Chapter 1
Epidemiology of the Association Between Bacterial Infections and Cancer

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Abstract The role of infectious agents such as bacteria, viruses, fungi etc. has been of interest for many years. Many studies have linked chronic bacterial infection with subsequent development of cancer at a number of different sites in the body.

Most cancers have a multifactorial aetiology with a number of different steps between the normal and the malignant cell. One example of this is stomach cancer where it has been postulated that bacteria play a role at a number of stages but will also be true of cancers at other sites.

This chapter summarises those situations where cancers occur as a possible result of bacterial infection and covers oesophageal, stomach, colorectal, gallbladder, pancreatic, bladder and lung cancer.

Keywords Bacteria • Bacterial infections • Cancer • Epidemiology • Esophagus • Stomach • Colon • Rectum • Gallbladder • Pancreas • Bladder • Lung • Review • Cancer prevention • Infection

1.1 Introduction

It has been postulated that over 80% of cancers are caused by environmental factors (Higginson 1968) many of which factors are non-infectious such as diet and exposure to radiation. However the number of cancers caused by infectious agents is likely to rise with further research; for example until recently, it was thought that the acidic conditions of the stomach resulted in a sterile environment whereas in relatively

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recent times one of the most important infectious agents found to increase the risk of cancer, *Helicobacter pylori* was identified (Eslick 2010). Currently, more than 20% of cancer have been postulated to be linked to infectious agents (zur Hausen 2009). Of these, the majority of the causative agents are viruses, which make up nearly two thirds of the infectious causes (human papilloma virus linked to squamous cell carcinoma of the ano-genital region and nasopharynx, Epstein Barr virus linked to Burkitt's lymphoma and hepatitis B and C viruses linked to hepatocellular carcinoma) (zur Hausen 2009). Smaller numbers of tumours are related to infections from human herpes virus, liver flukes and schistosomes (Parkin 2006). Additionally, immuno-suppression caused iatrogenically, in patients with autoimmune disease and organ transplants, but also by HIV and HTLV results in higher rates of Kaposi's sarcoma, lip, vulval and penile cancers as well as non-Hodgkin's lymphoma compared to non-immuno-compromised subjects. Rates of salivary gland, eye, tongue, thyroid and cervical cancer are also higher than in non immuno-compromised controls (Ruprecht et al. 2008).

Overall, if the infectious causes of cancer were prevented there would be 26.3% fewer cancers in developing countries and 7.7% in developed countries (Parkin 2006).

The major bacterial cause of human cancer is *Helicobacter pylori*. This organism was classified as being carcinogenic for humans in 1994 (IARC Working Group 1994). It is causally associated with gastric carcinoma and gastric lymphoma as well as a number of other malignancies (Wu et al. 2009b). *Helicobacter pylori* infection is generally acquired during childhood, with a gradual increase in prevalence towards middle age (Parkin 2006; Robins et al. 2008). Its prevalence varies globally and in some countries is greater than 75% with overall prevalence of 74% in developing countries and 58% in developed countries (Parkin 2006). This organism has been implicated in one third of cancers caused by infective agents (including virus-caused cancers) and is found in 80% of patients with gastric cancer (zur Hausen 2009). In 2002, there were estimated to be 592,000 cases of gastric adenocarcinoma and 11,500 cases of gastric lymphoma attributable to *Helicobacter pylori* (Parkin 2006).

There are a huge number of bacteria living symbiotically with the human host (10^{15} in the alimentary tract flora (Ouwehand and Vaughan 2006)) and their presence is crucial for normal human physiological function.

The effects of bacteria are not ubiquitously harmful and the dichotomy of bacterial protection versus harm is illustrated by the relative protective effects of *Helicobacter pylori* infection of the stomach with regards to reduction of oesophageal cancer, but increased risk of gastric adenocarcinoma and lymphoma (Nakajima and Hattori 2004). Colonisation by bacterial species does not indicate a true infection and bacteria may colonise the abnormal host environment around a tumour. Additionally, some bacterial toxins have been used in anti-cancer therapy as chemotherapeutic agents (Patyar et al. 2010).

1.2 Oesophageal Cancer

The two major types of oesophageal cancer, squamous cell carcinoma and adenocarcinoma have different aetiologies. Squamous cell carcinoma develops most frequently in patients who smoke and have high alcohol intake or long standing achalasia. Adenocarcinoma is associated with gastro-oesophageal reflux and columnar metaplasia ("Barrett's oesophagus") (Allum et al. 2002).

The oesophageal mucosa is continuously bathed in swallowed saliva and food boluses have a rapid transit time due to the organ's coordinated peristalsis and appropriate lower oesophageal sphincter relaxation minimising the contact time of carcinogenic agents with the organ. In normal subjects a small volume of gastro-oesophageal reflux occurs with low frequency, however in patients with defective antireflux mechanisms and inadequate lower oesophageal muscular clearance, the lower oesophagus may be bathed in swallowed boluses and gastric contents for more prolonged periods (Gatenby and Bann 2009). The highest risk of oesophageal adenocarcinoma is seen in patients with the most frequent and prolonged reflux symptoms (Lagergren et al. 1999) and those with metaplastic columnar-lined oesophagus (Barrett's oesophagus) which has an annual incidence of adenocarcinoma of 0.69% per annum (Gatenby et al. 2008).

There has been a worldwide increase in the incidence of oesophageal cancers over the last 50 years, the oesophagus being the eighth commonest site of primary carcinoma in 2000 (Parkin 2001). This increase has been demonstrated specifically in the United Kingdom (Newnham et al. 2003; Kocher et al. 2001; Powell and McConkey 1992; Johnston and Reed 1991; McKinney et al. 1995) as well as in other countries (Ries et al. 2004; Daly et al. 1996; Liabeuf and Faivre 1997; Tuyns 1992; Moller 1992; Hansen et al. 1997). The histological type of these tumours has changed, from historically a strong predominance of squamous cell carcinomata (Bosch et al. 1979; Puestow et al. 1955; Turnbull and Goodner 1968; Webb and Busuttil 1978) to the present time, when adenocarcinomata comprise the majority of oesophageal tumours in the United States and United Kingdom (Gelfand et al. 1992; Putnam et al. 1994; Rahamim and Cham 1993; Chalasani et al. 1998; Johnston and Reed 1991; Devesa et al. 1998; Powell and McConkey 1992). Furthermore, current trends are predictive of a continued rise in oesophageal cancer in the UK (Gatenby et al. 2011; Moller et al. 2007) which is likely also to be seen in other countries, especially those with high proportions of adenocarcinoma (Curado et al. 2007). However globally, squamous cell carcinoma is still the predominant histological type (Curado et al. 2007).

Swallowed bacteria from normal oral flora include *Streptococcus*, *Neisseria*, *Veillonella*, *Fusobacterium*, *Bacteroides*, *Lactobacillus*, *Staphylococcus* and *Enterobacteriaceae* (Sjosted 1989). A difference has been noted in the oesophageal flora in patients with oesophageal cancer compared to the normal oesophagus (Eslick 2010) and Barrett's oesophagus compared to the normal oesophagus

(MacFarlane et al. 2007). However it is likely that the majority of the changes in microbiological flora occurs due to opportunistic colonisation of the altered host environment of the cancer rather than earlier in the process of carcinogenesis as causative agents, with the exception of *Campylobacter concisus* and *Campylobacter rectus* which have been associated with the development of adenocarcinoma in patients with columnar metaplasia of the oesophagus via mutagenic effects including nitrite, N-nitroso and nitrous oxide mediated damage (MacFarlane et al. 2007).

Streptococcus anginosus infection has been found in 44% of oesophageal cancer tissue samples (Morita et al. 2003), but a role in the development of cancer has not been demonstrated.

Treponema denticola, which is associated with gingivitis and periodontitis is frequently found in oesophageal cancer specimens. This was the most frequent organism found in resected oesophageal cancer specimens in one series (Narikiyo et al. 2004).

Helicobacter pylori infection results in stomach inflammation and reduced gastric acid production and its eradication has been shown to increase reflux oesophagitis and metaplastic columnar-lined oesophagus (Labenz et al. 1997; Corley et al. 2008). The EUROGAST group has demonstrated that the ratio of cases of squamous cell carcinoma of the oesophagus: adenocarcinoma of the oesophagus is higher in centres with higher population prevalence of *Helicobacter pylori* infection (14 centres total), but that the strain of *Helicobacter pylori* did not have a clear relationship with histological type (Robins et al. 2008). The FINBAR study demonstrated that the rate of *Helicobacter pylori* positivity was lower in patients with reflux oesophagitis (42.4% positive), Barrett's oesophagus (47.4% positive) and adenocarcinoma (51.9% positive) compared to control subjects (59.3% positive). Cag A positivity (the strain most strongly associated with peptic ulcer disease and development of gastric tumours) was lower in Barrett's oesophagus and oesophageal adenocarcinoma patients than in patients with reflux oesophagitis or control subjects. When the oesophageal cancer group was divided into those with true oesophageal tumours to tumours at the oesophagogastric junction, rates of *Helicobacter pylori* and the Cag A strain were similar in patients with junctional tumours and control subjects, but lower in true oesophageal tumours (Anderson et al. 2008).

Three meta-analyses have been published on the relationship between *Helicobacter pylori* infection and the Cag A strain in the last 4 years. Rokkas et al. (2007) demonstrated an odds ratio of 0.52 (95% confidence interval 0.37–0.73) for *Helicobacter* positive compared to negative patients in development of adenocarcinoma (with similar findings for *Helicobacter* positivity and Barrett's oesophagus). The odds ratio for Cag A positive *Helicobacter pylori* and development of adenocarcinoma was 0.51 (95% confidence limits 0.31–0.82). There was no significant relationship between *Helicobacter pylori* positivity and squamous cell carcinoma (odds ratio 0.85, 95% confidence limits 0.55–1.33). Zhuo et al. (2008) demonstrated that in 12 case-control studies, the odds ratio for development of oesophageal adenocarcinoma (9 studies, 684 cases oesophageal adenocarcinoma and 2,470 controls of which 259 cases and 1,287 controls were *Helicobacter pylori* positive) with

Helicobacter pylori infection was 0.58 (95% confidence interval 0.48–0.70) and for squamous cell carcinoma (5 studies, 644 cases squamous cell carcinoma and 2,021 controls of which 355 cases and 1,150 controls were *Helicobacter pylori* positive) was 0.80 (95% confidence interval 0.45–1.43). For the Cag A strain-infected subjects compared to non-Cag A strain-infected subjects the odds ratio for development of adenocarcinoma was 0.54 (95% confidence interval 0.40–0.73) and the odds ratio for development of squamous cell carcinoma was 1.20 (95% confidence interval 0.45–3.18) (Zhuo et al. 2008). Islami and Kamangar (2008) demonstrated that in their meta-analysis of 13 studies (840 cases and 2,890 controls) that infection with the *Helicobacter pylori* was associated with reduced risk of oesophageal adenocarcinoma odds ratio 0.56 (95% confidence interval 0.45–0.69). The effect was also seen in the single study undertaken in a non-Western country (Iran), (but the result of this small study just fell short of statistical significance). The odds ratio of development of oesophageal adenocarcinoma with the Cag A strain was 0.56 (95% confidence interval 0.46–0.68) and no difference was seen between *Helicobacter* negative subjects and Cag A negative *Helicobacter pylori* positive subjects. No significant effect was seen with squamous cell carcinoma (Derakhshan et al. 2008).

A further large case-control study from Taiwan (where squamous cell carcinoma accounts for 95% of oesophageal cancers) has demonstrated that the odds ratio of *Helicobacter pylori* infection with squamous cell carcinoma of the oesophagus was 0.470 (95% confidence interval 0.340–0.648) and 0.375 (0.277–0.508) when compared to two hospital control groups and 0.802 (95% confidence interval 0.591–1.089) compared to a community control group (Wu et al. 2009b).

Within patients with established columnar-lined oesophagus there does not appear to be a difference in the risk of cancer development between those who had evidence of *Helicobacter pylori* infection and those who had not been infected (Ramus et al. 2007).

Overall it is possible that the protective effects are secondary to *Helicobacter pylori* induced gastric atrophy and hypochlorhydria, both of which reduce acid exposure of the lower oesophagus (Blaser 2008) and the overall results demonstrate that infection with *Helicobacter pylori* and particularly the Cag A strain are associated with reduced risk of oesophageal adenocarcinoma development, but no clear effect is seen on the risk of squamous cell carcinoma development.

Eradication of *Helicobacter pylori* would subsequently be likely to increase the risk of oesophageal adenocarcinoma, but eradication also reduces the risk of gastric cancers. Using an algorithm based on data from a systematic review, Nakajima and Hattori (2004) estimated that in patients with atrophic gastritis (the macroscopic state most closely associated with development of gastric cancer), eradication of *Helicobacter pylori* would reduce the annual incidence of gastric adenocarcinoma by 5.9 times. The annual incidence of oesophageal cancer was modelled at 1% per annum with 16.5% of patients who had undergone eradication developing gastro-oesophageal reflux disease and 12% of these patients developing columnar metaplasia of the oesophagus. The overall risk of development of oesophageal adenocarcinoma was 0.18% per annum in patients who had undergone eradication. In the presence of atrophic gastritis and columnar metaplasia of the oesophagus,

there was still an overall benefit seen in eradication with the combined incidence of gastric and oesophageal cancers being reduced from 1.4% to 1% per annum (Nakajima and Hattori 2004). Anand and Graham (1999) estimated that the risk of development of oesophageal adenocarcinoma following *Helicobacter pylori* eradication was 10–60-fold lower than the risk of development of gastric adenocarcinoma if eradication was not undertaken.

1.2.1 Viral, Parasitic and Fungal Infection

Expression of JC viral protein has been shown in a small study of oesophageal cancer cells, but not in normal oesophageal cells (where viral DNA was also found). The authors suggest that JC virus may have a role in oesophageal cancer development (Del Valle et al. 2005). Studies have not shown a relationship between Epstein Barr Virus infection and risk of oesophageal cancer (Eslick 2010).

No studies have examined the role of human herpes simplex virus in oesophageal cancer development (Eslick 2010). Human papilloma virus has been linked with squamous cell cancer of the oesophagus, with HPV 16 being the type most strongly associated and frequently studied (Eslick 2010).

Chaga's disease (protozoal infection with *Trypanosoma cruzi*) has been associated with both higher and lower rates of oesophageal cancer (Garcia et al. 2003; de Rezende et al. 1985) This occurs several decades after the initial infection with dysfunction of the nervous control of the gastrointestinal tract with development of a dilated mega-oesophagus with poor peristaltic function and oesophageal emptying (Matsuda et al. 2009). However, there is a common finding of coinfection with *Helicobacter pylori* (Barbosa et al. 1993; de Rezende et al. 1985; Eslick et al. 1999; El-Omar et al. 2000) and the overall number of cancers caused by this protozoan is likely to be small compared to the effects of *Helicobacter pylori* infection on oesophageal cancer development.

The data on fungal causes of oesophageal cancer are largely circumstantial, with linkage of several mycotoxins to oesophageal cancer, but no good epidemiological studies (Eslick 2010).

1.3 Gastric Cancer

A hypothesis for the sequence of changes that lead from normal gastric mucosa to gastric cancer was first proposed by Correa et al. (1975). Although this sequence has since been added to and changed, the essential hypothesis (shown in Fig. 1.1) remains the same. Bacterial colonisation/infection would appear to play a role by two different pathways. One pathway is normal mucosa progressing to gastric atrophy, at which stage the stomach would become hypochlorhydric resulting in chronic bacterial colonisation, and the production of N-nitroso compounds. The other pathway is as a result of *Helicobacter pylori* infection.

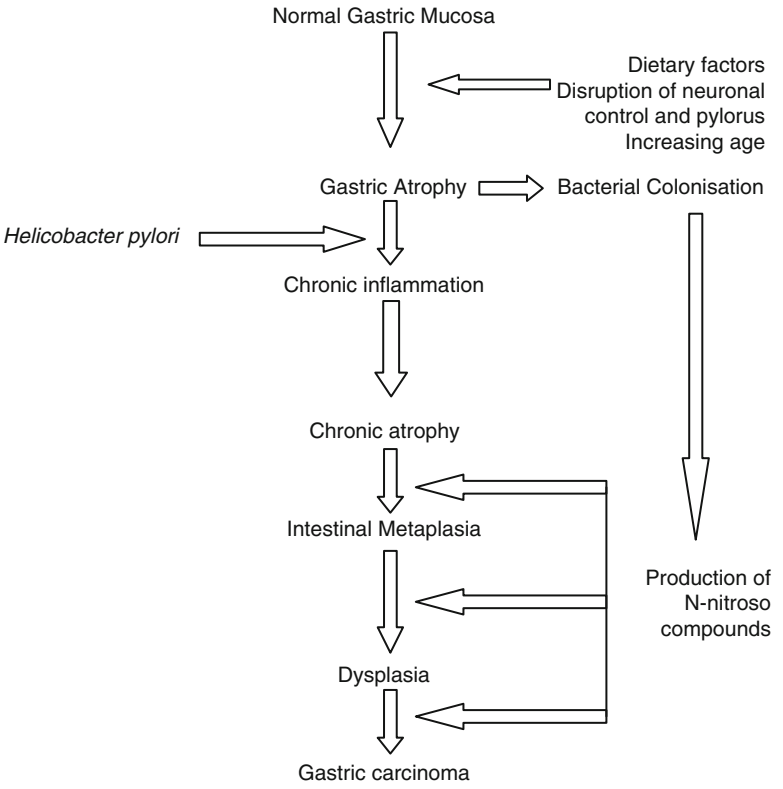

Fig. 1.1 The pathogenesis of gastric cancer

1.3.1 Helicobacter pylori Infection

Helicobacter pylori is a gram-negative bacterium which colonises gastric epithelium. It has evolved the ability to overcome the highly acidic environment of the stomach by metabolising urea to ammonia, thus generating a neutral environment (Wroblewski et al. 2010). *Helicobacter pylori* infection is associated with low socioeconomic status and crowded living conditions, especially in childhood (Malaty and Graham 1994). Approximately half the world's population is infected (with most children in developing countries being infected by the age of 10) (Smith and Parsonnet 1998) with the majority of these developing coexisting chronic inflammation (Wroblewski et al. 2010). In contrast, in developed countries, infection in children is uncommon and only 40–50% of adults are affected. There is a clear age-related increase in prevalence which is probably due to a cohort effect in that, H. *pylori* infection in childhood was more common in the past than it is today (Parsonnet et al. 1992; Banatvala et al. 1993). The route of transmission of *Helicobacter pylori* remains controversial with circumstantial evidence suggesting it probably occurs through person to person transmission.

Studies comparing rates of *Helicobacter pylori* infection in different populations with rates of gastric cancer in the same populations have mostly correlated well (Forman et al. 1993). In addition, as *Helicobacter pylori* infection has declined over time so has the rate of gastric cancer incidence (Parsonnet et al. 1992; Banatvala et al. 1993). It is considered that the gastric inflammatory response due to colonisation by *Helicobacter pylori* is the single strongest risk factor for peptic ulceration and gastric cancer. However only a fraction of those colonised go on to develop cancer (Peek et al. 2010).

Retrospective studies should be viewed with caution in view of the hypothesis that the cancerous stomach may lose its ability to harbour *Helicobacter pylori* (Osawa et al. 1996) but evidence from 2 meta-analyses of all case-control studies (Huang et al. 1998; Eslick and Talley 1998) indicate a 2-fold increase in the risk of gastric cancer in instances of *Helicobacter pylori* infection.

Prospective case-control using stored serum from populations, and thus knowing that infection by *Helicobacter pylori* preceded gastric cancer, has provided more concrete evidence of a link (Parsonnet et al. 1991; Forman et al. 1991; Lin et al. 1995; Siman et al. 1997). It has also been shown that in those infected with *Helicobacter pylori*, and followed up for a period of 10 years or more, risk of gastric cancer was increased 8-fold (Forman et al. 1994).

In a recent review of *Helicobacter pylori* infection and gastric cancer in the Middle East, Hussein (2010) reported that although *Helicobacter* infection rates in childhood were high, gastric cancer rates differ markedly from very high in Iran (26.1/100,000) to low in Israel (12.5/100,000) and very low in Egypt (3.4/100,000). Atherton (2006) concluded that *H. pylori* infection, distribution of virulence factors, diet and smoking could not explain the differences in gastric cancer rate even taking into account the accuracy of the data due to differences in diagnostic methods, limitations in medical services etc.

Whether eradication of *Helicobacter pylori* is an effective strategy for prevention of gastric cancer is still controversial (Selgrad et al. 2010). Some studies show this to be the case (Malfertheiner et al. 2005; Fry et al. 2007) but others do not (De Vries and Kuipers 2007). The effectiveness of *Helicobacter pylori* eradication as a means of protection against gastric cancer is dependant on the extent of preneoplastic changes (gastric atrophy, intestinal metaplasia etc.) at the time (Selgrad et al. 2010). Wu et al. (2009a) reported that the earlier *Helicobacter pylori* is eradicated after peptic ulcer disease, the smaller the risk of gastric cancer. Development of a vaccine to be used as primary prevention, especially with infant vaccination was discussed (Selgrad et al. 2010).

1.3.2 Chronic Bacterial Overgrowth of the Stomach

The normal stomach is acidic with a pH of 2. However in certain pathological conditions such as pernicious anaemia (caused by a lack of intrinsic factor and thus a failure to secrete gastric acid) and surgery for peptic ulcer, or as part of the ageing

process, the gastric pH may rise to 4.5 or above on a permanent basis. This would result in chronic bacterial overgrowth of the stomach.

In the case of peptic ulcer, the aim of surgical treatment, either by gastrectomy or by vagotomy, was to decrease acid secretion in order to allow the ulcer to heal. In the case of gastrectomy the lower, acid secreting, part of the stomach was removed by a variety of procedures, and in vagotomy the vagal nerves, which control acid secretion, were severed. Both these procedures resulted in loss of gastric acidity within a year, and in both there was an increased risk of gastric cancer (Caygill et al. 1984, 1986).

1.3.3 Pernicious Anaemia

An increased risk of gastric cancer had been reported in several series of pernicious anaemia patients (Blackburn et al. 1968; Brinton et al. 1989). A study by Caygill et al. (1990) showed an overall 5-fold excess risk of gastric cancer in pernicious anaemia patients. It was not possible to ascertain the onset of pernicious anaemia accurately from patients records as it may be present for some years before diagnosis, therefore the period after diagnosis was divided into 0–19 years and 20+ years and it was found that the excess risk of gastric cancer was 4-fold in the first time period and 11-fold in the second time period.

1.3.4 Surgery for Peptic Ulcer

Table 1.1 is a summary of cohort studies which have shown an increased risk of gastric cancer in peptic ulcer patients who have undergone surgery to remove the ulcer, or in the case of vagotomy to stop secretion of stomach acid. In the study by Caygill et al. (1986), cancer risk for those undergoing a gastrectomy for gastric ulcer was analysed separately from those who had the operation for duodenal ulcer. The risk was analysed by time interval. They found that in the case of duodenal ulcer there was a decrease in risk in the first 19 years followed by an increase in risk thereafter. In contrast in the gastric ulcer patients there was a 3-fold increase in risk immediately after, and presumably prior to surgery, and this rose to over 5-fold 20 or more years after surgery. The pattern of an initial decrease in risk in those operated for duodenal ulcer has been confirmed by Arnthorsson et al. (1988), Moller and Toftgaard (1991), Lundegardh et al. (1988) and Eide et al. (1991). This difference in behaviour between duodenal ulcer and gastric ulcer patients needs to be rationalised. It was hypothesised that prior to surgery duodenal ulcer patients would have good acid secretion and the effect of surgery would be to induce hypochlohydric within a year of surgery. On the other hand many gastric ulcer patients would be hypochlorhydric for varying number of years prior to the operation.

Table 1.1 Cohort studies examining gastric cancer risk following surgery for peptic ulcer

References	Study population (*n*)	Excess risk	Latency (years)
Ross et al. (1982)	779	None	19
Watt et al. (1984)	735	3-fold	15
Tokudome et al. (1984)	3,827	None	–
Caygill et al. (1986)	4,466	4-fold	20
Viste et al. (1986)	3,479	3-fold	20
Arnthorsson et al. (1988)	1,795	2-fold	15
Lundegardh et al. (1988)	6,459	3-fold	30
Offerhaus et al. (1988)	2,633	5-fold	15 females 3 males
Toftgaard (1989)	4,131	2-fold	25
(vagotomy cohort) Caygill et al. (1991)	1,643	1.6	20

1.3.5 Possible Mechanism for Gastric Carcinogenesis in Instances of Hypochlorhydria

The histopathological seqence from the normal to the neoplastic stomach proposed by Correa et al. (1975) and reviewed by Correa (1988) has been generally accepted. They postulated that the first stage, gastric atrophy, progresses to chronic atrophic gastritis. Atrophic gastritis is at increased risk of developing intestinal metaplasia which in turn carries an elevated risk of progressing through increasingly severe dysplasia to cancer. It was suggested that this progression was a result of the action of carcinogenic N-nitroso compounds. Gastric atrophy results in the loss of gastric acid secretion allowing bacterial colonisation of the stomach. The bacteria react with nitrate, present in many foods and in drinking water, and convert it to nitrite. The nitrite further reacts with nitrosatable amines to form a variety of N-nitroso compounds. If this hypothesis is correct then the loss of gastric acidity, with consequent chronic bacterial overgrowth, from any cause (surgical, metabolic, clinical, genetic or environmental) should, after a latency period of 20 years or more, lead to an increased risk of gastric cancer as has been shown in patients with pernicious anaemia and those undergoing gastrectomy or vagotomy (see Fig 1.1). This also offers an explanation for the difference in cancer risk in those operated on for a gastric ulcer or for duodenal ulcer. Gastric ulcer patients, as a result of their hypoacidity prior to operation, will have bacterial overgrowth for variable lengths of time which would contribute to the latency period, whereas those with duodenal ulcer will only become hypochlorhydric after their operation, thus their increase in risk would only start to manifest itself 20 years later.

1.4 Colorectal Cancer

As in many cancers the progression from the normal epithelium to malignancy is a multi-stage process. There are at least three distinct histological stages prior to malignancy and metastatic disease. These are adenoma formation, adenoma growth and increasingly severe dysplasia (Hill et al. 1978, 2001; Hill 1991). The evidence for this was reviewed by Morson (1974) and Morson et al. (1983). Benign adenomas are very common in both men and women in western populations and their prevalence has been found to be approximately 50% in males and 30% in females by the age of 70 in post mortem studies. Most are very small (around 3–5 mm) but some can be greater than 20 mm in diameter. The risk of finding malignant cells in a small adenoma is very small (less than 1 per 1,000 for those with a diameter less than 3 mm) but high in those with a diameter greater than 20 mm (Morson et al. 1983). Thus one of the most important steps in the adenoma-carcinoma sequence is adenoma growth.

1.4.1 Faecal Bacteria Present in the Colon

There are differences within the colon in subsite distribution of small adenomas, large adenomas and colorectal cancers. A very large number of postmortem studies have shown that small adenomas are evenly distributed around the colon and rectum whereas large adenomas and cancers are concentrated in the distal colon and rectum, (Hill 1986). The implication being that the causal agents are delivered via the vascular system; and indeed the colon lumen is a rich source of potential carcinogens, produced *in situ* by bacterial action on benign substrates (Caygill and Hill 2005). Although not proved, this is consistent with the hypothesis that the factors causing adenomas to increase in size and in severity of epithelial dysplasia are luminal products of bacterial metabolism. There is further support for this by the fact that adenomas regress after diversion of the faecal stream.

1.4.2 Streptococcus bovis

Several *Streptococci* have been linked to chronic infections of the colon and subsequent increased risk of colorectal cancer (Kim et al. 2002; Siegert and Overbosch 1995). An association between *Streptococcus bovis* and colorectal cancer was first reported by Roses et al. (1974) and has been validated by more recent studies (Biarc et al. 2004; Gold et al. 2004). The incidence of *Streptococcus bovis* associated with colorectal cancer has been determined as being between 18% and 62% (Zarkin et al. 1990).

1.4.3 E. coli and Inflammatory Bowel Disease

The intestinal flora in patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) differs from control subjects with increased *E. coli* (Martin et al. 2004). These patients have a marked increase in rate of colorectal cancer development which is highest in those with chronic severe inflammation (Munkholm 2003). Small studies have demonstrated increased mucosa-associated and intramucosal bacteria in Crohn's disease (79% and 71% respectively) and colon cancer (71% and 57% respectively) compared to non inflamed controls (42% and 29% respectively), but no difference between controls and ulcerative colitis. These *E. coli* commonly expressed haemagglutinins (39% Crohn's, 38% cancers, and 4% controls) and the resulting pro-inflammatory cytokines may be implicated in carcinogenesis (Martin et al. 2004).

1.5 Gallbladder Cancer

Cancer of the gallbladder has a very poor prognosis. The highest incidence is in the Andean countries of South and Central America and in American Indian groups (Misra et al. 2003) but is rare in Western countries. The etiology is not well understood, but the major risk factor is the presence of gallstones which are involved in 70–80% of cases (Lazcano-Ponce et al. 2001). Risk factors include obesity, reproductive factors and environmental exposure to certain chemicals (Lazcano-Ponce et al. 2001; Wistuba and Gazdar 2004).

However, the major risk factors are those which involve chronic bacterial infection such are previous polya partial gastrectomy for peptic ulcer, gallstone carriage, chronic infection with *Salmonella typhi/paratyphi* and with *Helicobacter species*.

1.5.1 Gallstones

Although it has been known for some years that gallstones are the most important risk factor for gallbladder cancer (Devor 1982; Zatonski et al. 1997; Randi et al. 2006), the nature of this association is not clear. Gallstones are, however associated with bacterial infection of the gallbladder (England and Rosenblatt 1977).

1.5.2 Polya Partial Gastrectomy

The routine treatment for persistent peptic ulcer, gastric or duodenal, was surgery using a variety of partial gastrectomy operations. These remove much of the lower part (including most of the acid secreting section) of the stomach. As a result, the stomach became hypochlorhydric attaining a pH of around 4.5.

This is a perfect milieu for bacterial overgrowth and formation of N-Nitroso compounds (Hill 1996) which have been shown to be carcinogenic in all species in which they have been studied. Polya partial gastrectomy is associated with a 10-fold excess risk of gallbladder cancer with a 20 year latency period (Caygill et al. 1988).

1.5.3 Infection with Salmonella typhi/paratyphi

There is a growing body of evidence that typhoid carriers are at an increased risk of biliary tract cancer. The New York City Health Department conducted a very large case–control study of 471 registered carriers and 942 age- and sex-matched controls which showed that chronic carriers were six times as liable to die of hepatobiliary cancer as controls (Welton et al. 1979). This finding has been confirmed by others (Mellemgaard and Gaarslev 1988; Caygill et al. 1994; Nath et al. 1997, 2008; Shukla et al. 2000).

Caygill and co-workers studied long-term cancer risk in two Scottish cohorts – one a cohort of 386 acute typhoid cases from a single outbreak which occurred in Aberdeen in 1964 and the other 83 typhoid carriers from a number of different outbreaks (Caygill et al. 1994, 1995). In case of acute infection in Aberdeen, there was neither excess risk for cancer of the gallbladder nor indeed for any other cancer.

In the cohort of patients with chronic infection there was an almost 200-fold excess risk of cancer of the gallbladder and an excess risk of cancer of the pancreas (Table 1.2).

1.5.4 Infection with Helicobacter species

Helicobacter species colonising the biliary tract have been associated with gallbladder cancer (Leong and Sung 2002; Kobayashi et al. 2005).

There is no doubt that gallbladder cancer has a multi-factorial aetiology. Although a proportion of any risk may well be an individuals environmental and life style exposure, the most important risk factor appears to be exposure to chronic, but not acute bacterial infection.

1.6 Pancreatic Cancer

Cancer of the pancreas has a relative low incidence but a very poor prognosis even if diagnosed early and ranks eighth in a world listing of cancer mortality. International incidence rates vary in different countries, implying that environmental factors are important. Smoking is the best documented etiologic agent and accounts for approximately about 25% of all cases. Little is known about dietary factors. The incidence

Table 1.2 Deaths from "cancer" in patients with chronic infection with typhoid/paratyphoid (Caygill et al. 1994)

Site of cancer	ICD no	Observed (O)	Expected (E)	O/E	95% CI
Gallbladder	1,560	5	0.03	167*	(54–391)
Pancreas	157	3	0.37	8.1*	(1.7–23.7)
Colorectum	152–4	3	1.00	3.8	(0.6–8.8)
Lung	162	5	1.98	2.5	(0.8–5.9)
All neoplasms	140–208	20	7.80	2.6*	(1.6–4.0)

ICD International Classification of Disease, *O* observed, *E* expected
*$P<0.001$

is strongly age dependent thus as the population of western countries ages we can anticipate an increasing number of cases (Lowenfels and Maisonneuve 2006). Cancer of the pancreas is also linked with bacterial infection.

1.6.1 Surgery for Peptic Ulcer

Surgery for peptic ulcer with the resultant hypochlorhydria results in bacterial overgrowth of the stomach. The bacteria thus formed react with ingested nitrates in food and converts them to nitrites. This is the perfect milieu for the formation of N-nitroso compounds which are formed when nitrite and nitrosatable amines are present together. These highly reactive compounds which can combine with nitrosatable amines, also present in food, and form a range of nitrosamines (Caygill et al. 1984; Preussmann 1984). Nitrosamines have been found to be carcinogenic in a number of animals (Pour and Lawson 1984) and are both species and target organ specific. This could well be the explanation for the finding of an excess risk for cancer of the pancreas after surgery for peptic ulcer (Caygill et al. 1987; Mack et al. 1986; Eide et al. 1991; Tersmette et al. 1990; Ross et al. 1982; Luo et al. 2007), the excess risk being greater in gastric ulcer than in duodenal ulcer patients (Caygill et al. 1987).It must be noted however that, Inokuchi et al. (1984), Watt et al. (1984) and Moller and Toftgaard (1991) did not find an excess risk of cancer of the pancreas in patients who had undergone operations for peptic ulcer.

1.6.2 Helicobacter species Infection

In recent years there have been a number of studies investigating a possible association between *Helicobacter species* infection and cancer of the pancreas. *Helicobacter species* ribosomal DNA was detected in the pancreas of 75% of pancreatic cancer patients (Nilsson et al. 2006) and *Helicobacter pylori* was found to be associated with an increased risk of pancreatic cancer in studies by Raderer et al. (1998) and

Stolzenberg-Solomon et al. (2001). A study by Risch et al. (2010) also found an association but only in individuals with non-O blood types. However studies by de Martel et al. (2008) and Lindkvist et al. (2008) could find no such association. Luo et al. (2007) found a modest increased risk of pancreatic cancer in patients with gastric ulcer or gastric resection and hypothesised that colonisation of the corpus by *H. pylori*, together with atrophic gastritis resulting in bacterial overgrowth and nitrosamine formation may contribute to pancreatic carcinogenesis.

1.6.3 Typhoid Carriage

In a study examining cancer risk in those infected with typhoid and in typhoid carriers, Caygill et al. (1994) found a large excess (23-fold) in cancer of the pancreas in a cohort of 83 typhoid carriers, not in 386 acute cases of typhoid who did not become carriers. The mechanism is uncertain, but pancreatic cancer has been associated with bile reflux from the common bile duct (Wynder 1975).

1.7 Bladder Cancer

Industrial exposure to naphthylamines, benzidine and a range of aromatic amines, contained in chemical dyes, has long been known to be associated with cancer of the bladder and explained the reason why men in industrialised countries were most at risk. However, a proportion of bladder cancer cases do not have an industrial origin. Early anecdotal evidence suggested an excess risk of bladder cancer following chronic bladder infection and this was confirmed by Radomski et al. (1978). Bladder infections are very common, and often asymptomatic (Sinclair and Tuxford 1971); the data on cancer risk reported by Radomski et al. (1978) concerns chronic symptomatic infection resistant to therapy, but many of his controls might have had asymptomatic bladder infections and so the magnitude of the excess risk would have been underestimated.

There is copious evidence that carcinogenic N-nitroso compounds are produced *in situ* in the bladder by infecting organisms, which is to be expected since the urine is the route of excretion of the substrates for N-nitroso compounds production – nitrate and nitrosatable amines. Thus Radomski et al. (1978) suggested that N-nitroso compounds, produced by bacterial action on these substrates were the cause of the cancer.

1.7.1 Schistosoma haematobium

Bilharzial (*Schistosoma haematobium)* infection is a major risk factor for bladder cancer, and such infections are accompanied by a profuse secondary bacterial infection of the bladder. Hicks et al. (1977) showed strong evidence that the

bladder cancer associated with bilharzial infection was in fact due to the N-nitroso compounds produced by the secondary bacterial infection. This has been supported by others who have shown a similar association (El-Mawla et al. 2001; Bedwani et al. 1998; Saad et al. 2006). Hicks et al. (1977) also produced evidence that the excess risk of bladder cancer in paraplegia was due to the same mechanism – N-nitroso compounds produced by a chronic bacterial infection of the bladder.

1.7.2 Tuberculosis

Increased bladder cancer risk has also been found amongst tuberculosis sufferers in Korea, a country where the prevalence of tuberculosis is particularly high (Kim et al. 2000).

1.8 Lung Cancer

The major risk factor for lung cancer is smoking, however infection by a number of bacteria also has a role.

1.8.1 Pulmonary Tuberculosis

Before 1950 most TB patients died when relatively young, thus any risk of lung cancer would not have became manifest. It was not till TB treatment was sufficiently successful to give the patient a reasonable life-expectancy that the association was noted. Indeed, as a result of early studies there was a theory (Rokitansky 1854) that the two diseases were antagonistic. Since then there have been numerous reviews of the association between tuberculosis and subsequent lung cancer. Aoki (1993) reviewed the epidemiological studies between 1960 and 1990 and confirmed that patients with active pulmonary tuberculosis have an excess risk of dying of lung cancer even though they already had a high mortality from tuberculosis. The excess was 5–10-fold depending on age, and was greater in women than in men. Patients with active disease were the most likely to develop lung cancer and he also found that they also had an excess risk of other cancers such as colon, lymphoma, myeloma etc.

The mechanism for the association is not clear, and there are no good hypotheses to explain it. Attempts to stimulate the immune system in animal with BCG resulted in an increased, rather than decreased, cancer risk (Martin et al. 1977). This may explain the reason for the increased risk of cancer at distant sites seen by Aoki (1993).

1.8.2 Chlamydia pneumonia

There have been a number of reports of a connection between lung cancer and infection with *Chlamydia pneumonia* (Laurila et al. 1997; Kocazeybek 2003; Littman et al. 2004). However accurate assessment of past *Chlamydia pneumonia* infection is difficult as there is no serological test to specifically identify persons with chronic infection (Littman et al. 2005).

In 2010, Chaturvedi et al. evaluated the relationship of *Chlamydia pneumoniae* infection with prospective lung cancer risk using serologic markers for both chronic and acute Chlamydial infection and concluded that chronic infection 2–5 years before was associated with an increased risk of lung cancer. They highlight the potential for lung cancer reduction through treatments targeted towards *Chlamydia pneumoniae* infections.

1.8.3 Helicobacter pylori Infection

Lung cancer has been associated with *Helicobacter pylori* infection in a number of studies (Gocyk et al. 2000; Ece et al. 2005; Zhou et al. 1992), however Philippou et al. (2004) found no such association. The mechanism is unknown but *Helicobacter pylori* may contribute by upregulating gastrin and COX-2 thus stimulating tumour growth. Also increased plasma gastrin concentrations may increase the risk of lung cancer by inducing proliferation of mucosal cells in the bronchial epithelium (Kanbay et al. 2007).

1.9 Conclusion

Bacteria play a significant role in the aetiology of cancer development, but less than viral infection. The strongest association has been seen in gastric cancer with *Helicobacter pylori* and this bacterium has been associated with the development of other tumours as well as having an inverse association with the development of oesophageal cancer. Chronic infection with ongoing insult from the infecting bacterium has been most strongly demonstrated with typhoid infection and also *Helicobacter pylori.* Eradication of bacterial agents which are causes of cancer may result in a reduction in one quarter of cancers in developing countries and a smaller proportion in developed countries.

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