



ELISAH

*European Linkage of Initiative
from Science to Action in Health*

DELIVERABLE

TASK 3.2 GEOGRAPHIC ANALYSIS

VERSION V. 1.0

AUTHORS

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VERSION CONTROL SHEET

• PROJECT SUMMARY

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DISCLAIMER

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ABBREVIATIONS

CR: Population-based cancer registry

ASRW: Age-standardised rate in relation to World population

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EXECUTIVE SUMMARY

This document aims to outline the development of Task 3.2 – Geographic Analysis. Geographic variations in age-standardised rates (ASRWs) are crucial indicators from a public health perspective, as they can uncover locally determined risk factors that could be counteracted. Many studies have compared international variations in ASRWs, while others have compared regional differences within countries. However, research into variations at local levels is limited. In this study, we sought to address the following question: Do geographic variations in ASRWs at the local level (such as city neighbourhoods or clusters of villages) hold significance for public health? To analyse these variations, we divided the counties covered by cancer registries participating in the ELISAH project into within-county districts and calculated the ASRWs for each district. Following this calculation, we created an “Inequality Indicator”, defined as the ratio of the mean ASRW in the upper decile of the ASRW distribution (areas with the highest incidence rates) to the mean ASRW in the lowest decile (areas with the lowest incidence rates). Our analysis indicated that ASRW variations at the local level were greater than those at higher geographic levels, designating geography as an important source of inequalities. The Inequality Index highlights those variations that can be addressed through public health interventions and stresses the importance of sharing information about ASRWs at this geographic level. We also observed an association between breast cancer rates and artificial surfaces as classified by the CORINE database, emphasising the need to counteract the ongoing increase in land use.

1. INTRODUCTION

In 2022, an estimated 2.29 million new cases of breast cancer were diagnosed worldwide [1], including 557,000 cases in Europe. While there is extensive knowledge about breast cancer risk factors, the population-based application of scientific research results has not yielded the anticipated outcomes, as evidenced by the rising age-standardised breast cancer rates across Europe [2]. The ELISAH project (European Linkage of Initiative from Science to Action in Health) aims to identify knowledge gaps regarding the distribution of breast cancer risk factors among European populations and to develop innovative actions and interventions that could reduce the impact of breast cancer on these populations. Geographic variations in age-standardised rates (ASRWs) are regarded as an important topic by ELISAH researchers. Cancer incidence varies significantly between countries and groups of countries, and this variation has been extensively studied. However, it is associated with risk factors that may vary within countries and may subsist in highly localised geographic areas [3-4]. A previous study [5] found that all-cancer ASRW variations within Latin-language countries were 70% higher than variations between those countries. We hypothesised that investigation at the micro level of cancer registry (CR) areas could reveal incidence variations and geographic inequalities that may not be evident at the macro level. The identification of areas with high ASRWs is important from a public health point of view, as it can highlight the presence of avoidable risk factors that public health authorities may be able to address. The comparison of geographic inequality indicators among provinces in a vast area such as that covered by the ELISAH project could pave the way for targeted public health interventions and identify actions that might have been missed at the macro level. The aim of Task 3.2 of WP3 is to examine within-province variations between small districts where the population-based CRs participating in ELISAH collect their cases. We analysed the type of land use (forest, agricultural land, grassland and urban settlements) as an explanatory variable for ASRW variations. The relationship between land use and breast cancer incidence is not well studied, even though it could provide valuable insights into the factors contributing to breast cancer [6]. We decided to go beyond the traditional distinction between urban and rural areas by using the concept of "land use" as expressed by the CORINE Land Cover dataset provided by EU Copernicus [7].

2. CONTENT

2.1 Study design and data sources

We conducted a retrospective study on a cohort of women diagnosed with primary breast cancer, using individual-level data. The cases were archived by the population-based CRs participating in Task 3.2 of the ELISAH project, including the CRs of the Basque Countries, Girona, Granada, Tarragona (Spain), Lazio, Veneto (Italy), Ivano-Frankivsk (Ukraine) and Attica (Greece). We launched a pilot initiative in Greece to set up a Greek population-based breast cancer registry. A sample of registered cases from the Attica region was included in this analysis after verifying population representativeness. A search conducted by CR personnel using the site code C50 and malignant epithelial morphology codes M8010–M8575 of the International Classification of Diseases for Oncology (ICD-O-3) [8] retrieved a total of X primary breast cancer cases diagnosed within the specified study period (2010-2021). No age-based selection was applied; all breast cancer cases were included in the analysis. Our aim was to analyse ASRWs by examining small districts within each CR region. The level of geographic units to be examined was a fundamental choice in the project's development. We needed to choose units of geographic analysis that could be compared between countries and be replicated in other parts of Europe. Municipalities were too heterogenous for our purpose, with populations ranging from a few hundred to several million. In Spain, we opted to use districts for which a national definition was available. In Greece and Italy we used zip code areas, given the lack of geographic units comparable to the Spanish districts; and in Ukraine we used Raions (districts) as unit of geographical analysis. Both zip code areas and districts divide large cities into subsections, enabling us to consider areas with comparable population sizes and square kilometres at a more localised level than provinces. Since the stability of ASRWs cannot be guaranteed in such small areas, we calculated ASRWs by aggregating data from multiple years (ranging from 2 to 12 years) based on the availability of data from CRs. We used the term "provinces" for second level administrative units within regions and above municipalities.

2.2 Data management and statistical analysis

ELISAH Task 3.2 was designed as an individual-level cohort study focusing on women diagnosed with breast cancer. For the purpose of the study, ELISAH researchers identified the district or zip code areas (hereafter referred to as districts) where these women resided at the time of their diagnosis. This information was included in the working database to

calculate the district-specific ASRWs. We defined person-years as the sum of the population counts by age group in the district under analysis. We used files detailing population counts by age group along with digital maps from DigiAtlas [9] for Italy, Greece and Ukraine, and from INA [10] for Spain.

We estimated the ASRW for each district per 100,000 individuals using the direct method standardised to the World Standard Population. This involved calculating the weighted average of the age-specific rates, with the weights derived from the World Standard Population expressed per 100,000 person-years. Poisson confidence intervals are provided along with their corresponding ASRWs. The variation in ASRWs within a province was measured using the ASRW decile ratio (p_{90}/p_{10}) as a dispersion metric. We chose this metric because it effectively highlights the gap between the top and bottom of a distribution. It is calculated by the following procedure: a) ranking of the districts according to their ASRWs; b) computation of the overall ASRW for the 10% of the population living in districts with the highest ASRWs; c) computation of the overall ASRW for the 10% of the population living in districts with the lowest ASRWs; d) computation of the ratio between the two ASRWs. We created maps that divide the areas into three parts: the lowest decile (coloured green), the highest decile (coloured red) and the area between the two extremes (coloured yellow). We assessed the exposure of the women in the cohort to land cover and land use by means of the CORINE Land Cover digital maps (shapefiles) provided by the EU Copernicus programme. These were the steps we followed:

- a) selection of districts where women of the cohort resided at the time of diagnosis
- b) intersection of the district shapefile with the CORINE shapefile
- c) computation of the percentage of forest, agricultural land, grassland and urban settlements (km^2) within any district relative to the total area of the district.

Negative binomial regression models were used to assess the incidence rate ratios and 95% confidence intervals for every CORINE category.

2.3 Results

We collected 105,470 cases from participating CRs. In Table 1, we present a description of the geographic areas involved, the years for which incidence data were available, the average population size, the computed person-years, the number of cases, the size of the geographic area in km^2 , the population size by district, and the crude and standardised rates along with their confidence intervals. The average population in different districts of Ukraine varied significantly, ranging from 10,939 to 120,976. In Italy the range was from 74 women to 108,646. The districts in Spain were smaller and numerically more homogeneous than

those in Ukraine and Italy, with populations ranging from 14 to 1,917 women. The mean district size was 13,912 km² in Ukraine, 3,808 km² in Greece, 2,865 km² in Italy, and 5,665 km² in Spain. In Table 2 we present the computation of the median ASRWs, the mean ASRWs for the lower and upper deciles of the ASRW distribution, and the Inequality Index by province for participating CRs. The median ASRW by province varied significantly between countries, ranging from 68.83 to 124.92 in Italy and from 50.69 to 71.48 in Spain. This highlights a substantial difference between the two countries, as well as a greater variation in ASRWs within Italy compared to Spain. In Ukraine, the ASRW varied from 17.62 to 58.93. In Greece, we collected samples by district, which also exhibited significant variations, despite some sampling uncertainty. When examining within-province differences (which we could only do for Italy and Spain, as we had data on multiple provinces in those countries) and measuring them by the Inequality Index, we observed significant variations: from 1.40 to 8.50 in Italy and from 3.85 to 5.28 in Spain. Across the broad area analysed by ELISAH, the Inequality Index ranged from 1.49 to 8.49. The lowest value of 1.49 is significant because it indicates that the area with the highest ASRW experienced a nearly 50% increase compared to the area with the lowest ASRW. These results highlight that the province level exhibits the highest level of geographic variation of all geographic levels we analysed in the ELISAH project. In Figures 1a-7a we present Inequality Index map maps of Lazio, Veneto, Paìs Vasco, Girona, Granada, Tarragona and Ivano Frankivsk, that illustrate the marked geographic blending between the three levels of inequality index. In figures 1b-7b we present maps of land cover/use of the same provinces. The incidence rate ratio calculated using the negative binomial model indicated a 0.4% increase in ASRWs for every 1% rise in artificial surfaces, with a confidence interval ranging from 0.2 to 0.6, indicating statistical significance.

2.4 Discussion

According to the results from WP2 of the ELISAH project, Belgium had the highest breast cancer incidence in the 2013-2017 period, with 188.1 cases per 100,000 people, while Turkey recorded the lowest incidence at 69.9 cases per 100,000 people. At the level of individual registries, the highest incidence was estimated to be in the Lille-Métropole region of France, at 188.7 cases per 100,000 people, while the lowest was found in Erzurum, Turkey, at 48.1 cases per 100,000. The results presented here show that the ASRW variations within provinces are at least comparable to the differences between countries, and in some cases they are even greater. To our knowledge, no study has performed international comparisons of ASRW variations between districts. Some studies have analysed

between-district disparities in cancer mortality in one country [11]. A previous study analysed all-cancer ASRW variations within countries compared to those between countries, showing that the former were greater than the latter. Only one study, conducted in California, has examined the association between land use and breast cancer incidence, reporting results similar to ours.

2.5 Further development

2.5.1 Link of gap analyses to action in the ELISAH project

A primary objective of the ELISAH project is to propose an integrated vision of breast cancer prevention by connecting scientific knowledge to population health and presenting a clear plan that aligns the gap analysis outlined in this document with actionable interventions. The results of this study are linked to the analysis and actions we are conducting for WP6 – Urban Environment and Breast Cancer Risk – in which we examine the urban assets of twelve European cities in relation to breast cancer prevention and develop action proposals in three of these cities. The results we have presented reinforce our goal of proposing actions at the neighbourhood level for WP6 and are valuable for optimal planning.

2.5.2 Generalisability of results

These results are generalisable to cancers other than those of the breast due to the shared risk factors between breast and other types of cancer. The generalisability of the results to other diseases and outcomes is supported by local studies with findings that were similar to ours. For example, a study on general mortality by district in the city of Genoa, Italy, illustrates this point [12].

2.5.3 Long-term sustainability of the project

This project was developed using routinely collected data from population-based cancer registries that opted to participate, as well as the publicly available CORINE-Copernicus database on land cover and use in Europe. We also utilised the publicly available dataset from the Instituto Nacional de Estadística to identify geographic districts in Spain. Thanks to the availability of these information sources it will be feasible to continue the project beyond the HADEA funding period.

3. CONCLUSIONS

The results of this study highlight significant within-province variations, which are more pronounced than those observed at both the international and national levels, as well as between counties. These variations demonstrate geographic inequalities in the distribution of risk factors, which can change rapidly in locations susceptible to public health interventions, paving the way for action and interventions to address specific inequalities.

We suggest the following actions:

- At the EU and national policy levels, policymakers should establish recommendations for public health authorities to provide cancer rate data to population, citizen and patient associations at the district level, in municipalities with small populations ($\leq 10,000$ persons), and within city neighbourhoods.
- Due to the significant geographic variations in cancer rates, it is crucial for municipalities to incorporate actions against more easily addressable risk factors into their policy plans.
- Citizen, patient and scientific associations should request the dissemination of data on cancer rates at the district level.
- Land use is linked to breast cancer incidence: areas with a greater presence of artificial surfaces have higher cancer incidence rates. We recommend that EU and national parliaments and governments limit the expansion of this type of surface.

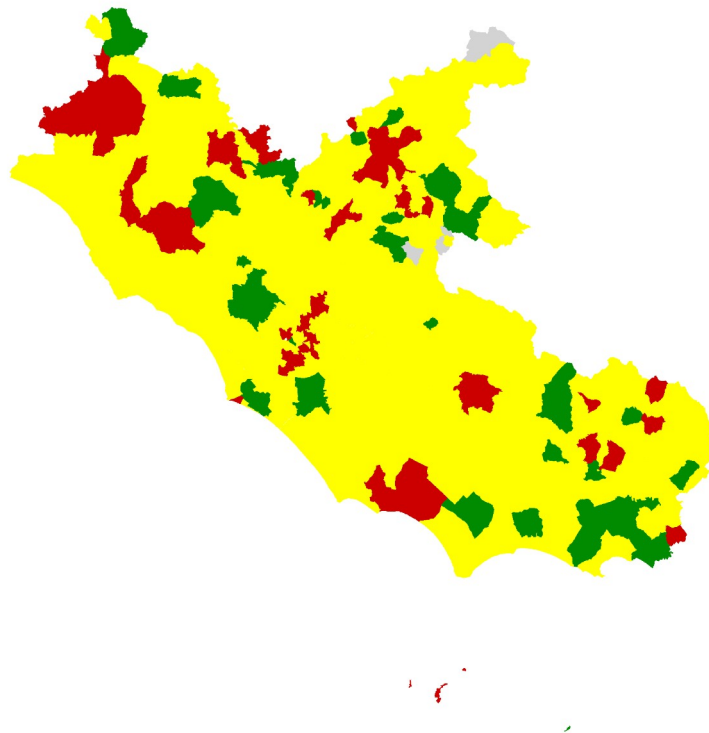
Country	Registry	Province	Year_inc	Population (women)	Person-years	Cases	Km ²	crude.rate	adj.rate	lci	uci	mean	District f_pop min	max
Italy	Lazio	Frosinone Latina Rieti Roma Viterbo	2013-2019	2938269	20567883	33244		161.63	86.49	85.42	87.57			
			7	234572	1642004	2311	3247	140.74	78.31	74.65	82.21	5864	721	22395
			7	285141	1995987	2405	2259	120.49	67.56	64.53	70.78	13578	305	65085
			7	74886	524202	864	2750	161.39	80.77	74.51	87.92	2080	177	23285
			7	2188012	15316084	25927	5367	169.28	90.28	89.02	91.56	16328	423	108646
			7	155658	1089606	1737	3616	159.42	82.94	78.43	87.85	5765	1151	33979
	Veneto	Belluno Padova Rovigo Treviso Venezia Verona Vicenza	2014-2021	2458874	19670992	39420		200.4	99.62	98.47	100.8			
			8	100579	804632	1739	3610	216.12	101.61	95.83	107.95	3725	554	18444
			8	473633	3789064	7617	2144	201.03	101.09	98.44	103.83	8028	895	89365
			8	115109	920872	2108	1824	228.91	106.08	100.59	112.07	4263	583	25671
			8	442941	3543528	7137	2480	201.41	102.41	99.65	105.27	9040	1106	44111
Spain	Andalucia	Granada	2010-2021											
			11 (2010-2020)	468653	5155183	5194	12011	100.75	62.9	61.05	64.82	2147	64	30500
			12 (2010-2021)	391572	4698864	5510	5937	117.26	69.22	67.23	71.28	1499	40	18874
			10 (2010-2019)	411882	4118820	5283	6165	128.26	79.42	77.08	81.85	1661	14	21011
			10 (2010-2019)	169186	1691860	2186	5958	129.21	77.64	73.99	81.53	2807	61	31255
	Cataluña	Girona Tarragona	10 (2010-2019)	596445	5964450	8065	2164	135.22	73.95	72.12	75.85	3400	77	30431
			10 (2010-2019)	371015	3710150	5079	1760	136.89	77.61	75.22	80.1	3032	52	22259
			10 (2010-2019)	169186	1691860	2186	5958	129.21	77.64	73.99	81.53	2807	61	31255
			10 (2010-2019)	596445	5964450	8065	2164	135.22	73.95	72.12	75.85	3400	77	30431
			10 (2010-2019)	371015	3710150	5079	1760	136.89	77.61	75.22	80.1	3032	52	22259
Ukraine	Ivano-Frankiv's'ka Oblast		2018-2020											
			3	742854	2228562	1107	13912	49.67	34.4	32.3	36.65	39098	10939	120976
			2019-2025											
Greece	Attica		7	1835833	12850829	382	3808	2.97	2.39	2.14	2.69	6119	15	26010

Table 1. Cohort description

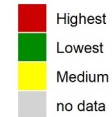
Country	Registry	Province	Inequality Index	MIN Adj.rate	MAX Adj.rate
Italy	Lazio	Frosinone	1.86	55.83	103.9
		Latina	1.45	52.71	76.43
		Rieti	2.37	41.05	97.37
		Roma	8.38	27.99	234.69
		Viterbo	1.56	63.66	99.14
	Veneto	Venezia	2.04	72.5	148.08
		Treviso	1.42	84.6	120.32
		Belluno	1.6	76.35	122.49
		Padova	1.75	79.61	139.34
		Vicenza	1.51	74.14	112.14
		Verona	2.88	55.04	158.72
		Rovigo	1.85	76.64	141.87
Spain	Andalucía	Granada	3.12	30.41	95.03
	Cataluña	Girona	2.29	42.34	96.91
		Tarragona	2.56	50.61	129.49
	País Vasco	Araba/Álava	1.76	51.11	89.8
		Bizkaia	2.06	45.97	94.64
		Gipuzkoa	2.05	49.61	101.68
Ukraine	Ivano-Frankivs'ka Oblast'		3.34	17.62	58.93
Greece	Attica		6.80	1.14	7.72

Table 2. Inequality index

Italy, Lazio



BREAST CANCER RATES



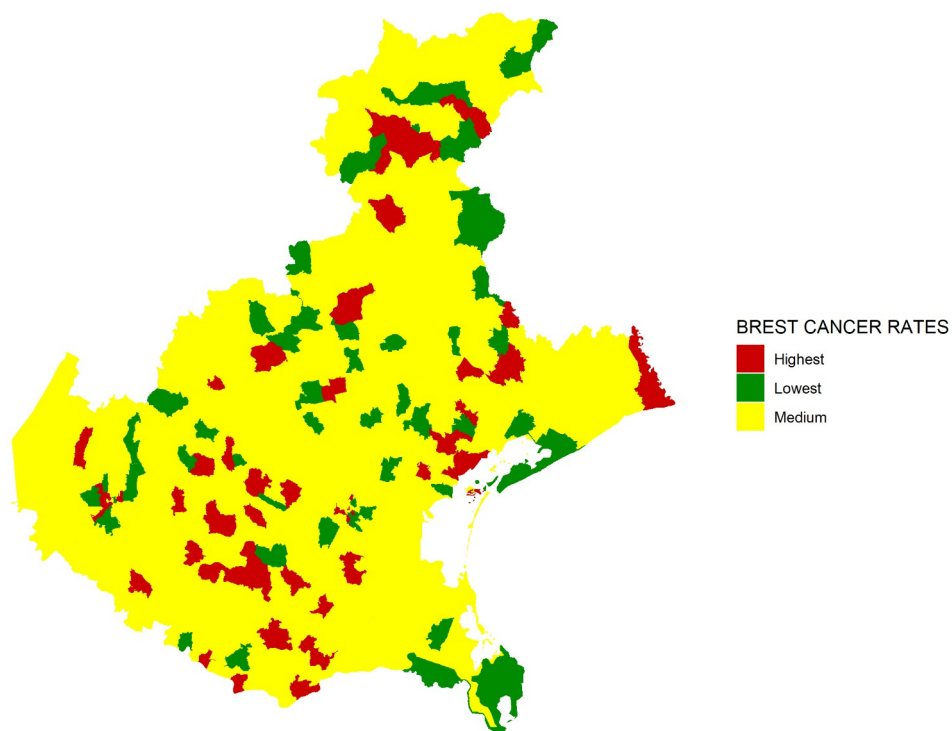
Italy, Lazio



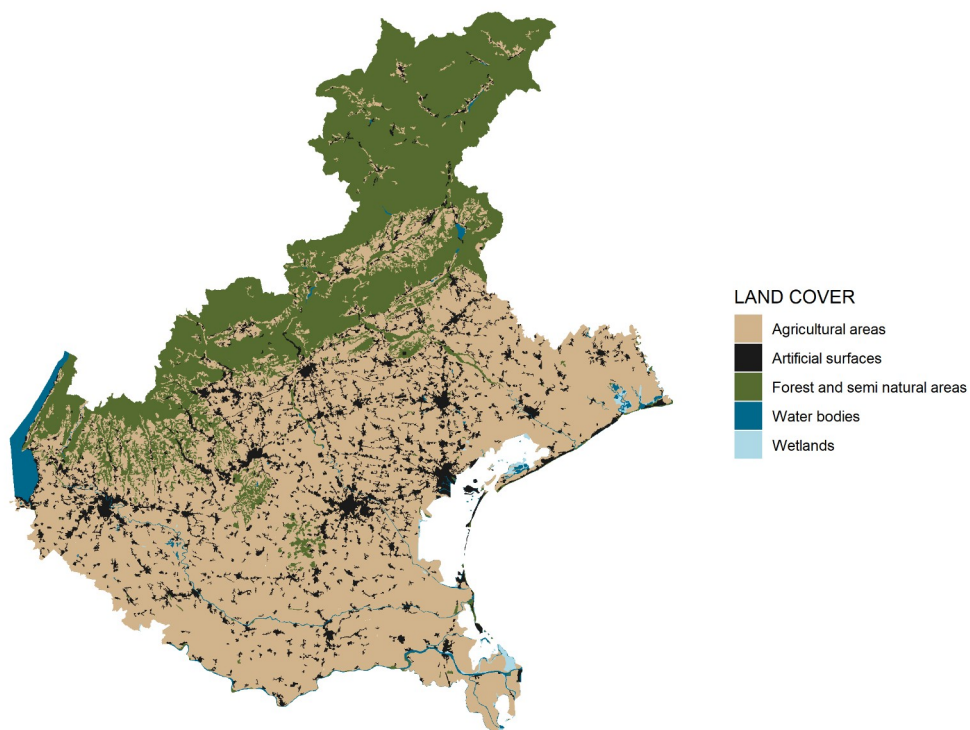
LAND COVER



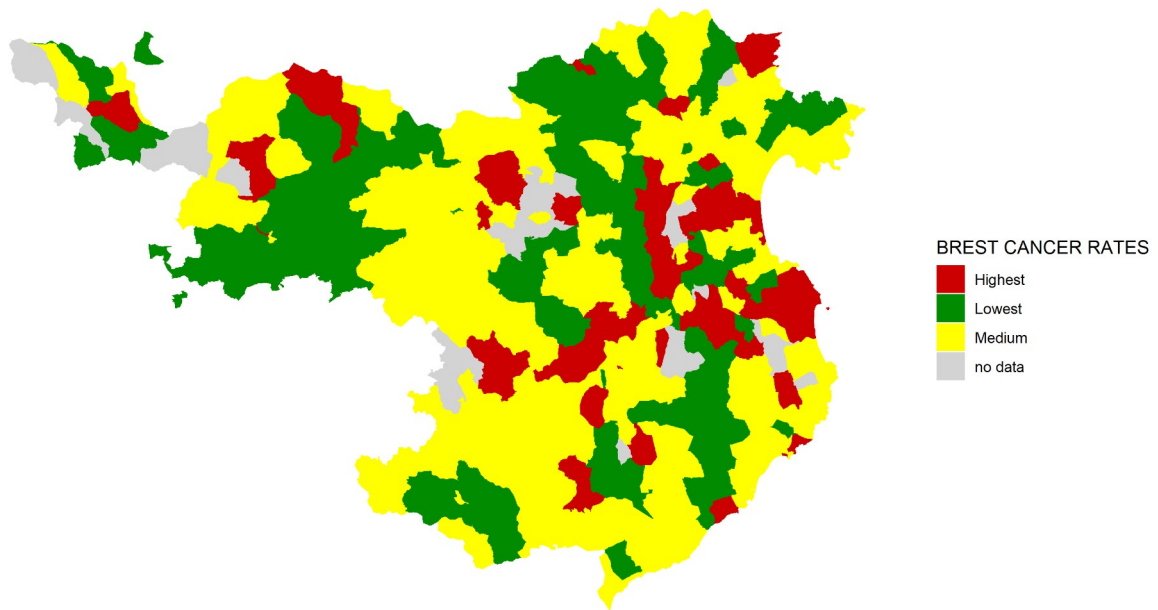
Italy, Veneto



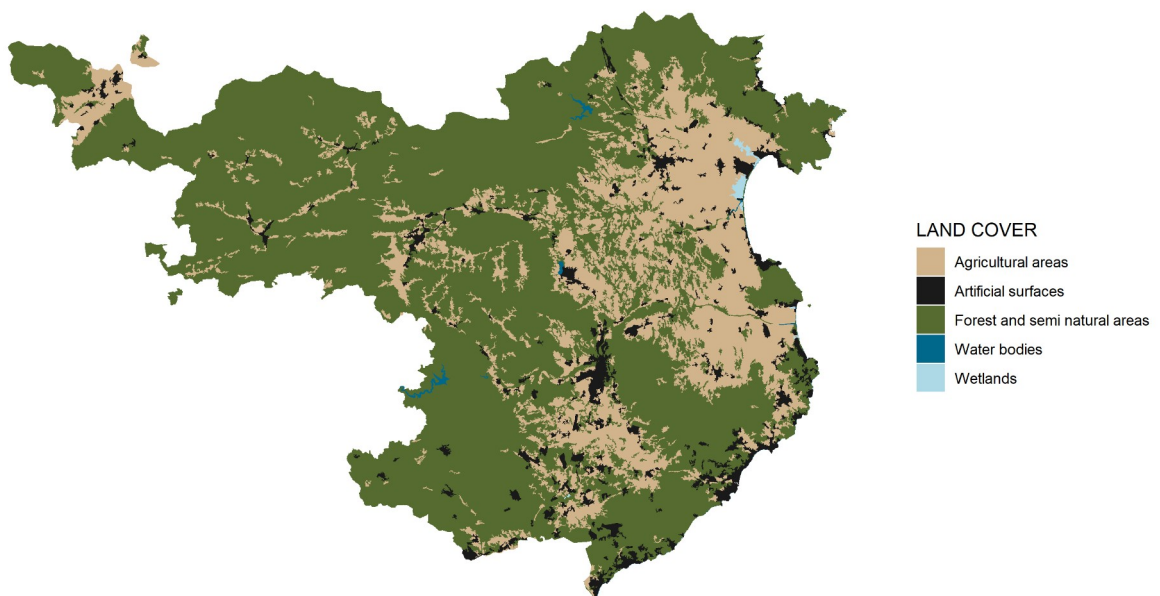
Italy, Veneto



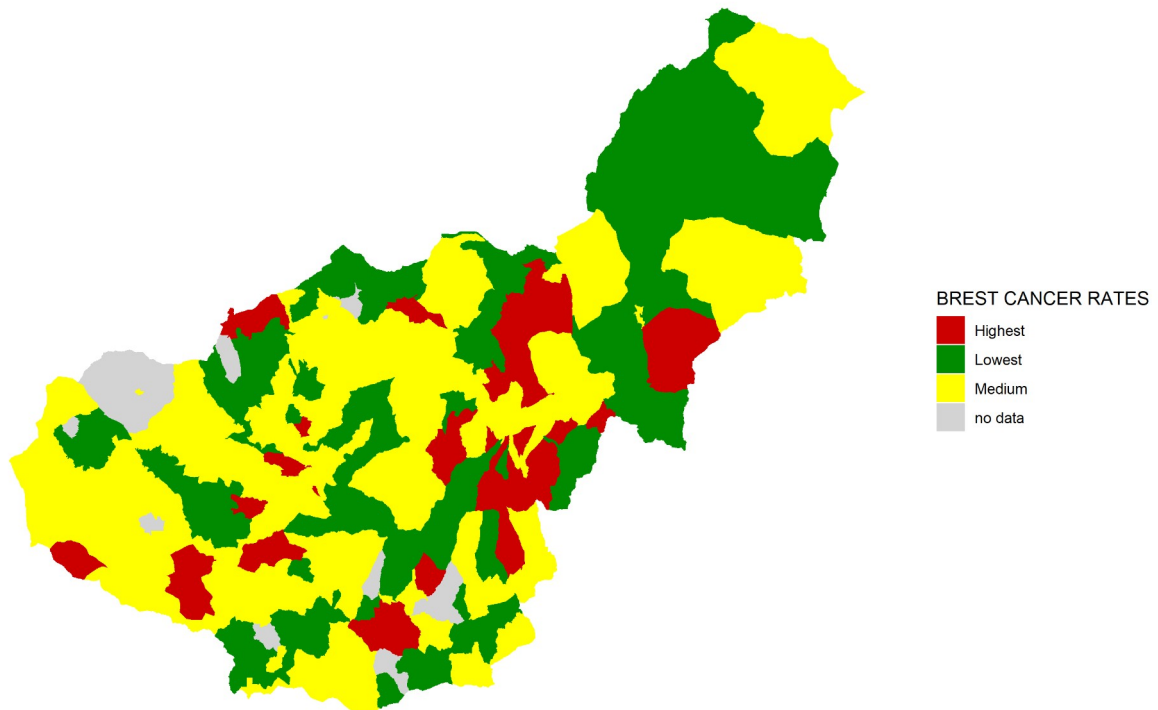
Spain, Girona



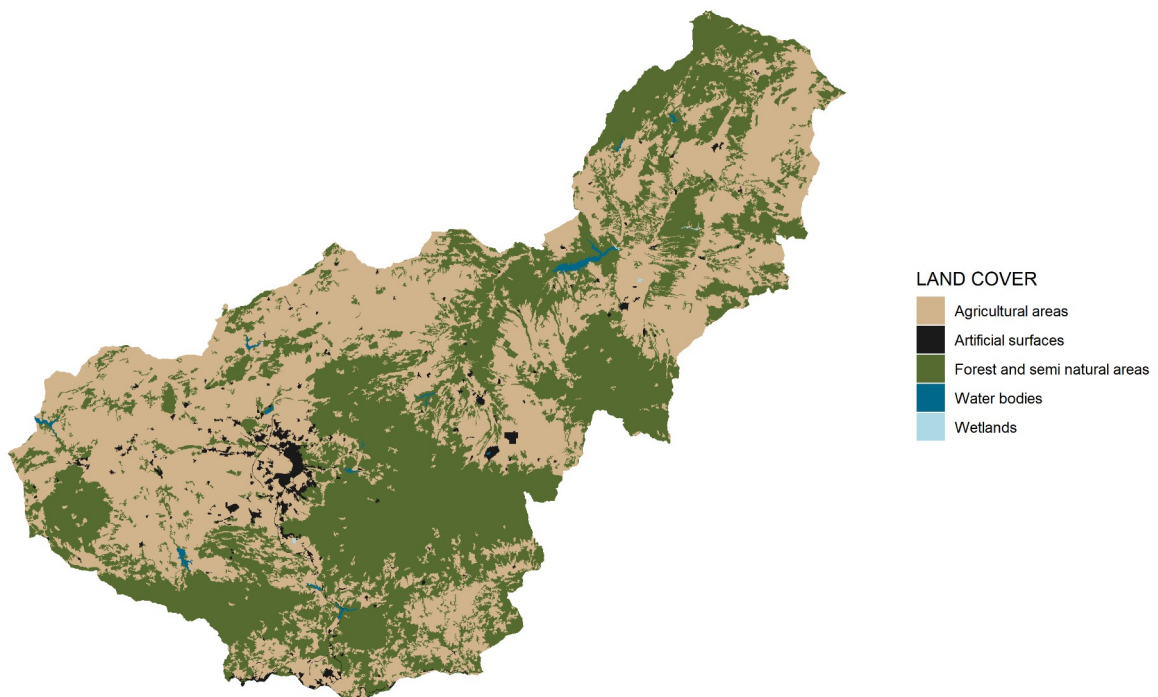
Spain, Girona



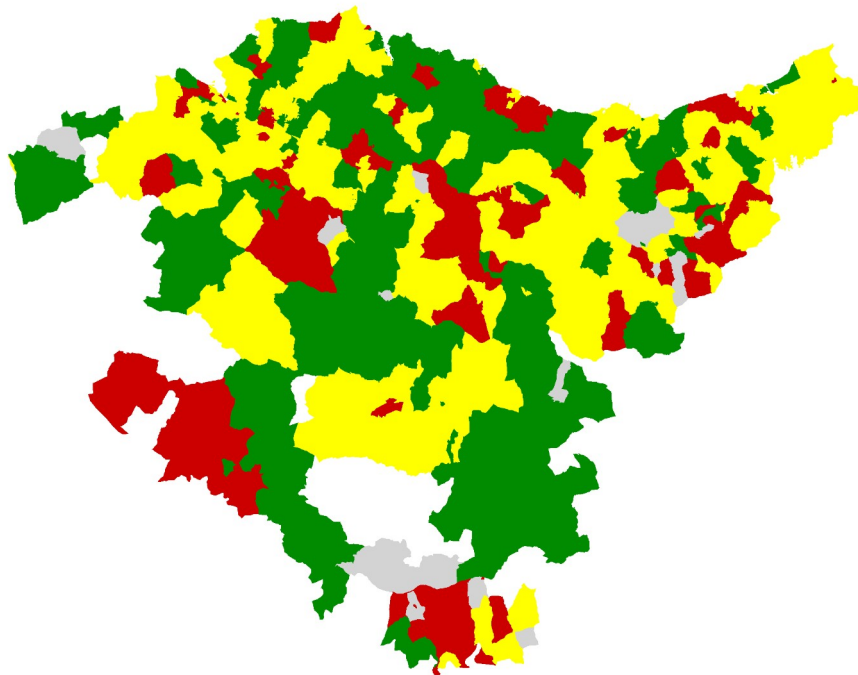
Spain, Granada



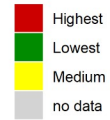
Spain, Granada



Spain, País Vasco



BREST CANCER RATES



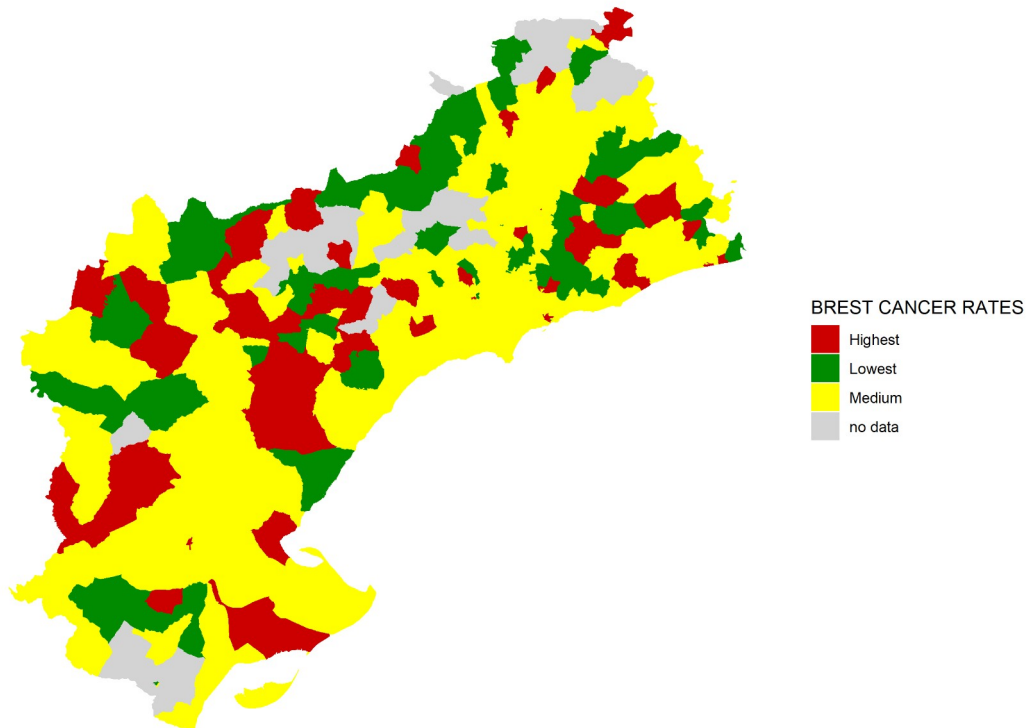
Spain, País Vasco



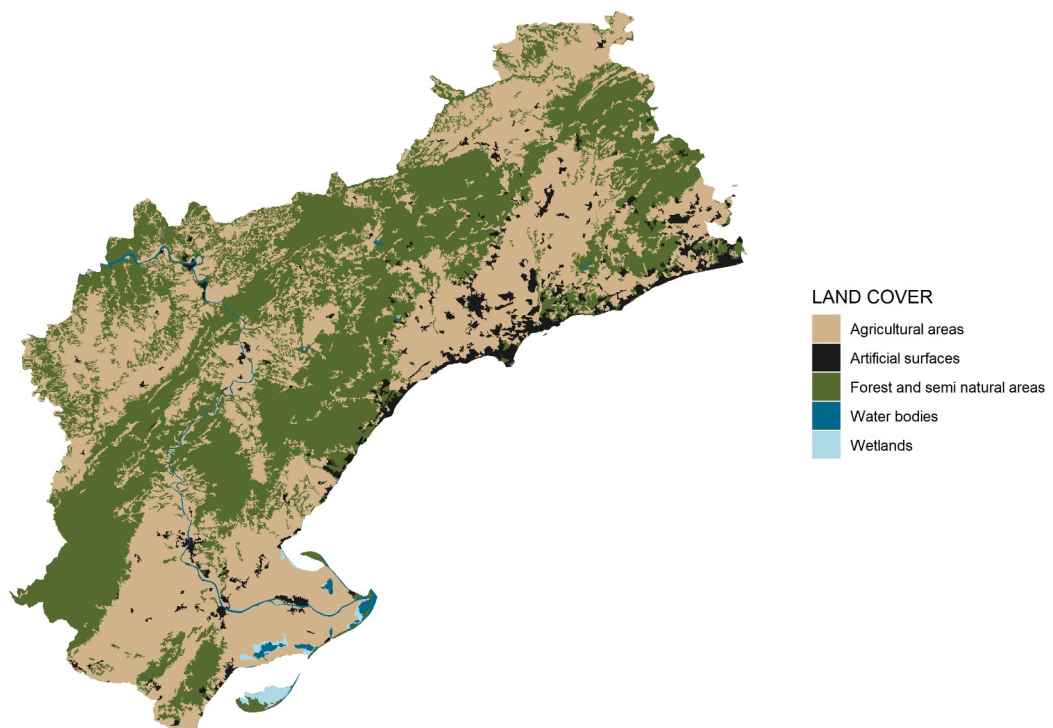
LAND COVER



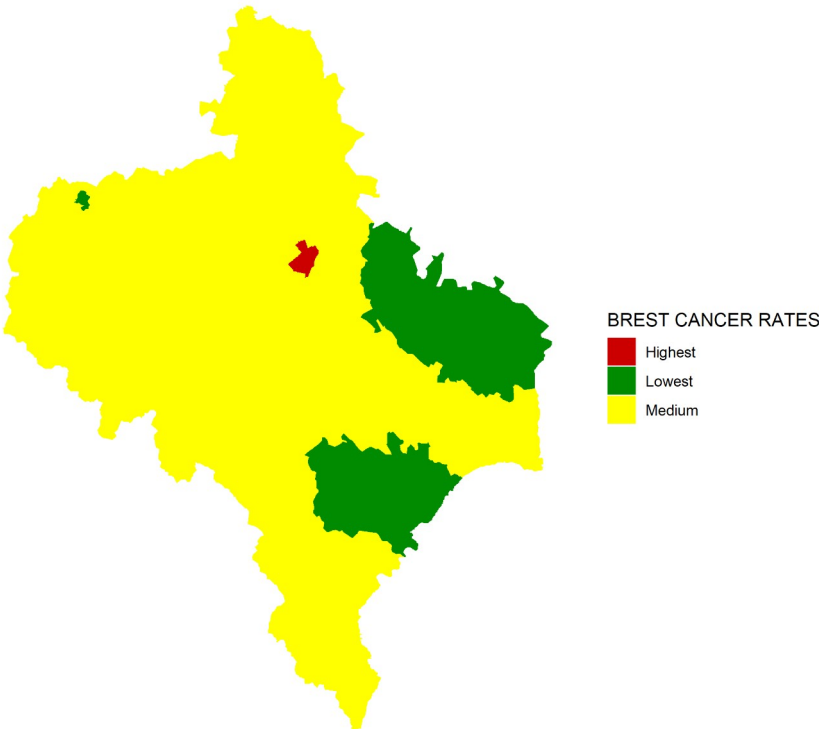
Spain, Tarragona



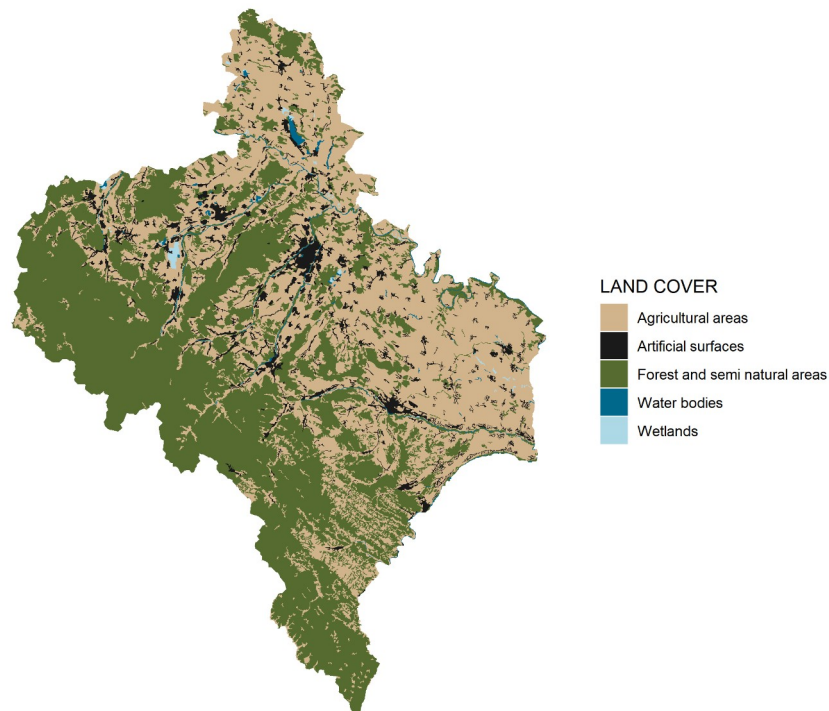
Spain, Tarragona



Ukraine, Ivano-Frankivs'ka oblast'



Ukraine, Ivano-Frankivs'ka oblast'



P

Public health implications and recommendations

Geographic inequalities are, in our view, very important because they serve as a comprehensive indicator of various risk factors that interact synergistically at the local level. For example, a study conducted by Venter et al. [13] revealed significant spatial inequality in exposure to urban nature, air pollution and heat in Oslo. This inequality is directly linked to an increased risk of breast cancer and comorbidities that worsen the prognosis of women diagnosed with the disease. Similarly, socioeconomic status displays significant geographic variations at the district level, as does access to both healthy and unhealthy foods [14]. Geographic inequality studies typically start by analysing the spatial distribution of risk factors, either individually or in combination. We believe that a complementary and useful approach would be to start by analysing the distribution of disease rates, as this may reveal unexpected patterns.

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5. ANNEXES

None