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Cancer incidence (2000–2020) among individuals under 35: an emerging sex disparity in oncology

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Abstract

Background Aggressive malignancies, such as pancreatic cancer, are increasingly impacting young, female populations. Our investigation centered on whether the observed trends in cancer incidence were unique to pancreatic cancer or indicative of a broader trend across various cancer types. To delve deeper into this phenomenon, we analyzed cancer incidence trends across different age and sex groups. Furthermore, we explored differences in cancer incidence within specific young subgroups aged 18 to 26 and 27 to 34, to better understand the emerging incidence trend among young individuals.

Methods This study collected cancer incidence data from one of the Surveillance, Epidemiology, and End Results cancer registry databases (SEER22), with 10,183,928 total cases from 2000 to 2020. Data were analyzed through Joinpoint trend analysis approach to evaluate sex- and age-specific trends in cancer incidence. Exposure rates were reported as Average Annual Percentage Changes (AAPCs).

Results The analysis revealed significant age and sex-specific disparities, particularly among individuals aged 18–26 and 27–34. Pancreatic cancer incidence rates increased more in females aged 18–26 (AAPC, 9.37% [95% CI, 7.36–11.41%]; $p < .0001$) than in males (4.43% [95% CI, 2.36–6.53%]; $p < .0001$). Notably, among gender, age, and other malignancies, young females had the highest AAPCs for pancreatic cancer. Additionally, the incidence of gastric cancer, myeloma, and colorectal malignancies also showed higher AAPCs in young females compared to males.

Conclusions Recognizing emerging risk populations for highly lethal malignancies is crucial for early detection and effective disease management.

Keywords Pancreatic cancer, Gastrointestinal cancer, Incidence data, Young population, Age-sex differences, Risk populations, Early-onset cancer

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Background

The existence of a significant sex gap in cancer incidence is a recurring theme in descriptive epidemiology. It has become increasingly apparent that disparities between sexes significantly influence cancer occurrence, with males recognized as having greater vulnerability to the development of cancer [1–5]. This notion has been challenged by recent studies revealing a higher incidence trend of pancreatic cancer (PC) among females aged 15–34 years compared to males [6], indicating the emergence of a novel risk population for this aggressive cancer. This observation is concerning as pancreatic cancer is currently the fourth leading cause of cancer-related death worldwide [1], and it is anticipated to become one of the deadliest cancers by 2030, primarily due to limited therapeutic advancements [7].

Early disease detection in populations at risk of PC may reduce the mortality rate. Pancreatic cancer primarily affects older adults, with approximately 90% of cases diagnosed in patients older than 55 years [8, 9]. In addition, males appear to have higher incidences than females, with this disparity being most pronounced in developed nations [9]. Hence, the emerging trend of increasing pancreatic cancer incidence among young female individuals was noteworthy since it underscores an increasing trend of the early onset of a devastating disease that has traditionally been considered to primarily affect the older adults. The observed trend of higher pancreatic cancer (PC) incidence in females aged 15–34 years compared to males was unexpected, as it deviates from common epidemiological trends typically seen in pancreatic cancer. As a possible explanation of such cancer incidences, sex-based disproportional exposure to known or unknown risk factors has been suggested [6]. Possibly, differences in exposure trends by age and sex to risk factors for pancreatic cancer, such as cigarette smoking, obesity, and diabetes, could have impacted the population over the last decades. Recently, Yan et al. analyzed the age-dependent association of risk factors with pancreatic cancer by implementing prospective cohorts with patients aged over 30 years, demonstrating that established risk factors such as cigarette smoking, obesity, and diabetes were most strongly associated with earlier-onset pancreatic cancer in the population aged 60 years or younger [10].

A deeper understanding of this epidemiological trend in cancer incidence among young populations is crucial for the early detection or prevention of PC and other aggressive cancers. This is particularly significant for the increasing number of younger individuals who are diagnosed with cancer. Our primary objective was to determine whether the increase in cancer incidence among young individuals, stratified by sex and age, was specific to pancreatic cancer or if it extended to other malignancies. Secondly, we aimed to investigate sex differences in cancer incidence within young subgroups to better delineate the emerging risk population among the young. To achieve this, we conducted an analysis of the SEER22 database, which reports cancer cases from 2000 to 2020.

Methods

Cancer incidence trend analysis

The Surveillance, Epidemiology, and End Results (SEER) Program is a National Cancer Institute (NCI) instrument used for cancer surveillance. It collects cancer data from several locations and sources throughout the USA, covering almost 50% of the US population. For the aims of this study, SEER*Stat version 8.4.2 was used to calculate delay-adjusted cancer incidence rates per year. In particular, we considered pancreatic cancer, stomach cancer, lung and bronchus cancers, brain and other nervous system cancers, myeloma, colon and rectum cancers, melanoma, cervical cancer, ovarian cancer, breast cancer (female cases only), prostate cancer, and testicular cancer from the SEER22 database, spanning from 2000 to 2020. The patients were stratified into multiple age-sex non-overlapping groups. Then, Joinpoint Command version 4.9.0.0 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) was implemented in R to run all trend analyses. Briefly, the simplest Joinpoint models were fit through Monte Carlo permutation tests on incidence rate data, and then Average Annual Percentage Changes (AAPCs) were estimated along with 95% confidence intervals; the significance of AAPC values was tested with 2-sided *t*-tests, and pairwise comparisons were carried out to evaluate the significance of sex as an interaction factor against it not being significant.

AAPCs measured in these analyses are summary estimates of the trend over a pre-specified fixed interval. They allow us to use a single number to describe the average APCs over a period of multiple years. They are computed as a weighted average of the APCs from the Joinpoint model, with the weights equal to the length of the APC interval. More info on the AAPC method can be found here: https://surveillance.cancer.gov/help/joinpoint/setting-parameters/method-and-parameters-tab/apc-aapctau-confidence-intervals/average-annual-percent-change-AAPC.

Statistical analysis

P-values computed for AAPCs and for sex interactions were corrected for multiplicity using the Benjamini-Hochberg (BH) methodology. In all cases, the results were considered statistically significant when

the adjusted *p*-values resulting from BH correction were < 0.05.

Results

PC incidence in females aged 18 to 34 years (henceforth defined as the young group) had a higher Average Annual Percentage Change (AAPC) increase in incidence (AAPC, 6.22% [95% CI, 5.2–7.24%]; $p < 0.0001$) than young males (AAPC, 4.04% [95% CI, 2.84–5.26%]; $p < 0.0001$) with non-parallel trends ($p = 0.017$) (Fig. 1A and Table 1). The AAPC for PC in females aged 18 to 34 years was higher than that in females aged 35 to 54 years (hereafter referred to as the "Adult group") (AAPC, 1.53% [95% CI, 1.24–1.82%]; $p < 0.0001$). Additionally, adult females had a higher AAPC compared to adult males (AAPC, 0.67% [95% CI, 0.4–0.95%]; $p = 0.0001$), with non-parallel trends ($p = 0.0058$). Overall, the AAPC of PC among young individuals was significantly higher than that among adults. Furthermore, the AAPC of PC incidence in the 55 + years age group was lower compared to young groups in both females (AAPC, 0.64% [95% CI, 0.54–0.75%]; $p < 0.0001$) and males (AAPC, 0.74% [95% CI, 0.58–0.9%]; $p < 0.0001$) (Fig. 1A and Table 1).

We then examined the time-trend incidence statistics for various types of cancer. Among the analyzed tumor types, young females showed a more significant percentage increase in the incidence of stomach cancer (AAPC, 2.37% [95% CI, 0.47–4.31%]; $p = 0.019$) compared to males (AAPC, -0.17% [95% CI, -1.05–0.72%]; $p = 0.704$), with non-parallel trends ($p = 0.024$). Similarly, in myeloma, young females exhibited a higher AAPC (AAPC, 2.82% [95% CI, 1.06–4.60%]; $p < 0.0045$) than males (AAPC, -0.16% [95% CI, -1.52–1.22%]; $p < 0.814$), also with non-parallel trends ($p = 0.0073$). Colorectal cancer also demonstrated a moderate relative increase in incidence rates among young females (AAPC, 3.95% [95% CI, 1.85–6.09%]; $p = 0.0003$) compared to males (AAPC, 3.22% [95% CI, 2.84–3.59%]; $p < 0.0001$), with non-parallel trends ($p = 0.0058$). In contrast, AAPC studies on lung and bronchus cancers, brain and nervous system cancers, and melanoma did not reveal a similar sex-specific trend of incidence growth in the young population (Fig. 1A and Table 1). Of note, in the 35–54 age group, females also showed higher AAPC than males for pancreatic and stomach cancer, myeloma, and melanoma.

To investigate whether the heightened incidence was specific to certain tumor types or indicative of a shift in cancer incidence rates based on sex, we also examined the trend in the incidence of sex-specific cancers over the same period. Young females did not show a substantial percentage increase in the incidence rate of cervical cancer (AAPC, -1.0% [95% CI, -1.69 – -0.3%]; $p = 0.0068$), ovarian cancer (AAPC, 0.71% [95% CI, 0.28–1.13%]; $p = 0.0036$), or breast cancer (AAPC, 1.16% [95% CI, 0.98–1.13%]; $p < 0.0001$) (Fig. 1A and Additional file1: Tables S1). Additionally, the analysis of sex-specific tumors in young males revealed a mild yet significant increase in AAPC for testicular cancer (AAPC, 1.0% [95% CI, 0.48–1.53%]; $p = 0.0003$) (Fig. 1A and Additional file1: Tables S1). Overall, AAPC for pancreatic cancer, gastrointestinal (GI) cancers, and myeloma in young females ranked the highest among the investigated sex and age groups, as well as in comparison to other malignancies (Fig. 1B). These data are particularly relevant, given that these tumors are among the most lethal types.

To further investigate sex differences in cancer incidence among young subgroups, individuals aged less than 34 years were divided into two age subgroups: 18–26 years and 27–34 years. Remarkably, females aged 18 to 26 years exhibited the highest relative increase in incidence rates of pancreatic cancer (AAPC, 9.37% [95% CI, 7.36–11.41%]; $p < 0.0001$) compared to males (AAPC, 4.43% [95% CI, 2.36–6.53%]; $p = 0.0005$), with non-parallel trends ($p = 0.041$). Females aged 27 to 34 years showed a trend of increasing incidence similar to males (AAPC, 4.46% [95% CI, 3.62–5.31%]; $p < 0.0001$), with parallel trends (Fig. 2 and Table 2). Therefore, the change of the incidence of pancreatic cancer over time among females was highest in the 18 to 26 age subgroup. Additionally, a substantial increase in AAPC was observed in the 27 to 34 age subgroup, albeit not differing by sex.

In the 18–26 age subgroup, females also exhibited higher AAPC for colorectal cancer incidence rates (AAPC, 6.18% [95% CI, 2.91–9.55%]; $p = 0.0004$) compared to males (AAPC, 5.15% [95% CI, 4.23–6.07%]; $p < 0.0001$), with non-parallel trends ($p = 0.0056$) (Table 2).

(See figure on next page.)

Fig. 1 Time trend of incidence for twelve cancer types, including pancreatic cancer, by sex and age. **A** Sex- and age-specific age-adjusted incidence rates per 100,000 population for 12 cancer types in the USA, as extracted from SEER22 data. Sex and age are grouped into six categories: 18–34-year-old (yo) males, 18–34yo females, 35–54yo males, 35–54yo females, 55 + yo males, and 55 + yo females. **B** Sex- and age-specific AAPC values of 2000–2020 cancer incidence trends for 12 cancer types in the USA. Sex and age are grouped into six categories: 18–34yo males, 18–34yo females, 35–54yo males, 35–54yo females, 55 + yo males, and 55 + yo females. Bars represent 95% CI. Statistical significance of AAPC values is labeled (ns: $p \geq 0.05$; *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; ****: $p < 0.0001$)

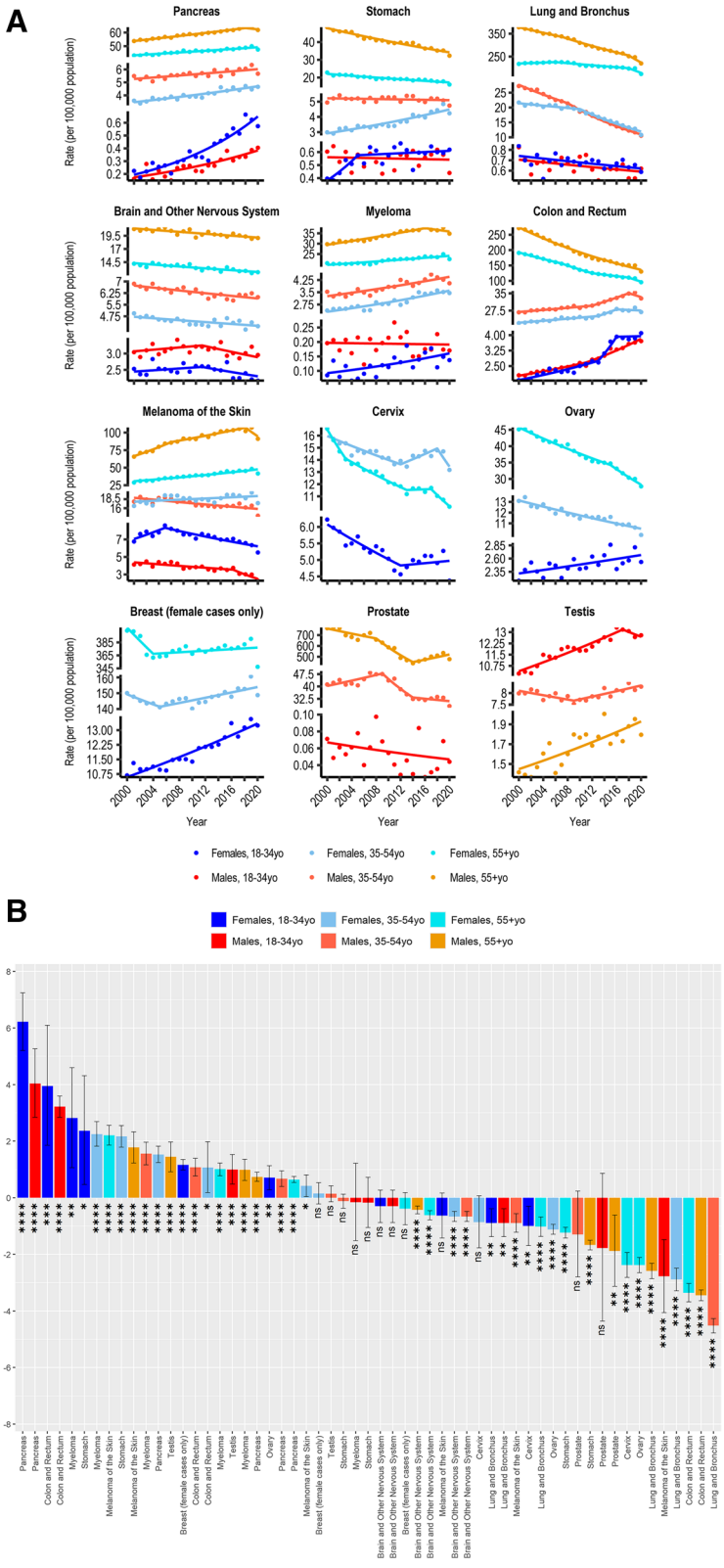

Fig. 1 (See legend on previous page.)

Table 1 Sex- and age-specific trends of 2000–2020 cancer incidence for seven cancer types in the US, as extracted from SEER22 data and calculated using Joinpoint

			Average Annual Percentage Change			Gender Interaction		
			AAPC [95% CI]	p-value	pADJ	Model	p-value	pADJ
Pancreas	18-34 yo	Females	6.22 [5.2 to 7.24]	< 0.0001	< 0.0001	NP	0.0109	0.017
		Males	4.04 [2.84 to 5.26]	< 0.0001	< 0.0001			
	35-54 yo	Females	1.53 [1.24 to 1.82]	< 0.0001	< 0.0001	NP	0.0022	0.0058
		Males	0.67 [0.4 to 0.95]	0.0001	0.0001			
	55+ yo	Females	0.64 [0.54 to 0.75]	< 0.0001	< 0.0001	NP	0.0013	0.0046
		Males	0.74 [0.58 to 0.9]	< 0.0001	< 0.0001			
Stomach	18-34 yo	Females	2.37 [0.47 to 4.31]	0.0144	0.0191	NP	0.0173	0.0242
		Males	-0.17 [-1.05 to 0.72]	0.692	0.7043			
	35-54 yo	Females	2.17 [1.79 to 2.55]	< 0.0001	< 0.0001	NP	0.0002	0.0008
		Males	-0.12 [-0.37 to 0.13]	0.3362	0.3549			
	55+ yo	Females	-1.23 [-1.42 to -1.04]	< 0.0001	< 0.0001	NP	0.0027	0.0063
		Males	-1.67 [-1.84 to -1.5]	< 0.0001	< 0.0001			
Lung and Bronchus	18-34 yo	Females	-0.89 [-1.38 to -0.39]	0.0009	0.0013	P	0.2844	0.2986
		Males						
	35-54 yo	Females	-2.89 [-3.29 to -2.49]	< 0.0001	< 0.0001	NP	0.0002	0.0008
		Males	-4.52 [-4.78 to -4.27]	< 0.0001	< 0.0001			
	55+ yo	Females	-1.02 [-1.37 to -0.68]	< 0.0001	< 0.0001	NP	0.0002	0.0008
		Males	-2.59 [-2.86 to -2.32]	< 0.0001	< 0.0001			
Brain and Other Nervous System	18-34 yo	Females	-0.3 [-0.88 to 0.27]	0.2997	0.3285	P	0.2529	0.2795
		Males						
	35-54 yo	Females	-0.66 [-0.84 to -0.48]	< 0.0001	< 0.0001	P	0.9531	0.9531
		Males						
	55+ yo	Females	-0.62 [-0.78 to -0.46]	< 0.0001	< 0.0001	NP	0.024	0.0315
		Males	-0.43 [-0.57 to -0.29]	< 0.0001	< 0.0001			
Myeloma	18-34 yo	Females	2.82 [1.06 to 4.6]	0.0032	0.0045	NP	0.0038	0.0073
		Males	-0.16 [-1.52 to 1.22]	0.8139	0.8139			
	35-54 yo	Females	2.25 [1.82 to 2.69]	< 0.0001	< 0.0001	NP	0.0113	0.017
		Males	1.56 [1.16 to 1.96]	< 0.0001	< 0.0001			
	55+ yo	Females	1.01 [0.78 to 1.23]	< 0.0001	< 0.0001	NP	0.0036	0.0073
		Males	0.99 [0.61 to 1.36]	< 0.0001	< 0.0001			
Colon and Rectum	18-34 yo	Females	3.95 [1.85 to 6.09]	0.0002	0.0003	NP	0.0022	0.0058
		Males	3.22 [2.84 to 3.59]	< 0.0001	< 0.0001			
	35-54 yo	Females	1.07 [0.18 to 1.98]	0.0189	0.0245	NP	0.0367	0.0428
		Males	1.08 [0.77 to 1.39]	< 0.0001	< 0.0001			
	55+ yo	Females	-3.36 [-3.68 to -3.03]	< 0.0001	< 0.0001	NP	0.034	0.042
		Males	-3.45 [-3.64 to -3.26]	< 0.0001	< 0.0001			
Melanoma of the Skin	18-34 yo	Females	-0.63 [-1.42 to 0.17]	0.1233	0.1464	NP	0.0084	0.0147
		Males	-2.78 [-4.06 to -1.48]	< 0.0001	0.0001			
	35-54 yo	Females	0.42 [0.04 to 0.81]	0.033	0.0417	NP	0.0002	0.0008
		Males	-0.89 [-1.22 to -0.56]	< 0.0001	< 0.0001			
	55+ yo	Females	2.21 [1.86 to 2.56]	< 0.0001	< 0.0001	NP	0.0002	0.0008
		Males	1.78 [1.23 to 2.33]	< 0.0001	< 0.0001			

Sex and age are grouped into six categories: 18–34yo males, 18–34yo females, 35–54yo males, 35–54yo females, 55+yo males, and 55+yo females. AAPC (95% CI) = Average Annual Percent Change (95% confidence interval). *p*-value (Average Annual Percentage Change) = *p*-value yielded by testing the significance of the difference of the AAPC from 0. pADJ (Average Annual Percentage Change) = *p*-value yielded by correcting for multiplicity *p*-values from the *p*-value (Average Annual Percentage Change) column, using the BH procedure. Values corrected account for both sexspecific and non-sex-specific cancer types ($N = 57$). Model = modeling of the difference between males and females cancer incidence trends. "NP" indicates the difference is statistically different, thus the trends are "Not-Parallel"; "P" indicates the difference is not statistically different, thus the trends are "Parallel". *p*-value (sex interaction) = *p*-value yielded by testing the significance of the difference between males and females trends. pADJ (Ssex Iinteraction) = *p*-value yielded by correcting for multiplicity *p*-values from the *p*-value (sex interaction) column, using the BH procedure. Values corrected account for non-sex-specific cancer types ($N = 21$)

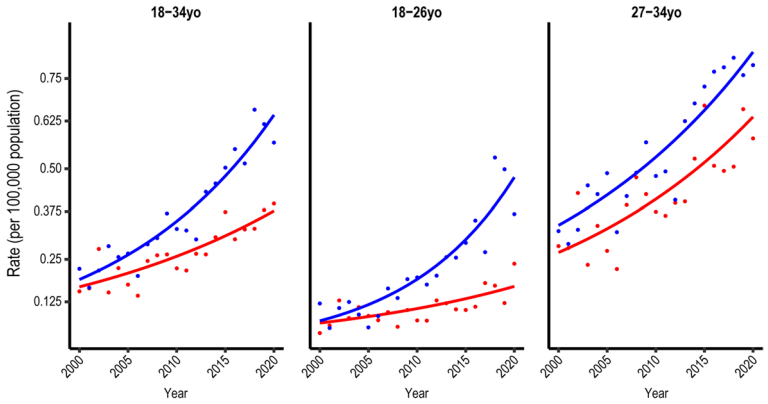

Fig. 2 Time trend of incidence for pancreatic cancer by sex in young subgroups. Sex- and age-specific age-adjusted incidence rates per 100,000 population for pancreatic cancer in the USA, as extracted from SEER22 data. Sex and age are grouped into six categories: 18–34yo males, 18–34yo females, 18–26yo males, 18–26yo females, 27–34yo males, and 27–34yo females. Males = red line; females = blue line

On the other hand, the AAPC of incidence for stomach cancer and myeloma showed the highest rate increase among females within the 27–34 age subgroup. For stomach cancer, the AAPC was 2.65% (95% CI, 0.06–5.32%) ($p=0.084$) for females and -0.28% (95% CI, -1.23% to 0.68%) for males ($p=0.66$), with non-parallel trends ($p=0.075$). The differences were statistically significant when tested individually, yet they did not remain significant after correction for multiplicity (Table 2). Regarding myeloma, the AAPC was 2.8% (95% CI, 1.03–4.61%) ($p=0.0076$) for females and -0.35% (95% CI, -1.83–1.15%) for males ($p=0.727$), with non-parallel trends ($p=0.015$) (Table 2).

Notably, the increase in PC incidence among females 18 to 26 subgroups, nearly a 10% annual percentage change, was the highest among all demographic groups and tumor types investigated in this study.

Discussion

The data confirmed the emergence of an unexpected sex gap in oncology, particularly among individuals younger than 35 years old. There are possible explanations for the above phenomenon: it is possible that changes in youth lifestyle over the past two decades have resulted in increased exposure to risk factors for pancreatic cancer and other gastrointestinal malignancies, previously relevant to the lifestyles of adults and seniors. There is a widespread belief that the young population is increasingly exposed to risk factors for cancer, yet a database-driven, systematic investigation is lacking. For instance, chronic pancreatitis or gastric inflammation are significant risk factors for digestive tract cancers [11, 12]. Alongside, longstanding diabetes, obesity, cigarette smoking, and heavy drinking are consolidated modifiable risk factors for both PC and GI cancers [13–15]. Therefore, addressing the prevalence of these risk factors in at-risk populations becomes crucial. Establishing a registry that documents chronic inflammations, such as pancreatitis, along with other identified risk factors, annotated with age, sex, and demographic information, could greatly contribute to our pathological understanding of PC and GI cancers in young individuals at risk. Previous studies have shown sex-dependent differences in pancreatic cancer risk factors exposure [16–18]. Other studies have suggested an enrichment of risk factors for pancreatic cancer among younger cases [19–21], which partly supports the differential etiology of pancreatic cancer by age at diagnosis. Obesity is a significant risk factor for pancreatic cancer. A more pronounced correlation between higher body mass index (BMI) and the risk of pancreatic cancer in men, possibly because of variations in fat distribution and hormonal factors has been found [22]. Furthermore, Genkinger and colleagues reported that being obese throughout early adulthood carries a greater risk compared to gaining weight later in life, highlighting the significance of the length of time a person is obese in relation to cancer development [23]. Diabetes, namely type 2 diabetes, has been recognized as a risk factor for pancreatic cancer [24]. Meta-analysis studies showed that diabetes had a more pronounced correlation risk for pancreatic cancer with both genders [25]. Although several studies have addressed age- and sex-dependent differences in exposure to risk factors for pancreatic cancer, these studies focused mainly on population aged > 30/40 years, and there is a lack of research that systematically investigates the pattern of young individuals' exposure to risk factors for pancreatic or gastrointestinal cancers.

We present data on time trend incidence among different types of cancer by sex and age. Caution is necessary

Table 2 Sex- and age-specific trends of 2000–2020 cancer incidence for seven cancer types in the US, as extracted from SEER22 data and calculated using Joinpoint

			Average Annual Percentage Change			Gender Interaction		
			AAPC [95% CI]	p-value	pADJ	Model	p-value	pADJ
Pancreas	18-26 yo	Females	9.37 [7.36 to 11.41]	< 0.0001	< 0.0001	NP	0.0176	0.0411
		Males	4.43 [2.36 to 6.53]	0.0002	0.0005			
	27-34 yo	Females	4.46 [3.62 to 5.31]	< 0.0001	< 0.0001	P	0.2818	0.3945
		Males						
Stomach	18-26 yo	Females	1.21 [-0.02 to 2.45]	0.0534	0.088	P	0.1582	0.2461
		Males						
	27-34 yo	Females	2.65 [0.06 to 5.32]	0.0452	0.0845	NP*	0.0376	0.0752
		Males	-0.28 [-1.23 to 0.68]	0.5492	0.6685			
Lung and Bronchus	18-26 yo	Females	0.17 [-0.88 to 1.23]	0.7408	0.7978	P	0.4782	0.5882
		Males						
	27-34 yo	Females	-1.21 [-1.79 to -0.63]	0.0002	0.0004	P	0.5898	0.6352
		Males						
Brain and Other Nervous System	18-26 yo	Females	-0.41 [-0.86 to 0.03]	0.0683	0.1006	P	0.0982	0.1718
		Males						
	27-34 yo	Females	-0.15 [-0.51 to 0.2]	0.3874	0.493	P	0.5042	0.5882
		Males						
Myeloma	18-26 yo	Females	0.19 [-2.77 to 3.24]	0.8983	0.8983	P	0.7553	0.7553
		Males						
	27-34 yo	Females	2.8 [1.03 to 4.61]	0.0038	0.0076	NP	0.0056	0.0157
		Males	-0.35 [-1.83 to 1.15]	0.6232	0.7271			
Colon and Rectum	18-26 yo	Females	6.18 [2.91 to 9.55]	0.0002	0.0004	NP	0.0004	0.0056
		Males	5.15 [4.23 to 6.07]	< 0.0001	< 0.0001			
	27-34 yo	Females	3.58 [3.03 to 4.13]	< 0.0001	< 0.0001	NP	0.0022	0.0103
		Males	2.68 [2.43 to 2.94]	< 0.0001	< 0.0001			
Melanoma of the Skin	18-26 yo	Females	-1.89 [-2.71 to -1.07]	< 0.0001	< 0.0001	NP	0.0042	0.0147
		Males	-3.62 [-4.38 to -2.86]	< 0.0001	< 0.0001			
	27-34 yo	Females	-1.03 [-2.44 to 0.39]	0.1541	0.2158	NP	0.0022	0.0103
		Males	-2.34 [-3.49 to -1.19]	0.0001	0.0002			

Sex and age are grouped into four categories: 18–26yo males, 18–26yo females, 27–34yo males, and 27–34yo females. AAPC (95% CI) = Average Annual Percent Change (95% Cconfidence linterval). *p*-value (Average Annual Percentage Change) = *p*-value yielded by testing the significance of the difference of the AAPC from 0. pADJ (Average Annual Percentage Change) = *p*-value yielded by correcting for multiplicity p-values from the *p*-value (Average Annual Percentage Change) column, using the BH procedure. Values corrected account for all cancer types ($N = 28$). Model = modeling of the difference between male and female cancer incidence trends. "NP" indicates the difference is statistically different, thus the trends are "Not-Parallel"; "P" indicates the difference is not statistically different, thus the trends are "Parallel". *p*-value (sex interaction) = *p*-value obtained by testing the significance of the difference between male and female trends. pADJ (sex interaction) = *p*-value yielded by correcting for multiplicity *p*-values from the *p*-value (sex interaction) column, using the BH procedure. Values corrected account for all cancer types ($N = 14$). "NP*" indicates the difference is statistically different when tested alone, but not after correction for multiplicity

when comparing incidence time trends among different tumor types due to the distinct epidemiological pathways and preventive measures affecting certain tumors, particularly when compared to pancreatic cancer. Indeed, in addition to the changing exposure to risk factors, the altered trend in cancer incidence over the years can also be related to other factors that are peculiar to each tumor type, such as participation in early-detection screening programs, changes in diagnostic methods, or tumor prevention campaigns. In certain cases, particularly colorectal, cervical, and breast cancer, participation in early-detection cancer screening programs, preventive vaccination campaigns, and a higher awareness about the role of active prevention in cancer have changed and reduced the age of cancer diagnosis. This is the case of the anti-HPV vaccination campaign against cervical cancer that has greatly reduced cervical cancer incidence among young women and has specifically influenced the trend of age-dependent cancer incidence. Consequently, while cancer incidence may be rising among females

overall, the trends for certain tumors, such as cervical cancer, are uniquely influenced by the success of ongoing screening programs for early disease detection or prevention and do not necessarily reflect trends of exposure to risk factors. It is also important to recall that participation in cancer prevention or early detection programs might only partially explain the observed trends in cancer-type incidence within age-specific groups. This is because the recommended initiating screening ages are often different among cancer types and age groups. For example, in 2016, the United States Preventive Services Task Force (USPSTF) recommended screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The USPSTF changed its guidelines in 2021 to recommend initiating screening at 45 years due to an increasing incidence of young-onset colorectal cancer. Therefore, screening programs might have influenced the prevalence of diagnoses for colorectal cancer by increasing the number of individuals diagnosed before the age of 54 and decreasing the risk for those over 54. However, the extent to which these screening programs influence the diagnosis of individuals aged 18 to 35 is unknown and probably restricted to certain tumor types [26]. Similarly, the HPV vaccine is recommended for routine vaccination at age 11 or 12 years. It is also recommended for everyone through age 26 years if not adequately vaccinated when younger. However, HPV vaccination is not recommended for individuals older than 26 years. Thus, preventive vaccination might have a peculiar age-dependent impact and should be considered. Furthermore, due to the lack of nationwide screening initiatives and established guidelines for early detection of pancreatic cancer, gastric cancer, and myeloma, the influence of screening programs on the incidence of these diseases among the overall population is probably limited. Conversely, heightened knowledge regarding the symptoms, genetic susceptibility, and family history associated with cancer could have increased both physician and population consciousness regarding targeted diagnostic methodologies. This, in turn, could have facilitated the early detection of the disease and impacted the variability observed in early-disease diagnosis trends.

Data presented here prompts the question of whether a sex disparity in cancer-associated risk among young individuals, particularly concerning exposures to risk factors for various malignancies including PC, may exist. Most studies examining the association between cancer risks, exposure to risk factors, and age typically focus on individuals aged 30 and above. Therefore, conducting additional ad hoc surveys is imperative to explore whether a discernible asymmetry in cancer-associated risk between sexes exists among the younger population, especially in relation to risk behaviors prevalent among adolescents.

While lifestyle choices and exposure to risk factors contribute to some sex disparities in cancer incidence, others are likely influenced by hormonal fluctuations, genetic, epigenetic, and immune-related factors, including differences in sex chromosomes [4, 27–30]. As for hormonal influences, a protective role of estrogens has been described, while testosterone and other androgens promote cellular proliferation and inhibit apoptosis, leading to increased cancer risk. Genetic differences between men and women can also play a significant role in the sex disparities observed in pancreatic cancer incidence [30]. Several genetic polymorphisms and mutations are associated with pancreatic cancer risk, and these can differ based on sex. Similarly, BRCA2 mutations are associated with a higher risk of pancreatic cancer, and the prevalence of these mutations can differ between men and women [30]. Furthermore, differences in immune response, particularly in terms of inflammation and immune surveillance, further explain the disparity in pancreatic cancer incidence between men and women. Sex differences in immune response to cancer can also be related to sex hormones or sex chromosome-associated genes impacting immune cells such as myeloid cells and T cells to shape the tumor microenvironment of both innate and adaptive immunity. For example, sex hormones can differentially regulate macrophage polarization with estrogen controlling the tumor-suppressive (M1) state, while androgens induce pro-inflammatory, tumor-promoting (M2) polarization of macrophages, a key event associated with pancreatic cancer progression [29, 30].

How can the insights provided here contribute to the prevention of pancreatic and GI cancers at earlier stages and reduce the mortality rate? Firstly, it is suggested that future targeted media campaigns should raise awareness about the correlation between behavioral risks and disease incidence among individuals aged 18 to 34 years. Secondly, these findings can serve as a foundation for the development of precise screening programs aimed at the early detection of pancreatic and GI cancers in emerging risk populations. Such programs can be tailored to specific sex and age subgroups, particularly those with heightened susceptibility to cancer or increased exposure to risk factors.

Conclusions

Recognizing these emerging risk groups for early-onset malignancies is crucial for early detection and reducing the overall lethality of cancer. The data presented here also hint at the initiation of debates concerning gender medicine, preventive medicine, and health program management—all crucial competencies for addressing the future impact of the rising incidence of early-onset malignancies, which unfortunately still bear the highest lethality rate.

Abbreviations

PC	Pancreatic cancer
GI	Gastrointestinal
AAPC	Average Annual Percentage Change
CI	Confidence interval
SEER	Surveillance, Epidemiology, and End Results
NCI	National Cancer Institute
BH	Benjamini-Hochberg

Supplementary Information

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Additional file 1. Table S1. Age-specific trends of 2000-2020 cancer incidence for five sex-specific cancer types in the US, as extracted from SEER22 data and calculated using Joinpoint. Sex and age are grouped into six categories: 18-34yo males, 18-34yo females, 35-54yo males, 35-54yo females, 55+yo males, and 55+yo females. AAPC [95% CI] = Average Annual Percent Change [95% Confidence Interval]. *p*-value (Average Annual Percentage Change) = *p*-value yielded by testing the significance of the difference of the AAPC from 0. pADJ (Average Annual Percentage Change) = *p*-value yielded by correcting for multiplicity *p*-values from the *p*-value (Average Annual Percentage Change) column, using the BH procedure. Values corrected account for both sex-specific and non-sex-specific cancer types ($N = 57$).

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Authors' contributions
A.C. and L.C. conceptualized the study and were responsible for data curation and analysis. A.C. developed and implemented the formal analysis methodology. Both A.C. and L.C. drafted the original manuscript and wrote the first draft of the paper. Additionally, L.C. played a key role in securing the necessary funding for the research project and provided guidance and oversight throughout its execution to ensure smooth progress. L.C. edited the final version of the manuscript. C.A. and D.G. contributed to data analysis and methodology, as well as to editing the first draft of the paper. All authors read and approved the final manuscript.

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Availability of data and materials
The data underlying this article were generated by using publically available data retrieved from the Surveillance, Epidemiology, and End Results (SEER) database, which is a National Cancer Institute (NCI) instrument used for cancer surveillance activities. Data extracted from publically available databases and according to the provided licensing have been extracted and analyzed as described in Methods. Further details regarding the statistical analysis and study protocols for all pertinent variable analyses can be obtained by contacting the authors, A. Cavazzani (cavazzani.alessandro@gmail.com) and L. Cardone (luca.cardone@cnr.it).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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