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Early-Onset Gastrointestinal Cancers
A Review

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IMPORTANCE Early-onset gastrointestinal (GI) cancer is typically defined as GI cancer diagnosed in individuals younger than 50 years. The incidence of early-onset GI cancer is rising globally, and early-onset GI cancers represent the most rapidly increasing early-onset cancer in the US.

OBSERVATIONS Worldwide, among early-onset GI cancers reported in 2022, colorectal cancer (CRC) was the most common (54.3%; 184 709 cases), followed by gastric cancer (23.8%; 80 885 cases), esophageal cancer (13.2%; 45 056 cases), and pancreatic cancer (8.6%; 29 402 cases). In the US, among early-onset GI cancers reported in 2022, 20 805 individuals were diagnosed with early-onset CRC, 2689 with early-onset gastric, 2657 with early-onset pancreatic, and 875 with early-onset esophageal cancer. Most early-onset GI cancers are associated with modifiable risk factors including obesity, poor-quality diet (eg, sugar-sweetened beverages, ultraprocessed foods), sedentary lifestyle, cigarette smoking, and alcohol consumption. Nonmodifiable risk factors include family history, hereditary syndromes (eg, Lynch syndrome), and inflammatory bowel disease for patients with early-onset CRC. Approximately 15% to 30% of early-onset GI cancers have pathogenic germline variants in genes such as DNA mismatch repair genes and *BRCA1/2*. All patients with early-onset GI cancers should undergo germline and somatic genetic testing to guide treatment, screen for other cancers (eg, endometrial cancer in Lynch syndrome), and assess familial risk. Treatment for early-onset GI cancers are similar to later-onset GI cancers and may include chemotherapy, surgery, radiation, and therapies such as poly–adenosine diphosphate ribose polymerase inhibitors for *BRCA*-associated pancreatic cancer. Compared with GI cancers diagnosed after age 50 years, patients with early-onset GI cancers typically receive more treatments but often have similar or shorter survival. Specialized centers and multidisciplinary teams can support patients with challenges around fertility preservation, parenting with cancer, financial difficulty, and psychosocial distress. Currently, screening is not recommended for most early-onset GI cancers, although in the US, screening for CRC is recommended for average-risk individuals starting at age 45 years. High-risk individuals (eg, those with Lynch syndrome, a first-degree relative with CRC, or advanced colorectal adenoma) should begin CRC screening earlier, at an age determined by the specific risk factor.

CONCLUSIONS AND RELEVANCE Early-onset GI cancers, typically defined as cancer diagnosed in individuals younger than 50 years, are among the largest subset of early-onset cancers globally. Treatment is similar to later-onset GI cancers and typically involves a combination of chemotherapy, surgery, and radiation, depending on the cancer type and stage. The prognosis for patients with early-onset GI cancers is similar to or worse than that for patients with later-onset GI cancers, highlighting the need for improved methods of prevention and early detection.

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Early-onset gastrointestinal (GI) cancers are GI cancers diagnosed in adults younger than 50 years.[1] Worldwide, among early-onset GI cancers reported in 2022, colorectal cancer (CRC) was the most common (54.3%; 184 709 cases), followed by gastric cancer (23.8%; 80 885 cases), esophageal cancer (13.2%; 45 056 cases), and pancreatic cancer (8.6%; 29 402 cases). In the US, among early-onset GI cancers reported in 2022, 20 805 individuals were diagnosed with early-onset CRC, 2689 with early-onset gastric, 2657 with early-onset pancreatic, and 875 with early-onset esophageal cancer.[2,3] From 2010 to 2019, the age-standardized incidence rate of early-onset GI cancers in the US increased from 11.49 to 13.65 per 100 000 population, corresponding to an annual percentage change (APC) of 2.16% (95% CI, 1.66%-2.67%; $P < .001$) and representing the most rapidly rising type of early-onset cancer.[4] The increasing incidence of early-onset colorectal cancer (CRC) led the US Preventive Services Task Force (USPSTF) to lower the recommended age for initiating CRC screening from 50 years to 45 years for average-risk individuals (described in the Screening section of the text for early-onset CRC) in 2021.[5] The increase in early-onset GI cancers follows a birth cohort effect, with generational variation in risk,[6] suggesting a potential association with changes in environmental exposures.[7]

Colorectal, pancreatic, and esophagogastric cancers are the most common early-onset GI cancers,[8] but recent reports also suggest a rising incidence of early-onset appendix,[4] small bowel,[4] biliary tract,[4] and neuroendocrine cancers.[9] However, published data on these rarer early-onset GI cancers are limited to small, single-center retrospective studies and are therefore not discussed in this Review. Although the incidence of GI cancers has also increased among children and adolescents,[10] this Review summarizes current evidence on adults aged 18 to 49 years with early-onset colorectal, early-onset pancreatic, and early-onset esophagogastric cancers. The **Box** provides some commonly asked questions and answers about early-onset gastrointestinal cancers.

Box. Commonly Asked Questions About Early-Onset Gastrointestinal (GI) Cancers

Which Early-Onset GI Cancers Are Increasing in Incidence?
Since 2010, the incidence of early-onset GI cancers (diagnosed in individuals aged <50 years) has been rising globally, predominantly in high-income countries. The highest incidence rates are in colorectal, pancreatic, and esophagogastric cancers; however, bile duct, gallbladder, appendix, neuroendocrine, and small intestine cancers have also been increasing worldwide.

What Are the Risk Factors for Early-Onset GI Cancers?
There are modifiable and nonmodifiable risk factors that contribute to development of early-onset GI cancers. Modifiable risk factors include obesity, low-quality diet (eg, high consumption of processed meats, sugar-sweetened beverages, and ultraprocessed foods), sedentary lifestyle, cigarette smoking, and alcohol consumption. Nonmodifiable risk factors include hereditary cancer syndromes such as Lynch syndrome and inflammatory bowel disease.

How Are Early-Onset GI Cancers Treated?
Treatment of early-onset GI cancers is similar to that of later-onset GI cancers. However, all patients with early-onset GI cancer should undergo germline genetic testing to identify underlying hereditary syndromes and somatic genomic profiling to identify actionable genomic variants (eg, *BRCA1/2* and *BRAF* V600E variants). Patients with early-onset GI cancer benefit from multidisciplinary care and should be offered referral for fertility counseling and preservation and psychosocial support for anxiety, depression, parenting concerns, and financial concerns.

Methods

A PubMed search was performed for English-language clinical trials, meta-analyses, systematic reviews, observational studies, narrative reviews, and guidelines on early-onset colorectal, pancreatic, and esophagogastric cancers published between January 1, 2014, and March 7, 2025. We prioritized recent, high-quality original research and excluded studies that did not include individuals aged 18 to 50 years. Of the 1693 articles retrieved, 115 were included (1 clinical trial, 6 meta-analyses, 2 systematic reviews, 83 observational studies, 7 narrative reviews, and 16 guidelines). We also used 3 publicly available cancer statistics databases: the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute,[8] the US Cancer Statistics Data Visualizations Tool,[11] and the GLOBOCAN 2022 database version 1.1 from the International Agency for Research on Cancer.[2,3]

Early-Onset CRC

Epidemiology

Although CRC incidence among US individuals of all ages has declined by 1.3% to 4.2% annually since the mid-1990s,[12] the incidence of early-onset CRC has increased by approximately 2% annually[12] and currently represents 14% of all CRC cases.[8] The age-adjusted incidence rate (AAIR) and average APC (AAPC) of early-onset CRC from SEER are presented in **Table 1**. Similarly, while CRC-associated mortality in the US has decreased by 1.7% per year, likely due to increased screening and improved treatments,[13] early-onset CRC–associated death rates increased by 1% per year in 2011-2020.[14] In 2022, among US individuals aged 20 to 49 years, CRC was the leading cause of cancer-related death among men (2073 deaths) and the second leading cause among women (1604 deaths).[13] Although lowering the CRC screening age to 45 years may improve early detection and prevention of early-onset CRC, the steepest increase in annual early-onset CRC rates are among those younger than 40 years[15] (from 4.1 to 5.5 per 100 000 [2013-2022]; AAPC, 3.4%; 95% CI, 2.4%-3.8%).[8]

Early-onset CRC incidence has also been increasing globally since the 1990s, particularly in high-income countries, including Australia, New Zealand, and South Korea.[16] Worldwide, there were 184 709 new early-onset CRC cases reported in 2022, representing 40% of all early-onset GI cancers,[2,3] with the largest increases in New Zealand (AAPC, 3.97%; 95% CI, 2.44%-5.52 [2007-2017]).[16]

Compared with females, US males have a higher incidence of early-onset CRC (male-to-female incidence rate ratio, 1.20; 95% CI, 1.18-1.22).[14] Rates are increasing in all racial and ethnic groups. From 2013 to 2022, the AAPC in early-onset CRC incidence was 4.7% for non-Hispanic Black individuals (AAIR, 8.2 to 10.4 per 100 000), 5.1% for Hispanic individuals (AAIR, 5.5 to 8.9 per 100 000), and 3.3% for non-Hispanic White individuals (AAIR, 7.8 to 10.9 per 100 000).[8] Compared with later-onset CRC, patients with early-onset CRC are

Table 1. Annual Incident Cases of Early-Onset Gastrointestinal Cancers and Incidence per 100 000 in the US by Sex and AAPCs as Reported in the SEER Registry[a]

Organ site	Female		Male	
	Annual incident cases (incidence per 100 000), 2022, age <50 y[b]	AAPC, % (95% CI), 2018-2022	Annual incident cases (incidence per 100 000), 2022, age <50 y[b]	AAPC, % (95% CI), 2018-2022
Colon and rectum	4570 (9.8)	5.1 (3.4 to 4.4)	4972 (10.5)	3.5 (3.1 to 4.2)
Stomach	826 (1.8)	4.0 (3.5 to 4.9)	772 (1.6)	2.6 (0.3 to 5.8)
Pancreas	688 (1.4)	2.8 (1.1 to 4.7)	636 (1.4)	1.0 (0.6 to 1.5)
Liver and intrahepatic bile duct	361 (0.8)	1.4 (1.0 to 2.0)	594 (1.3)	−2.8 (−3.3 to −2.4)
Small intestine	319 (0.7)	3.5 (3.0 to 4.1)	319 (0.7)	2.6 (2.1 to 3.2)
Esophagus[c]	91 (0.2)	5.7 (−1.5 to 13.7)	305 (0.7)	1.1 (−1.4 to 4.4)
Anus, anal canal, and anorectum	192 (0.4)	−0.6 (−1.2 to −0.1)	178 (0.4)	−3.4 (−4.7 to −2.5)
Gallbladder	95 (0.2)	0.8 (−0.1 to 1.8)	28 (0.1)	−6.3 (−12.8 to 2.1)

Abbreviations: AAPC, average annual percentage change; SEER, Surveillance, Epidemiology, and End Results.

[a] This table includes individuals younger than 50 years and is not restricted to ages 20 to 49 years due to the availability of data. The data represent nationally representative cancer statistics obtained from the SEER program of the National Cancer Institute. The table is ordered by declining annual incidence per 100 000, standardized to the 2000 US standard population.[8] Positive AAPC values denote an increasing trend in incidence over the time period, while negative values represent a decline.

[b] Incidence rates per 100 000 population are age adjusted.

[c] Combines esophageal adenocarcinoma and squamous cell carcinoma.

more likely to be Black (15% vs 11%) or Hispanic (9% vs 5%) than White (70% vs 80%).[17]

Risk Factors

Modifiable risk factors associated with early-onset CRC (**Table 2**) include exposure to carcinogens, such as cigarette smoke[33] and alcohol,[30] and certain dietary and lifestyle exposures starting in early life, such as processed meat, sugar-sweetened beverages,[25,27,35,36] obesity,[28] and sedentary behavior.[31] In the Nurses' Health Study (NHS) II prospective cohort of 29 474 women, individuals in the highest quintile of Western dietary pattern,[37] including intake of processed meat (eg, canned meat, sausages), red meat, butter, high-fat dairy products (eg, heavy cream, desserts), eggs, and refined grains (eg, white bread, white rice), had a significantly increased risk of early-onset high-risk colorectal adenomas, with 300 cases identified in the highest intake group compared with 183 cases in the lowest intake group (odds ratio, 1.67; 95% CI, 1.18-2.37).[27] Among 95 464 women in the NHS II prospective cohort, consumption of 2 or more servings per day of sugar-sweetened beverages was associated with a higher risk of early-onset CRC compared with less than 1 serving per week (16 cases per 138 469 person-years vs 45 cases per 536 446 person-years; relative risk, 2.18; 95% CI, 1.10-4.35).[25] Conversely, among 116 429 women in the NHS II, higher total vitamin D (dietary and supplemental) intake (≥450 IU/d vs <300 IU/d) was associated with a lower risk of early-onset CRC (27 cases per 406 189 person-years vs 64 cases per 528 107 person-years; hazard ratio, 0.49; 95% CI, 0.26-0.83).[36]

Obesity, an established CRC risk factor,[38] may be contributing to increasing early-onset CRC rates given the rising prevalence of both childhood and adult obesity worldwide.[39,40] Proposed mechanisms of adiposity-induced carcinogenesis include chronic inflammation and insulin resistance, among others.[41] In a meta-analysis of 12 studies with 242 561 participants aged 55 years or younger, the odds ratio for early-onset CRC was 1.32 (95% CI, 1.19-1.47) among individuals with overweight (body mass index [BMI; calculated as weight in kilograms divided by height in meters squared], 25-29.9) and 1.88 (95% CI, 1.40-2.54) with obesity (BMI >30) vs those with a BMI of less than 25.[28] Moreover, childhood and adolescent obesity (hazard ratio, 1.53; 95% CI, 1.17-2.0)[42] and maternal obesity (hazard ratio, 2.51; 95% CI, 1.05-6.02)[43] are also associated with increased early-onset CRC risk.

Inflammatory bowel disease is also more common among individuals with early-onset CRC (3%) compared with later-onset CRC (0.4%) (odds ratio, 2.97; 95% CI, 1.16-6.63).[44] Although most early-onset CRC is sporadic, a higher proportion of patients with early-onset CRC (14%-34%) report a family history of CRC diagnosed at any age compared with later-onset CRC (8%-19%) across multiple studies.[9,45-49]

Molecular Features

The prevalence of germline variants is higher among patients with early-onset CRC (16%-25%) vs later-onset CRC (approximately 10%), primarily due to Lynch syndrome.[46,50-52] Compared with later-onset CRC, early-onset CRC tumors more often harbor a high level of microsatellite instability due to germline alterations in DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) that characterize Lynch syndrome, or less commonly, through sporadic *MLH1* methylation.[46,50-53] These genetic alterations lead to defective DNA replication and accumulation of short tandem repeats (microsatellites). Other hereditary syndromes include familial adenomatous polyposis, *MUTYH*-associated polyposis, and hamartomatous polyposis syndromes.[54] Studies have reported a higher frequency of somatic genomic alterations involving *TP53* and *CTNNB1* and a lower frequency of *APC*, *KRAS*, and *BRAF* variants among individuals with microsatellite-stable early-onset CRC compared with later-onset CRC.[53,55,56]

Screening

In 2021, the USPSTF lowered the recommended age for initiation of CRC screening with stool-based tests (eg, fecal immunochemical test) and/or direct visualization tests (eg, colonoscopy, flexible sigmoidoscopy) from 50 years to 45 years for average-risk individuals (ie, those with no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease and no personal or family history of genetic disorders predisposing to CRC).[5] The modeling study informing this update reported that lowering the screening age from

Table 2. Screening Recommendations and Modifiable Risk Factors for Early-Onset Gastrointestinal Cancers[a]

	Type of early-onset gastrointestinal cancer		
	Colorectal	Pancreatic	Esophagogastric
Screening recommendations	While some countries, such as Austria and Italy, start screening at age 40 years,[18] and the US at age 45 years (USPSTF guidelines),[5] most other countries start screening at age 50 years. Recommendations vary by region and risk factors.[b]	Both US guidelines (American College of Gastroenterology,[19] American Gastroenterology Association[20]) and international guidelines (International Cancer of the Pancreas Screening Consortium[21]) recommend screening only for high-risk individuals (eg, those with inherited genetic syndromes, familial pancreatic cancer), with age varying by risk factors (eg, begin at age 50 years or 10 years younger than the initial age of familial onset; age 40 years in *CKDN2A* and *PRSS1* gene variant carriers with hereditary pancreatitis; age 35 years with Peutz-Jeghers syndrome)[20]	Routine EGD screening for early-onset esophagogastric cancer is not currently performed in most countries. However, in South Korea, biennial screening for gastric cancer with EGD or upper gastrointestinal series begins at age 40 years.[22] The American College of Gastroenterology recommends a single screening EGD for individuals with chronic gastroesophageal reflux disease symptoms and at least 3 of the following risk factors: male sex, age >50 years, White race, tobacco use, obesity, and family history of Barrett esophagus or esophageal adenocarcinoma in a first-degree relative.[23] Taipei Global Consensus guidelines endorse mass screening and eradication of *Helicobacter pylori* in individuals aged 20-40 years in regions with a high incidence or high risk of gastric cancer.[24]
Associated risk factors[c]			
Diet			
Sugar-sweetened beverages	RR, 2.18 (95% CI, 1.10-4.35; *P* = .02) for sugar-sweetened beverage consumption ≥2 servings per day vs <1 serving per week[25]	Not available	Beef and canned, smoked, and salted food: OR, 2.1 (95% CI, 1.3-2.8)[26]
Western dietary pattern	OR, 1.67 (95% CI, 1.18-2.37; *P* < .03) for high-risk adenomas (highest vs lowest quintile for Western diet score)[27]	Not available	Not available
Obesity (body mass index >30)[d]	OR, 1.88 (95% CI, 1.40-2.54)[28]	OR, 1.85 (95% CI, 1.19-2.88)[29]	OR, 1.7 (95% CI, 1.5-2.0)[26]
Alcohol consumption	RR, 1.71 (95% CI, 1.62-1.80) for highest defined category in studies compared with never drinkers[30]	Not available	OR, 2.0 (95% CI, 1.3-2.6) for alcohol consumption vs none[26]
Physical activity	Sedentary behavior: RR, 1.69 (95% CI, 1.07-2.67; *P* = .03); television viewing >14 h/wk vs <7 h/wk[31]	Physical activity (protective): HR, 0.25 (95% CI, 0.07-0.93) for active vs inactive participants per study criteria[32]	Not available
Smoking	OR, 1.33 (95% CI, 1.17-1.52) for current smoking vs nonsmoking[33]	HR, 1.84 (95% CI, 1.29-2.62) for ever smoking vs nonsmoking[29]	OR, 1.5 (95% CI, 0.6-2.3) for smoking vs nonsmoking[26]
MASLD (fatty liver index >30)[e]	HR, 1.14 (95% CI, 1.06-1.22)[34]	HR, 1.23 (95% CI, 1.09-1.40)[34]	HR, 1.14 (95% CI, 1.06-1.24)[34]
Infection	Not available	Not available	*H pylori*: OR, 2.3 (95% CI, 1.4-3.2)[26]
Others			
Hyperlipidemia	RR, 1.61 (95% CI, 1.22-2.13)[30]	Not available	Not available
Breastfed as infant	OR, 1.46 (95% CI, 1.16-1.83) for high-risk adenomas among those breastfed in infancy vs not breastfed[35]	Not available	Not available
Vitamin D intake	HR, 0.49 (95% CI, 0.26-0.83) for total vitamin D intake including dietary and supplemental intake (protective) of ≥450 IU/d vs <300 IU/d[36]	Not available	Not available

Abbreviations: EGD, esophagogastroduodenoscopy; HR, hazard ratio; MASLD, metabolic dysfunction–associated steatotic liver disease; OR, odds ratio; RR, relative risk; USPSTF, US Preventive Services Task Force.

[a] Preference was given to high-quality meta-analyses and large prospective cohort studies where available. Definitions of terms are included where available. Early onset is defined as an age at diagnosis <50 years and later onset is defined as an age at diagnosis ≥50 years unless otherwise noted.

[b] Individuals with a personal history of colorectal cancer, inflammatory bowel disease, hereditary colorectal cancer syndromes, other colorectal cancer–predisposing conditions, or a family history of colorectal cancer.[5]

[c] The ORs, RRs, and HRs in this section apply to groups with vs without exposure to risk factors unless otherwise specified. Definitions per the cited studies are included where available. The risk factors are ordered by descending numerical value for early-onset colorectal cancer and prioritizing those with the most data across cancers.

[d] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[e] Referred to as "nonalcoholic fatty liver disease" in the study.[34]

50 years to 45 years resulted in an estimated 22 to 27 additional life-years gained per 1000 individuals, with a minimal increase in complications (0.1 to 2 per 1000 individuals).[57] The US Multi-Society Task Force recommends that people with a family history of CRC (including early-onset CRC) or advanced adenoma (defined as adenoma ≥1 cm, high-grade dysplasia, or villous elements) in a first-degree relative younger than 60 years or 2 first-degree relatives at any age undergo screening colonoscopy every 5 years, beginning 10 years before the age at diagnosis of the youngest affected relative or at age 40 years, whichever is earlier.[58] Persons with a single first-degree relative diagnosed with CRC at age 60 years or older or an advanced adenoma should be offered CRC screening beginning at age

40 years.[58] Some high-income countries, such as Austria and Italy, initiate CRC screening at age 40 years. However, most other countries recommend starting at age 50 years for average-risk individuals, commonly with stool-based tests.[18]

Clinical Presentation and Diagnosis

The most common presenting symptoms of early-onset CRC are hematochezia (45%), abdominal pain (40%), and altered bowel habits such as constipation or diarrhea (27%),[59] which may be attributed to a higher prevalence of left-sided colon and rectal cancer among young patients (75%-80% of early-onset CRC vs 60% of later-onset CRC).[60] Unlike hemorrhoids, which typically present with blood on toilet paper, bleeding due to CRC may present as blood mixed in the stool, although the bleeding pattern may be nonspecific.[61] The American Society for Gastrointestinal Endoscopy guidelines recommend that all adults with hematochezia should be evaluated by history, physical examination, and endoscopy (flexible sigmoidoscopy or colonoscopy) because presence of hemorrhoids may not exclude additional pathology in the colon or rectum.[61] Colonoscopy should be pursued if no bleeding source is identified during flexible sigmoidoscopy or if patients have iron deficiency anemia, weight loss, bowel habit changes, or CRC risk factors.[61] In 1 analysis, 253 patients with early-onset CRC had a longer time from symptom onset to diagnosis (median, 128 days vs 79 days; $P < .05$) and more advanced-stage tumors at diagnosis (72% vs 63%; $P = .03$) compared with 232 older patients.[48] To prevent delay in diagnosis, all individuals experiencing hematochezia, abdominal pain, altered bowel habits, unexplained iron deficiency anemia, or unintentional weight loss should be referred for colonoscopy.[1] Compared with patients with later-onset CRC, those with early-onset CRC are more likely to have poorly differentiated tumors and signet ring cell histology.[9,62]

Treatment

Early-onset CRC should be treated similarly to later-onset CRC according to the Delphi Initiative for Early-Onset Colorectal Cancer International Management Guidelines, the first evidence-based consensus recommendations for early-onset CRC.[1] The National Comprehensive Cancer Network guidelines also do not differentiate CRC treatment by age.[63] However, compared with patients with later-onset CRC, those with early-onset CRC often undergo more aggressive therapy, including combination chemotherapy regimens,[64] surgical resections,[65] and radiation treatments.[66]

Treatment recommendations for patients with early-onset CRC include (1) universal germline genetic testing to guide treatment, screening for other cancers, and familial risk assessment; (2) somatic genomic profiling to identify variants that may be treated with targeted therapies (eg, *BRAF* V600E inhibitors); (3) microsatellite instability testing to predict response to immunotherapy; (4) consideration of organ-sparing surgery (preservation of the rectum to avoid radical resection and permanent colostomy) and pelvic radiation-sparing approaches in selected patients for treatment of localized rectal cancer to minimize morbidity and preserve fertility and sexual function; and (5) referral for fertility counseling prior to treatment initiation.[1]

Prognosis

Some studies suggest that patients with early-onset CRC experience similar or improved cancer-specific survival compared with later-onset CRC, possibly due to more intensive multimodality therapy, while others report no difference or decreased survival (**Table 3**).[62,66,71] Among 15 982 patients diagnosed with stage III CRC, a higher percentage of those with early-onset CRC received multiagent chemotherapy after surgery compared with later-onset CRC (86% vs 73%; odds ratio, 1.75; 95% CI, 1.58-1.93), with only marginal improvement in adjusted 5-year relative survival (73.7% vs 71.0%; relative risk, 0.89; 95% CI, 0.81-0.97).[64] In a randomized clinical trial of 2326 patients with metastatic CRC, those with early-onset CRC did not have improved overall survival compared with later-onset CRC (median, 27.07 [95% CI, 25.04-30.06] months vs 26.12 [95% CI, 24.94-27.30] months; $P = .12$), despite receiving a higher chemotherapy dose intensity.[71]

Early-Onset Pancreatic Cancer

Epidemiology

The incidence of early-onset pancreatic cancer (defined as age <50 years) increased in the US from 2013 to 2022 (from 1.1 to 1.4 per 100 000; AAPC, 2.4%; 95% CI, 1.7%-3.0%; $P < .01$)[8] and globally from 2001 to 2018 (AAPC, 2.82%-8.75%), most notably among high-income countries.[82] In the US, there were 1324 incident cases of early-onset pancreatic cancer in 2022 (Table 1), representing 5.2% of all pancreatic cancer cases reported in SEER.[8] From 2013 to 2022, early-onset pancreatic cancer in the US increased predominantly among women (from 1.0 to 1.4 per 100 000; AAPC, 2.8%; 95% CI, 1.7%-3.8%) compared with men (from 1.3 to 1.4 per 100 000; AAPC, 1.0%; 95% CI, 0.6%-1.5%).[8] While the AAIR of early-onset pancreatic cancer was highest among non-Hispanic Black individuals (1.7 per 100 000 in 2022) compared with Hispanic and non-Hispanic White individuals (AAIR, 1.4 per 100 000), the largest increases in incidence rates (2013-2022) occurred among Hispanic individuals (AAPC, 4.6%; 95% CI, 3.6%-5.3%) and non-Hispanic White individuals (AAPC, 1.6%; 95% CI, 1.1%-2.0%) compared with non-Hispanic Black individuals (AAPC, 1.0%; 95% CI, 0.5%-1.6%).[8] Although pancreatic ductal adenocarcinoma accounts for most pancreatic cancers (90%), pancreatic neuroendocrine tumors comprise approximately 5%,[83] and recent data indicate increasing incidence of early-onset pancreatic neuroendocrine tumors in the US (among women: AAPC, 7.3%; among men: AAPC, 7.5% [2001-2020]).[84]

Risk Factors

Risk factors for early-onset pancreatic cancer include alcohol consumption, smoking, sedentary behavior, obesity, and metabolic dysfunction–associated steatotic liver disease (Table 2). In a study of 5232 individuals, alcohol consumption of more than 26 g/d (ie, 2 drinks per day) vs 26 g/d or less was associated with early-onset pancreatic cancer (defined as age <60 years; 213 cases among 1954 individuals; odds ratio, 1.49; 95% CI, 1.2-1.84), particularly among those younger than 45 years (25 cases among 226 individuals; odds ratio, 2.18; 95% CI, 1.17-4.09).[85] A prospective study of 167 483 patients reported that multiple risk factors were more strongly associated with early-onset pancreatic cancer (defined as age ≤60 years) than later-onset pancreatic cancer, including smoking (98 cases per 1 265 695 person-years vs 378 cases per 619 032 person-years), obesity (24 cases per 201 523 person-years vs 98

Table 3. Studies Evaluating Survival Outcomes of Patients With Early-Onset vs Later-Onset GI Cancer[a]

Source	Country (study design)	Cancer stage	Study population, No.[b]		Survival outcome, early-onset vs later-onset GI cancer
			Early-onset GI cancer	Later-onset GI cancer	
Early-onset colorectal cancer					
Jeri-Yabar et al,[67] 2024	US (SEER database analysis)	IV	4141	19 137	Overall survival: median, 30 mo vs 18 mo (P < .001)
Liao et al,[68] 2024	Taiwan (retrospective cohort study)	IV	1240	4464	5-Year cause-specific survival: 32.8% vs 51.9% (P = .01)
Rashad et al,[69] 2024	Egypt (retrospective cohort study)	All	Aged ≤45 y: 555	Aged ≥65 y: 755	5-Year disease-free survival: 38.2% vs 36.3% (P = .43); overall survival: median, 53.2 mo vs 81.0 mo (P = .99)
Hutajulu et al,[70] 2024	Indonesia (single-center retrospective analysis)	All	Aged <40 y: 149	Aged ≥40 y: 1127	5-Year overall survival: 34.2% vs 36.9%
Lipsyc-Sharf et al,[71] 2022	US (population enrolled in Cancer and Leukemia Group B and SWOG 80405 phase 3 clinical trial)	IV	514	1812	Progression-free survival: median, 10.87 mo vs 10.55 mo (P = .67); overall survival: median, 27.07 mo vs 26.12 mo (P = .12)
Cheng et al,[62] 2021	US (National Cancer Database analysis)	All	102 168	78 812	10-Year overall survival: 53.6% vs 54.3% (P < .001)
Fontana et al,[72] 2021	Global (IDEA database)	III	1564	14 785	3-Year relapse-free rate: 54% vs 65%; 5-year cancer-specific mortality rate: 24% vs 20%
Cercek et al,[60] 2021	US (single-center retrospective analysis)	IV	Aged ≤35 y: 110; aged 36-49 y: 455	Aged ≥50 y: 574	• Radiographic response to first-line chemotherapy: ≤35 y, 71.9%; 36-49 y, 61.8%; ≥50 y, 66.5% • Overall survival, median: ≤35 y: 46.9 mo; 36-49 y: 56.4 mo; ≥50 y: 54.5 mo
Early-onset pancreatic cancer					
Mendis et al,[73] 2024	Australia, New Zealand, and Singapore (prospective database analysis)	All	112	1571	• Overall survival: median, 23.4 mo vs 10.3 mo • Resected cancer group: median, 65.6 mo vs 31.3 mo • Locally advanced unresectable group: median, 17.3 mo vs 10.6 mo • Metastatic disease group: median, 9.3 mo vs 5.4 mo
Whitley et al,[74] 2023	Czech Republic (national registry analysis)	All	1324	17 564	Overall survival: median, 5.9 mo vs 4.5 mo (P < .01)
Castet et al,[75] 2023	Spain (retrospective cohort study)	All	Aged ≤50 y: 139	Aged ≥70 y: 197	Overall survival: median, 18.7 mo vs 17.6 mo
Takeda et al,[76] 2022	Japan (single-institution retrospective analysis)	All	127	1519	Progression-free survival: median, 4.4 mo vs 5.3 mo (P = .65); overall survival: median, 11.5 mo vs 9.5 mo (P = .18)
Saadat et al,[77] 2021	US (National Cancer Database analysis)	All	15 710	232 924	1-Year overall survival: stage 0/I/II, 72% vs 53%; stage III, 48% vs 38%; stage IV, 25% vs 15%
Early-onset esophagogastric cancer					
Lumish et al,[78] 2024	US (single-institution retrospective analysis)	All	219	904	Overall survival: median, 22.7 mo vs 22.1 mo (P = .78)
Radkiewicz et al,[79] 2023	Sweden (population-based cohort study)	All	2576	25 278	5-Year relative survival: esophageal, 20% vs 16%; cardia gastric, 23% vs 19%; noncardia gastric, 25% vs 18%
Rompen et al,[80] 2023	Germany (single-institution retrospective analysis)	All	129	609	Gastric cancer overall survival: median, 50.5 mo vs 58.9 mo (P = .92)
Torrejon et al,[81] 2022	US (National Cancer Database analysis)	All	Gastric cancer: 16 368; esophageal cancer: 9765	Gastric cancer: aged 50-69 y, 65 897; aged >70 y, 76 334; esophageal cancer: aged 50-69 y: 71 939; aged >70 y, 57 506	• Gastric cancer survival, median: overall, 15.34 mo; 50-69 y: 16.39 mo; >70 y: 9.99 mo (P < .001) • Esophageal cancer survival, median: overall, 15.24 mo; 50-69 y: 15.34 mo; >70 y: 10.18 mo (P < .001)

Abbreviations: GI, gastrointestinal; SEER, Surveillance, Epidemiology and End Results.

[a] Studies selected from the literature review at authors' discretion prioritizing seminal works on the topic, global representation across disease stages, recent large administrative databases, and high-quality meta-analyses where available.

[b] Early onset is defined as an age at diagnosis <50 years and later onset is defined as an age at diagnosis ≥50 years unless otherwise noted.

cases per 146 839 person-years), diabetes (14 cases per 41 165 person-years vs 127 cases per 124 844 person-years), tall height (≥167 cm for women and ≥181 cm for men; 69 cases per 833 464 person-years vs 213 cases per 357 342 person-years), and non-O blood group (106 cases per 459 562 person-years vs 251 cases per 402 869 person-years).[29] Presence of 3 to 5 of these risk factors (vs 0) was associated with a hazard ratio for pancreatic cancer of 9.24 (95% CI, 4.11-20.77) for age 60 years or younger vs 3.00 (95% CI, 1.85-4.86) for age 61 to 70 years and 1.46 (95% CI, 1.10-1.94) for older than 70 years.[29] The hazard ratios for early-onset pancreatic cancer were 1.85 (95% CI, 1.19-2.88) for obesity, 3.85 (95% CI, 2.07-7.18) for diabetes, and 1.68 (95% CI, 1.21-2.33) for tall height.[29] Non-O blood group was more strongly associated with pancreatic cancer risk among participants aged 70 years or younger (hazard ratio, 1.84; 95% CI, 1.30-2.61) vs those older than 70 years (hazard ratio, 1.18; 95% CI, 0.97-1.44).[29] The mechanism by which non-O blood group[86] contributes to pancreatic cancer is unknown but may involve altered glycosylation (addition of carbohydrates to proteins), resulting in abnormal proteins on pancreatic cells resembling blood group antigens and escape from immune surveillance.[87] In a pooled analysis of 1954 individuals with early-onset pancreatic cancer (defined as age <60 years) and 3278 age- and sex-matched controls, those with early-onset pancreatic cancer were more likely to have a family history of pancreatic cancer in a first-degree relative (diagnosed at any age) compared with control participants (7% vs 2%; odds ratio, 2.53; 95% CI, 1.77-3.61).[85]

Molecular Features

Although most patients with early-onset pancreatic cancer do not have a hereditary predisposition, approximately 30% have germline variants in DNA damage repair genes such as *BRCA1/2* and *PALB2*, compared with 15% of patients with later-onset pancreatic cancer.[75] Other genetic syndromes that confer increased risk of pancreatic cancer include Peutz-Jeghers syndrome (*STK11* gene variants), hereditary pancreatitis (mostly *PRSS1* gene variants), familial atypical multiple mole melanoma syndrome (*CDKN2A* gene variants), and Lynch syndrome.[20] Compared with later-onset pancreatic cancer, early-onset pancreatic cancer has a higher prevalence of *KRAS* wild-type tumors (20% vs <10%) and genetic variants that can be treated with targeted therapies, such as *NTRK* fusions and *IDH1* variants.[75,88-91] Early-onset pancreatic cancers with high microsatellite instability[92] should be identified, as these genetic variants predict response to immunotherapy.[93]

Screening

Guidelines do not recommend screening for pancreatic cancer among adults considered at average risk.[20] However, the American College of Gastroenterology,[19] American Gastroenterology Association,[20] and International Cancer of the Pancreas Screening Consortium[21] recommend screening of high-risk individuals, including those with inherited genetic syndromes such as *BRCA2* or Peutz-Jeghers syndrome or with a family history of pancreatic cancer in a first-degree relative.[20] Screening modalities include abdominal magnetic resonance imaging and endoscopic ultrasound, with screening age and intervals determined by the high-risk indication (eg, starting age of 40 years in *CKDN2A* variant carriers and 35 years for Peutz-Jeghers syndrome).[20]

Clinical Presentation and Diagnosis

Most patients (85%) with early-onset pancreatic cancer present with symptoms, including abdominal pain (67%), obstructive jaundice (45%), weight loss (18.8%), gastric outlet obstruction (6.3%), and new-onset diabetes (1.8%).[73] Young adults with these symptoms should be evaluated with abdominal computed tomography.[91] Young patients with new-onset diabetes or worsening of preexisting diabetes (prevalent in 14%-17%)[73,89] who are at high risk of pancreatic cancer should engage in shared decision-making with their clinicians regarding pancreatic cancer workup or change in surveillance intervals.[20,91] Compared with later-onset pancreatic cancer, early-onset pancreatic cancer is associated with larger tumor size,[94] poorly differentiated histology (19% vs 15%),[95] and advanced-stage presentation (stage III or IV disease in 62% vs 55%).[96]

Treatment and Prognosis

Current treatment guidelines do not differ between early-onset pancreatic cancer and later-onset pancreatic cancer.[97] However, in a study of 248 634 patients with pancreatic cancer, more individuals with early-onset pancreatic cancer received cancer treatment compared with later-onset pancreatic cancer (81% vs 61%) and more often with multimodality therapies (21% vs 15%; adjusted odds ratio, 3.89; 95% CI, 3.66-4.15).[77] In a retrospective study of 336 patients with pancreatic cancer, 44% with early-onset pancreatic cancer received intensive chemotherapy (eg, FOLFIRINOX, consisting of fluorouracil, irinotecan, and oxaliplatin) vs 15% with later-onset pancreatic cancer.[75] Due to a higher frequency of germline DNA damage repair variants and actionable somatic alterations in early-onset pancreatic cancer, targeted therapies such as poly–adenosine diphosphate ribose polymerase inhibitors may be used.[75] In the same study, those treated with targeted therapies had significantly longer overall survival compared with those not receiving targeted therapies (median overall survival, 41.3 months vs 16.7 months; hazard ratio, 0.34; 95% CI, 0.12-0.93) (Table 3).[75] Therefore, all patients with early-onset pancreatic cancer should undergo germline and somatic genetic sequencing to detect hereditary syndromes and identify therapeutic options.[75]

Early-Onset Esophagogastric Cancer

Epidemiology

In the US, early-onset gastric cancer comprises 10.5% of all gastric cancer cases.[2,3] From 2013 to 2022, early-onset gastric cancer incidence increased in both females (AAIR, 1.2 to 1.8 per 100 000; AAPC, 4.0%; 95% CI, 3.5%-4.7%) and males (AAIR, 1.5 to 1.6 per 100 000; AAPC, 1.7%; 95% CI, 0.3%-2.8%) (Table 1).[8] Early-onset esophageal cancer represents approximately 5.1% of esophageal cancer cases in the US, including 282 cases of adenocarcinoma and 87 cases of squamous cell carcinoma in 2022, with AAIRs of 0.3 and 0.1 per 100 000, respectively.[8] The incidence rates of early-onset esophageal cancer increased between 2016 and 2022 (AAIR, 0.3 to 0.4 per 100 000; APC, 1.8%; 95% CI, −0.6% to 6.5%).[8]

Although the global incidence of esophagogastric cancer has declined over the last several decades,[98] early-onset gastric cancer increased globally from 2015 to 2019 (APC, 1.39%; 95% CI, 0.06%-2.74%; $P = .04$ in individuals aged <40 years).[99] The incidence increased in Central America, East Asia, and China from 1990 to 2019

but decreased in South Korea and Japan, likely due to opportunistic screening (performed per patient preference rather than via a screening program), *Helicobacter pylori* eradication, and improved access to health care.[99] Globally, early-onset esophageal cancer accounted for 45 056 incident cases and 39 196 deaths, with corresponding age-standardized rates of 0.05 and 0.04 per 100 000, respectively, in 2022.[2,3]

Risk Factors

Helicobacter pylori is classified as a class I carcinogen (strong evidence of carcinogenicity in humans).[100] A cluster-randomized trial of 180 284 individuals in China who were screened for *H pylori* reported that *H pylori* treatment decreased the incidence of gastric cancer (hazard ratio, 0.86; 95% CI, 0.74-0.99) vs symptomatic management alone, with crude rates of 0.58 and 0.68 per 1000 person-years, respectively. The incidence of gastric cancer was further reduced among those who had confirmed *H pylori* eradication over 11.8 years of follow-up (hazard ratio, 0.81; 95% CI, 0.69-0.96) vs no eradication (hazard ratio, 1.02; 95% CI, 0.83-1.26; crude rates, 0.54 vs 0.78 per 1000 person-years, respectively).[101] Other modifiable risk factors for early-onset gastric cancer include consumption of smoked and salted foods such as pickled vegetables and salt-preserved fish and meat (odds ratio, 2.1; 95% CI, 1.3-2.8), alcohol use (odds ratio, 2.0; 95% CI, 1.3-2.6), and obesity (odds ratio, 1.7; 95% CI, 1.5-2.0) (Table 2).[26] Nonmodifiable risk factors such as family history and hereditary factors are also associated with early-onset esophagogastric cancer risk, although they do not account for most cases.[78]

The rising incidence of esophageal adenocarcinoma[102] is likely due to increasing obesity rates[39] and gastroesophageal reflux disease,[103] both of which may cause Barrett esophagus, a strong risk factor for esophageal adenocarcinoma.[104,105] In contrast, primary risk factors for esophageal squamous cell carcinoma are smoking and heavy alcohol consumption (variably defined as >17 or >35 drinks per week).[106,107] Declining trends in smoking have contributed to reduced incidence of esophageal squamous cell carcinoma.[108]

Molecular Features

Patients with early-onset esophagogastric cancer have a higher prevalence of pathogenic germline alterations compared with later-onset esophagogastric cancer.[78] In a study of 466 patients with gastric cancer, the prevalence of germline alterations was 20.7% with early-onset esophagogastric cancer vs 16.1% with later-onset esophagogastric cancer.[78] Common hereditary syndromes leading to increased gastric cancer risk include hereditary diffuse gastric cancer (*CDH1* and, rarely, *CTNNA1* variants), Peutz-Jeghers syndrome, Lynch syndrome, and familial adenomatous polyposis. Pathogenic germline variants in *BRCA2* and *PALB2* may also occur.[109] Early-onset gastric cancer is characterized by fewer somatic tumor variants (8% vs 23% with later-onset gastric cancer), with fewer tumors having high microsatellite instability (3%-6% vs 23%) despite the higher frequency of Lynch syndrome.[78,110,111] Somatic alterations in *CCNE1* and *CDH1* are more common in early-onset esophagogastric cancer.[78]

Screening

Screening for gastric cancer is not routinely performed in most countries. However, in South Korea, biennial screening with esophagogastroduodenoscopy (EGD) or upper GI series begins at age 40 years.[22] The American College of Gastroenterology recommends a single screening EGD for individuals with chronic gastroesophageal reflux disease symptoms and 3 or more additional risk factors: male sex, age older than 50 years, White race, tobacco use, obesity (BMI ≥30), and family history of Barrett esophagus or esophageal cancer in a first-degree relative.[23] This conditional recommendation is based on low-quality evidence, and efforts are ongoing to refine risk criteria and screening strategies.[23] The Taipei Global Consensus also recommends *H pylori* screening and eradication in individuals aged 20 to 40 years in regions with high gastric cancer incidence.[24]

Clinical Presentation and Diagnosis

Most patients are symptomatic at presentation, commonly with pain (54%), weight loss (40%), and swallowing difficulty (29%).[78] Patients with new-onset dysphagia, GI bleeding (eg, melena), recurrent aspiration or regurgitation, weight loss, early satiety, and/or anorexia should undergo EGD.[112] Barium esophagram[113] may be used instead in patients at high risk of perforation with endoscopy or with limited local access to endoscopy.[112] Computed tomography of the chest, abdomen, and pelvis; upper endoscopic ultrasound; and positron emission tomography/computed tomography scans should be obtained for staging. If no metastases are detected and surgical resection is considered, diagnostic laparoscopy may be performed along with peritoneal washings to assess for intraperitoneal metastatic disease.[114,115] Based on SEER data of 75 225 patients with gastric cancer (1973-2015), those with early-onset gastric cancer had more poorly differentiated tumors (55% vs 47%), signet ring cell histology (19% vs 10%), diffuse histology (26% vs 15%), and metastatic disease at presentation (50% vs 41%) (all $P < .01$) compared with later-onset gastric cancer.[110]

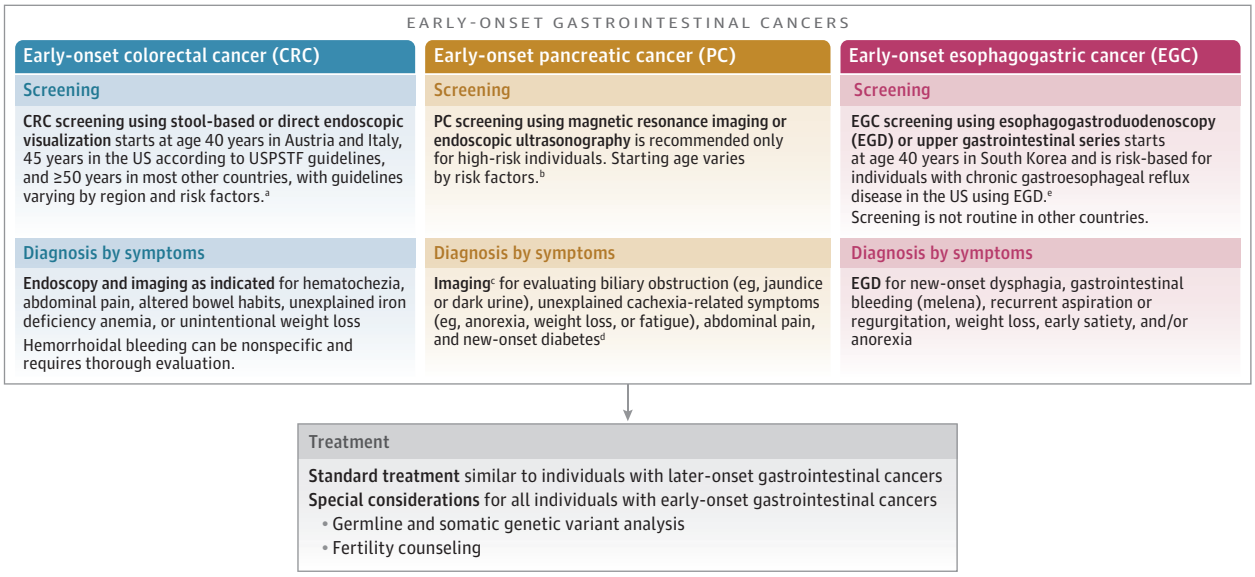
Treatment and Prognosis

Medical management of early-onset esophagogastric cancer is similar to that of later-onset esophagogastric cancer, although young patients with localized gastric cancer tend to receive more treatment. In a retrospective cohort study of 738 patients with gastric cancer undergoing curative surgery, those with early-onset gastric cancer more frequently received neoadjuvant therapy (63% vs 44%; $P < .001$) and radical surgery (68% vs 56%; $P = .006$), although overall survival was similar (median, 50.5 months vs 58.9 months; $P = .91$) compared with those with later-onset gastric cancer (Table 3).[80] In a National Cancer Database analysis of 158 599 patients with gastric cancer, median overall survival was 15.34 months (95% CI, 14.95-15.70 months) for patients with early-onset gastric cancer vs 16.39 months (95% CI, 16.16-16.62 months) for patients aged 50 to 69 years and 9.99 months (95% CI, 9.82-10.15 months) for those aged 70 years or older ($P < .001$ across all groups).[81] Among 139 210 patients with esophageal cancer, median overall survival was 15.24 months (95% CI, 14.72-15.80 months) for patients with early-onset esophageal cancer vs 15.34 months (95% CI, 15.15-15.54 months) for those aged 50 to 69 years and 10.18 months (95% CI, 9.99-10.35 months) for those aged 70 years or older ($P < .001$ across all groups).[81]

Practical Considerations

Given evidence from randomized clinical trials and cohort studies supporting the benefits of CRC screening on incidence and mortality, adherence to screening guidelines is a critical issue.[5] In 2022, the

Figure. Screening and Diagnostic Algorithm for Early-Onset Gastrointestinal Cancers



The figure illustrates the diagnostic pathway for early-onset gastrointestinal cancers from detection to treatment, including screening-based detection where applicable and symptom-driven diagnosis, which remains the most common presentation. USPSTF indicates US Preventive Services Task Force.

[a]While some countries, such as Austria and Italy, start screening at age 40 years[18] and the US at age 45 years[5], most countries lack guidelines for early-onset CRC screening in average-risk individuals (individuals without a personal history of CRC, inflammatory bowel disease, hereditary CRC syndromes, other CRC-predisposing conditions, or a family history of CRC).[5]

[b]Includes individuals at high risk of developing PC (eg, inherited genetic syndrome, family history of PC).[20,21] Starting age of screening (with abdominal magnetic resonance imaging or endoscopic ultrasound) varies by risk factors (eg, begin at age 50 years or 10 years younger than the initial age of familial onset; age 40 years in *CKDN2A* and *PRSS1* variant carriers with hereditary pancreatitis; age 35 years in the setting of Peutz-Jeghers syndrome).[20]

[c]Imaging modality selected based on clinical evaluation at clinician discretion.

[d]New-onset diabetes or worsening of preexisting diabetes may be a sign of PC and warrants appropriate evaluation.[20]

[e]Routine EGD screening for early-onset EGC is not currently performed in most countries, with South Korea being an exception, where biennial screening for gastric cancer with endoscopy or upper gastrointestinal series begins at age 40 years.[22] The American College of Gastroenterology recommends a single screening EGD for individuals with chronic gastroesophageal reflux disease symptoms and at least 3 of the following additional risk factors for Barrett esophagus: male sex, age >50 years, White race, tobacco use, obesity, and family history of Barrett esophagus or esophageal adenocarcinoma in a first-degree relative.[23] Taipei Global Consensus guidelines endorse mass screening (large-scale screening of whole population groups) and eradication of *Helicobacter pylori* in individuals aged 20 to 40 years in regions with a high incidence or high risk of gastric cancer.[24]

Table 4. Identified Needs of Patients With Early-Onset Gastrointestinal Cancer and Supportive Resources

Themes identified[a]	Key features in specialized centers
Feeling overwhelmed by the health care system and the need for navigation	• Dedicated program coordinator for patient navigation • Multidisciplinary evaluation for fertility, parenting concerns, nutrition, sexual health, and integrative oncology • Liaison to clinical and research teams
Isolation and the need for caregiver and patient peer support	• Customized (by disease stage) support groups for patients to establish peer connection and support including one-to-one programs • Caregiver support group: curriculum-based learning—regular webinars on relevant topics; patient and family forum with expert panels, 4 patient representatives, and research presentations
Life disruption and juggling many different roles and the need for psychosocial support	• Comprehensive psychosocial support and financial assistance program • Dedicated social worker on the care team with expertise in young patients, one-to-one counseling, and psychosocial counseling • Virtually accessible platform for services
Enthusiasm about research participation and germline genetic testing	• Prospective data collection and biobanks to elucidate underlying biological mechanisms and facilitate development of novel therapies • Education on research opportunities and germline genetic testing at first oncology appointment with regular check-ins • Availability of clinical trials • Utilize social media platforms to directly engage and partner with patients to accelerate research

[a] These primary themes highlight the specific needs of young patients with cancer identified in a qualitative study.[119]

screening rate was 72.2% among US adults aged 50 to 75 years[11] and in 2021 was 19.7% for those aged 45 to 49 years.[116] Among commercially insured US adults aged 45 to 49 years, CRC screening uptake increased from 0.50% (SD, 0.02%) to 1.51% (SD, 0.59%) between 20 months before and 20 months after the May 2021 USPSTF guideline change ($P < .001$).[117] The various pathways for screening and symptom-based diagnosis of early-onset GI cancers are outlined in the **Figure**.

In a systematic review of 2031 patients with early-onset CRC, 69.6% reported anxiety and 37.8% reported psychosocial distress.[118]

Concerns about fertility, parenting during cancer and treatment, and financial concerns are also common. Therefore, specialized centers with multidisciplinary teams, including reproductive health specialists, genetic counselors, psychosocial clinicians, and financial counselors, can substantially enhance care. **Table 4** summarizes the recommended components and services for specialized centers based on a qualitative study of patients with early-onset CRC and their caregivers at the Young-Onset Colorectal Cancer Center at Dana-Farber Cancer Institute.[119]

Limitations

This Review has several limitations. First, it is not a systematic review, and the quality of included literature was not formally evaluated. Second, some relevant studies may have been missed. Third, this Review does not include information about less common early-onset GI cancers such as early-onset appendix, small bowel, biliary tract, and neuroendocrine cancers, and it does not cover early-onset GI cancers in children and adolescents.

Conclusions

Early-onset GI cancers, typically defined as cancer diagnosed in individuals younger than 50 years, are among the largest subset of early-onset cancers globally. Treatment is similar to later-onset GI cancers and typically involves a combination of chemotherapy, surgery, and radiation, depending on the cancer type and stage. The prognosis for patients with early-onset GI cancers is similar to or worse than that for patients with later-onset GI cancers, highlighting the need for improved methods of prevention and early detection.

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