British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(11): 55172
https://doi.org/10.31083/BJHM55172

Article

Global Altitude Patterns in the Burden of Major Digestive System Cancers: An Ecological Study of 185 Countries

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Academic Editor: Kassem Sharif
Submitted: 22 June 2026 Revised: 29 August 2026 Accepted: 17 September 2026 Published: 12 November 2026

Abstract

Aims/Background: The association between high altitude and the burden of digestive system cancer remains controversial, often lacking rigorous control for specific risk factors. This study assesses the ecological association between altitude—quantified as population-weighted mean elevation (PWME)—and the global burden of five major digestive system cancers. **Methods:** Cross-sectional data from the Global Cancer Observatory (GLOBOCAN) 2022 were integrated with longitudinal trends from the Global Burden of Disease Study 2021 across 185 countries. The association between PWME and cancer burden was assessed using multivariable linear regression models adjusting for socioeconomic, environmental, and cancer-specific confounders, e.g., red meat and alcohol consumption, obesity, and the prevalence of diabetes, *Helicobacter pylori*, hepatitis B, and hepatitis C infections. Longitudinal trends from 1990 to 2021 were assessed using joinpoint regression, and average annual percent changes were compared between high- and low-PWME strata. **Results:** In the fully adjusted GLOBOCAN 2022 models, PWME was inversely associated with the age-standardized incidence rate (ASIR) of colorectal cancer ($B = –0.4192$ per 100 m, 95% CI: –0.6676 to –0.1709, $p = 0.0011$) and positively associated with the ASIR of esophageal cancer ($B = 0.1177$ per 100 m, 95% CI: 0.0044 to 0.2311, $p = 0.0418$). These incidence-related associations were also observed in GBD 2021 and were retained in the registry quality–restricted sensitivity analysis. Mortality-related findings and associations for gastric, liver, and pancreatic cancers were less consistent across datasets and sensitivity analyses. In descriptive longitudinal analyses, average annual percent change comparisons suggested divergent temporal trajectories between high- and low-PWME groups across several cancer burden metrics. **Conclusion:** Higher PWME was inversely associated with colorectal cancer incidence and positively associated with esophageal cancer incidence at the country level. These ecological associations are hypothesis-generating and should be interpreted cautiously because altitude may capture multiple environmental, socioeconomic, lifestyle, healthcare, and data quality factors.

Keywords: digestive system neoplasms; altitude; Global Burden of Disease; ecological study

1. Introduction

Digestive system cancers have persistently high morbidity and mortality rates, thus posing substantial threats to global public health. According to global cancer statistics for 2022, five major digestive system malignancies—colorectal, stomach, liver, esophageal, and pancreatic cancers—collectively accounted for nearly 24% of all new cancer cases worldwide [1]. Although genetic predisposition plays a role, the substantial geographic variation in incidence rates underscores the pivotal influence of environmental exposures and lifestyle determinants on tumorigenesis [2,3]. Among these environmental factors, high altitude has attracted considerable epidemiological interest [4,5], not least because population-level observations show that communities residing at different elevations often present with varying disease profiles. Importantly, altitude should be viewed not as a single causal exposure or directly modifiable intervention target but rather as a stable geographic context that integrates multiple coexisting environmental and contextual factors, including hypobaric hypoxia, lower ambient temperature, elevated solar radiation, settlement patterns, dietary accessibility, socioeconomic conditions, and healthcare access. In this sense, al-

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titude may serve as an ecological marker for a broader set of geographically patterned exposures that are difficult to capture individually in global comparative studies. Evaluating altitude-related cancer burden patterns may therefore help identify populations and regions requiring more targeted etiological investigation and geographically tailored cancer control strategies [6,7].

The association between altitude and the risk of digestive system cancer is drawing increasing attention but remains fragmented and paradoxical. Previous studies have yielded heterogeneous results, sparking debate regarding the directionality of this relationship. Epidemiological data from Austria demonstrate an inverse association between elevation and age-standardized incidence and mortality rates of colorectal cancer in men [8], whereas other studies suggest that high-altitude adaptations may exacerbate cancer risk or progression [9,10]. The existing literature is constrained by several methodological limitations that preclude definitive conclusions, including the application of unweighted elevation proxies susceptible to exposure misclassification, reliance on geographically confined datasets, and inadequate adjustment for tumor-specific risk factors.

To bridge these gaps, this study provides a comprehensive assessment of the ecological association between altitude and the burden of five major digestive cancers for 185 countries. Using data from GLOBOCAN 2022 and the Global Burden of Disease (GBD) 2021, we used population-weighted mean elevation (PWME) as a core country-level geographic metric that integrates geographic elevation with population distribution for ecological comparisons [11,12,13]. Hierarchical multivariable regression models adjusting for general socioeconomic, environmental, and cancer-specific covariates are applied, and long-term temporal trends across PWME strata are compared. Thus, this study aims to characterize global altitude-related ecological patterns in digestive cancer burden and generate hypotheses for future etiological and population-level studies.

2. Methods

2.1 Study Design

The analytical framework integrated complementary cross-sectional and longitudinal methodologies. Cross-sectional analysis utilized data from GLOBOCAN 2022 and GBD 2021, employing hierarchical multivariable regression to evaluate the ecological association between PWME and age-standardized incidence and mortality rates with adjustment for multidimensional socioeconomic, environmental, and cancer-specific risk factors. Complementing this evaluation, longitudinal analysis leveraged GBD data to quantify the spatiotemporal trajectories and long-term epidemiological trends of these malignancies across distinct PWME strata.

2.2 Population-Weighted Mean Elevation (PWME)

To summarize the country-level geographic elevation at which national populations are distributed, we used PWME as the core ecological geographic metric, following the geospatial analysis framework established by Tremblay and Ainslie [14]. Geospatial data preprocessing and calculations were performed using the Quantum Geographic Information System (QGIS) software (version 3.4.0; QGIS Development Team, Open Source Geospatial Foundation, Beaverton, OR, USA). Data source selection was performed in strict compliance with the current standards for global high-altitude population estimation. Elevation data were extracted from the Global Multiresolution Terrain Elevation Data (GMTED2010) utilizing mean elevation data with a spatial resolution of 30 arc seconds (~1 km^2 at the equator). The corresponding population distribution data were obtained from the LandScan Global 2019 dataset published by Oak Ridge National Laboratory. This dataset, which shares the same high spatial resolution of 30 arc seconds, employs multisource auxiliary data to precisely model ambient population distribution and is regarded as the community standard in this field. National administrative boundary vector data were acquired from the Database of Global Administrative Areas (GADM, version 3.6).

PWME was determined as follows. The GMTED2010 elevation raster and LandScan population raster were spatially coregistered within the QGIS environment to ensure that both datasets shared the same geographic coordinate system and that pixels were strictly aligned. Subsequently, a population–elevation product layer was generated using Raster Calculator, with each pixel value representing the product of the population count and corresponding mean elevation for that location. Based on the national boundaries provided by GADM, the Zonal Statistics tool was applied to extract the total population (ΣP_i) and sum of the population–elevation product ($\Sigma(P_i \times E_i)$) for each country. Finally, the PWME for each country was calculated as the ratio of these two sums:

$$PWME = \frac{\Sigma_{i=1}^{n}(P_i \times E_i)}{\Sigma_{i=1}^{n} P_i},$$

where P_i and E_i represent the population count and elevation height of the i^{th} raster cell, respectively. This population-weighting strategy reduced the influence of uninhabited highlands or mountainous areas compared with simple geographic mean elevation and provided a country-level summary of population-weighted geographic elevation. However, PWME should not be interpreted as correcting all sources of systematic errors or directly measuring individual-level hypoxic exposure, environmental exposure, residential history, or physiological adaptation to altitude.

2.3 Data Sources for Digestive System Cancers

Cancer epidemiological data were retrieved from two global databases: GLOBOCAN 2022, published by the International Agency for Research on Cancer (IARC), and GBD 2021, established by the Institute for Health Metrics and Evaluation at the University of Washington. GLOBOCAN 2022 was used as the primary data source for cross-sectional regression analyses because it provides the most recent IARC estimates of cancer incidence and mortality for 2022 across 185 countries or territories. GBD 2021 was used as an additional source for cross-database validation and longitudinal trend analysis because it provides internally consistent annual estimates from 1990 to 2021, including incidence, mortality, prevalence, and disability-adjusted life years (DALYs). The key differences between GLOBOCAN 2022 and GBD 2021 are summarized in **Supplementary Table 1**.

GLOBOCAN 2022 was accessed via IARC's "Cancer Today" online platform, providing the most recent estimates of incidence and mortality rates for 36 cancer types across 185 countries or territories. These estimates are generated using a hierarchical estimation framework according to data availability and quality, including direct observations based on high-quality national cancer registry data, extrapolation from subnational or regional registry data, incidence estimation using mortality-to-incidence ratio models, and estimates based on data from neighboring countries or regions where local data are limited. Age-standardized incidence rates (ASIRs) and age-standardized mortality rates (ASMRs) were extracted for five major digestive system cancers. To eliminate the confounding effects of varying age structures across countries, all rates were standardized using Segi's world standard population.

GBD 2021 data were obtained using the GBD Results Tool provided by the Institute for Health Metrics and Evaluation (IHME, Seattle, WA, USA). In the GBD framework, cause-specific mortality estimates were primarily generated using the Cause of Death Ensemble model (CODEm) and reconciled with the all-cause mortality envelope through CoDCorrect, while cancer incidence estimates were derived from the final mortality estimates using modeled mortality-to-incidence ratios (MIRs). The GBD study integrates data from cancer registries, vital registration systems, verbal autopsies, and relevant covariates to estimate disease burden across 204 countries and territories. In addition to incidence and mortality metrics, we extracted DALYs from GBD 2021 to comprehensively assess the burden of premature mortality and disability attributable to cancer.

To ensure data comparability between the two databases, cancer sites were strictly defined according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). The ICD-10 codes of the five digestive system cancers included in the analysis are C15 (esophageal cancer), C16 (stomach cancer), C18–C21 (colorectal cancer), C22 (liver cancer), and C25 (pancreatic cancer).

2.4 Data Sources of Covariates

To adjust for potential confounding in the association between altitude and cancer burden, we incorporated a set of established covariates, which were grouped into three main categories, namely socioeconomic and environmental factors (Human Development Index (HDI) and average annual temperature), lifestyle and metabolic parameters (smoking prevalence, per capita alcohol consumption, red meat intake, obesity prevalence, and diabetes prevalence), and cancer-specific infectious agents (*Helicobacter pylori* (*H. pylori*), hepatitis B virus (HBV), and hepatitis C virus (HCV)). The definitions, measurement years, primary data sources, and website links for all covariates are summarized in **Supplementary Table 2**.

National-level aggregate data were extracted from internationally recognized authoritative databases or the most recent global systematic reviews. For socioeconomic and environmental factors, the HDI was obtained from the Human Development Report published by the United Nations Development Programme, serving as a composite metric of overall development and integrating life expectancy, educational attainment, and gross national income per capita. Additionally, long-term average annual surface temperature data were retrieved from the World Bank Climate Change Knowledge Portal to adjust for climatic variations that may influence pathogen dynamics and health outcomes.

For lifestyle and metabolic parameters, data were synthesized from multiple specialized global health observatories to ensure optimal data quality and comparability. Smoking prevalence data were sourced from the World Health Organization Global Health Observatory (GHO), employing the age-standardized prevalence of current tobacco use among persons aged ≥15 years, which integrates findings from the Global Adult Tobacco Survey. Alcohol consumption was quantified using data from the GHO and defined as the total alcohol consumption per capita among individuals aged 15 years and older, expressed as liters of pure alcohol and calculated as a three-year average (SDG Indicator 3.5.2). Although individual-level dietary survey data are available from resources such as the Global Dietary Database and national health and nutrition surveys, their country coverage is incomplete, survey years are not fully consistent, and dietary assessment methods vary across countries. Therefore, these data sources are difficult to harmonize for global cross-country ecological comparisons. In contrast, the Food and Agriculture Organization Statistics Database (FAOSTAT) food supply data provide a broader country coverage, continuous annual estimates, and more standardized definitions. Accordingly, red meat exposure was approximated using FAOSTAT "Food Supply Quantity" data (kg per capita per year) as a country-level proxy, aggregating the supply of bovine, mutton, goat,

pig, and other meats. The age-standardized prevalence of obesity among adults (body mass index ≥30 kg/m^2) was obtained from the GHO, while the age-standardized prevalence of diabetes was extracted from GBD 2021. Diabetes was defined according to the GBD 2021 diabetes mellitus prevalence estimates using the GBD reference case definition based on fasting plasma glucose ≥7.0 mM (126 mg/dL) or current use of insulin or other glucose-lowering medication.

Regarding cancer-specific infectious agents, prevalence estimates for HBV and HCV infections were derived from GBD 2021. HBV prevalence was defined as the GBD 2021 country-level prevalence estimate of HBV infection, primarily informed by hepatitis B surface antigen seroprevalence. HCV prevalence was defined as the GBD 2021 country-level prevalence estimate of HCV infection, informed by anti-HCV seroprevalence and, where applicable, estimates of viremic HCV infection. For *H. pylori*, owing to the lack of a single annual global monitoring system, national prevalence estimates were extracted from the results of the most comprehensive recent global analysis [15]. The available country-level *H. pylori* estimates were reported as crude prevalence estimates rather than age-standardized prevalence estimates. To ensure temporal consistency, all covariate data were matched to the time points closest to cancer incidence data.

2.5 Statistical Analysis

To systematically assess the ecological association between altitude and cancer burden, we performed Spearman's rank correlation analysis and then constructed multivariable linear regression models. A hierarchical modeling strategy was adopted to rigorously control for potential confounders and evaluate the contribution of different covariate categories through stepwise inclusion. Model 1 included the PWME as the sole predictor to assess the crude association. Model 2 expanded upon Model 1 by adjusting for the HDI, smoking prevalence, and average annual temperature. Model 3—the fully adjusted model—further incorporated cancer-specific risk factors relevant to each tumor type. The regression results were reported as unstandardized regression coefficients (*B*) with 95% confidence intervals (CIs). For improved interpretability, PWME was rescaled by dividing the original meter-based value by 100, and the coefficients therefore represent the absolute change in age-standardized cancer rate per 100,000 population associated with a 100-m increase in PWME. As country-level ASIRs and ASMRs may show skewed distributions and include extreme values, diagnostic assessments were performed for the fully adjusted multivariable regression models. Standardized residuals, leverage values, and Cook's distances were examined to identify residual outliers and potentially influential observations. Cook's distance >1 was considered indicative of a potentially influential observation. Because ASIR and ASMR are continuous age-standardized rates, the primary regression analyses were conducted on the original rate scale to preserve the direct interpretability of the unstandardized coefficients as absolute rate differences per 100,000 population associated with a 100-m increase in PWME. Therefore, no data transformation was applied in the primary analysis. Multicollinearity among covariates in fully adjusted models was assessed using variance inflation factors (VIFs) and tolerance values. VIF >5 was considered suggestive of moderate collinearity, whereas VIF >10 or tolerance value <0.10 was considered indicative of severe multicollinearity. To assess the potential influence of cancer registration quality, we conducted registry quality–restricted sensitivity analyses separately for incidence and mortality outcomes. Countries were classified according to the GLOBOCAN 2022 country-specific data source and estimation method. For ASIR models, countries with higher-quality incidence estimates based on national cancer registry data or one or more subnational population-based cancer registries were retained, whereas countries whose incidence estimates were mainly derived from mortality-to-incidence modelling, neighbouring-country rates, regional extrapolation, or unclear sources were excluded. For ASMR models, countries with higher-quality mortality estimates were retained according to the corresponding GLOBOCAN 2022 mortality data quality classification. After applying these restrictions, 94 countries were retained and 91 countries were excluded for ASIR models, whereas 93 countries were retained and 92 countries were excluded for ASMR models. The fully adjusted models were then refitted in the corresponding restricted datasets.

For longitudinal analysis, temporal trends in cancer burden from 1990 to 2021 were evaluated using joinpoint regression models. A log-linear model was used with a logarithmic transformation of age-standardized rates [$\ln(y) = xb$]. The grid search method was applied to identify candidate joinpoint locations. The minimum and maximum numbers of joinpoints were set to zero and five, respectively. The optimal number of joinpoints was selected using the Monte Carlo permutation test with an overall significance level of 0.05 and 4499 permutations. Parametric methods were used to calculate CIs for annual percent changes (APCs) and average annual percent changes (AAPCs). AAPCs and their 95% CIs were calculated to describe long-term epidemiological trajectories over the past three decades. In addition to AAPCs, segment-specific APCs and their 95% CIs were extracted from each joinpoint model. The identified joinpoint years were reported as the boundaries between adjacent temporal segments. To assess geospatial disparities, countries were stratified into high-PWME (top quintile) and low-PWME (bottom quintile) groups, which allowed comparison between countries with the most contrasting population-weighted altitude profiles. The two-sided Mann–Whitney U test was used for comparisons of age-standardized rates between high-PWME and

low-PWME countries in box plots because country-level cancer rates were not assumed to follow a normal distribution. Differences in AAPCs between high-PWME and low-PWME groups were evaluated using a Z test based on AAPC estimates and their standard errors (SEs):

$$Z = \frac{(\mathrm{AAPC_{High}} - \mathrm{AAPC_{Low}})}{\sqrt{\mathrm{SE_{High}}^2 + \mathrm{SE_{Low}}^2}}.$$

Estimated annual percentage changes (EAPCs) were calculated as complementary summary metrics to facilitate comparison with previous GBD-based epidemiological studies. For each cancer type, burden metric, and PWME stratum, a log-linear regression model was fitted as ln(age-standardized rate) = $\alpha + \beta \times$ calendar year + ε. EAPC was calculated as $100 \times [\exp(\beta) - 1]$, and the corresponding 95% CI was calculated as $100 \times [\exp(\beta \pm 1.96 \times \mathrm{SE}) - 1]$, where β and SE represent the regression coefficient and SE for a calendar year, respectively. These analyses were used to compare descriptive temporal patterns across PWME strata, and time-varying country-level covariates were not incorporated into the joinpoint models. Statistical significance was determined by evaluating whether the AAPC significantly deviated from zero and directly comparing the difference in AAPC trajectories between high- and low-PWME strata.

To further explore the potential future public health relevance of the observed temporal patterns, exploratory medium-term projections of age-standardized rates were performed using autoregressive integrated moving average (ARIMA) models. Annual ASIRs, ASMRs, and age-standardized disability-adjusted life year rates (ASDRs) from 1990 to 2021 were used as input time series for each cancer type and PWME stratum. For each time series, a nonseasonal ARIMA model was fitted, and the optimal model was selected according to the corrected Akaike information criterion. Model adequacy was assessed using residual autocorrelation diagnostics and the Ljung–Box test. The fitted models were used to project age-standardized rates from 2022 to 2035, with uncertainty summarized using 95% prediction intervals. As these projections were based on age-standardized rates rather than age-specific counts and projected population structures, they were interpreted as exploratory rate-based projections rather than formal age–period–cohort burden forecasts.

All statistical analyses were performed using SPSS (version 29, IBM Corp., Armonk, NY, USA), R (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria), and the Joinpoint Regression Program (version 5.0.2, National Cancer Institute, Bethesda, MD, USA). Graphical visualizations were generated using R and GraphPad Prism (version 10, GraphPad Software, Boston, MA, USA). A two-sided p value of <0.05 was considered statistically significant.

3. Results

3.1 Global Burden of Digestive Cancers and Geospatial Distribution of Population-Weighted Elevation

In 2022, colorectal, liver, stomach, esophageal, and pancreatic cancers ranked among the top 10 causes of cancer mortality (Fig. 1A), with colorectal and liver cancers ranking among the top five. The geospatial distribution of the combined ASMR for these five cancers showed marked global heterogeneity (Fig. 1B). In terms of incidence, these five digestive cancers also ranked within the top 15 for ASIR globally (Fig. 1C), with colorectal cancer ranking as the fourth most incident cancer overall. The geospatial distribution of the combined ASIR for these five cancers also varied across countries, with higher rates observed in East Asia, Central Europe, and parts of South America (Fig. 1D).

Regarding the geospatial distribution of population-weighted elevation, our demographic analysis showed that a substantial portion of the global population resides in areas at or above selected elevation thresholds, including ≥1500, ≥2500, and ≥3500 m (Fig. 1E). Ethiopia and China are among the top 10 countries in terms of the absolute size of the population residing above these elevation thresholds, with China accounting for the largest absolute population residing above 3500 m. When considering the proportion of the national population, countries in the Andean region showed particularly high percentages of residents at the ≥2500 m and ≥3500 m thresholds. To provide a country-level summary of population-weighted geographic elevation, we established PWMEs for 185 countries. The global map of PWME demonstrated marked spatial variation in population-weighted elevation across countries (Fig. 1F).

3.2 Bivariate Associations Between Altitude and Digestive Cancer Burden

To systematically explore the potential link between altitude and digestive system malignancies, Spearman's rank correlation analyses and high-PWME versus low-PWME group comparisons were conducted using data derived from GLOBOCAN 2022 (Fig. 2) and GBD 2021 (**Supplementary Fig. 1**). The bivariate findings showed both shared patterns and database-specific differences; therefore, these results were interpreted as exploratory associations rather than definitive evidence of cross-database consistency. For colorectal cancer, ASIR and ASMR exhibited significant negative correlations with PWME in GLOBOCAN 2022 (Fig. 2A), and countries in the top 20% quintile of PWME had significantly lower ASIRs and ASMRs than those in the bottom 20% quintile (Fig. 2B). Similar inverse patterns were observed in the GBD 2021 dataset (**Supplementary Fig. 1A,B**). In contrast, no significant correlations were observed between PWME and the ASIR or ASMR of liver cancer, and no significant differences were found between high-PWME and low-PWME

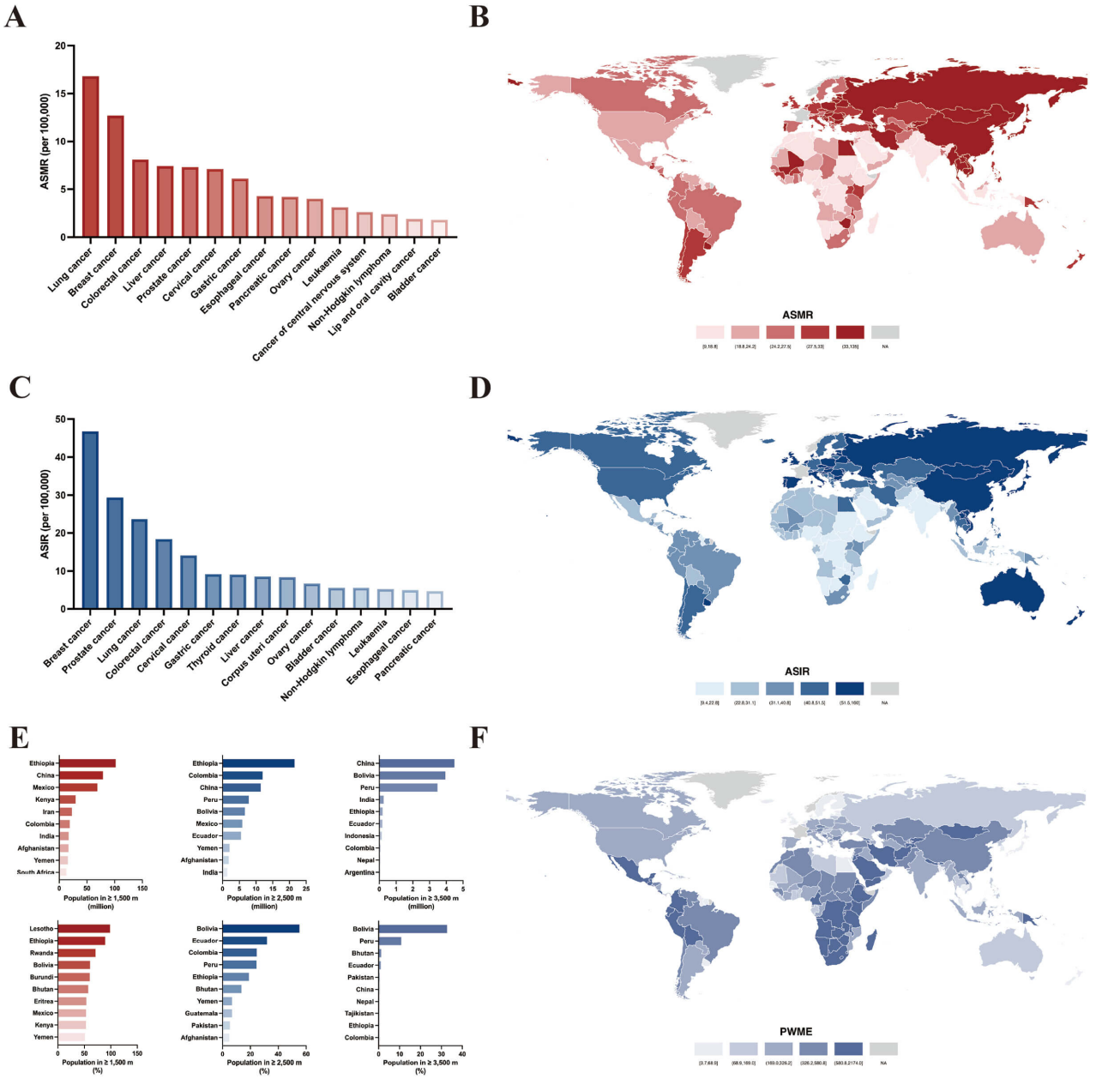


Fig. 1. Global burden of major digestive system cancers and geospatial assessment of high-altitude exposure. (A) Global rankings of the five digestive system malignancies (colorectal, liver, stomach, esophageal, and pancreatic cancer) among the leading causes of cancer-related mortality in 2022. (B) Geospatial heatmap depicting the global distribution of the age-standardized mortality rate (ASMR) for the five selected digestive cancers grouped together in GLOBOCAN 2022. (C) Global rankings of the five selected digestive malignancies among the leading causes of cancer incidence globally in 2022. (D) Geospatial heatmap illustrating the global distribution of the grouped age-standardized incidence rate (ASIR) for the five selected digestive cancers in GLOBOCAN 2022. For panels B and D, the five cancer types were selected simultaneously using the "Grouped" function in GLOBOCAN, and the corresponding grouped ASMR and ASIR reported by GLOBOCAN were used. (E) Top 10 countries with the largest populations residing at ≥1500, ≥2500, and ≥3500 m. Upper row: absolute population size in millions. Lower row: percentage of national population. (F) Global spatial distribution of population-weighted mean elevation (PWME) across 185 countries. Data sources: GLOBOCAN 2022 for global cancer incidence and mortality estimates in (A–D); GMTED2010, LandScan Global 2019, and GADM version 3.6 for altitude-related population exposure and PWME estimates in (E,F).

countries in either dataset (Fig. 2C,D; **Supplementary Fig. 1C,D**). For gastric cancer, ASIR was not significantly correlated with PWME, whereas ASMR showed a significant positive correlation with PWME in both datasets (Fig.

2E,F; **Supplementary Fig. 1E,F**). For esophageal cancer, the GLOBOCAN 2022 bivariate correlation results did not show statistically significant associations between PWME and ASIR or ASMR, although high-PWME countries had higher ASIRs and ASMRs than low-PWME countries in the extreme-quintile comparison (Fig. 2G,H). In contrast, in the GBD 2021 dataset, esophageal cancer ASIR and ASMR were significantly positively correlated with PWME and were higher in high-PWME countries than in low-PWME ones (**Supplementary Fig. 1G,H**). For pancreatic cancer, ASIR and ASMR were significantly negatively correlated with PWME in GLOBOCAN 2022 and GBD 2021, and countries in the top 20% PWME quintile had significantly lower ASIRs and ASMRs than those in the bottom 20% quintile (Fig. 2I,J; **Supplementary Fig. 1I,J**).

3.3 Multivariable Analysis of Altitude and Cancer Burden

Hierarchical multivariable linear regression models were constructed to evaluate the adjusted ecological associations between PWME and digestive cancer burden. PWME was rescaled per 100 m for improved interpretability, and regression results were reported as unstandardized coefficients with 95% CIs (Table 1, **Supplementary Table 3**).

Using GLOBOCAN 2022 as the primary dataset for contemporary cross-sectional regression analysis and GBD 2021 as a validation dataset, the fully adjusted models showed that the associations between PWME and digestive cancer burden varied by cancer type, burden metric, and database (Table 1, **Supplementary Tables 3,4**, Fig. 3). Among incidence outcomes, two findings were observed in both datasets and supported by registry quality–restricted sensitivity analysis. PWME was inversely associated with colorectal cancer ASIR in GLOBOCAN 2022 (B = –0.4192, 95% CI: –0.6676 to –0.1709, p = 0.0011) and GBD 2021 (B = –0.3160, 95% CI: –0.6308 to –0.0012, p = 0.0492), and this association was retained after restricting the analysis to countries with higher-quality cancer registration data (B = –0.3772, 95% CI: –0.7512 to –0.0033, p = 0.0481). PWME was positively associated with esophageal cancer ASIR in GLOBOCAN 2022 (B = 0.1177, 95% CI: 0.0044 to 0.2311, p = 0.0418) and GBD 2021 (B = 0.1795, 95% CI: 0.0187 to 0.3402, p = 0.0289), and this association was also retained in the registry quality–restricted sensitivity analysis (B = 0.3296, 95% CI: 0.1460 to 0.5133, p < 0.001). These results suggest that the PWME-related patterns for colorectal and esophageal cancers were more consistently observed for incidence than for other burden metrics.

Mortality-related findings were less consistent across analyses. Although PWME was positively associated with esophageal cancer ASMR in the fully adjusted models of GLOBOCAN 2022 and GBD 2021, this association was not observed in the registry quality–restricted sensitivity analysis. Similarly, colorectal cancer ASMR was inversely associated with PWME in GLOBOCAN 2022, but this association was not reproduced in the GBD 2021 fully adjusted model. For gastric cancer, PWME was positively associated with ASMR in the GLOBOCAN 2022 fully adjusted model (B = 0.1804, 95% CI: 0.0433 to 0.3175, p = 0.0103), whereas the association with ASIR did not reach statistical significance (B = 0.1739, 95% CI: –0.0090 to 0.3569, p = 0.0622). In the GBD 2021 fully adjusted models, PWME was positively associated with both gastric cancer ASIR and ASMR. However, these gastric cancer associations were not reproduced in the registry quality–restricted sensitivity analysis and were therefore interpreted cautiously. Pancreatic cancer showed inverse associations with PWME in GLOBOCAN 2022 primary analysis, whereas these associations were not observed in GBD 2021 fully adjusted models. Liver cancer was not significantly associated with PWME in the fully adjusted GLOBOCAN 2022 primary analysis or GBD 2021 validation analysis for ASIR or ASMR. Although liver cancer ASMR was significant in the registry quality–restricted sensitivity analysis, this finding was not reproduced across datasets and was therefore interpreted cautiously.

After applying the registry-quality restrictions, 94 countries were retained and 91 countries were excluded for ASIR models, whereas 93 countries were retained and 92 countries were excluded for ASMR models. Diagnostic assessments of the fully adjusted models identified residual outliers in several cancer-specific models, with the most pronounced deviations observed in liver cancer models (**Supplementary Table 5**). In particular, liver cancer models showed maximum absolute standardized residuals of approximately 9–10 and Cook's distances >1, indicating that at least one country deviated substantially from the model-predicted liver cancer burden and may have exerted considerable influence on the fitted models. Therefore, liver cancer regression results were interpreted cautiously. In contrast, Cook's distances for the main incidence findings of colorectal and esophageal cancers remained below 1 in both GLOBOCAN 2022 and GBD 2021, suggesting that these primary incidence patterns were unlikely to be driven by a single highly influential country. Multicollinearity diagnostics showed that most fully adjusted models had VIFs of <5. Moderate collinearity was observed in liver cancer models, mainly related to the HDI, but no model showed severe multicollinearity based on VIF >10 or tolerance <0.10 (**Supplementary Table 6**).

3.4 Longitudinal Trends and Regional Disparities in Digestive Cancer Burden

We analyzed the spatiotemporal evolution of digestive system cancers across different PWME strata using longitudinal data from 1990 to 2021. The temporal trajectories of ASIR, ASMR, age-standardized prevalence rate (ASPR), and ASDR revealed distinct epidemiological patterns between altitude groups (Fig. 4). Generally, high-PWME and low-PWME countries exhibited divergent epi-

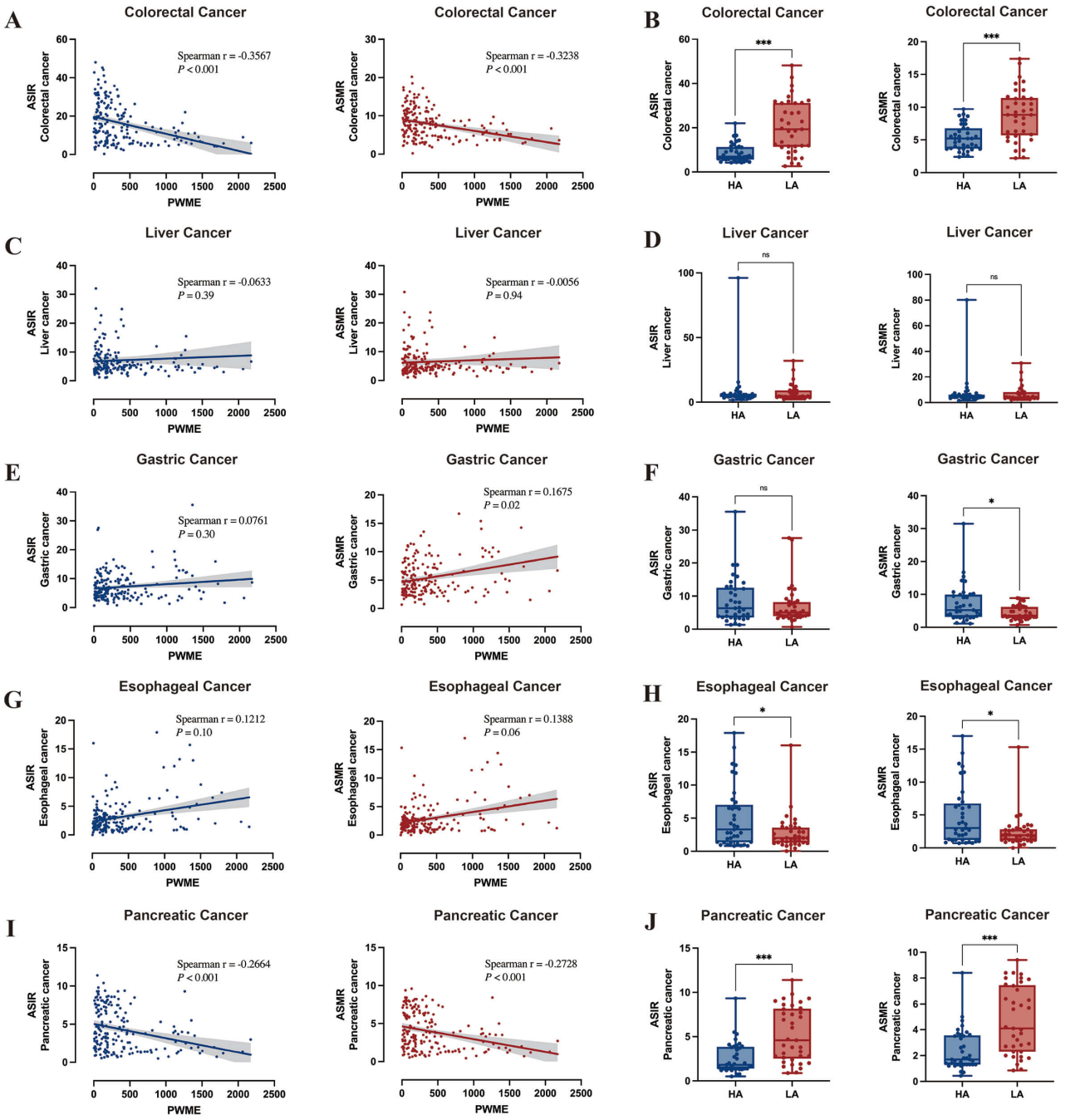


Fig. 2. Bivariate associations between PWME and the burden of five major digestive system cancers. (A) Spearman's rank correlation analyses evaluating the relationship between PWME and colorectal cancer ASIR and ASMR. (B) Box plots comparing the ASIR and ASMR of colorectal cancer between countries in the top 20% quintile (high altitude, HA) and the bottom 20% quintile (low altitude, LA) of PWME. (C) Spearman's rank correlation analyses evaluating the relationship between PWME and liver cancer ASIR and ASMR. (D) Box plots comparing liver cancer ASIR and ASMR between HA and LA countries. (E) Spearman's rank correlation analyses evaluating the relationship between PWME and gastric cancer ASIR and ASMR. (F) Box plots comparing gastric cancer ASIR and ASMR between HA and LA countries. (G) Spearman's rank correlation analyses evaluating the relationship between PWME and esophageal cancer ASIR and ASMR. (H) Box plots comparing esophageal cancer ASIR and ASMR between HA and LA countries. (I) Spearman's rank correlation analyses evaluating the relationship between PWME and pancreatic cancer ASIR and ASMR. (J) Box plots comparing pancreatic cancer ASIR and ASMR between HA and LA countries. Shaded regions in scatter plots represent the 95% confidence intervals (CIs) of regression lines. Statistical significance in box plots is indicated as $*p < 0.05$, $***p < 0.001$, ns, not significant. Data source: GLOBOCAN 2022.

Table 1. Association between PWME and age-standardized rates of incidence and mortality in digestive system cancers (GLOBOCAN 2022) with adjusted for different covariates.

Cancer burden	Model 1[1]			Model 2[2]			Model 3[3]		
	PWME coefficient	95% CI	*p* value	PWME coefficient	95% CI	*p* value	PWME coefficient	95% CI	*p* value
ASIR									
Colorectal cancer	–0.8916	–1.2147 to –0.5685	<0.001	–0.2493	–0.4843 to –0.0143	0.0377	–0.4192	–0.6676 to –0.1709	0.0011
Liver cancer	0.0942	–0.1695 to 0.3579	0.4820	0.0222	–0.2677 to 0.3122	0.8799	–0.0368	–0.3699 to 0.2962	0.8274
Gastric cancer	0.1541	–0.0034 to 0.3116	0.0551	0.2869	0.1213 to 0.4525	<0.001	0.1739	–0.0090 to 0.3569	0.0622
Esophageal cancer	0.1933	0.1005 to 0.2862	<0.001	0.1745	0.0716 to 0.2773	<0.001	0.1177	0.0044 to 0.2311	0.0418
Pancreatic cancer	–0.1861	–0.2719 to –0.1004	<0.001	–0.0131	–0.0772 to 0.0509	0.6859	–0.0807	–0.1432 to –0.0183	0.0117
ASMR									
Colorectal cancer	–0.2931	–0.4123 to –0.1740	<0.001	–0.1033	–0.2090 to 0.0024	0.0553	–0.1285	–0.2432 to –0.0139	0.0283
Liver cancer	0.083	–0.1478 to 0.3139	0.4790	–0.0164	–0.2681 to 0.2353	0.8979	–0.0561	–0.3442 to 0.2321	0.7010
Gastric cancer	0.2062	0.0913 to 0.3212	<0.001	0.2557	0.1307 to 0.3806	<0.001	0.1804	0.0433 to 0.3175	0.0103
Esophageal cancer	0.1961	0.1084 to 0.2837	<0.001	0.1664	0.0699 to 0.2630	<0.001	0.1193	0.0122 to 0.2263	0.0292
Pancreatic cancer	–0.1676	–0.2436 to –0.0916	<0.001	–0.0156	–0.0728 to 0.0416	0.5910	–0.0736	–0.1298 to –0.0175	0.0105

PWME, Population-Weighted Mean Elevation; CI, Confidence Interval.

Data source: GLOBOCAN 2022.

Coefficients are unstandardized regression coefficients (*B*) and represent the absolute change in age-standardized rates per 100,000 population associated with a 100-m increase in PWME.

[1] Model 1 was unadjusted.

[2] Model 2 was adjusted by HDI, smoking, and average annual temperature (AAT).

[3] Model 3 was adjusted by HDI, smoking, AAT, and cancer-specific confounders. Colorectal cancer was further adjusted by red meat consumption, alcohol consumption, obesity (body mass index [BMI] ≥30), and diabetes prevalence. Liver cancer was further adjusted by alcohol consumption, HBV prevalence, and HCV prevalence. Gastric cancer was further adjusted by *H. pylori* infection prevalence. Esophageal Cancer was further adjusted by alcohol consumption. Pancreatic Cancer was further adjusted by alcohol consumption, obesity (BMI ≥30), and diabetes prevalence.

demiological trajectories. For colorectal and pancreatic cancers, standardized rates in low-PWME regions consistently exceeded those in high-PWME regions. However, a notable upward trend in colorectal cancer ASIR was observed in high-PWME countries, gradually narrowing the gap with low-PWME ones. Conversely, for esophageal cancer, ASIR and ASMR in high-PWME countries remained higher than those in low-PWME countries over the past three decades but did not consistently exceed global estimates (Fig. 4). The absolute numbers of incidence cases, deaths, prevalent cases, and DALYs showed heterogeneous changes from 1990 to 2021 across cancer types, burden metrics, and PWME strata, with increases observed for several cancer–metric combinations but decreases or relative stability observed for others (**Supplementary Fig. 2**). To further characterize phase-specific changes in these temporal trajectories, segment-specific APCs and the corresponding joinpoint years were extracted from each joinpoint model (**Supplementary Tables 7–10**). These joinpoint analyses identified distinct temporal phases, with the timing and magnitude of segment-specific trend changes differing across cancer types, burden metrics, and PWME strata. To enhance comparability with previous GBD-based epidemiological studies, we calculated EAPCs for ASIR, ASMR, ASPR, and ASDR across different strata and provided an additional long-term trend metric complementary to the joinpoint-derived AAPC and APC estimates (**Supplementary Table 11**).

The quantification of the magnitude and speed of changes in incidence rates from 1990 to 2021 (Table

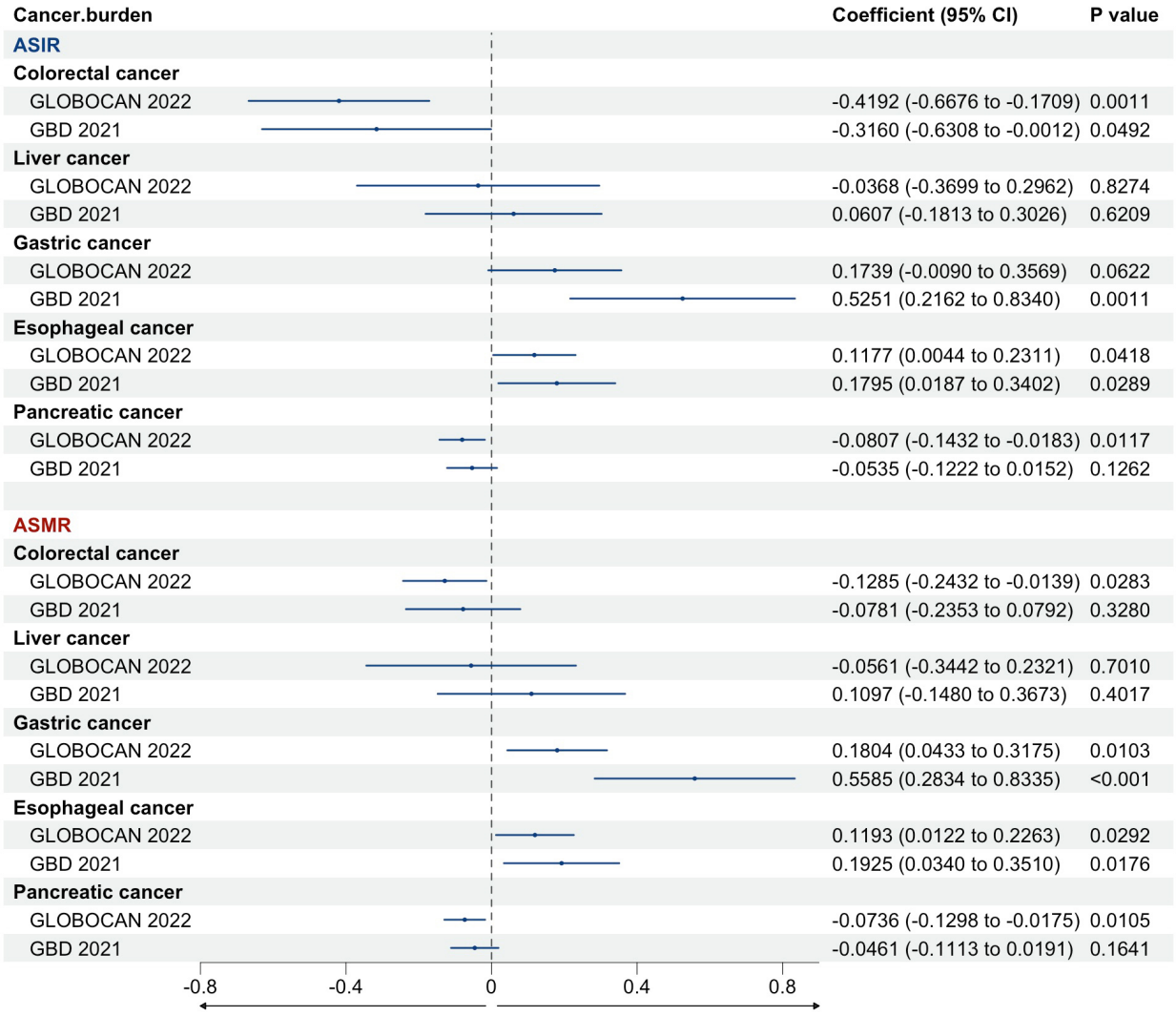


Fig. 3. Multivariable linear regression analysis of the adjusted ecological associations between PWME and digestive cancer burden. Forest plot presenting the unstandardized regression coefficients (*B*) per 100-m increase in PWME and 95% CIs for the ASIRs and ASMRs of the five digestive cancers. Results are derived from the fully adjusted model (Model 3) across GLOBOCAN 2022 and GBD 2021 with adjustment for socioeconomic, environmental, lifestyle/metabolic, and cancer-specific covariates. Blue dots represent point estimates, and horizontal lines denote 95% CIs. The vertical dashed line at zero indicates no association; coefficients positioned to the left or right denote a negative or positive association with PWME, respectively. The results of registry quality–restricted sensitivity analyses based on GLOBOCAN 2022 are presented separately in **Supplementary Table 4**. Data sources: GLOBOCAN 2022 and GBD 2021.

2) revealed significant heterogeneity in incidence trends between altitude groups. For colorectal cancer, cross-sectional analysis indicated a negative association between altitude and incidence at the baseline, while longitudinal data showed a greater relative increase in high-PWME countries. Specifically, these countries experienced a relative change of 29.29% in ASIR with an AAPC of 0.798 (95% CI: 0.698 to 0.898, $p < 0.001$). In contrast, low-PWME countries, which maintained higher absolute incidence rates, showed a relative change of 2.54% and a plateauing trend (AAPC = 0.039, $p = 0.626$). This difference in growth rate was statistically significant ($p < 0.001$). Thus, although high-PWME countries currently have a lower absolute burden of colorectal cancer, their faster relative growth is progressively narrowing the incidence gap. For gastric and esophageal cancers, although ASIRs declined globally, the reduction was significantly slower in high-PWME countries. For instance, the AAPC for gastric cancer ASIR was –1.420 in high-PWME countries and –3.078 in low-PWME countries, i.e., the decline was more rapid in the latter case ($p < 0.001$). For liver cancer, ASIR showed heterogeneous temporal patterns across strata. At the global level, liver cancer ASIR showed a slight but statistically significant increasing trend (AAPC =

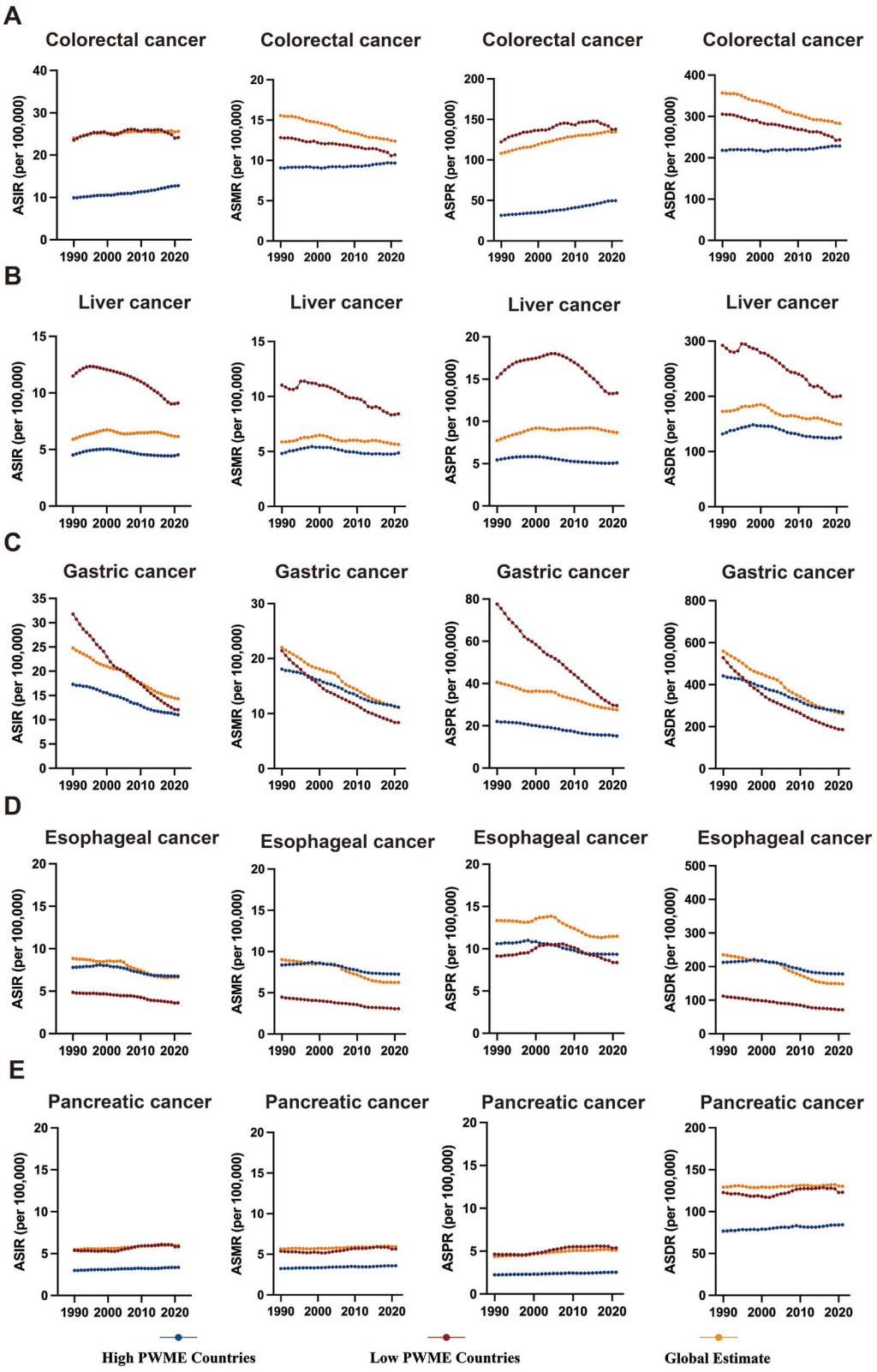


Fig. 4. Longitudinal trends in the burden of major digestive system cancers by altitude strata from 1990 to 2021. Line graphs illustrate the temporal trajectories of ASIR, ASMR, age-standardized prevalence rate (ASPR), and age-standardized disability-adjusted life year rate (ASDR) per 100,000 people. Trajectories are compared across high-PWME countries (blue lines), low-PWME countries (red lines), and the global estimate (yellow lines). (A) Colorectal cancer. (B) Liver cancer. (C) Gastric cancer. (D) Esophageal cancer. (E) Pancreatic cancer. Data source: GBD 2021.

0.115, $p < 0.001$), whereas ASIR decreased in low-PWME countries (AAPC = –0.780, $p < 0.001$), which maintained higher absolute incidence rates than high-PWME countries throughout the study period (Fig. 4, Table 2). Pancreatic cancer showed increasing trends in both groups, with high-PWME countries exhibiting a slightly faster rise, although the difference in AAPC was not significant.

Long-term trends in mortality rates highlighted divergent patterns (Table 3). Similar to the corresponding incidence, colorectal cancer mortality exhibited directional disparities. Low-PWME countries showed a significant decline in ASMR (AAPC = –0.614), whereas high-PWME ones showed a significant increase (AAPC = 0.205). This difference was highly statistically significant, reflecting a concerning upward trajectory in mortality for high-altitude regions. For liver cancer, ASMR declined in low-PWME countries but remained relatively stable in high-PWME ones, showing a nonsignificant upward trend (AAPC = 0.012, 95% CI: –0.132 to 0.157). For gastric and esophageal cancers, ASMRs declined in both high-PWME and low-PWME countries, but the decline was slower in the former. For esophageal cancer, the decline in mortality in high-PWME countries (AAPC = –0.466) was significantly slower than that in low-PWME countries (AAPC = –1.181). For pancreatic cancer, ASMR remained higher in low-PWME countries than in high-PWME countries throughout the study period; however, both high-PWME and low-PWME countries showed statistically significant increasing ASMR trends, in contrast to the declining mortality trends observed for gastric and esophageal cancers (Fig. 4, Table 3).

Prevalence and DALY analyses provided additional perspectives on the living and overall health loss burdens of digestive system cancers (**Supplementary Tables 12,13**). Regarding prevalence, colorectal cancer showed the most prominent increase in high-PWME countries, with ASPR increasing by 57.59% from 1990 to 2021 and an AAPC of 1.473 (95% CI: 1.361 to 1.585, $p < 0.001$). This increase exceeded that in low-PWME countries (12.57%; AAPC = 0.364, 95% CI: 0.129 to 0.600, $p = 0.002$; between-group $p < 0.001$). Liver cancer showed a more pronounced difference in ASPR between the high- and low-PWME strata, whereas the corresponding between-stratum differences for gastric and esophageal cancers were comparatively smaller. Gastric cancer ASPR declined in both strata, but the reduction was smaller in high-PWME countries (–30.91% versus –61.86%; between-group $p < 0.001$). These findings indicate that differences in prevalence across PWME strata varied substantially by cancer type rather than following a uniform pattern. DALY analyses showed divergent patterns across cancer types. For colorectal cancer, ASDR increased by 4.76% in high-PWME countries but decreased by 20.27% in low-PWME ones. For liver, gastric, and esophageal cancers, ASDRs declined in both strata, but the relative reductions were smaller in high-PWME countries. For pancreatic cancer, ASDR increased more clearly in high-PWME countries (9.91% versus 0.24%; between-group $p < 0.001$). These findings indicate that prevalence and DALY metrics complement incidence and mortality results and provide a more balanced description of digestive cancer burden across PWME strata.

These longitudinal findings should be interpreted in the context of descriptive ecological trend analysis. The observed faster increase in colorectal cancer burden and slower decline in upper gastrointestinal cancer burden in high-PWME countries may be influenced by broader country-level transitions over time, including changes in population age structure, cancer detection, registry completeness, screening implementation, socioeconomic development, and lifestyle-related exposures. Therefore, AAPC, segment-specific APC, and EAPC analyses primarily describe historical age-standardized rate trajectories across PWME strata rather than causal effects.

3.5 Exploratory Projections of Digestive Cancer Burden to 2035

Exploratory ARIMA-based projections were established to extend the observed age-standardized rate trajectories from 2022 to 2035 (**Supplementary Fig. 3** and **Supplementary Table 14**). By 2035, colorectal cancer ASIR in high-PWME countries was projected to continue increasing, reaching 14.43 per 100,000 population (95% prediction interval [PI]: 13.34 to 15.52), while ASDR was projected to reach 233.35 per 100,000 population (95% PI: 224.91 to 241.79).

For liver cancer, the projected trajectories differed between PWME strata. In high-PWME countries, ASIR was projected to increase from 4.63 per 100,000 in 2022 to 6.98 per 100,000 in 2035, accompanied by modest increases in ASMR and ASDR, which were projected to reach 5.18 and 135.89 per 100,000, respectively, by 2035. In contrast, liver cancer ASIR, ASMR, and ASDR in low-PWME countries were projected to decline, reaching 7.35, 7.28, and 160.52 per 100,000, respectively, by 2035.

Gastric and esophageal cancer projections generally suggested continued declines in age-standardized rates; however, gastric cancer ASDR in low-PWME countries showed a projected increase despite its long-term decline from 1990 to 2021. This apparent reversal may reflect the time-series dynamics captured by the selected ARIMA model, which extrapolates the autocorrelation and differenced structure of the observed series rather than being constrained to preserve the direction of the long-term AAPC. Given the relatively wide prediction intervals for gastric cancer in low-PWME countries, this projected reversal should be interpreted cautiously.

Pancreatic cancer rates were projected to remain relatively stable, with a modest increase in high-PWME ASDR to 87.73 per 100,000 population expected in 2035 (95% PI: 84.34 to 91.11). Overall, these projections should

Table 2. Baseline burden, relative change, and long-term trends in digestive system cancer incidence by PWME, 1990–2021.

Group	Number in 1990 (95% UI)	Age-standardized rate in 1990 (95% UI)	Number in 2021 (95% UI)	Age-standardized rate in 2021 (95% UI)	Relative change of numbers from 1990 to 2021 (%)	Relative change of age-standardized rate from 1990 to 2021 (%)	AAPC (95% CI)	p^1	p^2
Colorectal cancer									
Global	916,584 (873,755 to 959411)	24.0 (22.8 to 25.3)	2,194,143 (2,015,084 to 2,373,202)	25.6 (23.5 to 27.7)	139.38%	6.67%	0.204 (0.158 to 0.250)	<0.001	
High PWME	23,967 (22,346 to 25,589)	9.9 (9.2 to 10.7)	88,343 (83,646 to 93,041)	12.8 (12.1 to 13.4)	268.60%	29.29%	0.798 (0.698 to 0.898)	<0.001	<0.001
Low PWME	118,906 (115,046 to 122,767)	23.6 (22.8 to 24.4)	288,467 (269,046 to 307,888)	24.2 (23.0 to 25.4)	142.60%	2.54%	0.039 (–0.119 to 0.197)	0.626	
Liver cancer									
Global	244,689 (222,813 to 266,566)	5.9 (5.4 to 6.4)	529,203 (472,448 to 585,957)	6.2 (5.5 to 6.8)	116.28%	5.08%	0.115 (0.070 to 0.159)	<0.001	
High PWME	11,917 (10,790 to 13,044)	4.5 (4.0 to 5.0)	27,525 (25,425 to 29,626)	4.5 (4.1 to 5.0)	130.97%	0.00%	–0.003 (–0.053 to 0.046)	0.894	<0.001
Low PWME	44,656 (41,125 to 48,187)	11.5 (10.2 to 12.8)	81,048 (74,333 to 87,763)	9.1 (8.2 to 10.0)	81.49%	–20.87%	–0.780 (–0.849 to –0.710)	<0.001	
Gastric cancer									
Global	980,899 (890,435 to 1,071,364)	24.8 (22.6 to 27.0)	1,230,233 (1,051,423 to 1,409,042)	14.3 (12.2 to 16.4)	25.42%	–42.34%	–1.763 (–1.889 to –1.638)	<0.001	
High PWME	43,839 (41,763 to 45,914)	17.3 (16.5 to 18.1)	73,873 (69,467 to 78,278)	11.0 (10.3 to 11.8)	68.51%	–36.42%	–1.420 (–1.494 to –1.347)	<0.001	<0.001
Low PWME	148,901 (142,818 to 154,983)	31.8 (30.1 to 33.4)	146,568 (134,420 to 158,717)	12.1 (11.2 to 12.9)	–1.57%	–61.95%	–3.078 (–3.237 to –2.918)	<0.001	
Esophageal cancer									
Global	354,731 (319,030 to 390,432)	8.9 (8.0 to 9.7)	576,529 (508,451 to 644,608)	6.7 (5.9 to 7.4)	62.53%	–24.72%	–0.940 (–1.058 to –0.823)	<0.001	
High PWME	18,205 (17,168 to 19,241)	7.8 (7.4 to 8.3)	33,929 (31,963 to 35,895)	6.8 (6.3 to 7.2)	86.37%	–12.82%	–0.456 (–0.513 to –0.399)	<0.001	<0.001
Low PWME	19,735 (18,782 to 20,688)	4.9 (4.4 to 5.3)	37,945 (35,502 to 40,388)	3.6 (3.3 to 3.9)	92.27%	–26.53%	–0.916 (–1.125 to –0.706)	<0.001	

Table 2. Continued.

Group	Number in 1990 (95% UI)	Age-standardized rate in 1990 (95% UI)	Number in 2021 (95% UI)	Age-standardized rate in 2021 (95% UI)	Relative change of numbers from 1990 to 2021 (%)	Relative change of age-standardized rate from 1990 to 2021 (%)	AAPC (95% CI)	p^1	p^2
Pancreatic cancer									
Global	207,905 (197,341 to 218,470)	5.5 (5.2 to 5.8)	508,533 (465,974 to 551,091)	6.0 (5.4 to 6.5)	144.60%	9.09%	0.276 (0.165 to 0.387)	<0.001	
High PWME	7505 (7200 to 7810)	3.0 (2.9 to 3.1)	23,838 (22,615 to 25,061)	3.4 (3.2 to 3.5)	217.63%	13.33%	0.398 (0.273 to 0.522)	<0.001	0.090
Low PWME	26,080 (25,220 to 26,941)	5.4 (5.2 to 5.6)	72,282 (66,142 to 78,422)	5.8 (5.5 to 6.2)	177.15%	7.41%	0.253 (0.141 to 0.365)	<0.001	

PWME, Population-Weighted Mean Elevation; UI, Uncertainty Interval; CI, Confidence Interval; AAPC, Average Annual Percent Change.

Data source: GBD 2021.

p^1 indicates the statistical significance of the AAPC.

p^2 indicates the statistical significance of the difference in AAPC trajectories between the High PWME and Low PWME groups.

Table 3. Baseline burden, relative change, and long-term trends in digestive system cancer mortality by PWME, 1990–2021.

Group	Number in 1990 (95% UI)	Age-standardized rate in 1990 (95% UI)	Number in 2021 (95% UI)	Age-standardized rate in 2021 (95% UI)	Relative change of numbers from 1990 to 2021 (%)	Relative change of age-standardized rate from 1990 to 2021 (%)	AAPC (95% CI)	p^1	p^2
Colorectal cancer									
Global	570,319 (539,757 to 600,881)	15.6 (14.6 to 16.5)	1,044,072 (959,081 to 1,129,063)	12.4 (11.4 to 13.4)	83.07%	–20.51%	–0.717 (–0.806 to –0.627)	<0.001	
High PWME	20,476 (18,968 to 21,985)	9.1 (8.4 to 9.8)	57,299 (54,469 to 60,129)	9.7 (9.1 to 10.2)	179.83%	6.59%	0.205 (0.071 to 0.339)	0.003	<0.001
Low PWME	57,139 (55,259 to 59,020)	12.8 (12.3 to 13.3)	119,628 (110,140 to 129,115)	10.7 (10.1 to 11.3)	109.36%	–16.40%	–0.614 (–0.689 to –0.540)	<0.001	
Liver cancer									
Global	238,969 (216,809 to 261,129)	5.9 (5.3 to 6.4)	483,875 (433,987 to 533,764)	5.6 (5.1 to 6.2)	102.48%	–5.08%	–0.113 (–0.350 to 0.124)	0.348	
High PWME	12,059 (10,913 to 13,205)	4.8 (4.3 to 5.3)	28,513 (26,363 to 30,663)	4.9 (4.4 to 5.4)	136.45%	2.08%	0.012 (–0.132 to 0.157)	0.867	<0.001
Low PWME	40,054 (36,571 to 43,537)	11.0 (9.7 to 12.4)	68,147 (62,573 to 73,721)	8.4 (7.5 to 9.3)	70.14%	–23.64%	–0.942 (–1.387 to –0.494)	<0.001	
Gastric cancer									
Global	854,185 (770,641 to 937,728)	22.0 (19.9 to 24.1)	954,374 (820,461 to 1,088,287)	11.2 (9.6 to 12.8)	11.73%	–49.09%	–2.187 (–2.339 to –2.036)	<0.001	
High PWME	43,989 (41,929 to 46,048)	18.1 (17.2 to 18.9)	71,488 (67,304 to 75,671)	11.1 (10.4 to 11.9)	62.51%	–38.67%	–1.526 (–1.598 to –1.455)	<0.001	<0.001
Low PWME	89,974 (85,909 to 94,039)	21.4 (20.1 to 22.7)	92,325 (84,392 to 100,259)	8.4 (7.7 to 9.0)	2.61%	–60.75%	–3.013 (–3.156 to –2.870)	<0.001	
Esophageal cancer									
Global	356,263 (320,868 to 391,659)	9.0 (8.1 to 9.9)	538,602 (474,871 to 602,333)	6.3 (5.5 to 7.0)	51.18%	–30.00%	–1.197 (–1.326 to –1.068)	<0.001	
High PWME	18,912 (17,839 to 19,985)	8.4 (7.9 to 8.9)	35,156 (33,116 to 37,197)	7.3 (6.8 to 7.7)	85.89%	–13.10%	–0.466 (–0.558 to –0.374)	<0.001	<0.001
Low PWME	16,899 (15,979 to 17,818)	4.5 (4.0 to 4.9)	29,117 (27,014 to 31,220)	3.1 (2.7 to 3.4)	72.30%	–31.11%	–1.181 (–1.323 to –1.039)	<0.001	

Table 3. Continued.

Group	Number in 1990 (95% UI)	Age-standardized rate in 1990 (95% UI)	Number in 2021 (95% UI)	Age-standardized rate in 2021 (95% UI)	Relative change of numbers from 1990 to 2021 (%)	Relative change of age-standardized rate from 1990 to 2021 (%)	AAPC (95% CI)	p^1	p^2
Pancreatic cancer									
Global	211,613 (200,632 to 222,593)	5.7 (5.4 to 6.0)	505,752 (464,415 to 547,090)	5.9 (5.4 to 6.5)	139.00%	3.51%	0.160 (0.053 to 0.266)	0.003	
High PWME	7916 (7593 to 8239)	3.2 (3.1 to 3.4)	24,949 (23,669 to 26,229)	3.6 (3.4 to 3.8)	215.17%	12.50%	0.358 (0.236 to 0.480)	<0.001	0.026
Low PWME	25,557 (24,725 to 26,389)	5.4 (5.1 to 5.6)	67,836 (62,346 to 73,325)	5.7 (5.3 to 6.0)	165.43%	5.56%	0.159 (0.034 to 0.284)	0.013	

PWME, Population-Weighted Mean Elevation; UI, Uncertainty Interval; CI, Confidence Interval; AAPC, Average Annual Percent Change.

Data source: GBD 2021.

p^1 indicates the statistical significance of the AAPC.

p^2 indicates the statistical significance of the difference in AAPC trajectories between the High PWME and Low PWME groups.

be interpreted as exploratory extensions of historical age-standardized rate trajectories rather than definitive forecasts of future cancer burden.

4. Discussion

Although genetics matter, the striking geographic variation in cancer rates underscores the crucial role of environmental and lifestyle factors, among which high altitude has drawn much epidemiological interest. By establishing PWME and leveraging data from GLOBOCAN 2022 and GBD 2021, this study provides a systematic global assessment of the adjusted ecological associations between altitude-related geographic context and the burden of five major digestive system cancers [16]. Our core findings reveal distinct and bidirectional epidemiological patterns associated with specific tumor types. After adjustment for measured country-level confounders, PWME was inversely associated with colorectal cancer incidence and positively associated with esophageal cancer incidence. These findings should be interpreted as ecological associations rather than evidence of individual-level effects. The observed patterns may reflect the combined influence of altitude-related environmental conditions, socioeconomic context, lifestyle exposures, healthcare access, and cancer registration quality.

Previous epidemiological studies examining altitude and cancer have reported heterogeneous findings across populations and geographic settings. In an Austrian registry-based study, residence at moderate altitude was associated with lower incidence and mortality of colorectal cancer in men, which is directionally consistent with the inverse association between PWME and colorectal cancer incidence observed in the present study [8]. In contrast, an ecological study in Ecuador reported higher prevalence and mortality of colorectal, gastric, and hepatic/biliary cancers among populations living above 2000 m, whereas the gastric and liver cancer associations in our analyses were not consistently reproduced across databases and sensitivity analyses [17]. For esophageal cancer, a recent spatiotemporal study in Changzhi, China, identified a positive association between altitude and incidence, broadly consistent with our positive PWME–esophageal cancer incidence association [18]. Taken together, these differences across studies suggest that altitude–cancer patterns are unlikely to represent a uniform effect of altitude itself and may vary according to geographic setting, population characteristics, exposure definition, lifestyle and environmental factors, and data quality.

Registry quality–restricted sensitivity analysis supported main incidence findings. The preservation of the inverse association between PWME and colorectal cancer ASIR after excluding countries without direct registry-based incidence estimates suggests that the lower colorectal cancer incidence observed in higher-PWME settings cannot be fully explained by countries with lower-quality registration data. The positive association between PWME and esophageal cancer ASIR was also retained. In contrast, the mortality association for esophageal cancer was not preserved, which indicates that mortality-related findings may be more sensitive to differences in diagnostic capacity, cause-of-death ascertainment, healthcare access, or other country-level factors. An additional methodological consideration is that GBD 2021 applies the cause-of-death correction (CoDCorrect) algorithm to reconcile cause-specific mortality estimates with the all-cause mortality envelope, whereas GLOBOCAN 2022 uses cancer-specific mortality estimation procedures and does not apply the same cross-cause reconciliation framework. Consequently, ASMR estimates from the two databases are not methodologically identical, and differences in the magnitude or statistical significance of PWME–mortality associations may partly reflect database-specific mortality modelling rather than true epidemiological differences. Furthermore, longitudinal trend analysis highlighted a specific epidemiological transition in high-altitude regions. Although the absolute baseline burden of colorectal cancer remains relatively low, its incidence in high-altitude regions is accelerating significantly faster in relative terms than that in low-altitude regions. In contrast, although the burden of esophageal cancer remains heavy, the rate of its decline in high-altitude regions significantly lags behind that in low-altitude regions. These findings should be interpreted as ecological associations linked to altitude-related geographic context rather than as evidence that altitude itself is a direct causal factor or modifiable public health target. The practical value of PWME lies in its ability to summarize a population-weighted country-level geographic context in which environmental, socioeconomic, lifestyle, healthcare, and data quality factors may cluster. Therefore, the identified altitude-related patterns are best viewed as hypothesis-generating signals that may inform geographically targeted surveillance, risk factor assessment, and future individual-level research. These cross-sectional findings should be interpreted as time-specific ecological associations. Altitude itself is relatively stable, whereas national cancer incidence and mortality can change substantially over time because of epidemiological transition, screening implementation, diagnostic capacity, population aging, lifestyle changes, and improvements in cancer registration. In addition, some digestive system cancers comprise distinct histological or anatomical subtypes with divergent temporal patterns, such as esophageal squamous cell carcinoma and adenocarcinoma. Therefore, the associations observed using GLOBOCAN 2022 should be regarded as ecological patterns for the contemporary period rather than as the stable causal effects of altitude.

The observed temporal trends probably reflect the combined influence of demographic, healthcare system, socioeconomic, and risk factor transitions rather than altitude-related context alone. Population growth and aging can sub-

stantially increase the absolute numbers of incidence cases, deaths, prevalent cases, and DALYs, whereas changes in age-standardized rates may reflect shifts in underlying risk exposure, detection, survival, and data quality. Improvements in cancer registration and diagnostic capacity may increase the recorded incidence of some cancers, especially in settings where historical underdiagnosis or incomplete registration is more common. Screening programs may also shape temporal patterns by increasing short-term detection while potentially reducing advanced-stage disease and mortality over time. Socioeconomic development, urbanization, changes in diet, reduced physical activity, obesity, diabetes, alcohol consumption, smoking patterns, and other lifestyle-related exposures may contribute to the rising or slowly declining burden of colorectal and pancreatic cancers. Conversely, changes in major infection-related and environmental risk factors, including *H. pylori* control, hepatitis B vaccination, antiviral treatment for viral hepatitis, improved food preservation, reduced exposure to household solid fuels, and changing tobacco or alcohol exposure, may partly explain the declining trends observed for gastric, liver, and esophageal cancers in many regions. The slower improvement in some high-PWME strata may also reflect uneven access to screening, early diagnosis, specialized treatment, and long-term cancer care. Therefore, the observed temporal differences across PWME strata should be interpreted as the product of multiple interacting country-level transitions rather than as direct effects of altitude itself.

Additional prevalence and DALY analyses broaden the interpretation of digestive cancer burden beyond incidence and mortality. Prevalence reflects the number of individuals living with cancer and therefore captures survivorship, follow-up care, and long-term healthcare demand. The marked increase in colorectal cancer prevalence in high-PWME countries suggests a growing clinical management burden in these regions, even though their absolute colorectal cancer incidence remains lower than that of low-PWME countries. DALYs further integrate premature mortality and disability, providing a broader measure of population-level health loss. The slower decline in DALY rates for liver, gastric, and esophageal cancers, together with the increase in pancreatic cancer ASDR in high-PWME countries, indicates that improvements in digestive cancer outcomes may be uneven across PWME strata. These findings support the use of multiple GBD indicators to evaluate altitude-related cancer burden rather than relying only on incidence and mortality.

The exploratory ARIMA-based projections to 2035 extend these longitudinal findings by illustrating the potential medium-term trajectories of age-standardized digestive cancer burden across PWME strata. Consistent with the observed historical trends, colorectal cancer burden in high-PWME countries was projected to continue increasing, whereas gastric and esophageal cancer burdens were generally projected to decline. Pancreatic cancer showed relatively stable global trajectories but a modest projected increase in high-PWME ASDR. These findings may help identify cancer types and PWME strata that require sustained surveillance and prevention planning. However, these projections should be interpreted as exploratory rate-based extrapolations rather than deterministic predictions of future cancer burden.

The inverse association between PWME and colorectal cancer incidence observed herein should be interpreted as a country-level ecological pattern rather than as evidence of an individual-level inverse association of altitude [5]. High-altitude environments encompass multiple co-occurring ecological and social characteristics, including hypobaric hypoxia, lower ambient temperature, greater ultraviolet radiation, distinctive settlement patterns, dietary accessibility, and differences in healthcare access [19]. Some of these factors have been linked to biological pathways relevant to colorectal carcinogenesis, such as vitamin D metabolism, energy balance, chronic inflammation, and gut microbial ecology [20]. For example, greater ultraviolet exposure at higher altitudes may be related to population-level variations in vitamin D status, and hypobaric hypoxia is hypothesized to influence host metabolism and gut microbial composition [21,22,23,24,25,26,27]. However, these mechanisms were not directly assessed herein and should therefore be considered plausible explanatory hypotheses rather than evidence for high-altitude exposure itself reducing colorectal cancer risk [28,29,30]. Future individual-level studies integrating residential history, screening exposure, diet, physical activity, serum vitamin D levels, and microbiome data are needed to clarify whether these pathways contribute to the observed ecological association. However, the longitudinal results indicate that the cross-sectional pattern should be interpreted alongside ongoing epidemiological transitions. Although high-PWME countries had a lower baseline colorectal cancer burden, their ASIR increased more rapidly in relative terms over the past three decades [31]. This pattern may reflect a combination of demographic, healthcare, and lifestyle transitions rather than a single explanatory factor. Population aging, urbanization, improved diagnostic capacity, changes in cancer registry completeness, uneven implementation of colorectal cancer screening, and shifts to more energy-dense dietary patterns may all contribute to the observed temporal changes. Dietary transitions, including the increased consumption of red and processed meat and changes in other diet-related risk factors, may be one relevant component of this broader transition; however, it cannot be isolated as the primary driver in the present ecological analysis [32,33]. These findings suggest that colorectal cancer burden in high-PWME countries warrants continued surveillance as socioeconomic and healthcare transitions progress.

In contrast, PWME showed a positive association with esophageal cancer incidence in cross-sectional analyses,

which may reflect the clustering of altitude-related environmental, socioeconomic, and lifestyle contexts rather than a direct effect of altitude itself [34]. Several exposures more common in some high-altitude or cold-climate settings, including the consumption of very hot beverages, reliance on preserved or salted foods, limited access to fresh produce, and household solid fuel use, have been implicated in esophageal carcinogenesis in previous epidemiological studies [35,36,37,38,39]. These factors may coexist with lower screening availability, delayed diagnosis, and differences in healthcare access in some regions. However, the present ecological analysis cannot determine whether these exposures mediate the association between PWME and esophageal cancer burden. Moreover, esophageal cancer comprises biologically distinct histological subtypes, particularly esophageal squamous cell carcinoma and adenocarcinoma, which could not be separately assessed herein using the available country-level data. Therefore, the positive PWME–esophageal cancer association should be viewed as a hypothesis-generating geographic pattern that warrants further investigation using subtype-specific and individual-level data.

The methodological advantage of this study lies in the use of PWME, which provides a population-weighted country-level summary of geographic elevation rather than a simple unweighted geographic mean. By weighting elevation according to population distribution, PWME may reduce the influence of uninhabited highlands or mountainous areas in country-level altitude assessment. However, this approach does not eliminate systematic errors and may alter the pattern of exposure misclassification. Therefore, PWME should be interpreted as an ecological geographic indicator rather than a direct measure of individual-level hypoxic or environmental exposure. Another strength is the integration of two major global cancer data sources, GLOBOCAN 2022 and GBD 2021, which allowed the cross-database comparison of contemporary cancer burden and longitudinal trends. In addition, hierarchical regression models incorporating socioeconomic, environmental, lifestyle, metabolic, and infection-related covariates, together with registry quality–restricted sensitivity analyses, helped evaluate the robustness of the main ecological associations. However, these methodological features do not overcome the inherent limitations of ecological inference but rather strengthen the descriptive and hypothesis-generating value of the study while still requiring cautious interpretation at the population level.

Limitations and Future Directions

Several limitations should be considered when interpreting these findings. The first concerns the ecological design and spatial structure of the analysis. All exposures, outcomes, and covariates were assessed at the country level; therefore, the observed associations are subject to ecological fallacy and cannot be interpreted as individual-level effects or causal relationships. Despite adjustment for multiple country-level covariates, residual confounding from factors such as screening exposure, diet, physical activity, occupational exposures, genetic susceptibility, and healthcare access cannot be excluded. Within-country heterogeneity and population migration further limit the correspondence between PWME and individual lifetime altitude exposure. In addition, cancer burden may exhibit spatial autocorrelation across neighboring countries, and such spatial dependence was not explicitly modeled; consequently, conventional regression estimates of uncertainty should be interpreted cautiously.

A second limitation concerns the definition of altitude-related exposure and cancer outcomes. PWME is a population-weighted geographic indicator rather than a direct measure of individual hypoxic exposure, and it represents a composite geographic context in which hypobaric hypoxia, ultraviolet radiation, temperature, socioeconomic conditions, lifestyle factors, and healthcare characteristics may coexist. The present analysis therefore cannot disentangle the independent contributions of these components. Although geographic elevation itself is stable, PWME may also change over time with population redistribution, migration, and urbanization. Furthermore, the available country-level cancer data did not permit separation of relevant histological or anatomical subtypes, such as esophageal squamous cell carcinoma versus adenocarcinoma or distinct liver cancer subtypes, which may have different geographic distributions and risk-factor profiles.

A third limitation relates to data quality and temporal comparability. Cancer registry coverage, diagnostic capacity, and completeness of case and death ascertainment vary across countries. Although the principal colorectal and esophageal cancer incidence findings were generally retained in the registry quality–restricted sensitivity analysis, residual bias from underdiagnosis, differences in screening, and incomplete registration cannot be excluded. In addition, country-level *H. pylori* prevalence was available as crude rather than age-standardized estimates, which may have introduced additional residual confounding in the gastric cancer models. The primary cross-sectional analyses reflect the contemporary burden represented by GLOBOCAN 2022 and should not be assumed to characterize other calendar periods. Moreover, the high- and low-PWME longitudinal strata were defined using the upper and lower quintiles to maximize exposure contrast; this approach does not use the middle range of the PWME distribution and should therefore be interpreted together with the primary analyses in which PWME was modeled continuously.

Finally, several analytical limitations warrant consideration. Cancer rates were analyzed on their original age-standardized scale to preserve interpretability, but some distributions were skewed and contained extreme observations. Model diagnostics identified particularly large residuals and potentially influential observations in the liver

cancer models, and these results should therefore be interpreted cautiously. In addition, the ARIMA projections were derived solely from historical age-standardized rate trajectories and did not incorporate future changes in population structure, screening, diagnostic capacity, treatment, lifestyle exposures, registration completeness, or health policy. The projections should thus be regarded as exploratory extrapolations of historical time-series patterns rather than formal age–period–cohort forecasts or deterministic predictions of future cancer burden.

Future studies should move beyond ecological comparisons and use complementary designs to test the hypotheses generated by this analysis. First, causal inference approaches, such as Mendelian randomization, may help evaluate whether altitude-related biological mediators or major cancer-related risk factors, including vitamin D status, metabolic traits, inflammatory pathways, alcohol use, smoking, obesity, diabetes, viral hepatitis, and *H. pylori* infection, causally contribute to digestive cancer risk. Second, large individual-level prospective cohorts incorporating lifetime residential altitude history, migration status, screening exposure, diet, physical activity, socioeconomic status, healthcare access, infection status, tumor subtype, and multiomics profiles are needed to validate the observed ecological patterns and clarify population heterogeneity. Third, machine learning–based predictive models integrating geographic, environmental, socioeconomic, healthcare, lifestyle, infection-related, and molecular features may help identify high-risk populations, evaluate nonlinear interactions, and improve geographically tailored cancer surveillance strategies. These future approaches would help determine whether the PWME-related patterns observed herein reflect causal mechanisms, correlated contextual factors, or both.

5. Conclusion

Using PWME and data from GLOBOCAN 2022 and GBD 2021, this study identified heterogeneous altitude-related ecological patterns in the global burden of five major digestive system cancers. After adjustment for measured country-level confounders, higher PWME was inversely associated with colorectal cancer incidence and positively associated with esophageal cancer incidence, with these patterns generally supported across databases and registry quality–restricted sensitivity analyses. In contrast, associations for gastric, pancreatic, and liver cancers were less consistent across datasets and sensitivity analyses. Mortality-related findings were also less consistent than incidence findings and should be interpreted cautiously. Overall, the observed associations varied by cancer type and burden metric, arguing against a uniform relationship between altitude-related geographic context and digestive cancer burden. These findings should be regarded as hypothesis-generating ecological evidence that may reflect the combined influence of environmental, socioeconomic, lifestyle, healthcare, and data-quality factors rather than individual-level causal effects of altitude.

Key Points

• This global ecological study used PWME to assess altitude-related patterns in the burden of five major digestive system cancers across 185 countries.

• PWME-related associations varied by cancer type, burden metric, and database, with the most consistent cross-database patterns observed for colorectal and esophageal cancer incidence.

• After adjustment for measured country-level confounders, higher PWME was inversely associated with colorectal cancer incidence and positively associated with esophageal cancer incidence.

• In sensitivity analysis restricted to countries with higher-quality cancer registration data, the main incidence findings for colorectal and esophageal cancers were generally preserved.

• Longitudinal analysis suggested a divergence in temporal trajectories between high- and low-PWME countries, supporting the interpretation of these findings as hypothesis-generating ecological patterns rather than evidence of the causal effects of altitude.

Availability of Data and Materials

The datasets analyzed in this study are publicly available from GLOBOCAN 2022, GBD 2021, and the other sources described in the Methods and **Supplementary Materials**.

Author Contributions

WC: Conceptualization, Investigation, Data curation, Formal Analysis, Project administration, Software, Visualization, Writing—original draft. KH: Conceptualization, Project administration, Data curation, Formal Analysis, Supervision. KS: Conceptualization, Investigation, Formal Analysis, Data curation, Project administration. RX: Investigation. HZ: Investigation, Visualization. SL: Investigation, Visualization. DY: Investigation, Software. QX: Investigation. HX: Investigation. ZD: Investigation. BC: Investigation. JY: Investigation. HC: Conceptualization, Methodology, Project administration, Resources, Supervision. DW: Conceptualization, Funding acquisition, Project administration, Resources, Supervision. All authors contributed to revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study was supported by the Clinical Research Excellence Program for Research-Oriented Wards (BR-WEP2024W034010103), Science and Technology Projects of Xizang Autonomous Region, China (XZ202501JD0021, XZ202501ZY0072), and National High Level Hospital Clinical Research Funding (2025-PUMCH-C-048).

Conflicts of Interest

Given their roles as Associate Editor (Dong Wu) and Editorial Board Member (Kun He), both had no involvement in the peer-review of this article and have no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to Kassem Sharif. The other authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM55172.

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