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Spatial inequalities in cancer with special reference to lung cancer across Europe and their implications for environmental health policy

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Abstract

This study investigates spatial disparities in cancer and lung-cancer mortality across Europe through an integrative geospatial epidemiological framework. Using age-standardised Eurostat mortality data for 2022 at the NUTS-2 level, we combine Getis-Ord Gi* and Anselin Local Moran's I to detect statistically significant hot/cold spots, while multivariate regressions incorporate environmental and topographic predictors. Results reveal pronounced east-west and urban–rural gradients: persistent high-mortality clusters span Central and Eastern Europe, where historical industrialisation, elevated smoking prevalence, and structural healthcare gaps converge. By contrast, Southern European regions – Portugal, western Spain, and southern Greece – are associated with lower observed mortality levels, plausibly reflecting favourable behavioural profiles, environmental conditions, and healthcare accessibility. Spatial outliers identify territories where localised factors, such as air-pollution peaks or differential diagnostic capacity, modify broader regional patterns. Overall, the findings highlight geography as a structuring context for exposure, vulnerability, and access to care, rather than as a direct causal driver of cancer risk, and demonstrate the value of spatial epidemiology for territorial health governance, environmental monitoring, and urban planning. Policy relevance is twofold. First, the evidence supports region-specific interventions aligned with the Sustainable Development Goals (SDG) – especially SDG 3 (health), SDG 10 (reduced inequalities), and SDG 11 (sustainable cities). Second, the spatial outputs provide a robust empirical basis for informing the health-equity ambitions of Europe's Beating Cancer Plan and the environmental-justice agenda of the European Green Deal. By bridging granular geospatial evidence with EU-wide priorities, the study underscores the need for place-based, equity-oriented frameworks in cancer prevention and control across heterogeneous European landscapes.

Key words: spatial epidemiology; cancer mortality; lung cancer; geographic health inequalities; Getis-Ord Gi*; Anselin Local Moran's I; environmental exposure; european public health policy.

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Introduction

Cancer remains a leading cause of morbidity and mortality in Europe, accounting for over 1.2 million deaths annually and placing substantial strain on national health systems (European Commission, 2021). Lung Cancer (LC) is the most fatal, responsible for approximately 20% of global cancer-related deaths (Sung *et al.*, 2021). While individual-level risk factors – such as tobacco use, occupational exposures, and genetic predisposition – have been extensively documented, growing evidence highlights the role of environmental, spatial, and morphological determinants in shaping cancer outcomes (Brugge *et al.*, 2007; Raaschou-Nielsen *et al.*, 2013; Ciabattini *et al.*, 2021).

Despite advances in screening and treatment, substantial geographic inequalities in cancer mortality persist across Europe (Bambra *et al.*, 2019). These disparities are not fully explained by differences in healthcare access or health behaviours, but increasingly align with spatially embedded environmental conditions – such as air pollution, urban density, land use intensity, and topographic variation (Vienneau *et al.*, 2017; Alahmad *et al.*, 2023). Lowland urban-industrial zones tend to accumulate higher concentrations of air pollutants like $PM_{2.5}$ and NO_2, while highland or natural areas may offer mitigation through topography-driven microclimatic and dispersion effects (WHO, 2021; de Hoogh *et al.*, 2016). Health geography has evolved to view place not as a passive backdrop but as a structuring context for exposure, vulnerability, and access to health-promoting infrastructure (Curtis *et al.*, 2021; Bambra *et al.*, 2019). Geographic disparities in cancer mortality thus reflect not only unequal healthcare distribution or behavioural risk, but also the deeper imprint of ecological fragmentation, urban morphology, and biophysical characteristics. In this context, spatial epidemiology offers a critical framework for investigating inequalities, particularly when granular individual-level data are limited (Pearce *et al.*, 2010; Elliott & Wartenberg, 2004).

Environmental health justice and the urban–rural divide further reveal how spatial inequities reinforce social vulnerabilities, producing disproportionate health burdens in marginalized or isolated populations (Schlosberg, 2007; McKenzie *et al.*, 2013). These frameworks argue that disparities in cancer mortality are closely linked to spatial development trajectories, environmental degradation, and uneven exposure. Geographies of deprivation frequently coincide with limited diagnostic infrastructure and delayed treatment access, reinforcing cycles of disadvantage (Brulle & Pellow, 2006; Clougherty, 2010).

Landscape morphology and land cover also mediate human–environment interactions relevant to chronic disease exposure. The CORINE Land Cover (CLC) database provides standardized land use data, enabling differentiation between high-impact anthropogenic zones (*e.g*., urban, industrial), transitional areas (*e.g*., agricultural, semi-urban), and natural environments (*e.g*, forests, wetlands, water bodies). These features are associated with cancer outcomes through multiple pathways, including effects on pollution levels and exposure patterns, as well as indirect influences related to the built environment, socioeconomic structure, and healthcare access (Su *et al*., 2011; Nieuwenhuijsen *et al*., 2018).

However, studies that jointly consider topography, land cover, and spatial epidemiological modelling remain rare in cancer research. Most are confined to national scales or use aggregated data without accounting for spatial autocorrelation, clustering, or topographic heterogeneity (Woodruff *et al*., 2009; Yang & Geng, 2022). Moreover, pan-European analyses simultaneously addressing both total and lung cancer mortality in relation to environmental and morphological correlates are lacking. To address this gap, the present study conducts a spatial epidemiological analysis of cancer and lung cancer mortality across Europe at the NUTS-2 level. Drawing on standardized Eurostat mortality data, elevation stratification, and CORINE land cover indicators, we employ multiple linear regression and spatial statistical tools (including Getis-Ord Gi* and Anselin Local Moran's *I*) to: i) quantify associations between environmental–topographic factors and cancer mortality; ii) identify and visualize spatial clusters and outliers of high or low mortality; iii) compare mortality patterns between total and lung cancer, highlighting overlaps or divergences; and iv) explore spatial inequalities pointing to place-based cancer determinants. By adopting a multivariate and spatially explicit approach, this study contributes to the literature on geographical determinants of cancer and addresses public health imperatives to identify vulnerable regions where environmental exposures, morphological disadvantages, and land use history may converge to amplify cancer risk (O'Campo *et al*., 2015; Nieuwenhuijsen *et al*., 2018). In doing so, it supports the policy priorities of the European Green Deal and the European Commission's "Beating Cancer Plan", while directly contributing to Sustainable Development Goals 3 (Health and Well-being), 10 (Reduced Inequalities), and 11 (Sustainable Cities and Communities), which emphasize environmental justice, health equity, and place-based strategies for disease prevention.

Materials and Methods

Study area and spatial units of analysis

The spatial analysis was conducted across Europe using the NUTS-2 classification system of the European Commission (2018). These intermediate administrative units offer an effective compromise between spatial resolution and statistical reliability, enabling cross-national comparability while preserving intra-regional variability essential for analysing health disparities (European Commission, 2018; Svensson, 2019). Their use is well-established in spatial epidemiology for capturing multiscale environmental, demographic, and policy-related determinants of population health.

Mortality data

Cancer-related mortality data were retrieved from Eurostat (2022), which provides harmonized, age-standardized mortality statistics across European regions based on ICD-10 classifications. Two dependent variables were selected: i) age-standardized death rates (ASDR) from all malignant neoplasms (total cancer), ii) ASDR from lung cancer (ICD-10 codes C33-C34). Both indicators were calculated per 100,000 inhabitants and disaggregated by sex (male/female) and age group (<65, ≥65 years), yielding 18 dependent variables for modelling (Table 1).

In regions with missing data for 2022, a Last Observation Carried Forward (LOCF) technique was applied using the most recent available data from 2021 or, where necessary, 2018. This approach is consistent with standard practices in longitudinal health monitoring, especially in contexts of relatively stable mortality trends (Eurostat, 2022; Börsch-Supan *et al*., 2013).

Environmental predictors

Geomorphological indicators

Elevation data were obtained from a continental-scale Digital Elevation Model (DEM), processed to classify altitude into five physiographically meaningful bands, following the European Soil Data Centre convention (Pike *et al*., 2009; Table 1): i) Lowlands (LL): 0-200 m; ii) Uplands (UL): 200-600 m; iii) Lower Mountains (LM): 600-1500 m; iv) Mid Mountains (MM): 1500-3000 m; v) High Mountains (HM): > 3000 m. For each NUTS-2 region, the proportional land area falling within each elevation band was calculated using spatial overlay methods. These indicators act as proxies for geomorphological heterogeneity, which may be associated with pollutant accumulation, microclimate regulation, and infrastructural development (Pike *et al*., 2009; Malek & Verburg, 2020; de Hoogh *et al*., 2016).

Land use indicators

Land use patterns were derived from the CORINE Land Cover (CLC) inventory (European Environment Agency, 2018). To facilitate integration into epidemiological modelling, the 44 detailed CLC classes were aggregated into three analytically meaningful groups based on their environmental burden and presumed impact on cancer risk (WHO, 2020; Table 1): i) Group 1: Highly Burdened (CHB) – Dense anthropogenic and industrial surfaces (e.g., urban cores, transport and extraction areas; CLC codes: 111, 121-124, 131-133, 334); ii) Group 2: Moderately Burdened (CMB) – Transitional and mixed-use environments, including agricultural zones and discontinuous urban fabric (CLC codes: 112, 211-244, 331, 333); iii) Group 3: Neutral/Protective (CN) – Natural land covers with potential health-promoting attributes (e.g., forests, wetlands, water bodies; CLC codes: 141-142, 311-313, 321-324, 332, 335, 411-423, 511-523). Regional percentages of each land use group were computed and included as explanatory variables in the multivariate models.

Statistical analysis

Descriptive and correlation analyses

Descriptive statistics were used to summarize mortality and environmental variables across NUTS-2 regions. Bivariate associations between lung cancer mortality and each environmental factor were explored using Pearson correlation coefficients.

Multivariate regression modelling

To model the joint associations of elevation and land use, a series of multiple linear regression models were constructed – one for each of the 18 dependent variables. Each model included: i) the five elevation bands and three land use groups as main effects; ii) all 15 possible interaction terms between elevation and land use bands (*e.g.*, LL × CHB, UL × CMB), calculated as cross-products of their regional proportions. This interaction modelling approach enables the detection of non-additive effects between geomorphology and land use, reflecting synergistic or antagonistic influences on cancer mortality. This approach aligns with best practices in spatial health modelling that emphasize multivariate, interaction-aware designs (Anselin, 1995; Malek & Verburg, 2020; Yang & Geng, 2022).

Table 1. Coding and description of the mortality indicators and environmental characteristics used in the Pearson correlation analysis.

Abbreviation	Description
CT	Overall cancer mortality
CY	Cancer mortality <65 years
CO	Cancer mortality >65 years
CM	Cancer mortality in men
CMY	Cancer mortality in men <65
CMO	Cancer mortality in men >65
CF	Cancer mortality in women
CFY	Cancer mortality in women <65
CFO	Cancer mortality in women >65
LCT	Lung cancer mortality
LCY	Lung cancer mortality <65
LCO	Lung cancer mortality >65
LCM	Lung cancer mortality in men
LCMY	Lung cancer mortality in men <65
LCMO	Lung cancer mortality in men >65
LCF	Lung cancer mortality in women
LCFY	Lung cancer mortality in women <65
LCFO	Lung cancer mortality in women >65
LL	Percentage of lowlands (0-200m)
UL	Percentage of uplands (201-600m)
LM	Percentage of lower mountains (601-1500m)
MM	Percentage of mid mountains (1501-3000m)
HM	Percentage of high mountains (>3000m)
CHB	Percentage of high-burden areas (urban/industrial)
CMB	Percentage of moderately-burdened areas (agricultural/semi-urban)
CN	Percentage of neutral/protected areas (natural ecosystems)
P1: LL × CHB	Percentage of lowlands (0-200m) with urban/industrial areas
P2: UL × CHB	Percentage of uplands (201-600m) with urban/industrial areas
P3: LM × CHB	Percentage of lower mountains (601-1500m) with urban/industrial areas
P4: MM × CHB	Percentage of mid mountains (1501-3000m) with urban/industrial areas
P5: HM × CHB	Percentage of high mountains (>3000m) with urban/industrial areas
P6: LL × CMB	Percentage of lowlands (0-200m) with agricultural/semi-urban areas
P7: UL × CMB	Percentage of uplands (201-600m) with agricultural/semi-urban areas
P8: LM × CMB	Percentage of lower mountains (601-1500m) with agricultural/semi-urban areas
P9: MM × CMB	Percentage of mid mountains (1501-3000m) with agricultural/semi-urban areas
P10: HM × CMB	Percentage of high mountains (>3000m) with agricultural/semi-urban areas
P11: LL × CN	Percentage of lowlands (0-200m) with natural ecosystems
P12: UL × CN	Percentage of uplands (201-600m) with natural ecosystems
P13: LM × CN	Percentage of lower mountains (601-1500m) with natural ecosystems
P14: MM × CN	Percentage of mid mountains (1501-3000m) with natural ecosystems
P15: HM × CN	Percentage of high mountains (>3000m) with natural ecosystems

Spatial analysis

Given that health outcomes are inherently spatial, marked by geographic variability and clustering, advanced spatial statistical techniques were applied to examine lung cancer mortality patterns across Europe. This analytical step aimed to detect both global and local spatial inequalities and explore their association with underlying environmental characteristics.

Global cluster detection: hotspot analysis (Getis-Ord Gi)*

The Getis-Ord Gi* statistic was used to detect spatial clusters of elevated or reduced lung cancer mortality. This global method identifies regions with mortality rates significantly above or below their neighbours, indicating spatial autocorrelation (Getis & Ord, 1992). A fixed 200 km distance band defined neighbourhood structure, balancing sensitivity and generalizability (Hu *et al*., 2013), while row standardization ensured comparability across diverse regional geometries.

Local cluster and outlier detection: Anselin Local Moran's I

Complementing global clustering, Local Indicators of Spatial Association (LISA) were computed using Anselin's Local Moran's I statistic (Anselin, 1995). This local method classifies each region into: i) High–High (HH) clusters (hotspots); ii) Low–Low (LL) clusters (coldspots); iii) High–Low (HL) and Low–High (LH) outliers. This technique captures spatial discontinuities and detects micro-scale inequalities where neighbouring regions exhibit divergent mortality patterns, offering insight into localized environmental or policy-driven gradients.

Combined use of global and local spatial methods

The integrated use of Getis-Ord Gi* and Anselin Local Moran's I provides a dual-scale analytical perspective, enhancing the detection of both continental patterns and local anomalies (Nykiforuk & Flaman, 2011; Elliott & Wartenberg, 2004). This design strengthens inferential validity and supports more context-sensitive interpretations of spatial disparities in lung cancer mortality.

Technical and geodeticconsiderations

All spatial operations were conducted in ArcGIS 10.8.2, leveraging its geostatistical toolbox. To minimize distortion and ensure spatial comparability across Europe, all distance-based analyses were projected using the ETRS89 LAEA coordinate reference system (EPSG:3035), a standard in pan-European spatial research (EuroGeographics, 2020).

Policy relevance and strategic framing

Although fundamentally epidemiological, the methodological design of this study was guided by considerations of policy relevance. The multilevel spatial analysis of cancer mortality provides empirically grounded evidence for identifying regional vulnerabilities that can inform targeted interventions under the European Union's *Beating Cancer Plan* and the Sustainable Development Goals (SDG 3, 10, and 11). By structuring the analysis around scalable administrative units (NUTS-2) and ecologically grounded spatial predictors – namely land use composition and geomorphological heterogeneity – this study bridges spatial epidemiology with environmental governance and territorial public health planning.

Findings

This section presents the main results on cancer and lung cancer mortality across Europe, adopting a synthetic approach that integrates descriptive, correlational, regression, and spatial analyses (Getis-Ord Gi*, Anselin Moran's I). This structure facilitates immediate interpretation within each thematic axis, following best practices in spatial epidemiology (Cromley and McLafferty, 2012; Curtis *et al*., 2021). Emphasis is placed on the interplay between environmental and topographic factors and their role in structuring spatial health disparities.

Descriptive analysis

This section presents summary statistics and distributional characteristics of cancer and lung cancer mortality across European NUTS-2 regions, as well as of the key environmental predictors – elevation and land use. The descriptive findings provide essential epidemiological context for subsequent regression and spatial analyses, offering insights into age- and sex-specific disparities, as well as the ecological heterogeneity of the European landscape.

Cancer and lung cancer mortality profiles

Descriptive statistics revealed considerable variation in cancer-related mortality across the European continent. The mean total cancer mortality rate was 232.9 deaths per 100,000 inhabitants, with regional values ranging from 104.8 to 339.3. Lung cancer mortality followed a similar trend, averaging 47.9 deaths per 100,000, with a wider regional spread (range: 20.3-90.6), underscoring its contribution to the overall cancer burden (Tables 2-3).

Age-stratified analysis indicated sharp contrasts. For total cancer, mortality under age 65 averaged 63.1, compared to 933.5 among individuals aged 65 or older. A similar age gradient was observed for lung cancer (13.6 *vs* 189.7), confirming the influence of cumulative exposure and age-related vulnerability in shaping cancer outcomes (Bray *et al*., 2021; Pukkala *et al*., 2009). Gender disparities were equally pronounced, with males consistently exhibiting higher mortality rates than females across both cancer categories. Among those aged ≥65, the gap was stark: male total cancer mortality reached 1259.8 compared to 710.9 in females; in lung cancer, the gap widened further (281.3 *vs* 123.0, respectively). Mortality distributions exhibited moderate positive skewness, especially in younger populations, suggesting that a subset of regions carries a disproportionate share of early-onset cancer mortality. These skewed patterns are likely reflective of localized vulnerabilities linked to socioeconomic stressors, environmental exposures, or structural inequalities in healthcare access (Office for National Statistics, 2022).

Elevation patterns across regions

Geomorphological analysis revealed uneven distribution of elevation zones across Europe's NUTS-2 regions. Lowlands (LL, 0-200 m) accounted for the majority of land area (mean=50.2%, range=0-100%), followed by Uplands (UL, 200-600 m; mean=29%). Mountainous zones contributed less, with Lower Mountains (LM, 600-1500 m) averaging 16.3%, and Mid Mountains (MM, 1500-3000 m) only 4.5%. High Mountains (HM, >3000 m) were negligible (mean=0.1%; and 3 4). The distribution of elevation bands showed near-normal patterns in lower zones and high positive skewness and leptokurtosis in higher altitudes, indicating topographic concentration in select mountainous areas. These asymmetries reflect Europe's diverse terrain and may have implications for pollution dispersion, land development constraints, and differential environmental exposures (Lindley *et al*., 2011). Elevation thus emerges not as an isolated determinant, but as a modifier of ecological and urbanization gradients.

Land use composition by CORINE classification

Land use analysis, based on the CORINE Land Cover (CLC) typology, further illustrated Europe's spatial heterogeneity. Highly burdened anthropogenic zones (CHB) exhibited the lowest average coverage (2.7%), but showed extreme positive skewness, with values exceeding 50% in densely urbanized regions (Table 4). Moderately burdened landscapes (CMB) – predominantly agricultural and semi-urban areas – were most prevalent, averaging 57.6% and exhibiting broad geographic spread. Natural or neutral zones (CN) accounted for 39.7% on average, with values reaching up to 96.9%. The asymmetrical distribution of CHB highlights the spatial concentration of urban-industrial pressures, while the wider dispersion of CMB and CN categories reflects the transitional or ecological character of many European regions. These differences underscore the need to assess how land use gradients intersect with demographic and health profiles, particularly in relation to pollution exposure, healthcare infrastructure, and environmental risk mitigation (Nieuwenhuijsen *et al.*, 2018; Su *et al.,* 2011).

Synthesis and epidemiological implications

Together, the descriptive patterns suggest that cancer and lung cancer mortality across Europe reflecta combination of demographic structure, spatial morphology, and land use intensity. Age and sex remain dominant stratifiers of mortality risk, yet the contextual influence of topography and environmental configuration is evident. These structural features interact to produce geographically uneven distributions of cancer burden, reinforcing the rationale for spatially explicit modelling frameworks and geographically targeted public health interventions (Yang & Geng, 2022).

Correlation analysis: environmental and demographic predictors of cancer mortality

Bivariate correlation analysis was performed to examine initial associations between cancer mortality and key environmental predictors across European NUTS-2 regions. The results offered a preliminary statistical foundation for the subsequent multivariate models, highlighting potential interactions among demographic, topographic, and land use characteristics (*Supplementary materi-*

Table 2. Descriptive analysis of cancer mortality.

	CT	CY	CO	CM	CMY	CMO	CF	CFY	CFO
Mean	232.86	63.11	933.52	302.36	70.44	1259.76	183.88	56.23	710.86
Median	233.61	61.27	932.26	302.32	65.73	1262.68	183.75	55.96	720.21
Variance	1500.62	229.69	25587.11	2633.65	405.10	42950.33	1437.95	171.55	25312.15
Kurtosis	0.83	1.06	0.94	0.83	1.01	0.93	0.63	0.70	0.49
Skewness	-0.30	0.91	-0.53	0.26	0.98	-0.06	-0.49	0.43	-0.55
Range	234.52	83.13	988.33	313.93	113.59	1290.48	218.77	84.60	924.82
Minimum	104.80	34.86	384.78	152.59	31.07	610.38	69.24	15.97	227.27
Maximum	339.32	117.99	1373.11	466.52	144.66	1900.86	288.01	100.57	1152.09

Table 3. Descriptive analysis of lung cancer mortality.

	LCT	LCY	LCO	LCM	LCMY	LCMO	LCF	LCFY	LCFO
Mean	47.95	13.61	189.74	69.20	17.82	281.27	31.70	9.58	122.98
Median	46.07	13.36	181.05	67.90	16.90	274.73	30.17	9.12	114.18
Variance	126.97	23.23	2132.74	305.69	56.48	4526.80	176.05	16.95	3216.01
Kurtosis	1.06	2.05	0.65	1.01	0.53	0.56	0.31	0.83	0.37
Skewness	0.81	0.80	0.76	0.39	0.67	0.34	0.65	0.59	0.70
Range	70.32	34.29	275.54	124.10	45.12	450.79	75.99	25.58	322.35
Minimum	20.29	0.00	103.99	10.83	0.00	55.52	6.79	0.00	24.81
Maximum	90.61	34.29	379.53	134.93	45.12	506.31	82.78	25.58	347.16

Table 4. Descriptive analysis of lung cancer mortality.

	LL	UL	LM	MM	HM	CHB	CMB	CN
Mean	50.15%	28.99%	16.29%	4.47%	0.10%	2.70%	57.58%	39.72%
Median	47.56%	26.58%	3.47%	0.00%	0.00%	1.29%	59.17%	38.28%
Variance	1485.54	702.18	465.89	175.61	0.48	24.21	355.81	385.83
Kurtosis	-1.59	-0.22	1.23	19.17	112.56	37.74	-0.20	-0.23
Skewness	0.06	0.76	1.37	4.20	10.19	5.37	-0.43	0.46
Range	100.00%	99.39%	93.06%	88.52%	8.19%	50.80%	91.21%	93.24%
Minimum	0.00%	0.00%	0.00%	0.00%	0.00%	0.06%	3.06%	3.62%
Maximum	100.00%	99.39%	93.06%	88.52%	8.19%	50.87%	94.27%	96.85%

als, Table 1). Age emerged as the dominant correlation of total cancer mortality. The age-standardized death rate for individuals aged ≥65 exhibited a very strong positive correlation with overall cancer mortality (r=0.96), affirming the cumulative nature of cancer risk and its concentration among older populations. In contrast, the correlation for deaths under 65 was weaker (r=0.71), reflecting their smaller contribution to overall mortality. A similar gradient appeared when stratified by sex: older male and female cancer mortality correlated strongly with total cancer (r=0.97), while younger groups showed lower coefficients (r=0.76 for males under 65). Lung cancer mortality also correlated moderately with total cancer (r=0.73), consistent with its substantial contribution to the cancer burden. However, subgroup analysis revealed gender divergence: older men exhibited stronger correlation (r=0.82) than older women (r=0.66), likely due to historical differences in smoking rates, occupational exposures, and gendered health behaviours (Brennan & Bray, 2002; Bray *et al*., 2021).

Environmental variables showed weaker but directionally consistent correlations with mortality. Among topographic indicators, the proportion of lowland areas (LL) was positively correlated with lung cancer mortality (r=0.39), potentially reflecting higher population density, urbanization, and pollutant accumulation. Conversely, lower mountain zones (LM, 600-1500 m) showed a negative association (r=-0.35), consistent with conditions that may facilitate pollutant dispersion and reduced exposure (de Hoogh *et al*., 2013). Land use indicators revealed complementary patterns. Moderately burdened zones (CMB) correlated positively with lung cancer mortality (r=0.25), potentially reflecting agricultural emissions, semi-urban exposure profiles, or socio-spatial disadvantage. In contrast, natural or protective land uses (CN) were inversely associated with lung cancer (r=-0.27), consistent with evidence linking green environments to improved air quality and reduced carcinogen exposure (WHO, 2020; Nieuwenhuijsen *et al*., 2018).

Overall, these correlations confirm that while age and sex remain primary correlates, environmental and spatial context are associated with variations in cancer mortality. The significant relationships with elevation and land use underscore the contextual and modifying role of place-based exposures in spatial health inequalities.

Regression analysis: cancer mortality

Multivariate linear regression models were used to examine the associations between cancer mortality and environmental-topographic predictors, including land use categories and elevation bands. Eighteen models were developed to capture total cancer mortality disaggregated by sex and age, incorporating main effects and interaction terms to reflect synergies between physical geography and anthropogenic transformation (Table 5).

The models explained a modest but statistically significant share of the variance (R^2=0.11-0.14; p<0.001). Across models, urbanized and industrial zones (CHB) consistently showed negative associations with cancer mortality in low and mid-elevation areas (β=-17.6 to -28.1; p<0.01), consistent with a structural «urban health advantage.» This effect, particularly evident among older adults and in both sexes, likely reflects better healthcare access, earlier diagnosis, and medical infrastructure in urban areas (Borrell *et al.*, 2014; Ribeiro *et al*., 2018; Van Hemelrijck *et al*., 2021). In contrast, moderately burdened zones (CMB) – including agricultural and semi-urban areas – were positively associated with cancer mortality, especially among women and in lowland settings. The strongest effect appeared in females ≥65 years (β=+55.15, p=0.001), highlighting patterns of spatial disadvantage in transitional landscapes with overlapping environmental exposures, healthcare access barriers, and socioeconomic deprivation (Clougherty, 2010; Nieuwenhuijsen, 2015; Lawlor *et al*., 2006). Associations in male models were weaker or non-significant, suggesting gender-specific vulnerability.

Age stratification revealed stronger associations in the ≥65 group, with higher explanatory power (R^2 up to 0.14) and more pronounced land use effects. Models for individuals <65 yielded lower R^2 values (~0.08) and fewer significant predictors, consistent with a potentially greater role for behavioural or genetic factors in early-onset cancer (Institute of Medicine, 2002; Carvalho *et al*., 2018). CHB zones at mid-elevation were associated with lower mortality for older men(β=-111.2, p=0.007) and women (β=-70 to -172, p<0.03), revealing age-structured spatial inequalities in exposure and healthcare reach. While elevation alone did not consistently predict cancer mortality, its interaction with land use was significant. CHB zones at higher altitudes showed weaker associations, while those at low elevations provided the strongest negative associations.This is consistent with elevation operating as a contextual modifier rather than a direct determinant (de Hoogh *et al*., 2013). Neutral land use zones (CN) were not significantly associated with cancer mortality in any model, suggesting that natural landscapes alone may not confer protection without adequate healthcare infrastructure or access. In sum, these findings highlight the value of incorporating environmental morphology and land use in spatial epidemiological models of cancer. While age and sex remain dominant predictors, the spatial structuring of exposure and healthcare access reinforces the need for targeted, equity-oriented public health strategies (Ben-Shlomo & Kuh, 2002; Saurel-Cubizolles *et al*., 2009; Van Hemelrijck *et al*., 2021; Ni *et al*., 2024).

Regression analysis: lung cancer mortality

Multivariate models assessing lung cancer mortality revealed stronger and more consistent spatial patterns than those for total cancer, underscoring stronger spatial and environmental associations for this site-specific cancer (Table 6). Overall explanatory power was higher, with adjusted R^2 values between 0.18 and 0.27, especially in older populations and female subgroups. Highly bur-

Table 5. Statistical regression results examining the relationship between geomorphological and environmental factors and overall cancer mortality. disaggregated by age group (<65. ≥65) and sex.

	CT	CY	CO	CM	CMY	CMO	CF	CFY	CFO
Multiple R	0.37	0.28	0.37	0.33	0.27	0.33	0.37	0.29	0.37
R^2	0.14	0.08	0.14	0.11	0.08	0.11	0.14	0.09	0.13
Adjusted R^2	0.10	0.03	0.09	0.07	0.03	0.06	0.10	0.04	0.09
Standard error	36.39	14.73	150.40	49.01	19.60	198.30	35.63	12.68	149.87

dened land use zones (CHB) were negatively associated with lung cancer mortality in multiple configurations, particularly at mid-elevation. Among women aged ≥65, CHB zones at moderate altitudes showed the strongest negative association (β=-146.51, p<0.001), while in men, significant negative associations were observed across various topographic strata (β range: -102.5 to -128.3, p<0.01). These findings suggest that urban infrastructure at mid-altitude may be associated with lower observed mortality, potentially reflecting differences in healthcare access, ventilation, or pollution dispersion (Raaschou-Nielsen *et al.*, 2013; de Hoogh *et al*., 2016). In contrast, moderately burdened zones (CMB) were robustly linked to higher lung cancer mortality, especially among older women. The highest positive effect appeared in females ≥65 in lowland areas (β=+73.8, p=0.002), indicating patterns of heightened vulnerability in semi-urban and agricultural regions where pollution, pesticide exposure, and healthcare access intersect (Ciabattini *et al*., 2021; WHO, 2021). Male models also showed positive coefficients, though with weaker significance, possibly reflecting sex-specific differences in exposure or resilience (Brulle & Pellow, 2006; Clougherty, 2010).

Topographic effects alone were limited, but their interactions with land use were significant. Lowland–CMB combinations consistently predicted higher mortality in both sexes, reinforcing the interpretation that geographic context conditionsanthropogenic exposure effects. These additive and interactive dynamics emphasize the importance of spatial context in epidemiological risk modelling (Anselin, 1995; Malek & Verburg, 2020).

Protective land uses (CN) did not show significant associations in any model, suggesting that natural spaces may not sufficiently buffer cumulative risks at the regional scale. This challenges assumptions of universally beneficial "green exposure" and underscores the need for finer-scale studies on environmental quality and mobility (Nieuwenhuijsen *et al*., 2018; Su *et al*., 2011).

Older populations showed stronger spatial sensitivity to land use and elevation, with models for age ≥65 yielding higher adjusted R^2 (up to 0.27), consistent with lifetime exposure and reduced resilience (Ben-Shlomo & Kuh, 2002; Institute of Medicine, 2002).

Overall, lung cancer mortality proved more spatially structured than total cancer, with sharper gradients and stronger land use interactions. Urban mid-elevation zones are associated with relatively lower observed mortality, while semi-rural lowlands exhibit higher mortality levels, particularly for older women. These patterns support the development of place-sensitive cancer prevention and environmental health policies targeting spatial disparities (Schlosberg, 2007; Yang & Geng, 2022).

Comparative synthesis: total versus lung cancer mortality

A comparative analysis of regression models for total and lung cancer mortality revealed both convergences and divergences in spatial patterns and environmental correlations. While both outcomes share structural correlates, lung cancer shows greater spatial sensitivity to environmental and morphological conditions.

Lung-cancer models consistently demonstrated higher explanatory power (adjusted R^2=0.18-0.27) than those for total cancer (adjusted R^2=0.08-0.14), particularly among older populations. This reinforces the stronger environmental associations observed for lung cancer as a site-related disease influenced by external exposures such as airborne pollutants and land-use characteristics (Ciabattini *et al*., 2021; WHO, 2021). In contrast, total-cancer mortality reflects a broader aetiology involving less spatially structured factors such as genetic predisposition, diet, and comorbidities (Ben-Shlomo & Kuh, 2002; Carvalho *et al*., 2018). For instance, in Upper Silesia (Poland) – a low-elevation coal-mining basin – lung-cancer models explained almost 25 % of the regional variance, compared with <10 % for total cancer.

Highly burdened (CHB) urban-industrial zones were negatively associated with mortality in both outcomes, but the negative association was more pronounced in lung-cancer models, especially at mid-elevations. This suggests that urban infrastructure – such as advanced healthcare systems and routine screening – may be associated with lower observed lung-cancer mortality, a disease with relatively high preventability and responsiveness to early detection (Bray *et al*., 2021; Van Hemelrijck *et al*., 2021). The CHB–elevation interaction is exemplified by Lombardy's mid-altitude urban core (Milan/Bergamo), where strong healthcare coverage appears to coincide with lower-than-expected lung-cancer mortality despite industrial exposures.

Moderately burdened (CMB) landscapes exhibited positive associations with mortality in both models, but were stronger and more significant in lung cancer, especially in semi-urban and agricultural lowland areas. These areas with higher observed mortalitylikely reflect a convergence of ambient exposures (e.g., pesticides, emissions) and limited access to specialised care (Raaschou-Nielsen *et al*., 2013; Clougherty, 2010).

Topographic variables alone had limited predictive value, yet their interaction with land use was crucial. Lowland–CMB combinations consistently emerged as clusters of higher mortality – particularly for lung cancer – underscoring the synergistic effects of geography and anthropogenic transformation (Malek & Verburg, 2020).

Stratified models revealed gender- and age-related spatial dynamics. Total-cancer mortality in men showed broader but less consistent associations with land use, whereas lung-cancer models for older women exhibited the most robust spatial gradients. This highlights the gendered nature of environmental risk, shaped by cumulative exposure, occupational history, and differential healthcare access (Clougherty, 2010; Saurel-Cubizolles *et al*., 2009). A contrasting pattern is visible in Thessaloniki (Greece), where female lung-cancer mortality remains relatively low despite elevated male rates, pointing to sex-specific exposure histories and screening uptake.

In sum, lung-cancer mortality emerges as a more spatially

Table 6. Statistical regression results examining the relationship between geomorphological and environmental factors and overall lung cancer mortality. disaggregated by age group (<65. ≥65) and sex.

	LCT	LCY	LCO	LCM	LCMY	LCMO	LCF	LCFY	LCFO
Multiple R	0.23	0.29	0.23	0.27	0.29	0.26	0.37	0.36	0.38
R^2	0.05	0.08	0.05	0.07	0.08	0.07	0.14	0.13	0.15
Adjusted R^2	0.01	0.04	0.01	0.03	0.04	0.02	0.10	0.09	0.10
Standard Error	11.23	4.72	45.99	17.25	7.37	66.59	12.62	3.93	53.68

responsive outcome than total cancer, with sharper gradients and clearer environmental associations. While both outcomes are associated with land use and topography, the strength, direction, and interactions differ, underscoring the need for cancer-specific geospatial research. These findings provide a robust evidence base for geographically targeted cancer-control strategies that advance Sustainable Development Goals 3 (Good Health and Well-being), 10 (Reduced Inequalities), and 11 (Sustainable Cities and Communities), while aligning with the European Green Deal's commitment to regional health equity and environmental justice.

Hotspot analysis

Global spatial patterns in cancer and lung cancer mortality

The Getis-Ord Gi* analysis revealed substantial spatial clustering of cancer mortality across Europe, identifying zones with significantly high or low values. For total cancer mortality (Figure 1), hotspots at the 99% confidence level were primarily located in Central and Eastern Europe, notably in Germany, Poland, Czechia, Hungary, Romania, and the Western Balkans. This concentration aligns with prior research linking elevated mortality to industrial legacies, environmental degradation, and socioeconomic disadvantages (Borrell *et al.*, 2014; Carvalho *et al.,* 2018).

In contrast, pronounced cold spots (95-99%) were observed in the Iberian Peninsula (Portugal and southern Spain) and eastern Turkey, suggesting the presence of favourable contextual factors related to lifestyle, diet, or healthcare infrastructure (Bray *et al.*, 2021). Southern Scandinavia (Sweden, Norway, Finland) showed 99% confidence hotspots, while northern zones appeared as non-significant or cold, likely reflecting urban–rural divides and environmental contrasts (Pukkala *et al*., 2009; Vienneau *et al*., 2017). Northern Italy and much of France emerged as moderate hotspots (90%-95%), consistent with dense urban-industrial development and detailed health reporting. For lung cancer mortality (Figure 2), a clearer west–east and north–south divide emerged. Hotspots concentrated in Germany, the Netherlands, and the UK were consistent with historical patterns of tobacco use, industrial emissions, and air pollution (Raaschou-Nielsen *et al*., 2013; Ciabattini *et al*., 2021). Cold spots (99%) were evident across Sweden, Norway (especially coastal and northern areas), the Iberian Peninsula, and eastern Turkey – regions where environmental and lifestyle profiles may be associated with lower observed mortality. Notably, parts of Central Greece, including the mainland and the Peloponnese, appeared as 90-95% hotspots for lung cancer mortality. These may reflect localized industrial emissions or disparities in early diagnostic services (Bambra *et al*., 2019; WHO, 2020). This variation reinforces the need for micro-regional assessment in epidemiological studies.

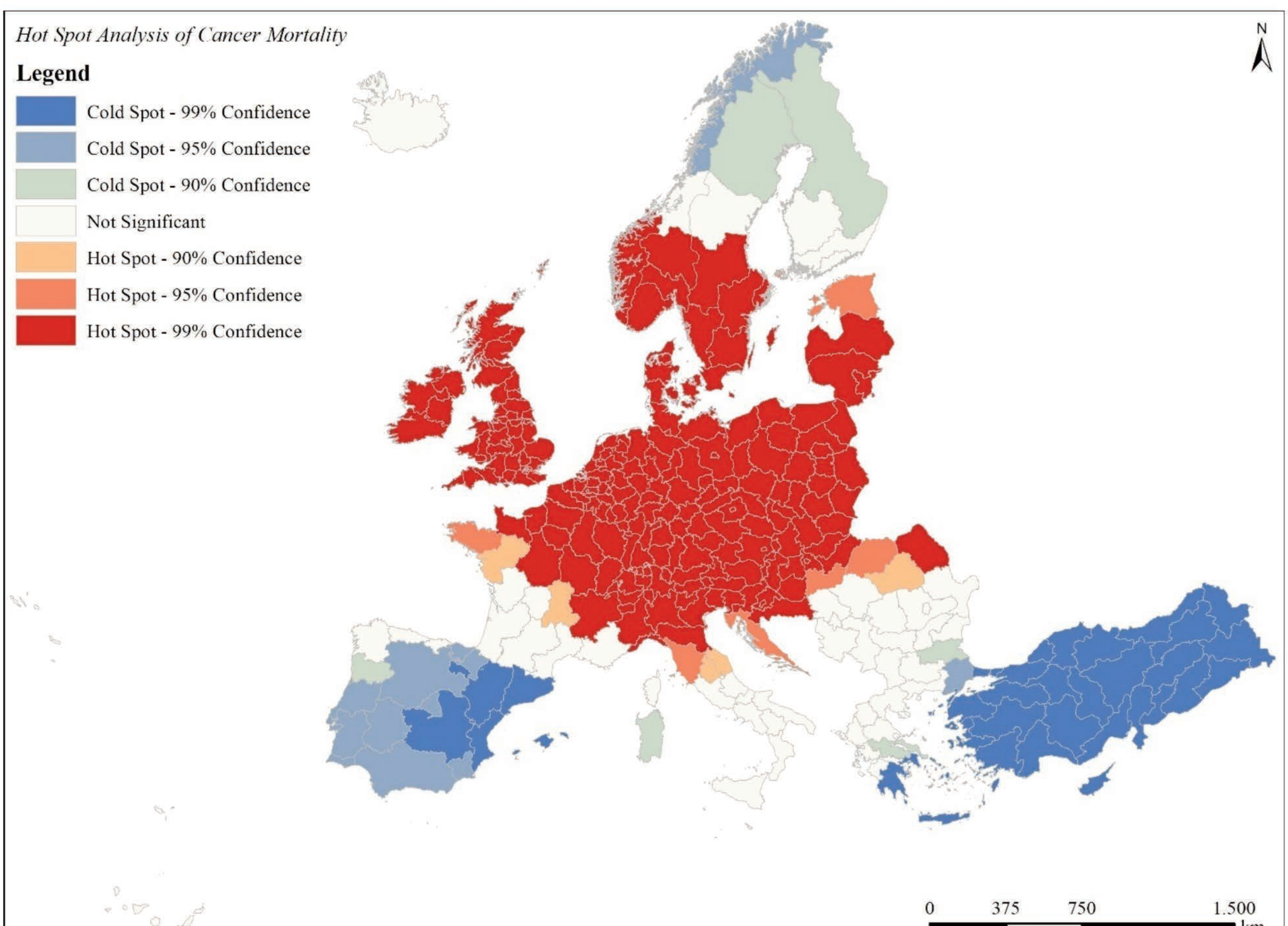

Figure 1. Hotspot analysis of age-standardized cancer mortality in Europe (NUTS-2 level).

In sum, the Getis-Ord Gi* results confirm that cancer and lung cancer mortality exhibit significant spatial clustering and are associated with environmental exposure, topography, and social structure. These patterns underscore the utility of spatial epidemiology in identifying priority regions for targeted cancer prevention and environmental health policy (Elliott & Wartenberg, 2004; Nieuwenhuijsen *et al*., 2018).

Overlaps: comparative spatial patterns between cancer and lung cancer mortality

The comparative spatial analysis of total and lung cancer mortality, based on Getis-Ord Gi* hotspot results (Figures 1 and 2), revealed substantial yet incomplete regional overlap. Simultaneous mapping of both indicators enabled identification of zones with converging or diverging mortality risks, enriching interpretations of spatial health inequalities across Europe.

Strong spatial convergence appeared across several NUTS-2 regions in Central and Eastern Europe, particularly in Germany, Poland, Czechia, Slovakia, and Hungary. These consistently emerged as high-significance hotspots ($p<0.01$) for both outcomes, suggesting that lung cancer is a major contributor to total cancer mortality in these areas. This alignment likely reflects long-term industrial emissions, high historical smoking prevalence, and lingering environmental risks from urban-industrial transitions.

Parts of the Western Balkans, including Serbia and western Bulgaria, also exhibited dual clustering, reinforcing the presence of cumulative regional risks. These overlapping hotspots likely reflect shared structural correlates, such as late diagnoses, under-resourced public health systems, and localized environmental burdens. Conversely, overlapping cold spots ($p<0.01$) appeared in southwestern Europe – Portugal, western and southern Spain – and parts of Eastern Turkey and southern Greece. These areas exhibited low mortality for both indicators, likely due to favourable demographics, healthier lifestyles, and reduced industrial pollution.

However, important divergences were also noted. In Nordic and Baltic countries – especially southern Norway, Sweden, and Finland – lung cancer mortality formed cold spots, while total cancer mortality showed no clustering. This may indicate a higher contribution from other malignancies, such as prostate or colorectal cancer. Similarly, in Italy and France, several areas emerged as hotspots for total cancer mortality without corresponding clustering for lung cancer, likely due to higher incidence of non-pulmonary cancers like breast or gastrointestinal types. Overall, while lung cancer significantly contributes to total cancer mortality in many regions, its spatial distribution does not fully mirror broader cancer patterns. These distinctions highlight the need for disease-specific, spatially targeted cancer control strategies that reflect regional environmental and sociodemographic dynamics.

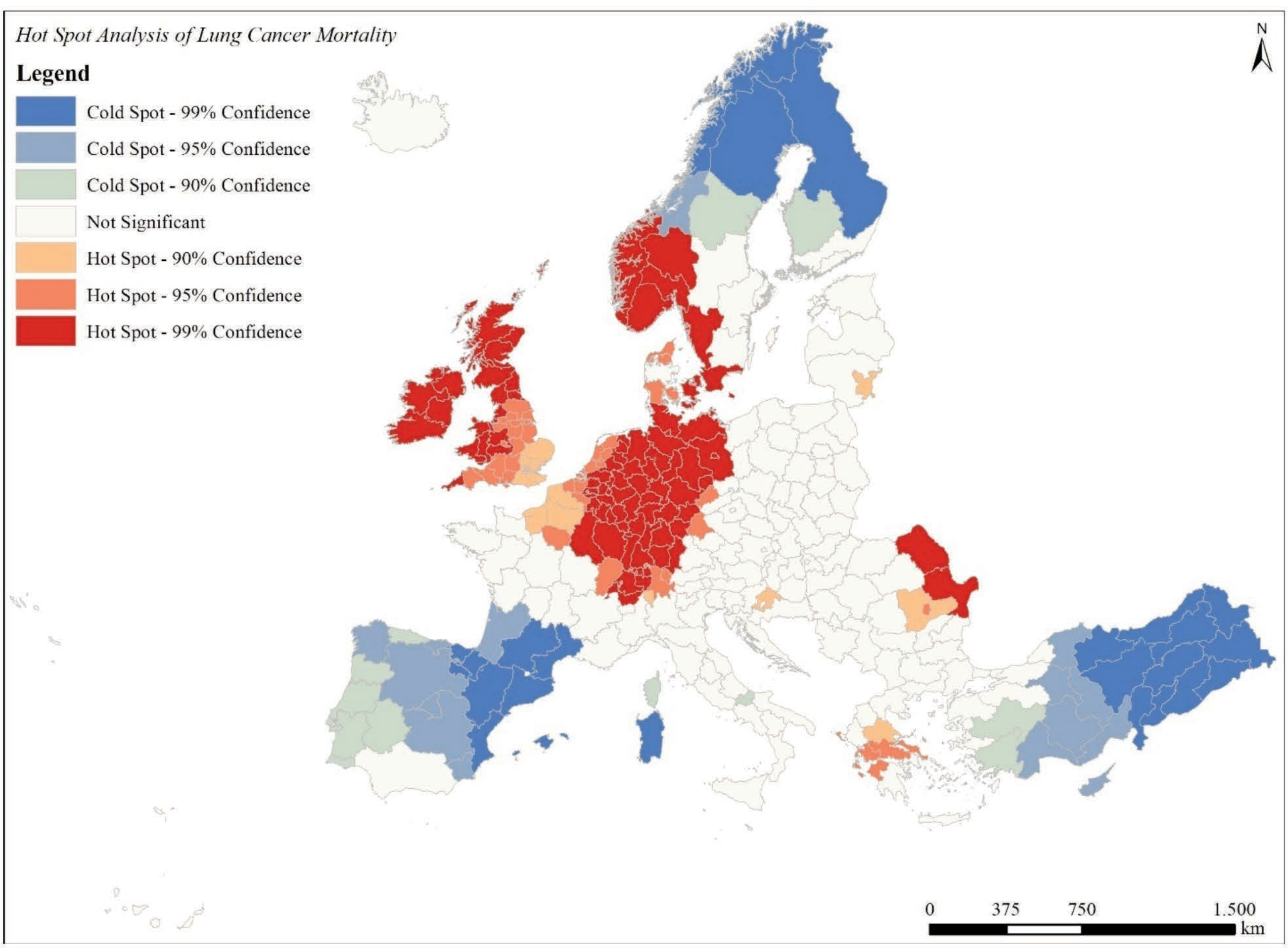

Figure 2. Hotspot analysis of age-standardized lung cancer mortality in europe (NUTS-2 level).

Cluster and outlier analysis (Anselin Local Moran's I)

Global spatial patterns in cancer and lung cancer mortality

Anselin Local Moran's I enabled the identification of statistically significant local clusters and spatial outliers in cancer and lung cancer mortality across European NUTS-2 regions, offering finer-grained insight beyond the broader patterns detected by Getis-Ord Gi*. For total cancer mortality (Figure 3), distinct high–high clusters (*i.e.*, regions with high mortality surrounded by similarly high neighbours) appeared across Central and Eastern Europe – especially in Germany, Czechia, Hungary, and the Western Balkans. These patterns are consistent with entrenched regional disadvantages rooted in industrial pollution, underinvestment in healthcare, and socioeconomic vulnerability (Carvalho *et al.*, 2018; Borrell *et al.*, 2014). Low–low clusters – areas with low mortality surrounded by similarly low neighbours – were observed in southwestern Europe, including Spain, Portugal, southern Greece, Sardinia, and parts of eastern Turkey. These align with the associations with healthier lifestyles, diets, and lower industrial density (Bray *et al*., 2021).

High–low outliers (high mortality amid lower-burden neighbours) were found in northern Norway, eastern Greece (e.g., Thrace and parts of the Aegean), and southeastern Europe, possibly indicating localized burdens driven by lagging infrastructure or exposure sources. Conversely, low–high outliers – regions with low mortality surrounded by high-mortality neighbours – were identified in southern Germany, Czechia, north-eastern Romania, and parts of France and Poland. These may reflect local resilience, early detection, or health system effectiveness.

For lung cancer mortality (Figure 4), high–low outliers concentrated in southern France, central and northern Italy, northern Spain, and the fringes of Turkey and Norway. These locally elevated mortality levels relative to surrounding regions may stem from localized pollution patterns or disparities in tobacco control (Ciabattini *et al*., 2021; WHO, 2020). In contrast, low–high outliers were found in Poland, Romania, Ireland, the UK, and southern Scandinavia, suggesting effective mitigation policies or favourable sociodemographic conditions.

Low–low clusters for lung cancer were notable in northern Italy, Switzerland, southern France, northern Scandinavia, and eastern Turkey, consistent with persistently lower observed lung cancer mortality. These results complement global patterns while highlighting micro-regional anomalies essential for policy planning.

In sum, LISA results reveal spatial discontinuities and cross-border contrasts not always evident in global analyses. These pat-

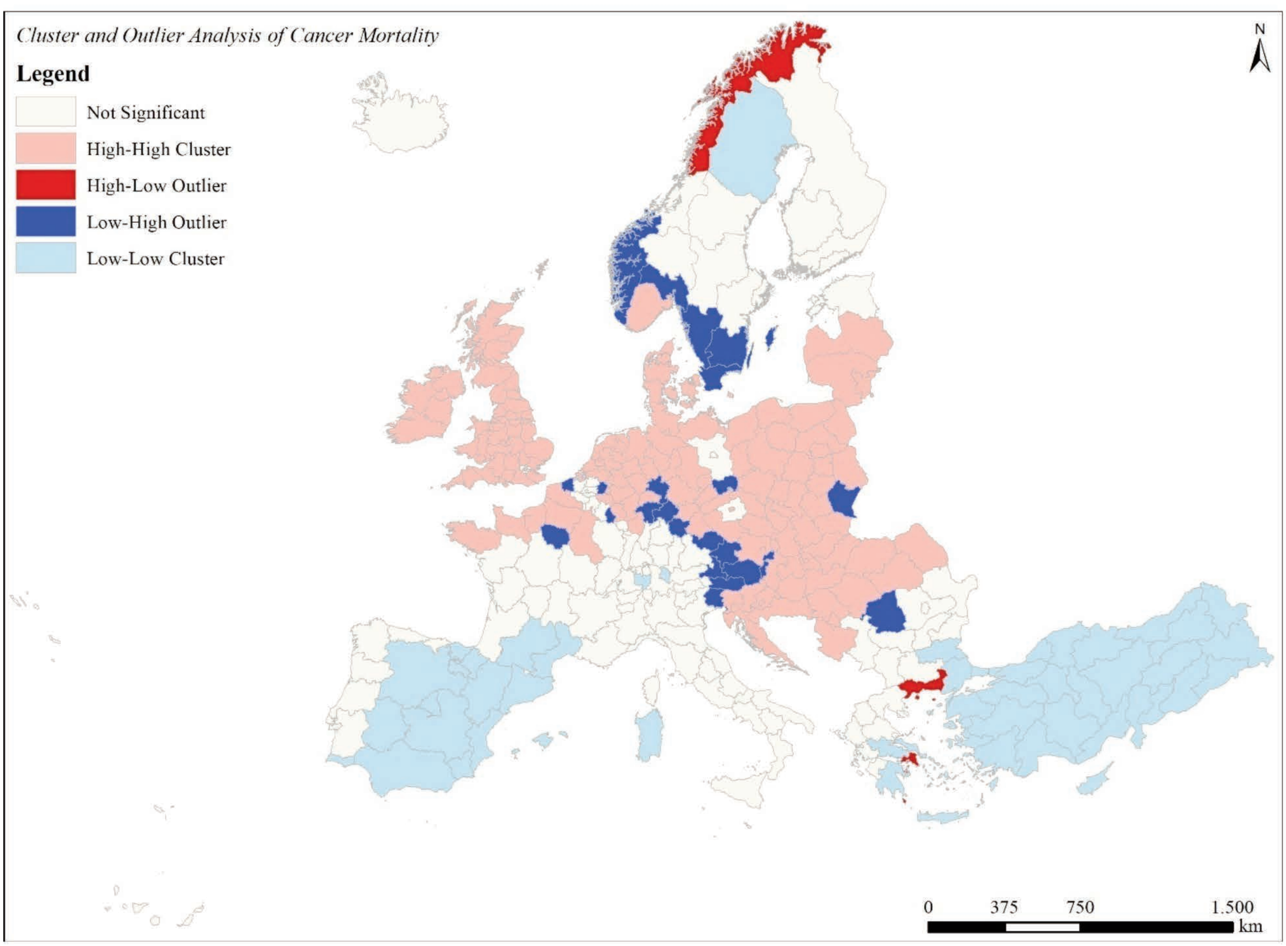

Figure 3. Cluster and outlier analysis of age-standardized cancer mortality in Europe (NUTS-2 level).

terns help identify priority regions for targeted screening, communication, and public health action, especially where overall and lung cancer mortality diverge. The combined use of cluster and outlier detection strengthens the spatial epidemiological framework for understanding cancer mortality inequalities in Europe (Anselin, 1995; Nykiforuk & Flaman, 2011).

Overlaps: Comparative Spatial Patterns between Cancer and LungCancer Mortality

The comparative application of Anselin Local Moran's I to total and lung cancer mortality revealed notable overlap in spatial clustering, alongside key divergences offering epidemiological insight. Several NUTS-2 regions in Central and Eastern Europe – particularly Poland, Czechia, Hungary, and southern Germany – consistently appeared as high–high clusters for both cancer types. These areas exhibited elevated mortality surrounded by similarly high-burden neighbours, indicating entrenched structural vulnerabilities linked to aging populations, delayed screening, historical smoking, and sustained industrial exposure (Raaschou-Nielsen *et al*., 2013; Carvalho *et al.*, 2018). Such zones highlight the need for geographically targeted interventions and improved screening infrastructure. Conversely, low–low clusters for both mortality types were identified in southwestern Europe, including western and southern Spain, Portugal, parts of southern Italy, and eastern Turkey. These areas likely reflect favourable contextual factors such as healthier diets, lower urban-industrial density, and reduced historical tobacco use (Bray *et al*., 2021; Nieuwenhuijsen *et al*., 2018).

Despite these parallels, important asymmetries were observed. High–low outliers – regions with elevated mortality surrounded by low-burden areas – emerged in southern France, northern Spain, and northern Italy. These may reflect localized industrial sources, healthcare under-diagnosis in rural neighbours, or historical inequalities in service provision. Conversely, low–high outliers – regions with lower mortality than adjacent high-burden areas – were found in Sweden, Scotland, and southern Germany, possibly indicating more robust healthcare systems, early detection, or favourable age structures (Bambra *et al*., 2019; WHO, 2020).

Overall, the spatial congruence between total and lung cancer mortality reveals coherent regional health gradients. However, mismatches highlight that lung cancer does not fully mirror broader cancer trends, showing greater sensitivity to localized occupational, environmental, and behavioural factors. These results stress the need for disease-specific public health strategies, as uniform prevention approaches may not address spatially discordant cancer burdens.

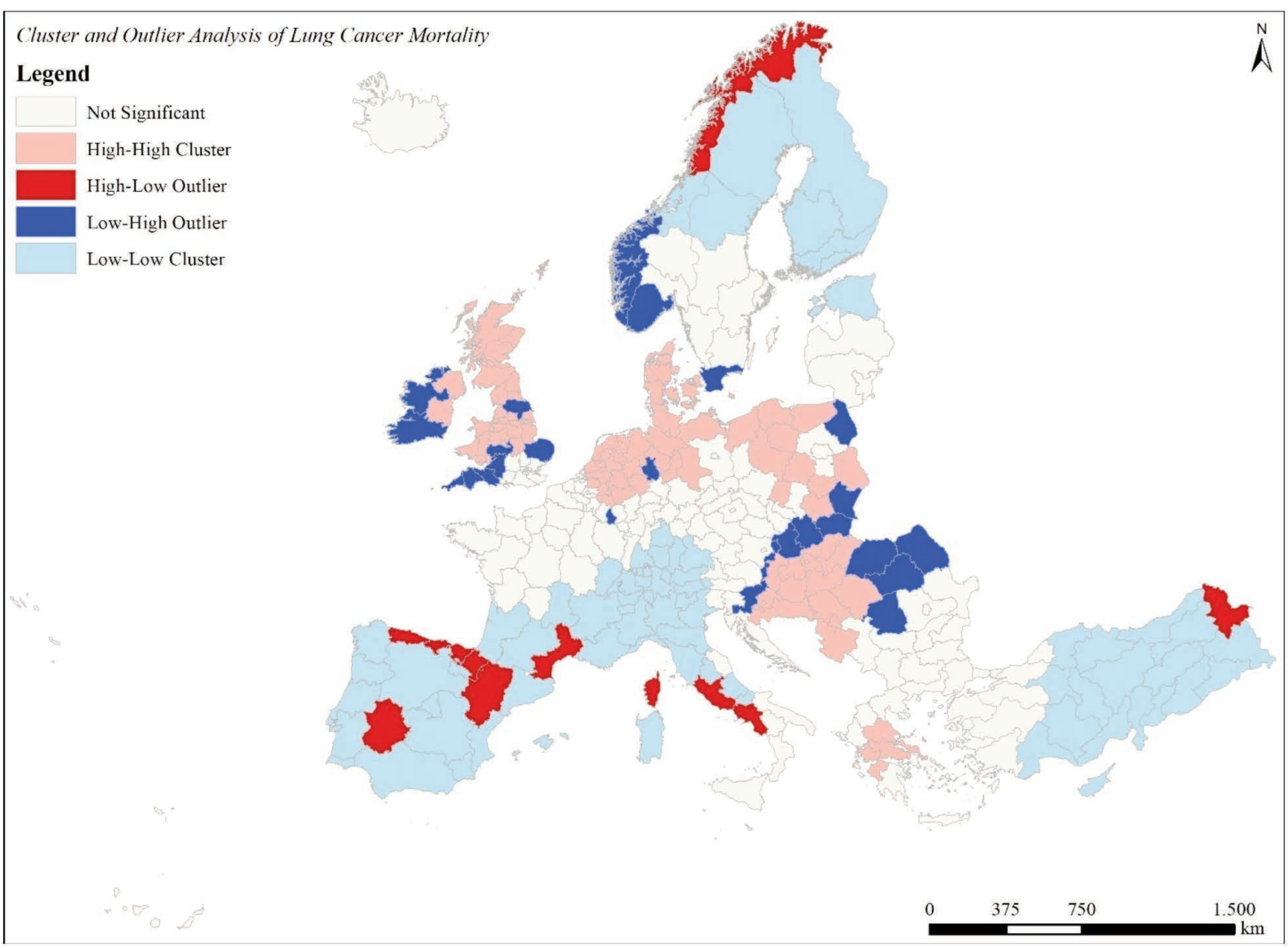

Figure 4. Cluster and Outlier Analysis of Age-Standardized Lung Cancer Mortality in Europe (NUTS-2 Level).

Divergences and residual spatial inequalities

Despite considerable spatial overlap between total and lung cancer mortality clusters, several regions show significant divergences, pointing to residual spatial inequalities and context-specific factorsbeyond shared environmental or behavioural risks. These mismatches underscore the pitfalls of assuming homogeneous cancer burdens across adjacent regions and highlight the interplay between place-specific exposures, healthcare access, and demographic dynamics.

Notably, parts of Northern Italy, Southern France, and Eastern Greece consistently appeared as high–low or low–high outliers, depending on cancer type. These anomalies may stem from hidden spatial processes such as undocumented occupational exposures, local variations in screening uptake, or differences in cause-of-death registration practices. Cross-border inconsistencies – such as those along the German–French or Italian–Swiss frontiers – suggest that administrative boundaries may mask underlying gradients of environmental or social vulnerability.

Such residual disparities also reflect the limits of aggregate regional indicators. For instance, lung cancer clusters may diverge from overall cancer mortality in areas where other cancers (e.g., breast, colorectal, prostate) dominate due to region-specific demographic or lifestyle profiles (Bray *et al*., 2021; Pukkala *et al*., 2009). Inversely, regional outliers may indicate pockets of resilience – such as effective public health campaigns or strong healthcare systems – that suppress mortality despite elevated environmental risk.

Ultimately, these divergences emphasize the need to move beyond national averages and employ spatially disaggregated epidemiological models. Integrating multilevel analyses with place-based environmental and sociodemographic data can better elucidate the multifactorial nature of cancer mortality. Addressing these residual inequalities requires tailored cancer control strategies sensitive to regional differences in exposure, vulnerability, and healthcare capacity (Elliott & Wartenberg, 2004; Yang & Geng, 2022).

Discussion

This study provides robust and policy-relevant evidence of pronounced spatial inequalities in cancer and lung-cancer mortality across Europe. By integrating Geographically Weighted Regression with advanced spatial clustering techniques (Getis-Ord Gi* and Anselin Local Moran's I) and illustrative case-study vignettes (*e.g*., Upper Silesia, Lombardy, Thessaloniki), we revealed both continent-wide patterns and localised outliers – territories where mortality diverges dramatically from surrounding regions, signalling areas of embedded structural vulnerability.

A clear evidence of spatially patterned cancer and lung cancer mortality across Europe, with consistent clusters of elevated risk in Central and Eastern European regions, is presented. The application of both global (Getis-Ord Gi*) and local (Anselin Local Moran's I) spatial statistics revealed substantial heterogeneity in mortality burdens, highlighting the important role of geographic context in structuring cancer outcomes. In particular, NUTS-2 regions in Germany, Poland, Czechia, Hungary, and parts of the Western Balkans emerged as persistent high-risk clusters for both cancer indicators. Specific regional examples – such as Upper Silesia in Poland and Lombardy in Italy – illustrate how industrial legacy, air pollution, and socioeconomic marginalization co-occur with elevated mortality burdens (Borrell *et al*., 2014; Carvalho *et al*., 2018; Ciabattini *et al*., 2021). In Upper Silesia, coal combustion and high $PM_{2.5}$ coincide with inadequate screening infrastructures, whereas in Lombardy, urban healthcare networks partially mitigate risks, resulting in paradoxically lower lung cancer mortality in metropolitan Milan–Bergamo compared to adjacent rural districts.

Conversely, southwestern Europe – including Portugal, western Spain, southern Italy, and parts of Greece such as Thessaloniki – consistently appeared as cold spots for both mortality types. These regions likely benefit from a constellation of protective factors, such as healthier dietary patterns (e.g., the Mediterranean diet), lower historical smoking rates, and reduced exposure to ambient pollutants (Bray *et al*., 2021; Nieuwenhuijsen *et al*., 2018). For instance, the Alentejo region in southern Portugal combines low traffic density with traditional plant-based diets, coinciding with some of the lowest NO_2 concentrations and cancer mortality rates in the dataset. Similarly, within Central Macedonia, lung cancer mortality gradients between urban Thessaloniki and its rural hinterlands underscore intraregional heterogeneity rooted in mobility, land use, and healthcare access.

Importantly, the observed discrepancies between cancer and lung cancer mortality patterns – particularly in countries like France, Italy, and parts of Scandinavia – highlight that lung cancer does not uniformly drive overall cancer mortality. For example, areas such as southern Norway and Sweden exhibited cold spots for lung cancer but not for total cancer mortality, suggesting that other cancers (e.g., breast, colorectal, or prostate) may dominate in these settings. Similarly, hotspots for total cancer in France and Italy, without corresponding clustering in lung cancer, point to the importance of non-pulmonary cancer drivers within specific regional contexts (Pukkala *et al*., 2009; Sung *et al*., 2021).

These findings underscore the multidimensional nature of cancer risk, where age structure, occupational exposures, tobacco history, and healthcare-system characteristics interact within specific spatial configurations. The consistent identification of high–high clusters across spatial models further validates the robustness of spatial clustering as a proxy for cumulative exposure and structural vulnerability (Anselin, 1995; Nykiforuk & Flaman, 2011). By making these spatial inequities visible, this study provides an actionable evidence base for geographically targeted cancer control interventions. In doing so, it supports key priorities of the Sustainable Development Goals – namely SDG 3 (Good Health and Well-being), SDG 10 (Reduced Inequalities), and SDG 11 (Sustainable Cities and Communities) – and aligns with the European Green Deal's territorial equity agenda, while informing implementation of Europe's Beating Cancer Plan.

Methodological strengths and limitations

A core strength of this study lies in its spatially explicit design, integrating high-resolution mortality data with advanced spatial statistics to examine geographic disparities in cancer and lung cancer outcomes. The complementary use of Getis-Ord Gi* and Anselin Local Moran's I enabled detection of both global and local clusters, allowing the identification of robust hot/coldspots as well as spatial outliers. This dual approach enhanced interpretive capacity, revealing regional patterns that remain obscured in traditional non-spatial epidemiological analyses (Anselin, 1995; Elliott & Wartenberg, 2004; Nykiforuk & Flaman, 2011).

Utilizing NUTS-2 level data ensured cross-national comparability in line with Eurostat standards (European Commission, 2018), while retaining sufficient spatial granularity to detect regional inequalities. The reliance on age-standardized death rates further improved comparability by controlling for demographic structure. Nonetheless, several limitations must be acknowledged.

The cross-sectional nature of the dataset limits causal inference, as the observed spatial patterns may reflect legacy exposures, contextual influences, or lagged effects not captured in contemporary data. Additionally, the ecological framework precludes individual-level analysis, raising the risk of ecological fallacy. Within-region variation in socioeconomic, behavioural, or genetic characteristics may influence outcomes but remain unobservable at the aggregate scale. While spatial clustering techniques capture the non-random distribution of disease, they do not clarify the underlying mechanisms driving these patterns. The absence of integrated behavioural or environmental exposure data – such as smoking prevalence, occupational histories, or fine-scale air pollution measures – constrains explanatory depth. Although prior studies link air pollution to lung cancer risk (Raaschou-Nielsen *et al*., 2013; Ciabattini *et al*., 2021), this analysis was not designed to directly quantify such exposures.

Additional methodological caveats include the Modifiable Areal Unit Problem (MAUP) and edge effects, which may distort cluster identification along borders or coastal regions. Furthermore, while the spatial statistics employed are effective for pattern detection, they are not suited to modelling causal processes or temporal dynamics (Lee & Lawson, 2014; Reich *et al*., 2021).

In sum, the study offers a valuable framework for regional cancer surveillance in Europe. Beyond advancing spatial epidemiology, it supports geospatial health monitoring systems aligned with Sustainable Development Goal 3 on non-communicable disease reduction and Goal 10 on inequality reduction. Its integration of spatial clustering into environmental health research also complements the European Green Deal's strategic vision for territorial cohesion and health equity. Findings should therefore be interpreted within the boundaries of ecological, cross-sectional, and cluster-based designs. Future research should integrate longitudinal methods, individual-level data, and spatially resolved exposure indicators to better elucidate the processes underlying these persistent geographical disparities.

Policy and public health implications

The spatial disparities in cancer and lung-cancer mortality revealed in this study highlight the need for geographically tailored public-health strategies. Regions with persistent high–high clusters and overlapping hotspots – particularly in Central and Eastern Europe – would benefit from targeted interventions that address cumulative industrial exposure, historical tobacco use, and systemic healthcare gaps (Borrell *et al*., 2014; Carvalho *et al*., 2018; Raaschou-Nielsen *et al*., 2013). Effective cancer prevention in such contexts should incorporate environmental-risk reduction, occupational-safety reforms, and equitable access to early diagnosis and treatment (WHO, 2020; Bray *et al*., 2021). The coal-mining basin of Upper Silesia, for example, combines high particulate pollution with limited screening infrastructure – illustrating a setting where intensive air-quality remediation and mobile-clinic programmes could be prioritized.

Conversely, cold-spot clusters in south-western Europe and eastern Turkey point to protective health determinants, including healthier diets, lower smoking prevalence, and reduced industrial activity (Nieuwenhuijsen *et al*., 2018). These regions offer transferable models for promoting lifestyle-based prevention in higher-risk areas. Recent initiatives in Barcelona – such as low-emission zones and "super-block" traffic schemes – demonstrate how urban greening and active-mobility policies may contribute to long-term reductions in cancer-related risk (Nieuwenhuijsen *et al*., 2018; Vienneau *et al*., 2017).

Spatial outliers – regions with high mortality surrounded by lower-burden neighbours – warrant detailed investigation through community-engaged and qualitative methods. Such mismatches may reflect local infrastructure deficits, diagnostic delays, or marginalized populations that remain invisible in national-level data (Bambra *et al*., 2019; Brulle & Pellow, 2006). The port city of Thessaloniki exemplifies this pattern: industrial-site proximity and congested traffic corridors coincide with higher male lung-cancer mortality, underscoring the need for targeted emission-control measures and gender-sensitive screening strategies.

This study also affirms the strategic value of geospatial methods for guiding cancer control. Integrating spatial epidemiology with land-use regression models and environmental-monitoring systems, as in de Hoogh *et al*. (2016), can support early-warning efforts and more equitable resource distribution. The European Commission's Beating Cancer Plan explicitly supports region-specific actions aligned with such spatially grounded insights (European Commission, 2021). A pan-European "Cancer Geo-Dashboard", pooling Eurostat, Copernicus air-quality layers, and hospital-registry feeds, could help operationalise this early-warning capacity. The Horizon Europe Cancer Mission offers a suitable funding framework for piloting these geospatial tools in applied regional programmes, while evidence platforms such as ESPON on territorial cohesion can assist in benchmarking cross-border health gaps and guiding smart-specialisation strategies in oncology. Such geographically targeted interventions are consistent with Sustainable Development Goals 3 (Good Health and Well-being), 10 (Reduced Inequalities), and 11 (Sustainable Cities and Communities), and resonate with the European Green Deal's commitment to territorial health equity and environmental justice.

Ultimately, public-health responses must adopt an inter-sectoral perspective, encompassing healthcare, urban planning, environmental governance, and social protection. Addressing structural health disparities – especially in vulnerable communities – requires upstream policy integration consistent with principles of environmental justice and spatial equity (Brulle & Pellow, 2006; Lindley *et al*., 2011). Cross-border platforms such as the Alpine Cancer Observatory or the Baltic Health Network could further facilitate knowledge transfer and harmonize monitoring standards across high- and low-burden regions.

General limitations and future directions

Although this study provides a comprehensive spatial assessment of cancer and lung cancer mortality across Europe, several methodological limitations must be acknowledged. First, the analysis was conducted at the NUTS-2 level, which, while standardized for cross-national comparability, may obscure intra-regional disparities and localized environmental or sociodemographic risks (European Commission, 2018; Nieuwenhuijsen *et al*., 2018). Finer spatial disaggregation – such as NUTS-3 or municipal units – would be better suited for detecting neighbourhood-level health inequalities and for informing precision-targeted interventions aligned with the *Leave No One Behind* principle of the SDGs.

As an ecological study, this analysis cannot establish causal inference at the individual level. The relationships between spatial clusters and explanatory factors (e.g., pollution, lifestyle, healthcare access) are inherently correlational. While spatial clustering techniques such as Getis-Ord Gi* and Anselin Local Moran's I are powerful for pattern detection, they fall short in elucidating underlying mechanisms. Future research may benefit from adopting spatially explicit causal inference frameworks – such as Bayesian hierarchical models or spatio-temporal exposure designs – to further narrow the gap between association and causation (Reich *et* *al*., 2021; Lee & Lawson, 2014).

Additionally, although Eurostat provides harmonized cause-of-death data, variation in national reporting standards, coding practices, and healthcare quality may introduce cross-country inconsistencies (Eurostat, 2022; Bray *et al*., 2021). Moreover, mortality data alone may underestimate the total cancer burden, particularly in regions with high survival rates, limited diagnostic infrastructure, or delays in cancer registration. Including incidence rates and stage-at-diagnosis indicators could substantially enhance the interpretive power of geospatial cancer surveillance.

Environmental exposures such as air pollution were not directly measured but inferred from spatial typologies. Although previous research has firmly established links between fine particulate matter ($PM_{2.5}$) and lung cancer (de Hoogh *et al*., 2016; Ciabattini *et al.*, 2021), incorporating high-resolution pollution maps, satellite-based land-cover changes, and personal exposure proxies would improve explanatory depth and policy relevance. These enhancements are particularly relevant for advancing SDG 3 (Good Health and Well-being) and SDG 11 (Sustainable Cities and Communities), as well as for operationalising the Zero Pollution Action Plan of the European Green Deal.

Furthermore, the cross-sectional nature of the analysis restricts temporal insight. It precludes evaluation of dynamic processes such as environmental remediation, policy reform impacts, or evolving health inequalities. Longitudinal spatial analyses are therefore important for tracking trends, evaluating the implementation of Europe's Beating Cancer Plan, and monitoring progress toward EU territorial equity goals (European Commission, 2021).

In summary, future research should pursue the following priorities: i) disaggregation to finer spatial scales (*e.g*., NUTS-3, urban neighbourhoods); ii) longitudinal and multilevel modelling frameworks; iii) integration of direct environmental and behavioural exposure data, including air quality, occupation, and lifestyle patterns; and iv) expansion of outcome metrics to include quality of life, economic costs, and survivorship disparities. By advancing these directions, spatial epidemiology can more effectively support equitable cancer control strategies that are scientifically robust, environmentally informed, and policy-relevant across diverse European geographies.

Policy recommendations

The spatial disparities in cancer and lung cancer mortality revealed in this study underscore the need for geographically differentiated public health strategies across Europe. The persistence of hotspots in Central and Eastern Europe – contrasted with cold spots in regions of the Iberian Peninsula and Eastern Turkey – illustrates the insufficiency of uniform, pan-European approaches to cancer control. A spatially stratified framework is essential to account for the complex interplay between environmental exposures, demographic aging, socioeconomic vulnerabilities, and healthcare system capacity.

High-burden clusters – notably in Poland, Czechia, Hungary, Germany, and the Western Balkans – represent priorities for targeted interventions. These regions exhibit enduring legacies of industrialization, elevated environmental risks, and strained preventive infrastructures. Policy responses may encompass intensified screening efforts, anti-smoking campaigns, and environmental remediation programs, supported by both national health ministries and coordinated EU action (Carvalho *et al*., 2018; Bray *et al*., 2021; WHO, 2020). These initiatives align with SDG 3 (Good Health and Well-being) and SDG 10 (Reduced Inequalities), offering a framework for equity-driven resource allocation.

Enhanced environmental surveillance is also needed, especially in high–low outlier zones such as southern France and northern Italy, where localized emission sources and regulatory gaps may distort observed spatial exposure–risk relationships. Micro-scale assessments of air pollution, land use transitions, and industrial zoning can inform adaptive urban planning policies that reduce cancer risks in line with the Zero Pollution Action Plan of the European Green Deal (Raaschou-Nielsen *et al*., 2013; de Hoogh *et al*., 2016).

Resource reallocation based on spatial need is paramount. Drawing on deprivation indices and epidemiological clustering, public health authorities can optimize funding mechanisms, infrastructure investments, and workforce deployments to underserved populations (Borrell *et al*., 2014; Ribeiro *et al*., 2018). This form of place-sensitive policy architecture helps to redress structural imbalances in cancer prevention and care access, especially in areas marked by cumulative disadvantage.

EU-wide frameworks such as *Europe's Beating Cancer Plan* should more explicitly embed spatial epidemiological insights into strategic design and implementation. The integration of Geographic Information Systems (GIS), spatial regression outputs, and health–environment interaction models can enhance the geographical precision and contextual sensitivity of EU cancer control strategies when interpreted alongside healthcare and behavioural determinants (European Commission, 2021; Nieuwenhuijsen *et al*., 2018). Moreover, cross-border knowledge transfer is vital. Regions exhibiting favourable cancer outcomes – such as Portugal, southern Sweden, or parts of Spain – offer valuable templates of integrated environmental–health governance that could be replicated or adapted to high-risk contexts. These models emphasize multi-sector collaboration, preventive health promotion, and pollution abatement, reinforcing principles of SDG 11 (Sustainable Cities and Communities) and environmental justice (Vienneau *et al.*, 2017; Bambra *et al*., 2019).

In sum, this study provides a compelling spatial evidence base for redesigning cancer prevention through territorially adaptive, equity-oriented public health interventions. Bridging epidemiological knowledge with environmental governance is essential to mitigating spatial health disparities and promoting sustainable cancer control across European geographies.

Conclusions

Health geography – beyond its descriptive role – provides a valuable analytical framework for advancing territorial health equity. It equips policymakers with evidence to address entrenched inequalities and supports public-health planning that is more equitable, anticipatory, and spatially attuned. Achieving this vision requires sustained investment in open spatial data, cross-border collaboration, and a culture of territorial health equity across Europe.

A central insight is that low-lying, densely populated regions – despite heavier environmental loads – often display lower mortality rates, a pattern likely reflecting stronger healthcare systems and earlier diagnostic access. In contrast, peripheral and upland regions, particularly those in Central and Eastern Europe, exhibit heightened mortality burdens, especially among older adults and women, reflecting cumulative environmental stressors and persistent gaps in healthcare equity – as seen in Upper Silesia's coal basin and other industrial heartlands. Elevation did not act as a primary predictor but functioned as a contextual modifier, shaping how land use and demography interact to structure uneven health outcomes. Lung-cancer mortality emerged as more spatially asymmetric than total cancer, exhibiting sharper local gradients and stronger environmental associations; this divergence is exemplified by the steep within-region contrast between Lombardy's urban core and its rural periphery. Such findings reinforce the necessity for disease-specific geographies of risk and undermine assumptions of uniform cancer-burden distributions.

A key contribution of this research lies in its interdisciplinary lens – merging spatial epidemiology, environmental-exposure science, and demographic-vulnerability frameworks. While spatial context alone cannot fully explain mortality variability, its inclusion substantially enhances our capacity to map and interpret cancer risk, particularly in marginalized territories overlooked by standard models. Future research must move beyond static ecological associations to incorporate behavioural data (e.g., smoking prevalence), high-resolution environmental metrics (e.g., $PM_{2.5}$), and multilevel spatial models that trace interactions between micro- and macro-level forces. Only then can we more effectively unravel the causal chains linking geography to disease and design interventions that are truly place-based and person-centred.

From a policy perspective, these spatial insights align directly with the strategic aims of Europe's Beating Cancer Plan, the European Green Deal, and the Horizon Europe Cancer Mission. Collectively, they advance SDG 3 (Health), SDG 10 (Inequality), and SDG 11 (Sustainable Cities), while operationalizing the Green Deal's zero-pollution ambition. By identifying persistent hotspots and spatial outliers, this study delivers actionable intelligence to guide geographically precise screening, early detection, and environmental remediation.

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Online supplementary materials
Table 1. Correlation analysis between cancer mortality and environmental characteristics.
Appendix A
Table A1. Regression results examining the relationship between geomorphological and environmental factors with overall cancer mortality (CT).
Table A2. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality <65 years (CY).
Table A3. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality >65 years (CO).
Table A4. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality in men (CM).
Table A5. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality in men <65 (CMY).
Table A6. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality in men >65 (CMO).
Table A7. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality in women (CF).
Table A8. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality in women <65 (CFY).
Table A9. Regression results examining the relationship between geomorphological and environmental factors with cancer mortality in women >65 (CFO).
Table A10. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality (LCT).
Table A11. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality <65 (LCY).
Table A12. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality >65 (LCO).
Table A13. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality in men (LCM).
Table A14. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality in men <65 (LCMY).
Table A15. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality in men >65 (LCMO).
Table A16. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality in women (LCF).
Table A17. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality in women <65 (LCFY).
Table A18. Regression results examining the relationship between geomorphological and environmental factors with lung cancer mortality in women >65 (LCFO).

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