Epidemiology of gastrointestinal tract tumours

Overall, tumours of the gastrointestinal (GI) tract (International Classification of Diseases for Oncology [ICD-O] codes C15-C26) represent about one quarter of all cancers diagnosed in Europe.

In Europe, about 900 000 new cases of tumours of the GI tract were diagnosed in 2018, out of the more than 3.5 million new cases of cancer overall.

Half of GI tract tumours are colorectal cancers (CRCs), followed by cancers of the stomach and pancreas (14% each), and finally liver and oesophageal cancers.

Among GI tumours, only those from the colon and rectum have a relatively good prognosis. The 5-year survival is slightly over 60% (average for Europe).

Other tumours within this group show relatively poor prognosis, with 5-year survival below 20%, including pancreatic cancer, where 5-year survival is still below 10%.

CRC survival has increased by ~5% (patients diagnosed in 2010-2014 compared with 2000-2007), but improved only by 1%-1.5% for the remaining GI tumours in the same period.

REVISION QUESTIONS
1. What proportion of all cancers diagnosed in Europe represents tumours of the GI tract?
2. Across all tumour types, why is the mortality from GI tumours higher than the incidence?
3. Which tumours of the GI tract have a poor prognosis, according to their survival rates?
Oesophageal cancer

Oesophageal cancer (OC) comprises two distinct diseases: oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma (OAC), each with different risk factors and incidence trends.

OC is the eighth most common cancer worldwide. Whereas OSCC incidence is declining, the incidence of OAC is rising in developed countries, such as Canada, USA (White population) and Scotland.

Latin American countries, Asia, and Black populations of the USA have the highest incidence of OSCC, particularly in the ‘OC belt’ (Northern China to Northern Iran).

Smoking, low fruit and vegetable intake and high intake of processed meat increase the risk of both OSCC and OAC. Alcohol consumption only increases the risk of OSCC.

Hot beverages increase the risk of both. Human papillomavirus (HPV) 16 infection may increase the risk of OSCC, while Helicobacter pylori (H. pylori) infection may reduce the risk of OAC. Obesity, GORD and BE increase the risk of OAC.

Genome-wide association studies (GWAS) of OSCC in Chinese populations showed associations with different single nucleotide polymorphisms (SNPs). The Cancer Genome Atlas (TCGA) showed genomic amplification of different chromosomes.

Precursor dysplastic lesions are detectable for OAC/OSCC. Repeated exposure to high-temperature drinks or gastro-oesophageal reflux disease (GORD) may cause inflammation.

Barrett’s oesophagus (BE) is a probable intermediate stage between GORD and OAC, in which squamous cells are replaced by columnar epithelial cells, due to chronic injury.

OACs arise from glandular cells at the lower end of oesophagus. OSCCs arise from epithelial cells that are exposed to irritation and carcinogens in foods and drinks.

REVISION QUESTIONS

1. Are there geographical differences in the distribution of the two histological types of OC?
2. Are there differences in the risk factors associated with OAC and OSCC?
3. Is alcohol consumption associated with the risk of both OAC and OSCC?
Gastric cancer

The high-risk areas for gastric cancer (GC) are Japan, China, Eastern Europe and certain countries in Latin America. Low-risk areas are North America, India, some Western European countries and most of Africa.

About 70% of cases occur in less developed countries, although in Europe there are high-risk areas in Portugal, central areas of Spain and Italy, and Eastern European countries.

Incidence rates have been declining worldwide, except for cardia GC, which has shown an increase in some developed countries, though it is still the fifth most common cancer worldwide.

A multifactorial and multistep model of gastric carcinogenesis is currently accepted, with different factors involved at different stages in the cancer process.

Pathogenesis differs between cardia and non-cardia GC. *H. pylori* is probably a necessary condition for non-cardia GC, but it is not associated with cardia GC.

**Environmental, dietary and lifestyle factors that are or may be associated with gastric cancer risk**

<table>
<thead>
<tr>
<th>Factors</th>
<th>Decreases risk</th>
<th>Increases risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious factors</td>
<td></td>
<td><em>H. pylori</em> (non-cardia)</td>
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<tr>
<td>Tobacco</td>
<td></td>
<td>Smoking</td>
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<tr>
<td>Dietary factors</td>
<td></td>
<td>Salt and salty foods</td>
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<tr>
<td>Body mass index</td>
<td></td>
<td>Obesity (cardia)</td>
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<tr>
<td>Hormones</td>
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<td>Anti-inflammatory drugs</td>
<td></td>
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<tr>
<td>Occupational exposure</td>
<td></td>
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<tr>
<td>Blood group</td>
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</tbody>
</table>

Fig. 1.7

Several factors are, or may be, associated with either a decreased or increased risk of GC, including infections, tobacco use, dietary factors, high alcohol intake and body mass index (cardia GC).

SNPs (involved in inflammatory responses, activation of chemical compounds, DNA repair) might modify the effect of environmental exposures and could explain geographical variations.

Germline mutations in *CDH1* and *CTNNA1* cause the rare (1%-3%) familial form of diffuse GC. GWAS in Asia have found a significant association with several genes, the most relevant being *PSCA* and *MUC1*.

**REVISION QUESTIONS**

1. Which are the high-risk areas for GC in Europe?
2. Do you agree that *H. pylori* infection is probably a necessary condition of non-cardia GC?
3. What are the main factors that increase and decrease the risk of GC?
Epidemiology, risk factors and pathogenesis

Colorectal cancer

CRC is the third most common cancer worldwide, and the second leading cause of cancer death (1.8 million cases and 881 000 deaths in 2018).

Incidence and mortality rates vary geographically, with the highest rates in the most developed countries. These rates are ~25% lower in women than in men.

An overall decline or stabilisation in the risk of CRC has been noted in high-income countries. In contrast, a worrying rise has been observed in patients <50 years old.

### Lifestyle and environmental factors associated with colorectal cancer risk

<table>
<thead>
<tr>
<th>Factors</th>
<th>Increases risk</th>
<th>Decreases risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body fatness</td>
<td>Both general and abdominal obesity, as marked by body mass index, waist circumference and waist-to-hip ratio</td>
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<tr>
<td>Physical activity</td>
<td>All types (including occupational and recreational). Restricted to colon; no clear effect for rectal cancer</td>
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<tr>
<td>Processed meat</td>
<td>18% increased risk for each 50 grams per day (IARC group 1 of carcinogens)</td>
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<tr>
<td>Alcoholic drinks</td>
<td>For alcohol intakes above 30 grams per day (two drinks)</td>
<td></td>
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<tr>
<td>Tobacco use</td>
<td>Increased risk with cigarettes/day and duration in current smokers; decreased risk in former smokers</td>
<td></td>
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<tr>
<td>Medication</td>
<td>Long-term use of aspirin and NSAIDs; hormonal therapy in postmenopause</td>
<td></td>
</tr>
<tr>
<td>Other diseases</td>
<td>Inflammatory bowel disease (Crohn’s disease, ulcerative colitis)</td>
<td></td>
</tr>
<tr>
<td>Dietary factors</td>
<td>Red meat</td>
<td>Dietary fibre, wholegrains, dairy products (all types), calcium intake (dietary and/or supplements)</td>
</tr>
</tbody>
</table>


CRC exemplifies stepwise progression as it develops initially as a benign precursor lesion (adenoma), which can progress to an invasive lesion (adenocarcinoma).

The lesion arises from an intestinal clonogenic precursor cell through the accumulation of multiple genetic abnormalities. There are three major precursor lesion pathways: the chromosomal instability (conventional) pathway (~80%), the microsatellite instability pathway (2%-7%) and the sessile serrated (CpG island methylator, ~15%).

### REVISION QUESTIONS

1. What are the trends in CRC risk in high-income countries?
2. What are the most important modifiable risk factors of CRC?
3. Which is the most common precursor lesion pathway of CRC?
Pancreatic cancer

Cancer of the pancreas is the 12th most common cancer worldwide and the 7th most common cause of cancer death. About 460,000 cases and 430,000 deaths were estimated in 2018.

The risk is higher in men than in women and increases with age; it is mainly a disease of high-income countries. Trends in incidence have remained fairly stable over time.

The early stages do not usually produce symptoms, so the disease is generally advanced when it is diagnosed, which accounts for relatively low survival rates.

<table>
<thead>
<tr>
<th>Risk factors associated with pancreatic cancer risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors</strong></td>
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<tr>
<td>Tobacco smoking</td>
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<tr>
<td>Risk increases with intensity (cigarettes/day) and duration, and decreases with time since cessation in former smokers</td>
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<tr>
<td>Body fatness</td>
</tr>
<tr>
<td>Greater body mass index, waist circumference, adult weight gain</td>
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<tr>
<td>Other diseases</td>
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<tr>
<td>Diabetes (new-onset type 2 diabetes) and chronic inflammatory pancreatitis</td>
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<tr>
<td>Family history and genetic syndromes</td>
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<tr>
<td>Family history of pancreatic cancer increases risk, particularly when more than one family member is involved. Besides rare germline mutations in susceptibility genes, common variants confer modest risk (i.e. carriers of A or B blood groups relative to group O)</td>
</tr>
<tr>
<td><strong>Factors with limited evidence of association with risk of pancreatic cancer</strong></td>
</tr>
<tr>
<td>Dietary factors</td>
</tr>
<tr>
<td>High consumption of red meat, processed meat, alcohol, foods containing saturated fatty acids, foods and drinks containing fructose</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>The role of infection with <em>H. pylori</em> is the subject of ongoing research</td>
</tr>
</tbody>
</table>

About 95% of pancreatic cancers occur in the exocrine pancreas, the most common being the infiltrating ductal adenocarcinoma. Other pancreatic neoplasms include neuroendocrine tumours.

Intraductal papillary mucinous neoplasms and mucinous cystic neoplasms are curable precursor lesions that can progress to an incurable invasive carcinoma.

The molecular pathology of pancreatic cancer is dominated by activating mutations in KRAS and inactivating mutations of TP53, CDKN2A and SMAD4.

Cigarette smoking is the leading modifiable cause of pancreatic cancer. It is estimated to cause 20%-25% of pancreatic cancers.

Body fatness, reflected by greater body mass index, including abdominal obesity and adult weight gain, is a cause of pancreatic cancer.

Other risk factors include chronic pancreatitis and diabetes. Family history and rare genetic syndromes (5%-10% of cases) also carry increased risk.

**REVISION QUESTIONS**

1. Identify the population groups with higher risk of pancreatic cancer according to age, sex and geography.
2. What are the most important modifiable risk factors for pancreatic cancer identified so far?
3. Which are the tumour suppressor genes commonly involved in the pathology of pancreatic cancer?
Summary: Epidemiology, risk factors and pathogenesis

- Taken together, the cancers of the intestinal tract are the most frequent tumours in humans, accounting for around one quarter of all cancer cases and almost one third of all cancer-related deaths. ~50% of these tumours are CRCs
- Except for CRC, with a 5-year survival of 60%, the remainder of GI tumours have a poor prognosis, the worst of which is pancreatic cancer, with 5-year survival <10%
- There are extreme geographical differences in the incidence of OC (more than for any other tumour). Incidence rates vary globally by more than 15-fold in men and almost 20-fold in women
- Smoking, alcohol, low fruit and vegetable intake and low income explain almost 99% of the attributable risk for OSCC in the USA and are strong risk factors in European countries, but tobacco and alcohol are weak risk factors in the highest risk areas of the world (Asian OC belt), where the aetiology of OSCC remains speculative
- *H. pylori* is the most common cause of non-cardia GC, though why *H. pylori* causes GC in only a minority of those infected remains unknown
- Given that GC is a multi-step process, the identification of patients with preneoplastic lesions with a high risk of progression and their periodic endoscopic surveillance represents the most effective method of early GC diagnosis
- There has been a substantial increase in the incidence of CRC in people <50 years old in several high-income countries. However, further studies are needed to establish the causes of this rising incidence and identify potential preventive and early-detection strategies
- CRC may be considered as a lifestyle disease: its risk is higher in countries with a diet high in calories and animal fat and a largely sedentary population with increased levels of overweight and obesity. However, there is still a lack of precise knowledge as to how multiple factors interact and contribute to risk
- Pancreatic cancer has one of the poorest prognoses among the major types of GI tumours. The most clearly established modifiable risk factors for pancreatic cancer are tobacco smoking and body fatness
- The carcinogenesis of pancreatic cancer remains largely unknown. However, some potentially curable precursor lesions and a set of significantly mutated oncogenes or tumour suppressor genes have been identified

Further Reading


González CA, Agudo A. Carcinogenesis, prevention and early detection of gastric cancer: where we are and where we should go. Int J Cancer 2012; 130:745–753.


