of developing colorectal cancer compared with the general population was 2.4 in this study.

The generally accepted mechanism for the increased risk of intestinal cancer associated with inflammatory disease is that long-standing inflammation promotes oncogenesis locally (Wong et al. 2001). This concept has been questioned for carcinoid tumours occurring in relation to inflammatory disease (Greenstein et al. 1997) and it has been suggested that the seemingly increased risk of carcinoid in CD rather is the result of distant cytokine effects (West et al. 2007).
Medical risk-factors

As adenocarcinomas of the small bowel seem to have a predilection to proximal parts such as the duodenum, it has been claimed that bile might be an important carcinogen (Lewis et al. 1972; Lowenfels 1978; Ross et al. 1991). Bile emptying is accelerated after cholecystectomy (Madacsy et al. 1999); therefore, patients who have undergone cholecystectomy could be at increased risk of developing small intestinal malignancies. In a population-based retrospective cohort study, the SIR for small bowel adenocarcinoma and carcinoid after cholecystectomy was 1.8 and 1.7 respectively (Lagergren et al. 2001). In a population-based case-control study no association between cholecystectomy and adenocarcinoma was seen (Kaerlev et al. 2001). Carcinoid of the small intestine has been associated with previous cholecystectomy, but only within two years after surgery, indicating that these results are caused by detection bias (Kaerlev et al. 2002a). Peptic ulcer disease (Chen et al. 1994) and ovariectomy (Kaerlev et al. 2001; Kaerlev et al. 2002a) have also been suggested as risk-factors for adenocarcinoma and carcinoid, again results are probably due to detection bias.

Coeliac disease

The association between coeliac disease and malignant lymphoma is well established in the literature (Askling et al. 2002; Smedby et al. 2005). There are few population-based studies of reasonable size addressing the risk of other malignancies, as small intestinal adenocarcinoma and carcinoid. In a case-control study from Denmark including 95 patients with small intestinal adenocarcinoma and 3335 controls, 2 cases and 0 controls had coeliac disease although one case was diagnosed at the same time as the small intestinal malignancy (Kaerlev et al. 2001). Smaller cohort studies have failed to demonstrate increased incidence of small intestinal malignancy in patients with coeliac disease (Card et al. 2004; Viljamaa et al. 2006; Anderson et al. 2007) whereas in a large cohort study of patients hospitalized for coeliac disease the risk was increased ten-fold (Askling et al. 2002). Furthermore, there are indications that small intestinal cancers associated with coeliac disease have poorer prognosis (Howdle et al. 2004).

Diagnosis

Adenocarcinomas and carcinoids of the small intestine may present with a variety of clinical symptoms ranging from occult gastrointestinal bleeding from a small adenocarcinoma, to the carcinoid syndrome in the case of liver metastases from a carcinoid tumour. The choice of diagnostic procedure for these patients evidently depends totally on the manifestation of the disease.
In clinical practice, a multimodal approach is usually needed for the correct diagnosis, staging and follow-up of small intestinal malignancies. Attempts of standardisation of imaging procedures has been done for neuroendocrine tumours (Ricke et al. 2001).

Conventional radiographic methods

The length and looped configuration contribute to the difficulties in diagnosing tumours in the small bowel with conventional radiographic methods. Previously, small-intestinal follow-through and various double-contrast techniques (enteroclysis), sometimes combined with angiography were the methods available for patients with suspected small bowel tumours (Henriksen et al. 1979; Ekberg et al. 1980; Martin et al. 1980). These methods are still in clinical use today, although the small-intestinal follow through is seldom used as a diagnostic tool for suspected small bowel tumours except in the emergency setting with manifest intestinal obstruction. Bessette and co-workers reported a sensitivity for detecting small bowel neoplasms by enteroclysis as high as 95% compared with 61% for the small intestinal follow-through (Bessette et al. 1989).

Computed tomography

Computed tomography (CT) was earlier used mainly as a tool for staging a known malignancy or in the clinical work-up for unspecific symptoms as abdominal pain. It has been suggested that carcinoid tumours involving the small intestinal mesentery have a typical radiographic appearance with rounded mesenteric masses with small linear radiodensities (Cockey et al. 1985). Multidetector or multisclice CT available today may detect small intestinal carcinoids confined to the bowel wall (Gore et al. 2005). Recently CT enteroclysis and enterography has been introduced as valuable methods in both diagnosis and staging of small bowel neoplasms (Paulsen et al. 2006; Pilleul et al. 2006; Minordi et al. 2007).

Endoscopy

Direct visualization of the small bowel mucosa can be accomplished by small bowel endoscopy. Initially a sonde-type endoscope introduced transnally was used (Tada et al. 1977). The procedure is time-consuming and there is no therapeutic capability. Furthermore, complete passage to the ileocecal valve is not always accomplished (Lewis et al. 1991b), and even with complete intubation only 50-70% of the mucosa is examined (Lewis et al. 1987). Push-enteroscopy using a standard colonoscope allows for therapeutic measures and biopsy of suspected lesions (Parker et al. 1983) although the reach of the instrument limits diagnostic yield (Foutch et al. 1990). Lewis
and co-workers reported 258 patients with obscure gastrointestinal bleeding evaluated with a combination of push-enteroscopy and small bowel enteroscopy with the sonde-type enteroscope (Lewis et al. 1991a). In 50 %, no diagnosis was made. In 13 patients, the cause of bleeding was a small bowel tumour, although for patients less than 50 years of age, neoplasms was the most common source of obscure gastrointestinal bleeding in this study. Yamamoto and co-workers has described a modified technique of small bowel endoscopy with a double-balloon endoscopy system and reported successful examination of the entire small bowel in 86% of investigated patients (Yamamoto et al. 2004). In this study, a combination of antegrade and retrograde intubation was used, and few patients were completely evaluated by the antegrade route alone. For the patients with obscure gastrointestinal bleeding the source could be identified in 50 of 66 patients; 10 patients had small intestinal tumours. The major advantage of this procedure is the capability of diagnostic and therapeutic measures under direct visualisation.

**Video capsule endoscopy**

Iddan and co-workers introduced video capsule endoscopy in 2000 (Iddan et al. 2000). This procedure has mostly been evaluated in the setting of obscure gastrointestinal bleeding. Pennazio and co-workers reported 100 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding when no source was found after standard endoscopy (Pennazio et al. 2004). Positive findings were observed in 47 % of included patients and capsule endoscopy revealed the source of bleeding in 32 of 36 patients with a final positive diagnosis confirmed by surgery or further work-up. One patient in this study had a small bowel tumour. In a recent study of 260 patients with obscure gastrointestinal bleeding, diagnostic yield for capsule endoscopy was 53 %, (Carey et al. 2007). The number of identified small bowel tumours was not exactly stated in this study. Two meta-analyses found capsule endoscopy superior to conventional radiography and push enteroscopy although there was no statistically significant difference in the diagnostic yield for small bowel tumours (Marmo et al. 2005; Triester et al. 2005). A recent meta-analysis including 8 trials and 277 patients found capsule endoscopy equal to double-balloon endoscopy for diagnosis of various small bowel diseases if a combined oral and anal insertion approach was used (Chen et al. 2007). Cobrin and co-workers retrospectively evaluated the effectiveness of capsule endoscopy in diagnosing small bowel tumours (Cobrin et al. 2006). The majority of the 562 patients included suffered from gastrointestinal bleeding. Diagnostic yield was 49.3 % including 8 adenocarcinomas and 10 carcinoids. The patients with tumours (neoplastic and non-neoplastic) had undergone extensive non-diagnostic work-up prior to capsule endoscopy. Capsule endoscopy has also been evaluated for patients with metastatic neuroendocrine tumours with unknown primary (Johanssen et al. 2006; van
Tuyl et al. 2006). Although small, these studies suggest that video capsule endoscopy may be valuable in this setting, especially for its ability to differentiate between intestinal and mesenterial location of a tumour found with nuclear imaging.

Somatostatin receptor scintigraphy
As discussed in more detail below, neuroendocrine tumours in the small intestine express somatostatin receptors. The use of radiolabelled somatostatin analogues for localisation of neuroendocrine tumours was originally proposed by Krenning and co-workers (Krenning et al. 1989). This method was soon recognized as a valuable tool for identification of primary tumours as well as metastatic disease not recognized with conventional methods (Westlin et al. 1993). An analysis of 194 patients with neuroendocrine tumours of various origins (57 patients had small bowel carcinoids) reported a sensitivity of over 90 % for both primary and metastatic lesions (Raderer et al. 2000). Indium-111 is the most commonly used radioligand, and the addition of single photon emission computed tomography (SPECT) is generally recommended to give better anatomic visualization compared with planar views (Schillaci et al. 1996). Somatostatin receptor scintigraphy is limited by its inability to detect small lesions and tumours not expressing somatostatin receptors (Oberg et al. 2005).

Positron emission tomography
As malignant cells in general, have a higher than normal glycolytic rate, positron emission tomography (PET) using fluorodeoxyglucose (FDG) labelled with a positron emitter as fluorine-18 or carbon-11 is useful for identifying various malignancies, as well as monitoring changes in tumour glucose metabolism during treatment (Messa et al. 1992; Findlay et al. 1996). Most neuroendocrine tumours in the small intestine are well-differentiated neoplasms with low metabolic rate, and PET with this method is of little value (Adams et al. 1998). PET using amine precursors as 5-hydroxytryptophan and dihydroxyphenylalanine as tracers has been evaluated recently, and seem to have major advantages compared with computed tomography and somatostatin receptor scintigraphy (Orlefors et al. 2005; Koopmans et al. 2006).

Biochemical markers
5-hydroxyindoleacetic acid
5-hydroxytryptamine (5-HT), or serotonin, (Rapport 1949; Erspamer 1954), is present in high concentrations in small intestinal carcinoids (Lembeck
1953). Increased levels of serotonin in blood, and of its major metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in urine, have been recognized in the carcinoid syndrome (Pernow et al. 1954; Page et al. 1955). Twenty-four hour urine collection of 5-HIAA is used as a diagnostic test, mainly for patients with symptoms associated with the carcinoid syndrome. Reported sensitivity is between 35 % and 76 %, and specificity between 89% and 100 % (Feldman 1986; Feldman et al. 1986; Tormey et al. 1995; Janson et al. 1997; Nuttall et al. 1998; Bajetta et al. 1999; Seregni et al. 2001). Most authors include neuroendocrine tumours of divergent origin and statistical methods for estimating the clinical usefulness of 5-HIAA as a diagnostic test vary. Meijer and co-workers evaluated 5-HIAA levels in 51 patients with mid-gut carcinoid (in this study defined as jejunum, ileum, appendix, and the ascending colon) compared with healthy controls as well as subjects with clinical symptoms suggestive of carcinoid disease, but with no evidence of carcinoid tumour at follow-up (Meijer et al. 2000). Different cut-off values were used for urinary 5-HIAA. Sensitivity was 68 % and specificity was 89 % for low-level values, and 52 % and 98 % respectively for high-level cut-off values. Corresponding positive predicting values for the presence of a carcinoid tumour was 58 % and 87 %. Because of the relatively low discriminating capacity of 5-HIAA, it is mainly used for monitoring therapy.

**Chromogranin A**

In 1965 Banks and Helle identified a soluble protein released from chromaffin granules in the isolated bovine adrenal gland (Banks et al. 1965). Blaschko and co-workers later reported the release of this protein together with catecholamines *in vivo*, and suggested the term ‘chromogranin’ (Blaschko et al. 1967). Chromogranins belong to a family of secretory proteins consisting of several subtypes. Chromogranin A (CgA) has been identified in normal polypeptide producing tissues as well as in various tumours of neuroendocrine origin (O'Connor et al. 1983; Deftos et al. 1988). It is widely used in immunohistochemical analyses of neuroendocrine tumours. Circulating levels of CgA has been recognized as a valuable marker of neuroendocrine tumours (O'Connor et al. 1986; Eriksson et al. 1989). Reported sensitivity and specificity vary in the literature, mainly because of the use of different cut-off values and choice of reference population as well as the inclusion of various neuroendocrine tumours in the study population. Furthermore, different assays used for measuring CgA levels give divergent results (Stridsberg et al. 2003). In a recent study, Campana and co-workers analysed CgA levels in 238 patients with neuroendocrine tumours (85 patients had gastrointestinal neuroendocrine tumours) compared with 48 healthy participants (Campana et al. 2007). In this setting, sensitivity was 85.3 % and specificity 95.8 %. In earlier studies, sensitivity and specificity was 47-84 % and 84-100 %, respectively (Nobels et al. 1997; Bajetta et al. 1999; Cimitan et al. 2003; Peracchi et al. 2003). Syversen and co-workers
reported CgA levels in 153 consecutive patients in whom CgA was analysed mainly because of symptoms suggestive of a neuroendocrine tumour (Syversen et al. 2004). Elevated CgA levels were found in 44 patients, and 19 had neuroendocrine tumours. Well-known causes for elevated CgA levels in the absence of neuroendocrine tumours are chronic atrophic gastritis, use of proton-pump inhibitors and impaired renal function (Nobels et al. 1997; Sanduleanu et al. 1999; Campana et al. 2007). CgA levels correlate with tumour load in animal models (Kolby et al. 2004) as well as in humans (Janson et al. 1997; Nobels et al. 1997; Bajetta et al. 1999; Campana et al. 2007; Zatelli et al. 2007). To avoid the problem of falsely elevated CgA levels in clinical practice, complementary measurement of chromogranin B has recently been suggested (Stridsberg et al. 2007).

Treatment
Surgery

Adenocarcinoma
There are no evidence-based data in the literature regarding surgical strategy in small intestinal adenocarcinoma. Most authors agree that standard surgical treatment is wide excision of the lesion with en bloc removal of regional lymph nodes for jejunal and proximal ileal tumours, right sided hemicolectomy for distal ileal tumours, and pancreaticoduodenectomy for duodenal tumours (Darling 1959; Morgan 1977; Ouriel et al. 1984; Ashley et al. 1988). Pancreaticoduodenectomy is only advocated in the absence of regional lymph node metastases and gastrojejunostomy for all others although massive bleeding will usually require at least palliative resection (Ouriel et al. 1984). The proportion of patients operated with curative intent as compared with those undergoing palliative procedures is commonly reported as ‘resection rate’ in the literature. Reported resection rates for jejunal and ileal carcinomas vary between 39 % and 90 % (Rochlin et al. 1961; Southam 1962; Pagtalunan et al. 1964; Hancock 1970; Vuori 1971; Wilson et al. 1974; Bridge et al. 1975; Treadwell et al. 1975; Mittal et al. 1980; Farmilo et al. 1988; Kusumoto et al. 1992; Bauer et al. 1994; Frost et al. 1994; Naef et al. 1999; Talamonti et al. 2002; Dabaja et al. 2004; Lepage et al. 2006; Agrawal et al. 2007) and between 28% and 70% for duodenal lesions (Rochlin et al. 1961; Sakker et al. 1973; Morgan 1977; Alwmark 1980; Ouriel et al. 1984; Kusumoto et al. 1992; Bauer et al. 1994).

Carcinoid
Most of the general principles outlined above regarding surgery for small intestinal adenocarcinomas apply for small intestinal carcinoids. A major difference is that over time, surgical treatment for neuroendocrine tumours
has become more aggressive. Surgery is the only approach that can achieve complete cure (Oberg 2003). Intestinal resection and removal of mesenteric lymph nodes is usually recommended even in the presence of liver metastases, and debulking and palliative procedures are commonly applied (Makridis et al. 1990; Soreide et al. 1992; Makridis et al. 1996; Hellman et al. 2002). As lymph node metastases often grow to considerable size with fibrosis surrounding the mesenteric vessels, lymphadenectomy can be technically difficult (Ohrvall et al. 2000). There is some evidence that removal of lymph node metastases as well as liver metastases relieves symptoms and improves survival (Soreide et al. 1992; Hellman et al. 2002; Sarmiento et al. 2003). Cytoreductive techniques in the presence of non-resectable metastases may relieve symptoms in the presence of the carcinoid syndrome and even prolong survival (Que et al. 2002). Eriksson and co-workers recently presented the successful use of radiofrequency ablation and liver resection in 37 patients with liver metastases from mid-gut carcinoids (Eriksson et al. 2008). Both treatment modalities were effective in controlling the carcinoid syndrome and complications were relatively few. Liver transplantation has been described for patients with liver metastases, especially for well-differentiated tumours with low proliferating index (Ahlman et al. 2004; Blonski et al. 2005). Recent guidelines for the management of small intestinal carcinoids (or GEP NETs originating in the small intestine) all emphasize the role of surgery even in patients with advanced disease (Oberg et al. 2004b; Ramage et al. 2005; Maroun et al. 2006).

Non-surgical treatment

Adenocarcinoma

Randomized controlled trials addressing the value of chemotherapy of small intestinal adenocarcinoma, in the adjuvant or palliative setting are lacking in the literature (Singhal et al. 2007). Since it has been clearly demonstrated that adjuvant chemotherapy in stage III colon cancer decreases recurrence and mortality (Moertel et al. 1990), it is tempting to assume that adjuvant chemotherapy is as effective for small intestinal adenocarcinoma. Despite the sparse evidence, the use of chemotherapy for patients with adenocarcinoma has been described in several papers. Although some authors conclude that chemotherapy is almost uniformly unsuccessful (Wilson et al. 1974; Jigyasu et al. 1984), more recent reports give a more optimistic outlook. In a retrospective cohort study of 217 patients with small intestinal adenocarcinoma, adjuvant chemotherapy was administered in 59 (27 %) patients and 48 (22%) received palliative chemotherapy (Dabaja et al. 2004). Adjuvant therapy did not improve overall survival although palliative chemotherapy seemed to be of benefit for patients who did not undergo surgery or who had distant metastases. There was no information on the type of cytotoxic drugs
used in this report. Crawley and co-workers reviewed the efficacy of protracted infusion of 5-fluorouracil-based chemotherapy for advanced small intestinal adenocarcinoma (Crawley et al. 1998). In conclusion, the treatment was well tolerated, and an overall response rate of 37.5 % was seen. In a phase II study of 5-fluorouracil, doxorubicin, and mitomucin for metastatic small bowel adenocarcinoma, response rates of 18.4 % was seen although toxicity was common and the studied combination did not achieve a response rate or overall survival (8 months median overall survival) superior to historical controls (Gibson et al. 2005). A review of a regimen with 5-fluorouracil and platinum compounds reported an overall response rate of 21 % and median overall survival of 14 months, with tolerable side-effects (Locher et al. 2005). In a recent chart review of 113 patients with locally advanced or metastatic disease, 46% received some form of chemotherapy (Fishman et al. 2006). The authors concluded that response rates with newer chemotherapeutic agents are 30 %, and furthermore an improved survival was seen in the palliative setting. A similar review of patients treated with various chemotherapy agents (mostly 5-fluorouracil-based) reported an overall response rate of no more than 6 % for patients treated with palliative intent (Czaykowski et al. 2007). An apparent survival benefit was seen for patients receiving chemotherapy versus patients receiving no treatment, although the difference is probably explained by selection bias. In a recent case-control study of 11 patients with small intestinal adenocarcinoma and 581 controls with colorectal-cancer, treated with either with capecitabine combined with oxaliplatin as palliative treatment or with adjuvant 5-fluorouracil, response rates in the palliative group (n=7) were 14 % compared with 35 % for colorectal cancer patients (Thomsen Lonborg et al. 2007). Adjuvant treatment was not of benefit in this analysis, although this study was too small to draw any firm conclusions.

**Carcinoid**

For many years standard medical treatment for carcinoid tumours was chemotherapy, mostly streptozocin combined with fluorouracil, with a response rate of 33% (Moertel et al. 1979), and purely symptomatic therapy in the presence of the carcinoid syndrome (Grahame-Smith 1968; Davis et al. 1973). As most small intestinal carcinoids are neuroendocrine tumours with low proliferative capacity, cytotoxic treatment is generally of little benefit for these patients (Oberg 2003). Nevertheless, oxaliplatin and capecitabine in combination has recently been proposed for well differentiated neuroendocrine tumours after progression following biotherapy (Bajetta et al. 2007).

**Somatostatin**

Somatostatin was isolated from bovine hypothalamus by Brazeau and co-workers in 1972, and it is an inhibitor of various endogenous peptides (Brazeau et al. 1973). Some years later somatostatin was reported to be ef-
effective in controlling the effects associated with the carcinoid syndrome (Frolich et al. 1978; Thulin et al. 1978). Since natural occurring somatostatin has short half-life in vivo, a synthetic somatostatin analogue, octreotide, was developed (Bauer et al. 1982) and was shown to be equally effective in the treatment of the carcinoid syndrome (Kvols et al. 1985; Kvols et al. 1986). Five somatostatin receptors have been characterized and cloned; sst1-5 (Yamada et al. 1992a; Yamada et al. 1992b; Yamada et al. 1993). Somatostatin binds to all somatostatin receptors whereas the two commercially available analogues, octreotide and lanreotide, mainly bind to receptor subtypes 2 and 5 (Patel et al. 1994). Neuroendocrine tumours in the small intestine generally express all somatostatin receptors, possibly with a predominance of ssr2 (Patel et al. 1994; Reubi et al. 1996). Somatostatin analogues have antisecretory effects in the presence of the carcinoid syndrome and possibly antiproliferative effects although response rates vary widely in the literature (Kvols et al. 1986; Öberg et al. 1991; Arnold et al. 1992; di Bartolomeo et al. 1996). Clear evidence is lacking for improved survival although there is some evidence of improved progression free survival for patients receiving somatostatin analogue therapy when compared with historical controls (Saltz et al. 1993). Somatostatin analogues in higher than conventional doses bind to receptor subtype 3 in addition to subtypes 2 and 5 (Lamberts et al. 1996). Eriksson and co-workers treated 19 patients with advanced GEP NETs with high-dose lanreotide with no better results than those achieved with standard doses (Eriksson et al. 1997). The authors reported apoptosis or programmed cell death in tumours of responding patients. It has been shown earlier that apoptosis is mediated by receptor subtype 3 (Sharma et al. 1996). A high-dose formula of octreotide, octreotide pamoate, has recently been evaluated by Welin and co-workers to further improve response rates for patients with advanced small intestinal neuroendocrine tumours and progressive disease (Welin et al. 2004). Improvement of symptoms and stabilization of hormone production, as well as tumour growth was seen in 75 % of the 12 patients included, although no signs of apoptosis were seen. A somatostatin analogue, pasireotide (SOM230) with affinity for receptor subtypes 1,2,3 and 5 has been identified (Bruns et al. 2002). Recently a phase II clinical trial has been conducted showing that pasireotide was effective in controlling diarrhoea and flushing in 27 % patients with metastatic carcinoid tumours who did not respond to octreotide (Kvols et al. 2006). The use of subtype specific antibodies against somatostatin receptors expressed in neuroendocrine tumours has been proposed as a way of individualizing somatostatin analogue therapy (Kulaksiz et al. 2002). Well-accepted indications for somatostatin analogue therapy in small intestinal neuroendocrine tumours include the presence of the carcinoid syndrome and progression of metastatic disease (Oberg et al. 2004c).
Interferon

In 1957 Isaacs and co-workers described the existence of a factor they called ‘interferon’, capable of inducing resistance to infection through interference with homologous or heterologous viruses (Isaacs et al. 1957a; Isaacs et al. 1957b). Although initially presented as an anti-viral drug; in 1969 interferon was shown to have anti-tumour effects (Gresser et al. 1969). Interferon is a cytokine that regulates various cellular functions. There are different types and subtypes of which interferon type I, subtypes alpha and beta, are the two predominant forms (van Boxel-Dezaire et al. 2006; Pestka 2007; Vilcek 2007). The treatment of small intestinal carcinoid tumours with interferon-alpha was first proposed by Oberg and co-workers (Oberg et al. 1983). At that time, interferon was known to enhance natural-killer cell activity (Herberman et al. 1982), and deficient natural-killer cell activity had been demonstrated in patients with disseminated cancer (Kadish et al. 1981). Nine patients with small intestinal carcinoids and progressive disease were treated with interferon-alpha in this pilot study, with effects on symptoms and amine levels in seven patients (Oberg et al. 1983). Furthermore, abnormalities in the interaction between natural-killer cells and interferon were shown in these nine patients (Funa et al. 1983). Since then, the various effects of interferon-alpha on neuroendocrine tumours have been thoroughly explored; in summary it acts via antiproliferative effects and inhibition of tumour angiogenesis (Sangfelt et al. 2000; Rosewicz et al. 2004) as well as immuno-modulatory effects (Vilcek et al. 1980). Several reports have been published reporting the effects of interferon-alpha in clinical practice, demonstrating biochemical response rates of 40-50 %, symptomatic response rates of 40-50 % and antiproliferative effects in 10-15% (Moertel et al. 1989; Creutzfeldt et al. 1991; Oberg et al. 1991; Valimaki et al. 1991; Bajetta et al. 1993; di Bartolomeo et al. 1993; Dirix et al. 1996). There is some evidence of a survival benefit for patients with advanced small intestinal neuroendocrine tumours treated with interferon-alpha. Oberg and co-workers reported a median survival of over 80 months compared with mere 8 months for historical controls treated with chemotherapy alone at the same institution. The patient population was heterogeneous regarding origin of the primary neuroendocrine tumour although the majority of patients in this study were classified as ‘mid-gut carcinoid tumours’ (Oberg et al. 1991). Further evidence towards interferon treatment and increased survival comes from a study including 42 patients with mid-gut carcinoid tumours and liver metastases (Jacobsen et al. 1995). Patients were initially treated with interferon-alpha for one year and then randomized to continue or to stop therapy, with a statistically significantly increased cumulative 5-year survival for patients who continued therapy.

Adverse reactions as flu-like symptoms, fatigue, weight loss and anaemia are common during treatment with interferon-alpha (Oberg et al. 1991), and
autoimmune reactions have been described (Ronnblom et al. 1991). Most adverse reactions seem to be dose-dependent, and consequently, trials using higher than conventional dosage has reported increased incidence of serious side effects without therapeutic gain (Moertel et al. 1989).

Treatment with interferon has been compared with chemotherapy with streptozocin and 5-fluorouracil in a randomized trial including 20 patients with carcinoid tumours (Oberg et al. 1989). Although this study was small and included neuroendocrine tumours of diverse origin, the authors concluded that interferon was the treatment of choice. The combination of interferon and chemotherapy has also been explored in a randomized trial showing no benefit from combination therapy compared with interferon alone (Janson et al. 1992). The addition of interferon-alpha to somatostatin analogue treatment has been suggested to further improve response rates and minimizing the adverse effects of interferon by lowering interferon dosage (Tiensuu Janson et al. 1992). In randomized trials, although small, no clear-cut advantage has been presented for the use of combination therapy with interferon-alpha and somatostatin analogues (Faiss et al. 2003; Kölby et al. 2003; Arnold et al. 2005).

Liver artery embolization
In the presence of multifocal or disseminated liver metastases, conventional liver resection is seldom an option. The blood supply to liver metastases comes almost entirely from the hepatic artery, whereas the blood supply to normal hepatic tissue is derived from portal blood flow (Breedis et al. 1954). With this knowledge in mind ligation of the hepatic arterial vessels was explored as treatment of metastases to the liver from carcinomas as well as carcinoids (Nilsson 1966; Nilsson et al. 1967; Aune et al. 1972). To avoid the complications associated with open surgery, arterial embolization was developed and initially proposed for unresectable hepatomas (Yamada et al. 1980). Since then several authors have described embolization of liver metastases from carcinoids with response rates around 50% (Eriksson et al. 1998; Strosberg et al. 2006). To further improve response rates, intra-arterial chemotherapy has been used in combination with embolization (chemoembolization) without any obvious advantage compared with embolization alone (Ruszniewski et al. 2000; Gupta et al. 2003).

Peptide receptor radionuclide therapy
The use of radiolabelled somatostatin analogues for diagnostic purposes is part of routine clinical work up for patients with carcinoid tumours. Tumour targeted therapy was initially described using high doses of octreotide labelled with indium-111, which was normally used for diagnostic purposes (Valkema et al. 2002). Since then somatostatin analogues with higher receptor affinity has been developed and combined with radionuclides with more favourable physical characteristics such as yttrium-90 (Waldherr et al. 2001)
and lutetium-177 (Kwekkeboom et al. 2003). In a recent trial using octreotide labelled with yttrium-90, 33 out of 58 patients experienced some improvement of their disease (Valkema et al. 2006). Partial response was achieved in just over 10% and overall median survival was 36.7 months. The patient cohort included various GEP-NETs and the majority of patients had advanced disease with liver metastases. Thirty patients in this study were classified as mid-gut carcinoids. In a study using a somatostatin analogue with higher affinity to somatostatin receptor subtype 2 and a different radionuclide (lutetium -177), a partial response of 20% was achieved for carcinoid tumours (Kwekkeboom et al. 2005). Overall, median time to progression for patients with either stable disease or some kind of radiological response was over 36 months. Again, the cohort was heterogeneous regarding primary tumour site, although in 64 of 70 patients with carcinoid tumours, the site of origin was the small intestine. Severe side-effects are rare in peptide receptor nuclide therapy although toxic effects of radiation affecting mainly the kidneys and bone-marrow are commonly described (Forrer et al. 2007). There are no randomized controlled trials evaluating the role of peptide receptor nuclide therapy in the literature although a trial comparing treatment with a somatostatin analogue labelled with lutetium-177 alone or in combination with capecitabine has recently started (van Essen et al. 2008).

Survival

There are few population-based analyses, and numerous case series in the literature describing survival in small intestinal adenocarcinoma and carcinoid. Several reports from referral centres have been published over the years with the obvious problem of selection bias inherent to a single-institution study. Nevertheless, detailed analyses of patients from specialized centres provide valuable information of prognostic factors not readily available in population based tumour registries as well as the possibility of evaluating the impact of therapeutic strategies on survival. Some population-based series do not analyse the different histological subtypes separately, and especially in the published analyses of carcinoids, cases with primary tumours of different origin are analysed together. Furthermore, methods used for analysis of survival vary widely between authors. Moreover, the earlier lack of a uniform system for staging and classification of gastrointestinal neuroendocrine tumours makes analysis of data from different time-periods difficult.

Only a selection of single-centre studies of special interest will be referred to in detail below.
Short summary of statistical methods in survival analysis

Reports of patient survival are common in the medical literature. The presentation of 5-year survival is frequently used in cancer research when describing single populations or comparing two or more groups, subject to different treatment modalities. In some reports, ‘5-year survival’ may simply denote the proportion of patients surviving at least 5 years after study entry, which can be date of diagnosis, date of surgery or some other entry point. In most instances, the event of interest (e.g. death) will not have occurred for all patients at the end of the study period. These are called censored observations. Censoring also occurs when subjects are lost to follow-up. Common statistical methods for comparison of survival times in different groups as a continuous variable are not useful in the presence of censored data. Even in the case of complete follow-up, such methods are of little use, as survival times in study populations are not normally distributed. Moreover, patients experiencing the event of interest before 5 years of observation contribute valuable information which is lost if the analysis is done merely by dividing the number of patients alive after 5 years of observation by the total number included (Cutler et al. 1958). Survival analysis or ‘failure-time’ analysis is a descriptive method to estimate times to different events as progression of disease, recurrence or death in a sample (Peto 1984). Survival curves in the medical literature are usually estimated by non-parametric methods as the life-table method (Cutler et al. 1958) or the Kaplan-Meier method (Kaplan et al. 1958) and show the probability at different times of not experiencing the event of interest. While the Kaplan-Meier method calculates the probability for the event at the time it occurs, the life-table method uses grouped data, by months or years. In both methods, cases with censored data are included in the population at risk until censoring occurs in the subsequent calculations of probability of survival. Commonly used terms in descriptions of patient outcome are ‘overall’ survival and ‘disease-specific’ survival. In analyses of ‘overall’ survival, all deaths during the study period are considered as events. Censoring occurs in the absence of death before the end of the study period. This method is obviously dependent on the age of the study population as it evaluates deaths from all causes. ‘Disease-specific’ (or ‘cancer-specific’, or ‘corrected’) survival is used to exclusively study deaths from the disease (e.g. cancer) under study. Deaths by other causes are thus censored in the analysis. This method is highly dependent on correct information on causes of death, which is commonly withdrawn from death certificates in population-based studies.

The most frequently applied method of comparing survival curves of two or more groups is the logrank test (Kalbfleisch et al. 2002; Bland et al. 2004). This test is appropriate when the relative mortality (and risk of censoring) between study groups does not change over time; the proportional hazard assumption. Crossing survival curves is an indication that the propor-
tional hazard assumption is violated, and alternative tests of significance should be considered. The logrank test is computed by comparing the observed number of deaths in each group to the number that would be expected if the death rates were the same in the two groups. A simplified way of calculating the test statistic is by \( \chi^2 (\text{logrank}) = \sum (O - E)^2 / E \), where \( O \) and \( E \) are the total number of expected (E) and observed (O) events in each group to be compared. The p-value is extracted from a table of the \( \chi^2 \) –distribution, where the degrees of freedom are the number of compared groups minus one. The logrank test is merely a test of significance and does not estimate the magnitude of the difference between the compared groups.

Modelling of survival is usually done through the hazard function. The hazard function measures the instantaneous death rate at a specific time for an individual surviving up to that time. This is also referred to as the ‘instantaneous death rate’, ‘force of mortality’ or hazard rate. The most widely used regression method is the Cox proportional hazards model (Cox 1972; Gill 1982). It allows analysing the effects of several risk factors on survival (or hazard) simultaneously. This method gives a quantitative measure of the difference in survival times between different groups of interest. Results are commonly reported as relative hazards or relative risks. The Cox model assumes proportional hazards, i.e., the ratio between the hazards of included groups is the same at any time, although there are methods of including time-varying covariates into the model.

Due to the inherent problems in analysing overall and cause-specific survival, reports of survival in population-based studies often describe relative survival (Ederer et al. 1961; Hakulinen 1982). Relative survival is estimated from life-tables as the ratio of the observed survival of the patients to the expected survival of a comparable group. Expected survival is derived from nationwide life-tables stratified by age, sex, and calendar-time. Relative survival is a measure of the excess mortality for patients with the disease of interest, irrespective of whether the excess mortality is directly or indirectly attributable to the disease.

Modelling of relative survival is through the hazard function which is modelled as the sum of the expected hazard, and the excess hazard due to the studied disease (i.e. cancer) (Dickman et al. 2004). Results are reported as excess hazard ratios or relative excess risks, which denotes the excess mortality associated with the disease of interest. An excess hazard ratio of 2 for one study group compared with another, means that the excess mortality associated with the disease of interest is 100% higher for the first group.
Adenocarcinoma

Population-based studies

Howe and co-workers presented data from the National Cancer Data Base (NCDB) in the United States (Howe et al. 1999). Although the NCDB formally is not a population-based registry as data is gathered on a voluntary basis, it provides information from a large number of hospitals of different sizes. A total of 4995 cases of small intestinal adenocarcinoma were identified in the NCDB 1985-95. Disease specific survival for 1866 patients was analysed with the life-table method under the assumption that patients who died with disease died of disease. Almost 20 % were lost to follow-up within 5 years. The proportion surviving at 5 years was 30.5 %. Cox proportional hazards analysis was used to evaluate the independent effects on survival of different variables. Old age, regional or distant tumour spread and tumour location in duodenum was associated with poor survival. No information on trends in survival over time was available in this study.

Pashayan and co-workers gathered 2563 cases of small intestinal adenocarcinoma from the National Cancer Registry including patients from England and Wales (Pashayan et al. 2006). Relative survival was analysed by age, sex, anatomic localisation and period of diagnosis. As different morphologic subtypes were analysed together, there are no conclusions to be drawn on the effects of these variables on relative survival for patients with adenocarcinoma from this study. Five-year relative survival for duodenal, jejunal, and ileal adenocarcinoma was 15 %, 26 %, and 25 %, respectively. Relative survival was statistically significantly lower for duodenal tumours.

DiSario and co-workers reported a review of the Utah Cancer Registry, including 80 patients with small intestinal adenocarcinoma diagnosed 1966 through 1990 (DiSario et al. 1994). Five-year relative survival was 25 %. No analysis of prognostic factors was reported in this study.

An analysis of 135 cases of small intestinal adenocarcinoma derived from a cancer registry in Burgundy, France, was reported by Lepage and co-workers (Lepage et al. 2006). Five-year relative survival was 27 %, and overall 5-year survival was 24 %. Again, in the analysis of prognostic factors as age as gender, age at diagnosis, period of diagnosis and stage, no stratification for the different histological subtypes was made.

In conclusion, data from population-based studies indicate a disease specific 5-year survival of around 30 %, relative 5-year survival estimates of around 25 %, and overall survival 24 %. Tumour site in duodenum, distant tumour spread, and old age are probably factors associated with poor prognosis. There are no available reports on time-trends in survival for patients with small intestinal adenocarcinoma.
Single-centre studies

Dabaja and co-workers presented a detailed retrospective analysis of 217 patients with small intestinal adenocarcinoma diagnosed between 1978 and 1998 at M. D. Anderson Cancer Centre, Houston, Texas (Dabaja et al. 2004). Overall survival was analysed with the Kaplan-Meier method. Five year overall survival was 26 %. Median overall survival for duodenal tumours was 18 months for duodenal tumours and 26 months for tumours in jejunum/ileum. The difference in survival between sites was not statistically significant. Lymph-node metastases and distant metastases were associated with poor survival. Age did not correlate with survival, and neither did gender or histology grade in this study.

Similar results come from an analysis of 80 patients with small intestinal adenocarcinoma from Chang Gung Memorial Hospital, Taiwan (Wu et al. 2006). Overall 5-year survival was 17.5 % and advanced tumour stage was a predictor of poor survival. Disease free 5-year survival for patients who had undergone curative resection was 27.4 %.

Veyrières and co-workers analysed 100 patients with jejunal and ileal adenocarcinomas (Veyrières et al. 1997). Five- and ten-year overall survival was 38 % and 27 % respectively. Corresponding overall survival after curative resection was 54 % and 40 %. Moreover, preoperative anaemia corresponded with favourable outcome for these patients. It is likely that patients presenting with anaemia are diagnosed at an earlier stage compared with cases with weight loss, obstruction, or when the malignancy is discovered at surgery for bowel obstruction. Tumour factors as site, size, differentiation, serosal involvement and lymph node status did not correlate with survival.

An analysis from the same research group included 66 patients with duodenal adenocarcinoma (Rotman et al. 1994). The impact of numerous clinical and pathological characteristics on survival for patients operated with curative intent was analysed. None correlated with survival. As in the previous studies, curative surgery correlated with a more favourable outcome compared with palliative procedures when the analysis included all patients. Overall survival at 5 years was 33 %.

In an analysis of 64 patients with adenocarcinoma in duodenum, jejunum and ileum, disease-specific 5-year survival was 22 % (Contant et al. 1997). Tumour stage did not correlate with survival for the 28 patients who underwent curative resection, although the number of cases in each group was obviously very small.

Agrawal and co-workers recently presented 64 patients treated at their institution 1971-2005 (Agrawal et al. 2007). Advanced local tumour stage (T4 versus T1-T3) and distant metastases were independent predictors of poor survival, whereas tumour differentiation, sex, age and site of primary tumour (duodenum versus jejunum/ileum) where not. Overall 5-year survival was
21.1 % in this series, and 45 % for the 30 patients operated curatively with no residual disease.

In a series of 58 patients presented by Ito and co-workers, overall 5-year survival was 26 % (Ito et al. 2003). Again, 5-year survival was statistically significantly better for patients who underwent curative resection compared with mere palliative procedures (46.9 % versus 12.5 %). Analysis of prognostic factors for curatively resected patients identified local tumour stage and nodal status as prognostic factors. No attempt was made to identify independent predictors of survival in this study.

It is not possible to analyse time-trends in survival from data available in published single-institution series. For comparison, Barclay and co-workers reported a series of 74 patients with small intestinal adenocarcinoma diagnosed 1950-79 (Barclay et al. 1983). Overall 5-year survival was 22.5 %, which seems equal to data presented in more recent series.

In summary, data on overall 5-year survival from single institution series vary widely. Tumour stage seems to correlate with survival. 5-year survival around 50 % for patients operated with locally radical resections is commonly reported, although most series are too small to draw any firm conclusions.

Carcinoid

Population-based studies

Goodwin presented the first attempt of a population-based analysis of small intestinal carcinoids in 1975 (Goodwin 1975). Cases were collected from the End Results Group in the United States, which at that time included some 100 hospitals from three states. As with some of the above-mentioned registry studies, formally this registry is not population based. From 1950-1969, 367 cases of small intestinal (including 14 ileocecal cases) carcinoids were identified. Although the statistical method used is not clearly stated, five-year relative survival was 54 %. Five-year relative survival for localized, regional and distant disease was 75 %, 59 %, and 19 % respectively. For patients with ileal tumours and regional disease, old age was a predictor of poor survival in this often-cited study.

The report by DiSario and co-workers cited above also included 136 small intestinal carcinoids (DiSario et al. 1994). Five-year relative survival was 83 %.

Modlin and co-workers identified 3105 patients with small intestinal carcinoids diagnosed 1973-1999 from the SEER Database, which covers approximately 14 % of the United States population (Modlin et al. 2003). Overall 5-year survival for patients diagnosed 1973-1991 and 1992-1999 was 52 % and 60 % respectively. For cases with distant metastases, corresponding overall 5-year survival was 36 % and 50 %.
The SEER database has also been analysed by Crocetti and Paci (Crocetti et al. 2003). Relative 5-year survival for the 1788 patients diagnosed 1992-1999 was 77%. Analyses were made to evaluate disease stage and time-period of diagnosis as prognostic factors. All possible primary tumour sites were analysed together, and accordingly, no conclusions can be drawn for small intestinal carcinoids in this respect.

Another analysis of the SEER database was presented by Maggard and co-workers (Maggard et al. 2004). Gastrointestinal carcinoids diagnosed 1973-1999 were presented. The cohort included 2778 small intestinal carcinoids. Age adjusted 5-year cause-specific survival was 76.1%. Corresponding survival when all causes of deaths were taken into account was 54.6%. Advanced tumour-stage (regional or distant disease) was associated with poor prognosis compared with local disease.

The report by Pashayan and co-workers referred to above also included patients with small intestinal carcinoids (Pashayan et al. 2006). The authors use the term ‘endocrine tumours’ which probably is synonymous to carcinoid. Notably, these tumours were remarkably few. The registry file contained 5612 patients with small intestinal tumours of various morphologies, and only some 800 cases were ‘endocrine tumours’. Five-year relative survival for these patients was 46%.

Data from the Burgundy Digestive Cancer Registry reported by Lepage and co-workers included 102 patients with ‘endocrine tumours’ (Lepage et al. 2006). Five-year relative survival was 57% and overall survival 46%. As mentioned above, morphologic subtypes were not analysed separately for prognostic factors as gender, age, period of diagnosis and stage. However, from the presented multivariate model of relative survival in this study, it can be concluded that old age and advanced stage are prognostic factors associated with poor survival regardless of morphology.

Modlin and co-workers have recently presented the most up to date analysis of the SEER data (Modlin et al. 2007). Although not comprehensively described, five-year survival in this study is probably analysed as the proportion surviving after at least 5 years of follow-up. From 1973 to 2002, 3911 patients with small intestinal carcinoids were reported. Overall five-year survival was 63% for the whole time-period. Overall 5-year survival was 54% for patients diagnosed 1973-1977, and 68% for patients diagnosed 1993-97. This increase in survival was not considered as statistically significant. Five-year survival for patients with localized, regional, and distant disease was 84%, 72%, and 43% respectively. These differences were considered as statistically significant. Histological grading was available in some 600 patients. Five-year survival for well-differentiated, moderately differentiated, and poorly differentiated tumours was 71%, 62%, and 29% respectively.

Recently, Perez and co-workers presented data from the Florida Cancer Data System (FCDS) (Perez et al. 2007). The FCDS covers 6% of the United States population. Reporting is mandatory for all Florida physicians...
and medical facilities. From 1981 through 2001, 1500 small bowel carcinoids were identified. In the analyses of predictors of survival, the authors chose to describe the results for mid-gut tumours (small-bowel, appendix, colon to the splenic flexure, and omentum) as a separate entity; altogether 2130 cases. Overall 5-year survival by the Kaplan-Meier method for small bowel carcinoids was 37 %. For mid-gut tumours, 5- year overall survival for patients over 60 years of age at diagnosis was statistically significantly lower than for younger patients; 26% versus 52 %. Men with mid-gut tumours had statistically significantly worse prognosis than women. Furthermore, black race was associated with poor prognosis compared with white race, although only 69 patients in the cohort were black. In the analyses of tumour stage as a predictive factor, analyses were not stratified for primary tumour site.

To conclude, data from population-based studies does not suggest that prognosis for small intestinal carcinoids have improved over time. However, there are indications of a more favourable outcome for patients with advanced disease in more recent calendar time-periods. Old age and male gender seem to be predictors of poor prognosis.

**Single-centre studies**

Norheim and co-workers analysed 103 patients with metastatic carcinoid tumours treated at Uppsala University Hospital 1978-1986 (Norheim et al. 1987). Primary tumours of various locations were included, although in 80 patients the primary tumour was located in the small intestine. The number of tumours at each of the other sites was very low. Despite advanced disease, 5-year overall survival was around 65 %, and median survival was 14 years. Most patients were treated with interferon-alpha, and some with somatostatin-analogues.

An evaluation of survival and prognostic factors for patients with carcinoid tumours was presented by Janson and co-workers (Janson et al. 1997). They included 256 patients with ‘midgut’ carcinoids referred to Uppsala University Hospital 1978-1993. The vast majority of primary tumours were probably located in the small bowel. Most patients had lymph node and/or liver metastases. Overall 5-year survival for all patients from the time of diagnosis was 63 %. Old age (53 years or older), more than five liver metastases, the presence of the carcinoid syndrome, elevated 5-HIAA levels and elevated levels of CgA were associated with poor prognosis. In a multivariate Cox proportional hazards model, only old age and elevated CgA remained as statistically significant prognostic factors, although complete data on all variables was only available in 71 patients and consequently, confidence intervals were wide.

In 1996, Wängberg and co-workers presented 64 consecutive patients with disseminated (regional or distant disease) ‘midgut’ carcinoid tumours, treated at Sahlgrenska University Hospital in Gothenburg during an 8-year
period (Wängberg et al. 1996). All patients had elevated 5-HIAA levels and symptoms in accordance with the carcinoid syndrome. Date of diagnosis of the carcinoid syndrome was used as entry point in the survival analyses. Disease-specific 5-year survival was 69% for all patients, and corresponding relative survival was 58%. Five-year disease specific survival for the 14 patients who underwent radical surgery was 100% and corresponding relative survival just over 90%. For the patients who were subject to palliative surgical procedures and medical treatment, with or without liver-embolization, 5-year survival was markedly lower.

Schindl and co-workers reviewed 58 patients with small intestinal carcinoids, treated at a referral centre (Schindl et al. 2002). Disease specific 5-year survival for all patients was 76%. Prognosis was statistically significantly worse for patients with lymph node metastases or distant metastases (5-year disease specific survival 83% and 64% respectively). Local radical surgery in the presence of liver metastases did not correlate with a more favourable prognosis. Multimodal treatment with somatostatin analogues, liver embolization, interferon-alpha and chemotherapy was given in various combinations to 28 of 36 patients with distant metastases. No statistically significant difference in disease-specific survival was noted between the treated and untreated group. 5-year survival was just above 60% for these patients.

Hellman and co-workers reviewed 314 patients with ‘midgut’ carcinoids treated at Uppsala University Hospital during 1975-1997 (Hellman et al. 2002). Virtually all were small intestinal tumours. Most patients had lymph node metastases or liver metastases. Disease-specific 5-year survival for all patients was 67%. Fifty-two patients did not undergo surgery for various reasons. Five-year disease-specific survival for these patients was 42%. Regardless of whether liver metastases were present or not, resection of the primary tumour and affected lymph nodes was associated with a more favourable outcome. High levels of 5-HIAA and CgA were associated with poor survival, as was preoperative weight loss.

To further evaluate the impact on survival of resection of the primary carcinoid tumour in the presence of liver metastases, Givi and co-workers presented a retrospective analysis of 84 patients diagnosed 1995 through 2006 (Givi et al. 2006). Sixty patients underwent resection of the primary tumour. Most tumours in the resected group were situated in the small intestine. Four patients in each group had ‘foregut’ or ‘hindgut’ tumours. In the non-resected group, the site of the primary was unknown in half of the patients. Even though the two groups were comparable regarding age, gender, symptoms, chromogranin levels (as a marker of tumour burden) and non-surgical treatment, 5-year overall survival for the group of patients who underwent resection of the primary was 81%, compared with 21% for the non-resected group. The authors concluded that their data indicates that resection of the
primary tumour should be considered for patients with carcinoid tumours with liver metastases even for non-symptomatic primary tumours.

Nykjaer and co-workers presented a referral centre series including 56 patients with ‘midgut’ carcinoids (Nykjaer et al. 2007). Overall 5-year survival was 72% for all patients. Five-year survival for patients operated with no residual disease was 85% and corresponding survival for patients with residual disease was 68%. CgA levels at referral did not correlate with survival, although the number of patients in this study was probably far too small to detect any difference in this respect. Five-year survival for patients with less than five or multiple liver metastases was 100% and 50% respectively. Although the number of patients in each group was small (10 versus 15), the authors reported this difference to be statistically significant.

Cunningham and co-workers recently analysed 81 patients with well-differentiated neuroendocrine carcinomas (Cunningham et al. 2007). The authors used the term ‘malignant ileocecal serotonin-producing carcinoid tumours’ and consequently included small intestinal carcinoids as well as tumours originating in the proximal colon. Appendiceal tumours were not included. The patients were surgically treated between 1980 and 2004 at Uppsala University Hospital, and all but three had metastases at the time of surgery. During follow-up, all developed metastases. Survival was analysed in relation to growth pattern and Ki67 mitotic index. Solid growth pattern and an average Ki67 index ≥ 1% was clearly associated with poor prognosis. Most patients in this series were treated with interferon-alpha or somatostatin analogues or both agents, and 5-year survival (from date of surgery) was around 30% and 50% respectively, for patients with Ki67 index above or under 1%. These results are in disagreement with recent classifications where a Ki67 index of 2% or less is used to differentiate benign tumours from tumours with malignant behaviour.

Turner (Turner et al. 2006) and co-workers presented 139 patients with ‘midgut’ carcinoids, with most primary tumours situated in the small intestine. In 19 patients, the site of the primary tumour was unknown. Fifty-two patients had liver metastases, and in total 111 had metastatic disease at the time of diagnosis (lymph node and/or liver metastases). The primary tumour was removed in 110 patients. Urinary 5-HIAA levels correlated with the presence of liver metastases as well as the number of liver metastases (<5 versus ≥ 5) as did the levels of plasma neurokinin K (Norheim et al. 1986). Overall 5-year survival was 53% for all patients. Raised plasma neurokinin K, raised urinary 5-HIAA, increasing age, ≥ 5 liver metastases, lack of resection of primary tumour and breach of serosal surface correlated with poor survival. In multivariate analysis using a Cox proportional hazards model, including 111 patients and the variables age, serosal breach, resection of primary, and ≥ 5 liver metastases, age at diagnosis was the only independent prognostic factor. Further subgroup analyses showed plasma neurokinin K to be a prognostic marker, at least for patients with ≥ 5 liver metastases. Fur-
thermore, reduction of neurokinin K levels during somatostatin-analogue treatment seemed to predict a more favourable outcome.

Van der Horst-Schrivers and co-workers evaluated prognostic factors for patients with disseminated ‘midgut’ carcinoid tumours (van der Horst-Schrivers et al. 2004). They included 76 patients treated at a referral centre 1992-2003. Forty-seven patients had primary tumours in the small bowel, and in 22 patients, the site of the primary was unknown. Sixty-one patients had liver metastases, although it was not described in what way the disease in the remaining patients was disseminated. Only 11 patients received treatment with somatostatin-analogues, and one patient was treated with interferon. Overall 5-year survival from diagnosis was 57%. The impact on overall 5-year survival since referral of age at diagnosis, gender, liver metastases, resection of primary tumour, gamma-glutamyltransferase levels, alkaline phosphatase levels and 5-HIAA levels was analysed in a multivariate Cox proportional hazards model. In this analysis, age, elevated levels of gamma-glutamyltransferase and elevated 5-HIAA were independent predictors of poor survival.

To summarize, available data from single-centre series indicates that tumour stage (localized, regional, distant) and tumour burden in general, correlates with outcome. Even though most patients in series from referral centres have fairly advanced disease, most authors report overall 5-year survival around 65%. There is some evidence of a survival benefit for patients undergoing resection of the primary tumour even in the presence of liver metastases. The value of biochemical markers as independent prognostic factors remains unclear, as they may merely reflect tumour burden. Old age is probably a factor associated with poor survival.

Comparison of different series must be undertaken with great care as patient selection as well as statistical methods used vary greatly, and most series are small. Detailed analyses of population-based series with application of modern classification would be of great interest.

As for small intestinal adenocarcinomas, no conclusions can be drawn regarding time-trends in survival from available single-centre series. Notably, in the fairly large series presented by Barclay and co-workers in 1983, including 94 patients with malignant small intestinal carcinoids, overall 5-year survival for patients with regional or distant metastasis was 59% (Barclay et al. 1983).

Second primary tumours

Second malignant neoplasms associated with tumours of the small intestine have been recognised in autopsy studies (Alexander et al. 1968) and numerous relatively small case series (Awrich et al. 1980; Lanzafame et al. 1982;
Barclay et al. 1983; Ciccarelli et al. 1987; Frost et al. 1994; Ripley et al. 1995). 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 statistically significant excess risks of cancer of the liver and biliary tract and statistically non-significant excess risks of colorectal and pancreatic cancers (Lynge et al. 1985). 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 (Hoar et al. 1985). These studies were not stratified for histolopathologic subtype of the small bowel neoplasms. In a recent report of data from the SEER data base it was noted that 29% of patients with small intestinal carcinoid had associated malignancies (Modlin et al. 2003). 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 (Neugut et al. 1993). 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 (Scélo et al. 2006).

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 (Schottenfield 1982). Excess risk of small intestinal malignancies has been reported following colorectal cancer (Enblad et al. 1990; Neugut et al. 1993; Hemminki et al. 2001b). Increased relative risk of small intestinal carcinoid have been reported following prostate cancer (Thellenberg et al. 2003) and after thyroid and other endocrine gland tumours (Hemminki et al. 2001a).

Causes of death
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 (Makridis et al. 1997). 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 (Agrawal et al. 2007).
Aims of the investigation

To clarify the survival experience for patients with adenocarcinoma and midgut carcinoid tumours in a population based material

To investigate associations between small intestinal tumours and other malignancies, in order to identify potential common etiologies

To explore the causes of death for these patients, to possibly generate hypotheses regarding etiology for the surprisingly rare small intestinal malignancies

To specifically evaluate an often stated association between Crohn’s disease and small intestinal tumours
Patients and methods

Patients

The Swedish Cancer Registry and Causes of Death Registry

The Swedish Cancer Registry was established in 1958. Physicians, pathologists and cytologists are obliged by law to report all cases of diagnosed malignant tumours to the registry. The information from death certificates is supplied from the Causes of death Registry and merged into the files of the Cancer Registry supplying date, and cause of death (The Swedish Cancer Registry 2008).

Data on causes of deaths in Sweden have been systematically collected and classified according to the International classification of Diseases (ICD) in the 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) (The Cause of Death Registry 2008).

The Swedish Patient Registry

The population based Swedish Patient Registry (In-patient statistics) contains individual information on inpatient care countywise since 1964 and nationwide since 1987. The register included only six counties at its start in 1964, representing 20 percent of the Swedish population. More counties were added successively and since 1987, the register has included data from all Swedish hospitals. For every hospital discharge, information on discharge diagnoses and surgical procedures is recorded according to the ICD, versions 7–10 (The Swedish Patient Registry 2008).

Paper I

We identified all patients with primary adenocarcinoma in the small intestine (histopathological type 096, ICD-VII 152.0-152.9) diagnosed between 1960 and 1988 and reported to the Swedish Cancer Registry. Follow-up was available until end of 1990. Only cases in which the diagnosis was made in vivo from histological analysis were included into the study, whereby diagnosis incidentally at autopsy as well as by clinical or mere cytological ex-
amination were excluded (Table 1). Moreover, tumours of the ampulla of Vater (ICD 155.3) were disregarded. Tumours in jejunum and ileum were treated as one group, and altogether, 263 cases with duodenal lesions and 663 with jejunal/ileal tumours were included. Table 2 shows the patient distribution by sex, age and year of diagnosis.

Validity of the Cancer Registry was analysed by review of pathologists’ original reports and re-examination of available microscopic slides in a randomised sample of 200 cases of small intestinal adenocarcinoma. Records of 172 (86%) of them could be retrieved and in 136 cases, the slides were examined. In 21 cases, the pathologist’s report could not be found due to closure of hospitals and/or disposal of old archives. There was no answer to our request for the records from three hospitals (5 cases) and another case could not be found due to lack of information on the reporting laboratory and hospital in the Cancer Registry file. In one case, the reporting laboratory could not be located. Most common causes for disagreement between registry and hospital records were ICD-coding mistakes (n=10), since unequivocal non-small intestinal adenocarcinoma was diagnosed by the reporting pathologist as well as by review of the available records and microscopic slides. In two cases, the lesion was diagnosed incorrectly by the reporting pathologist and in another four, primary tumour sites was equivocal due to massive overgrowth on adjacent organs (Table 3). The misclassifications were not correlated to patient sex, age or period of diagnosis. The misclassified cases from the sample were excluded from further analyses.

Table 1. Number of cases recruited from the Cancer Registry and exclusions due to lack of diagnosis in vivo

| Small intestinal tumours reported | 4188 |
| Adenocarcinomas | 1139 |
| Autopsy diagnosis | 205 |
| Clinical or cytological diagnosis | 8 |
| Cases included | 926 |
| Tumours in duodenum | 263 |
| Tumours in jejunum/ileum | 663 |
Table 2. Distribution by sex, age, and period of diagnosis for the patients with adenocarcinoma in the small intestine

<table>
<thead>
<tr>
<th></th>
<th>Duodenum</th>
<th>Jejunum/ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>130 (49%)</td>
<td>338 (51%)</td>
</tr>
<tr>
<td>Period of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1960-70</td>
<td>53 (20%)</td>
<td>165 (25%)</td>
</tr>
<tr>
<td>1971-77</td>
<td>46 (17%)</td>
<td>172 (26%)</td>
</tr>
<tr>
<td>1978-84</td>
<td>86 (33%)</td>
<td>179 (27%)</td>
</tr>
<tr>
<td>1985-88</td>
<td>78 (30%)</td>
<td>147 (22%)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-50</td>
<td>28 (11%)</td>
<td>95 (14%)</td>
</tr>
<tr>
<td>51-59</td>
<td>44 (17%)</td>
<td>114 (17%)</td>
</tr>
<tr>
<td>60-67</td>
<td>61 (23%)</td>
<td>140 (21%)</td>
</tr>
<tr>
<td>68-74</td>
<td>71 (27%)</td>
<td>148 (22%)</td>
</tr>
<tr>
<td>75-</td>
<td>59 (22%)</td>
<td>166 (25%)</td>
</tr>
</tbody>
</table>

Table 3. Discordant diagnoses in hospital records compared with the Cancer Registry file for 172 examined cases selected at random

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown site of primary tumour</td>
<td>4</td>
<td>Incorrect ICD-coding</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>3</td>
<td>Incorrect ICD-coding</td>
</tr>
<tr>
<td>Carcinoid tumour</td>
<td>2</td>
<td>Incorrect ICD-coding</td>
</tr>
<tr>
<td>Tumours of the papilla of Vater</td>
<td>2</td>
<td>Incorrect ICD-coding</td>
</tr>
<tr>
<td>Secondaries from colonic carcinoma</td>
<td>1</td>
<td>Incorrect ICD-coding</td>
</tr>
<tr>
<td>Neurofibrosarcoma</td>
<td>1</td>
<td>Incorrect ICD-coding</td>
</tr>
<tr>
<td>Reticular-cell sarcoma</td>
<td>1</td>
<td>Incorrect ICD-coding</td>
</tr>
<tr>
<td>Tumour of endocrine origin</td>
<td>1</td>
<td>Misdiagnosed by pathologist</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
<td>Misdiagnosed by pathologist</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>16</strong></td>
<td></td>
</tr>
</tbody>
</table>
Paper II

We identified all patients with primary carcinoid tumour in the small intestine (histopathologic type 086, ICD-7 152.0-152.9) diagnosed during 1960 through 2000, and reported to the Swedish Cancer Registry. Follow-up was available until end of 2001. Only histologically verified cases in which the diagnosis was made \textit{in vivo} were included. Cases diagnosed incidentally at autopsy or by clinical or by cytological examination alone were excluded, as were those with the same date of diagnosis and death (Table 4). Altogether 89 cases with duodenal lesions and 2437 with jejunal/ileal tumours were included. Data on causes and date of death was available until end of 2001. Mean follow-up was 6.8 years (range 0.1-40 years) and median follow-up 4.6 years. A total of 1801 patients died during the study period. In 457 cases, the cause of death was small intestinal carcinoid. Table 5 shows the patient distribution by sex, age, and site.

Validity of diagnoses coded in the Cancer Registry was analysed by reviewing the pathologists’ original reports. Three hundred cases of small intestinal carcinoid tumour were selected at random from the registry file. Records of 252 cases (84%) could be retrieved and reviewed. Twenty (8%) turned out to be discordant diagnoses that were incorrectly coded as carcinoid in the registry file.

Table 4. Cases recruited from the Cancer Registry and exclusions due to lack of histological diagnosis \textit{in vivo}

<table>
<thead>
<tr>
<th></th>
<th>Duodenum</th>
<th>Jejunum/ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of tumours reported</td>
<td>1172</td>
<td>5587</td>
</tr>
<tr>
<td>Carcinoid tumours</td>
<td>151</td>
<td>3590</td>
</tr>
<tr>
<td>Autopsy diagnosis or date of diagnosis same as death date</td>
<td>61</td>
<td>1135</td>
</tr>
<tr>
<td>Clinical or cytological diagnosis only</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>No. of cases included</td>
<td>89</td>
<td>2437</td>
</tr>
</tbody>
</table>
Table 5. Distribution by sex, age, and period of diagnosis for patients with carcinoid tumours in the small intestine

<table>
<thead>
<tr>
<th></th>
<th>Duodenum</th>
<th>Jejunum/ileum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>52 (58%)</td>
<td>1307 (54%)</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>15 (11%)</td>
<td>276 (11%)</td>
</tr>
<tr>
<td>51-59</td>
<td>20 (17%)</td>
<td>370 (15%)</td>
</tr>
<tr>
<td>60-69</td>
<td>20 (23%)</td>
<td>767 (31%)</td>
</tr>
<tr>
<td>70-74</td>
<td>11 (27%)</td>
<td>408 (17%)</td>
</tr>
<tr>
<td>≥ 75</td>
<td>23 (22%)</td>
<td>616 (25%)</td>
</tr>
<tr>
<td>Period of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1960-1970</td>
<td>15 (17%)</td>
<td>385 (16%)</td>
</tr>
<tr>
<td>1971-1980</td>
<td>17 (19%)</td>
<td>542 (22%)</td>
</tr>
<tr>
<td>1981-1990</td>
<td>25 (28%)</td>
<td>709 (29%)</td>
</tr>
<tr>
<td>1991-2000</td>
<td>32 (36%)</td>
<td>801 (33%)</td>
</tr>
</tbody>
</table>

Paper III

We studied all cases of primary adenocarcinoma and carcinoid in the small intestine (ICD-7 152.0-152.9, WHO/HS/CANC/24.1 Histology Code 096 and 086), 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 6). 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-VII): 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.

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 7. 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.
Table 6. Cases recruited from the Swedish Cancer Registry and exclusions due to lack of diagnosis in vivo

<table>
<thead>
<tr>
<th></th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number reported</td>
<td>1982</td>
<td>3741</td>
</tr>
<tr>
<td>Date of diagnosis same as death date</td>
<td>153</td>
<td>686</td>
</tr>
<tr>
<td>Included</td>
<td>1829</td>
<td>3055</td>
</tr>
</tbody>
</table>

Table 7. Causes of death grouped according to ICD in relation to time-periods

<table>
<thead>
<tr>
<th></th>
<th>ICD 7 (58-68)</th>
<th>ICD 8 (69-86)</th>
<th>ICD 9 (87-96)</th>
<th>ICD 10 (96-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious diseases</td>
<td>001-138</td>
<td>000-136</td>
<td>000-139</td>
<td>A00-B99</td>
</tr>
<tr>
<td>Neoplasms, except 152</td>
<td>140-151, 153-239</td>
<td>140-151, 153-239</td>
<td>1401151, 153-239</td>
<td>C00-C16, C18-D46</td>
</tr>
<tr>
<td>Haematological diseases</td>
<td>290-299</td>
<td>280-289</td>
<td>279-289</td>
<td>D50-D89</td>
</tr>
<tr>
<td>Endocrine, nutritional and metabolic diseases</td>
<td>250-289</td>
<td>240-279</td>
<td>240-279</td>
<td>E00-E79</td>
</tr>
<tr>
<td>Diseases of the nervous system</td>
<td>340-369</td>
<td>320-358</td>
<td>320-359</td>
<td>G00-G99</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>400-468</td>
<td>390-429, 440-458</td>
<td>390-429, 440-459</td>
<td>I00-I52, I70-I99</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>470-520</td>
<td>460-519</td>
<td>460-519</td>
<td>J00-J99</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>530-588</td>
<td>520-577</td>
<td>520-579</td>
<td>K00-K93</td>
</tr>
<tr>
<td>Urogenital diseases</td>
<td>590-638</td>
<td>580-629</td>
<td>580-629</td>
<td>N00-N99</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>330-334</td>
<td>430-438</td>
<td>430-438</td>
<td>I60-I69</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>157</td>
<td>157</td>
<td>157</td>
<td>C25</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>153-154</td>
<td>153-154</td>
<td>153-154</td>
<td>C18-C20</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>410-413, 421</td>
<td>395-398, 424</td>
<td>394-397, 424</td>
<td>I05-I08, I34-I39</td>
</tr>
<tr>
<td>Other causes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Paper IV

We identified all patients discharged with a diagnosis of CD affecting the small bowel between 1 January 1964 and 31 December 2004. The following ICD-codes were included: 5720 (ICD 7), 5630 (ICD 8), 555A, 555C, 555X (ICD9), K500, K508, and K509 (ICD10). We identified the first discharge (index admission to hospital) with CD for each affected person. The date of first discharge was used as date of diagnosis of CD. Patients were followed until death, diagnosis of small intestinal malignancy or end of study period (31 December 2004). Only small intestinal adenocarcinoma (ICD7 152, histopathologic code 096) and carcinoid (ICD7 152, histopathologic code 089) were included in the analysis. A total of 100,928 registry entries with a discharge diagnosis of CD were obtained. Only the first registry entry for each patient was included, and after exclusion of 2,886 registry entries with
missing identity, information or registration errors there remained information on 23,393 CD patients for the analyses. Fifteen patients acquired small intestinal adenocarcinoma before diagnosis of CD, and were excluded in the final analysis regarding the risk of subsequent adenocarcinoma. Correspondingly, 18 patients with carcinoid occurring before the diagnosis of CD were excluded. Median age at diagnosis of CD was 35.2 years and median follow-up was 12.2 years. There were 11,034 men, and 12,359 women (table 8).

Table 8. Patients discharged with a diagnosis of CD in Sweden 1964-2004. Patients with Crohn colitis only excluded

<table>
<thead>
<tr>
<th>Sex (%)</th>
<th>Male 11034 (47)</th>
<th>Female 12359 (53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>3461 (15)</td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>10123 (43)</td>
<td></td>
</tr>
<tr>
<td>40-59</td>
<td>5594 (24)</td>
<td></td>
</tr>
<tr>
<td>60-79</td>
<td>3443 (15)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>772 (3)</td>
<td></td>
</tr>
</tbody>
</table>

Median age 35.2

<table>
<thead>
<tr>
<th>Period (%)</th>
<th>1964-80 6095 (26)</th>
<th>1981-95 9520 (41)</th>
<th>1996-04 7778 (33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cohort</td>
<td>23393 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methods

Paper I

Overall and corrected survival rates (i.e. small intestinal malignant tumour or malignant tumour of the digestive tract not otherwise specified as the main or contributory cause of death) were calculated with life-table methods (Cutler et al. 1958). The analyses were made by sex, age and year of diagnosis separately for duodenal and jejunal/ileal tumours. Ninety-five per cent confidence intervals of the estimates are given. The log-rank test was utilized to assess differences between survival curves; p<0.05 was considered statistically significant. Cox’ proportional hazards analysis was used to study the independent effect on survival of each variable (Cox 1972). In the Cox models period of diagnosis was coded with dummy variables using 1960-70 as reference category. In trend analyses of time-period of diagnosis, the
categories were represented as 0 to 3, beginning with 1960-1970. Age at
diagnosis was used as a continuous variable. Analyses were made using
SAS/STAT software.

Paper II

Overall and cause-specific survival (i.e. small intestinal malignant tumour as
the cause of death) was calculated with the Kaplan-Meier method (Kaplan et
al. 1958). Cases with cause of death other than small intestinal malignant
tumour were thus censored at the time of death in the analyses of cause-
specific survival. Analyses were made by site, sex, age and period of diagno-
sis. The log-rank test was utilized to assess differences between survival
curves; a p-value less than 0.05 was considered statistically significant and
95% confidence limits for the estimates are given. Uni- and multivariate
Cox’ proportional hazards analysis was used to study the effect on survival
of each variable (Cox 1972). In the Cox models, age at diagnosis was coded
with dummy variables using age \( \leq 50 \) as reference. Correspondingly, 1960-
1970 was used as reference in the analyses of period of diagnosis. Analyses
were made using SPSS software.

Relative survival (Ederer et al. 1961) was calculated using the program
provided by the Finnish Cancer Registry (Voutilainen et al. 2000) with
modifications by Brenner et al. (Brenner et al. 2002). The relative survival
was derived as the ratio of absolute (overall) survival divided by the ex-
pected survival of subjects of the corresponding age and sex observed during
the same calendar time in the general population. Analyses were made by
site, sex, age and period of diagnosis and 95% confidence limits were esti-
mated. To assess differences in relative survival between the groups previ-
ously defined, we used an additive hazards model where the total hazard is
written as the sum of the known baseline hazard and the excess hazard asso-
ciated with a diagnosis of small intestinal carcinoid. An excess hazard ratio
of, for example 1.5 for males compared with females implies that the excess
hazard associated with a diagnosis of carcinoid is 50% higher for males than
for females (Dickman et al. 2002).

Stratified analyses were not performed for duodenal carcinoids because of
the small sample size.

Paper III

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 multipli-
cation of person-years 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 standardised incidence ratio (SIR) was defined as the ratio of observed numbers of a second malignancy to the expected numbers. Analyses were made by sex, period of diagnosis and time from diagnosis of the small bowel malignancy.

Correspondingly, the standardised mortality ratio (SMR) was calculated using data from the Swedish Causes of Death Registry. Detailed analyses of SMR by gender, age, period of diagnosis and follow-up were made only for causes of death with enough data to permit stable calculations.

The 95% confidence intervals (CI) for the SIRs and SMRs were established by assuming that the observed cases have a Poisson distribution using Byar’s normal approximation (Breslow et al. 1987). All the statistical analyses were carried out using the SAS version 8.2.

**Paper IV**

Each cohort member contributed person-time at risk for small bowel tumours from the first discharge diagnosis of CD until the date of small bowel tumour, death or December 31, 2004, whichever came first. The date of death was obtained by linking the CD cohort patients, by their unique national identification number, to the Causes of Death Registry in Sweden. Person-years at risk were summed for cohort members and tabulated in strata of sex, age (5-year intervals), and calendar year. Stratum-specific person-years were then multiplied by the corresponding stratum-specific small bowel tumour rates in the general population and summed over strata to yield the expected numbers of small bowel tumours in the cohort.

SIRs of adenocarcinoma and carcinoid in the small bowel were calculated as ratios of the observed to the expected number of patients with a diagnosis of the tumours in the CD cohort, with expected numbers based on background rates in the general population. The background rates in the general population were based on information on the number of tumours diagnosed according to the Swedish Cancer Registry.

The 95% confidence intervals (CI) for the SIRs were established by assuming that the observed cases have a Poisson distribution (Breslow et al. 1987). Analyses were made using Stata 9 software (Stata Statistical Software: Release 9. 2007). Differences between strata were assessed with a chi-squared test for unequal SMRs (heterogeneity) and a score test for a linear trend in SMR against strata.
Results

Paper I. Survival in small intestinal adenocarcinoma

Overall 5- and 10-year survival was 24% and 17% for duodenal tumours, and 28% and 20% for tumours in jejunum/ileum. The difference in prognosis between the sites was not statistically significant (p=0.09). Corresponding corrected survival was 39% and 37% for duodenal tumours and 46% and 41% for those in jejunum/ileum (p=0.16 for difference between sites). Survival curves are illustrated in figure 1.

![Survival curves](image)

*Figure 1. Overall (OS) and corrected (CS) survival for patients with adenocarcinoma in duodenum and jejunum/ileum.*

Women with tumours in jejunum/ileum had a more favourable prognosis than men. Five- and 10-year corrected survival was 52% and 48% for the
women and 40% and 34% for the men (p=0.0095 for difference between sexes). The relation between sex and corrected survival was not found for patients with duodenal tumours.

Corrected survival correlated with age at diagnosis for duodenal tumours (p=0.03377) but not for those in jejunum/ileum.

There was no difference in survival when comparing periods of diagnosis in neither duodenal nor jejunal/ileal tumours (p=0.12 and 0.22, respectively for corrected survival).

In the univariate proportional hazards analysis, sex was a statistically significant (p=0.04) predictor of corrected survival for all patients with adenocarcinoma of the small intestine (Table 9). Furthermore, diagnosis later than 1984 was associated with significantly lower relative hazards (p=0.01). Since the life table analyses indicated qualitative differences between duodenal and jejunal/ileal tumours, the multivariate analyses were stratified by site (Table 9). In the multivariate models including gender, period of diagnosis and age at diagnosis, men with adenocarcinoma in jejunum/ileum had significantly (p=0.01) higher relative hazards than women, while there was no difference in this respect (p=0.92) for duodenal tumours. Age at diagnosis remained a significant predictor of survival in patients with duodenal tumours. The decrease in relative hazards for cases diagnosed in the period 1985-88 in the univariate model was also found in the multivariate model, although the difference was not formally statistically significant for tumours in jejunum/ileum (p=0.06). Test for trend by time-period revealed clearly statistically significant results in the univariate analysis, and in the multivariate analysis for duodenal tumours.

Table 9. Relative hazards with 95 % confidence limits in uni- and multivariate Cox proportional hazards analysis of corrected survival

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Small bowel</td>
<td>Duodenum</td>
<td>Jejunum/ileum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>Male (vs. female)</td>
<td>1.2 (0.7, 1.0)</td>
<td>0.04</td>
<td>1.0 (0.7, 1.4)</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1960-1970</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1971-1977</td>
<td>0.9 (0.7, 1.0)</td>
<td>0.23</td>
<td>0.7 (0.4, 1.2)</td>
</tr>
<tr>
<td>1978-1984</td>
<td>0.8 (0.7, 1.1)</td>
<td>0.17</td>
<td>0.6 (0.4, 0.9)</td>
</tr>
<tr>
<td>1985-1988</td>
<td>0.7 (0.5, 0.9)</td>
<td>0.18</td>
<td>0.5 (0.3, 0.8)</td>
</tr>
<tr>
<td>Test for trend</td>
<td>0.02</td>
<td>0.005</td>
<td>0.08</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.1 (1.0, 1.1)</td>
<td>0.18</td>
<td>1.3 (1.1, 1.5)</td>
</tr>
<tr>
<td>Jejunum/ileum (vs. duodenum)</td>
<td>0.9 (0.7, 1.1)</td>
<td>0.20</td>
<td></td>
</tr>
</tbody>
</table>
Paper II. Long-term survival of patients with small intestinal carcinoid tumours

The overall 5-, 10- and 15- year survival was 60%, 46% and 28 % for duodenal tumours, and 56%, 36% and 23 % for tumours in jejunum/ileum. For duodenal tumours, the 5-, 10- and 15 year cause-specific survival was 94 % respectively, i.e. cause-specific survival did not decline beyond approximately 1 year of observation. The cause-specific 5-, 10- and 15-year survival was 87%, 80% and 77 % for tumours in jejunum/ileum. The difference in cause-specific survival between sites was statistically significant (p=0.02) although overall survival did not differ statistically significantly (p=0.14).

The relative 5-, 10- and 15- year survival was 72%, 67% and 51% for duodenal tumours, and 67%, 54% and 44% for jejunal/ileal tumours (Table 10). There was no statistically significant difference in relative survival between sites.

Median overall survival for patients with duodenal tumours was 7.2 years and for jejunal/ileal tumours 6.2 years.

Relative survival ratio, together with probability of overall and cause-specific survival for tumours in the jejunum/ileum is illustrated in figure 2.

![Figure 2](image-url)  
*Figure 2.* Overall (OS), cause-specific (CS), and relative survival (RS) for patients with carcinoid in jejunum/ileum.
There were only small and not statistically significant differences in survival between men and women with small intestinal carcinoid. The difference in relative survival between sexes at 5 and 10 years of follow-up was not statistically significant although the excess hazard ratio for men at 15 years was 0.8 (p=0.0472). Gender was not a predictor of cause-specific survival in the proportional hazards analyses (Table 11).

Cause-specific survival correlated with age at diagnosis for patients with jejunal/ileal tumours, with a more favourable outcome in younger age groups. The regression model used to estimate relative survival revealed significant differences in relative survival at 5 years of follow up when comparing age at diagnosis, although these differences did not remain at 10 and 15 years of follow-up. In the Cox model, age at diagnosis remained a significant predictor of survival with increasing relative hazards in elderly patients (Table 11).

When comparing time-periods of diagnosis, patients diagnosed more recently had statistically significant better prognosis in the analyses of overall survival, disease-specific survival and relative survival. Furthermore, time-period of diagnosis was an independent predictor of prognosis in the Cox proportional hazards model (Table 11).

Table 10. Relative survival ratios (with 95% confidence limits) for patients with carcinoid in jejunum/ileum.

<table>
<thead>
<tr>
<th>Gender</th>
<th>5-year survival</th>
<th>10-year survival</th>
<th>15-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>68 (63; 72)</td>
<td>57 (53; 62)</td>
<td>48 (43; 54)</td>
</tr>
<tr>
<td>Female</td>
<td>66 (63; 70)</td>
<td>51 (46; 55)</td>
<td>40 (35; 46)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>83 (79; 88)</td>
<td>76 (70; 82)</td>
<td>67 (60; 70)</td>
</tr>
<tr>
<td>51-59</td>
<td>76 (71; 81)</td>
<td>64 (58; 69)</td>
<td>51 (43; 58)</td>
</tr>
<tr>
<td>60-69</td>
<td>65 (61; 69)</td>
<td>46 (41; 51)</td>
<td>35 (29; 41)</td>
</tr>
<tr>
<td>70-74</td>
<td>57 (51; 63)</td>
<td>41 (33; 49)</td>
<td>22 (12; 32)</td>
</tr>
<tr>
<td>75+</td>
<td>61 (55; 68)</td>
<td>51 (40; 62)</td>
<td>26 (8; 44)</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1960-70</td>
<td>59 (53; 65)</td>
<td>47 (40; 54)</td>
<td>43 (35; 51)</td>
</tr>
<tr>
<td>1971-80</td>
<td>61 (56; 66)</td>
<td>49 (43; 55)</td>
<td>37 (30; 43)</td>
</tr>
<tr>
<td>1981-90</td>
<td>66 (62; 71)</td>
<td>55 (50; 61)</td>
<td>45 (38; 51)</td>
</tr>
<tr>
<td>1991-00</td>
<td>77 (73; 82)</td>
<td>60 (53; 67)</td>
<td>---------------</td>
</tr>
</tbody>
</table>
Table 11. Relative hazards (with 95 % confidence limits) in univariate and multi-variate analysis of cause-specific survival for patients with carcinoid in the jejunum/ileum.

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (vs. female)</td>
<td>1.1 (0.9; 1.4)</td>
<td>1.0 (0.8; 1.3)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>51-59</td>
<td>1.5 (1.0; 2.4)</td>
<td>1.5 (1.0; 2.4)</td>
</tr>
<tr>
<td>60-67</td>
<td>1.4 (1.1; 1.9)</td>
<td>2.0 (1.3; 3.0)</td>
</tr>
<tr>
<td>68-74</td>
<td>2.1 (1.6; 2.7)</td>
<td>2.5 (1.7; 3.9)</td>
</tr>
<tr>
<td>≥75</td>
<td>1.4 (1.1; 1.9)</td>
<td>2.8 (1.8; 4.3)</td>
</tr>
<tr>
<td>p for trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1960-70</td>
<td>1.0 (ref.)</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>1971-80</td>
<td>0.7 (0.8; 1.0)</td>
<td>0.7 (0.5; 0.8)</td>
</tr>
<tr>
<td>1981-90</td>
<td>0.6 (0.5; 0.7)</td>
<td>0.5 (0.4; 0.7)</td>
</tr>
<tr>
<td>1990-00</td>
<td>0.2 (0.1; 0.3)</td>
<td>0.2 (0.1; 0.3)</td>
</tr>
<tr>
<td>p for trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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

Adenocarcinoma

Second primary malignancies

Patients with adenocarcinoma had increased risk of acquiring other gastrointestinal malignancies (Table 12). For both sexes combined, 36 cases were seen compared with 24 expected (SIR 1.5; 95 % CI 1.1-2.1, for the whole study period). Statistically significantly increased risks were only seen for men. For all patients with small intestinal adenocarcinoma the most common second gastrointestinal tumours were cancers of the pancreas and lower gastrointestinal tract. SIRs for these tumours were statistically significantly raised although increased incidence of pancreatic cancer was seen only for cases diagnosed 1960 to 1980 (Table 12). Again, a statistically significant increase in SIR was only seen for male gender. For women, tumours of the female genital system and breasts were seen more frequently than anticipated (Table 12). The gynaecological site most commonly affected was the ovaries. The SIR for ovarian cancer was 3.9 (95% CI 2.0-7.0) for the whole
study period and an increased risk of breast cancer was seen in the early study period (SIR 2.7; 95% CI 1.1-5.4) but not in recent years (Table 12). No increase in male breast cancer was seen. For both sexes combined, an increased risk of skin cancer was seen but the excess risk was only confined to the earlier study period and only related to non-melanoma tumours (Table 12). The SIR for prostate cancer and malignancies of the respiratory system and brain did not differ statistically significantly from unity (Table 12).

**Causes of death**

In the cohort with adenocarcinoma, 1754 patients (88% of the cohort with adenocarcinoma) died during the study period and in 899 patients, the cause of death was the primary small bowel malignancy. 396 patients died within 30 days from diagnosis of the primary malignancy and 153 had the same death date as date of diagnosis.

The patients with small bowel adenocarcinoma had increased risk of dying from other malignant diseases (Table 13). The overall SMR was 9.5 (95% CI 8.6-10). Such lethal malignancies were largely dominated by colon and pancreatic cancer (34% and 17% respectively of all deaths from malignant diseases). The SMRs for pancreatic cancer and colorectal cancer were 24 and 26 respectively and the increased incidence was most pronounced during the first year of follow-up. The SMR for gastrointestinal diseases was statistically significantly raised (Table 13). It mainly related to duodenal ulcer (29% of deaths from gastrointestinal disease).

Endocrine disorders were overrepresented as cause of death for patients with adenocarcinoma of the small bowel (Table 13). The increased SMR was most pronounced for men, and during the early study period. Furthermore, a significant increase in SMR was only seen the first year of follow-up and not for patients older than 68 years. Diabetes was stated as cause of death in 50 % of deaths related to endocrine disease.

**Carcinoid**

**Second primary malignant tumours**

The incidence of prostate cancer subsequent to carcinoid tumour was higher than expected. Seventeen cases were seen versus six expected during the earlier study period (SIR 2.8; 95 % CI, 1.6-4.6, Table 12). During the later study period, there was no increase in the incidence of prostate cancer. For men and women combined, the incidence of malignant melanoma and other skin malignancies was statistically significantly increased for patients with carcinoid but only when analyzing cases diagnosed 1960-1980 (SIR 6.3 and 3.6 respectively, Table 12). The risk of acquiring malignancies in other endocrine organs was statistically significantly increased during the whole
study period (SIR 2.2; 95% CI 1.1-3.8). Twenty percent of these malignancies were thyroid cancers and 40 percent were adrenal malignancies.

**Causes of death**

In the cohort with carcinoid tumours, 3011 (80% of the cohort with carcinoid) died during the study period and 613 patients died of their primary malignancy. 1210 died within 30 days from diagnosis of the primary malignancy and 686 had the same death date as date of diagnosis.

Patients with carcinoid had increased overall risk to die from malignant diseases (SMR 4.3; 95 % CI 4.0-4.6) (Table 13). These neoplasms were dominated by colorectal cancer (23%), although in 44 % the cause of death was stated as ‘disseminated malignant tumour’. The increase in risk of dying from malignant disease was most pronounced during the early study period and during the first year of follow-up. The risk of dying from cardiovascular disease was slightly increased (SMR 1.1; 95% CI 1.0-1.3). It mainly related to ischemic heart disease (62 %) and was most pronounced during the early study period, and during the first year of follow-up. Seven percent of deaths from cardiovascular disease were related to heart failure whereas 9 % were registered as caused by heart valve disease. The SMR for heart valve disease was 3.1 (Table 13). Thirty percent were registered as mitral valve disease, 25% as aortic valve disease and 35% as ‘unspecified heart valve disease’. The SMR for gastrointestinal disorders was statistically significantly increased (Table 13). The overall risk was 2.8 (95% CI 2.1-3.6). Twenty-four percent of the deaths from gastrointestinal disorders were duodenal or gastric ulcers and 12 % were caused by intestinal obstruction. The risk of dying from endocrinological disorders was increased during the whole study period (overall SMR 14; 95% CI 12-17, table 13). In 97% of these cases, the endocrinological disorder in question was not specified in the Causes of Death Registry.
<table>
<thead>
<tr>
<th>Second tumour (ICD-7)</th>
<th>Period</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>O/E</td>
<td>PYR</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1960-80</td>
<td>13/5.3</td>
<td>1205</td>
</tr>
<tr>
<td>(1500-1549)</td>
<td>1981-00</td>
<td>23/13</td>
<td>2640</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1960-80</td>
<td>10/3.3</td>
<td>1205</td>
</tr>
<tr>
<td>(1530-1549)</td>
<td>1981-00</td>
<td>21/9.9</td>
<td>2658</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1960-80</td>
<td>4/0.5</td>
<td>1257</td>
</tr>
<tr>
<td>(1579)</td>
<td>1981-00</td>
<td>3/1.2</td>
<td>3014</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>1960-80</td>
<td>-/0.3</td>
<td>1258</td>
</tr>
<tr>
<td>(1551-1552)</td>
<td>1981-00</td>
<td>2/0.5</td>
<td>3007</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1960-80</td>
<td>-/0</td>
<td>1258</td>
</tr>
<tr>
<td>(1509)</td>
<td>1981-00</td>
<td>-/0.2</td>
<td>3017</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1960-80</td>
<td>7/2.6</td>
<td>1233</td>
</tr>
<tr>
<td>(1600-1649)</td>
<td>1981-00</td>
<td>2/6.4</td>
<td>3005</td>
</tr>
<tr>
<td>Breast</td>
<td>1960-80</td>
<td>3/1.9</td>
<td>1253</td>
</tr>
<tr>
<td>(1700-1709)</td>
<td>1981-00</td>
<td>4/8.8</td>
<td>2963</td>
</tr>
<tr>
<td>Gynaecologic</td>
<td>1960-80</td>
<td>9/1.4</td>
<td>1241</td>
</tr>
<tr>
<td>(1710-1760)</td>
<td>1981-00</td>
<td>9/3.2</td>
<td>2898</td>
</tr>
<tr>
<td>Ovary</td>
<td>1960-80</td>
<td>5/0.7</td>
<td>683</td>
</tr>
<tr>
<td>(1750-1759)</td>
<td>1981-00</td>
<td>6/1.5</td>
<td>1567</td>
</tr>
<tr>
<td>Skin</td>
<td>1960-80</td>
<td>4/0.9</td>
<td>1256</td>
</tr>
<tr>
<td>(1910-1919)</td>
<td>1981-00</td>
<td>6/5.1</td>
<td>2977</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1960-80</td>
<td>1/0.4</td>
<td>1258</td>
</tr>
<tr>
<td>(1900-1909)</td>
<td>1981-00</td>
<td>3/2.2</td>
<td>2998</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1960-80</td>
<td>5/2.5</td>
<td>1133</td>
</tr>
<tr>
<td>(1800-1819)</td>
<td>1981-00</td>
<td>5/6.9</td>
<td>2970</td>
</tr>
<tr>
<td>Prostate</td>
<td>1960-80</td>
<td>3/1.6</td>
<td>2385</td>
</tr>
<tr>
<td>(177)</td>
<td>1981-00</td>
<td>10/6.8</td>
<td>1360</td>
</tr>
<tr>
<td>Endocrine</td>
<td>1960-80</td>
<td>-/0.4</td>
<td>1252</td>
</tr>
<tr>
<td>(1940-1959)</td>
<td>1981-00</td>
<td>2/1.4</td>
<td>2989</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1960-80</td>
<td>-/0.1</td>
<td>1259</td>
</tr>
<tr>
<td>(1940-1949)</td>
<td>1981-00</td>
<td>1/0.2</td>
<td>3013</td>
</tr>
</tbody>
</table>
Table 13. *Standardised mortality ratios (SMR) with 95% confidence interval (CI) for the causes of deaths studied for patients with adenocarcinoma and carcinoid in the small intestine.*

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Adenocarcinoma</th>
<th></th>
<th>Carcinoid</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O/E</td>
<td>SMR</td>
<td>95 % CI</td>
<td>O/E</td>
</tr>
<tr>
<td>Infectious diseases</td>
<td>2/1.5</td>
<td>1.3</td>
<td>(0.3-5.2)</td>
<td>4/4.6</td>
</tr>
<tr>
<td>Neoplasms, except 152</td>
<td>403/42</td>
<td>9.5</td>
<td>(8.6-10)</td>
<td>569/133</td>
</tr>
<tr>
<td>Haematological diseases</td>
<td>2/0.5</td>
<td>3.8</td>
<td>(0.9-15)</td>
<td>2/1.6</td>
</tr>
<tr>
<td>Endocrine, nutritional and metabolic diseases</td>
<td>8/3.9</td>
<td>2.0</td>
<td>(1.0-4.1)</td>
<td>167/12</td>
</tr>
<tr>
<td>Diseases of the nervous system</td>
<td>1.0/2.3</td>
<td>0.4</td>
<td>(0.1-3.1)</td>
<td>7/6.9</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>100/88</td>
<td>1.3</td>
<td>(0.9-1.3)</td>
<td>306/269</td>
</tr>
<tr>
<td>Diseases of the respiratory system</td>
<td>12/15</td>
<td>0.7</td>
<td>(0.4-1.2)</td>
<td>56/47</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>17/6.5</td>
<td>2.6</td>
<td>(1.6-4.2)</td>
<td>54/19</td>
</tr>
<tr>
<td>Urogenital diseases</td>
<td>4/3</td>
<td>1.3</td>
<td>(0.5-3.4)</td>
<td>9/10</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>26/24</td>
<td>1.1</td>
<td>(0.7-1.5)</td>
<td>64/70</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>68/2.9</td>
<td>24</td>
<td>(19-30)</td>
<td>18/8.8</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>137/5.4</td>
<td>26</td>
<td>(22-30)</td>
<td>130/16</td>
</tr>
<tr>
<td>Heart valve disease</td>
<td>2/2.2</td>
<td>0.9</td>
<td>(0.2-3.7)</td>
<td>20/6.4</td>
</tr>
<tr>
<td>Other causes</td>
<td>10/15</td>
<td>0.8</td>
<td>(0.4-1.2)</td>
<td>48/45</td>
</tr>
<tr>
<td>Endocrine, nutritional and metabolic diseases except ICD8=258</td>
<td>6/3.9</td>
<td>1.5</td>
<td>(0.7-3.4)</td>
<td>9/11</td>
</tr>
</tbody>
</table>
Paper IV. Small intestinal adenocarcinoma and carcinoid in Crohn’s disease

Adenocarcinoma

The overall standardised (age, sex, and calendar year) incidence rate for small intestinal adenocarcinoma was 9.5/100000 (95% CI 6.7-13) in the CD cohort. Median age at diagnosis of CD for patients who subsequently developed small intestinal adenocarcinoma was 46.2 years (range 23.7-82.6), as opposed to the 35.2 years in the whole cohort. Median age at diagnosis of small intestinal adenocarcinoma in the cohort was 57.3 years (range 37.4-86.1).

We identified 31 patients with adenocarcinoma in the small intestine in the cohort and the expected number was 2.3 (SIR 13; 95% CI 9.4-19) (Table 14). There was no difference in SIR between sexes (Table 14). The risk of adenocarcinoma was statistically significantly increased for age groups older than 20 years at diagnosis of CD. SIRs did not differ statistically significantly between patients diagnosed with CD in different age groups (table 14). SIR was statistically significantly increased for all calendar time-periods, furthermore the analyses revealed a linear trend against different calendar time-periods with the highest SIR in later years (table 14). The most pronounced increase in SIR was seen for patients diagnosed during the first six months after diagnosis of CD (SIR 116; 95% CI 50-229). There was a statistical significant linear trend with decreasing SIRs after longer time since diagnosis (table14). The risk remained statistically significantly increased after 20-30 years of follow-up (table 14).

Carcinoid

The overall standardised (age, sex and calendar year) incidence rate for small intestinal carcinoid was 7.9/100000 (95% CI 5.4-12) in the CD cohort. Median age at diagnosis of CD for patients who subsequently developed small intestinal carcinoid was 64.7 years (range 37.4-86.0). Median age at diagnosis of small intestinal carcinoid in the cohort was 65.9 years (range 37.4-86.1).

Patients in the cohort with Crohn’s disease had statistically significantly increased risk of carcinoid in the small intestine. Twenty-six cases were identified compared with 3.6 expected (SIR 7.2; 95% CI 4.9-11, table 14). There was no difference in SIR between sexes (Table 14). The SIRs for patients who were diagnosed with CD before 40 years of age did not differ from unity. Patients older than 40 at diagnosis of CD had statistically significant higher SIRs when analysing for heterogeneity over strata of age at diagnosis of CD (table 14). When analysing SIR by calendar time-period of diagnosis of CD the highest SIR was seen for patients with their first admis-
sion for CD in the later calendar time-period (1996-2004) (table 14). There
was a linear trend against different calendar time-periods of diagnosis with
the highest SIR in later years (table 14).
The risk for carcinoid was highest during the first six months of follow-up
(SIR 160; 95% CI 95-253 (table 14). Beyond 2 years since diagnosis of CD,
there was no increase in SIR.

Table 14. Standardised incidence ratios (SIR) for adenocarcinoma and carcinoid in
the small intestine for patients with CD (CD) affecting the small bowel. Analyses by
sex, age at CD diagnosis, period of CD diagnosis, and years since CD diagnosis.

<table>
<thead>
<tr>
<th></th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O/E SIR 95 % CI PYR p</td>
<td>O/E SIR 95 % CI PYR p</td>
</tr>
<tr>
<td>Total</td>
<td>31/2.3 13 9.4-19 327119</td>
<td>26/3.6 7.4 4.9-11 327113</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19/1.2 16 9.4-24 152041</td>
<td>16/2.0 7.8 4.8-13 151978</td>
</tr>
<tr>
<td>Female</td>
<td>12/1.1 11 5.6-19 175078</td>
<td>10/1.5 6.5 3.5-12 175235</td>
</tr>
<tr>
<td>Age</td>
<td>0.335</td>
<td>0.651</td>
</tr>
<tr>
<td>&lt;20</td>
<td>0/0.04 0.0 0.0-93 55992</td>
<td>0/0.06 0 55992</td>
</tr>
<tr>
<td>20-39</td>
<td>9/0.6 17 7.6-32 173138</td>
<td>1/0.8 1.3 0.2-9.5 173149</td>
</tr>
<tr>
<td>40-59</td>
<td>11/0.9 12 6.1-22 70112</td>
<td>8/1.4 5.6 2.8-11 70099</td>
</tr>
<tr>
<td>60-79</td>
<td>10/0.8 13 6.4-25 25302</td>
<td>15/1.2 12 7.5-20 25305</td>
</tr>
<tr>
<td>≥80</td>
<td>1/0.1 10 0.3-46 2574</td>
<td>2/0.1 14 3.5-56 2566</td>
</tr>
<tr>
<td>Period</td>
<td>0.798</td>
<td>0.002</td>
</tr>
<tr>
<td>1964-80</td>
<td>8/1.0 7.7 3.3-15 156473</td>
<td>7/1.6 4.3 2.0-8.9 154478</td>
</tr>
<tr>
<td>1981-95</td>
<td>18/1.0 17 7.9-32 139239</td>
<td>9/1.6 5.7 3.0-11 139260</td>
</tr>
<tr>
<td>1996-04</td>
<td>5/0.3 19 6.4-46 31407</td>
<td>10/0.4 27 14-49 31373</td>
</tr>
<tr>
<td>Follow-up</td>
<td>0.042</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0-0.5</td>
<td>8/0.07 116 50-229 11413</td>
<td>18/0.1 160 100-253 11409</td>
</tr>
<tr>
<td>0.5-1</td>
<td>2/0.1 31 3.7-110 11038</td>
<td>2/0.1 19 2.1-64 11033</td>
</tr>
<tr>
<td>1-2</td>
<td>1/0.1 8.0 0.2-45 21142</td>
<td>3/0.2 15 2.9-4.1 21130</td>
</tr>
<tr>
<td>2-5</td>
<td>4/0.3 12 3.3-31 56716</td>
<td>2/0.5 3.8 0.4-13 56686</td>
</tr>
<tr>
<td>5-10</td>
<td>8/0.5 17 7.4-34 75962</td>
<td>0/0.7 0 0.0-5.0 75969</td>
</tr>
<tr>
<td>10-20</td>
<td>5/0.7 6.8 2.2-16 100961</td>
<td>1/1.1 0.9 0.02-5.0 100990</td>
</tr>
<tr>
<td>20-30</td>
<td>3/0.3 6.8 1.4-20 44024</td>
<td>0/0.7 0 0.0-5.6 44037</td>
</tr>
<tr>
<td>&gt;30</td>
<td>0/0.1 0 0.0-43 6130</td>
<td>0/0.1 0 0.0-29 6130</td>
</tr>
</tbody>
</table>

1Chi-squared test for unequal SIRs (heterogeneity), 2scoretest for linear trend in SIRs.
Discussion

In the present thesis we took advantage of three population-based registries in Sweden; the Cancer Registry, the Causes of Death Registry, and the Patient Registry. Accuracy and completeness of the Cancer Registry and Causes of Death Registry have been carefully investigated in earlier studies. Less than 2% of histologically confirmed cancer cases known from death certificates are missing in the Cancer Registry (Mattsson et al. 1984). Moreover concordance between Cancer Registry diagnosis and certified causes of death is approximately 87% with the greatest discrepancy for sites of prevalent metastases (Mattsson et al. 1985b).

In paper I, we reviewed a randomised sample from the Cancer Registry file including patients with small intestinal adenocarcinoma. We performed a detailed review of microscopic slides and pathologists’ reports. The diagnosis of small intestinal adenocarcinoma could not be verified in 9%. This modest misclassification mostly depended on ICD miscodings and was not associated with the investigated determinants of prognosis. The misclassification may have slightly influenced the overall results if tumours with generally better or worse prognosis than small intestinal adenocarcinoma selectively had been included. There was no evidence for any strong tendency in any direction. The misclassification should not bias the comparison between genders, site, time-period or age in any other way than making differences more difficult to detect. Correspondingly, we reviewed a randomised sample from the cohort with small intestinal carcinoid in paper II. Although we merely evaluated the pathologists’ reports, misclassification seemed modest. Evidently, cases incorrectly diagnosed as carcinoids by the pathologist cannot be safely identified without reviewing the microscopic slides or preferably, histopathological re-examination of the entire tumour material.

In Paper III, patients with second malignant tumours occurring after the diagnosis of small intestinal adenocarcinoma or carcinoid were identified in the Cancer Registry. The correctness of the diagnoses for individuals reported to suffer from multiple malignancies in the Swedish Cancer Registry has been analyzed 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 (Frodin et al. 1997).

The analysis of causes of death in Paper III is highly dependent on correctness of death-certificates issued by clinicians. It is well known that diag-
nostic errors are discovered at routine autopsies (Britton 1974b), and that there is disagreement between hospital discharge records and death certificates (Johansson et al. 2000). Earlier studies of autopsy series indicate that clinicians frequently interpret symptoms and signs preceding death as a consequence of previously known diagnoses (Britton 1974a). Furthermore, four different versions of the ICD have been used during the period 1960-2000, making evaluation of time-trends regarding causes of deaths difficult. Possibly, most of these errors will lead to an underestimation of the risk of dying from causes not directly related to small intestinal malignancy.

All patients in Paper IV were identified through the population-based Swedish Patient Registry. As the registry only includes patients hospitalised for CD, less severe cases could have been excluded. However, an analysis of the Danish hospital system, similar to the Swedish Patient Register, revealed acceptable completeness and validity regarding CD (Fonager et al. 1996).

**Survival**

In paper I and II, we analysed survival in small intestinal adenocarcinoma and carcinoid. Women with adenocarcinoma of jejunum/ileum had better prognosis than the men and increased age correlated with poorer prognosis in duodenal but not in jejunal/ileal tumours. The favourable relationship between female sex and survival has been found in a number of epithelial tumours. An explanation proposed for this phenomenon is that female sex hormones have a role in modulating tumour dissemination (Adami et al. 1990). The reason for sex not being a prognostic factor in adenocarcinoma of the duodenum is not clear. Hypothetically, it may relate to a higher incidence of peptic ulcer disease among men during the study period with greater frequency of endoscopic investigations of the upper gastrointestinal tract, which could facilitate earlier cancer diagnosis. In the analysis of carcinoid, tumours there were no detectable difference in overall, cause-specific or relative survival between men and women.

The analyses of prognosis in relation to different calendar periods of diagnosis for patients with adenocarcinoma revealed a trend towards improved survival in the late eighties compared with 1960-1970. An increased use of upper gastrointestinal endoscopy during the study period could explain this improvement as it was most convincing for duodenal adenocarcinomas. No novel therapies or surgical strategies have otherwise emerged for this disease to our knowledge. Most likely, the improved prognosis is caused by a general improvement in health care systems at all levels and better surgical and intensive care. Similarly, overall, cause-specific and relative survival has increased during recent years for small intestinal carcinoids, according to the present investigation. During recent years, there has been a rapid development and implication of new diagnostic, medical and surgical approaches.
The improvement of diagnostic tools in recent years may result in earlier diagnosis of these lesions, which yields increased curability as the tumours are found in earlier stages. However, lead-time bias may result in seemingly improved survival as the time from diagnosis to death increases irrespective of medical or surgical treatment. Somatostatin analogues and interferon has been used routinely for some 20 years, which may have improved survival, at least for the more advanced cases, although this is yet to be proved in randomised trials. Surgery of midgut carcinoid tumours has been more standardised and aggressive during the last 10-15 years, and the recent development of a more active approach towards the commonly present liver metastases may further increase survival in the future. Notably, the improvement in relative survival for small intestinal carcinoids was only confined to the estimates at 5-years of follow-up.

Young age at diagnosis was associated with better survival for both adenocarcinomas and carcinoids. For adenocarcinomas, the correlation of young age and a more favourable prognosis was confined to tumours in the duodenum. This may possibly relate to the ability of younger patients to tolerate extensive radical surgery. A similar difference in prognosis between age groups was seen for carcinoids in jejunum and ileum. Furthermore, analysis of relative survival performed for patients with carcinoids in Paper II showed similar results although the difference in survival between age groups was not statistically significant at 10 and 15 years of follow-up.

Population-based studies of prognostic factors in small intestinal adenocarcinomas are rare in the literature. Reported 5-year survival from such studies is between 25 and 30 %, which is in accordance with our results (Howe et al. 1999; Lepage et al. 2006; Pashayan et al. 2006). Furthermore there are some data from population based studies indicating old age and tumour site in the duodenum as predictors of poor outcome (Howe et al. 1999). It is unknown if prognosis for these patients has improved in recent years, and in this context our own data on small intestinal adenocarcinoma obviously need to be updated.

Available population-based reports of survival for patients with small intestinal carcinoid, indicates overall 5-year survival between 50 % and 60 %, disease-specific 5-year survival just below 80 %, and relative 5-year survival between 50 % and 83 % (Goodwin 1975; DiSario et al. 1994; Crocetti et al. 2003; Modlin et al. 2003; Maggard et al. 2004; Lepage et al. 2006; Pashayan et al. 2006; Modlin et al. 2007; Perez et al. 2007). The figures are comparable with the results in our analyses. Old age and male gender has been associated with poor prognosis in some studies (Goodwin 1975; Lepage et al. 2006; Perez et al. 2007). None of the available studies have reported improved prognosis in later time-periods.

Analyses of overall survival are independent of cause of death but are unreliable when studying age at diagnosis in relation to survival or evaluation of improvement in prognosis over time. In the analyses of corrected (or dis-
ease-specific survival), we used slightly different definitions of events and censoring. In the analyses of adenocarcinomas (Paper I), deaths from small intestinal malignant tumour or unspecified gastrointestinal tumour was defined as events, whereas in the analyses of carcinoids (Paper II), deaths from small intestinal malignant tumour only was considered as events. The definition used in paper II most probably overestimates survival although there is no reason to believe that it affects the analysis of any of the studied determinants of survival. Cause-specific or corrected survival is highly dependent on correct registration of cause of death on the death certificates issued by clinicians. Furthermore, there are numerous ways of defining disease-specific deaths and bias may occur if the individuals under study are affected by more than one cancer, as is the case for some patients with small intestinal tumours in the present analyses (Boer et al. 2003). Moreover, death of small intestinal malignancy was defined as an event in the analysis of cause-specific survival, which inevitably, leads to overestimation of survival. The advantage of relative survival is that information on cause of death is not required and that it measures excess mortality irrespective of whether it is directly or indirectly attributable to the disease of interest. Chueng et al have recently addressed method of choice when analysing age at diagnosis in relation to survival (Cheung et al. 2003). They concluded that analysis of relative survival is appropriate when studying age as an indicator of tumour aggressiveness whereas the Cox proportional hazards model using time since diagnosis as time-scale describes age as a predictor of mortality. In Paper II both methods were used, which generally is advisable when analysing data from population-based registries.

Second malignant primary tumours

In Paper III, we describe increased risks of acquiring gastrointestinal malignancy and genital or breast malignancy for patients with small bowel adenocarcinoma, while carcinoid tumour of the small intestine couple to increased risk of prostate cancer, melanoma and malignancies of other endocrine organs.

Adenocarcinomas and carcinoids were analysed separately because of the differences in clinical presentation between these tumours and their probable divergence in histogenic origin (Enblad et al. 1988) as well as most likely different etiological pathways. However, because of the relatively small number of observed cases, second tumours and causes of death were pooled into larger groups, although attempts to perform a detailed analysis were made even though this includes lower number of cases and more difficulties to identify relevant associations.

Generally, second malignancies were diagnosed within the first year after diagnosis of the small bowel tumour, possibly due to increased activity in the
clinical workup. The increased risk of acquiring other gastrointestinal malignancies noted in men with adenocarcinoma could be due to misclassification of metastatic disease or local recurrences, at least during the first years of observation. Tumours of the small intestine generally cause vague symptoms and are difficult to diagnose. Thus, before correct localisation of the disease, patients have often undergone extensive clinical and laboratory investigations (Maglinte et al. 1991). Earlier studies have also indicated an increased risk of acquiring cancers of the liver and biliary tract as well as the digestive system (Hoar et al. 1985; Lynge et al. 1985; Neugut et al. 1993). It is, however, unclear why this increase should be isolated to men and thus a chance finding cannot be excluded.

Previously, an association between small intestinal malignancy, especially for carcinoids, and cancer of the prostate has been noted (Hoar et al. 1985; Thellenberg et al. 2003). These findings induce a need for further exploration of the pathogenetic pathways for prostate cancer and carcinoid tumours, including the role of vitamin D deficiency (Mikhak et al. 2007). The association between genital and breast cancer in females and adenocarcinoma of the small intestine has not been noted before. Detection bias cannot be ruled out and the excess risk was mostly confined to the earlier study period. Breast cancer cases and female genital cancers may largely be represented by in situ cancers, as they have become part of screening programmes. Although we did not formally exclude in situ cancers, less than 4 % of all tumours diagnosed after the index small intestinal malignancy were registered as in situ. No gynaecologic cancers diagnosed after the primary small bowel tumour were non-invasive. Breast cancer and prostate cancer have with time lost their association to small bowel malignancy, possibly as an effect of screening, at least in the case of breast cancer. Formally, there are no regular screening programmes in Sweden for prostate cancer, although in later years there has been a tendency for ‘wild screening’ initiated by patients as well as physicians. If, hypothetically, the study population with small bowel malignancies, are less prone to attend screening programmes than the general population, changes in the relation between the number of observed versus expected cases could affect the result due to the relatively small number of observed second malignancies.

The increased risk of second tumours in this study could possibly be explained by the misinterpretation of a recurrence from the small intestinal malignancy as a new gastrointestinal cancer. A more plausible explanation is that basal genetic disturbances including microsatellite instability or defect DNA repair mechanisms may be present in these patients (Blaker et al. 2002) generating a true increase in second malignancies and possibly a more adverse course of the disease. For carcinoids, death in colorectal cancer was significant although acquiring this cancer was not. A plausible explanation may be that the treatment for the carcinoid tumour affects the course of this type of malignancy. Interferon may be one possible factor. However, inter-
feron may also be an explanation to why the incidence of melanoma is reduced as second malignancy 1980-2000 compared with 1960-1980 for patients with carcinoid tumours (Ringborg et al. 2007).

**Causes of death**

Malignant disorders, cardiovascular and gastrointestinal diseases were overrepresented as causes of death for both study cohorts, although the increased mortality in cardiovascular disease was most convincing for patients with carcinoid. The lethal malignancies were dominated by cancers of the lower gastrointestinal tract and pancreas in the cohort with adenocarcinoma, and colorectal cancer in the cohort with carcinoid tumours. Notably, in the latter cohort, a substantial number of cases were registered with the diagnosis ‘disseminated malignant tumour’ as the cause of death. It is thus unknown if this diagnosis represents a second malignancy or a late manifestation of the original disease, that has been misclassified in the Causes of Death Registry.

The marked difference between the number of pancreatic and colorectal cancers recorded respectively as incident cases and deaths in is striking. The file acquired from the Cancer Registry for the present study, contains all patients with small intestinal adenocarcinoma and carcinoid from 1960 to 2000. Furthermore, the file contains all registered malignant tumours for these patients during the study period, before as well as after diagnosis of the small intestinal malignancy. Thus, an explanation for the discrepancy between incident cases in the analysis of risk of colorectal cancer as second malignancy, and the number of deaths caused by colorectal cancer, could be that most cases of colorectal cancer associated with small intestinal carcinoid as well as adenocarcinoma were diagnosed before diagnosis of the small intestinal malignancy. These cases are obviously not included in the analysis of SIR.

For pancreatic cancer, data should be interpreted with caution. In the case of primary adenocarcinoma, 80 % of index tumours were situated in the duodenum. The physician responsible for issuing the death certificate could have misdiagnosed these cases as pancreatic cancers at the time of death. On the other hand it is well known from the Causes of Death Registry that a substantial amount of patients are registered with pancreatic cancer as cause of death without previous records in the Cancer Registry (Mattsson et al. 1985a).

For the patients with carcinoid tumours, endocrine disorders were also overrepresented as causes of death, although the majority (97%) were registered as ‘non-specified endocrine disorder’, and may potentially represent misclassifications of the carcinoid syndrome. Most of these cases were coded according to ICD 8 as 258. When excluding this diagnosis there remained no increase in SMR for endocrine disorders.
The increased risk of cardiovascular deaths could possibly be accounted for if exposure to smoking is more common in patients with small intestinal malignancies, as previously noted in epidemiological studies (Chen et al. 1994; Wu et al. 1997; Kaerlev et al. 2000b; Kaerlev et al. 2002a). However, this possibility is partly contradicted by the fact that we could not find any increased risk for cancers of the respiratory system, and another investigation of small bowel malignancy does not implicate smoking as a risk factor (Chow et al. 1993). Other known cardiovascular risk factors such as hyperlipidemia and hypertension have not been thoroughly investigated in these patients. To date, there is only a vague or even absent hereditary factor in small intestinal adenocarcinoma and carcinoid, arguing against a common genetic etiology between cardiovascular disease and either of the small bowel malignancies. A detailed analysis of valve disturbances occurring in the carcinoid cohort reveals that not only right-sided, but also defect left-sided valves – mitral and aortic valves – are present in high frequency.

The increased risk of dying in gastrointestinal disorders gives further arguments to speculations that other gastrointestinal diseases could be on the etiologic pathway for small bowel malignancy.

A detailed analysis of causes of death in a population-based cohort of small intestinal malignancies has not been presented before in the literature. Cause of death in malignancy is high in both histological types studied. This is not surprising, as patients with small bowel adenocarcinoma as well as carcinoid, frequently had a history of malignant disease before diagnosis of the small bowel malignancy. In fact, compared with cancers registered after the index small bowel tumour, there are twice as many malignancies registered before the small bowel malignancy. Although not analysed in the present study, this indicates that patients with small bowel adenocarcinomas and carcinoids may have an increased lifetime risk of developing malignant diseases of any kind. There is also an increased risk to die of cardiovascular disease, and similarly to the analysis of second malignancies, there are differences between the two types.

Crohn’s disease as a risk factor for small intestinal adenocarcinoma and carcinoid

Patients hospitalised with CD had increased risk of acquiring adenocarcinoma of the small intestine. The risk remained significantly elevated 20-30 years after diagnosis of CD although the most pronounced increase in SIR was seen the first six months of observation. No statistically significant increase in SIR was seen for patients with their first admission for CD before 20 years of age. Calendar-period of diagnosis of CD influenced the risk of
subsequent adenocarcinoma with a more pronounced increase in SIR in recent years.

The SIR of carcinoid was generally elevated but the risk dropped to statistically non-significant levels during the first two years of follow-up. No increase in SIR for carcinoid was seen for patients in the youngest age group at diagnosis. Stratification for calendar-period of diagnosis of CD revealed a more pronounced increase in SIR of carcinoid in the later time-period.

Two earlier studies from Sweden generated conflicting results regarding the risk of small intestinal cancer after diagnosis of CD. Ekbom et al (Ekbom et al. 1991a) found no increased risk of small bowel malignancy. In this study, patients with CD were not stratified based on disease location. Thus, their cohort included cases with Crohn colitis possibly at a smaller risk of developing malignancies in the small bowel. In the present study, ICD-codes representing Crohn colitis were excluded although codes representing CD without specification of location were included. Thus, it is possible that some patients included in the cohort have CD only confined to the large bowel, which could lead to an underestimation of the risk of small bowel malignancy. In Sweden approximately 25% of patients with CD have CD in colon only (Ekbom et al. 1991b) and it is likely that a majority of these patients are registered with the ICD-code for Crohn colitis. It is not possible to report the exact number of patients with Crohn colitis in the present cohort without going into the individual patient records.

Persson et al (Persson et al. 1994) did find an increased risk of small bowel cancer after CD (SIR 15.6; 95% CI 4.3-40) but as the cohort was rather small, confidence limits were wide. In the present study, which includes cases from the two Swedish studies, an overall increased risk was seen for both adenocarcinoma and carcinoid in the small intestine. The observed numbers of small intestinal adenocarcinomas and carcinoids in our analysis was 57 compared with 1 and 4 respectively in the earlier Swedish studies (Ekbom et al. 1991a; Persson et al. 1994).

In the present study, the relatively large cohort allowed stratification by histological subtype which is not reported before in the literature. We chose to include only the two most frequent small intestinal malignancies. In our study, the risk for both adenocarcinoma and carcinoid was markedly higher during the first year of follow-up. Jess et al found no relationship between duration of CD and small bowel cancer; again the observed number of cancers was small (Jess et al. 2004). The most striking difference between adenocarcinoma and carcinoid was the rapid decline in SIR for carcinoid tumours the first year of follow-up. A plausible explanation could be that patients were misdiagnosed primarily. A stricture found in the small bowel during the radiological work up for gastrointestinal symptoms may well be interpreted as a Crohn stricture even though the underlying cause is carcinoid. The pattern of extreme SIR the first year of follow up was also seen for
adenocarcinomas although SIR remained significantly elevated for more than 20 years.

As date of first hospital submission was used as date of diagnosis of CD, the true disease duration is unknown. Time from first discharge or submission for CD to diagnosis of small intestinal malignancy was used as a surrogate for disease duration, resulting in a possible underestimation of time at risk for the cohort with CD. Some patients were probably diagnosed with CD before they were in need of hospitalisation. This could be an explanation for the high SIRs during the first year after diagnosis. Furthermore, some patients in the cohort were probably hospitalised for the first time, before the start of the Swedish Patient Registry.

It has been argued that the risk of small bowel malignancy as well as colorectal cancer in association with CD has decreased in recent years due to a more active maintenance treatment policy (Jess et al. 2004). In the present analysis, no such time trends were revealed. In contrast, we found a trend towards an increase in SIR for both adenocarcinoma and carcinoid in recent years. A more conservative attitude towards surgery for CD among physicians and surgeons in recent years, has left patients on various maintenance therapies during longer periods of time (Pearson et al. 2000; Alfadhli et al. 2005; Sandborn et al. 2005). Hypothetically, this could explain the increased risk of small bowel malignancy, as it is assumed that chronic inflammation causes cancer (Itzkowitz et al. 2004). Furthermore, most medical therapies used in CD as various immunomodulators and immunosuppressants, could theoretically make these patients more susceptible to cancer (Karran et al. 2008).

The seemingly increased risk for small intestinal cancer in later years could also be explained by changes in ICD-coding routines. Later ICD-versions allows a more exact classification of CD location. More patients with ambiguous disease extent in the earlier periods, possibly including relatively more patients with Crohn colitis could potentially lead to an underestimation of risk of malignancy in the small intestine.
Conclusions

Prognosis for patients with small intestinal adenocarcinomas and carcinoids has improved in later years, although the explanation is open for discussion. Treatment protocols for gastrointestinal neuroendocrine tumours have become more aggressive during the past 25 years, and several novel medical therapies have evolved. On the other hand, a similar development in treatment modalities has not been noted for small intestinal adenocarcinomas.

Our results support an increased risk of other second malignancies after diagnosis of small bowel tumours, and clearly demonstrate differences between adenocarcinomas and carcinoids disease in this respect.

The association between prostate cancer and carcinoids as well as the novel finding of increased risk of cause of death in colorectal cancer and pancreatic cancer in these patients mandates further investigations.

Patients with CD have increased risks of small intestinal adenocarcinoma as well as carcinoid. The risk is most pronounced during the early period after first admission for CD. The risk for small intestinal malignancy in CD has increased for patients diagnosed in later years.
Elakartade tumörer i tunntarmen är relativt ovanliga. Tunntarmen utgör ca 90 % av ytan i mag-tarmkanalen. Det är därför förvånande att endast 2 % av elakartade tumörer i mag-tarmkanalen är tunntarmscancer. Orsaken till att det är så ovanligt med tumörer i tunntarmen är inte känt. Ett flertal förslag och spekulationer har framkommit genom åren. Innehållet i tunntarmen är tunnflytande vilket, möjligen gör att slemhinnan utsätts för mindre expone-ring av ämnen som kan stimulera cancerutveckling genom att de späds ut. Den snabba passagen av eventuella cancerframkallande ämnen leder till att de är i kontakt med slemhinnan under kortare tid jämfört med andra platser i mag-tarmkanalen där cancer är vanligare. En del bakterier i mag-tarmkanalen har förmågan att omvandla gallsyror till cancerframkallande ämnen. Antalet bakterier i tunntarmen är relativt litet, vilket skulle kunna bidra till den låga förekomsten av tumörer. Vävnad som innehåller celler som är inblandade i immunförsvarvare är vanlig i tunntarmen, vilket kan ha en skyddande effekt.

Elakartade tunntarmstumörer finns av flera olika typer. Adenocarcinom och carcinoid är de två vanligaste i vår del av världen, men lymfom, leiomyosarcom, gastrointestinala stromacellstumörer och andra mycket ovanliga typer förekommer också. Adenocarcinom utgår från körtelceller i tarmen och liknar mikroskopiskt tjocktarmscancer. Carcinoid utgår från så kallade neuroendocrina celler i tarmen. Den här tumörtypen är speciell genom att den har förmågan att utsöndra olika hormonliknande ämnen.

Varje år insjuknar ungefär 150-200 personer i adenocarcinom eller carcinoid i tunntarmen. Insjuknandet i tunntarmstumörer varierar kraftigt när man jämför olika länder. I Afrika och större delen av Asien är tunntarmstumörer betydligt ovanligare än i Europa och Nordamerika. Insjuknandet i tunntarmstumörer har möjligen ökat i vissa delar i världen, men i Sverige finns ingen tydlig sådan tendens. I de flesta material är adenocarcinom vanligast i tolfingertarmen, medan carcinoid är vanligast i slutet på tunntarmen.

Tunntarmstumörer ger ofta diffusa symptom i tidiga stadier. Tidig diagnos är relativt ovanligt. Symptomen vid adenocarcinom är ofta buksmärta, stopp i tarmen eller blödning. Carcinoid ger likartade symptom i tidigt stadium även om blödning är ovanligt. En betydande andel av patienter med adenocarcinom eller carcinoid i tunntarmen har avancerad sjukdom vid diagnos.
Ett särdrag hos carcinoider är förmågan att utsöndra hormonliknande ämnen som kan ge upphov till carcinoidsyndromet. Typiska tecken är ansiktstöd med svettningar, diarré, ärrbildning i hjärtklaffar och ibland sammandragning av luftvägarna. Carcinoidsyndromet uppstår som regel när tumören spridit sig till levern, men förekommer även vid större spridning till lymfkörtlar nära tarmen.

Även om orsaken till elakartade tunntarmstumörer är okänd har ett antal riskfaktorer föreslagits för båda tumörtyperna. Länder med hög förekomst av tjocktarmscancer har hög frekvens av tunntarmscancer, vilket kan tala för att det föreligger gemensamma riskfaktorer bakom de två tumörtyperna. Även om orsakerna till tjocktarmscancer inte heller är fullständigt kända, talar mycket för att faktorer i kosten spelar stor roll. Det finns studier som indikerar att stort intag av rött eller rökt kött och socker ökar risken för tunntarmscancer. Åtfällda sjukdomar som orsakar ökad polybildning i tarmsystemet verkar innebära ökad risk för tunntarmscancer. Någon enstaka studie har påvisat att fisk, grönsaker och frukt verkar ha en skyddande effekt. Resultaten av de flesta studierna får anses som mycket osäkra. Rökning och alkoholintag föreslås som riskfaktorer i vissa studier medan andra inte kunnat påvisa några sådana samband. Vissa yrken har föreslagits innebära ökad risk men även de resultaten är osäkra och svåra att tolka. Sjukdomar som innebär kronisk inflammation (till exempel Crohns sjukdom) i tunntarmen samt glutenintolerans ökar möjligen risken för utveckling av cancer, även om motstridiga uppgifter förekommer i litteraturen.


Behandlingen av adenocarcinom och carcinoid är ganska likartad i tidiga stadier och innebär kirurgiskt avlägsnande av tumören och intilliggande lymfkörtlar. När det gäller adenocarcinom har det inte utvecklats några nya behandlingsmetoder av mer avancerade tumörer under de senaste 20-30 åren. Man har gjort försök med cellgiftsbehandling utan övertygande effekt. Den kirurgiska behandlingen av carcinoider har under senare tid blivit allt mer aggressiv. Det lönar sig troligen att avlägsna ursprungstumören även vid mycket spridd sjukdom och kirurgisk behandling av tumörer som spridit sig till lymfkörtlar och lever verkar också inverka positivt på förloppet. Soma-


I många rapporter har man noterat att patienter med tunntarmstumörer har ökad frekvens av andra elakartade tumörer. Orsaken till den ökade risken att utveckla andra tumörer kan vara att det finns gemensamma riskfaktorer hos tunntarmstumörer och de andra tumörtyperna eller att behandlingen som patienterna erhållit i sig ger upphov till nya cancerformer. Hypotetiskt kan man även tänka sig att patienter som får tunntarmscancer har en allmän bemägenhet att utveckla elakartade tumörer.

Arbete I
Vi studerade faktorer som kan påverka överlevnaden hos patienter med adenocarcinom i tolvfingertarmen (263 patienter) och resten av tunntarmen (663 patienter). Patienterna identifierades via Cancerregistret. Femårsoverlevnaden för patienter med tumör i tolvfingertarmen var 24 % och för tumörer i tunntarmen 28 %. Det var ingen statistiskt säkerställd skillnad mellan de två tumörlokalisationerna. Kvinnor med adenocarcinom i tunntarmen hade bättre överlevnad än män medan det inte fanns någon skillnad mellan könen för tumörer i övriga tunntarmen. Äldre patienter hade sämre prognos än yngre. Överlevnaden verkar ha blivit bättre under senare år, åtminstone för tumörer i tolvfingertarmen.

Arbete II
Vi studerade faktorer som kan påverka prognosen för patienter med carcinoid i tunntarmen. Från Cancerregistret identifierade vi 89 patienter med carcinoid i tolvfingertarmen och 2437 patienter med carcinoid i övriga tunntarmen. Femårsoverlevnaden för patienter med tumör i tolvfingertarmen var 60 % och för patienter med tumör i övriga tunntarmen 56 %. Möjligt är prognosen bättre för tumörer i tolvfingertarmen jämfört med övriga tunntar-

Arbete III
Vi studerade risken jämfört med normalbefolkningen att utveckla andra elakartade tumörer för patienter som fått adenocarcinom eller carcinoid i tunntarmen. Vi analyserade också om patienter med adenocarcinom och carcinoid i tunntarmen har ökad risk att dö av andra sjukdomar än tunntarmstumor jämfört med normalbefolkningen.


Patienter med adenocarcinom hade ökad risk jämfört med normalbefolkningen att dö av elakartade tumörer och av andra sjukdomar i mag-tarmkanalen såsom magsår och tarmvred. Patienterna med carcinoid hade ökad risk att dö av elakartade tumörer, sjukdomar i mag-tarmkanalen och av hjärt-kärl-sjukdomar.

Resultaten talar för att patienter med adenocarcinom och carcinoid i tunntarmen har en allmän benägenhet att utveckla andra elakartade sjukdomar. Möjligen finns det gemensamma faktorer som påverkar uppkomsten av tunntarmscancer och andra tumörformer.

Arbete IV
Vi studerade risken att utveckla adenocarcinom eller carcinoid i tunntarmen hos patienter med Crohns sjukdom. Vi identifierade 23393 patienter som vårdats för Crohns sjukdom via Patientregistret. Risken jämfört med normalbefolkningen att utveckla både adenocarcinom och carcinoid var kraftigt ökad. Risken verkar ha ökat för patienter som vårdats för Crohns sjukdom under senare år.
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