

Environmental and lifestyle drivers of early-onset cancer

Received: 30 April 2025

Accepted: 1 April 2026

Published online: 07 May 2026

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Early-onset cancer (EOC) of the oesophagus, stomach, colorectum, biliary tract, liver, pancreas, kidney, prostate, uterine corpus, breast, bone marrow, and head and neck has shown an increasing incidence worldwide. This Review summarizes current evidence for epidemiological and molecular pathological features of rising EOC overall and in each organ-specific cancer type, underscoring not only their shared aetiologies but also their dissimilarities. Although the contributions of enhanced screening, diagnostics and early detection to the rise of EOC are difficult to quantify, a genuine increase in EOC development seems likely in certain EOC types exhibiting mortality increases or aggressive tumoural features compared to later-onset counterparts. Evidence suggests that this trend reflects decades-long influences of environmental, lifestyle, systemic and metabolic factors that begin in early life. Polygenic influences with associated gene–environment interactions on cancer risks appear more pronounced in younger ages. However, identifying specific aetiological factors remains difficult due to prolonged latency, confounding and limited availability of long-term exposure data. Nonetheless, EOC tumour profiling efforts provide pathogenic clues to genomic, epigenomic, microbial and immune contributions. Integrative research frameworks, such as molecular pathological epidemiology, combined with the prospective cohort incident-tumour biobank method, comprehensive biorepositories and artificial intelligence-empowered analytical tools, offer promising opportunities to clarify pathophysiological mechanisms.

Numerous studies, based on various global and regional databases, indicate that cancer across multiple organs increasingly affects young populations^{1–4}. This phenomenon calls for a deeper understanding of the aetiology and pathobiology of EOC.

According to the Global Burden of Disease (GBD) and Global Cancer Observatory (GLOBOCAN) databases, the global rising incidence of EOC has been documented across a broad spectrum of organ systems, including the gastrointestinal system (oesophagus, stomach, colorectum, biliary tract, liver and pancreas), kidney and bone marrow (multiple myeloma), with variable incidence trends across cancer types and countries^{2,3}. The rising incidence has also been observed

in sex-specific cancers, including breast, endometrial and prostate cancers^{2,3}. Across EOC types, unhealthy diet (for example, high in red meat and low in fruits), alcohol drinking and tobacco appear to be major risk factors^{2,3}. The rise of EOC may be in part, but not fully, explained by increased availability of screening tests, with some EOC types also showing increases in disease-specific mortality. A cancer trend analysis across US birth cohorts in 1920–1990 revealed increased incidence of several cancer types in newer generations, finding that the cohort born in 1990 experienced 2–3 times higher age-matched incidence for liver, pancreatic and kidney cancers than the 1955 cohort (a phenomenon known as the ‘birth cohort effect’)^{4–6}.

Table 1 | Possible and putative risk factors for EOC

Cancer type	Possible and putative risk factors ^a
Oesophageal cancer	<ul style="list-style-type: none"> • Obesity, recurrent GERD and smoking for oesophageal adenocarcinoma^{37,38} • Germline variants in apoptosis-related genes (<i>NOS3</i>, <i>BCL2</i>, <i>TNFRSF10A</i>, <i>CASP8</i>) for oesophageal adenocarcinoma⁴¹ • Poor oral hygiene, second-hand tobacco smoke exposure, pest infestation of grain and/or nuts and consumption of hot beverages for oesophageal squamous cell carcinoma³⁹
Stomach cancer	<ul style="list-style-type: none"> • <i>H. pylori</i> infection, alcohol, high sodium diets, smoking and obesity^{3,44,45,193} • <u>Family history of stomach cancer</u> or prostate cancer and <u>germline variants in <i>CDH1</i>, <i>CTNNA1</i> and <i>CTNND1</i></u> (refs. 46–48).
Colorectal cancer	<ul style="list-style-type: none"> • Obesity^{67–70}, sedentary behaviour⁶², <u>metabolic conditions</u> (type 2 diabetes, hyperlipidaemia, metabolic syndrome)^{63,66,67}, dietary factors (red meat⁶⁵, sugary beverages⁷¹, insufficient vitamin D intake⁷²), <u>alcohol</u>^{63–65}, <u>family history of colorectal cancer</u>^{63,75,76} and <u>genetic variants</u>^{76,75–78}
Biliary tract cancer	<ul style="list-style-type: none"> • Biliary cysts/stones, liver cirrhosis, HBV/HCV infections and <u>pancreaticobiliary maljunction</u> for bile duct cancer^{94,194} • Female gender¹⁹⁵, <u>Asian/Latin American ethnicities</u>^{196,197}, cholelithiasis¹⁹⁸, porcelain gallbladder¹⁹⁸, anomalous junction of the pancreatic and biliary ducts¹⁹⁸, chronic bacterial cholangitis, primary sclerosing cholangitis, obesity and genetic variant in <i>PARP1</i> for gallbladder cancer^{197–199} • <u>Pancreaticobiliary maljunction</u> for extrahepatic biliary tract cancer^{94,95}
Hepatocellular carcinoma	<ul style="list-style-type: none"> • <u>Chronic HBV infection</u>, <u>metabolic conditions</u> (MASLD, non-alcoholic steatohepatitis, obesity, diabetes), <u>smoking</u> and family history of hepatocellular carcinoma^{99,103,104} • Germline <i>SPRTN</i> variants¹⁰⁵
Pancreatic cancer	<ul style="list-style-type: none"> • <u>Smoking</u>, <u>obesity</u>, diabetes, tall height, non-O blood group, genetic variants, male sex, Black ethnicity and <u>alcohol</u>^{111,112,115,200}
Kidney cancer	<ul style="list-style-type: none"> • <u>Obesity</u>^{119,120}, family history of renal cell carcinoma¹²¹ and genetic variants¹²²
Prostate cancer	<ul style="list-style-type: none"> • High-fat diet¹²⁶ • Germline mutations in <i>ATM</i>, <i>ATR</i>, <i>BRCA1</i>, <i>BRCA2</i>, <i>BRIP1</i>, <i>CHEK2</i>, <i>ERCC5</i>, <i>FANCA</i>, <i>HOXB13</i>, <i>MRE11</i>, <i>MSH6</i>, <i>PALB2</i>, <i>PMS2</i> and <i>WRN</i>¹³⁰
Endometrial cancer	<ul style="list-style-type: none"> • <u>Obesity</u>^{137–140}, hyper-oestrogenic states¹⁴¹, <u>nulliparity</u>^{137,140}, prolonged duration of menses¹³⁷ and <u>family history of endometrial or any cancer</u>^{140,142,143}
Breast cancer	<ul style="list-style-type: none"> • <u>Hormonal/reproductive factors</u> (early menarche, contraceptive use, nulliparity, higher age at first pregnancy and lack of breastfeeding)^{152–154}, high waist-to-hip ratio²⁰¹, high muscle mass-to-weight ratio²⁰², <u>alcohol</u>^{156,157}, <u>physical inactivity</u>^{158,159}, high fat intake¹⁶⁰, tall height²⁰³, family history of breast cancer²⁰⁴ and <u>genetic variants</u>^{161,162}
Head and neck cancer	<ul style="list-style-type: none"> • Smoking, alcohol, family history of EOC and low consumption of fruits and vegetables¹⁶⁷
Multiple myeloma	<ul style="list-style-type: none"> • <u>High BMI during young adulthood</u>^{173,174}

^aRisk factors supported by multiple studies or a single large study (with a sample size of >500 EOC cases) are underlined.

In this Review, we summarize the current evidence on the incidence, potential risk factors and characteristics of EOC overall and in various organ systems (Tables 1 and 2). There are shared aetiologies as well as dissimilarities across multiple rising EOC types. Although the contributions of enhanced screening, diagnostics and early detection to the rise of EOC are difficult to quantify, a genuine increase in EOC development seems likely in certain EOC types, especially those that have accompanied mortality increases and aggressive tumoural features compared to later-onset counterparts. In general, we use the commonly used age 50 cut-off to define EOC. In women's cancers, menopausal status—typically transitioning around ages 45–55—also provides a biologically based classifier. Importantly, beyond the dichotomies, future studies should consider detailed age assessments based on the 'age-continuum' model to gain better insights into age-related differences^{2,7}.

Diagnosics and risk factors

Diagnostic practice changes

The rise of EOC may be attributable, at least in part, to the increasing availability and diagnostic performance of screening tests. Low-dose computed tomography replaced chest X-ray in some countries as the primary modality for lung cancer screening in the 2010s. For colorectal cancer (CRC), colonoscopy became increasingly common since the late 1990s. However, the rising incidence of EOC of the endometrium, liver (in women), biliary system and colorectum, in which disease-specific mortality has increased^{1,2}, is not fully explained by enhanced screening practices. By contrast, early-onset thyroid, prostate and non-melanoma skin cancers have shown rising incidence in young people without corresponding increases in mortality, underscoring the need to distinguish detection-related age shifts from true disease burden³.

Mortality in young patients is difficult to quantify because disease-specific deaths (for example, of young women with non-advanced

breast cancer) often occur many years after diagnosis. Considerable fractions of thyroid and prostate carcinomas are inconsequential and non-lethal². Widespread use of neck ultrasonography inflated early-onset thyroid cancer incidence through overdiagnosis in South Korea⁸ and likely other countries. Prostate cancer screening based on KLK3 (HGNC:6364; kallikrein-related peptidase 3, also known as prostate-specific antigen (PSA); standardized nomenclature recommended by the expert panel⁹) test has led to overdiagnosis of indolent tumours. A related issue is the overtreatment of pre-invasive neoplasms, such as breast ductal carcinoma in situ, non-invasive papillary urothelial carcinoma and gastrointestinal intramucosal carcinoma. Overtreatment can lead to physical and psychological morbidities.

Birth cohort effect and early-life risk factors

The 'birth cohort effect' phenomenon (Fig. 1)^{4–6} implies that a newer birth cohort exhibits higher EOC incidence at a given age, likely reflecting increases in risk factor exposures over the past several decades. Harmful changes in early-life exposures take 2–4 decades to manifest as an increase in EOC incidence, which will likely continue to increase in the future. In addition, when the current young generations get older, far more of them may develop cancer compared to prior generations.

Numerous studies indicate that carcinogenic processes may start in early life (that is, from the prenatal period to adolescence), extending into young adulthood before cancer becomes clinically evident^{10,11}. Most EOC cases likely arise from interactive influences of environmental, lifestyle, metabolic, genetic and other risk factors starting from early life³. Maternal, prenatal, perinatal and neonatal factors appear to influence cancer risks in later adulthood^{12–14}. Recognizing that disease processes may originate from conception and continue to affect cells and tissues across the entire trajectory of growth is pivotal to a better understanding of EOC.

Table 2 | Clinical and tumour characteristics of EOC compared to later-onset cancer

Cancer type	Clinical characteristics ^a	Tumour characteristics ^a
Oesophageal cancer	<ul style="list-style-type: none"> Advanced disease stages but inconsistent findings on survival for adenocarcinoma^{36,40,205} Single nucleotide polymorphisms in apoptosis-related genes (<i>NOS3</i>, <i>BCL2</i>, <i>TNFRSF10A</i> and <i>CASP8</i>) for adenocarcinoma⁴¹. Multiple oesophageal tumours and concurrent upper aerodigestive tract cancers for squamous cell carcinoma⁴² 	<ul style="list-style-type: none"> Not reported
Stomach cancer	<ul style="list-style-type: none"> Female sex, localization in the gastric body and antrum pylorus^{51–53} Advanced disease stages and comparable survival outcome^{49–53} Epstein–Barr virus infection^{50,54} 	<ul style="list-style-type: none"> Mutations in <i>CDH1</i> and <i>TGFBR1</i> and less frequent <i>RHOA</i> mutation^{55,56} Hypermethylation of the <i>EIF4E</i> promoter²⁰⁶ Frequent genomically stable subtype and less frequent MSI subtype⁵⁰
Colorectal cancer	<ul style="list-style-type: none"> Localization in the distal colon and rectum and advanced disease stages at diagnosis⁹⁰ Inconsistent findings on survival^{207–213} Unique patterns of treatment-related adverse events (increased nausea and vomiting; decreased diarrhoea, fatigue and neutropenia)²¹¹ 	<ul style="list-style-type: none"> Aggressive tumour morphological findings (poor differentiation, signet-ring cell morphology and increased lymphovascular invasion)^{179,80} and differential immune infiltration^{79–81,214} Frequent MSI-high status, infrequent CIMP-high status and few <i>BRAF</i> mutations^{75,76,79,183,215}, observed consistently across most tumour subsites from caecum to rectum²¹⁶ Frequent <i>FBXW7</i> and <i>POLE</i> mutations in metastatic tumours²¹⁷ Frequent <i>TP53</i> and <i>CTNNB1</i> mutations in non-MSI-high cancer and frequent <i>APC</i> and <i>KRAS</i> mutations with infrequent <i>BRAF</i> mutations in MSI-high cancer²¹⁵ <i>LINE-1</i> and global DNA hypomethylation^{182,183,218}, high TMB²¹⁴ and increased DNA repair features²¹⁴ Increased expression of microRNAs (<i>MIR193A</i>, <i>MIR210</i>, <i>MIR513A</i> and <i>MIR628</i>)²¹⁹ High FAP expression in tissues⁸⁵ Colibactin-induced mutational signatures (SBS88 and ID18)^{86,87,220} Differential tumour microbiome, including enrichment for <i>Akkermansia</i>⁸⁸ and <i>Bacteroides</i>⁸⁸
Biliary tract cancer	<ul style="list-style-type: none"> Intrahepatic localization, larger tumours, lymph node positivity and stage IV disease^{96–98} Favourable survival outcome^{96–98} 	<ul style="list-style-type: none"> Frequent fusions involving <i>FGFR2</i> or <i>NIPBL</i> and frequent mutations in <i>BRAF</i> and <i>ATM</i>^{97,98} IFNG and T cell-inflamed transcriptomic signatures⁹⁸
Hepatocellular carcinoma	<ul style="list-style-type: none"> Less cirrhosis and unfavourable survival outcome^{106,107} 	<ul style="list-style-type: none"> HBV DNA integration into chromosome 8q24, leading to overexpression of <i>MYC</i>, <i>PVT1</i> and <i>MIR1204</i> (ref. 106). Mutations in <i>JAK1</i>, <i>BRCA1</i> and <i>HDAC2</i>, amplifications in <i>MDM2</i>, <i>IL7R</i> and <i>TERT</i>, deletions in <i>EP300</i>, <i>CDH1</i> and <i>PALB2</i>, and Hippo signalling pathway¹⁰⁸
Pancreatic cancer	<ul style="list-style-type: none"> Advanced disease stages at diagnosis, high neutrophil-to-lymphocyte ratios and better overall performance at diagnosis^{114,115} Inconsistent findings on survival^{113–115} 	<ul style="list-style-type: none"> Poorly differentiated morphology and perineural invasion¹¹³ Fewer mutations in <i>KRAS</i>, <i>RNF43</i> and <i>SF3B1</i> (refs. 114,116). Enrichment with actionable genomic alterations, including <i>PALB2</i> and <i>BRCA2</i> mutations and MSI-high status^{114,116} Fewer <i>TP53</i> mutations and more frequent <i>MET</i> and <i>NRG1</i> fusions in <i>KRAS</i> wild-type tumours¹¹⁶ Increased infiltration of natural killer cells, CD8⁺ T cells, monocytes and M2 macrophages in tumour microenvironment¹¹⁶
Kidney cancer	<ul style="list-style-type: none"> Non-white ethnicity¹²³ Trend towards favourable 10-year survival outcome after surgery¹²⁴ 	<ul style="list-style-type: none"> Smaller tumour sizes, less advanced stages, lower rates of lymph node and distant metastasis¹²⁴ Non-clear-cell histology¹²²
Prostate cancer	<ul style="list-style-type: none"> Aggressive disease phenotypes and unfavourable survival outcome¹³¹ 	<ul style="list-style-type: none"> High prevalence of <i>TMPRSS2::ERG</i> fusions, kataegis by APOBEC3-driven mutational processes, recurrent duplications of <i>ESRP1</i> and AR-driven transcriptional regulation^{132,133}
Endometrial cancer	<ul style="list-style-type: none"> Favourable survival outcome¹³⁷ 	<ul style="list-style-type: none"> Type I tumour, well differentiated and with concomitant endometrial hyperplasia¹³⁷ Frequent <i>CTNNB1</i> and <i>BRCA2</i> mutations and infrequent <i>FGFR2</i> and <i>PIK3R1</i> mutations^{144,145} DNA methylation alterations in WNT signalling pathway genes¹⁴⁵ Exposome-related mutational signature, characterized by <i>CTNNB1</i> and <i>SIGLEC10</i> mutations¹⁴⁶
Breast cancer	<ul style="list-style-type: none"> Large tumour size, lymph node positivity and poor survival outcome^{163–165} 	<ul style="list-style-type: none"> High histological grade, poor differentiation and lymphovascular invasion^{163–165} Low ESR1 (HGNC:3467; also known as ER) immunohistochemical positivity, <i>ERBB2</i> (HGNC:3430; also known as HER2) overexpression and high MKI67 (HGNC:7107; also known as Ki-67) proliferation indices^{163–165} Low mRNA levels of <i>ESR1</i>, <i>ESR2</i> and <i>PGR</i> (HGNC:8910; also known as PR) and high mRNA levels of <i>ERBB2</i> and <i>EGFR</i>¹⁶³ Frequent somatic alterations in <i>GATA3</i> and <i>ARID1A</i> and less frequent <i>PIK3CA</i> somatic alterations in luminal A cancer¹⁶⁶
Head and neck cancer	<ul style="list-style-type: none"> Localization in the oral tongue and oral cavity^{167,169} Favourable survival outcome¹⁶⁹ 	<ul style="list-style-type: none"> Low EZH2 expression¹⁷⁰ Enriched oxidative stress responses and activation of the MAPK and JAK–STAT pathways, accompanied by increased TAMs, MDSCs and plasma cells¹⁷¹ Vascular mimicry and tertiary lymphoid structures at the invasive front¹⁷¹
Multiple myeloma	<ul style="list-style-type: none"> Inconsistent findings on survival^{175,176} 	<ul style="list-style-type: none"> Light chain subtype¹⁷⁵

^aCharacteristics supported by multiple studies or a single large study (with a sample size of >500 EOC cases) are underlined. AR, androgen receptor; CAF, cancer-associated fibroblast; CIMP, CpG island methylator phenotype; ID, indel; HGNC, Human Genome Organisation Gene Nomenclature Committee; LINE-1, long interspersed nucleotide element-1; MDSC, myeloid-derived suppressor cell; SBS, single base substitution; TAM, tumour-associated macrophage; TMB, tumour mutation burden.

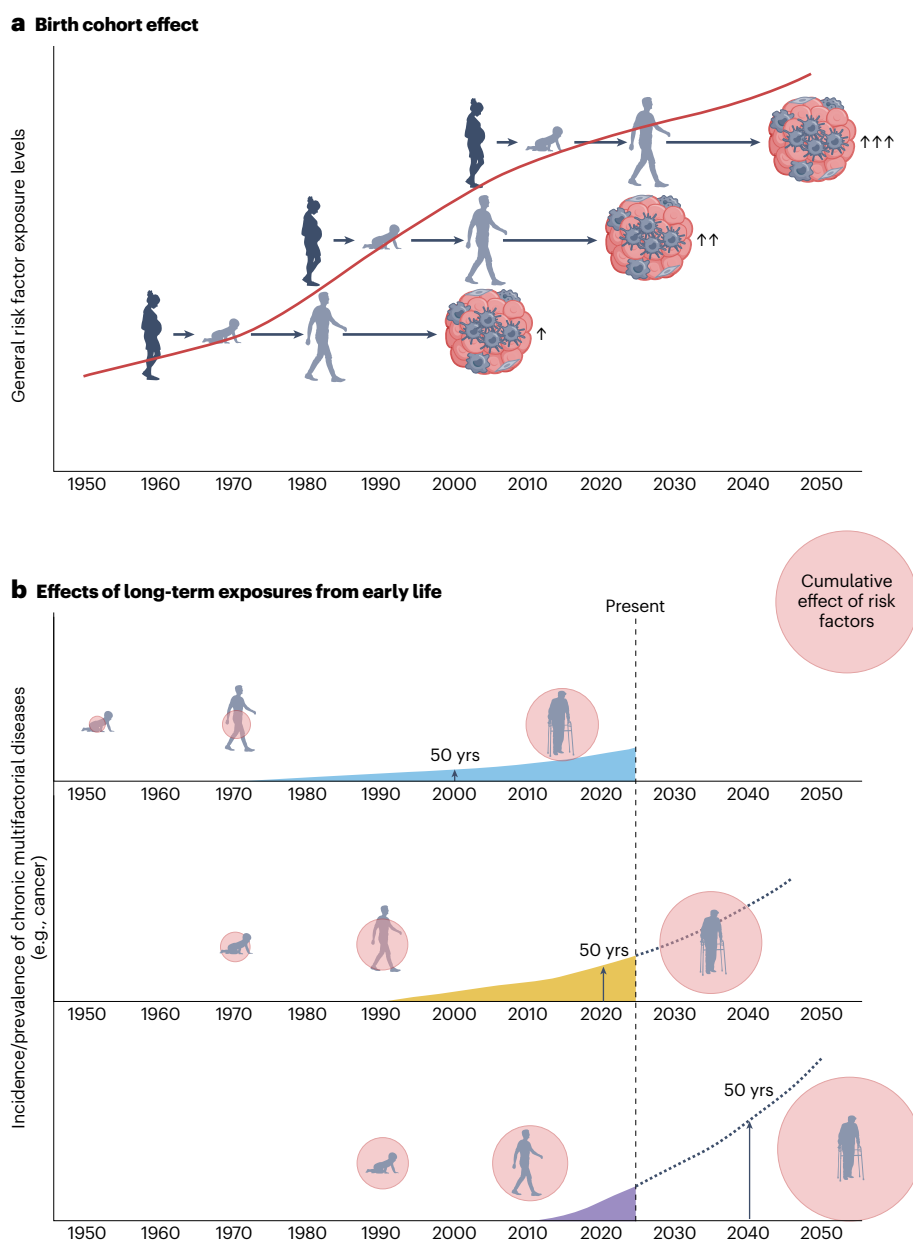


Fig. 1 | Birth cohort effect and increasing incidence of EOC. a, Birth cohort effect is illustrated. With increasing risk factor levels in a population over calendar time, cohorts of individuals born later experience higher EOC incidence at a given age. **b,** With the birth cohort effect, cohorts of individuals born later experience higher incidence of not only EOC at a given age (for example,

40 years) but also later-onset cancer (if there is no prevention effect). The cancer-promoting effect of unfavourable early-life exposures has a latency period of 1–5 decades. It is also possible that we may only recognize the current EOC epidemic as a ‘tip of the iceberg’ that predates a much larger future epidemic of all-age cancers.

Exposome changes

Since the mid-20th century, the exposome that encompasses diet, lifestyle, environment and intracorporeal factors has changed, preceding the surge of EOC incidence starting in the 1990s². Some putative contributing factors—including Western-style diets (characterized by high consumption of sugars, ultra-processed foods, saturated and animal fats, red and processed meats, refined carbohydrates and energy-dense desserts, together with low consumption of vegetables, wholegrains and legumes), alcohol drinking, physical inactivity, sedentary lifestyle, disturbed sleep patterns, bright light at night, ionizing radiation exposure (for example, from radiological imaging) and various chemicals (including food additives, pollutants, pesticides, herbicides, drugs, microplastics and nanoplastics)—might have contributed to the increase in EOC incidence^{2,15,16}. Increased incidence or prevalence of

various health conditions and factors, including obesity, insulin resistance, type 2 diabetes mellitus, inflammatory bowel disease, fatty liver diseases, other metabolic and inflammatory disorders, and reproductive practice changes, might have further contributed to this trend.

The underlying mechanisms of exposure effects seem complex. The westernization of diets has paralleled a notable surge in paediatric and adolescent obesity and type 2 diabetes, which are themselves putative risk factors for EOC¹⁷. Physical inactivity, extended screen time and sleep disturbances might compound metabolic imbalances conducive to oncogenesis¹⁸. Furthermore, alcohol and smoking (inclusive of early-life second-hand smoke) contribute to carcinogenesis^{19,20}. Antibiotics use, which is associated with colorectal neoplasia risk²¹, has increased in many countries²². Antibiotics and other medications may cause intestinal dysbiosis, thereby enhancing pathogenic bacterial effects.

Table 3 | Features of prospective cohort study design compared to case–control study design in EOC research

Prospective cohort study design	Case–control study design
Can prospectively collect long-term time-varying exposure data.	Not designed to obtain reliable long-term exposure data.
Can collect early-life exposure data prospectively if participants enrol at young ages.	Not designed to obtain reliable early-life exposure data.
Can capture a source population that gives rise to cancer cases, thereby reducing selection bias of cancer cases.	Cases have selection bias and may not be close to a random sample from cancer cases in the general background population.
Can reduce measurement errors in long-term exposure data if information is repeatedly obtained during follow-up.	Measurement errors in remote past exposures may be high.
By design, no differential recall bias exists in pre-diagnosis phase exposures in cancer cases versus cancer-free persons.	Differential recall bias in cancer cases versus controls is present.
There is low risk for reverse causation when using long-term pre-diagnosis exposures.	Cancer may influence patients' behaviour and exposure information, which is typically obtained after cancer diagnosis.
Can prospectively collect biospecimens before cancer diagnosis.	Not designed to collect pre-diagnosis biospecimens.
Multiple cancer types can be studied in a single study.	Not designed to study multiple cancer types in a single study. Optimal only for the cancer type to be studied.
Multiple other chronic multifactorial diseases, many of which are cancer risk factors, can be studied in a single study.	Not designed to study multiple other diseases that are cancer risk factors. Optimal only for the cancer type to be studied.
The sample size of cancer cases is determined by cohort size and may be limited for rare cancers and rare subtypes.	Can study rare cancer types and subtypes. The sample size of cancer cases can be large.
Not designed to collect freshly procured tumour tissue specimens.	Can be designed to collect freshly procured tumour tissue specimens.
Long-term follow-up of participants is needed.	No follow-up is required.

The human body is host to a dynamic and complex ecosystem of commensal microorganisms, encompassing bacteria, viruses, fungi and parasites. Numerous studies indicate that these microorganisms may provoke carcinogenesis in the gastrointestinal tract and other organs²³. The microbiota is progressively established from early life and plays a fundamental role in shaping systemic metabolism and immune homeostasis²⁴. Importantly, maternal exposures, including diet, smoking, alcohol consumption and medications, together with early-life feeding practices, exert profound and lasting effects on the infant gut microbiome²⁵. All these exposures may influence the future risk of developing EOC.

While some EOCs arise in the context of well-known familial or monogenic syndromes, they do not account for increasing fractions of EOC cases. Studies have shown that polygenic risk scores using common cancer risk variants identified by genome-wide association studies are more strongly associated with early-onset colorectal cancer (EO-CRC) compared to later-onset CRC, suggesting an enhanced effect of gene–environment interactions on EO-CRC development^{26,27}. Studies using the UK Biobank²⁸ and Sister Study²⁹ showed that both genetic and lifestyle factors influenced EOC risk. Missing genetic contributors, encompassing moderate-penetrance variants and small-effect alleles in known familial cancer-predisposition genes, may further interact with exposures to increase EOC risk.

Study design considerations

A paucity of prospective longitudinal cohort studies has curtailed robust epidemiological investigations. Case–control studies have critical limitations, as exposure and biomarker data are typically collected after cancer diagnosis (Table 3). There exists differential recall bias in exposure information between cases and cancer-free controls. Furthermore, the presence of subclinical cancer might biologically influence systemic conditions, behaviours, anthropometrics and biomarker measures, leading to potential 'reverse causation'. Given the important aetiological roles of early-life factors, confounding of early-life factors must be considered to accurately assess exposure–outcome causal relationships (Fig. 2). Whether the adulthood exposure has a causal effect on EOC development can be examined only by research on both early-life and adulthood factors.

Role of tumour profiling

Cancer is a multifactorial disease caused by transformed neoplastic cells with influences from environmental, systemic and tissue microenvironmental conditions³⁰. Systemic conditions together with genetic, environmental and lifestyle factors create a microenvironmental milieu that provides selective advantages to particular somatic cells or clones to proliferate and become a malignant neoplasm^{31,32}. To gain pathogenic insight, profiling of tumours and their microenvironment can be performed by various techniques, including in situ, bulk-tissue and/or single-cell-based analyses. When EOCs exhibit specific tumour characteristics (especially aggressive features) different from later-onset counterparts, it provides evidence for distinct pathobiologies of EOC, arguing against the hypothesis that early detection is the only cause of the rise of EOC. Furthermore, tumour profiling information can be integrated into large-scale epidemiological research to study the effects of risk factors on tumour cellular and microenvironmental alterations, using the molecular pathological epidemiology approach^{10,33,34}.

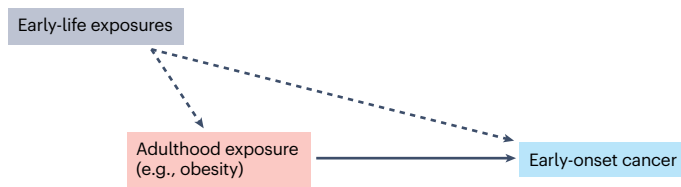
Characteristics of EOC across organs

In certain cancer types, patients with EOC generally exhibit better physical status while EOC tumours generally exhibit greater aggressiveness, compared with later-onset counterparts. This section discusses the features of increasing EOC types (summarized in Tables 1 and 2). Many findings were derived from a single database or study and therefore warrant validation.

Early-onset oesophageal cancer

Despite a global decline in early-onset oesophageal cancer overall, according to the GBD database³⁵, multiple US population-based studies indicate that the incidence is rising, with a notable increase in adenocarcinoma and among women^{4,36}. Oesophageal adenocarcinoma typically develops based on gastroesophageal reflux disease (GERD) and Barrett's metaplasia. Early-onset tumours have been more strongly associated with recurrent GERD and obesity compared to later-onset tumours³⁷. Increasing GERD and obesity prevalence in high-income countries is linked to the rise of early-onset oesophageal adenocarcinoma. The absence of *Helicobacter pylori* infection is associated with oesophageal adenocarcinoma risk, suggesting its potential protective role³⁸.

a An adulthood exposure appears to be a risk factor without analysing a true causal risk factor (confounder) in early life



b Whether an adulthood exposure is a causal risk factor or not can be determined only by studying early-life exposures (confounders)

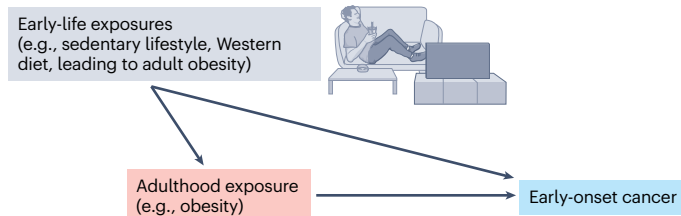


Fig. 2 | Potential bias due to a lack of accounting for influences of early-life exposures. **a**, Most current EOC aetiological studies focus on adulthood factors and may identify apparent risk factors in adulthood (for example, obesity). **b**, Considering multiple pieces of evidence, the aetiological roles of early-life factors need to be examined. In the depicted example, true causal EOC risk factors are exposures (for example, physical inactivity and Western-style diets) in early life spanning from the prenatal period to adolescence that lead to adulthood obesity. In this setting, the aetiological role of adulthood obesity needs to be clarified by longitudinal studies that have accumulated data on early-life exposures/confounders. The adjustment for confounding factors in early life is mandatory for the accurate identification and quantitative assessment of true causal risk factors for EOC.

Early-onset oesophageal squamous cell carcinoma predominates in Eastern Africa and Asia³⁹. Its potential risk factors include poor oral hygiene, tobacco smoke (including second-hand smoke), hot beverages and pest infestation of grain and/or nuts³⁹.

Early-onset oesophageal adenocarcinoma is more frequently diagnosed at advanced stages, although survival outcome correlates are inconclusive^{36,40}. Single nucleotide polymorphisms in apoptosis-related genes (*NOS3*, *BCL2*, *TNFRSF10A* and *CASP8*) are associated with early-onset oesophageal adenocarcinoma⁴¹. Early-onset oesophageal squamous cell carcinoma is characterized by a higher prevalence of multiple oesophageal tumours and concurrent upper aerodigestive tract cancers compared to its later-onset counterpart⁴².

Early-onset stomach cancer

Stomach cancer is classified into cardia (upper stomach) and non-cardia (middle and distal stomach) subtypes. Non-cardia stomach cancer is strongly associated with *H. pylori* infection and is prevalent in Eastern and Central Asia and Eastern Europe, whereas cardia cancer, associated with obesity, is more common in North America and Western Europe. Although the global incidence of stomach cancer has declined over the past 50 years, likely due to *H. pylori* treatment, the Cancer Incidence in Five Continents data suggest that the incidence of early-onset stomach cancer increased in various countries (including Belarus, Chile, the Netherlands, Canada and the United Kingdom) with a less pronounced pattern among women⁴³.

Early-onset stomach cancer has distinct risk factors and genetic predispositions. While *H. pylori* infection remains a substantial risk factor, its prevalence has declined in developed countries⁴³. Changes in lifestyle factors, including alcohol consumption, high sodium diets, smoking and obesity, may play roles in early-onset stomach cancer^{3,44,45}. A family history of stomach or prostate cancer also increases the risk,

with germline variants in *CDHI*, *CTNNA1* and *CTNND1* conferring familial cancer risk^{46–48}.

Early-onset stomach cancer is associated with women, non-cardia localization, advanced disease stages and poorly differentiated and Lauren diffuse-type morphology, including signet-ring cell components, with survival outcomes comparable to its later-onset counterpart^{49–53}. Epstein–Barr virus infection has been implicated in a subset of early-onset cases^{50,54}. Early-onset diffuse-type stomach cancer has been associated with *CDHI* and *TGFBR1* mutations and fewer *RHOA* mutations compared to later-onset counterparts^{55,56}. Early-onset stomach cancer is associated with genomically stable non-microsatellite instability (MSI)-high status⁵⁰.

Early-onset CRC

While CRC incidence has stabilized or even declined among older adults in high-income countries⁵⁷, multiple global databases indicate that the incidence of EO-CRC has increased, especially in North America, Europe and Oceania^{1–3,6}. The increasing incidence of early-onset rectal cancer is more pronounced than early-onset colon cancer in the United States⁵⁸, although a similar pattern has not been observed in many countries⁵⁹. In the United States, all-age CRC incidence among individuals born in the late 19th and early 20th centuries began increasing in the 1950s, whereas EO-CRC incidence among those born in the mid-20th century began to increase in the early 1990s^{4–6}. These age-related trends were also documented in Oceania^{5,6}.

The modifiable risk factors for EO-CRC include physical inactivity^{60,61}, sedentary behaviour⁶² and alcohol^{63–65}, as well as adverse metabolic conditions (including obesity, type 2 diabetes, hyperlipidaemia, hyperglycaemia and metabolic syndrome)^{63,66–70}. Other putative risk factors include dietary and nutritional factors such as sugary beverages⁷¹, red meat⁶⁵, vitamin D insufficiency⁷² and hyperinsulinaemia-associated dietary and lifestyle patterns⁷³. Maternal obesity¹⁴ and being breastfed in infancy⁷⁴ have been associated with increased incidence of CRC, suggesting the carcinogenic role of in utero and early-life exposures. Many of these factors are characteristics of a westernized lifestyle.

While CRC family history is associated with EO-CRC, only a fraction of patients with EO-CRC have hereditary cancer syndromes. Studies showed that 16–20% of patients with EO-CRC carried pathogenic germline mutations, with 5–8% having Lynch syndrome and 5% having polyposis syndromes^{75,76}. The aetiological role of common genetic variants in EO-CRC has been increasingly recognized^{75–77}. A polygenic CRC risk score is associated more strongly with EO-CRC than with later-onset CRC⁷⁷. Susceptibility loci for EO-CRC appear related to chromatin assembly and DNA replication pathways⁷⁸. The top EO-CRC-specific variant, *rs12794623*, might drive cell proliferation by allele-specific *POLA2* overexpression⁷⁸. Recent genomic studies suggest the pathogenic contributions of education level, body size, alcohol, insulin signalling, and immune and infection-related pathways in EO-CRC²⁶.

Clinicopathological features associated with EO-CRC, compared with its later-onset counterpart, include distal colorectal localization, advanced disease stage, poor differentiation, signet-ring-cell histology and distinct molecular features, including infrequent *BRAF* mutations, long interspersed nucleotide element-1 (LINE-1) hypomethylation and little lymphocytic reaction (reviewed in refs. 2,79). Because patients with Lynch syndrome often present with early-onset MSI-high/mismatch repair (MMR)-deficient CRCs, data analyses limited to non-MSI-high/MMR-proficient tumours are crucial to examine the EO-CRC features. EO-CRC is associated with an immunosuppressed microenvironment characterized by fewer tumour-infiltrating lymphocytes, less T cell clonal expansion and hypovascularity of CD34⁺LAMBI⁺ vessels^{80–84}. Spatial transcriptomic and proteomic profiling revealed overexpression of FAP (HGNC:3590; fibroblast activation protein- α) in tissues of EO-CRC⁸⁵. Growing evidence implicates the role of specific microorganisms (such as colibactin-producing *pks*⁺ *Escherichia*

coli, *Akkermansia*, *Bacteroides* and *Flavonifractor plautii*) in EO-CRC pathogenesis^{86–92}.

Early-onset biliary tract cancer

Biliary tract cancer originates from the epithelial cells of the intrahepatic, perihilar or extrahepatic bile ducts or the gallbladder. The incidence of gallbladder and extrahepatic bile duct cancers is rising across all age groups, with a more rapid increase in younger populations⁴. Early-onset intrahepatic cholangiocarcinoma has increased in women while remaining stable in men⁴. According to the GBD database, the increase in early-onset cases was pronounced in countries with middle to low sociodemographic indices⁹³.

Pancreaticobiliary maljunction is frequently observed in early-onset biliary tract cancers, with higher prevalence in distal cholangiocarcinoma (18.5%) and gallbladder carcinoma (19.3%) compared to intrahepatic or perihilar cholangiocarcinoma (4.4%)⁹⁴, suggesting a potential aetiological role in distal cholangiocarcinoma and gallbladder carcinoma. The minor allele G of the *PARP1* rs1136410 (A/G) single nucleotide polymorphism has been linked to gallbladder carcinogenesis and an earlier disease onset⁹⁵.

Clinically, early-onset biliary tract cancer is characterized by intrahepatic localization, larger tumours, lymph node positivity and stage IV disease, yet shows better survival outcomes^{96–98}. Molecularly, early-onset biliary tract cancer shows frequent fusions involving *FGFR2* or *NIPBL*, along with mutations in *BRAF* and *ATM*, and pronounced *IFNG* and T cell-inflamed transcriptomic signatures^{97,98}. The improved survival in younger patients is potentially influenced by the higher prevalence of *FGFR2* fusion (15.7% versus 5.9%) compared to later-onset cases⁹⁸.

Early-onset HCC

According to the GBD database, the incidence of early-onset liver cancer is increasing, particularly in East Asia, with hepatocellular carcinoma (HCC) being the most common type⁹⁹. The global prevalence of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), as established risk factors for HCC, has been declining due to vaccination and direct-acting antivirals, respectively (except for HCV in Eastern Europe)^{100,101}. Other risk factors include alcohol consumption, type 2 diabetes, obesity, metabolic dysfunction-associated steatotic liver disease (MASLD) and smoking¹⁰². Early-onset HCC cases have a lower prevalence of cirrhosis than later-onset cases. Chronic HBV infection plays a key role in early-onset HCC development, with smoking and HCC family history further amplifying this risk^{103,104}. Metabolic conditions, including MASLD, obesity and diabetes, are increasingly recognized as key contributors to the global increase in early-onset HCC, especially when coupled with HBV infection⁹⁹. Genetic predisposition is evident in early-onset HCC, with germline variants in *SPRTN* (related to sustained DNA replication stress) linked to familial cases¹⁰⁵.

Early-onset HCC typically presents with less cirrhosis and carries a poor prognosis compared to its later-onset counterpart^{106,107}. In early-onset HCC associated with HBV, viral DNA is typically integrated into specific genomic regions, such as the 8q24 locus between *MYC* and *PVT1*, potentially leading to the overexpression of *MYC*, *PVT1* and *MIR1204* for carcinogenesis¹⁰⁶. Early-onset HCC exhibits specific genetic alterations, including mutations in *JAK1*, *BRCA1* and *HDAC2*, amplifications of *MDM2*, *IL7R* and *TERT*, deletions of *EP300*, *CDHI* and *PALB2* (ref. 108) and hippo signalling pathway alterations¹⁰⁸.

Early-onset pancreatic cancer

Multiple datasets indicate that the incidence of early-onset pancreatic cancer has increased^{3,109,110}, particularly in high-income countries (based on data from the GBD database)³. In US-based prospective cohorts, smoking, obesity, diabetes, tall height and non-O blood group were more strongly associated with early-onset pancreatic cancer risk than later-onset cancer risk¹¹¹. Polygenic risk scores, male sex, Black

ethnicity and alcohol drinking were associated with early-onset pancreatic cancer^{111,112}.

Early-onset pancreatic cancer often presents with poorly differentiated morphology and perineural invasion, although their prognostic role remains uncertain^{113–115}. Compared to its later-onset counterpart, early-onset pancreatic cancer is inversely associated with mutations in *KRAS*, *RNF43* and *SF3B1* and positively with MSI-high/MMR-deficient status and actionable alterations in *BRCA2* and *PALB2* (ref. 116). *KRAS* wild-type early-onset pancreatic cancer is associated positively with *MET* fusions and *NRG1* fusions and inversely with *TP53* mutations and *BRAF* fusions¹¹⁶. Transcriptomic analyses indicate a distinct tumour microenvironment in early-onset pancreatic cancer, characterized by increased infiltration of natural killer cells, CD8⁺ T cells, monocytes and M2 macrophages¹¹⁶.

Early-onset kidney cancer

Kidney cancer includes several subtypes, with renal cell carcinoma (RCC) being the most prevalent. Over half of RCCs are detected incidentally on imaging studies performed for unrelated indications¹¹⁷, potentially resulting in the rising incidence observed in young populations. According to the GBD database, early-onset kidney cancer has increased, particularly in countries with high sociodemographic indices¹¹⁸. Obesity is a key risk factor, with increasing obesity rates correlating with rising incidence of early-onset kidney cancer globally¹¹⁹. A population-based cohort study suggested the role of adolescent obesity in the aetiology of RCC¹²⁰. RCC family history is another risk factor for early-onset RCC¹²¹. Genetic predisposition contributes to early-onset RCC, with germline pathogenic or likely pathogenic variants identified in 18% of cases, including mutations in RCC-associated genes (*FH*, *VHL* and *MET*) and DNA repair genes (*BRCA1*, *BRCA2*, *ATM* and *CHEK2*)¹²².

Compared to the later-onset counterpart, early-onset RCC has been associated with Black, Hispanic and Asian populations¹²³, smaller tumour sizes, less advanced stages, favourable survival¹²⁴, non-clear-cell histology (including unclassified RCC, chromophobe RCC and papillary RCC), *FH*-deficient RCC and translocation-associated RCC¹²².

Early-onset prostate cancer

According to the GBD database, the incidence of early-onset prostate cancer has shown a notable increase globally from 1990 to 2021, particularly in countries such as Vietnam, Saudi Arabia and Jordan that have recently increased the use of KLK3 (PSA)-based screening¹²⁵. The introduction of KLK3-based screening in the United States in the 1990s substantially increased detection, making it difficult to determine how much of the observed increase reflects a genuine incidence increase.

Potential risk factors for early-onset prostate cancer include dietary and reproductive factors. A high-fat diet has been implicated as a potential contributor¹²⁶. Additionally, men achieving fatherhood through assisted reproduction, particularly via intra-cytoplasmic sperm injection, may face a higher risk¹²⁷. Genetic factors are a substantial contributor, with an estimated heritability of 58%¹²⁸. The risk of early-onset prostate cancer increases with a greater number of affected first-degree relatives with prostate cancer, particularly when those relatives are diagnosed at a younger age¹²⁹. Germline mutations in *BRCA1*, *BRCA2*, *ATM*, *CHEK2* and other DNA repair genes, as well as *HOXB13*, are frequently identified in Black people with early-onset prostate cancer¹³⁰.

Compared to its later-onset counterpart, early-onset prostate cancer often presents with more aggressive phenotypes, including high Gleason scores and unfavourable survival¹³¹. Early-onset prostate cancer has been associated with *TMPRSS2::ERG* fusions, APOBEC3-driven mutational signature that might contribute to mutation clusters manifested as kataegis, and recurrent duplications of *ESRPI* that are linked to aggressive tumour behaviour and high Gleason scores^{132,133}. Additionally, chromatin breakpoints enriched near AR (HGNC:644;

Table 4 | The American Cancer Society recommendations for cancer screening for individuals under 50 years

Cancer type	Sex, age group	Recommendation
Breast cancer ¹⁸⁸	Women, 40–44 years	Mammogram (yearly, optional)
	Women (average risk), 45–54 years	Mammogram (yearly)
	Women (high risk ^a), 45–54 years	Mammogram and MRI (yearly)
Cervical cancer ¹⁸⁹	Women, 25 years	Start cancer screening
	Women, 25–65 years	Primary HPV test (every 5 years) Alternatively, HPV and Pap tests (every 5 years) or Pap test (every 3 years)
Colorectal cancer ¹⁹⁰	Women/men (average risk ^b), 45 years	Start screening with a stool-based test (faecal immunochemical test, yearly; highly sensitive guaiac-based faecal occult blood test, yearly; or multi-target stool DNA test, every 3 years) or a structural examination (for example, colonoscopy, every 10 years; CT colonography, every 5 years; or flexible sigmoidoscopy, every 5 years)
Endometrial cancer ¹⁹¹	Postmenopausal women	Education about cancer risk and symptoms
	Women with Lynch syndrome, by 35 years	Start endometrial biopsy (yearly)
Prostate cancer ¹⁹²	Men (very high risk ^c), 40 years	Consider screening with serum KLK3 protein (also known as PSA) ^d plus an optional digital rectal examination
	Men (high risk ^d), 45 years	

^aWomen with genetic predispositions or a history of radiation therapy to the chest. ^bIndividuals without a history of adenomatous polyps or colorectal cancer and an increased risk for colorectal cancer due to a family history of colorectal cancer, a confirmed or suspected hereditary colorectal cancer syndrome (such as familial adenomatous polyposis or Lynch syndrome), a history of abdominal or pelvic radiation therapy or a history of inflammatory bowel disease. ^cMen with two or more first-degree relatives diagnosed with prostate cancer before the age of 65 years. ^dBlack men and men with a first-degree relative diagnosed with prostate cancer before the age of 65 years. ^eThe nomenclature of genes and gene products follows the recommendation by an expert panel^e. CT, computed tomography; MRI, magnetic resonance imaging.

androgen receptor)-binding sites suggest an association with AR-driven transcriptional regulation¹³².

Early-onset endometrial cancer

Endometrial cancer is generally classified into types I and II. Type I tumours, typically low-grade endometrioid carcinomas, are primarily driven by unopposed oestrogen stimulation and constitute 60–80% of cases, whereas type II tumours, comprising high-grade endometrioid, serous and clear cell carcinomas, are generally oestrogen independent. The incidence of endometrial cancer, especially type I tumours, has been increasing among premenopausal women^{134,135}. Globally, the incidence of early-onset cases has increased, with exceptions in some countries (such as Denmark, the Czech Republic and the Netherlands) based on the Cancer Incidence in Five Continents data¹³⁶.

Key risk factors for early-onset endometrial cancer include obesity^{137–140}, hyper-oestrogenic states¹⁴¹, nulliparity^{137,140}, prolonged duration of menses¹³⁷ and a family history of reproductive organ or any cancers^{140,142,143}.

Premenopausal individuals with endometrial cancer exhibit better survival outcomes compared to their postmenopausal counterparts¹³⁷. Pathologically, early-onset endometrial cancer is characterized by type I and well-differentiated tumours and frequent concomitant endometrial hyperplasia¹³⁷. Compared to its later-onset counterpart, early-onset non-hypermethylated endometrial cancer is associated with a lower tumour mutational burden, higher frequencies of *CTNNB1* and *BRCA2* mutations, DNA methylation alterations in WNT signalling pathway genes and lower frequencies of *FGFR2* and *PIK3R1* mutations^{144,145}. A multi-omics study revealed an enrichment of exposome-related mutational signature, characterized by *CTNNB1* and *SIGLEC10* mutations, in early-onset endometrioid carcinoma¹⁴⁶.

Early-onset or premenopausal breast cancer

Multiple cohort studies suggest that the effects of potential risk factors on breast cancer risk may differ by menopausal status. Body mass index (BMI) has been associated inversely with breast cancer risk in premenopausal women but positively in postmenopausal women^{147,148}. According to the GLOBOCAN database, the global incidence of premenopausal breast cancer has been steadily increasing, with higher mortality in African countries¹⁴⁹. Whereas enhanced imaging and/or screening has improved early detection, this may not fully account for the rise^{150,151}.

Early menarche, contraceptive use, nulliparity, older age at first pregnancy and lack of breastfeeding are associated with premenopausal breast cancer risk^{152–154}, suggesting that declining fertility rates and delayed childbearing contribute to its rising incidence. High serum LEP (HGNC:6553; leptin) levels and obesity were associated with an increased risk of luminal A and triple-negative breast cancer subtypes in Black women under 45 years¹⁵⁵. Lifestyle risk factors for premenopausal breast cancer include alcohol consumption^{156,157}, physical inactivity^{158,159} and high fat intake¹⁶⁰. Data from the Surveillance, Epidemiology, and End Results (SEER) Cancer Registry showed that binge drinking was associated with early-onset luminal A and luminal B breast cancer types in women under 40 years¹⁵⁷. High-penetrance variants in *BRCA1* and *BRCA2* are the most common genetic risk factors, accounting for up to 40% of familial breast cancer¹⁶¹. Approximately 10% of breast cancers diagnosed under 40 years of age involve *BRCA1* or *BRCA2* germline mutations, whereas *TP53* and *PTEN* germline mutations appear in 1–7% and <1% of breast cancer cases under age 40, respectively^{161,162}. Variants in additional high-penetrance-variant-carrying genes, including *PALB2*, *STK11* and *CDH1*, may further elevate risk, particularly in young individuals^{161,162}.

Early-onset breast cancer is characterized by larger tumour size, higher rates of lymph node metastasis, higher histological grade, lower tumour differentiation, lymphovascular invasion and shorter survivals, compared to later-onset breast cancer^{163–165}. Molecularly, early-onset breast cancer is associated with lower *ESR1* (HGNC:3467; also known as ER) immunohistochemical positivity, more frequent *ERBB2* (HGNC:3430; also known as HER2) overexpression and higher *MKI67* (HGNC:7107; also known as Ki-67) proliferation indices^{163–165}. Compared to tumours identified at age ≥ 65 , tumours identified at age ≤ 45 were characterized by lower expression of *ESR1*, *ESR2* and *PGR* (HGNC:8910; also known as PR) and higher expression of *ERBB2* and *EGFR*¹⁶³. Additionally, luminal A tumours in women under 35 years exhibited more frequent somatic alterations in *GATA3* and *ARID1A* but showed less frequent somatic alterations in *PIK3CA* compared to those in women over 45 years¹⁶⁶.

Early-onset head and neck cancer

Although head and neck cancer typically affects individuals over 60 years, there is a rising incidence among young individuals³. According to the GBD database, early-onset nasopharyngeal cancer exhibited the fastest-growing trend among the cancer types³.

Risk factors for early-onset head and neck cancer include smoking, alcohol intake, EOC family history and lower fruit and vegetable consumption¹⁶⁷. The lower proportion of cases attributable to smoking and alcohol among younger adults may highlight additional risk factors¹⁶⁷. Recent sexual behavioural changes might have increased the prevalence of oral human papillomavirus (HPV) infection, potentially influencing the rise in early-onset oropharynx cancer¹⁶⁸.

Early-onset head and neck cancer predominantly affects the tongue and oral cavity^{167,169}. Although early-onset head and neck cancer generally exhibits favourable clinical outcomes, early-onset hypopharynx cancer has been associated with poorer survival than those in other locations¹⁶⁹.

EZH2 (HGNC:3527) expression may be generally low in early-onset head and neck cancer¹⁷⁰, potentially contributing to its less aggressive tumour behaviour. In early-onset tongue cancer, transcriptomic profiling showed enriched oxidative stress responses and activation of the MAPK and JAK–STAT pathways, accompanied by increased tumour-associated macrophages, myeloid-derived suppressor cells and plasma cells¹⁷¹.

Early-onset multiple myeloma

Early-onset multiple myeloma is increasingly reported across several countries^{1–3}. According to the GBD database, the burden of early-onset multiple myeloma was higher in men and in countries with high sociodemographic indices¹⁷². While this increase is partly attributed to more widespread screening for monoclonal gammopathy, evidence suggests that the rise in early-onset multiple myeloma may be a genuine upward trend.

Although specific risk factors for early-onset multiple myeloma are still unclear, BMI during young adulthood may have a stronger effect than BMI later in life^{173,174}.

In a systematic review, early-onset multiple myeloma accounts for approximately 10% of all multiple myeloma cases¹⁷⁵ and has been associated with earlier-stage disease and the light chain subtype, which may contribute to their favourable survival association¹⁷⁵. Another study found no significant differences in clinical characteristics, such as renal involvement, serum lactate dehydrogenase levels or overall survival¹⁷⁶.

Future directions

Coordinated aetiological research involving biobanking, collaboration and technological advancements is needed. Existing prospective cohort studies can be utilized for investigating EOC aetiology^{177,178}. Those include, but are not limited to, the All of Us Research Program, Avon Longitudinal Study of Parents and Children, 1958 National Child Development Study, 1970 British Cohort Study, Growing Up Today Study I and II, Nurses' Health Study 1–3, LifeCycle Project (EU Child Cohort Network), Japan Environmental and Children's Study, Millennium Cohort Study, National Longitudinal Study of Adolescent to Adult Health, Next Steps, Child Health and Development Studies and the UK Biobank.

Establishing comprehensive biobanks that integrate high-quality biospecimens and molecular data with detailed long-term exposure histories is crucial for advancing beyond epidemiological associations. Such integrative resources underpin molecular pathological epidemiology, a transdisciplinary research framework that leverages tumour molecular signatures to infer carcinogenic mechanisms^{30,34}. Incorporating biospecimens (blood, urine, stool, saliva, sputum, placenta and umbilical cord tissues) collected early in life can further enhance aetiological research. Longitudinal biobanking with sequential collections of biospecimens can also illuminate long-term pathophysiological alterations and potential points of intervention to prevent malignant transformation.

Integrative biobank research can contribute to a better understanding of EOC aetiologies, using EOC-associated tumour

biomarkers and new evidence synthesis methods¹⁷⁹. Analyses using the prospective cohort incident-tumour biobank method (PCIBM)¹⁸⁰ linked long-term folate deficiency and alcohol intake with increased incidence of all-age CRC with tumour LINE-1 hypomethylation¹⁸¹, which is a feature of EO-CRC^{182,183}. Alcohol has been linked to EO-CRC risk in Mendelian randomization research²⁶. Tumour LINE-1 hypomethylated CRC incidence has also been linked to individuals with CRC family history (most of whom were not individuals with familial cancer syndrome)¹⁸⁴, which is consistent with the importance of polygenic influences on EO-CRC risk^{26,77}. Taken together, long-term alcohol consumption and folate deficiency may increase EO-CRC incidence via epigenomic changes.

Various studies have shown the immunosuppressive tumour microenvironment as a feature of EO-CRC^{80–83}. A PCIBM-based study linked long-term inflammatory diets with increased incidence of immunosuppressed CRC¹⁸⁵, while long-term aspirin (anti-inflammatory drug) use has been associated with decreased incidence of immunosuppressed CRC¹⁸⁶. Taken together, long-term systemic inflammation may increase EO-CRC incidence via immunosuppressive effects on the tumour microenvironment.

Another PCIBM-based study linked long-term Western diets with increased incidence of CRC having colibactin-producing *pks*⁺ *Escherichia coli*¹⁸⁷. Colibactin can cause specific mutational signatures (SBS88 and ID18), which are commonly observed in EO-CRC^{86,87}. High glycaemic index, which is linked to Western diets, is associated with EO-CRC by Mendelian randomization research²⁶. Taken together, long-term Western diets may increase EO-CRC incidence via colibactin's mutagenic effect.

Various organizations, including the American Cancer Society (Table 4), have developed screening programmes aimed at detecting various types of EOC^{188–192}. Cost-effectiveness should be considered as well as controversies on when and how screening should be performed. Given the increased biological aggressiveness of EOC compared to later-onset cancer in certain organs, the implementation of screening programmes that can identify EOC at a curable stage, especially for high-risk individuals, may be considered. The existing guidelines should be re-evaluated based on the up-to-date data on the global rise in EOC incidence. Advances in biomarkers and imaging technologies should be leveraged to improve screening efficacy.

Conclusions

The rising incidence of EOC reflects broader shifts in global health, potentially heralding a larger burden of cancer across wide generations. Long-latency exposure effects and the complex interplay of genetic and environmental factors represent key challenges in aetiological research. To address these, cross-disciplinary collaborations, leveraging existing cohorts of young individuals and advanced integrative research frameworks, are essential. By investing in long-term, information-rich biobanks and harnessing new technologies, including artificial intelligence, to integrate diverse datasets, we can accelerate discoveries in EOC research.

Data availability

No datasets were generated or analysed in this article.

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Acknowledgements

This work was supported by the American Cancer Society Clinical Research Professor Award (CRP-24-1185864-01-PROF to S.O.)

Author contributions

T.H. and K.I. contributed equally as co-first authors. T.U. and S.O. contributed equally as co-last authors. All authors contributed to drafting, reviewing and revising the manuscript, and approved the final version of the manuscript. T.H., K.I. and S.O. are responsible for the overall content as guarantors.

Competing interests

S.O. served as a consultant for Sanofi Pasteur on unrelated subjects. The other authors declare no competing interests.

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Peer review information *Nature Health* thanks Xue Li and the other, anonymous, reviewer(s) for their contribution to their peer review of this work. Primary Handling Editor: Ben Johnson, in collaboration with the *Nature Health* team.

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