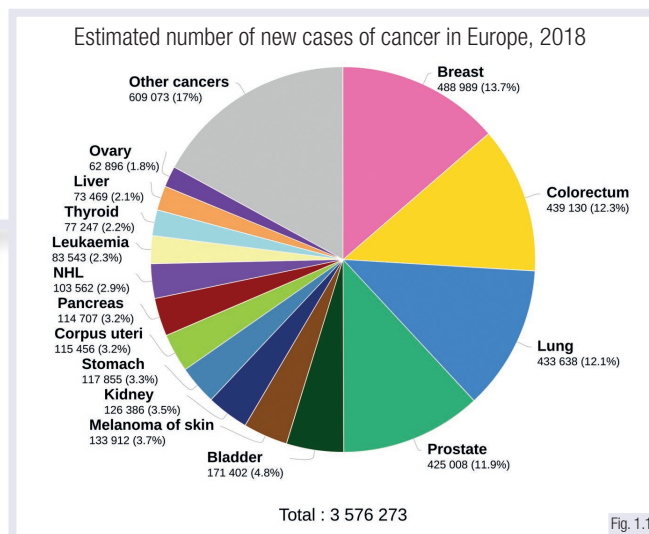# 1 Epidemiology, risk factors and pathogenesis
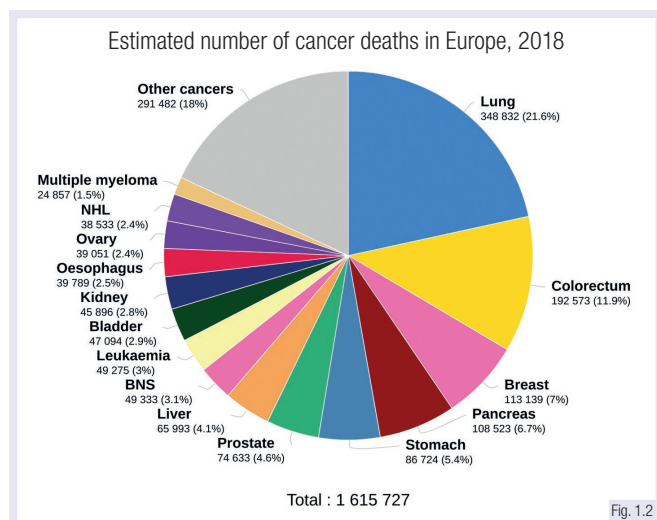
Epidemiology of gastrointestinal tract tumours

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.

Estimated number of new cases of cancer in Europe, 2018

Other cancers 609 073 (17%)
Ovary 62 896 (1.8%)
Liver 73 469 (2.1%)
Thyroid 77 247 (2.2%)
Leukaemia 83 543 (2.3%)
NHL 103 562 (2.9%)
Pancreas 114 707 (3.2%)
Corpus uteri 115 456 (3.2%)
Stomach 117 855 (3.3%)
Kidney 126 386 (3.5%)
Melanoma of skin 133 912 (3.7%)
Bladder 171 402 (4.8%)
Breast 488 989 (13.7%)
Colorectum 439 130 (12.3%)
Lung 433 638 (12.1%)
Prostate 425 008 (11.9%)

Total : 3 576 273

Fig. 1.1

NHL, non-Hodgkin lymphoma.

Estimated number of cancer deaths in Europe, 2018

Other cancers 291 482 (18%)
Multiple myeloma 24 857 (1.5%)
NHL 38 533 (2.4%)
Ovary 39 051 (2.4%)
Oesophagus 39 789 (2.5%)
Kidney 45 896 (2.8%)
Bladder 47 094 (2.9%)
Leukaemia 49 275 (3%)
BNS 49 333 (3.1%)
Liver 65 993 (4.1%)
Prostate 74 633 (4.6%)
Stomach 86 724 (5.4%)
Pancreas 108 523 (6.7%)
Breast 113 139 (7%)
Colorectum 192 573 (11.9%)
Lung 348 832 (21.6%)

Total : 1 615 727

Fig. 1.2

BNS, brain, central nervous system; NHL, non-Hodgkin lymphoma.

GI cancers account for almost one third of all cancer deaths, or about 600 000 deaths out of more than 1.6 million cancer deaths (Europe, 2018).

This relatively high proportion of deaths compared with incidence in GI cancers is due to the fact that these tumours include some cancers with poor prognosis.

CRC deaths account for ~40% of all GI cancer deaths, followed by pancreatic and stomach cancers (21% and 17%, respectively).

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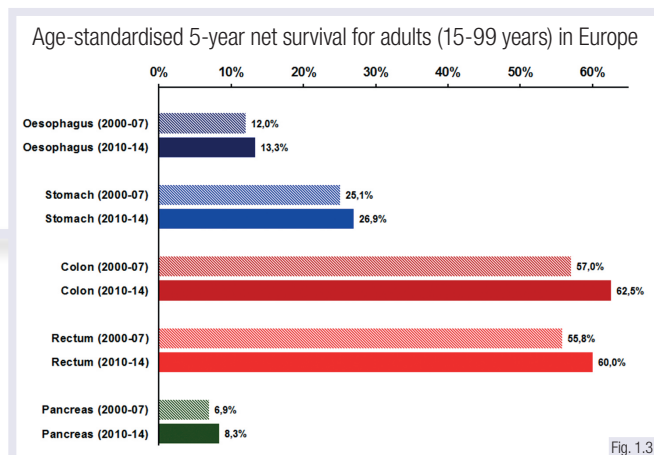
Other tumours within this group show relatively poor prognosis, with 5-year survival below 20%, including pancreatic cancer, where 5-year survival is still below 10%.

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.

Age-standardised 5-year net survival for adults (15-99 years) in Europe

	Survival
Oesophagus (2000-07)	12,0%
Oesophagus (2010-14)	13,3%
Stomach (2000-07)	25,1%
Stomach (2010-14)	26,9%
Colon (2000-07)	57,0%
Colon (2010-14)	62,5%
Rectum (2000-07)	55,8%
Rectum (2010-14)	60,0%
Pancreas (2000-07)	6,9%
Pancreas (2010-14)	8,3%

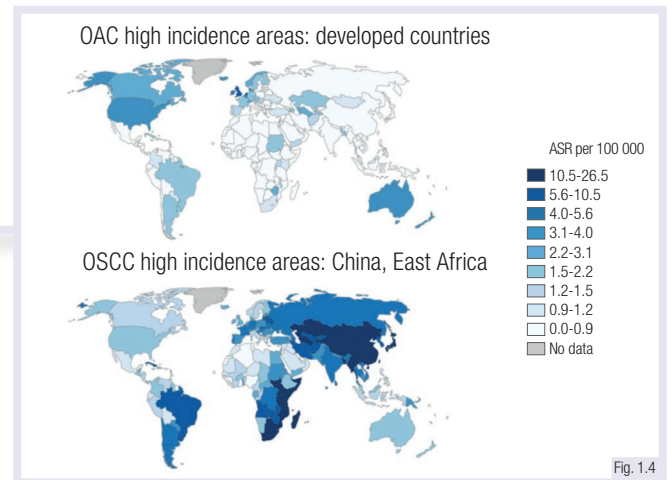Fig. 1.3

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).

OAC high incidence areas: developed countries

OSCC high incidence areas: China, East Africa

ASR per 100 000
- 10.5-26.5
- 5.6-10.5
- 4.0-5.6
- 3.1-4.0
- 2.2-3.1
- 1.5-2.2
- 1.2-1.5
- 0.9-1.2
- 0.0-0.9
- No data

Fig. 1.4

ASR, age-standardised rate; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

Development and progression of Barrett's oesophagus. Oesophageal injury, mainly due to gastrointestinal reflux, may lead to Barrett's oesophagus, a lesion that is characterised by replacement of the normal squamous epithelium by columnar epithelium, termed intestinal metaplasia. This pre-malignant condition might progress to dysplasia and oesophageal adenocarcinoma, which may invade the submucosa.
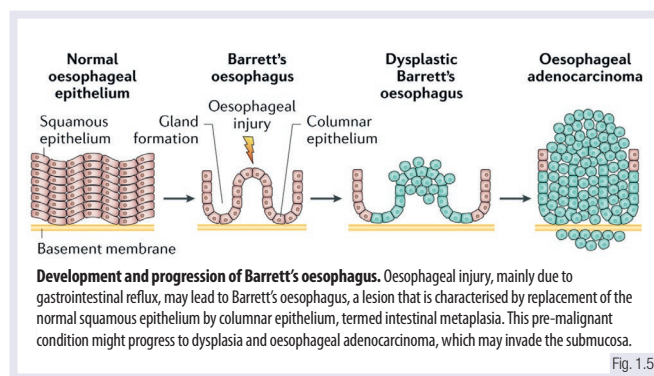
Fig. 1.5

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.

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.

Several factors are or may be associated with risk of OSCC and OAC			
Factors	OSCC Increases risk	OAC Decreases risk	OAC Increases risk
Tobacco	Smoking		Smoking
Dietary factors	Low fruit intake Low vegetable intake High alcohol intake High intake of processed meat		Low fruit intake Low vegetable intake High intake of processed meat
Infectious agents	HPV 16	*H. pylori* infection	
Hot beverages	Tea, mate		Tea, mate
Body mass index			
Other		Physical activity (1)	Gastro-oesophageal reflux disease Barrett's oesophagus

(1) OAC and OSCC combined.

Fig. 1.6

HPV, human papillomavirus; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.
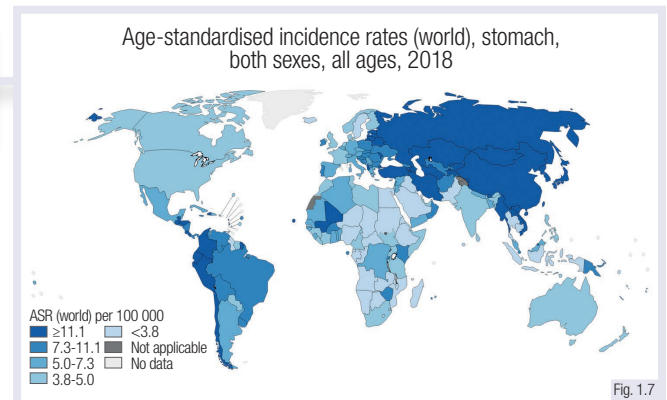
REVISION QUESTIONS

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?

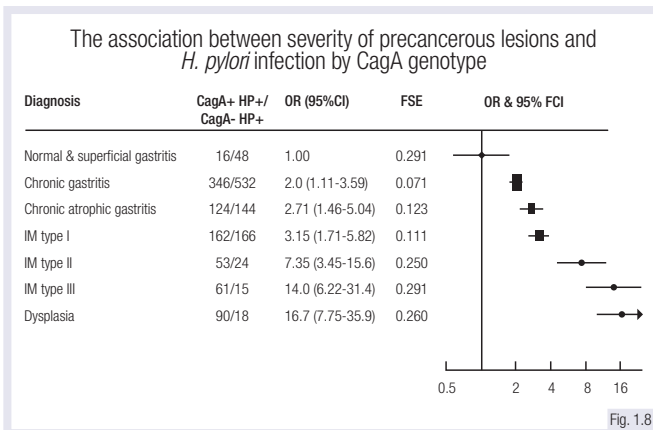*Epidemiology, risk factors and pathogenesis*

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.

Age-standardised incidence rates (world), stomach, both sexes, all ages, 2018

ASR (world) per 100 000
■ ≥11.1 □ <3.8
■ 7.3-11.1 ■ Not applicable
■ 5.0-7.3 □ No data
■ 3.8-5.0

Fig. 1.7

ASR, age-standardised rate.

The association between severity of precancerous lesions and
H. pylori infection by CagA genotype

Diagnosis	CagA+ HP+/ CagA- HP+	OR (95%CI)	FSE	OR & 95% FCI
Normal & superficial gastritis	16/48	1.00	0.291	
Chronic gastritis	346/532	2.0 (1.11-3.59)	0.071	
Chronic atrophic gastritis	124/144	2.71 (1.46-5.04)	0.123	
IM type I	162/166	3.15 (1.71-5.82)	0.111	
IM type II	53/24	7.35 (3.45-15.6)	0.250	
IM type III	61/15	14.0 (6.22-31.4)	0.291	
Dysplasia	90/18	16.7 (7.75-35.9)	0.260	

Fig. 1.8

CagA, cytotoxin-associated gene A; CI, confidence interval; FCI, floating confidence interval; FSE, floating standard error on a log scale; *H. pylori*, *Helicobacter pylori*; HP+, *H. pylori*-positive; IM, intestinal metaplasia; OR, odds ratio.

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

The GC development process undergoes a cascade from normal mucosae, through gastritis to atrophic gastritis, complete intestinal metaplasia (IM), incomplete IM, dysplasia and GC.

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.

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*.

Environmental, dietary and lifestyle factors that are or may be associated with gastric cancer risk		
Factors	**Decreases risk**	**Increases risk**
Infectious factors		*H. pylori* (non-cardia) (virulence factors: GagA, VacA s1, VacA m1, babA2, CagA EPIYA-C) Epstein-Barr virus (EBV)
Tobacco		Smoking
Dietary factors	Green-yellow vegetables Allium vegetables Fruits and citrus fruits Flavonoid Green tea	Salt and salty foods Smoked foods Pickled foods Nitrosamines and nitroso-compounds Alcohol (heavy intake) Red and processed meat (non-cardia) Haem iron (from fresh meat) Grilled meat and fish
Body mass index		Obesity (cardia)
Hormones	Oestrogens (female)	
Anti-inflammatory drugs	Aspirin use	
Occupational exposure		Industrial chemical exposure (rubber, coal mine)
Blood group		Blood group A

H. pylori, *Helicobacter pylori*.
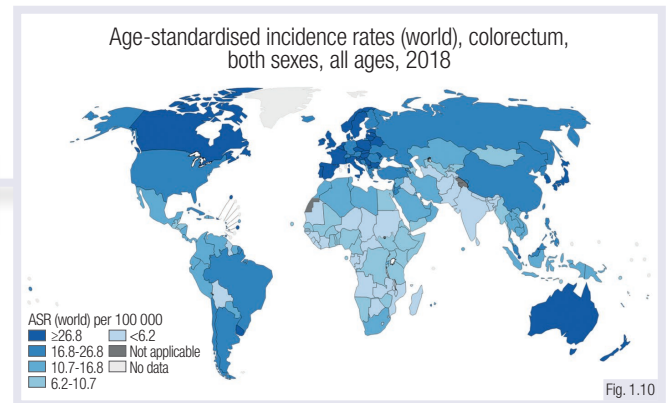
Fig. 1.9

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?

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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.

Age-standardised incidence rates (world), colorectum, both sexes, all ages, 2018

ASR (world) per 100 000
≥26.8 | <6.2
16.8-26.8 | Not applicable
10.7-16.8 | No data
6.2-10.7

Fig. 1.10

ASR, age-standardised rate.

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

IARC, International Agency for Research on Cancer; NSAID, non-steroidal anti-inflammatory drug.

Fig. 1.11

10%-20% of CRCs occur in people with positive family history, with varying risk depending on the number and degree of affected relatives.

About 5%-7% of cases are affected by hereditary conditions. The two major ones are hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP).

Obesity, lack of physical activity and some dietary factors are the major lifestyle factors contributing to CRC risk, but the underlying causative processes are not defined.
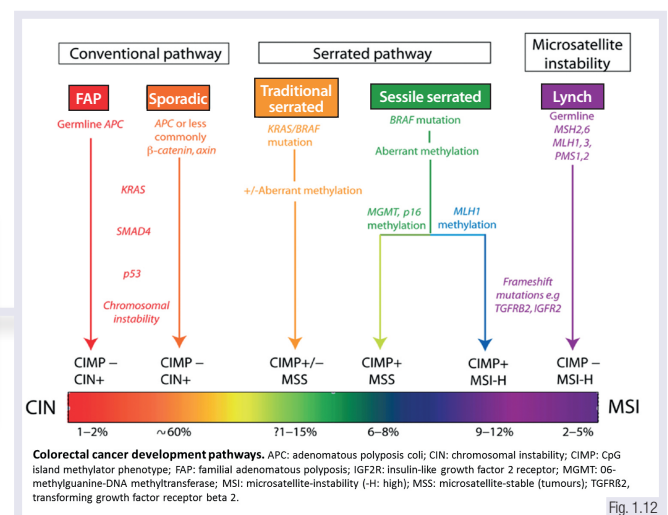
CRC exemplifies stepwise progression as it develops initially as a benign precursor lesion (adenoma), which can progress to an invasive lesion (adenocarcinoma).

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%).

Colorectal cancer development pathways. APC: adenomatous polyposis coli; CIN: chromosomal instability; CIMP: CpG island methylator phenotype; FAP: familial adenomatous polyposis; IGF2R: insulin-like growth factor 2 receptor; MGMT: 06-methylguanine-DNA methyltransferase; MSI: microsatellite-instability (-H: high); MSS: microsatellite-stable (tumours); TGFR82, transforming growth factor receptor beta 2.

Fig. 1.12

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.

Age-standardised (world) incidence and mortality rates of pancreatic cancer

Fig. 1.13

ASR, age-standardised rate.

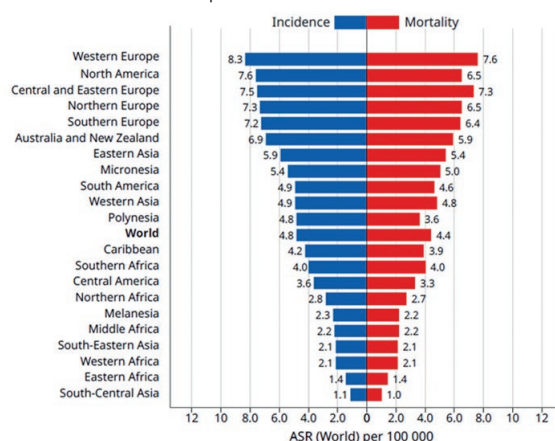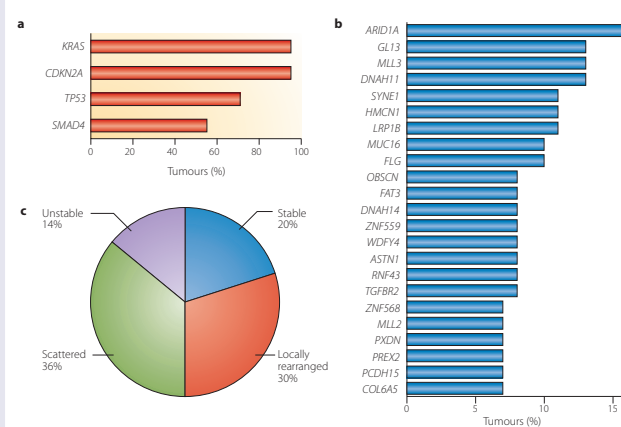| Risk factors associated with pancreatic cancer risk	
Factors	
Tobacco smoking	Risk increases with intensity (cigarettes/day) and duration, and decreases with time since cessation in former smokers
Body fatness	Greater body mass index, waist circumference, adult weight gain
Other diseases	Diabetes (new-onset type 2 diabetes) and chronic inflammatory pancreatitis
Family history and genetic syndromes	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)
Factors with limited evidence of association with risk of pancreatic cancer	
Dietary factors	High consumption of red meat, processed meat, alcohol, foods containing saturated fatty acids, foods and drinks containing fructose
Other	The role of infection with *H. pylori* is the subject of ongoing research

H. pylori, Helicobacter pylori.
Fig. 1.14

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.

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*.

Gene alterations in pancreatic cancer. **(a)** Commonly altered genes; **(b)** less commonly mutated genes; **(c)** pancreatic cancer subtypes proposed based on the number and location of structural rearrangements.
Fig. 1.15

ARID1A, AT-rich interaction domain 1A; CKN2A, cyclin-dependent kinase inhibitor 2A; DNAH11, dynein axonemal heavy chain 11; TGFBR2, transforming growth factor beta receptor 2.

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?

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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

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