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Aims and Scope

Cancer Screening and Prevention (CSP) publishes high-quality research and review articles related to cancer screening and prevention. It aims to provide a platform for studies that develop innovative and creative strategies and precise models for screening, early detection, and prevention of various cancers. Studies on the integration of precision cancer prevention multiomics where cancer screening, early detection and prevention regimens can precisely reflect the risk of cancer from dissected genomic and environmental parameters are particularly welcome. Specifically, CSP publishes epidemiological, translational, and clinical studies on screening, early diagnosis, prevention of various cancers, especially gastrointestinal cancers. Topics of particular interest include but are not limited to: epidemiology of cancers; new strategies or models; novel discoveries of biomarkers; novel devices and clinical application; innovative techniques and clinical application; novel theories and mechanisms; evidence-based medicine; early detection of cancer; precision cancer screening and prevention; future perspectives. The acceptable categories include original article, review article, systematic review, meta-analysis, short communication, letter to the editor, and invited editorial & commentaries on rapidly progressing areas within the scope. All articles published by CSP, both solicited and unsolicited, must have passed a rigorous peer review.

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Original Article

Age-period-cohort Analysis of Cutaneous Malignant Melanoma Incidence in the United States from 1987 to 2016

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Abstract

Background and objectives: The prevalence and fatality rates of cutaneous malignant melanoma (CMM) have been rising, particularly among the elderly. This study analyzes CMM incidence trends in the United States elderly population from 1987 to 2016 to inform prevention and management strategies.

Methods: Using incidence data from the Surveillance, Epidemiology, and End Results database spanning 1989 to 2008, we calculated the age-adjusted standardized population incidence rates for CMM in elderly individuals. The Joinpoint software was employed to estimate annual percent change and analyze trends in CMM incidence among elderly individuals from 1987 to 2016.

Results: The study included 56,997 elderly CMM patients from eight Surveillance, Epidemiology, and End Results registries, of whom 36,726 were male (64.4%). The age-adjusted CMM incidence rate from 2012 to 2016 was 0.99 per 1,000, a 2.8-fold increase from 1987–1991 (95% confidence interval: 2.7–2.9). Incidence rates increased with age and birth cohort, peaking at 1.53 per 1,000 males and 0.59 per 1,000 females aged 85+ during 2012–2016. Birth cohort effects also showed a continuous increase.

Conclusions: This study reveals a substantial increase in CMM incidence rates among the elderly from 1987 to 2016, particularly between 2012 and 2016. Incidence rates escalated with age and birth cohort, with the highest rates observed in individuals aged 85 and older.

Introduction

Skin cancer is the most prevalent malignancy in the United States, with malignant melanoma being a highly aggressive form that originates in melanocytes, the cells responsible for producing skin pigment. Despite advances in treatment that have improved survival rates, malignant melanoma remains the deadliest type of skin cancer, and its global incidence continues to rise. Malignant melanoma can develop in various locations, including the skin, mucous membranes, eyes, and even the meninges. The most common types are cutaneous melanoma, ocular melanoma, and mucosal melanoma.[1,2]

Cutaneous melanomas are further categorized into subtypes, including chronic malignant melanoma, superficial spreading melanoma, nodular melanoma, and acral lentiginous melanoma, each with distinct clinical and histological features.[1] While early diagnosis and appropriate treatment result in a five-year survival rate of 95% for most skin cancers, the incidence and mortality rates of cutaneous malignant melanoma (CMM) are notably higher, accounting for 65% of all skin cancer-related deaths.[3] Though patients with metastatic melanoma face a disheartening 5% long-term survival rate, early detection of CMM offers a much more favorable prognosis, often leading to a complete cure.[3]

The global incidence of malignant melanoma has been increasing, with significant demographic disparities. In Western countries such as New Zealand and Australia, the incidence rates are among the highest, with age-standardized rates of 40.2/100,000 and 37.7/100,000 for males, respectively.[4] In Canada, the national crude incidence rate is reported as 20.75 cases per 100,000 individuals per year.[5] In the United States, melanoma is the fifth most common cancer, with an annual incidence of 73,870 cases.[6] The lifetime risk of developing melanoma has increased dramatically,

Keywords: Age-period-cohort; Oldest-old; Cutaneous malignant melanoma; Incidence; Annual percent change; Incidence trends.

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from 1 in 1,500 in the 1930s to 1 in 59 today.[6] CMM, a recalcitrant and aggressive melanocyte malignancy, has demonstrated a conspicuous and continuous rise in incidence globally, drawing significant attention from public health and medical research communities.[7]

Since 1975, the incidence of malignant melanoma in the United States has increased by over 320%, a trend expected to continue until at least 2029.[8] From 2006 to 2017, the United States Hispanic population experienced a particularly rapid increase in melanoma incidence, with Hispanic whites exhibiting the highest incidence of acral lentiginous melanoma compared to other populations of color.[9]

The demographic landscape in the United States is also changing, with an increasing proportion of the population reaching advanced age. By 2050, the population aged 85 years and older is expected to more than double, from 5.7 million to 24 million, making it the fastest-growing demographic.[10] This shift underscores the importance of studying CMM incidence and mortality rates within this age group.[10]

CMM is the leading cause of death among skin tumors, and in recent years, both its incidence and mortality rates have been steadily rising, particularly among the elderly.[11] Older patients with CMM typically present with more aggressive disease characteristics, such as a higher prevalence of ulceration and deeper tumor invasion, as indicated by Breslow's index.[12] These factors often result in a more advanced stage of diagnosis compared to younger patients.[12] Additionally, older adults are more likely to present with melanoma on the head and neck, with lentigo malignant melanoma being more common in this age group.[13,14]

Elderly patients generally have a poorer prognosis, with reduced melanoma-specific survival compared to younger adults.[11] Understanding the differences in clinical presentation and outcomes in the elderly is crucial for optimizing prevention, diagnosis, and treatment strategies tailored to this population.

The Surveillance, Epidemiology, and End Results (SEER) database, maintained by the National Cancer Institute (NCI), is a comprehensive nationwide cancer registry system that aggregates clinical and epidemiological data from cancer patients across the United States. These data are vital for both cancer research and clinical practice, providing researchers with insights into the epidemiological characteristics of various cancers, treatment effectiveness, and patient survival rates.[15,16]

Age-adjusted standardized population rates are essential tools in epidemiological studies and public health assessments. These rates adjust for differences in age distribution across populations, allowing for meaningful comparisons of health outcomes such as disease incidence or mortality. By using a standard population as a reference, these rates offer a more accurate reflection of the true burden of a condition, making them crucial for evaluating health trends, informing policy decisions, and comparing outcomes across different regions or time periods.[17]

In this study, we leverage SEER Research Plus Data from 1987 to 2016, covering eight registries up to November 2021 (1975–2019). We employ an age-period-cohort analysis to explore trends in CMM incidence among the elderly population in the United States. The primary goal is to provide scientific evidence to support the development of strategies for CMM prevention and management in the elderly and to evaluate their efficacy.

The following sections will elaborate on the research methodologies, data analysis, and findings, offering a comprehensive understanding of CMM incidence trends in elderly Americans and the factors influencing these trends.

Materials and methods

The data for this study were obtained from the SEER Program, maintained by the NCI. The SEER database is a comprehensive source of population-based information, covering approximately 34.6% of the United States population. It collects data on cancer incidence, survival, and prevalence from various geographic areas representing a cross-section of the nation. The SEER program is renowned for its high-quality data, gathered from multiple registries across the United States, ensuring a broad and diverse representation of cancer patients.[18,19]

Patient selection

Data from the SEER Program, comprising eight registries, were queried for the period spanning 1987 to 2016. Patients diagnosed with CMM of the skin were identified based on histology using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) codes 8720/3-8722/3, 8730/3-8780/3, and ICD-O-3 codes C44, C60.9, C63.2. Inclusion criteria were as follows: (1) the primary tumor site was the skin; (2) patients were aged 65 years or older at the time of diagnosis; (3) the diagnosis was confirmed pathologically; (4) complete follow-up data were available, with survival times exceeding zero days; and (5) the diagnosis occurred between 1987 and 2016. Exclusion criteria included: (1) cases where the diagnosis was based solely on autopsy or death certificate information; (2) instances with indeterminate survival times; and (3) patients diagnosed with secondary or metastatic tumors rather than primary CMM.

Statistical analysis

An annual percentage change (APC) analysis was conducted using five-year age intervals and 5-year period intervals, resulting in five age groups (65–69 years, 70–74 years, 75–79 years, 80–84 years, and ≥85 years) and six period intervals (1987–1991, 1992–1996, 1997–2001, 2002–2006, 2007–2011, and 2012–2016). Birth cohorts were defined based on the midpoints of the age and period intervals. Age-adjusted incidence rates were calculated using the United States standard population in 2000. Ratios, with 95% confidence intervals (CIs), were calculated using the Tiwari 2006 revision in SEER*Stat 8.4.2 (NCI).[20]

To assess trends in CMM incidence rates among elderly individuals in the United States from 1987 to 2016, this study used the Joinpoint Regression Model. For population-based trends in cancer incidence and mortality rates, the logarithmic linear model is typically used.

The main outcomes of the Joinpoint model were the APC and the average annual percent change (AAPC), both with their respective 95% CI. In the logarithmic linear model, denoted as $In(y) = \beta_0 + \beta_1 x$, where x represents the year of diagnosis, the APC can be computed using the following formula expressed as follows:

$$APC = \left[\frac{y_{x+1} - y_x}{y_x} \right] * 100 = (e^{\beta_1} - 1) * 100$$

To analyze long-term trends in CMM incidence rates, we used version 5.0 of the Joinpoint program from the NCI, available at https://surveillance.cancer.gov/joinpoint/. This program uses the Monte Carlo permutation method to evaluate the statistical significance of changes in trends. The optimal joinpoint model was determined by analyzing log-transformed data. The APC for individual linear segments and the AAPC for each joinpoint model across the entire study period were calculated, with 95% CI determined using the normal approximation method.[21]

Table 1. Change in cutaneous malignant melanoma incidence rates over time

Variable	Rate (95% CI)		Rate ratio (95% CI)
	1987–1991	2012–2016	
Overall	0.36 (0.35–0.37)	0.99 (0.98–1.01)	2.8 (2.7–2.9)
Sex			
Male	0.52 (0.50–0.55)	1.53 (1.50–1.56)	2.9 (2.8–3.0)
Female	0.25 (0.24–0.27)	0.59 (0.57–0.60)	2.3 (2.2–2.4)
Race			
White	0.40 (0.39–0.42)	1.22 (1,20–1.24)	3.0 (2.9–3.1)
Black	0.07 (0.05–0.11)	0.04 (0.03–0.06)	0.6 (0.4–1.0)
Other	0.04 (0.02–0.05)	0.08 (0.07–0.10)	2.3 (1.5–3.8)
SEER registry			
San Francisco, California	0.385 (0.359–0.413)	1.032 (0.996–1.069)	2.7 (2.5–2.9)
Connecticut	0.398 (0.371–0.425)	0.866 (0.831–0.902)	2.2 (2.0–2.4)
Hawaii	0.228 (0.189–0.272)	0.793 (0.741–0.847)	3.5 (2.8–4.2)
Lowa	0.309 (0.286–0.334)	0.865 (0.828–0.903)	2.8 (2.6–3.1)
New Mexico	0.396 (0.352–0.444)	0.649 (0.609–0.691)	1.6 (1.4–1.9)
Seattle (Puget Sound)	0.345 (0.318–0.373)	1.110 (1.073–1.147)	3.2 (3.0–3.5)
Utah	0.413 (0.366–0.463)	1.506 (1.442–1.571)	3.6 (3.2–4.1)
Atlanta (Metropolitan)	0.385 (0.342–0.431)	1.100 (1.050–1.153)	2.9 (2.5–3.2)

CI, confidence interval; SEER, Surveillance, Epidemiology, and End Results.

In cases where a significant difference in the linear slope of the time trend was detected, the joinpoint model was used to determine whether the age-adjusted incidence rates were best described by a single linear segment or multiple segments. A statistically significant trend, indicated by the APC or AAPC, was classified as increasing (slope > 0) or decreasing (slope < 0). Parallelism tests were conducted to determine whether the direction of slope changes in trends was similar or different between groups. These tests allowed for an analysis of whether the fitted models for different groups (e.g., females and males) had similar shapes but were shifted along the x-axis (i.e., the year of diagnosis). The statistical significance (*P*-value) from this test indicated whether the two compared AAPCs were statistically distinct.[22] All tests were two-sided, with a significance level set at $\alpha = 0.05$.

Finally, the APC model was employed to identify patterns in long-term incidence rate trends, considering the age at CMM diagnosis (age), the year of CMM diagnosis (period), and the birth year (cohort). The APC model described associations between cancer incidence rates and age, period (calendar year of diagnosis), and birth cohort. Graphs generated from these models provided a visual representation of trends while controlling for competing effects, such as birth cohort influences that adjust for age and period effects. These models were fitted using the NCI's Age-Period-Cohort web tool, available at https://analysistools.cancer.gov/apc/. This tool provided estimates of net drift (the expected age-adjusted rate of change over time in the APC), local drift (the expected age-specific rate of change over time), and cohort rate ratios (RR, the ratio of age-specific rates for each birth cohort relative to a reference cohort). The tool also enabled the testing of the equality of observed trends.[23]

Results

Incidence rates

The study included a total of 56,997 cases, with 36,726 (64.4%) being male patients. During the period from 2012 to 2016, the overall age-adjusted incidence rate of CMM was 0.99 per 1,000 individuals (95% CI, 0.98–1.01), representing a striking 2.8-fold increase compared to the period from 1987 to 1991 (95% CI, 2.7–2.9), as shown in Table 1. When stratified by gender, the age-adjusted incidence rate for males during 2012–2016 was 1.53 per 1,000 (95% CI, 1.50–1.56), while for females, it was 0.59 per 1,000 (95% CI, 0.57–0.60). These findings highlight a significant increase since the initial cohort analysis (1987–1991), with the age-adjusted incidence rate for males rising 2.9 times (95% CI, 2.8–3.0), and for females increasing 2.3 times (95% CI, 2.2–2.4). Additionally, we examined the distribution of CMM incidence rates based on race/ethnicity and geographic location (Table 1). It is evident that CMM is more prevalent in the white population compared to black and other racial/ethnic groups. Among white individuals, the incidence rate of CMM escalated from 0.40 per 1,000 to 1.22 per 1,000 (rate ratio 3.0; 95% CI, 2.9–3.1) between 1987–1991 and 2012–2016. When stratified by geographic location, Utah, Seattle, and Atlanta reported higher CMM incidence rates (Utah: 1.506 per 1,000; 95% CI, 1.442–1.571; Seattle: 1.110 per 1,000; 95% CI, 1.073–1.147), and Atlanta (1.100 per 1,000; 95% CI, 1.050–1.153). The overall increase in incidence rates from 1987–1991 to 2012–2016 was 2.8 times (95% CI, 2.7–2.9).

APC analysis

Over the course of 30 years, from 1987 to 2016, a persistent upward trend in the incidence rate of CMM was observed. Based on the APC, this ascending trend can be divided into two distinct seg-

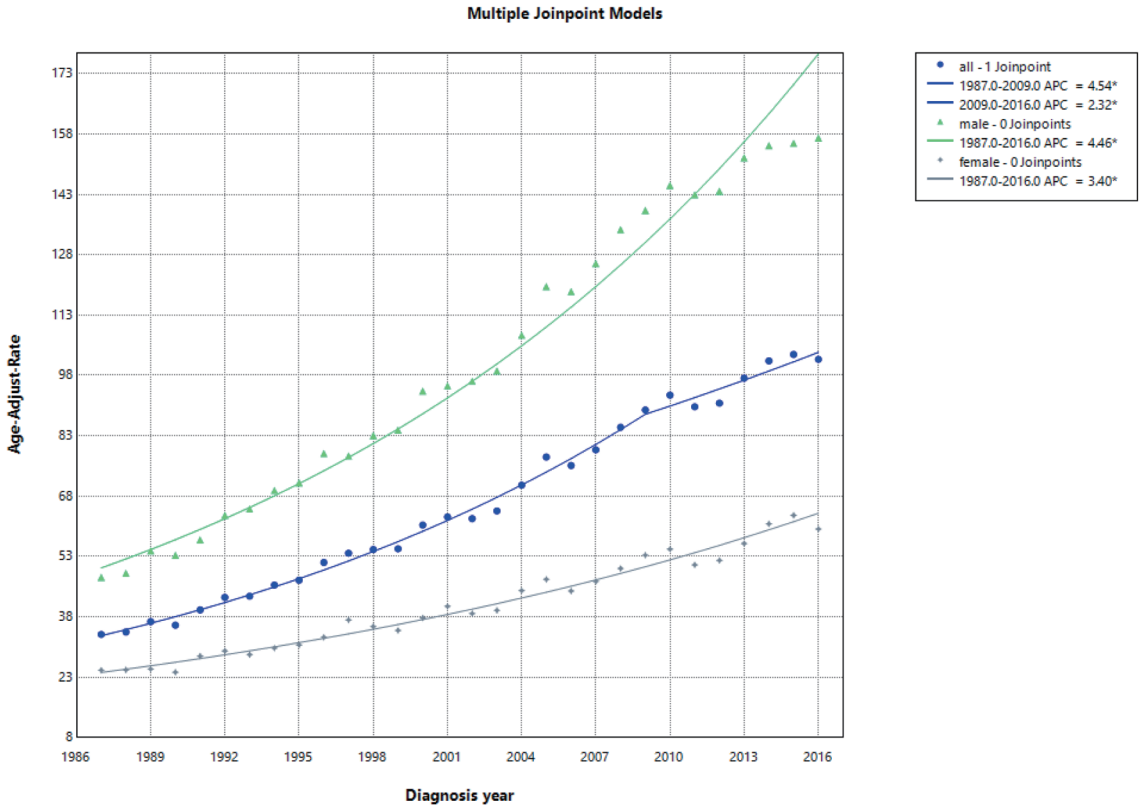

Fig. 1. Associations of age and calendar period of diagnosis with CMM incidence among all patients. CMM, cutaneous malignant melanoma.

ments, with a pivotal shift in 2009. Between 1987 and 2009, there was a pronounced upward trend, with a substantial APC of 4.45%. However, after 2009, the trend moderated, displaying a somewhat less steep incline compared to the earlier period (Fig. 1).

Period trends in age-adjusted CMM incidence rates

We began our analysis by examining the period trends in the evolving incidence rates of CMM in the United States. Figures 2a and b illustrate the fluctuations in age-specific CMM incidence rates across various observation periods (years) for American males and females from 1987 to 2016. Overall, CMM incidence rates tend to be higher in older age groups, regardless of the observation period. Across all five age groups, an upward trajectory in CMM incidence rates is evident over the years. Notably, the 80–84 age group among males exhibits a significantly pronounced upward trend, with an APC of 6.04%. Among females, the 75–79 age group shows a significant upward trend, with an APC of 3.69%. In the male population, the incidence rate of CMM in the 85+ age group initially declines, followed by an increase, with an inflection point in 1989. In contrast, the incidence rate in the 80–84 age group initially rises rapidly but decelerates post-2010, with an APC of 0.31%. Among females, the 75–79 age group shows an initial decline followed by an increase in CMM incidence rates, with the inflection point occurring in 1990.

Cohort trends in age-adjusted CMM incidence rates

Figures 3a and b provide insights into the fluctuations in age-specific CMM incidence rates based on birth cohorts for American males and females from 1987 to 2016. The results from the birth cohort models reveal that, particularly among males aged 65 and older, individuals of the same age but from different birth years show a gradual increase in CMM incidence rates as their birth years advance. In contrast, the differences in birth cohort trends were less pronounced between females and males. CMM incidence rates across various age groups generally show a gradual increase as birth years progress. However, in the elderly male population, the overall incidence rate of CMM exceeded that of elderly females. Notably, male CMM incidence rates, spanning different age groups and birth cohorts, surpassed 44, with males aged 85 and older showing the highest incidence rates.

Age-period-cohort models

As shown by the longitudinal age curve in Figure 4, the incidence rate of skin melanoma peaks in the older age groups. Figure 5a illustrates the rising trend over time, with a notable increase starting around 2000. Rates exceeding 1.0 after 2000 indicate that the incidence of CMM is increasing during these periods compared to the reference period. The shaded areas represent confidence intervals, highlighting a significant upward trend over time. Figure 5b demonstrates a steady rise in incidence rates among recent birth cohorts, indicating that individuals born more recently are at a higher risk of developing CMM than those from earlier cohorts. This increase is particularly sharp for cohorts born after 1940, with a pronounced risk for those born after 1950.

Discussion

The incidence rate of CMM among elderly individuals in the Unit-

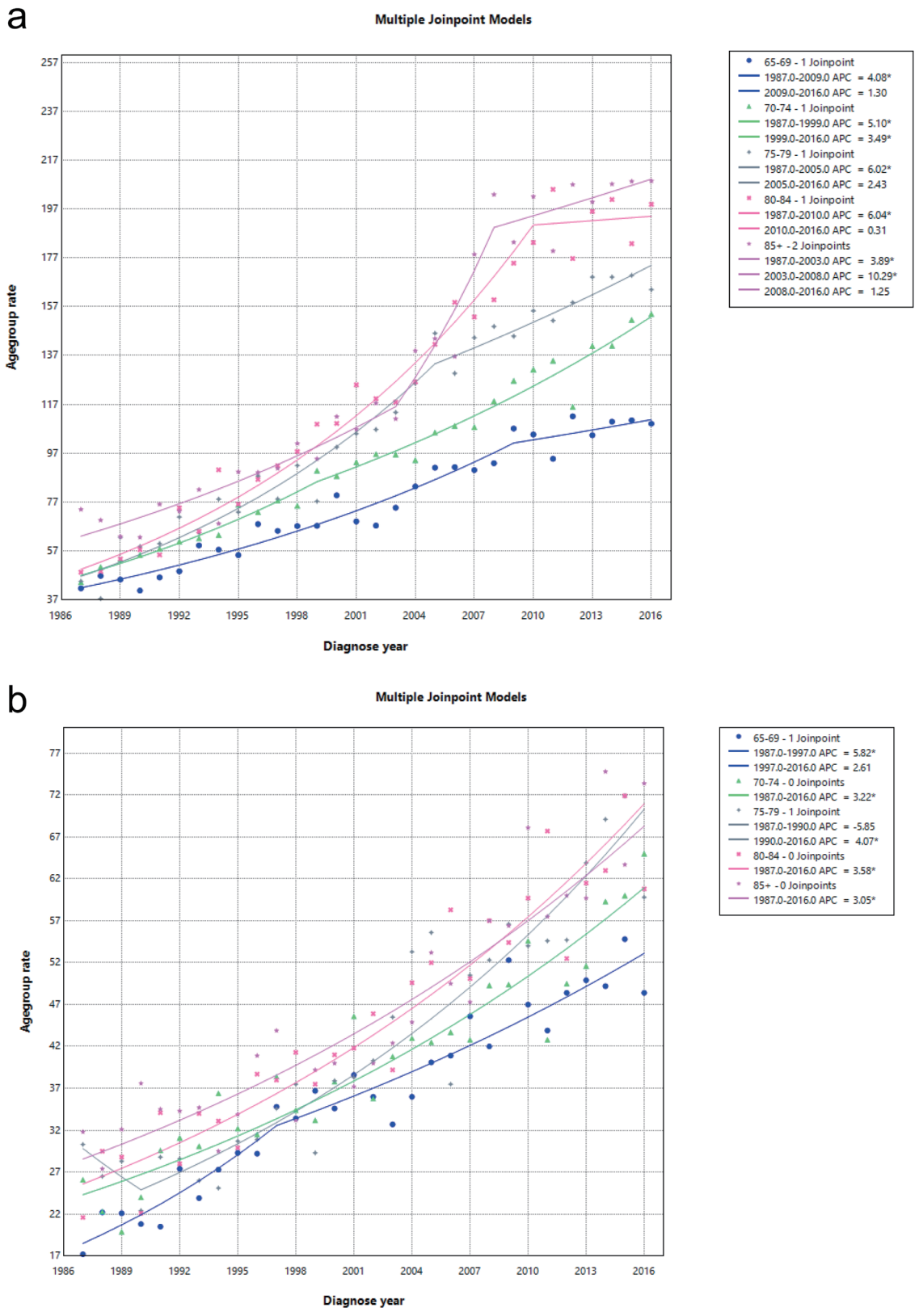

Fig. 2. Associations of age and period of diagnosis with CMM (cutaneous malignant melanoma). (a) Association of age and calendar period of diagnosis with CMM incidence among male patients. (b) Association of age and calendar period of diagnosis with CMM incidence among female patients.

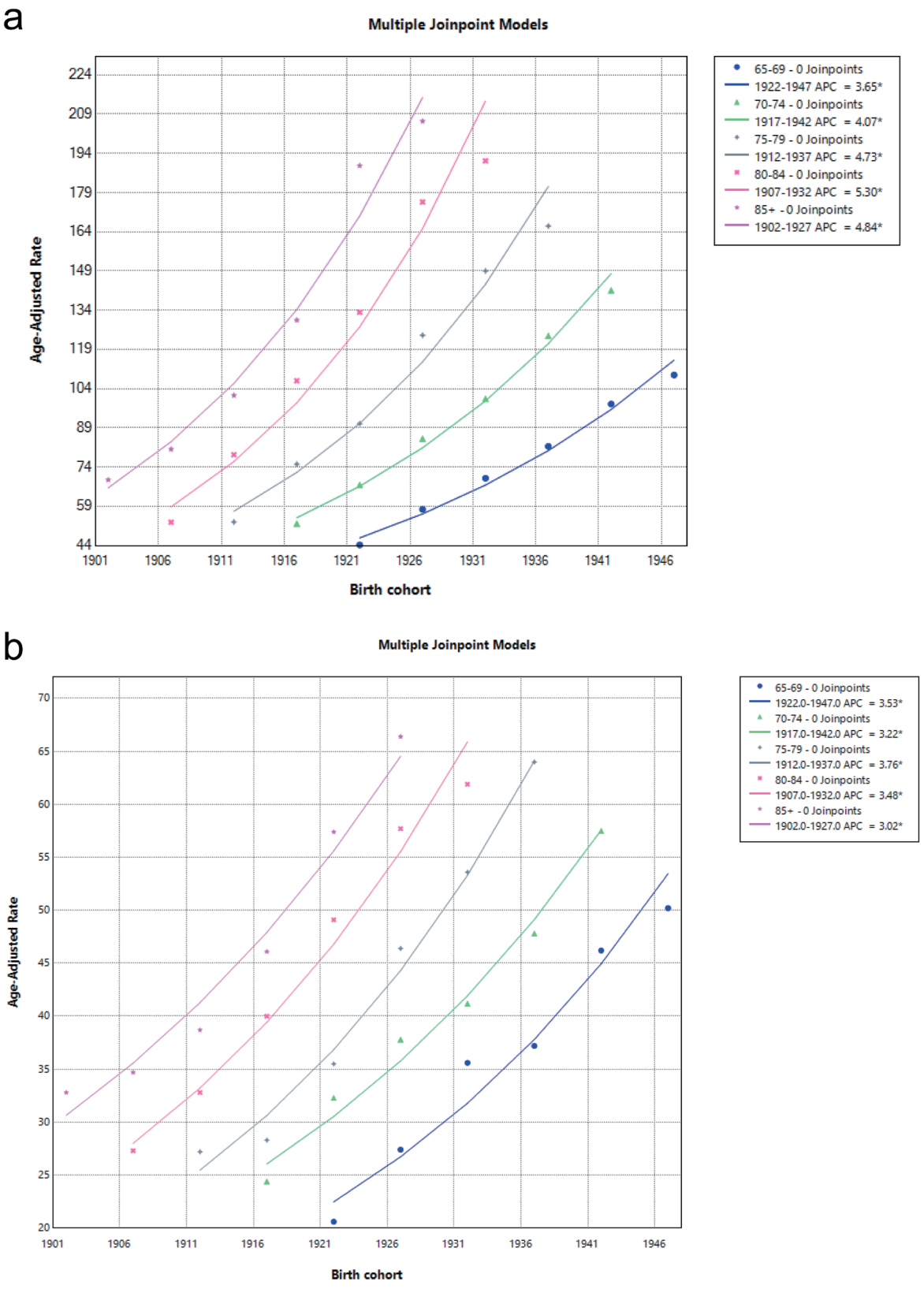

Fig. 3. Associations of age and birth cohort with CMM (cutaneous malignant melanoma). (a) Association of age and birth cohort with CMM incidence among male patients. (b) Association of age and birth cohort with CMM incidence among female patients.

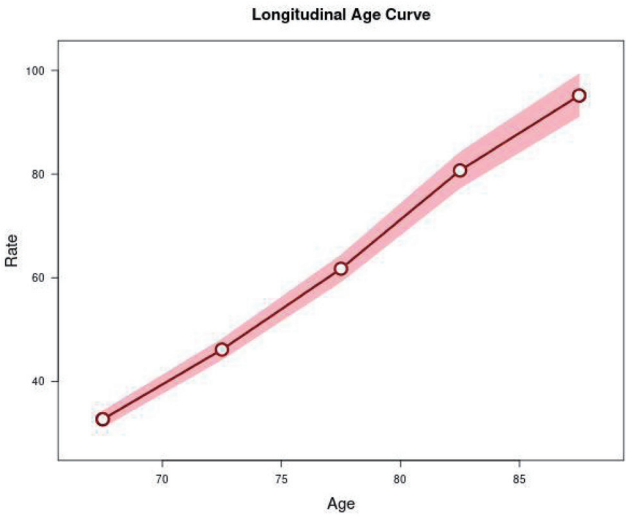

Fig. 4. Longitudinal age curves of CMM in SEER 8 from 1978 to 2016 and corresponding 95% CI. CI, confidence interval; CMM, cutaneous malignant melanoma; SEER, Surveillance, Epidemiology, and End Results.

ed States varies significantly across different genders, races, and geographic locations. Utah had the highest incidence of CMM in older adults from 2012 to 2016 (95% CI, 1.442–1.571). Both Hawaii and Utah show a high rate of increase in CMM incidence. In 2019, Utah had the highest incidence of distant melanoma among white women, with an incidence rate of 3.45 cases per 100,000.[24] This high incidence aligns with broader trends in the United States, where melanoma incidence has been rising, particularly among older adults.[25] The high prevalence in Hawaii and Utah may be related to lifestyle factors that increase Ultraviolet (UV) exposure, such as outdoor activities and tanning habits.[8] Changes in clothing styles and recreational behaviors over recent decades have also contributed to increased UV exposure, particularly in sunny states such as Hawaii.[26] A comparative analysis across different time periods reveals a notable upward trend in overall incidence rates in recent decades.

Utilizing Joinpoint regression to provide a detailed description and statistical analysis of temporal trends in CMM incidence rates among elderly individuals in the United States, this study uncovers a sustained upward trend in CMM incidence over the past three decades. Various factors may contribute to this trend, including prolonged exposure to ultraviolet radiation, indoor tanning, immunosuppression, the presence of moles (nevi), family history, and obesity.[8] This trend is also partly driven by an aging population in industrialized countries, where older individuals are more susceptible to melanoma due to cumulative sun exposure over their lifetimes.[12] A global study analyzing trends from 1990 to 2019 found that the age-standardized incidence rate of malignant skin melanoma increased in most countries, with a positive correlation between incidence rates and the Human Development Index.[27] In the United States, the incidence of melanoma in the lower limbs and hips increased significantly from 2000 to 2019, particularly among those over 50 years old, highlighting a rising trend in older age groups.[28] While the incidence of CMM in the elderly has risen rapidly, the rate of change has slowed since 2010. The inflection point in 2009 suggests that certain factors or interventions may have started impacting melanoma incidence trends after that year. Distinct trends in incidence rates were observed among different male age groups, with the 2009 inflection point, as seen in a melanoma epidemiology study in Hungary, signaling a potential shift influenced by various factors or interventions.[29] The slowdown in malignant melanoma incidence among older adults around 2010 can be attributed to changes in diagnostic practices, healthcare utilization, and demographic shifts. These factors have influenced the detection and management of melanoma in the elderly, potentially stabilizing incidence rates. This suggests that the rise in melanoma incidence prior to 2010 may partly reflect overdiagnosis rather than a genuine increase in disease prevalence. During this period, healthcare utilization increased, including more frequent dermatology visits and skin biopsies for Medicare beneficiaries. This enhanced surveillance may have led to the detection of more early melanomas, many of which do not progress to invasive disease. The stabilization of incidence rates in older adults may indicate efforts to address overdiagnosis, as the detection of non-invasive melanomas has increased without a corresponding rise in mortality, suggesting that many detected cases may not require aggressive treatment.[30]

After adjusting for age, the incidence of CMM exhibited an in-

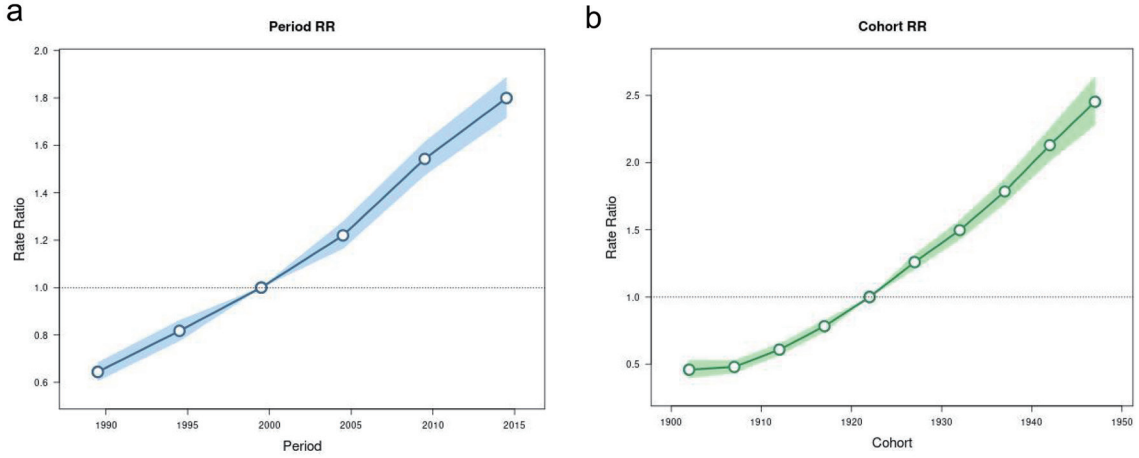

Fig. 5. Incidence rate ratios by period for CMM incidence in SEER 8 (a). Incidence rate ratios by birth cohort for CMM incidence in SEER 8 database (b). Shaded bands indicate the 95% CI. CI, confidence interval; CMM, cutaneous malignant melanoma; RR, rate ratio; SEER, Surveillance, Epidemiology, and End Results.

creasing trend over the observation period. However, in some age groups, notably the 80–84 age group, the growth rate of incidence slowed during a specific period. Incidence rates in elderly females were lower than in elderly males, and overall, the rate of increase in incidence among elderly females was less pronounced than among males. Studies by Bellenghi *et al*.[31] suggest that differences in incidence rates can be partially attributed to gender-related behaviors. Additionally, melanoma incidence in older men exceeds that of women, possibly due to lower rates of skin self-examination and fewer dermatologic visits among men.[32] Furthermore, in the elderly population, melanoma is more frequently located in the head and neck area, with specific subtypes such as lentigo malignant melanoma being more common, along with a higher Breslow index, presence of ulceration, and increased mitotic rate compared to younger individuals.[13] Recent findings indicate that biological variations, including genetic and epigenetic factors, play a crucial role. In recent years, the rate of incidence growth has decelerated, potentially reflecting increased awareness of skin health, more stringent sun protection measures, or improved early detection.[7]

CMM remains a substantial health concern, and according to other research, the number of cases of cutaneous malignant melanoma in the elderly population is expected to rise.[33] These findings underscore the continued importance of vigilance regarding CMM among the elderly and the necessity for prevention and early detection strategies. Age, time period, and birth cohort effects are all critical factors in comprehending the heightened incidence of CMM.

While this study provides valuable insights into the trends in CMM incidence among the elderly in the United States, several limitations must be acknowledged. First, the study relies on data that may be subject to reporting biases, particularly regarding the accuracy and completeness of melanoma diagnoses over time. Second, while Joinpoint analysis offers a robust method for identifying temporal trends, it does not account for potential confounding variables that might influence these trends, such as changes in public awareness, diagnostic technologies, or healthcare access. Third, the study does not differentiate between various histopathological subtypes of CMM, which could have different etiologies and prognoses, potentially leading to an oversimplification of the observed trends. Fourth, geographic variations in sun exposure, socioeconomic factors, and healthcare infrastructure across the United States may not be fully captured in the analysis, limiting the generalizability of the findings. Lastly, the observational nature of this study precludes the establishment of causal relationships between the identified trends and specific risk factors or interventions. Future research should address these limitations by incorporating more granular data, exploring the impact of specific interventions, and utilizing more sophisticated statistical techniques to account for potential confounders.

Conclusions

The incidence of CMM among the elderly population in the United States has shown a notable upward trend over the past three decades. This increase is influenced by a complex interplay of factors, including UV exposure, changes in healthcare practices, and demographic shifts. While the incidence rate continues to rise, particularly in certain geographic regions, there has been a recent deceleration in this trend, possibly due to increased awareness, early detection, and the potential impact of overdiagnosis. Despite this, CMM remains a significant health concern, especially among older adults, necessitating continued efforts in prevention, early diagnosis, and research into targeted interventions. Addressing the limitations identified in this study will be crucial for advancing our understanding of CMM trends and for developing more effective public health strategies to mitigate the burden of melanoma in the aging population.

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Conflict of interest

Jun Lyu is an editorial board member of *Cancer Screening and Prevention*. The authors report no other competing interests.

Author contributions

Conception and design (RFD), data collection and assembly (RFD, JYG), data analysis and interpretation, manuscript writing, and final approval of manuscript (RFD, JYG, JL, JLY). All authors have approved the final version and publication of the manuscript.

Ethical statement

We signed the "Surveillance, Epidemiology, and End Results Program Data-Use Agreement" in accordance with the requirements for using the Surveillance, Epidemiology, and End Results (SEER) database. Therefore, we obtained the data with permission and were able to download it from the SEER database. This article does not fall within the scope of ethics committee review and, according to current ethical standards, does not require ethical approval. The data used in this paper were collected from public databases and are considered public resources.

Data sharing statement

All data generated or analyzed during this study are included in this published article and its supplementary information files. All related information was derived from the SEER program using SEER*Stat version 8.4.1 (https://seer.cancer.gov/).

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Original Article

Helicobacter pylori Infection and Risk of Cardia Gastric Cancer in Asian Countries: A Systematic Review and Meta-analysis

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Abstract

Background and objectives: The incidence of cardia gastric cancer (CGC) is rising worldwide, particularly in East Asia. There has been a debate over whether *Helicobacter pylori* (*H. pylori*) constitutes a risk factor for CGC. This study aimed to evaluate the relative risk of *H. pylori* infection and CGC in Asian countries.

Methods: Relevant studies examining *H. pylori* and CGC were searched in PubMed, Embase, and Web of Science from their inception to June 30, 2024. Either a random-effect model or a fixed-effect model was used to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). Sensitivity analyses and assessments of publication bias were performed. The stability of results was evaluated in cases where publication bias was detected.

Results: A total of 24 studies were included in the meta-analysis. A significant association between *H. pylori* and CGC was observed (OR = 2.20, 95% CI 1.73–2.80). In a subgroup analysis of different countries, a significant association was observed in East Asian countries, including China (OR = 2.12, 95% CI 1.63–2.77), Japan (OR = 2.21, 95% CI 1.16–4.20), and Korea (OR = 2.36, 95% CI 1.58–3.54), but not in Iran (OR = 1.48, 95% CI 0.77–2.84). The pooled OR from five prospective cohort studies revealed a strong association between *H. pylori* and CGC (OR = 2.32, 95% CI 1.47–3.66).

Conclusions: East Asia bears a significant burden of *H. pylori*-related CGC. A clear association between *H. pylori* infection and CGC was observed in this region.

Introduction

According to statistical sources, there were more than 960,000 new cases of gastric cancer worldwide in 2022, with about 660,000 fatalities. Gastric cancer is the fifth most prevalent malignancy and the fifth leading cause of cancer-related death globally. It can be divided into two subsites based on anatomical location: cardia gastric cancer (CGC) and non-cardia gastric cancer (NCGC).[1] East Asia has the highest incidence of CGC in the world, and the incidence continues to show an upward trend.[2]

East Asia has a 54.1% overall *Helicobacter pylori* (*H. pylori*) infection rate, which is significantly higher than that of other regions. Furthermore, this region bears a high burden of gastric cancer related to *H. pylori* infection.[3] Several studies have identified a substantial connection between *H. pylori* infection and NCGC.[4] Correa described the progression from *H. pylori* infection, chronic gastritis, chronic atrophic gastritis, intestinal metaplasia, and atypical hyperplasia to cancer, a pathway widely recognized in NCGC.[5] Additionally, *H. pylori* eradication therapy has been shown to reduce the incidence of gastric cancer and related mortality.[6] However, the relationship between *H. pylori* and CGC has remained controversial due to the unique anatomical position of CGC. A previous meta-analysis found a positive correlation in East Asia (odds ratio (OR) = 2.9, 95% confidence interval (CI) 2.3–2.6) and a negative correlation in the West (OR = 0.8, 95% CI 0.6–1.0).[4] A recent multicenter prospective case-control study of 500,000 Chinese individuals found that at least 78% of NCGC

Keywords: Cardia gastric cancer; *Helicobacter pylori*; Risk factor; East Asia; Meta-analysis; Systematic review.

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and 62% of CGC can be attributed to *H. pylori*.[7] However, the latest meta-analysis included studies on duplicate populations, which may have affected the results.[4] Therefore, our goal was to more convincingly evaluate the relative risk of *H. pylori* infection and CGC in Asian populations.

Materials and methods

Search strategy

This systematic review and meta-analysis, registered in PROSPERO (CRD42023432339), was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement.[8] All relevant studies were retrieved from three databases, including PubMed, Embase, and Web of Science, from their inception up to June 30, 2024. The following search terms were utilized: ("cardia" OR "proximal" OR "esophagogastric junction" OR "gastroesophageal junction") AND ("neoplasm" OR "tumor" OR "cancer" OR "neoplasia" OR "carcinoma" OR "adenocarcinoma") AND ("*helicobacter pylori*" OR "*helicobacter nemestrinae*" OR "*campylobacter pylori*" OR "*H. pylori*"). The detailed search strategy is provided in Table S1. Additionally, reference lists of relevant studies were checked to identify additional eligible studies. Two collaborators independently retrieved and evaluated the included studies, with disagreements resolved through consensus.

Inclusion and exclusion

All studies investigating the association between *H. pylori* infection and CGC in Asian populations were considered for screening. *H. pylori* detection methods included histology, rapid urease testing, culture, serology, or carbon-urea breath testing. The inclusion criteria were carefully defined: (1) the study type included case-control, cross-sectional, or cohort studies; (2) the exposure variable was *H. pylori* infection; (3) the case group involved CGC, and the control group was free of gastric cancer; (4) the population was from Asian countries; (5) studies provided sufficient data to estimate ORs or risk ratios; and (6) studies were published in English with full text available. We attempted to exclude other types of gastroesophageal junction carcinoma, such as distal esophageal adenocarcinoma. Case reports, letters, comments, reviews, and duplicate publications were excluded.

Data extraction

Two authors extracted detailed information from each included study, including the first author, publication year, country, patient characteristics (age, sex), study design (study type, follow-up time, method of *H. pylori* detection), definition of CGC, and details of the case and control groups (sample size, *H. pylori* infection status, outcomes).

Quality assessment and risk of bias

The methodological quality of eligible studies was independently assessed by two authors using the Newcastle-Ottawa Scale for case-control and cohort studies. Studies with scores ranging from seven to nine points were considered high quality. The risk of bias was assessed using ROBINS-E, a tool for non-randomized exposure studies, across several domains, including confounding, participant selection, exposure measurement, post-exposure interventions, missing data, outcome measurement, and selection of reported results.[9] A study was considered to have a high risk of bias if bias was present in at least one of the seven domains.

Statistical analysis

Pooled ORs with 95% CIs were calculated to assess the association between *H. pylori* and CGC. The model used was based on heterogeneity results, which were analyzed using the chi-squared (χ^2) test (Cochran's Q) and the inconsistency index (I^2). A random-effect model was employed when significant heterogeneity was identified (χ^2 $P < 0.05$ or $I^2 > 50\%$); otherwise, a fixed-effect model was applied. The aim of our analysis was to investigate the association between *H. pylori* infection and the risk of CGC. Subgroup analyses were conducted to explore effect modification based on study-level factors such as country, detection time of *H. pylori*, publication year, and duration of follow-up. Sensitivity analyses were performed to explore potential sources of heterogeneity. Publication bias was evaluated using funnel plots (Begg's and Egger's regression tests). All analyses were performed using Review Manager V.5.4 and STATA 15, with statistical significance defined as $P < 0.05$.

Results

Literature search and study characteristics

The PRISMA flowchart is presented in Figure 1. The preliminary literature search yielded a total of 4,308 articles from PubMed, Embase, and Web of Science. After removing 1,829 duplicates and excluding 2,393 unrelated articles based on title and abstract screening, 86 studies remained for full-text review. Finally, 24 full-text articles were included in the final analysis,[7,10–32] after excluding six studies that used duplicate populations.[33–38] The analysis involved 2,529 CGC cases and 52,556 control subjects. The study populations of the 24 included studies were from Asian countries (eight in China, nine in Japan, five in Korea, and two in Iran). The characteristics and quality scores of the eligible articles are shown in Table 1. Using the ROBINS-E risk of bias tool, three studies were rated as high risk of bias, six as moderate risk, and the remainder as low risk (Fig. 2).

Pooled data

The pooled OR for the association between *H. pylori* and CGC in Asian countries was 2.20 (95% CI 1.73–2.80), with significant heterogeneity (I^2 = 66%, $P < 0.001$), based on a random-effect model (Fig. 3).

Subgroup analysis

Stratification by country

The included studies were from Asian countries. A significant association between *H. pylori* and CGC was observed in East Asian countries, including China (OR = 2.12 [95% CI 1.63–2.77], I^2 = 58%, $P < 0.001$), Japan (OR = 2.21 [95% CI 1.16–4.20], I^2 = 78%, $P = 0.02$), and Korea (OR = 2.36 [95% CI 1.58–3.54], I^2 = 15%, $P < 0.01$), but not in Iran (OR = 1.48 [95% CI 0.77–2.84], I^2 = 0%, $P = 0.24$) (Fig. 4a).

Stratification by detection time of *H. pylori*

It is possible that *H. pylori* infection could be cleared as the cancer progresses.[39,40] Identifying the status of *H. pylori* before malignancy develops can help reduce false-negative results to some extent. Seven articles, including five cohort studies and two nested case-control studies, detected the status of *H. pylori* before the onset of CGC. A comparable correlation was observed regardless of *H. pylori* detection time (OR = 2.03 [95% CI 1.32–3.12], I^2 = 69%,

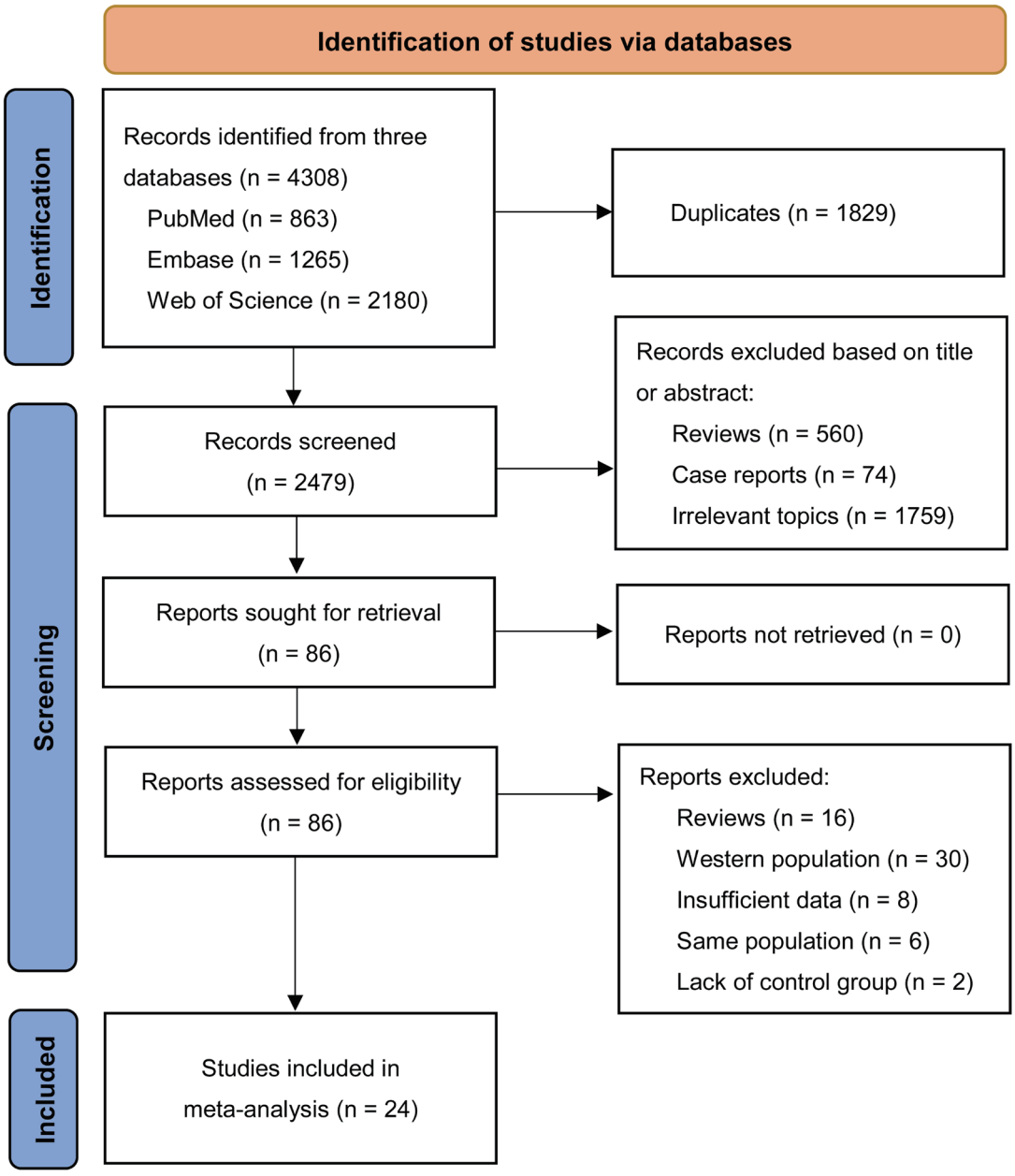


Fig. 1. Flowchart of the systematic search and selection process.

P = 0.001; OR = 2.27 [95% CI 1.67–3.09], I^2 = 66%, P < 0.001) (Fig. 4b).

Stratification by publication time

Between 1990–2000 and 2000–2010, there was a significant association between *H. pylori* and CGC (OR = 2.83 [95% CI 1.55–5.19], I^2 = 58%, P < 0.001; OR = 2.10 [95% CI 1.55–2.86], I^2 = 48%, P < 0.001). However, the pooled studies published from 2010 to 2020 showed no correlation (OR = 1.56 [95% CI 0.73–3.32], I^2 = 72%, P = 0.25) (Fig. 5a).

Stratification by follow-up time

Seven of the studies were retrospective or prospective cohort studies, with five being prospective studies with a follow-up period of more than five years. The pooled data analysis of five studies revealed a notable association between *H. pylori* and CGC (OR = 2.32 [95% CI 1.47–3.66], I^2 = 75%, P < 0.001), while no correlation was seen in two studies with follow-ups of less than five years (OR = 0.94 [95% CI 0.36–2.46], I^2 = 0%, P = 0.90) (Fig. 5b).

Publication bias and sensitivity analysis

Publication bias was evaluated using Begg's and Egger's tests. No substantial publication bias was observed (P-value of Begg's test = 0.980, P-value of Egger's test = 0.503) (Fig. S1). Furthermore, visual inspection of the funnel plot shapes revealed no significant evidence of asymmetry among the studies (Fig. 6). The study by

Table 1. Characteristics of 24 studies

First author	Year	Country	Design	Study period	Median follow-up (year)	H.pylori method	Age (year)	Male (%)	Number of CGC/ control	Definition of CGC	NOS
Chen[10]	2009	Taiwan, China	case-control	2000–2009	–	ELISA	CGC: 64.53 ± 2.17 Control: 63.27 ± 1.73	100 100	41/205	within 5mm to GEJ	8
Cho[11]	2010	Korea	case-control	2003.6–2007.4	–	ELISA	Case: 58.1 ± 12.0 Control: 53.0 ± 7.0	68.8 50.0	216/562	within 2cm distal to GEJ	8
Derakhshan[12]	2008	Iran	case-control	–	–	ELISA	CGC: 63.8 ± 7.1 Control:matched	69.8 –	53/53	within 2cm distal to GEJ	7
Gao[13]	2022	China	case-control	2010–2014	–	Immunoblot	CGC: 69.3 ± 7.9 Control: 66.3 ± 8.71	67.9 69.1	349/1,859	within 5cm to GEJ	8
Horii[14]	2011	Japan	case-control	2000.8–2009.1	–	histology/RUT/ELISA	CGC: 68.7 ± 9.5 Control: 61.7 ± 8.3	87.0 93.5	23/46	within 2cm to GEJ	8
Inoue[15]	2020	Japan	cohort	1993–1994	18	ELISA	56.7 ± 8.3	Case: 62.2 Control: 37.7	50/1,8511	anatomical position	7
Kamangar[16]	2007	China	case-cohort	1985–2001	10	ELISA	CGC: 55.5 ± 7.7 Control: 51.9 ± 8.9	60.3 45.3	582/992	proximal 3cm of the stomach	8
Kato[17]	2004	Japan	case-control	–	–	ELISA	–	–	86/6,578	–	7
Kikuchi[18]	1995	Japan	case-control	1988–1992	–	ELISA	GC: 20–40 Control: 15–44	45.7 43.6	35/203	–	7
Kikuchi[19]	2000	Japan	case-control	1993.6–1995.7	–	ELISA	matched	GC: 66.1 Control: 51.3	186/1,007	upper third of stomach	7
Kim[20]	1997	Korea	case-control	1994	–	histology/RUT	GC: 57.3 Control: 56.9	65 61.9	12/160	anatomical position	6
Kim[21]	2012	Korea	case-control	2003.6–2011.2	–	histology/RUT/ ELISA/tissue culture	Case: 60.3 ± 12.3 Control: 55.9 ± 11.9	67.3 33.7	60/270	within 2cm below GEJ	8
Komoto[22]	1998	Japan	case-control	1991–1996	–	ELISA	GC: 64.9 ± 1.2 Control: 62.4 ± 1.1	78.10 matched	14/105	within 20mm distal to GEJ	8
Lee[23]	1998	Korea	case-control	1992–1995	–	RUT	GC: 54.4 Control: 40.5	67.4 71.7	17/113	anatomical position	7
Shakeri[24]	2015	Iran	case-control	2004.12–2011.12	–	ELISA,multiplex serology	CGC: 66.3 ± 11.1 Mcontrol: 64.5 ± 9.1	78.2 77.2	142/276	-	8
Shibata[25]	1996	Japan	case-control	–	–	histology	GC: 62 Control: 61.8	74 74	5/50	upper third of stomach	6
Shin[26]	2005	Korea	nested case-control	1993–1999	2.6	ELISA	Cases: 63.0 Control:matched	66 matched	6/24	–	8

(continued)

Table 1. *(continued)*

First author	Year	Country	Design	Study period	Median follow-up (year)	H.pylori method	Age (year)	Male (%)	Number of CGC/ control	Definition of CGC	NOS
Suzuki[27]	2007	Japan	nested case-control	1970.1–2001.12	2	ELISA	CGC: 70 ± 11 Control: –	54.5 58.9	22/1,042	–	7
Wu[28]	2009	Taiwan, China	case-control	2000–2007	–	ELISA	GC: 63.2 ± 13.5 Control: 40.2 ± 6.2	62.8 51.6	29/395	within 3cm distal to GEJ	8
Xie[29]	2020	China	cross-sectional	2014.1–2016.6	–	13C	CGC: 62.65 ± 5.27 Control: 53.30 ± 7.94	41.96 60.87	23/1,225	–	8
Yamaoka[30]	1999	Japan	case-control	–	–	ELISA	GC: 64.5 Control: matched	72.7 matched	23/23	cardia and fundus	6
Yan[32]	2024	China	case-cohort	2015–2017	6.3	13C	54.7	41.8	76/18,233	–	8
Yang[7]	2021	China	case-cohort	2004.6–2008.7	10.1	Immunoblot	CGC: 61.2 ± 8.6 Control: 59.1 ± 9.9	75.0 69.0	436/500	–	8
Yuan[31]	1999	China	case-cohort	1986–1989	5.2	ELISA	GC: 63.4 ± 5.6 Control: matched	–	43/124	–	8

CGC, cardia gastric cancer; ELISA, enzyme linked immunosorbent assay; GC, gastric cancer; GEJ, gastroesophageal junction; NOS, Newcastle-Ottawa Scale; RUT, rapid urease test.

Fig. 2. Assessment of risk of bias using the ROBINS-E.

Kikuchi *et al*.[19] deviated from the line of symmetry, which could be attributed to the study population being primarily composed of patients under the age of 40. We assessed the contribution of each study to the overall pooled OR through a leave-one-out sensitivity

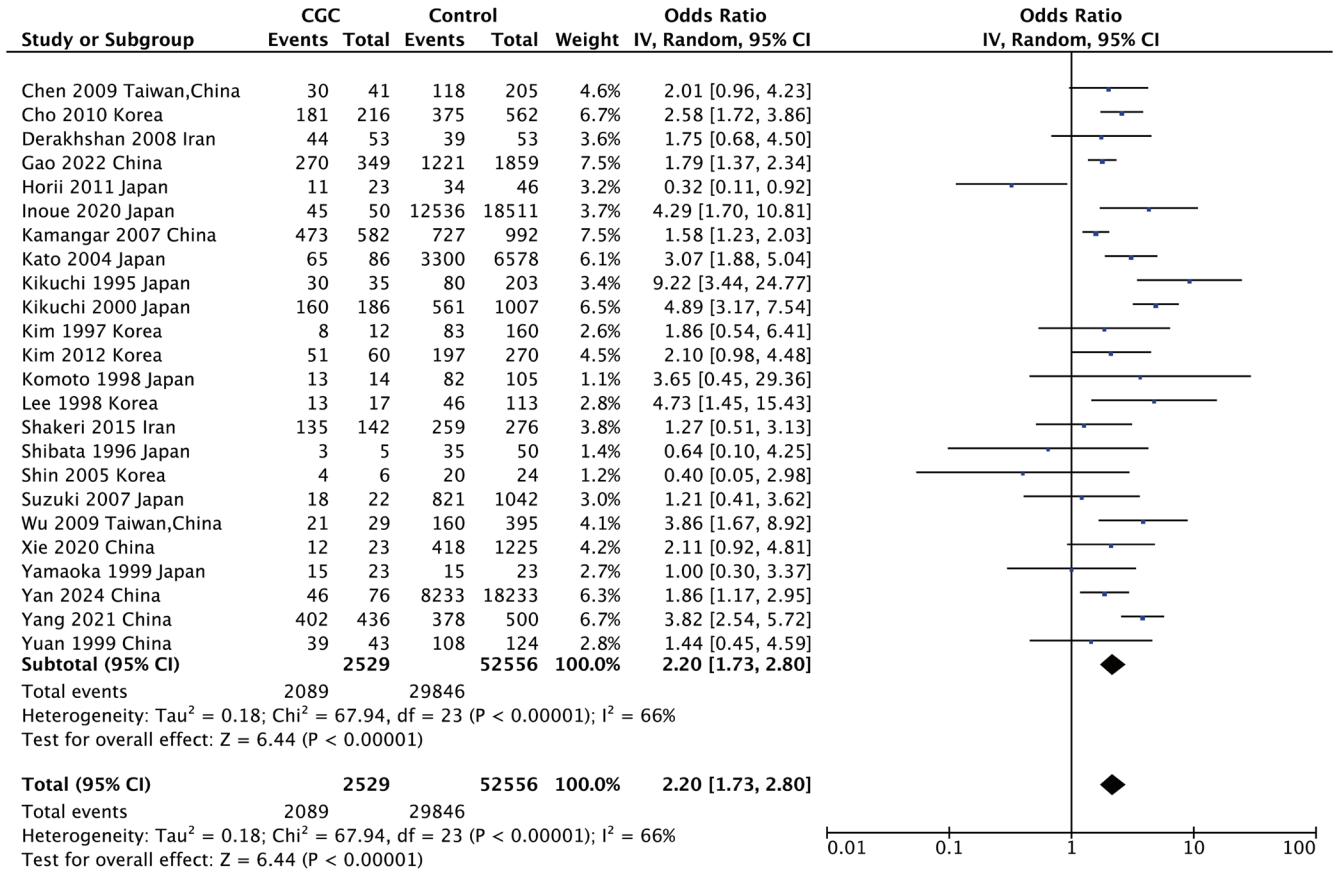


Fig. 3. Forest plot for *Helicobacter pylori* infection among cardia gastric cancer. CI, confidence interval; IV, inverse variance.

analysis. The stability of the results was confirmed, as no single study significantly influenced the pooled OR (Fig. 7). When combined with the results of the subgroup analysis, the heterogeneity was attributed to various factors, including differences in the definition of CGC, study population, and *H. pylori* detection methods.

Discussion

The incidence rate of CGC is increasing in Asian countries. The proportion of CGC in Japan has risen from 2.3% to 10.0% in recent years.[41] In high-incidence areas of China, the rate can reach 50/100,000.[42] The risk factors and etiology of CGC are debatable but appear to be related to geography and ethnicity. Previous studies have yielded contradictory conclusions about the relationship between *H. pylori* and CGC.[4,43–46] Han *et al*.[4] conducted a meta-analysis that demonstrated a significant association between *H. pylori* infection and CGC in East Asia, but the analysis included studies using duplicated populations. Moreover, the most recent meta-analysis by Gu *et al*.[47] completed the literature search in December 2021. Recent papers could significantly affect these conclusions. Therefore, we updated the literature and excluded studies using duplicated populations to analyze any new associations between *H. pylori* and CGC in Asia.

A total of 24 studies were included in our meta-analysis. The *H. pylori* infection rate in CGC cases was 2.20 times greater than that in the control group, confirming that *H. pylori* is a clear risk factor for CGC. At the same time, we conducted a subgroup analysis for different countries. The outcomes revealed that infected individuals from East Asia (China, Japan, and Korea) had a twofold higher risk of developing CGC than the control group, whereas no correlation was found in Iran. Our analysis only included two Western Asia-related studies from Iran. Western Asia has much lower age-standardized incidence rates of stomach and esophageal malignancies than Eastern Asia, which ranks first.[48] Additionally, several previous studies confirmed a null or negative correlation between *H. pylori* and CGC in Western populations or low-incidence regions.[4,43,44,46] Hence, a positive association between *H. pylori* and CGC was only observed in East Asia.

Because of the unique location of the esophagogastric junction (GEJ), CGC is likely a heterogeneous tumor originating from different mucosal types. Internationally, various definitions and classification standards exist. The Siewert classification, proposed in 1987 and extensively used, refers to adenocarcinomas located within 5 cm of the GEJ, including type I (located 1 to 5 cm above the GEJ), type II (located 1 cm above to 2 cm below the GEJ), and type III (located 2 to 5 cm below the GEJ).[49] The Kyoto International Consensus Report in 2022 stated that adenocarcinomas within 1 cm of the GEJ should be classified as "cardia cancer".[50] Several studies have found geographical variations in the pathogenesis of CGC. In the West, it is often associated with excessive gastric acid damage caused by gastroesophageal reflux disease, similar to esophageal adenocarcinoma. In East Asia, CGC is associated with gastric mucosal atrophy induced by *H. pylori* infection, similar to distal gastric cancer.[12,51,52] Urabe *et al*.[53] demonstrated

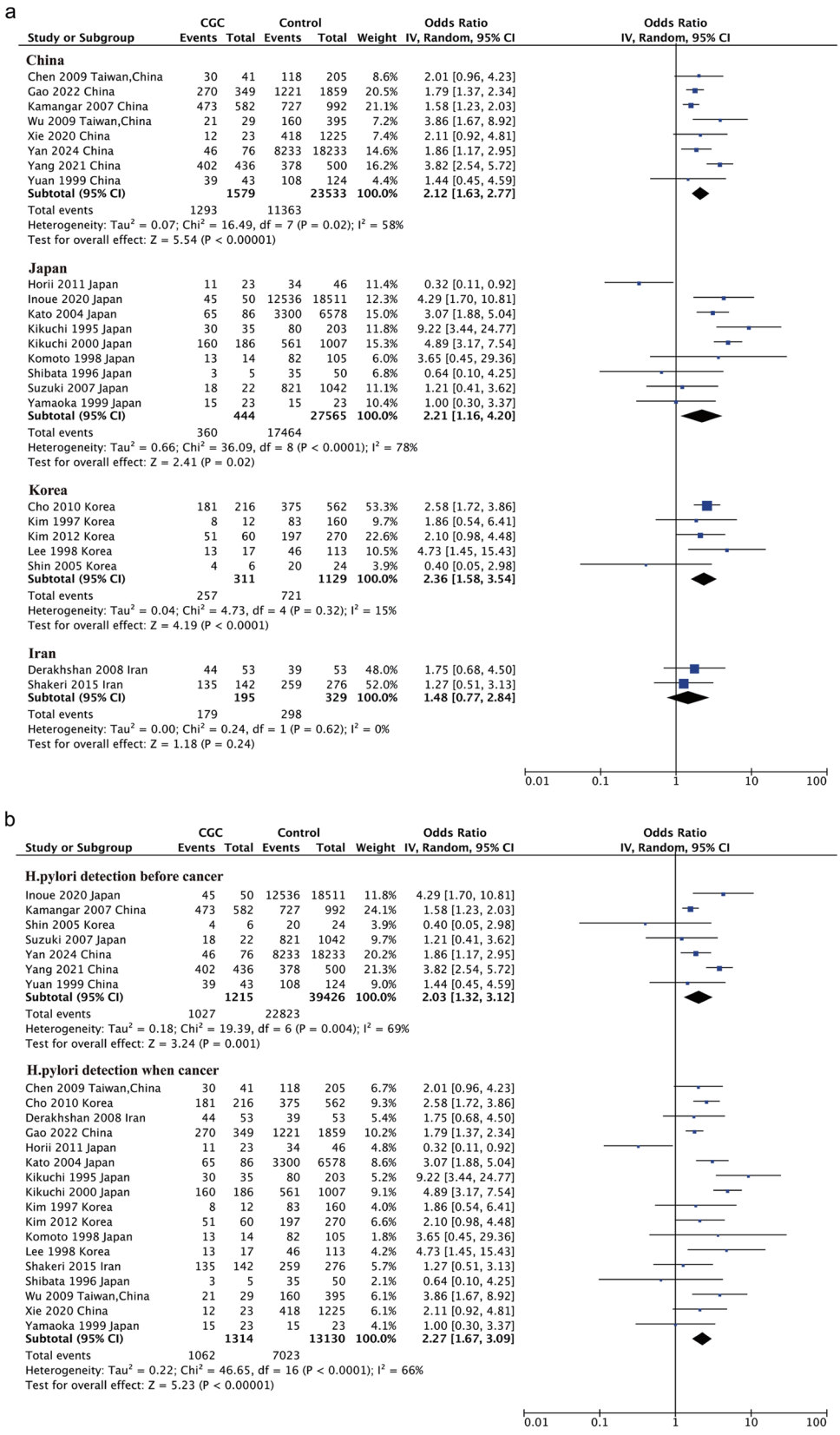
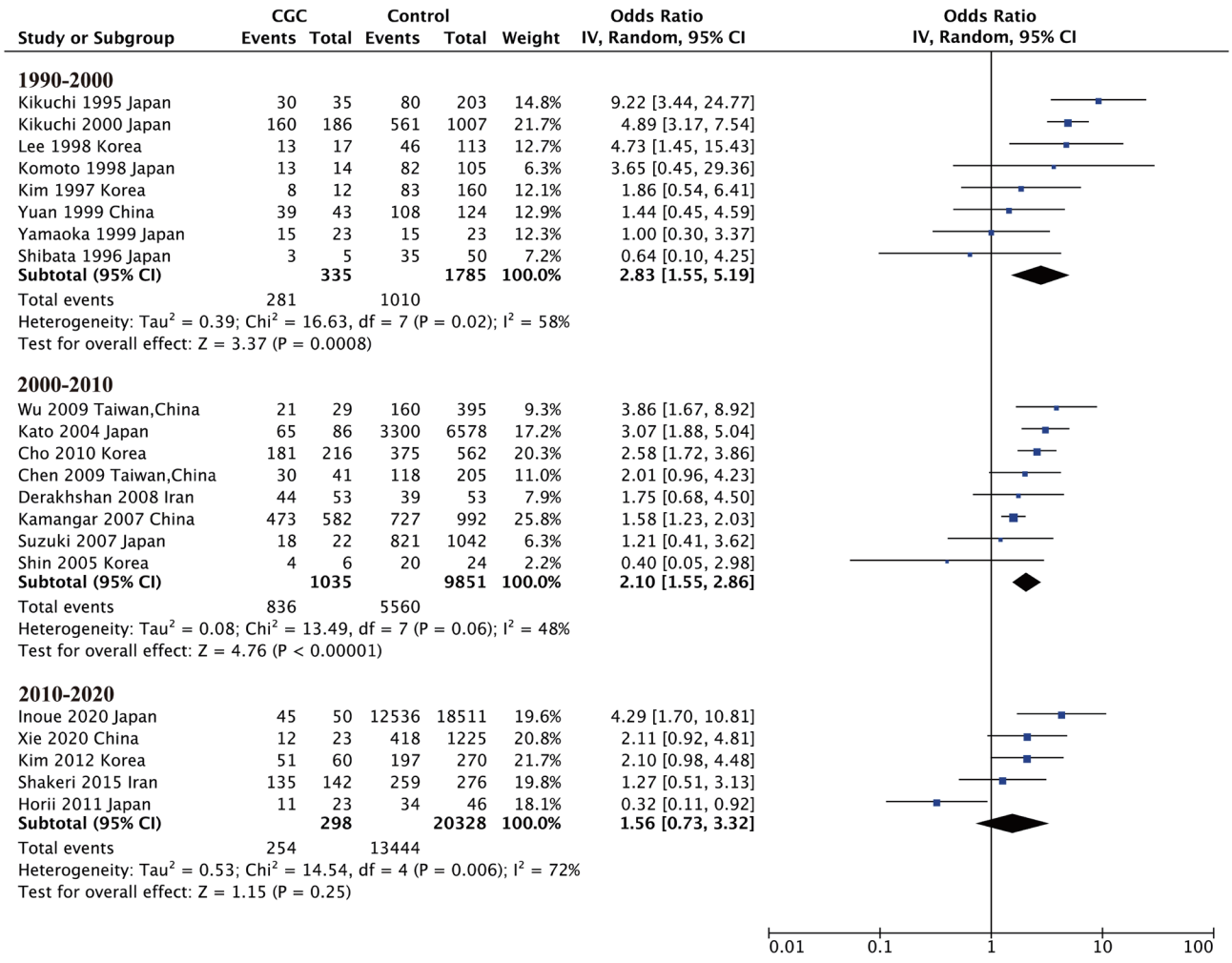


Fig. 4. Subgroup analysis (a) by countries; (b) by detection time of *Helicobacter pylori*. CGC, cardia gastric cancer; CI, confidence interval; IV, inverse variance,

a



b

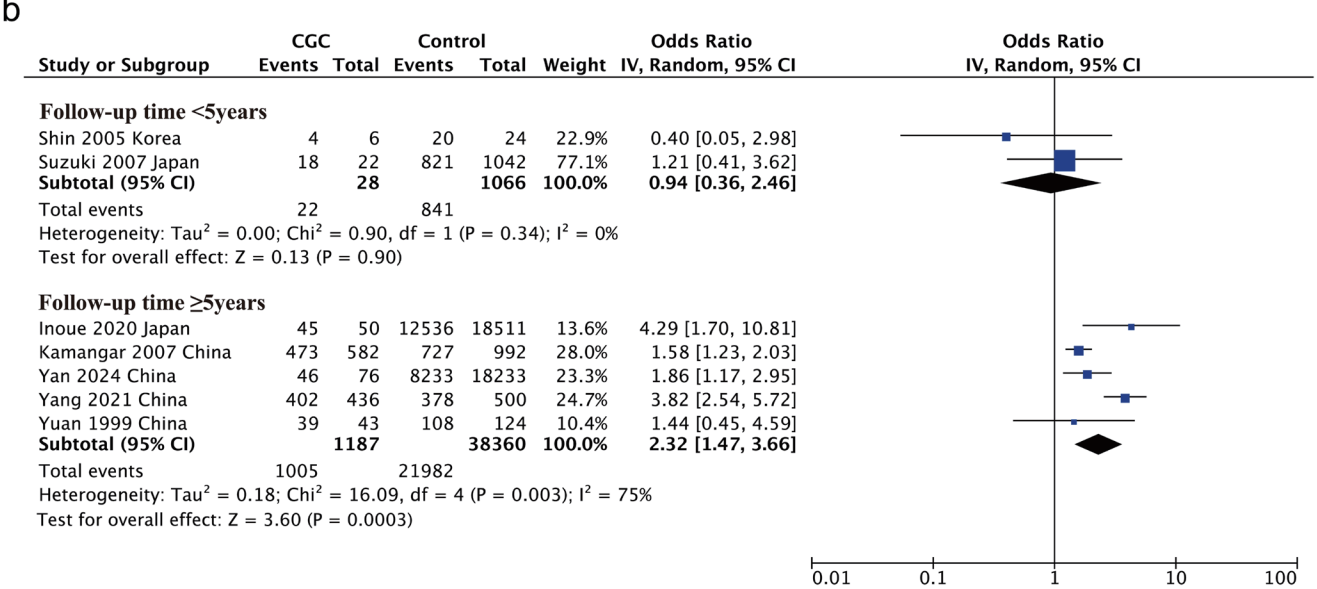


Fig. 5. Subgroup analysis (a) by publication time; (b) by duration of follow-up time. CGC, cardia gastric cancer; CI, confidence interval; IV, inverse variance.

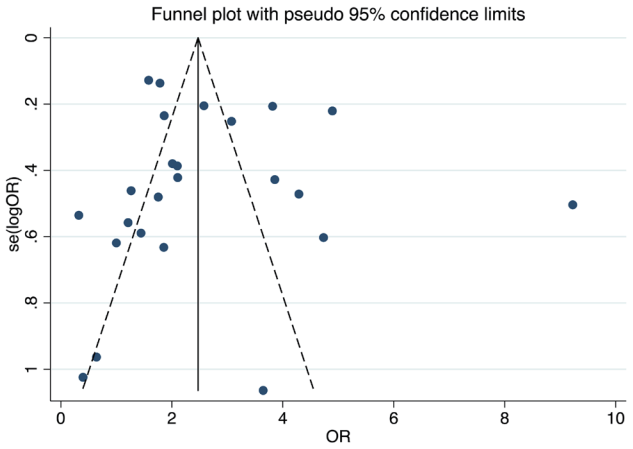


Fig. 6. Funnel plot. OR, odds ratio.

that gastric cancers and type III adenocarcinoma of the esophagogastric junction had a similar background mucosal type. Based on survey data from three high-incidence areas in China, the long-term morbidity and mortality risk of CGC increased as the severity of cardia mucosal lesions increased. Trend analysis revealed a positive correlation between the degree of mucosal lesions and the *H. pylori* infection rate.[54] To summarize, severe mucosal atrophy and intestinal metaplasia increase the risk of CGC to some extent. The question of whether its occurrence and development follow the path of Correa needs further exploration. Additionally, the strain type of *H. pylori* and host susceptibility also play roles in the complex process of carcinogenesis. Current clinical research has found that compared to NCGC, CGC tends to present at a later pTNM stage and has worse clinical outcomes.[55] Therefore, identifying risk factors, performing early screening, and implementing interventions are critical in clinical practice.

In addition, the accuracy of *H. pylori* status is affected by various factors. The first issue involves methodological limitations. In one prospective study, the relationship between *H. pylori* and the risk of NCGC assessed by immunoblot was more than threefold higher than that assessed by ELISA (enzyme linked immunosorbent assay),[56] indicating that detection techniques have different sensitivity levels. Secondly, anti-*H. pylori* therapy for atrophic gastritis prior to malignancy should be considered. Moreover, both histological infection and serological antibody titers of *H. pylori* may be cleared or decreased as cancer progresses.[39] As a result, the *H. pylori* infection rate may be underestimated due to the factors described above. We performed a subgroup analysis based on the detection time of *H. pylori* and found that there was a consistent correlation regardless of detection time, and heterogeneity was not primarily due to this factor. The results from five prospective cohort studies appear to be more reliable. We did not conduct a subgroup analysis of different detection methods because only a few studies employed the immunoblot method.

This meta-analysis has certain limitations. First, although we performed sensitivity analysis to evaluate the stability of the results, the source of heterogeneity remains somewhat difficult to explain. At least half of the studies contributed to the heterogeneity. On the one hand, the criteria for CGC in various studies have not been standardized, resulting in heterogeneity in study populations. Second, various methods were used to detect *H. pylori*. Studies focusing on younger patients may also have contributed to the heterogeneity. Third, the majority of the included studies were retrospective case-control studies, which are subject to selection bias

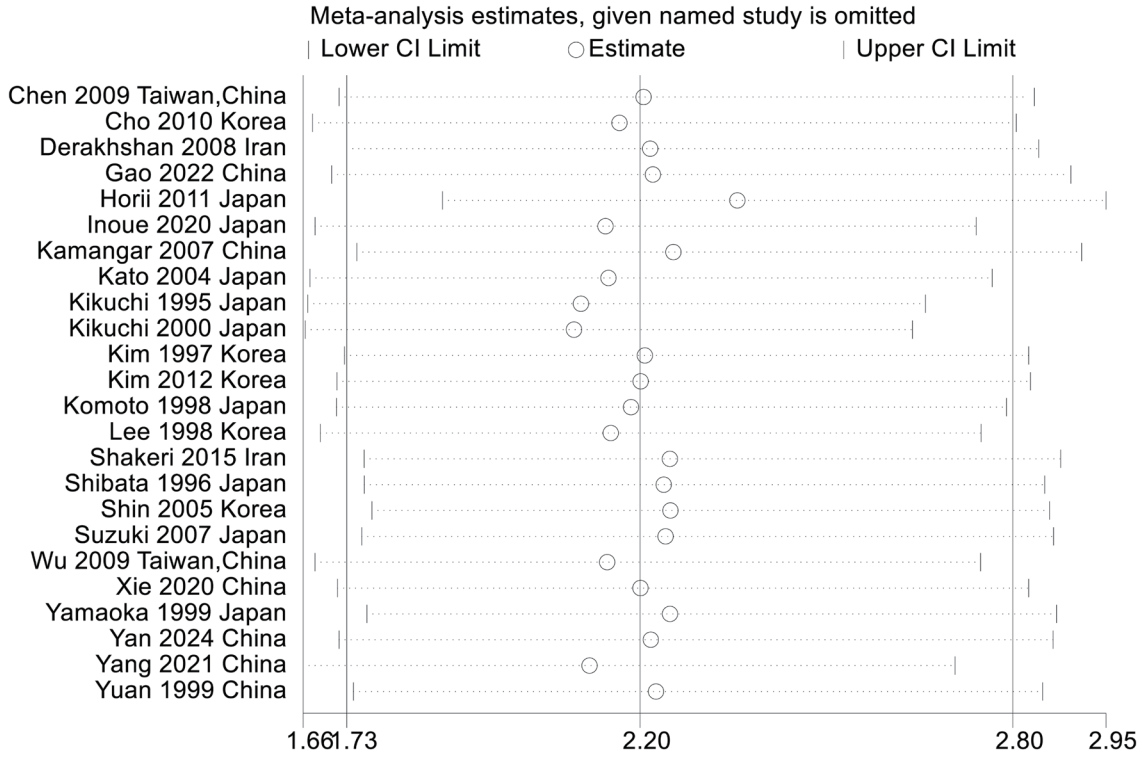


Fig. 7. Sensitivity analysis. CI, confidence interval.

and confounding variables. Although most studies were matched by age and gender, other risk factors, including diet, smoking, alcohol consumption, gastroesophageal reflux disease, and gastrointestinal ulcers, may confound the relationship between *H. pylori* and CGC.[57] Additional adjustments are required for these risk variables. Furthermore, our conclusions primarily focus on East Asian populations due to the lack of sufficient information from countries outside East Asia. Despite the constraints of our study, we updated the latest relevant literature. In addition, we identified and excluded studies using duplicate population cohorts, compared to a prior meta-analysis.[4] In summary, *H. pylori* infection is a risk factor for CGC in East Asia. It is meaningful to conduct early detection and intervention.

Conclusions

East Asia bears a significant burden of CGC, where a positive association between *H. pylori* infection and CGC has been observed. We anticipate the development of more reliable endoscopic techniques and pathology diagnostics to better identify the origin of cancer in the gastroesophageal junction area. Additionally, more valuable prospective cohort studies and randomized controlled trials are needed. Identification of risk factors and early intervention are critical for reducing the incidence of CGC.

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Conflict of interest

One of the authors, Prof. Ruihua Shi has been an associate editor of *Cancer Screening and Prevention* since March 2022. There are no other conflicts of interest regarding the publication of this paper.

Author contributions

Material preparation, data collection, and analysis (YNZ, YD), writing of the first draft of the manuscript (YNZ). All authors contributed to the study's conception and design and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data sharing statement

The datasets used in support of the findings of this study are available from the corresponding author at ruihuashi@126.com upon request.

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Review Article

Advances in Screening and Early Diagnosis of Pancreatic Cancer

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Abstract

Pancreatic cancer (PC) remains a formidable challenge in oncology due to its notoriously poor prognosis, often resulting from late-stage diagnosis. Early detection through effective screening methods is crucial not only to improving patient outcomes but also to enhancing their quality of life. This review focuses on the latest advancements in PC screening and early diagnostic strategies. Key areas include the integration of artificial intelligence in radiology, the search for novel biomarkers, and the development of predictive models. This review aimed to provide a comprehensive overview, serving as a stepping stone toward transforming early detection strategies for PC in the digital age.

Introduction

Aggressive progression and insidious symptoms often result in pancreatic cancer (PC) patients receiving diagnoses at late stages. Therefore, treatment landscapes and survival rates have remained pessimistic, even with advancements in oncology. According to Cancer Statistics 2024, PC ranked 4th among the leading causes of cancer death across all age groups in the United States, with an estimated 66,440 new cases and 51,750 deaths reported in 2024.[1] In China, 118,672 new PC cases were reported in 2022, with an incidence rate of 4.4 per 100 and a mortality rate of 3.9 per 100. In contrast, global statistics reported 510,992 new cases, an incidence rate of 4.7 per 100, and a mortality rate of 4.2 per 100.[2]

Ethnically, the Asian population may be more susceptible to PC in the presence of certain disease backgrounds, such as gallstones and Crohn's disease.[3,4] Additionally, the large number of PC patients and deaths in China has created significant medical and socioeconomic burdens, warranting immediate attention. PC patients require a considerable amount of healthcare resources, leading to a substantial number of hospitalizations and medical costs significantly higher than those for other cancer types.[5] The rising incidence and associated costs have contributed to PC's growing burden, especially in regions with rapid economic growth and aging populations, such as China.[6,7] PC's 5-year overall survival rate is currently 13%.[1] Early diagnosis, however, holds great promise for improving patient outcomes, overall survival rates, and associated costs. Studies have shown that patients diagnosed at an early stage exhibit significantly improved survival outcomes, with a median overall survival of nearly 10 years compared to 1.5 years for those diagnosed at later stages.[8] Consequently, it is imminent to implement prevention strategies and early detection programs to screen this disease early.[7]

The challenge of conducting effective early screening for PC stems from three main factors: 1. The lack of indicative risk factors; 2. the absence of reliable, specific, and sensitive screening protocols; and 3. the relatively low prevalence of PC in the general population. The mechanisms behind PC incidence and progression remain poorly understood,[9] hindering the identification of serum biomarkers strongly associated with early disease onset. While the development of endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiopancreatography has improved sensitivity and specificity in PC screening, issues such as a shortage of trained operators and long appointment wait times have failed to meet clinical needs.[10] Furthermore, the low sensitivity and laborious protocols of current detection methods present significant obstacles to large-scale screening efforts.[11] Although serum biomarker carbohydrate antigen 19-9 (CA19-9) is routinely used in clinics to diagnose PC, its limited sensitivity and specificity undermine its

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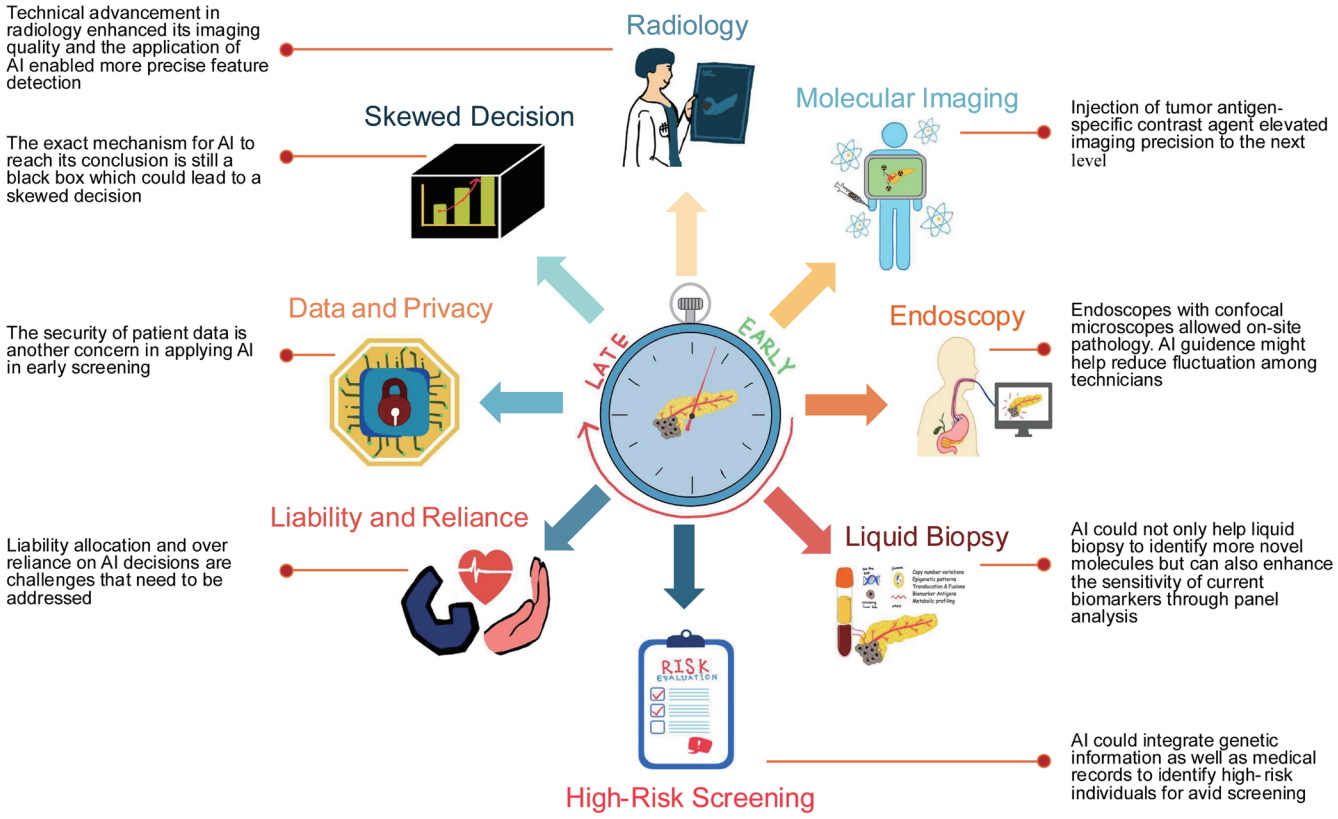

Fig. 1. An illustration of integrating artificial intelligence in various regimes to aid in identifying pancreatic cancer promptly. AI, artificial intelligence.

reliability in early detection despite widespread use.[12] Finally, the relatively low prevalence of PC makes extensive screening infeasible.[9] Therefore, further research into imaging techniques, early-stage biomarkers, and predictive risk factors is imperative for developing timely, specific, convenient, and cost-effective screening methods.

This review will discuss the latest advancements in early PC detection, including radiology, serum markers, and the incorporation of artificial intelligence (AI). By critically evaluating the strengths and limitations of existing technologies, this study endeavored to elucidate optimal strategies for early detection protocol development for scientists, engineers, and physicians (Fig. 1).

Advancements in diagnostic technologies

Significant strides have been made in radiology for screening pancreatic lesions in recent years. High-resolution computed tomography (CT), magnetic resonance imaging (MRI) with diffusion-weighted sequences, and EUS have emerged as front-line tools for identifying pancreatic lesions at early stages, when curative interventions may still be viable. EUS, particularly contrast-enhanced EUS, has enabled efficient imaging, differential diagnosis, and staging of pancreatic lesions that might otherwise be missed by other imaging modalities.[13,14] Concurrently, advancements in more sensitive molecular detection methods have rapidly expanded biomarker research, leading to the identification of reliable hematological indicators for early PC screening. Liquid biopsy, a non-invasive technique, can detect various biomarkers, from circulating tumor cells to tumor RNA, in blood, urine, and pancreatic juice.[15] As more novel biomarkers, including proteins, genetic signatures, DNA, RNA, and exosomes, are identified through liquid biopsy,[15] integrated data may help reveal the mechanisms of cancer development. Beyond screening, the application of liquid biopsy extends to monitoring treatment response, evaluating prognosis, and identifying therapeutic targets.[15]

In addition to developing more precise imaging and sampling methods, the integration of AI into nearly every aspect of early diagnostic tools has been unprecedented and indispensable. AI-driven approaches show promise in streamlining the diagnostic process. By synthesizing diverse sources of information from radiology, serum biomarker panels, health records, etc., AI programs can potentially identify high-risk individuals and early-stage pancreatic lesions with much greater accuracy than human capabilities.[8,16] Undoubtedly, the incorporation of AI will enhance the efficiency and precision of medical professionals' work. However, various concerns accompany these advancements, requiring comprehensive solutions to address biases, transparency, privacy, liability, and ethical considerations.[17]

CT, positron emission tomography (PET)-CT, & MRI

Diffusion-weighted imaging (DWI) and contrast were used to further enhance MRI scan details. By analyzing water molecules, DWI MRI can reveal tissue microstructures, enabling differentiation between healthy and pathological regions with increased sensitivity.[18] MRI with DWI significantly improves diagnostic accuracy and the detection of early-stage cancer.[19] Through the use of contrast agent injections, dynamic contrast-enhanced MRI (DCE-MRI) allows for both qualitative and quantitative assessments of

tumor lesions. Although quantitative DCE-MRI is currently limited to clinical trials, ongoing efforts are proposing standardized protocols for recruiting DCE-MRI to clinical practice.[20]

Fibroblast activation protein (FAP), predominantly found in activated fibroblasts associated with cancer, chronic inflammation, and fibrosis, is a type II transmembrane protease with both dipeptidyl peptidase and endopeptidase activities. FAP is involved in tissue remodeling, angiogenesis, and collagen degradation. The FAP inhibitor (FAPI) is a radiolabeled quinoline tracer designed for PET.[21] Specifically, [68Ga]Ga-FAPI-04 PET has demonstrated high expression in various cancers, including those with low [18F]-FDG affinity, and minimal uptake in most healthy tissues. Recent studies of [68Ga]Ga-FAPI-04 PET suggest its potential to predict tumor invasiveness, provide prognostic information, and assist in treatment decision-making.[22,23]

The increasing detail in medical imaging introduces an overwhelming amount of information, often indecipherable to the human eye, providing an opportunity for AI to excel. AI applications in medical imaging have ushered in a new era of early PC diagnosis, where robust feature detection and subtle pattern recognition are now possible. Machine learning and deep learning algorithms are particularly adept at analyzing complex imaging datasets from medical scans, including CT, MRI, and PET scans, giving rise to the new field of "radiomics".[24,25] These algorithms can detect subtle changes in pancreatic morphology and identify small, potentially malignant lesions that may escape traditional radiological interpretation, allowing clinicians to detect pancreatic abnormalities at an earlier and potentially more treatable stage. By training algorithms with CT or MRI scans labeled with PC lesions, they have shown higher sensitivity for PC diagnosis compared to radiologists.[26] Deep learning and radiomics not only enhance the accuracy and efficiency of PC diagnosis but also demonstrate a high level of generalizability, accommodating individuals from various ethnic backgrounds (The performance of AI models was evaluated using several key measures. The models achieved a mean accuracy of 89.4%, ranging from 71.6% to 99%. The area under the curve had a mean value of 88.05%, ranging from 86% to 95.3%. Precision averaged 69.1%, ranging from 14% to 99.5%. Sensitivity was high, with a mean of 91.3%, ranging from 60% to 99.9%, while specificity averaged 83.2%, with a range of 69.5% to 100%. These results indicate strong overall performance across different metrics).[16,26] Li *et al*.[27] also developed a novel causality-driven graph neural network to analyze CT scans. This innovative learning algorithm yielded promising results in enhancing the stability and generalization of early PC diagnosis and may serve as a valuable clinical tool in the foreseeable future. AI technologies undoubtedly hold great promise in developing automated systems to identify subtle features indicative of early-stage PC. While there is still a long way to go before AI technologies can function independently in medical diagnosis, they could significantly aid physicians in improving early detection rates and patient outcomes.[28]

In summary, enhanced visualization and AI integration in medical imaging have significantly improved the accuracy and efficiency of early detection, precise staging, and treatment planning for PC.

Molecular imaging

In addition to detecting PC early by analyzing image features, Zhu *et al*.[29] developed a nanoplatform to deliver MRI contrast agents with cancer specificity. These peptide-functionalized polymeric magnetic nanoparticles were selectively internalized by PC cells through specific bonding. This differential binding created a contrast enhancement between healthy and cancerous pancreatic tissue and holds promise for targeted imaging in the early diagnosis of PC.[29] A similar approach, where molecular-level targets were selected to enable specific and sensitive imaging, was applied in functional imaging techniques, including single-photon emission computed tomography and PET. Wang *et al*.[30] used a radioactively labeled inhibitor to integrin α5 (ITGA5), a protein specifically overexpressed in the pancreatic stroma, to enhance single-photon emission computed tomography/CT scans of PC in a mouse xenograft model. Though a preliminary study, this method offered valuable insights into how advances in imaging specificity and treatment specificity could complement each other.

AI also played a role in accelerating biomarker recognition that could be employed in molecular imaging. Combining AI with hyperpolarized magnetic resonance and multimodal imaging data facilitated the discovery of real-time biomarkers to detect PC early.[31] This fusion of AI with advanced imaging technologies holds great promise for transforming the early detection and management of PC.

Endoscopic ultrasonography

Challenges exist when applying EUS to the early detection of PC. Many different types of pancreatic lesions present with a similar hypoechoic appearance on EUS, making it difficult to differentiate between benign and malignant lesions based solely on images.[32] Moreover, for pancreatic tumors around 2–3 cm, EUS can achieve satisfying sensitivity compared to other radiological images, but this sensitivity drops rapidly as lesion size decreases.[33] It is especially challenging to widely adopt EUS for early diagnosis when lesions are usually minimal. Though EUS images alone sometimes fail to provide the sensitivity and accuracy desired for early PC diagnosis, its visual guidance is undoubtedly valuable and has led to advancements in operations, from biopsy of pancreatic tissue to treatment and symptom relief.[34]

The application of AI in EUS-related operations is also noteworthy. AI algorithms, incorporating artificial neural networks and region-based convolutional neural networks, have been used for early and precise PC identification. AI and endoscopists can help verify each other's judgments to avoid missed readings.[35] In a meta-analysis by Yin *et al*.,[36] AI-assisted image classification demonstrated an accuracy of 0.95 in PC prediction, a sensitivity of 93%, and a specificity of 90%. This high level of accuracy likely stems from AI's unbiased nature in reading image details, reducing the intrinsic variability among EUS operators.[37] Operating and interpreting EUS results require years of specialized training. Unequal distribution of EUS specialists can result in healthcare disparities, making certain populations more susceptible to missed early PC diagnoses. Certain AI algorithms have achieved specimen recognition levels comparable to EUS experts,[38] which could be crucial in reducing disparities in timely PC diagnosis due to a lack of specialists.

In conclusion, EUS and its associated procedures are foundational to the early diagnosis of pancreatic cancer, given their high diagnostic accuracy, safety, and versatility in obtaining tissue samples for cytological and histological assessments. AI image classification offers great support to endoscopists by providing additional security checks and could potentially reduce disparities in early PC diagnosis. Moreover, live AI-assisted EUS operations or training programs could help improve PC patient outcomes by reducing variability between skilled and less experienced EUS technicians.

Liquid biopsy

Exosomes are a significant liquid biopsy approach for the early diagnosis of PC due to their minimal invasiveness.[39] Research by Yu

et al.[39] developed a nanoliquid biopsy test to enhance PC exosome detection while addressing low specificity and sensitivity, labor-intensiveness, and technical obstacles. Liquid biopsy of cell-free DNA has also demonstrated its potential as an adjunct to standard care for PC patients.[40]

Piwi-interacting RNAs, which act as epigenetic modulators, were identified from pancreatic tissue through liquid biopsy to differentiate healthy individuals from PC patients. Additionally, the detection of Piwi-interacting RNAs enhanced the diagnostic potential of the serum marker CA19-9 for early PC detection.[41]

However, the effectiveness of liquid biopsies for early cancer detection varies greatly depending on the technique and tumor type. To improve performance, intensive inspections of the circulome and comprehensive profiling of a panel of biomarkers, including circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), extracellular vesicles, etc., could be applied, although the diagnostic validity and accuracy warrant further investigation.[42]

Liquid biopsy holds the potential to facilitate a prompt, minimally invasive, and accurate diagnosis of PC. As more molecules are discovered through liquid biopsy, understanding the genesis and progression of cancer will improve, expediting early PC detection.

Traditional serum markers

CA19-9 and carcinoembryonic antigen are widely used serum markers in clinical practice to screen PC, despite their unsatisfactory specificity and sensitivity.[43] CA19-9, the sole biomarker authorized by the United States Food and Drug Administration, is more indicative of treatment response monitoring than early PC detection.[44] Panel analysis of different biomarkers in combination with CA19-9 has enhanced the accuracy of early PC detection. Xiao *et al*.[45] created a detection panel consisting of the exosomal surface protein glypican-1, an exosomal cluster of differentiation-82, and serum CA19-9. This panel exhibited excellent diagnostic accuracy (AUC = 0.942) in distinguishing healthy individuals, pancreatitis patients, and PC patients, holding the potential to become a standard PC screening protocol.[45] Suehiro *et al*.[46] also evaluated the diagnostic performance of serum-methylated Homeobox A1 and methylated somatostatin in combination with CA19-9 using the combined restriction digital PCR assay. The sensitivity for stage I PC increased from 50% during a single-marker test of CA19-9 to above 85% when other biomarkers were included in the diagnosis.[46] This multiplex approach shows promise in improving the specificity and sensitivity of early PC screening.

Ongoing research is focused on identifying novel biomarkers and adjusting multi-marker panels. The diagnostic cocktail of traditional markers combined with other macromolecules and metabolic profiling data will further enhance screening methods to detect PC at earlier stages.

Other serum markers

Metabolomic profiling involves the comprehensive analysis of small-molecule metabolites in biological samples. Altered metabolic pathways in PC cells can lead to distinct metabolite profiles in patient biofluids and therefore could serve as a gateway for early detection and disease monitoring. Research has delved into the role of metabolites and genetic signatures, such as single nucleotide polymorphisms, in predicting PC risk to enable early diagnosis and therapeutic interventions.[47] Serum fatty acid synthase levels are significantly elevated in PC patients and have been proposed as a diagnostic marker for early PC detection.[48] However, it is still unclear how early fatty acid synthase levels rise in the bloodstream, which complicates determining an appropriate timeline for early PC diagnosis. Elevated levels of serum ferritin are also indicative of PC and could be applied to identify at-risk individuals for early intervention.[49]

Furthermore, chronic inflammation markers, including C-reactive protein, albumin, haptoglobin, and leukocytes, are associated with the risk of PC. Analysis of these expression patterns could potentially be used to assess PC risk.[50] Another notable advancement in isolating serum markers for PC involves utilizing a microfluidic immunoassay system for the rapid detection and semi-quantitative determination of the potential serum biomarker mesothelin.[51]

CTCs

Many CTCs enter the bloodstream early in tumorigenesis through passive shedding from the primary tumor site.[52] Therefore, CTCs are theoretically suitable for early cancer screening. CTCs were identified and analyzed in PC alongside other macromolecules through liquid biopsy for detection and early disease screening.[11] Vimentin was used as an antigen to extract serum CTCs in PC patients, presenting satisfactory diagnostic potency alongside CA19-9.[53] CTCs isolated from preoperative blood draws could predict the early recurrence of PC, rendering them a valuable tool for monitoring disease progression.[54] In addition to serum, CTCs and ctDNA from pancreatic juice have also been recognized for their contributions to early PC diagnosis.[55]

As more biomolecules become available through liquid biopsy, CTCs are increasingly evaluated alongside other biomarkers to provide more accurate and comprehensive information regarding early tumor genesis and disease progression.

Exosomes

Primarily extracted through liquid biopsy, tumor exosomes (T-Exos) have emerged as essential components of the biomarker panel for early PC diagnosis. Yu *et al*.[39] developed a nano-liquid biopsy assay to detect PC T-Exos with excellent specificity, ultrahigh sensitivity, and cost-effectiveness. T-Exos can be detected at concentrations as low as 78 pg/mL.[39] Moreover, Li *et al*.[56] employed a hierarchical surface-enhanced Raman scattering substrate and a rapid enrichment strategy using magnetic beads to successfully enhance the quantitative detection of exosomes specific to PC, even at early stages.

Circulating nucleotides

ctDNA is fragmented tumor DNA released from tumor sites and shows promise as a tumor-specific biomarker for PC.[57] ctDNA serves as a non-invasive tool for early diagnosis, molecular characterization, and monitoring of tumor progression in PC. While preoperative ctDNA is a prognostic marker for poor survival, postoperative ctDNA levels indicate minimal residual disease. ctDNA also shares genetic information with the primary tumor site, thus aiding in directing personalized treatment.[58]

Two main approaches to identifying genetic alterations in ctDNA are advanced PCR-based techniques, which are highly sensitive in targeting known mutations, and NGS-based techniques, which can analyze multiple alterations in a single experiment, albeit with a sacrifice of sensitivity.[59–61] Evaluation of ctDNA through liquid biopsy presents a promising tool for early diagnosis and personalized treatment of PC.[62] A recent study by Bayle *et al*.[63] found that ctDNA genetic testing could enhance and potentially substitute tissue testing, based on data from over 1,000 enrolled patients. However, detecting ctDNA at lower concentrations

remains challenging.[58] Additionally, normal aging and the accumulation of blood cell mutations could contribute to false positives in ctDNA analysis.[64]

Circular RNAs also show promise as biomarkers for early diagnosis. hsa_circ_0013587, identified through qRT-PCR, is elevated in serum samples of PC patients. Though detected in the early stages of PC, the expression of hsa_circ_0013587 is more upregulated in PC patients at later stages.[65] Therefore, guidelines and more reliable testing techniques are needed to ensure the detection of hsa_circ_0013587 at lower levels for early diagnosis. Long non-coding RNAs are also being explored as potential biomarkers for PC diagnosis and prognosis prediction, as they are involved in various cellular functions.[66]

Integration of information by AI

As tumor cells are a dynamic biological entity, it is nearly impossible to determine the existence of cancer-based on a singular result. Therefore, integrated information from a panel of multiple biomarkers, including proteins, genetic mutations, and epigenetic alterations, is being developed to improve diagnostic accuracy. To manage the overwhelming amount of information, AI has become a valuable tool for searching and interpreting non-invasive biomarkers for the timely detection and intervention of PC.[67]

A deep learning model, Pancreatic Cancer Detection with Artificial Intelligence, demonstrated high accuracy in detecting and classifying pancreatic lesions using non-contrast CT scans. Trained on a dataset of 3,208 patients from a single center, this model achieved an AUC ranging from 0.986 to 0.996 in a multicenter validation involving 6,239 patients across ten centers. It outperformed the average radiologist's performance by 34.1% in sensitivity and 6.3% in specificity for identifying pancreatic ductal adenocarcinoma. In real-world scenarios, the model achieved a sensitivity of 92.9% and a specificity of 99.9% in detecting lesions among 20,530 consecutive patients. Notably, the model's performance with non-contrast CT was comparable to radiology reports using contrast-enhanced CT when distinguishing common pancreatic lesion subtypes. This accuracy instills confidence in applying the model as a valuable tool for large-scale PC screening.[68]

Moreover, mass spectrometry, machine learning, and liquid biopsy have facilitated the identification of clusters of biomarkers for PC diagnosis.[69] By amalgamating multiple biomarkers, researchers aimed to overcome the limitations of existing screening tools and enhance the overall management of PC.

AI has been instrumental in compiling imaging data, biomarker profiles, and clinical information to identify subtle abnormalities indicative of PC.[16] Machine learning algorithms have helped integrate diverse data sources to enhance patient care.

Screening and identifying high-risk individuals

From an epidemiological perspective, it is impossible to screen the general population for PC. Therefore, medical professionals in primary care or community medical facilities must identify high-risk individuals to conduct routine and targeted screening. Routine EUS and/or MRI/magnetic resonance cholangiopancreatography (MRCP) are recommended for screening high-risk individuals once they are identified.[70]

The development of PC is influenced by both genetic and environmental factors.[7] Genetic factors include familial PC, hereditary pancreatitis, known genetic mutations, and syndromes that render certain populations more susceptible.[71] A genome-wide association study found that variants in the ABO locus are associated with a differential risk of PC, with blood types A and B contributing to a higher risk compared to blood type O.[72] SIK3 has been identified as a potential new susceptibility gene predisposing its carriers to PC.[73] Germline pathogenic variants of genes, including *BRCA1/2*, *PALB2*, *ATM*, and *RAD17*, are linked to familial PC cases.[74,75] Variations at the single nucleotide level also exerted an effect on PC risk; eight single nucleotide polymorphisms associated with increased susceptibility have been identified on chromosomes 13q22.1, 1q32.1, and 5p15.33.[76]

Furthermore, epigenetic modifications can alter PC risks. Joris *et al*.[75] investigated methylome data and identified 45 cytosine-phosphate-guanine (CpG) sites associated with PC risk. These genetic variations and their regulation predispose individuals to PC and can influence familial aggregation patterns, highlighting the importance of genetic testing in high-risk populations.

In addition to genetic factors, lifestyle choices such as alcohol consumption and smoking, medical histories such as diabetes and chronic pancreatitis, and environmental exposures play intricate roles in PC risk.[7] Interactions between genetic predisposition and environmental factors influence this risk. Significant associations have been found between poor oral hygiene and NR5A2 rs2816938, as well as between obesity and PDX1 rs9581943, highlighting gene-environment interactions.[51]

Collectively, lifestyle factors, medical histories, genetic polymorphisms, and gene-environment interactions influence the elevated risk of PC. Therefore, it is essential to conduct a comprehensive analysis of these various components. AI and machine learning can enhance patient risk stratification by integrating a range of input factors, streamlining the identification of high-risk individuals.[77] Risk models based on clinical characteristics, genetic polymorphisms, and biomarkers improve precision in disease recognition compared to models that rely solely on clinical factors.[78] Placido *et al*.[79] constructed AI models to retrospectively analyze clinical data from millions of patients in Denmark and the United States, identifying critical trajectories indicative of PC. These models can significantly enhance surveillance programs for at-risk patients to detect PC early.[79]

A combination of genetic, epigenetic, and environmental factors influences PC risk. Understanding the genetic backgrounds that predispose individuals to PC is crucial for early detection and intervention. Until widely available genetic testing and screening become a reality, AI algorithms that analyze medical records and lifestyle choices hold substantial promise in identifying at-risk individuals from the general population for further examination.

Challenges and advantages in applying AI to clinical settings

AI is a valuable tool that significantly enhances the early diagnosis of PC from various perspectives. Algorithms can efficiently identify at-risk individuals by processing substantial amounts of information from medical images, pathological examinations, biomarkers, and other factors.[8] AI algorithms equip medical professionals with precise decision-making tools for early screening, diagnosis, and management of PC.[80] This increased accessibility to convenient screening approaches may also help alleviate disparities in medical services for disease management.

However, the application of AI in clinical practice is not without concerns. Potential biases intrinsic to AI algorithms can lead to skewed outcomes and decisions.[81] A lack of transparency regarding information safety and associated risks is another major concern. Significant gaps in documentation about AI training data and ethical considerations raise issues of trust and accountabili-

ty.[82] Privacy concerns, challenges to job security among healthcare professionals, and over-reliance on AI must all be carefully addressed.[83] Additionally, the reallocation of responsibility between AI and healthcare providers should be optimized to ensure maximum patient safety.[83]

The new era of AI has prompted many professional fields to address issues of data bias, transparency, privacy, liability, and ethical considerations in clinical settings. By actively acknowledging these concerns, the integration of AI in the early diagnosis of PC can be continuously optimized.

Future directions

Successful early diagnosis of an insidious malignancy such as PC requires a multifaceted approach. Current challenges primarily consist of a lack of highly specific and cost-effective markers indicative of early stages, alongside high screening costs due to the relatively low incidence among the general public. Therefore, future research efforts should focus on developing low-cost, efficient, early, and specific screening strategies.

Studies on molecular pathways involved in early tumorigenesis and progression, including CIRBP, p53, and RAD51, represent significant advancements in developing early diagnostic regimens.[84,85] A deeper understanding of molecular mechanisms will aid in identifying markers that emerge at increasingly earlier stages of cancer development. As previously mentioned, these markers could be utilized in molecular imaging to generate highly tumor-specific scans, enabling radiologists to detect subtle changes that might otherwise be overlooked.

The discovery of molecular biomarkers hinges on the development of accurate and economical cell assays. Liquid biopsy has ushered in a new era for detecting a broad range of molecules at various cancer stages. However, its high material costs and complex procedures remain significant barriers to widespread application in routine screening. With AI's assistance, the utility and efficiency of liquid biopsy could be significantly amplified. AI could help identify and analyze key targets in a panel of biomarkers, potentially simplifying the number of biomarkers needed in a single test.

The development and application of AI tools for PC screening based on imaging results and medical records may be more achievable than addressing other technical challenges that require a deeper understanding of physical and life sciences. Collaboration among AI developers, government officials, and medical professionals is essential to resolve ethical and liability concerns and facilitate the broad application of AI-assisted screening programs.

Last but not least, screening and advocacy efforts from clinicians to improve patient education represent the most cost-effective yet significant strategies. The impact of social determinants of health on PC diagnosis and survival has garnered attention, with studies suggesting that addressing modifiable social risk factors could enhance early diagnosis rates and ultimately improve patient outcomes.[86] Understanding the interplay between social determinants of health and disease prognosis is crucial for developing holistic approaches to PC management that extend beyond traditional medical interventions.

Future directions in early diagnosis of PC lie in the collaboration of innovative biomarker identification, the application of artificial intelligence tools, and the dedicated efforts of medical personnel. Continued interdisciplinary collaboration and translational research are essential to realizing these transformative potentials and addressing the challenges posed by this devastating disease.

Despite the variety of advanced technologies available for early diagnosis of PC, notable limitations persist. Current research on these technologies is often superficial and lacks in-depth validation. While promising diagnostic tools, such as advanced imaging techniques, biomarkers, and liquid biopsies, have been developed, their clinical translation and prospects for general adoption remain limited. The gap between theoretical advancements and practical implementation in clinical settings needs to be narrowed.

Although this article proposes a novel early diagnostic model based on AI, the supporting research for its clinical application is sparse. Relatively few studies explore how AI-based models perform in real-world clinical environments, limiting our understanding of their efficacy and integration into routine practice. Addressing these gaps through more comprehensive research and clinical trials is essential for advancing the field and improving early diagnosis strategies for PC.

Conclusions

PC screening and early diagnosis are rapidly evolving due to advancements in imaging technologies, biomarker discovery, and artificial intelligence. Despite challenges such as cost, accessibility, and ethical concerns, ongoing research holds promise for improving early detection rates and patient outcomes. Continued interdisciplinary collaboration and the integration of innovative technologies are essential to translate these advancements into effective clinical practice.

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Conflict of interest

One of the authors, Prof. Taiping Zhang, has been an associate editor of *Cancer Screening and Prevention* since March 2022. The authors have no other conflicts of interest.

Author contributions

Study design (WHL), literature search (JW), study draft and revision (WHL, JW, HC, ZC, JDQ, YZL, GY, JXT, LYY, GHW, TL, HH, JCX, XYL, CD, YFF, YYW, MGZ), and supervision (LY, TPZ). All authors have approved the final version and publication of the manuscript.

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Review Article

Ferroptosis in Regulating Treatment Tolerance of Digestive System Tumors

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Abstract

Among all tumors worldwide, digestive tract tumors have a higher incidence rate and a significant disease burden. Esophageal cancer, gastric cancer, liver cancer, and colorectal cancer are often diagnosed at an advanced stage, and the prognosis remains poor. Currently, tumor treatment resistance is a major global challenge, with many underlying mechanisms. Ferroptosis has been shown to reverse drug resistance. This article reviews the mechanisms and recent advancements in ferroptosis related to reversing treatment resistance in gastrointestinal tumors, aiming to provide theoretical insights and research directions for the diagnosis and treatment of digestive tract tumors.

Introduction

Cancer has become the most serious public health issue in the world.[1,2] The incidence of digestive tract tumors accounts for 50% of all malignant tumors. Although new endoscopic techniques have improved the diagnosis and treatment rates for early gastrointestinal cancer, most patients with gastrointestinal tumors are diagnosed at an advanced stage and have a high mortality rate.[3] For these patients, medication is often the only option, but it can lead to treatment tolerance. While there are many mechanisms involved, the details are still unclear. Recent studies have shown that ferroptosis plays a key role in tumor suppression and offers new perspectives for tumor treatment. Inducing ferroptosis can reverse tumor treatment resistance,[4–7] but the mechanisms by which ferroptosis influences treatment resistance remain unclear. This article clarifies the relationship between ferroptosis and treatment resistance in various digestive tract tumors and explores the connection between ferroptosis-related mechanisms and treatment resistance, aiming to provide new research directions for the future treatment of gastrointestinal tumors.

Ferroptosis and tumor treatment resistance

Ferroptosis is a unique form of cell death driven by iron-dependent phospholipid peroxidation. It is regulated by multiple cellular processes, including redox balance, iron metabolism, and lipid metabolism.[8] The primary mechanism of ferroptosis involves the peroxidation of polyunsaturated fatty acid-containing phospholipids in the cell membrane under conditions rich in iron, reactive oxygen species (ROS), and lipid peroxidation.[9,10] The accumulation of lipid peroxides in the cell membrane eventually disrupts membrane integrity, leading to cell death. The molecular mechanisms of ferroptosis can be roughly divided into three pathways: the deletion or activation of glutathione peroxidase 4 (GPX4), iron metabolism, and lipid peroxidation (Fig. 1).[11]

Tumor cells can significantly enhance their defense against oxidative stress by regulating ferroptosis, which leads to treatment resistance.[12–14] Drug resistance in tumor cells is a major cause of cancer treatment failure. Currently, all tumor treatment drugs used in clinical practice can induce tumor cell resistance, resulting in tumor recurrence, metastasis, and ultimately, patient death. Studies have found that tumor resistance is primarily related to the activation of endogenous stress relief pathways by oncogenic stressors (e.g., starvation, DNA damage, dietary toxins, infection, or cancer therapy).[15,16] These pathways enable cells to better cope with stressors during development and renewal. Radiation therapy, chemotherapy, targeted therapy, and immunotherapy increase oncogenic stress, leading to further dependence of cancer cells on stress relief pathways. Cancer cells, as well as cells in the tumor microenvironment, rapidly adapt to relieve the stress caused by cancer treatments. These factors ultimately contribute to the resistance mechanisms of tumor treatment and provide new therapeutic targets,[17] with ferroptosis playing a key role in therapeutic resistance.[18] In tumor cell treatment resistance, persister cells (PCs) are particularly important.[19] PCs are tumor cells that survive after several rounds of chemotherapy and represent a treatment-resistant state.[20] The survival of PCs criti-

Keywords: Ferroptosis; Gastrointestinal tumors; Treatment resistance; Glutathione peroxidase 4 (GPX4); Reactive oxygen species (ROS); Chemotherapy; Targeted therapy.

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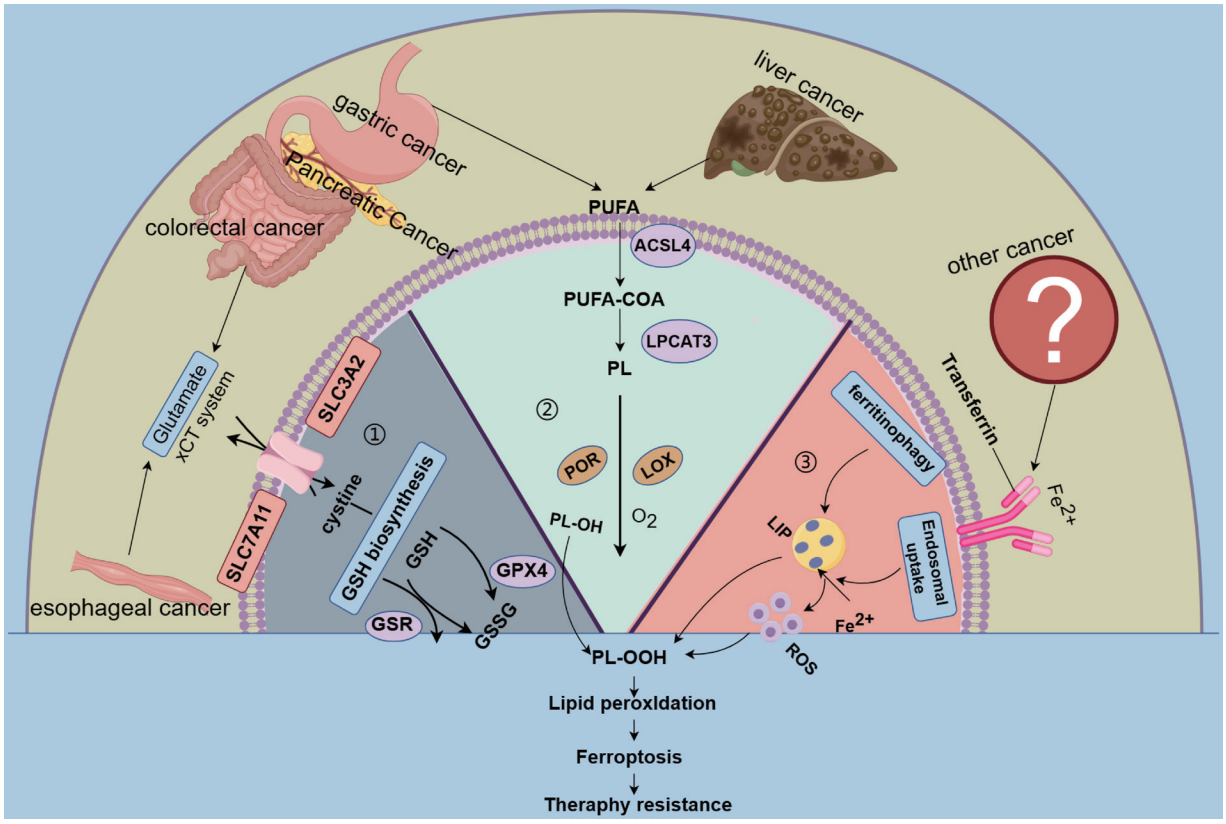

Fig. 1. The mechanism of gastrointestinal tumors involved in the ferroptosis pathway. ① Antioxidant pathway: Cysteine is imported into cells to synthesize GSH through the SLC7A11/SLC3A2 complex. GPX4 uses GSH as a substrate to reduce membrane phospholipid hydroperoxides to harmless lipid alcohols, thereby preventing the accumulation of lethal lipid ROS and inhibiting ferroptosis. ② Lipid peroxidation pathway: ACSL4 catalyzes the connection of long-chain polyunsaturated fatty acids to coenzyme A, and LPCAT3 promotes esterification and the incorporation of these products into membrane phospholipids (PL). PUFA-containing PL is oxidized by the iron-dependent enzymes LOX or POR, leading to lipid peroxidation, membrane damage, and subsequent ferroptosis. ③ Overexpression of nuclear receptor coactivator 4 increases intracellular LIP by increasing ferritin degradation. The increased intracellular LIP can generate free radicals (hydroxyl radicals) through the Fenton reaction and participate in the peroxidation reaction of phospholipids to generate PLOOH. Most intracellular production of reactive oxygen species is iron-catalyzed. The production of ROS triggers lipid peroxidation and ultimately leads to ferroptosis. ACSL4, acyl-CoA synthetase long chain family member 4; CoA, coenzyme A; GPX4, glutathione peroxidase 4; GSH, glutathione; GSR, glutathione-disulfide reductase; GSSG, glutathione oxidized; LIP, labile iron pool; LOX, lipoxygenase; PL, phospholipid; PLOH, phospholipid alcohol; PLOOH, phospholipid hydroperoxide; POR, cytochrome P450 oxidoreductase; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; xCT, cystine/glutamate antiporter.

cally depends on GPX4, and the downregulation of GPX4 levels can selectively induce ferroptosis in PCs. Additionally, ferroptosis can selectively target the unique metabolic and signaling pathways of cancer stem cells (CSCs), playing an important role in treatment resistance.[21,22] Erastin, an inhibitor of the cystine/glutamate transporter (SLC7A11), also known as xCT, is a component of the cystine/glutamate antitransporter (system Xc-).[23] SLC7A11 has a significant cytotoxic effect on CSCs and can reduce chemotherapy resistance in CSCs.[24] Therefore, ferroptosis offers hope for overcoming treatment resistance by modulating PCs and CSCs. Numerous studies have found that ferroptosis is involved in the treatment resistance of gastrointestinal tumors (Table 1).[6,9,10,21,24–34] This article will next introduce the relationship between ferroptosis and digestive tract tumors, focusing on colorectal cancer, gastric cancer, pancreatic cancer, and liver cancer (Fig. 1).[11,23,35,36]

Ferroptosis and gastric cancer treatment resistance

Studies have found that inducing ferroptosis may be a key strategy to address gastric cancer treatment resistance. ROS interferes with the cellular oxidative environment and induces cell death. The antioxidant enzyme peroxiredoxin 2 significantly increases cell sensitivity to cisplatin treatment by regulating ROS levels.[29] Silva found that resistance to chemotherapy in gastric cancer is associated with gene mutations that regulate apoptosis and elevated levels of glutathione (a substance that inhibits ferroptosis in cells),[37] and that ferroptosis inducers (FINS) can help overcome this resistance.[30] Another potential target for gastric cancer treatment is to block the ROS-activated general control nonderepressible 2 (GCN2)-eukaryotic initiation factor 2α subunit (eIF2α)-activation transcription factor 4 (ATF4)-xCT pathway, which causes mitochondrial dysfunction and enhances cisplatin tolerance.[29] Sorafenib, a tyrosine kinase inhibitor, plays an important anti-tumor role in gastric cancer as a FINS. Activating transcription factor 2 (ATF2), a member of the ATF/CREB transcription factor family, is associated with various cancer-related biological functions. Studies have shown that ATF2 is activated during sorafenib-induced ferroptosis in gastric cancer cells. ATF2 knockdown promotes sorafenib-induced ferroptosis, whereas ATF2 overexpression shows the opposite effect in gastric cancer cells.

Table 1. Specific mechanisms of cell ferroptosis and treatment tolerance in gastrointestinal tumors

Tumor type	Key pathways to ferroptosis	Mechanism	Tolerance type	Medicine	References
Gastric cancer	Lipid peroxidation	GCN2-eIF2α-ATF4-xCT	Chemotherapy	Cisplatin	Wang *et al*., 2016[29]
	Lipid peroxidation	Antioxidase peroxiredoxin 2	Chemotherapy	Cisplatin	Wang *et al*., 2016[29]
	Lipid peroxidation; Inhibit GPX4 activity	SIRT6	Targeted therapy	Sorafenib	Cai *et al*., 2021[34]; Xu *et al*., 2022[24]
	Lipid peroxidation	SLC7A11	Targeted therapy	Sorafenib	Wang *et al*., 2016[9,10]; Xu *et al*., 2023[10]
Colorectal cancer	Inhibit GPX4 activity	KIF20A/NUAK1/PP1β/GPX4	Chemotherapy	Oxaliplatin	Yang *et al*., 2021[31]
	GPX4	FAM98A	Chemotherapy	5-fluorouracil	Chen *et al*., 2020[21]
Liver cancer	Lipid peroxidation	Metallothionein-1G (MT-1G)	Targeted therapy	Sorafenib	Sun *et al*., 2016[30]
	Iron metabolism	miR-23a-3p	Targeted therapy	Sorafenib	Lu *et al*., 2022[33]
Pancreatic Cancer	Inhibit GPX4 activity	Activate p22-phox expression	Chemotherapy	Gemcitabine	Sporn *et al*., 2012[32]
	Lipid peroxidation	Nuclear translocation of NRF2 stimulates the production of partially encoded enzymes to catalyze glutathione (GSH) production	Chemotherapy	Gemcitabine	Sporn *et al*., 2012[32]

ATF4, activation transcription factor 4; eIF2α, eukaryotic initiation factor 2α subunit; FAM98A, family with sequence similarity 98 member A; GCN2, general control nonderepressible 2; GPX4, glutathione peroxidase 4; KIF20A, kinesin family member 20A; NUAK1, NUAK family kinase 1; PP1β, protein phosphatase 1 beta; SIRT6, recombinant Sirtuin 6; xCT, SLC7A11 (solute carrier family 7, (cationic amino acid transporter, y+ system) member 11).

Furthermore, results from tumor xenograft models indicate that ATF2 knockdown can effectively enhance sorafenib sensitivity *in vivo*.[24] Heat shock protein (HSP) overexpression inhibits erastin-mediated ferroptosis by reducing cellular iron uptake and lipid ROS production.[38] HSP regulates GPX4 degradation by inducing chaperone-mediated autophagy and plays a role in necroptosis and ferroptosis.[39] At the same time, HSP can negatively regulate ferroptosis by inhibiting GPX4 degradation.[40] Studies have shown that heat shock protein family member 1 (HSPH1) is a direct target of ATF2 and mainly acts as a molecular chaperone to prevent the aggregation of misfolded or unfolded proteins, thus maintaining protein homeostasis.[41] HSPH1 can also affect sorafenib-induced ferroptosis by regulating SLC7A11 stability. Further experiments have shown that knocking down HSPH1 can partially negate the effect of ATF2 overexpression on sorafenib-induced ferroptosis. Both ATF2 and HSPH1 are closely related to chemotherapy resistance in tumor cells. ATF2 knockdown or loss-of-function mutations in HSPH1 significantly increase the sensitivity of colorectal cancer and melanoma to oxaliplatin and 5-fluorouracil.[24] These findings suggest potential targets for overcoming drug treatment resistance in gastric cancer. Pathways such as GPX4 and lipid metabolism involved in ferroptosis are relevant to the treatment resistance of gastric cancer.

The role of ferroptosis in treatment resistance in colorectal cancer

The prognosis for patients with advanced colorectal cancer is poor due to resistance to anticancer drugs. Studies have found that interfering with the lipid metabolism involved in ferroptosis in colorectal cancer cells disrupts the metabolic balance of iron in these cells and enhances the chemosensitivity of drug-resistant cancer cells.[42–44] Ferroptosis plays a crucial role in both chemotherapy and targeted therapy.

The role of ferroptosis in chemotherapy resistance in colorectal cancer

Research has revealed that cysteine desulfurase (NFS1) deficiency synergizes with oxaliplatin to induce ferroptosis, increase intracellular ROS levels, and enhance the sensitivity of colorectal cancer cells to oxaliplatin. The KIF20A-NUAK1-PP1β-GPX4 signaling pathway can directly or indirectly inhibit ferroptosis in colorectal cancer cells,[45] playing an important role in reversing colorectal cancer resistance to oxaliplatin. FAM98A, a microtubule-associated protein involved in cell proliferation and migration, enhances the expression of xCT in stress granules, inhibits ferroptosis in colorectal cancer cells, and improves the tolerance of colorectal cancer to 5-fluorouracil.[31] Therefore, inducing ferroptosis through various mechanisms may be an effective strategy to overcome resistance to colorectal chemotherapy.

The role of ferroptosis in resistance to targeted therapy in colorectal cancer

Resistance to epidermal growth factor receptor (EGFR) therapy limits the effectiveness of EGFR-targeted treatments in colorectal cancer. Cetuximab, a monoclonal antibody targeting EGFR, can promote RAS-selective lethal 3 (RSL3)-induced ferroptosis by inhibiting the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway in kirsten rats arcomaviral oncogene homolog (KRAS) mutant colorectal cancer cells.[46,47] Additionally, β-elemene, a compound with broad-spectrum anticancer effects and a new type of FINs, can induce ferroptosis and inhibit epithelial-to-mesenchymal transition when combined with cetuximab, thereby improving treatment resistance in KRAS-

mutant colorectal cancer cells.[48] Vitamin C, an antioxidant that can induce oxidative stress at pharmacological doses, disrupts iron homeostasis and further increases ROS levels, ultimately leading to ferroptosis. The combination of cetuximab and Vitamin C can induce ferroptosis and reduce acquired resistance to anti-EGFR antibodies.[49] Therefore, modulating ferroptosis can reverse the treatment resistance effects of cetuximab.

The role of ferroptosis in treatment resistance in pancreatic cancer

Pancreatic cancer is often accompanied by lymph node invasion or distant organ metastasis at an early stage, with less than 20% of patients being eligible for surgical treatment once diagnosed.[50] For patients with unresectable pancreatic cancer, chemotherapy and radiotherapy are currently the main treatments. However, conventional chemotherapy regimens are prone to tumor cell resistance and strong chemotherapy side effects in the short term.[51] Consequently, the overall effectiveness of pancreatic cancer treatment has not improved obviously.[52] Previous studies have shown that FINS can inhibit pancreatic cancer growth by inducing cellular ferroptosis and, when combined with chemotherapy drugs, can increase tumor cell sensitivity to these drugs.[53]

Gemcitabine induces ROS accumulation during treatment.[54] In addition, knocking down GPX4 can increase lipid ROS production and induce ferroptosis. Gemcitabine can also induce ferroptosis by activating p22-phox expression in pancreatic ductal adenocarcinoma cells, which leads to NF-kB activation and NADPH oxidase (NOX) derived ROS accumulation. This may further enhance sensitivity to chemotherapy drugs. NRF2 is a major regulator of antioxidant molecules in cells. The nuclear translocation of NRF2 stimulates the production of enzymes that catalyze glutathione production, thereby reducing ROS levels. This mechanism can improve tumor cell resilience.[32] Therefore, combining NRF2 inhibitors with FINS may be a feasible strategy to reduce the resistance of pancreatic cancer cells to gemcitabine treatment. In summary, inducing ferroptosis through GPX4 and ROS accumulation may reverse resistance to chemotherapy drugs, providing a promising theoretical basis for the development of new treatments for pancreatic cancer. However, the role of ferroptosis in chemotherapy resistance in pancreatic cancer still requires further research.

The role of ferroptosis in treatment resistance in cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common primary liver tumor after hepatocellular carcinoma.[55] Ferroptosis has been found to be closely related to the occurrence and development of various cancers, including CCA.[11,56,57] Therefore, it is important to further explore the role of ferroptosis in CCA. Studies have found that abnormal expression of iron regulatory proteins is key to the development of CCA. Increased iron deposits correlate with a worse prognosis. Artemisinin can induce both cell apoptosis and ferroptosis in cancer cells by promoting ferritin autophagy and increasing intracellular free iron ions. Research by Wanna *et al*. demonstrated that dihydroartemisinin has a strong toxic effect on CCA cells, offering a new strategy for treating CCA.[58]

The role of ferroptosis in treatment resistance in liver cancer

Sorafenib is the first systemic treatment approved for patients with advanced liver cancer who are not suitable for surgical resection.[59] However, resistance to sorafenib can affect its efficacy in treating liver cancer. Compared with apoptosis inducers, the combined use of FINS and sorafenib can induce ferroptosis in liver cancer cells, thereby increasing the sensitivity of liver cancer to chemotherapy drugs. This ferroptosis mechanism is unique to sorafenib and is independent of its kinase inhibitory activity.

Lu *et al*.[33] found that miR-23a-3p negatively regulates sorafenib-induced ferroptosis by reducing iron overload and lipid peroxidation. Knockout or downregulation of miR-23a-3p significantly improved the responsiveness of orthotopic hepatocellular carcinoma (HCC) tumors and HCC cells to sorafenib treatment. Sun *et al*.[60] discovered that upregulating metallothione-1G (MT-1G) expression could protect HCC cells from the effects of sorafenib and promote cancer progression by inhibiting lipid peroxidation-mediated ferroptosis. This study suggests that regulating MT-1G expression is a potential therapeutic strategy to overcome the acquired resistance of HCC cells to sorafenib. These findings provide a promising therapeutic strategy for improving tolerance to sorafenib treatment in the future.[60,61]

The role of ferroptosis in treatment resistance in esophageal cancer

Patients with advanced esophageal cancer usually receive concurrent chemoradiotherapy and surgery. However, repeated use of chemotherapy drugs often leads to the development of treatment resistance in tumor cells, resulting in poor prognosis for these patients. Addressing therapy resistance in esophageal cancer can involve promoting ferroptosis in cells by targeting the system Xc-,[62] GPX4,[62] and NRF2, thereby inhibiting tumor proliferation and differentiation. Currently, there are few reports on the mechanism of ferroptosis in immunotherapy for esophageal cancer. As research on immunotherapy progresses, programmed death 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) targeted inhibitors have been used in the treatment of various tumors, including digestive tract tumors such as esophageal cancer, gastric cancer, colorectal cancer, and liver cancer. Liu J. *et al*. concluded that anti-PD-L1 antibodies can promote ferroptosis in tumor cells through the lipid peroxide pathway. Combining anti-PD-L1 antibodies with FINS can greatly inhibit tumor growth, with the mechanism related to cytotoxicity. T cells release interferon-γ, activate STAT1, inhibit xCT expression, and subsequently induce ferroptosis.[63] Few studies have explored the immunogenicity of esophageal cancer cells. Inducing ferroptosis in tumor cells can enhance their immunogenicity, thereby boosting the anti-cancer activity of immune cells.[64] These mechanisms of ferroptosis and treatment resistance in esophageal cancer offer new options and methods for the further treatment of patients with advanced esophageal cancer.

Limitations and future perspectives

Current research on ferroptosis and tumors has also been explored in other systemic tumors, such as non-small cell lung cancer,[65] and breast cancer.[66–68] The treatment of these tumors primarily utilizes ferroptosis-related mechanisms and pathways, including: (1) inhibiting the XC-glutathione/GPX4 axis by regulating antioxidants; (2) modulating the p62-Keap1-NRF2 pathway and NRF2 downstream antioxidant gene expression; (3) activating the ferroptosis axis by regulating the functions of lysosomes, ferritin, transferrin, and ferrophagosomes. Therefore, ferroptosis plays a crucial role in killing tumor cells and inhibiting tumor growth. Targeted induction of

ferroptosis may be a novel strategy to overcome tumor treatment resistance. However, clinical understanding of the factors involved in regulating cellular ferroptosis and treatment resistance remains limited. As alternative therapeutic targets, a deeper understanding of the initiation and transformation of ferroptosis and treatment resistance mechanisms in gastrointestinal tumors is needed.

Currently, ferroptosis represents a new clinical treatment direction and has garnered increasing attention in cancer therapy. Despite the growing research on ferroptosis, several issues remain: (1) Further exploration is needed to understand the unknown and regulatory mechanisms of ferroptosis in tumor treatment resistance; (2) Different tissues exhibit varying sensitivities to ferroptosis, making the correct application of ferroptosis in tumor treatment an important research direction; (3) Anti-tumor drugs are often used in combination, but the antagonistic or synergistic effects of these combinations are not yet fully understood, and substantial theoretical research support is still required; (4) While some drugs and compounds can induce ferroptosis, and new drug delivery systems such as exosomes and nanotechnology are being explored, clinical application remains a challenge. Further exploration and effort from scholars are needed.

The detection and application of ferroptosis in tumor drug resistance are crucial. Ongoing research and detection methods related to ferroptosis provide valuable tools for understanding and intervening in this process. For example, measuring the levels of specific lipid peroxides within cells, such as malondialdehyde and 4-hydroxynonenal, can help assess ferroptosis.[69] Additionally, detecting the activity of enzymes associated with ferroptosis, such as GPX4, is an important indicator of ferroptosis occurrence. The release of cytochrome C, changes in mitochondrial membrane potential,[70] and increases in intracellular iron ion levels are also key events in ferroptosis, detectable through biochemical experiments.[71] Techniques such as flow cytometry, fluorescence microscopy,[72] and Western blotting are widely used for detecting ferroptosis.[73,74] Although there is currently no single gold standard for detecting ferroptosis, combining these methods can provide a more comprehensive assessment. Future research may uncover new biomarkers and detection technologies, further improving the accuracy of ferroptosis detection and its clinical application feasibility.

Conclusions

We anticipate seeing more meaningful clinical and basic research in the near future. These studies will enhance our understanding of resistance mechanisms to ferroptosis reversal therapy and lead to more effective cancer treatments, thereby reducing the disease burden on patients and improving their quality of life.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Manuscript drafting (XQ), study concept and design (XQ, HW, MXZ), figures and tables (XQ, MXZ), English polishing (HL), critical revision of the important intellectual content for the manuscript (MXZ). All authors read and approved the final manuscript.

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Review Article

Gut Dysbiosis and Fecal Microbiota Transplantation in Pancreatic Cancer: Current Status and Perspectives

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease with difficulties in early diagnosis, poor prognosis, and limited effective therapies. Early detection and effective treatment offer the optimal chance to improve survival rates. Various studies have shown that gut microbiota dysbiosis is closely related to PDAC, with potential mechanism involving immune regulation, metabolic process impact, and reshaping the tumor microenvironment. A comprehensive understanding of the microbiota in PDAC might lead to the establishment of screening or early-stage diagnosis methods, implementation of cancer bacteriotherapy such as fecal microbiota transplantation, creating new opportunities and fostering hope for desperate PDAC patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal human malignancies. Through extensive efforts and prolonged research, the five-year survival rate has improved to approximately 10%.[1] Surgical resection offers a potential cure for patients with PDAC.[2] Due to the insidious onset and lack of specific early clinical manifestations, only 15–20% of patients are diagnosed with PDAC that can be removed using standard resection.[3] It is urgent to find effective biomarkers and clinical treatment strategies.

The gut microbiota, consisting of trillions of microorganisms inhabiting the intestinal tract, interacts with the host in various ways, playing crucial roles in host physiology, including immune regulation, metabolite exchange, and nutrient metabolism.[4,5] With the progress of metagenomics and the identification of gut bacterial compositions, studies on the role of gut microbiota in cancer have become an international hotspot. Growing research suggests a strong link between the gut microbiome and PDAC, indicating a critical role in the development, progression, and treatment of the disease.[6] Therefore, utilizing microbiota therapy to reconstruct the composition and quantity of the gut microbiome may be a potential therapeutic strategy for PDAC.[7,8]

Among all the approaches for interventions targeting the gut microbiome, fecal microbiota transplantation (FMT), which involves transferring functional microbiota from healthy donors into the gastrointestinal tract of patients, has shown initial clinical effects in cancer therapy.[9] Numerous clinical studies have demonstrated that FMT can significantly enhance the efficacy of tumor immunotherapy, chemotherapy, and radiotherapy, and mitigate adverse effects.[10] Nevertheless, concerns persist regarding the safety, efficacy, and precision of FMT procedures.

Herein, we provide an overview of the complex association between gut microbiota and PDAC, as well as the current research progress and prospects of FMT in the management of PDAC, with at least one published or ongoing FMT study in human or mouse models. Furthermore, we discuss recent challenges and offer future research directions.

The human gut microbiome

Under healthy conditions, the gut microbiota is stable, resilient, and maintains a mutually beneficial relationship with the host.[11,12] The composition of the gut microbiota is influenced by various factors, including diet, physical activity, daily routines, host age, gender, genetics, and the use of antibiotics, probiotics, and other microbiome-targeted interventions.[13] Consequently, defining the precise characteristics of a healthy gut microbiota is challenging. Generally, the human gut microbiota is dominated by five bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia.[13] Elderly individuals often show reduced levels of Bifidobacterium and elevated levels of Clostridium and Proteobacteria.[14] Additionally, based on the composition of the gut microbiota, individuals can be classified into three enterotypes,

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which are not influenced by gender, age, nationality, or geographical location. Enterotype 1 is characterized by Bacteroides as the indicative taxon; Enterotype 2 is driven by Prevotella; and Enterotype 3 is distinguished by the relative abundance of Firmicutes, primarily Ruminococcus.[15]

Gut dysbiosis in PDAC

Gut microbiome in PDAC

Dysbiosis of gut bacteria is a well-established phenomenon that contributes to several aspects of PDAC.[16] In recent years, multiple studies have analyzed the gut microbiota in stool samples obtained from PDAC patients and non-tumor controls through 16S ribosomal RNA sequencing and metagenomic sequencing, revealing notable differences in gut microbiota composition. Nagata and colleagues analyzed the gut microbiota of PDAC patients and controls from Japanese, Spanish, and German cohorts, finding a significant enrichment of Streptococcus and Veillonella spp., along with a reduced abundance of Faecalibacterium prausnitzii, as characteristic gut signatures associated with PDAC across all three cohorts.[17] A study conducted by Zhou and colleagues,[18] which included PDAC patients (32), autoimmune pancreatitis patients (32), and healthy controls (32), showed a marked increase in the phylum Proteobacteria and a decrease in the phylum Firmicutes in PDAC patients compared to autoimmune pancreatitis patients and controls. Additionally, meta-analyses and prospective cohort studies have suggested a positive correlation between Helicobacter pylori infection and PDAC, indicating that patients with Helicobacter pylori infection have a higher risk of developing PDAC.[19,20] The characteristics of gut microbiota in PDAC patients vary across different studies, which may be due to substantial geographical and ethnicity-specific heterogeneity of the gut microbiota, differences in fecal collection, and sequencing protocols. Therefore, larger-scale investigations are warranted to develop a comprehensive gut microbiota profile unique to PDAC.

The characteristic alterations observed in the gut microbiota of PDAC patients are being proposed as promising biomarkers for the diagnosis of PDAC. Kartal *et al*.[21] assessed the gut microbiota of 57 PDAC patients, 50 controls, and 29 chronic pancreatitis patients to construct fecal metagenomic classifiers based on 27 microbial species, achieving an accuracy of up to 0.84 in the area under the receiver operating characteristic curve (AUC), which accurately identified PDAC. Furthermore, when combined with CA199, the AUC increased to 0.94, demonstrating high predictive accuracy in 26 validation cohorts.[21] Similarly, Yang and colleagues, comparing the gut microbiota of 44 PDAC patients and 50 healthy individuals, identified Streptococcus as an accurate discriminator of PDAC (AUC = 0.927) and PDAC with liver metastasis (AUC = 0.796), suggesting its utility as an effective screening tool.[22] Considering the convenience and non-invasiveness of gut microbiota detection, along with high compliance in the initial screening population, gut microbiota-related markers hold promise as valuable tools for PDAC screening and early diagnosis.

Gut dysbiosis and immune regulation

The complex interplay between the gut microbiota and the immune system regulates host immunity via various pathways, leading to either immune activation or suppression, consequently impacting the onset and treatment of PDAC.[16,23] KRAS mutation is one of the initiating factors in PDAC.[24] Lipopolysaccharides, the major components of gram-negative bacterial cell walls, can activate Toll-like receptor signaling pathways and stimulate the secretion of cytokines such as IL-8 and TNF-α.[25] In mouse models of PDAC, gut microbiome depletion significantly reduced tumor volumes and the number of both primary and liver metastatic tumors, with an increase in interferon gamma-producing T cells and a corresponding decrease in interleukin 17A and interleukin 10-producing T cells in the tumor microenvironment.[26] Moreover, gut microbiota may migrate into the pancreas, exerting immunosuppressive effects. Pushalkar and colleagues found that intrapancreatic bacteria were elevated in PDAC compared with normal pancreatic tissue, and certain bacteria were selectively increased in PDAC compared with the gut.[27] Furthermore, bacterial ablation was shown to inhibit PDAC growth and was associated with immunogenic reprogramming of the tumor microenvironment, including a reduction in the activation of specific Toll-like receptors on monocytic cells and an increase in the polarization of tumor-protective M1 macrophages, which facilitated the infiltration and activation of T helper cells and cytotoxic T cells.[27] Alam *et al*.[28] discovered that the intratumoral fungal mycobiome drives IL-33 secretion, promoting type 2 immune responses and accelerating PDAC progression.

Microbiota-derived metabolites and their effects on PDAC

Metabolites produced by the gut microbiota play crucial roles in various physiological and pathological processes, including cell proliferation, differentiation, apoptosis, and even tumor treatment.[6] Short-chain fatty acids, primarily including acetate, propionate, and butyrate, are the most abundant microbial metabolites in the colonic lumen and are mainly produced by the microbial fermentation of prebiotics. Among short-chain fatty acids, butyric acid has been shown to activate differentiation and inhibit invasion in PDAC cells.[29–31] In PDAC patients, lower concentrations of butyrate and reduced relative abundance of butyrate-producing bacteria in the gut have been reported. More recently, indole-3-acetic acid, a tryptophan metabolite produced by Bacteroides fragilis and Bacteroides thetaiotaomicron, enhanced the efficacy of chemotherapy in PDAC. In combination with chemotherapy, it downregulates the reactive oxygen species-degrading enzymes glutathione peroxidase 3 and glutathione peroxidase 7, leading to the accumulation of reactive oxygen species and downregulation of autophagy in PDAC cells, thereby inhibiting cell proliferation.[32] Mirji *et al*.[33] identified that the gut microbe-derived metabolite trimethylamine N-oxide enhanced immunotherapy sensitivity, associated with an immunostimulatory tumor-associated macrophage and activated effector T cell response in the tumor microenvironment. Uro A, an intestinal microbial metabolite of ellagitannin, inhibited phosphorylation of AKT and p70S6K through the PI3K/AKT/mTOR pathway and induced strong antiproliferative and proapoptotic effects in PDAC, along with reduced levels of infiltrating immunosuppressive cell populations such as myeloid-derived suppressor cells, tumor-associated macrophages, and regulatory T cells.[34] Altogether, the biological activity of microbiota-derived metabolites in PDAC still needs to be further explored.

Gut dysbiosis and PDAC treatment

Systemic therapy, which includes chemotherapy as the primary treatment modality supplemented by radiotherapy, targeted therapy, immunotherapy, and other approaches, remains crucial in managing PDAC.[35] The gut microbiome has been shown to influence the efficacy of these treatments. For instance, gemcitabine, a commonly used chemotherapy drug for PDAC, may have reduced efficacy due to Gammaproteobacteria, which are suggested to migrate from the gut to pancreatic tumors.[36] FOLFIRINOX, consid-

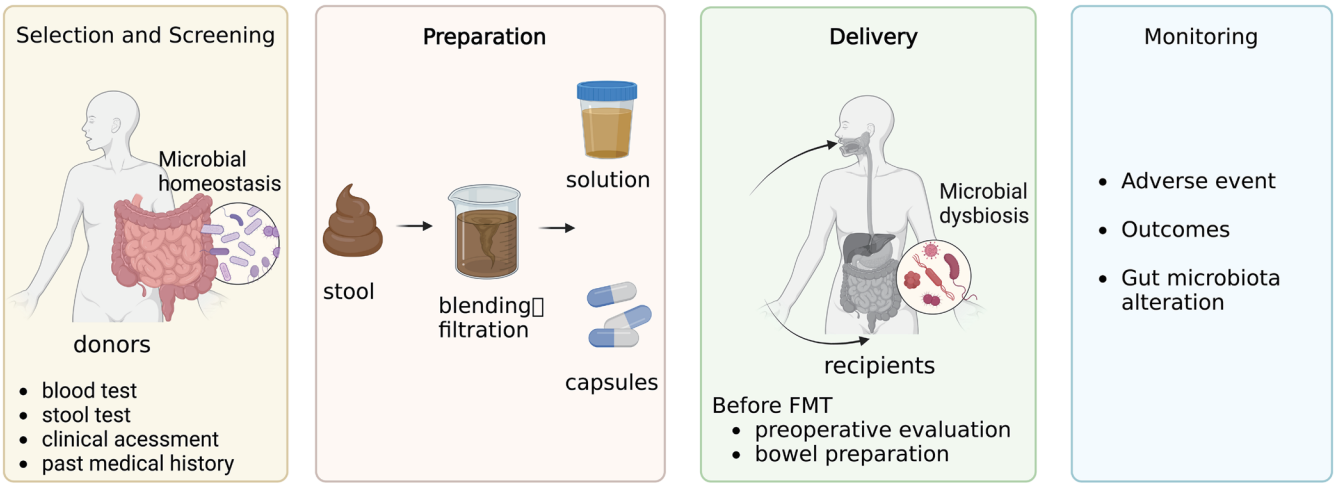

Fig. 1. The process of FMT (fecal microbiota transplantation). This includes (1) selection and screening for donors; (2) bacterial suspension and freeze-dried capsules preparation; (3) delivery via upper gastrointestinal routes (nasogastric tube, gastroscopy) or lower gastrointestinal routes (colonoscopy, sigmoidoscopy); (4) close post-transplant follow-up.

ered frontline therapy for advanced PDAC, consists of leucovorin, fluorouracil, irinotecan, and oxaliplatin. Irinotecan is metabolized in the liver to SN-38G, an inactive metabolite. However, in the intestines, bacterial β-glucuronidase enzymes produced by the commensal microbiota can convert SN-38G back into its active form, SN-38.[37,38] This activation process in the intestines can lead to delayed diarrhea.[39] Antibiotics have the potential to disrupt the gut microbiota's composition. A study involving 20 volunteers exposed to four common antibiotic regimens showed a significant decrease in species richness immediately after treatment. While most volunteers' microbiomes returned to pre-treatment richness after two months, the taxonomy and metabolism were altered.[40] However, some volunteers experienced a persistent reduction in microbiome diversity.[40] For tumor patients treated with immunotherapy, antibiotic administration is associated with poor progression-free survival and overall survival. Therefore, caution should be exercised when prescribing antibiotics to patients planning to undergo immunotherapy.[41–43] Park *et al*.[44] identified that the gut microbiota can promote responses to programmed death 1 (PD-1) checkpoint blockade by downregulating the programmed death ligand 2 (PD-L2)/repulsive guidance molecule b (RGMb) pathway in FMT. Interestingly, the gut microbiome could be linked to postoperative complications after pancreatic surgery. In a prospective clinical pilot study, Schmitt *et al*.[45] analyzed 116 stool samples from 32 patients before and after pancreatic surgery and revealed that distinct microbiome patterns are associated with surgical complications. Patients with a specific gut microbial composition pattern, characterized by an increase in Akkermansia, Enterobacteriaceae, and Bacteroidales, and a decrease in Lachnospiraceae, Prevotella, and Bacteroides, were found to be at a significantly higher risk for developing postoperative complications.[45] Overall, the intricate relationship between the gut microbiome and treatment outcomes in PDAC underscores the importance of preserving microbiome integrity during therapy.

An overview of FMT

FMT is a therapeutic approach that delivers the full spectrum of gut microbiota to patients to combat or alleviate microbial imbalances. Historical records in traditional Chinese medicine document the use of feces to treat illnesses, dating back approximately 1,700 years when Ge Hong used human fecal infusions to treat patients on the brink of death due to food poisoning, diarrhea, and fever.[46] In modern medicine, FMT was first approved for the treatment of multiply recurrent or refractory Clostridioides difficile infection.[47] In 2023, the first international Rome consensus conference on gut microbiota and fecal microbiota transplantation in inflammatory bowel disease was published.[48] Currently, in clinical practice, FMT has been applied to treat various diseases associated with intestinal dysbiosis, including inflammatory bowel disease,[49] irritable bowel syndrome,[50] diarrhea,[51] as well as disorders of the nervous and metabolic systems,[52–54] and cancer,[51,55] with its effectiveness and safety widely recognized.

Based on consensus from various regions, the implementation of FMT can be broadly divided into several steps (Fig. 1): donor selection, preparation of transplant material, recipient preparation, transplantation, and post-transplant follow-up management.[56,57] (1) Prior to FMT implementation, rigorous donor screening and regular assessment of donor health status are necessary; (2) Recipients must undergo comprehensive clinical evaluation before transplantation and prepare their intestines according to their individual conditions; (3) Transplant materials are typically in the form of a solution or freeze-dried capsules derived from donor feces. The method of transplantation varies depending on the type of transplant material, with options including infusion of the solution via upper gastrointestinal routes (nasogastric tube, gastroscopy) or lower gastrointestinal routes (colonoscopy, sigmoidoscopy) to introduce functional microbial communities into the patient's intestines; (4) Close post-transplant follow-up is essential to monitor the therapeutic efficacy of FMT and any associated adverse reactions.

Potential mechanisms of FMT

FMT has gained attention for its potential to treat cancer by altering the composition of gut microbiota. While the precise mechanisms underlying FMT are still under investigation, several potential pathways have been proposed (Fig. 2). FMT can replenish

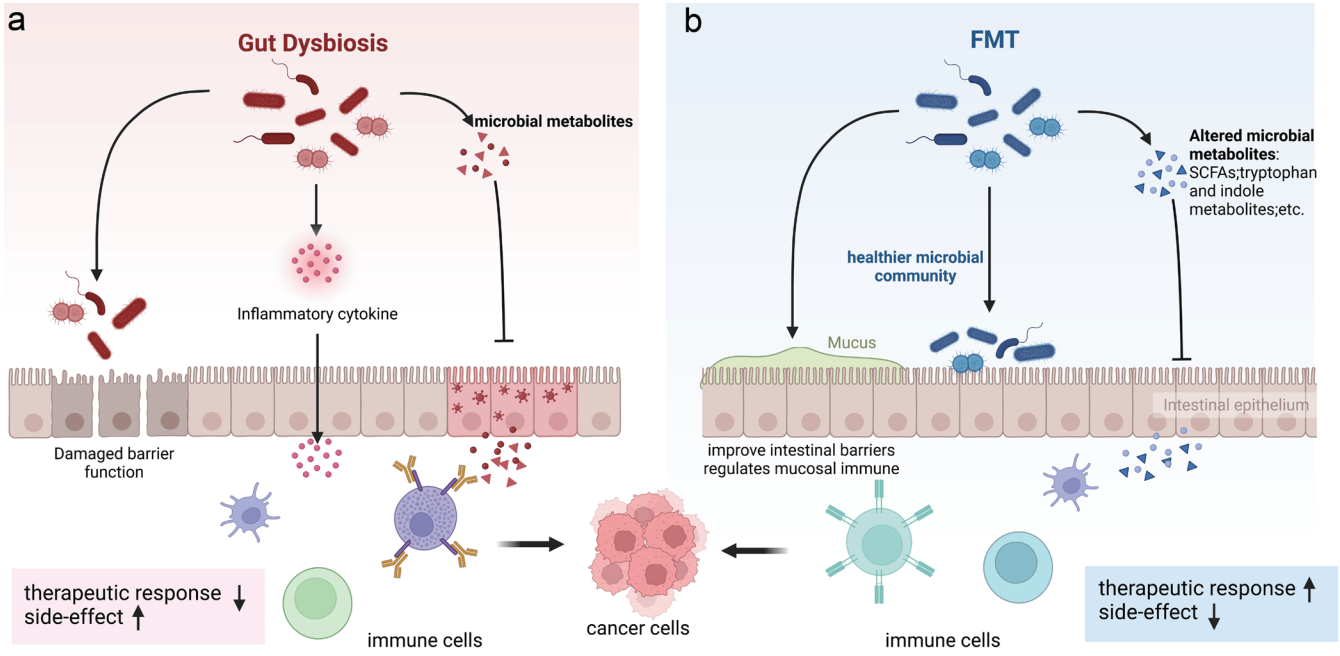

Fig. 2. Gut dysbiosis and fecal microbiota transplantation for cancer. (a) Potential mechanisms by which a disturbed gut microbiome contributes to cancer pathogenesis. (b) Proposed mechanisms by which FMT restores the gut microbiome and reestablishes microecosystem homeostasis. FMT, fecal microbiota transplantation; SCFA, short-chain fatty acids.

and diversify the recipient's gut microbiota, correcting imbalances and fostering a healthier microbial community, which improves intestinal barriers and regulates mucosal immunity. Huang *et al*.[58] discovered that FMT reduced gut inflammation by decreasing toll-like receptor 4. It also provided significant relief from intestinal mucosal injury and reduced intestinal permeability by increasing the expression of mucin and tight junction proteins.[58] The intestine, as the largest immune organ in the human body, plays a pivotal role in maintaining host balance and defense through its mucosal immune system. The intestinal microbiome promotes the differentiation of naive $CD8^+$ T cells into $CD4^+$ T cells in the large intestine.[59] FMT may also impact metabolites that regulate and alleviate tumors locally in the gut or systemically throughout the body. Inosine, a prominent microbial metabolite, in the presence of exogenous interferon-gamma, promotes T helper 1 cell differentiation by binding to the adenosine 2A receptor on the surface of T cells and significantly enhances the anticancer ability of T helper 1 cells in tumors.[60]

FMT and PDAC treatment

FMT is a potent approach to restoring gut microbiota, and several preclinical models have demonstrated its potential in treating PDAC. Pushalkar *et al*.[27] conducted mouse-to-mouse FMT experiments and observed that mice receiving fecal samples from PDAC mice exhibited accelerated tumor growth compared to those receiving samples from control mice. This suggests that FMT modulates tumor growth by altering the gut microbiota. Riquelme *et al*.[61] conducted FMT experiments in mice using samples from PDAC patients with short-term survival (STS), PDAC patients with long-term survival (LTS), and healthy controls. They found that mice receiving fecal samples from LTS patients exhibited significantly slower tumor growth compared to those transplanted with samples from STS patients ($P < 0.001$) or controls ($P = 0.02$). Moreover, there was a notable increase in the infiltration of $CD8^+$ T cells and activated T cells in the tumor microenvironment of mice that received FMT from LTS patients. Conversely, mice that received FMT from STS patients showed an increase in the infiltration of $CD4^+FOXP3^+$ cells and bone marrow-derived suppressor cells in the tumor. These findings indicate that FMT therapy can modulate the tumor immune microenvironment and the natural history of the disease.

FMT and chemotherapy

Chemotherapy is one of the primary methods for systemic treatment of PDAC; however, drug resistance limits its effectiveness and is a major cause of recurrence and poor prognosis in PDAC patients.[62,63] Recently, growing evidence suggests that microbes impact the efficacy of chemotherapeutic drugs in cancer therapies. Bacterial modification of pharmaceuticals might either potentiate desirable effects, compromise efficacy, or release harmful compounds, both directly and indirectly.[64] It is reported that bacteria can metabolize the chemotherapeutic drug gemcitabine (2′,2′-difluorodeoxycytidine) into its inactive form (2′,2′-difluorodeoxyuridine), which depends on the bacterial enzyme cytidine deaminase.[36] In a preclinical study, Tintelnot *et al*.[32] utilized patient-to-mouse FMT experiments and observed that mice receiving fecal samples from chemotherapy-responder patients exhibited increased sensitivity to chemotherapy compared to those receiving samples from chemotherapy-non-responder patients. Additionally, receiving fecal samples from healthy mice led to a reduction in tumor growth.[32] These studies lay the foundation for conducting clinical trials of FMT alongside chemotherapy for PDAC.

FMT and radiotherapy

Radiotherapy is an important modality for the local treatment of PDAC. However, the side effects of radiotherapy are associated with significant morbidity and mortality that impact patients' qual-

ity of life.[65] Radiation enteritis is a common complication of radiotherapy for abdominal and pelvic tumors, often manifesting as abdominal pain, diarrhea, and rectal bleeding, which are prone to recurrence and poorly responsive to traditional treatments.[66] In a case report, a 64-year-old female with cervical cancer and chronic radiation enteritis underwent two courses of FMT and then experienced short- and long-term relief from symptoms without adverse effects.[67] In a pilot study, FMT was performed on five patients with chronic radiation enteritis who were unresponsive to conventional treatment. Healthy donor gut microbiota was transplanted into the patients, and the patients' radiation toxicity, gastrointestinal symptoms, and changes in gut microbiota were regularly evaluated. After eight weeks, three patients showed improvement, one underwent surgery for other reasons, and one showed no improvement, with no FMT-related deaths or infectious complications.[68] In a prospective cohort study, researchers treated 20 patients with radiation enteritis complicated by intestinal obstruction with FMT and followed them up for six months.[69] Compared to the conventional treatment group (25 patients), the FMT group showed superior gastrointestinal quality of life scores, body mass index, total protein, and albumin levels, effectively improving the patients' early nutritional status and quality of life.[69] Another study involving 127 patients with radiation enteritis treated with FMT showed clinical cure rates of 61.4%, 56.5%, and 47.6% at three, 12, and 36 months, respectively.[70]

FMT and immunotherapy

The unique immune-suppressive microenvironment and low immunogenicity of PDAC make it challenging for immunotherapy to achieve desirable outcomes.[71–73] Improving responses to immunotherapy and developing effective immunotherapeutic strategies remain long-term tasks. Increasing evidence suggests that gut microbiota modulation plays a significant role in cancer immunotherapy.[74] For example, the gut microbiota metabolite trimethylamine-N-oxide has immunomodulatory effects and can enhance the sensitivity of PDAC to immune checkpoint inhibitors.[33] Compared to tumor patients who did not receive antibiotic treatment before and after their first PD-1/PD-L1 treatment, the group receiving antibiotic treatment showed significantly shortened progression-free survival and overall survival.[43,75] Moreover, immune checkpoint inhibitor-induced colitis, an adverse effect of immunotherapy treatment, could be ameliorated by FMT.[76,77] Although there are no clinical studies on FMT for immunotherapy in PDAC, initial successes have been achieved in immunotherapy for other cancers. Several FMT clinical trials have shown that transplanting gut microbiota from immunotherapy responders can reverse tumor resistance to PD-1/PD-L1 treatment,[55,78,79] and healthy individuals as donors can also reverse the refractoriness of tumors to immunotherapy.[80,81]

Based on the above research, combining FMT with existing therapies such as chemotherapy, radiotherapy, and immunotherapy holds promise for improving treatment efficiency and reducing side effects. Previous research on FMT in cancer treatment has primarily concentrated on its combination with immunotherapy, chemotherapy, and radiation therapy. The neoadjuvant therapy and perioperative periods may also present opportune times for combining FMT with treatment in the future, as earlier modulation of gut microbiota, immune function, and nutritional status in cancer patients could potentially enhance therapeutic outcomes against tumors. Although there is currently no publicly available clinical data on FMT for PDAC treatment, the enormous potential of FMT in treating PDAC cannot be denied. Several clinical trials are currently underway. In one preliminary study, researchers initiated FMT treatment four weeks before Whipple surgery for PDAC patients (NCT04975217). Other clinical trials are exploring the application of FMT in the treatment of advanced PDAC (ChiCTR2100049431) (Table 1).

Current issues in FMT treatment for PDAC

Complications of FMT treatment

Although FMT is recognized as a safe and low-risk medical innovation, it still carries the risk of complications. In a previous report, two recipients of FMT developed bacteremia caused by extended-spectrum beta-lactamase-producing Escherichia coli, with both cases linked to the same stool donor. One of the patients died, which was attributed to the donor not undergoing screening for multidrug resistance.[82] Therefore, ensuring the safety of transplant materials is crucial for the safety profile of FMT. Currently, guidelines and consensus on FMT have been developed, outlining donor screening and management protocols, as well as requirements for the preparation and quality control of transplant materials. Enhancing donor screening and daily management is a critical measure to ensure the quality and safety of transplants. Before FMT, a comprehensive assessment of the donor's recent health status is necessary, including medical history, clinical symptoms, blood tests, fecal microbial tests, and lifestyle and dietary habits. Additionally, cohabitation is an important factor in the transmission of microbes, with the median strain-sharing rates of gut and oral microbiota among cohabiting individuals being 12% and 32%, respectively. The impact of cohabitation duration on strain sharing is greater than that of age and genetics.[83,84] Therefore, it may also be necessary to focus on the gut microbiota health of cohabitants in the future. A systematic review of 129 FMT-related studies conducted from 2000 to 2020 found that most FMT-related adverse events were mild or moderate and self-limiting. The most common adverse events were diarrhea (10%) and abdominal discomfort/pain/cramping (7%); 1.4% of FMT recipients experienced severe adverse events, all related to mucosal barrier damage.[85] Thus, an accurate evaluation of the recipient's tolerance for FMT is essential before proceeding with the procedure. Moreover, selecting an appropriate route of FMT delivery, enhancing donor screening before transplantation, and regularly monitoring recipients throughout the process may help reduce risks to some extent.

Challenges and unresolved issues in FMT

FMT presents a double-edged sword, with potential risks of transmitting harmful microorganisms alongside the benefits of improving gut microbiota, underscoring the critical importance of establishing implementation guidelines. With its widespread application, FMT protocols have been established across different regions, but specific details have not been standardized. Donor screening and management are among the most challenging aspects of FMT implementation and are crucial factors affecting the safety and efficacy of the procedure. Strict donor screening criteria result in a screening success rate of only 1.7%, which is far from meeting clinical demands.[86] Additionally, rules for donor-recipient matching are still under exploration, and further discussion is needed on how to select suitable donors based on recipient-specific factors to maximize therapeutic effects. For example, should the recipient's gut microbiota characteristics be considered? Could the diversity of the recipient's gut microbiota potentially influence the outcomes of FMT? Donor–recipient enterotype matching and

Cancer Screen Prev

Table 1. The registered clinical trials about the therapeutic effects of fecal microbiota transplantation (FMT) in cancer

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Microbiota transplant to cancer patients who have failed immunotherapy using feces from clinical responders	NCT05286294	Melanoma; head and neck squamous cell carcinoma; cutaneous squamous cell carcinoma; clear cell renal cell carcinoma; non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	20	RECRUITING
Washed microbiota transplantation for the treatment of oncotherapy-related intestinal complications	NCT04721041	Cancer	INTERVENTIONAL	SINGLE_GROUP	/	40	RECRUITING
Utilization of microbiome as biomarkers and therapeutics in immuno-oncology	NCT04264975	Solid carcinoma	INTERVENTIONAL	SINGLE_GROUP	/	60	UNKNOWN
FMT in treating immune-checkpoint inhibitor induced-diarrhea or colitis in genitourinary cancer patients	NCT04038619	Malignant genitourinary system neoplasm; melanoma; lung cancer; ovarian cancer; uterine cancer; breast cancer; cervical cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	40	RECRUITING
FMT in checkpoint inhibitor-mediated diarrhea and colitis	NCT06206707	Malignant melanoma; kidney cancer	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	/	20	RECRUITING
FMT in patients with malignancies not responding to cancer immunotherapy	NCT05273255	Cancer	INTERVENTIONAL	SINGLE_GROUP	/	30	RECRUITING
Efficacy and safety of FMT in reducing recurrence of colorectal adenoma	NCT06205862	Colorectal adenoma	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	PHASE2	466	RECRUITING
FMT in metastatic melanoma patients who failed immunotherapy	NCT03353402	Melanoma	INTERVENTIONAL	SINGLE_GROUP	PHASE1	40	UNKNOWN
Preventing toxicity in renal cancer patients treated with immunotherapy using FMT	NCT04163289	Renal cell carcinoma	INTERVENTIONAL	SINGLE_GROUP	PHASE1	20	ACTIVE_NOT_RECRUITING
FMT with immune checkpoint inhibitors in lung cancer	NCT05502913	Metastatic lung cancer	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	80	RECRUITING
FMT in melanoma patients	NCT03341143	Melanoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	18	ACTIVE_NOT_RECRUITING

(continued)

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Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Inducing remission in melanoma patients with Checkpoint Inhibitor therapy using FMT.	NCT04577729	Malignant melanoma	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	/	5	TERMINATED
FMT to convert the response to immunotherapy	NCT05251389	Melanoma	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	24	RECRUITING
FMT and pembrolizumab for men with metastatic castration-resistant prostate cancer.	NCT04116775	Prostate cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	32	UNKNOWN
Chemotherapy and stool transplant in pancreatic ductal adenocarcinoma (PDAC)	NCT06393400	Unresectable or metastatic advanced pancreatic ductal adenocarcinoma	INTERVENTIONAL	SINGLE_GROUP	PHASE1	20	NOT_YET_ RECRUITING
FMT in patients with advanced gastric cancer	NCT06346093	Advanced gastric cancer	INTERVENTIONAL	PARALLEL; Masking: DOUBLE (PARTICIPANT, INVESTIGATOR)	/	66	RECRUITING
A single dose FMT infusion as an adjunct to Keytruda for metastatic mesothelioma	NCT04056026	Mesothelioma	INTERVENTIONAL	SINGLE_GROUP	EARLY_ PHASE1	1	COMPLETED
FMT in diarrhea induced by tyrosine-kinase inhibitors	NCT04040712	Renal cell cancer	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, CARE_PROVIDER, OUTCOMES_ASSESSOR)	/	20	COMPLETED
FMT for the treatment of pancreatic cancer	NCT04975217	Pancreatic ductal adenocarcinoma	INTERVENTIONAL	SINGLE_GROUP	EARLY_ PHASE1	10	RECRUITING
Microbiota transplant in advanced lung cancer treated with immunotherapy	NCT04924374	Lung cancer	INTERVENTIONAL	PARALLEL; Masking: NONET	/	20	RECRUITING
Prevention of dysbiosis complications with autologous FMT in AML patients	NCT02928523	Leukemia, myeloid, acute	INTERVENTIONAL	SINGLE_GROUP	PHASE2	20	COMPLETED
Fecal microbiota transfer in liver cancer to overcome resistance to atezolizumab/bevacizumab	NCT05690048	Immunotherapy	INTERVENTIONAL	PARALLEL; Masking: SINGLE (PARTICIPANT)	PHASE2	48	NOT_YET_ RECRUITING

(continued)

Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
FMT and re-introduction of anti-programmed death 1 (anti-PD-1) therapy (Pembrolizumab or Nivolumab) for the treatment of metastatic colorectal cancer in anti-PD-1 non-responders	NCT04729322	Metastatic colorectal adenocarcinoma	INTERVENTIONAL	PARALLEL; Masking: NONE	PHASE2	15	ACTIVE_NOT_RECRUITING
FMT capsule for improving the efficacy of anti-PD-1	NCT04130763	Gastrointestinal system cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	10	ACTIVE_NOT_RECRUITING
FMT+chemotherapy+Sintilimab as first-line treatment for advanced gastric cancer	NCT06405113	Gastric cancer	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR)	PHASE2	198	NOT_YET_RECRUITING
FMT with nivolumab in patients with advanced solid cancers who have progressed during anti-PD-1 therapy	NCT05533983	Solid carcinoma	INTERVENTIONAL	SINGLE_GROUP	/	50	NOT_YET_RECRUITING
Responder-derived FMT (R-FMT) and pembrolizumab in relapsed/refractory programmed death ligand 1 (PD-L1) positive non-small cell lung cancer	NCT05669846	Non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	26	NOT_YET_RECRUITING
A study of FMT in patients with acute myeloid leukemia allogeneic hematopoietic cell transplantation in recipients	NCT03678493	Acute myeloid leukemia	INTERVENTIONAL	PARALLEL; Masking: NONE	PHASE2	100	COMPLETED
FMT combined with immune checkpoint inhibitor and tyrosine kinase inhibitors in the treatment of colorectal cancer patients with advanced stage	NCT05279677	Colorectal neoplasms malignant	INTERVENTIONAL	SINGLE_GROUP	PHASE2	30	UNKNOWN
Intestinal microbiota transplant prior to allogeneic stem cell transplant trial	NCT06355583	Acute lymphoblastic leukemia	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR)	PHASE2	50	NOT_YET_RECRUITING
Pilot trial of FMT for lymphoma patients receiving axicabtagene ciloleucel therapy.	NCT06218602	Lymphoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	40	RECRUITING
FMT+immunotherapy+chemotherapy as first-line treatment for driver-gene negative advanced non-small cell lung cancer	NCT06403111	Non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	62	NOT_YET_RECRUITING

(continued)

Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Role of the gut microbiome and fecal transplant on medication-induced gastrointestinal complications in patients with cancer	NCT03819296	Melanoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	800	RECRUITING
Assessing the tolerance and clinical benefit of fecal transplantation in patients with melanoma	NCT04988841	Melanoma	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	60	RECRUITING
FMT to improve efficacy of immune checkpoint inhibitors in renal cell carcinoma	NCT04758507	Renal cell carcinoma	INTERVENTIONAL	PARALLEL; Masking: QUADRUPLE (PARTICIPANT, CARE_PROVIDER, INVESTIGATOR, OUTCOMES_ASSESSOR)	PHASE2	50	ACTIVE_NOT_RECRUITING
Gut microbiota reconstruction for immunotherapy	NCT05008861	Non-small cell lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	20	UNKNOWN
Impact of oral nutritional supplements on patients undergoing hematopoietic stem cell transplantation	NCT05460013	Hematological malignancy	INTERVENTIONAL	PARALLEL; Masking: SINGLE (PARTICIPANT)	NA	100	RECRUITING
RBX7455 before surgery for the treatment of operable breast cancer	NCT04139993	Breast cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE1	3	TERMINATED
FMT combined with atezolizumab plus bevacizumab in patients with hepatocellular carcinoma who failed to respond to prior immunotherapy	NCT05750030	Hepatocellular carcinoma	INTERVENTIONAL	SINGLE_GROUP	PHASE2	12	RECRUITING
Pembrolizumab/Lenvatinib with and without responder-derived FMT in relapsed/refractory melanoma	NCT06030037	PD-1 refractory advanced melanoma	INTERVENTIONAL	PARALLEL; Masking: NONE	PHASE2	56	NOT_YET_RECRUITING
Oral immunonutrition with synbiotics, Omega 3, and vitamin D in patients undergoing duodenopancreatectomy for tumoral lesion.	NCT05271344	Pancreatic cancer	INTERVENTIONAL	PARALLEL; Masking: TRIPLE (PARTICIPANT, INVESTIGATOR, OUTCOMES_ASSESSOR)	/	74	RECRUITING
Feasibility study of microbial ecosystem therapeutics to evaluate effects of fecal microbiome in patients on immunotherapy	NCT03686202	All solid tumors	INTERVENTIONAL	SINGLE_GROUP	PHASE2	65	ACTIVE_NOT_RECRUITING

(continued)

Table 1. *(continued)*

Study	Identifier	Diseases	Study type	Study design	Phases	Enrollment	Study status
Role of microbiome as a biomarker in locoregionally-advanced oropharyngeal squamous cell carcinoma 2	NCT03838601	Head and neck squamous cell carcinoma	INTERVENTIONAL	SINGLE_GROUP	/	30	ACTIVE_NOT_RECRUITING
Microbiota and pancreatic cancer cachexia	NCT05606523	Pancreatic cancer	OBSERVATIONAL	Observational Model	/	24	RECRUITING
Role of gut microbiome in cancer therapy	NCT05112614	Hematopoietic and lymphoid cell neoplasm; malignant solid neoplasm	OBSERVATIONAL	Observational Model	/	5,000	RECRUITING
The effect of gut microbiota on postoperative liver function recovery in patients with hepatocellular carcinoma	NCT04303286	Hepatocellular carcinoma	OBSERVATIONAL	Observational Model	/	200	COMPLETED
The gut microbiome in acute myeloid leukemia with FLT3 mutation undergoing allogeneic hematopoietic stem cell transplantation with or without sorafenib maintenance	NCT05601895	Acute leukemia	OBSERVATIONAL	Observational Model	/	60	RECRUITING
The mechanism of enhancing the anti-tumor effects of chimeric antigen receptor T-cell immunotherapy on pancreatic cancer by gut microbiota regulation	NCT04203459	Pancreatic cancer	OBSERVATIONAL	Observational Model	/	80	UNKNOWN
The gut microbiome in acute myeloid leukemia with FMS-like tyrosine kinase-3/internal tandem duplication (FLT3/ITD) mutation undergoing allogeneic hematopoietic stem cell transplantation with or without sorafenib maintenance after allogeneic hematopoietic stem cell transplantation	NCT05596981	Acute myeloid leukemia with FLT3/ITD mutation	OBSERVATIONAL	Observational Model	/	60	RECRUITING
The gut microbiome and sorafenib maintenance therapy in FLT3/ITD positive cute myeloid leukemia after allogeneic hematopoietic stem cell transplantation	NCT05596968	Acute myeloid leukemia with FLT3/ITD mutation	OBSERVATIONAL	Observational Model	/	37	RECRUITING
Multiple myeloma outcomes based on maintenance therapy post autologous stem cell transplant	NCT05271630	Multiple myeloma	OBSERVATIONAL	Observational Model	/	69	RECRUITING
Fecal bacteria transplantation in the treatment of patients with advanced cancer	ChiCTR2100049431	Liver, colon, gastric, pancreatic, and lung cancer	INTERVENTIONAL	SINGLE_GROUP	PHASE2	50	UNKNOWN

complementarity may contribute to the colonization of microbiota and the outcomes of FMT.[87,88] FMT transplant materials include liquid and capsule forms, with administration methods including upper gastrointestinal tract liquid injection, lower gastrointestinal tract liquid injection, and oral capsules. Currently, there is a lack of comparative studies on the efficacy of different administration methods in tumor patients, and no consensus exists on the optimal dosage for FMT. The infusion dosage, frequency, and duration of FMT treatment may vary considerably across different diseases and patients. In theory, greater quantities of donor microbes can enhance colonization of the recipient's gut, achievable through either increasing the microbial amounts per single FMT or the frequency of administration. In many clinical studies, long-term and repeated FMT have been considered more favorable for outcomes.[89–93] Therefore, a considerable number of clinical trials are still needed to further address these issues.

Conclusions

It is increasingly recognized that the intricate relationship between the gut microbiota and PDAC underscores the potential of microbiome-based strategies in the management of this devastating disease. The identification of specific microbial signatures associated with PDAC offers a promising avenue for the development of non-invasive diagnostic tools. These tools could facilitate early detection, thereby improving patient prognosis through timely intervention. Moreover, the modulation of the gut microbiota through targeted interventions, such as fecal microbiota transplantation, presents a novel therapeutic approach that could enhance the efficacy of current treatments and potentially alleviate treatment-related adverse effects. Nevertheless, FMT also faces numerous challenges, such as dosage optimization, patient acceptance, and the scientific matching of donors and recipients. Multiple exploration gaps remain in the FMT validity and its long-term consequences. However, for microbiota-based strategies to become more practical in clinical applications, there is still a long way to go.

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Conflict of interest

The authors report that there are no competing interests to declare.

Author contributions

Study concept and design, acquisition of the data, drafting of the manuscript (XH, CM), critical revision of the manuscript (XK). All authors have made a significant contribution to this study and have approved the final manuscript.

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Review Article

Disparities in Gastric Cancer Screening Worldwide

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Abstract

Gastric cancer is the third most common cause of cancer-related death globally. The highest incidence is encountered in Asia, followed by Europe which has the second highest incidence worldwide. In Europe, gastric cancer is typically diagnosed at an advanced stage, with an estimated five-year survival rate of 24%, compared to 59% in Japan. This disparity is largely attributed to the significant role of screening in Japan. Given the expected rise in absolute numbers of gastric cancer cases, there has been a demand for gastric cancer screening programmes in high-intermediate risk countries, advocated by the International Agency for Research on Cancer, the Science Advice for Policy by European Academies, the European Commission as part of the Europe Beating Cancer Plan, and the Maastricht VI/Florence consensus guidelines. This review article summarizes the current disparities in screening strategies between countries in the East and West and comments on future developments in population-based screening research in this field. The references for this article were identified through PubMed, the Cochrane Database of Systematic Reviews, and the Cochrane Controlled Register of Trials using the search terms "gastric cancer", "stomach cancer", "Helicobacter pylori", and "screening" over the period from 1995 until March 2024. Overall, this review identifies three potential approaches to screening: primary, secondary, and opportunistic. It highlights the lack of a uniform consensus on the best approach to screening, the disparity in the information available in different populations, and upcoming research to address this disparity.

Introduction

Over one million new cases and 770,000 deaths of gastric cancer were estimated in 2020, making it the 6th most common cancer worldwide.[1] While the prevalence has been decreasing, the absolute burden has increased due to the aging population. It is predicted that by 2040, the annual burden of gastric cancer will rise to nearly 2 million new cases and 1.3 million deaths globally.[2] However, not all regions are equally affected; higher incidence rates are encountered in Asia, Latin America, and Central and Eastern Europe (Fig. 1).[3] This discrepancy in incidence is thought to be driven predominantly by environmental risk factors, the most significant of which is *Helicobacter pylori (H. pylori)* infection.[4,5] Other environmental risk factors include smoking, alcohol consumption, high salt intake, ingestion of smoked or cured meat, poor housing sanitation, and exposure to chemicals such as nitrosamines. Regarding genetic causes, familial clustering is observed in approximately 10% of cases, with hereditary mutations accounting for only 1–3% of all gastric cancer cases.[6]

Over 90% of gastric cancers are adenocarcinomas, with the majority being classified as non-cardia tumors. Lauren's histopathologic classification, created in 1960, is the most frequently used histopathological classification system in gastric cancer classification in Europe.[7] It divides gastric cancers into 'intestinal type' and 'diffuse type' based on histopathological findings. The most frequent type is the 'intestinal type' because of its morphological similarity to adenocarcinomas arising in the intestinal tract. It is a slow-growing tumor typically seen in older male patients with severe atrophic gastritis and is strongly associated with intestinal metaplasia caused by persistent *H. pylori* infection. The less common type is diffuse-type gastric cancer, which is more commonly seen in younger age groups and tends to have a more aggressive disease course and poorer outcomes.

Screening and prevention of gastric cancer

The Wilson and Junger criteria

The Wilson and Junger criteria for screening, established in 1968,

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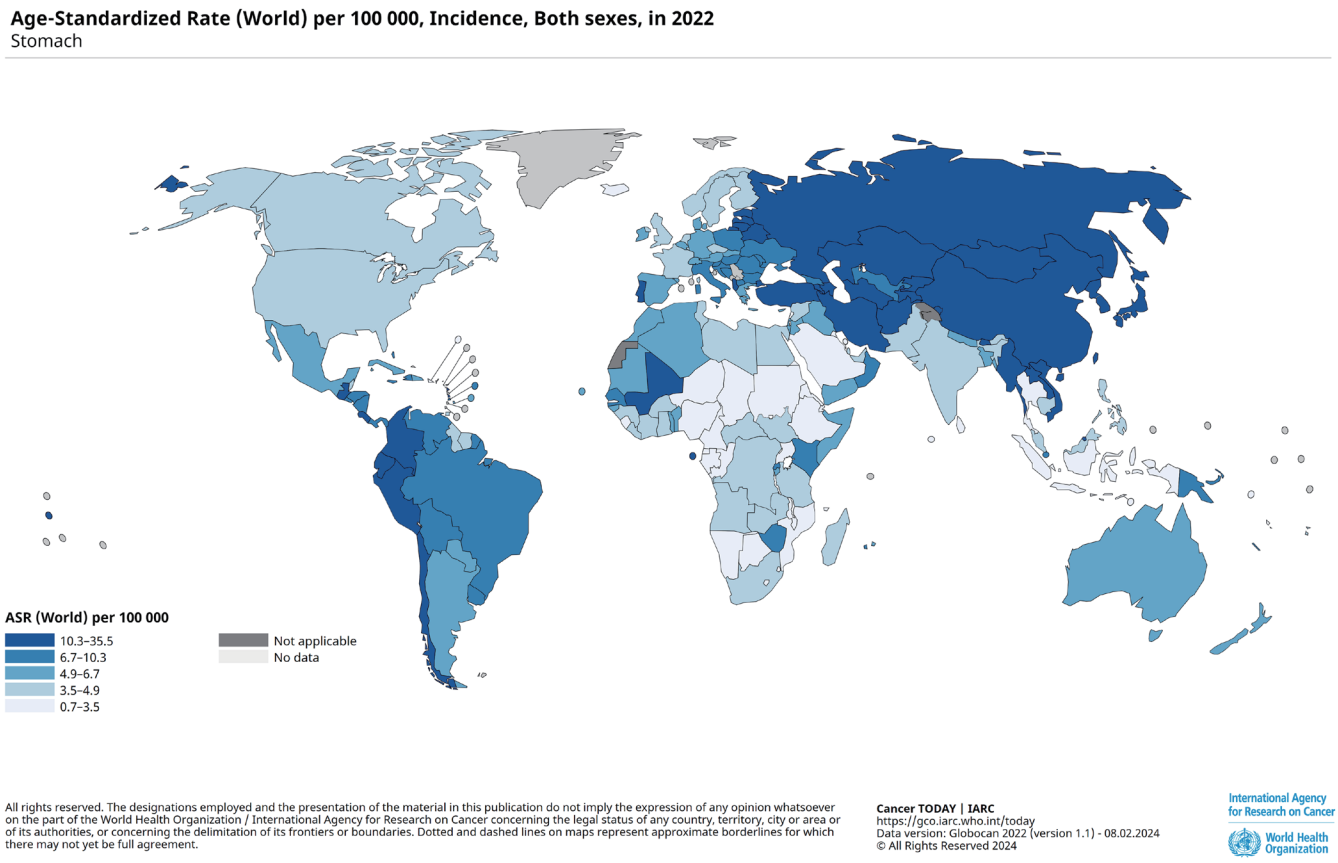

Fig. 1. The incidence of gastric cancer worldwide, GLOBOCAN 2022. License to use Figure 1 granted by the International Agency for Research on Cancer. Cancer TODAY | IARC https://gco.iarc.who.int/today. Data version: Globocan 2022 (version 1.1) - 08.02.2024© Date Accessed March 7, 2024.

outline key requirements for the development of an effective screening programme. These criteria include that the condition being screened for is an important health concern, that it has a recognizable early symptomatic stage, and that we understand the condition's natural course. It also requires the availability of a suitable test that is acceptable to the population and the availability of treatment and facilities for diagnosis and treatment.[8] In the case of gastric cancer, the disease pathway is detailed by the Correa cascade,[9] which describes the progression from normal mucosa through intestinal metaplasia, gastric atrophy, and ultimately, cancer. A significant promoter along this carcinogenic cascade is the presence of *H. pylori*. While *H. pylori* infection is not necessary for cancer development, it significantly promotes progression along this pathway. *H. pylori* can be tested for non-invasively using urea breath testing, stool antigen testing, or serology. Fortunately, effective treatment exists for this pathogen.[10] Notably, in countries with reducing *H. pylori* prevalence, there has been a corresponding reduction in gastric cancer cases (Figs. 2 and 3).[11]

Screening mechanisms

Three potential screening strategies have been suggested to target gastric cancer: primary prevention, secondary prevention, and opportunistic screening. A primary preventive strategy focuses on screening individuals for this carcinogenic bacteria before the development of preneoplastic lesions and treating it where present; this is known as a 'screen and treat' strategy.[12] A substantial body of evidence supports this approach, at reducing the risk of gastric cancer mortality and incidence. However, debate exists around the optimal age to begin screening. Recent studies have suggested the potential role of screening school-aged children, while others argue that infection in childhood rarely causes complications such as peptic ulcer disease.[13–15] A recent meta-analysis of randomized controlled trials using this 'screen and treat' approach in adult populations estimated the number needed to treat to prevent one case of gastric cancer as 72 and one cancer-related death as 135.[16] A significant body of observational data in Asia also supports this approach. The most notable of these is the Matsu Islands study. In this study, 7,000 adults over the age of 30 were screened and treated for *H. pylori*. Compared to the historical period from 1995 to 2003, there was a 53% reduction in gastric cancer incidence and a 23% reduction in mortality.[17] While limited, observational population data exists in a European population to support this approach. A systematic review conducted by Doorakkers *et al*.[18] on the Swedish database provided data associating *H. pylori* eradication with a reduction in gastric cancer in a Western population. The most significant benefit was observed when *H. pylori* infection was treated earlier, with a reported standardized incidence ratio over 5–7 years of 0.87.[19]

Secondary preventive strategies involve screening those in a high-risk age cohort when a pre-neoplastic or early neoplastic lesion has already occurred and endoscopically treating these before progression. Research on secondary prevention has primarily focused on endoscopic screening, the role of X-rays as part of an upper gastrointestinal series (UGIS), and serological markers. While both endoscopic screening and UGIS have limitations, me-

Fig. 2. The declining global prevalence of *Helicobacter pylori* infection.

ta-analysis supports the role of endoscopic screening over UGIS.[20] UGIS carries concerns over radioactivity, lack of biopsy capability, and low sensitivity and specificity compared to endoscopy, potentially resulting in lost opportunities to treat early-stage cancers endoscopically. Endoscopy, while both a screening and diagnostic test, is costly, comes with a small risk of significant complications, and requires considerable training to perform at a high quality. Despite these factors, UGIS has largely been replaced by endoscopic screening in national gastric cancer screening programmes in East Asian countries. However, in areas lacking facilities and trained endoscopy staff, UGIS can still be considered based on the patient's clinical situation.[21]

Research has been ongoing on the role of serological markers as a potential screening mechanism for decades.[22,23] *H. pylori* antibodies, pepsinogen I & II levels, gastrin-17, and anti-parietal cell antibodies have been studied for their potential role as a prescreening tool to determine who requires a gastroscopy. Support currently exists for the potential use of pepsinogen and *H. pylori* antibodies as a screening mechanism from the Kyoto Global Consensus; however, limitations exist in their application across popu-

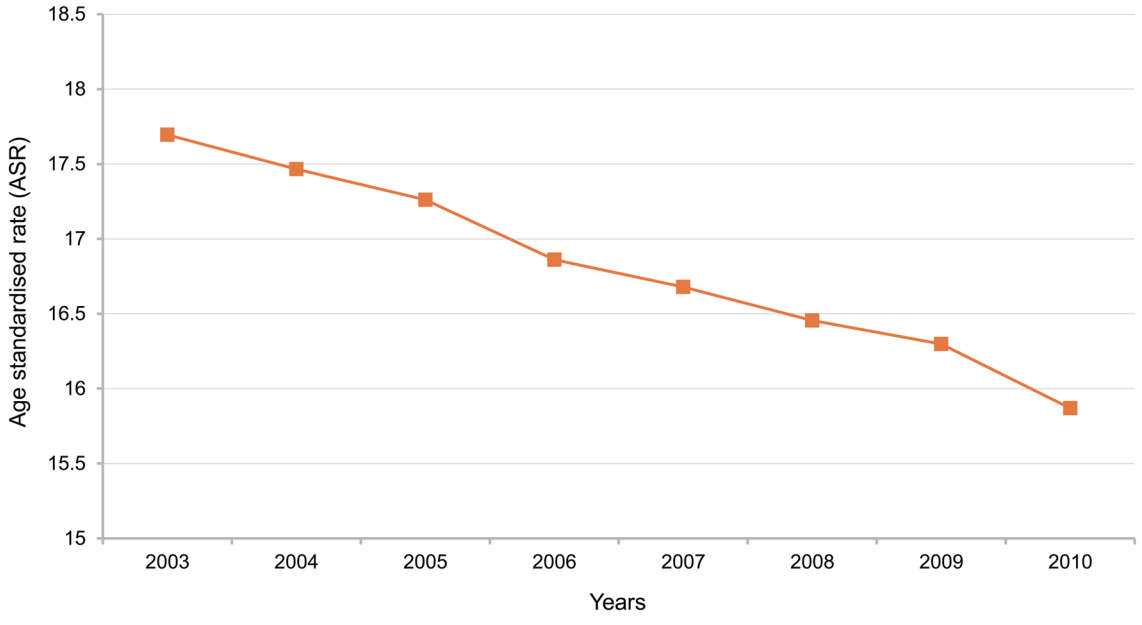

Fig. 3. The declining age standardized rate (ASR) of gastric cancer.

Table 1. A summary of existing screening strategies by country or region

Region	National screening programme available	Methods of screening
Japan	Yes	Endoscopic screening every 2–3 years from age 50
Korea	Yes	Endoscopic screening every two years for those aged 40–75
Mainland China	Targeted population screening: Individuals in selected high-risk rural areas; High-risk individuals in urban cities	Endoscopy from age 40–69
Europe	No	
North America	No	

lations.[24] Four key models have been proposed using these markers, including the ABC, ABCD, five-markers study, and the seven variables study. All scoring systems incorporate serology, with the more recent seven variables study also including recognized gastric cancer risk factors. The ABC and ABCD methods measure serum pepsinogen I, II, I/II ratio, and *H. pylori* antibody status.[25,26] The five-markers and seven variables methods measure *H. pylori* antibody status, pepsinogen I & II levels, gastrin-17 levels, and antiparietal cell antibodies. The seven variables method also assesses exposure to nitroso compounds such as pickled and fried food.[27,28] Out of these scoring systems, the seven variables method suggests a better discriminative ability to identify patients with gastric cancer than the other methods.[29] However, it is important to note differences in baseline risk in these study groups and variations in reproducibility of results in different populations. In Europe, a retrospective review by Gašenko *et al*.[30] found a poor correlation between changes in pepsinogen and gastrin-17 levels and gastric cancer, suggesting these serological markers have an uncertain application in a Caucasian population. Despite this, in countries where these markers are validated in the population being screened, they could potentially be used to select those who require gastroscopy, allowing for a 'work smart' approach to screening.

Vaccination against H. pylori

Research into the development of a vaccine against *H. pylori* has been ongoing for decades. While a significant body of knowledge about the bacteria has been developed, only one vaccine has reached a phase III clinical trial.[31] *H. pylori* possesses several strategies to survive hostile gastric environments and modify the host immune response to ensure its survival. As a result, no vaccine has successfully induced long-term protection against *H. pylori,* which is important since most infections occur in childhood.[32,33] Consequently, a vaccination strategy to reduce gastric cancer rates is not currently feasible.

Recommendations on gastric cancer screening from different societies

There has been a growing focus on adopting an evidence-based approach to gastric cancer screening. The 8th report from the International Agency for Research on Cancer Working Group strongly recommended that all nations incorporate gastric cancer into national cancer control programmes.[34] Their suggestion emphasized the importance of evaluating *H. pylori* prevalence and the potential effectiveness of prevention strategies tailored to each country.

The 2015 Kyoto Global Consensus Report on *H. pylori* gastritis further supported the importance of treatment, highlighting that eradicating *H. pylori* significantly diminishes the risk of developing gastric cancer.[24] This sentiment was echoed by the Taipei global consensus in 2020.[5]

The Maastricht/Florence VI guidelines propose incorporating gastric cancer screening in countries reporting an intermediate-high incidence of gastric cancer. They also support the role of mechanisms such as *H. pylori* screening in lower-incidence countries; however, they note that it may impact cost-effectiveness.[35] The Science Advice for Policy by European Academies network recommends implementing population-based screening and treatment programmes for *H. pylori* in regions with intermediate to high gastric cancer incidence.[36] Lastly, the European Commission identified gastric cancer as a target for an upcoming screening programme as part of the Europe Beating Cancer Plan.[37]

This collective body of recommendations from international organizations and academic reports underscores the global consensus on gastric cancer as a significant problem and the importance of evidence-based strategies for its screening and prevention. Notably, screening for gastric cancer is not a new concept, and certain countries have been screening for decades. This is explored further below and summarized in Table 1.

Screening strategies in high and intermediate-incidence countries and regions

Japan

Japan pioneered its inaugural gastric cancer screening initiative in the 1960s, and since then, screening initiatives have had a substantial influence on reducing mortality associated with gastric cancer. The 5-year survival rate in Japan stands at 59%, a stark contrast to Europe's lower rate of only 24%.[38] In 1983, the gastric cancer screening programme was expanded for all residents aged 40 years and older, involving an indirect UGIS using a barium meal. In 2018, the guidelines were updated to recommend biannual gastric cancer screening (using endoscopy) for individuals aged 50 and above.[39]

Korea

The Korean National Cancer Screening Programme for gastric cancer was launched in 2002, and the Korean National Guideline for gastric cancer screening was published in 2015. They currently recommend screening individuals aged 40–75 through endoscopy every two years.[40] They do not recommend screening those aged 75–84 due to insufficient evidence to assess the benefits and risks of screening in this age group and actively advise against screening adults over 85. While endoscopy is recommended as the screening test of choice, the guidelines allow for clinician judgment and patient preference, should they deem UGIS more appropriate in individual cases.

Mainland China

There is currently no nationwide screening programme in China; opportunistic screening with endoscopy is the primary method of early gastric cancer detection and prevention. Since 2005, two organized screening programmes for gastric cancer have been implemented in high-risk areas: the Cancer Screening Programme in Urban China and the Cancer Screening Programme in Rural Areas. These programmes focused on high-risk individuals in rural and urban areas.[21] High-risk individuals, as defined by the Chinese national guidelines, aged 40 years or above, were invited for upper gastrointestinal screening. Those with severe atrophic gastritis, intestinal metaplasia, and low-grade intestinal metaplasia at endoscopy were offered follow-up gastroscopy at least once within three years. By the end of 2018, more than 2 million rural people had undergone endoscopy, with a cancer detection rate of 2%, of which 70% were detected at an early stage.

Chinese Taiwan

Taiwan has no documented population-based screening strategy; however, several proposed methods to reduce gastric cancer incidence have been investigated. The most notable are the Matsu Island studies, detailed above and the Changhua County study.[17,41] The Changhua County study combined the national colorectal cancer screening strategy with screening for *H. pylori.* In this randomized controlled trial, stool samples were tested for fecal immunochemical testing and *H. pylori* in the intervention group, and those who tested positive were treated. This resulted in a 9% lower gastric cancer mortality rate in the intervention arm.

Europe

There is currently no population-based screening programme available in Europe despite it having the second highest incidence in the world after Asia. The current European guidelines, Management of Epithelial Precancerous Conditions and Lesions in the Stomach II, suggest opportunistic screening in those already identified as having premalignant lesions.[42] They do not make recommendations on screening the general population.

In comparison, the Maastricht VI/Florence consensus guidelines, published on behalf of the European Helicobacter and Microbiota Study Group, state that a population-based *H. pylori* 'screen and treat' programme is cost-effective in populations with an intermediate or high incidence of gastric cancer and that screening modalities for gastric cancer prevention (non-invasive or endoscopic) combined with colorectal cancer screening are a potential opportunity for screening.[35] The appetite for such recommendations has grown in response to the EU's Beating Cancer Plan.

Low-incidence countries and prevention studies

The United Kingdom (UK)

The UK lacks a standardized national screening programme for gastric cancer. Screening is currently based on recommendations by the British Society of Gastroenterology, which advises endoscopic screening for those over the age of 50 with risk factors for gastric cancer. These risk factors include pernicious anemia, a first-degree relative with a family history of gastric cancer, and other risk factors such as smoking and male gender.[43]

North America

No national gastric cancer screening programme is endorsed in North America. Furthermore, there is limited support for opportunistic screening in the guidelines from the American Gastroenterology Association. Currently, the support for endoscopic surveillance of intestinal metaplasia is debated and is generally only suggested for those at high risk of gastric cancer.[34] However, data does support the positive effect of *H. pylori* eradication on risk reduction for non-cardia gastric cancer eight years after treatment in a North American population.[44] Riquelme *et al*.[45] proposed measures for the Americas that could be used to control gastric cancer. These measures include promoting improvements in population-based cancer registry data to capture the burden of gastric cancer, supporting the development and dissemination of standards aimed at promoting quality endoscopy, enabling the training of healthcare workers specialized in gastric cancer, creating a *H. pylori* database to ensure optimal testing, follow-up and monitoring for resistance, ensuring endoscopic surveillance of patients with high-risk intestinal metaplasia, establishing quality research, and promoting population-based measures to reduce the incidence of gastric cancer such as strengthening smoking regulations, creating strategies to reduce salt intake, and promoting health literacy in the community.[45]

Future research developments in screening

Upcoming population-based screening

Research funded by the European Union is underway as part of the Eurohelican and the Towards Gastric Cancer Screening Implementation in the European Union (TOGAS) studies to determine the feasibility of a screening programme in member states. The Eurohelican research, based in Slovenia, seeks to evaluate the feasibility and cost-effectiveness of a primary preventive strategy towards gastric cancer.[46] The Towards Gastric Cancer Screening Implementation in the European Union trial is being run in 14 European countries with varying prevalence rates. The aim is to compare the feasibility and cost-effectiveness of primary and secondary preventive strategies amongst member states.[47] Two longitudinal studies evaluating the impact of screening in a European population are also underway. The *Helicobacter Pylori* Screening Study, a longitudinal study based in the UK that will conclude in 2024, aims to determine the potential impact of screening and treating *H. pylori* on gastric cancer risk over ten years in a low-incidence country.[48] The GISTAR study in Latvia will examine this effect in a high-incidence European country; it is due for completion in 2035.[49] These studies hold promise in offering valuable insights into the effectiveness of *H. pylori* screening and treatment strategies in an adult population in the context of low-intermediate and intermediate-high-risk European populations. In doing so, these studies will guide European member states in implementing local policies.

Other vital studies due for completion include the Linqu County study in China and the *Helicobacter Pylori* Eradication for Gastric Cancer Prevention in the General Population study from Korea.[36,50] These will provide data on the impact of *H. pylori* eradication on gastric cancer incidence. The clinical study by Gallardo *et al*.[51] in Chile, in which 14-18-year-olds are screened for *H. pylori*, will also provide data on the acceptability of this approach in a young adult cohort.

Requirement for the development of key performance indicators

Finally, future screening programmes will need to consider potential key performance indicators for gastric cancer screening, taking into account the mode of screening, cost of screening, and

diagnostic yield. In the case where a 'screen and treat' approach is adopted, consideration should be given to creating local registries that would allow for the audit of treatment compliance and effectiveness. If endoscopic screening is adopted, defining the minimum standards and markers of a 'quality screening endoscopy' will be required.

Conclusion

While the incidence of gastric cancer is falling, the absolute burden is rising, and it is estimated that there will be over a million cases by 2040. Despite the call for screening programmes, disparities still exist in the availability of gastric cancer screening. While national screening programmes have been created in high-incidence countries such as Japan and Korea, this contrasts with other high-incidence regions, such as Eastern Europe, where no national screening programme exists. This disparity is further exacerbated by the limited research available in Europe evaluating the feasibility of screening. Research is expected in the medium term that will aim to address this disparity.

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Conflict of interest

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Author contributions

Drafting of the manuscript (CD); critical revision of the manuscript for important intellectual content (COM, OK). All authors have made a significant contribution to this study and have approved the final manuscript.

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