PhD thesis

Spatio-temporal modelling of breast cancer incidence between 2000 and 2021 at sub-national levels in Iran: Bayesian disease mapping

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A thesis submitted to Middlesex University in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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Abstract

While in Iran trends in breast cancer incidence are generally monitored at the national level, little is known about sub-national variation in these trends. This project aims to assess levels and trends (2000-2021) of relative risk of breast cancer incidence and mortality at sub-national levels in Iran and their relation to key socioeconomic dimensions, to understand the full extent of geographical and social inequalities in the country associated with breast cancer morbidity and mortality. Data from the national cancer registry system of the Iranian Ministry of Health have been used, which is gathered on cancer incidence at provincial and district levels by age and sex. Census and Household Expenditure and Income Survey (HEIS) datasets have been then used to extract related covariates. The relative risk of breast cancer incidence was estimated in women aged 30+ years for all 316 districts in Iran from 2000 to 2010 using a Bayesian spatio-temporal model. Then, I've propagated uncertainty from the spatio-temporal model into the prediction model for the years from 2011 to 2021. The national relative risk of breast cancer incidence in Iran increased from 0.21 (95% credible interval (CrI): 0.19, 0.22) in 2000 to 0.66 (0.63, 0.68) in 2010 and 1.23 (1.18, 1.28) in 2021. The relative risk of breast cancer incidence was highest in Yazd (1.96 [1.63, 2.33]), Shiraz (1.90 [1.72, 2.09]) and Shemiranat (1.90 [1.12, 2.91]) in 2010 and Tehran (3.99 [3.86, 4.33]), Bushehr (3.89 [3.07, 4.77]) and Abadan (3.67 [2.99, 4.39]) in 2021. In contrast, Savojbolagh, Saravan and Nikshahr were found to have the lowest relative risks in both 2010 (0.11 [0.05, 0.20], 0.17 [0.08, 0.30] and 0.20 [0.09, 0.36], respectively) and 2021 (0.19 [0.10, 0.33], 0.34 [0.18, 0.54] and 0.35 [0.17, 0.62], respectively). The relative risk of breast cancer incidence was 60% higher across districts in the highest YOS quintile (average years of schooling: 3.9) than those in the lowest YOS quintile (average years of schooling: 2.2; relative index of inequality: 1.6). Results show that the relative risk of breast cancer incidence has increased over time (2000-2021) at national and sub-national levels in Iran. Breast cancer is one of the few diseases with a positive education gradient, with higher relative risk of breast cancer incidence among higher- compared to lower-educated women, probably due to better awareness of diagnostic approaches and access to those. While social inequalities are a major barrier to reducing the prevalence and incidence of breast cancer, it is important to track the progress made at the district level based on the characteristics of specific policies aimed at

reducing health inequalities. A scaling-up in the quality of healthcare services, national and sub-national policies addressing prevention and treatment, and more specialised training programs in women's health are needed.

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List of abbreviations

Abbreviation	Definition
ACS	American Cancer Society
AIC	Akaike Information Criterion
ASIR	Age-Standardised Incidence Rate
ASMR	Age-Standardised Mortality Rate
BGR	Brooks Gelman Rubin
BMI	Body-Mass Index
BSE	Breast Self-Examination
BYM	Besag, York and Molli
CBE	Clinical Breast Examination
CBT	Cognitive-Behavioural Therapy
DALY	Disability-Adjusted Life Years
DIC	Deviance Information Criterion
DRS	Death Registry System
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GNI	Gross National Income
GP	General Physician
HDI	Human Development Index
HEIS	Household Expenditure and Income Survey
HRT	Hormone Replacement Therapy
IBM	Incidence-Based Mortality
ICAR	Intrinsic Conditional Auto-Regressive
ICU	Intensive Care Unit
MCMC	Markov Chain Monte Carlo
MIR	Mortality to Incidence Ratio
MRI	Magnetic Resonance Imaging
NCDRC	Non-Communicable Disease Research Centre
NCR	National Cancer Registry
PCA	Principal Components Analysis
QoL	Quality of Life
SMR	Standardized Morbidity/Mortality Ratio
SSI	Social Security Insurance
WHO	World Health Organization
WI	Wealth Index
YLD	Years Lived with Disability
YLL	Years of Life Lost
YOS	Years of Schooling

Declaration of originality

I, at this moment, declare that the work in this thesis is my original research and that I have appropriately cited any work that is not my own.

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1 Introduction

1.1 Overview

As the leading cause of cancer-related Disability-Adjusted Life Years (DALYs), deaths, and Years of Life Lost (YLLs) globally in 2019, female breast cancer accounted for 20.3 million (95% Credible Interval (CrI): 18.7, 21.9 million) of 20.6 million (19.0, 22.2 million) total breast cancer-related DALYs (both sexes combined) in 2019, of which 93.3% (91.1%, 95.2%) came from YLLs and 6.7% (4.8%, 8.9%) from Years Lived with Disability (YLDs) (Kocarnik *et al.*, 2022). Globally, 689,000 (635,000, 740,000) of 701,000 (647,000, 752,000) breast cancer deaths and 1.98 million (1.81, 2.15 million) of 2.00 million (1.83, 2.17 million) breast cancer new cases occurred in females in 2019 (Kocarnik *et al.*, 2022). World Health Organization (WHO) breast cancer initiatives are valued efforts toward reducing the global breast cancer burden in combination with national-level cancer control planning (Anderson *et al.*, 2021). Still, international and local efforts require comprehensive assessments of breast cancer, which may be sparse or unavailable in some countries (Bray *et al.*, 2017).

The current project results suggest that the national and sub-national level of breast cancer in Iran is substantial and that there is a high level of heterogeneity across socioeconomic statuses; it also provides inclusive and comparable estimates that can potentially inform stakeholders' efforts toward the design and implementation of breast cancer control programmes in the country.

1.2 Background

Cancers are a crucial contributor to the burden of disease worldwide, and projections forecast that the global burden of cancer will continue to grow for at least the next two decades (Foreman *et al.*, 2018; Bray *et al.*, 2012). Recent estimates suggest 28.4 million cases in 2040, a 47% rise from 2020, driven mainly by a larger increase in the low and middle-income (64% to 95%) versus high-income (32% to 56%) countries due to demographic changes (Sung *et al.*, 2021). However, this may be further exacerbated by increasing risk factors associated with globalisation and a growing economy (Sung *et al.*, 2021). Accelerating the pace of cancer progress is crucial, now more than ever, given the ongoing

COVID-19 pandemic, which has led to interruptions in cancer diagnosis and treatment worldwide (Kuderer *et al.,* 2020; Maringe *et al.,* 2020; Sato *et al.,* 2021). Cancer accounted for 10.0 million (9.36, 10.6) deaths and 23.6 million (22.2, 24.9) new cases globally in 2019, according to the Global Burden of Disease (GBD) 2019 study (Kocarnik *et al.,* 2021). Breast cancer has been the leading cause of global cancer incidence in 2020 among women, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases (Sung *et al.,* 2021), making it one of the most severe burdensome cancer globally (James *et al.,* 2018; Giordano, 2018) even in terms of economic burden (Alefan *et al.,* 2020). Among women, breast cancer accounts for 1 in 4 cancer cases and 1 in 6 cancer deaths, ranking first for incidence in most countries (159 of 185 countries) and mortality in 110 countries (Sung *et al.,* 2021).

Several studies have considered the geographical distribution of breast cancer incidence and mortality (Bab *et al.,* 2019; Ghoncheh *et al.,* 2015; Ferlay *et al.,* 2015; Forouzanfar *et al.,* 2011; Bray *et al.,* 2004). Many new female breast cancer cases are now taking place in low and middle-income countries, with 60% of cases and 75% of deaths occurring in deprived societies (Chagpar and Coccia, 2019). Moreover, while the age-standardised female breast cancer mortality rate has declined over the past three decades in many high-income countries, this is not the case in low and middle-income countries (Anderson *et al.,* 2018; Azamjah *et al.,* 2019).

Despite advances in early detection and treatment for numerous cancers, socioeconomic inequalities persist in cancer incidence and mortality (Clegg *et al.,* 2002). Many high-income countries and regions have a higher incidence rate of breast cancer (Chagpar and Coccia, 2019; Engmann *et al.,* 2017; Coccia, 2013), which is likely due to better detection, with women in poor countries having a higher burden of breast cancer mortality, because of a series of barriers to breast cancer care such as accessing early detection programmes, receiving timely diagnosis and appropriate treatment (Bellanger *et al.,* 2018; Duport *et al.,* 2008; Coleman *et al.,* 2008). The lower breast cancer 5-year survival in low and middle-income countries (40-60%) compared to 80% in high-income countries can be attributed to advanced-stage presentation and poor access to systemic therapy (Coleman *et al.,* 2008). Insufficient healthcare resources in low and middle-income countries need to be used strategically to ensure timely, beneficial access to health care (Birnbaum *et al.,* 2018). Consequently, the high levels of geographical

heterogeneity in breast cancer incidence and mortality are partly explained by inequalities in implementation and access to screening and treatment (Tfayli *et al.*, 2010; Birnbaum *et al.*, 2018).

While breast cancer incidence and mortality trends are generally monitored at the national level (Bray *et al.*, 2018; Roux *et al.*, 2001), little is known about the distribution and variation in sub-national levels. Considering geographical variability in breast cancer incidence across small areas and over time is essential to facilitate appropriate sub-national allocation of resources to increase breast cancer screening and achieve better outcomes (Ji *et al.*, 2020; Schootman and Sun, 2004). Better geographic resource allocation, especially in low and middle-income settings, where resources are scarce, could maximise the impact of screening interventions and possibly reduce geographic variability in mortality (Schootman and Sun, 2004).

Cancers are the third most common cause of death in Iran after cardiovascular diseases and motor vehicle accidents (Bab *et al.*, 2019). Breast cancer is the most common cancer in women and the fifth most common cause of death among Iranian women (Farhood *et al.*, 2018). In 2019, the age-standardised breast cancer incidence rate was 34.1 per 100,000 women (30.7, 37.9), while the age-standardised mortality rate was 11.9 deaths per 100,000 women (10.8, 13.1), with a percentage change of 71.2% (27.9%, 118.3%) and 15.5% (-3.7%, 31.7%) respectively between 1990 and 2019 (Global Burden of Disease, 2019). Current trends highlight the need for robust estimates of the geographical and temporal patterns to support effective public health policies in a country characterised by insufficient financial resources and a lack of continuity of financing (Tabrizi *et al.*, 2017).

Population-based cancer registries are the first and undeniably essential source of information that can estimate cancer incidence and are the most robust basis for health policymaking and scientific research (Modirian *et al.*, 2014). Cancer registries also help public health professionals to program and implement policies to control the burden of cancers more effectively. In Iran, the Ministry of Health is the only entity that gathers data on cancer incidence (Modirian *et al.*, 2014). Here, breast cancer registered incidence and mortality cases in Iran for 11 years have been used to estimate national and sub-national levels (Appendix Table 1) of breast cancer incidence and mortality.

1.3 Bayesian disease mapping approach

Statistics provide essential inputs for evidence-based policy for social, economic, and environmental priorities (Asian Development Bank, 2020). In 2000, the Millennium Development Goals highlighted the critical role of statistics and data in tackling international development priorities (Asian Development Bank, 2020). Since then, national and international statistical systems have redoubled their efforts to use data to monitor development targets and ensure high-quality, accessible, timely, and reliable policy inputs (Asian Development Bank, 2020). Nowadays, due to the rising burden of non-communicable diseases worldwide, it is crucial to apply appropriate statistical methods and reliable surveillance strategies to detect trends and outline emerging non-communicable disease risk factors (Blangiardo *et al.*, 2020).

Bayesian disease mapping as a conservative approach with high specificity even in situations with scarce data, represents a statistical outline for modelling and mapping the geographic variation of disease rates or risks, considering the spatial structure and uncertainty in the data (Lawson, 2018; Waller and Carlin, 2010; Richardson *et al*., 2004). The Bayesian approach allows for the incorporation of prior knowledge, such as disease patterns in neighbouring regions, into the analysis. This information can be used to standardise the estimates and to provide more stable and accurate results, especially in areas with limited data. The models can also incorporate covariate information, such as environmental or demographic variables, to understand the factors that contribute to the spatial variation in disease estimations (Waller and Carlin, 2010; Richardson *et al*., 2004). The key strength of Bayesian disease mapping is the ability to provide measures of uncertainty for the disease rate or risk estimates, allowing for a more complete and transparent representation of the results (Waller and Carlin, 2010). This is particularly important for decision-making purposes, where it is necessary to know the level of confidence in the estimates (Waller and Carlin, 2010).

Bayesian disease mapping in early studies was typically performed on a large geographic scale with international or regional comparisons. Recently, the availability of local geographically health data has provided the opportunity of spatial analysis of a small geographic scale (Piel and Cockings, 2020; Hodgson *et al.*, 2020; Elliott *et al*. 2000). Better data availability can widen the scope and utility of

small-area studies. It can also lead to greater complexity, including choosing the optimal study area size and extent, the duration of study periods, and the range of covariates and confounders to be considered (Piel *et al.*, 2020). The lack of financial resources probably makes comprehensive data sources (e.g. death/cancer registries) infeasible over an entire country (Diggle and Giorgi, 2016). The challenge, therefore, in disease mapping is how best to use innovative approaches that take advantage of additional information to overcome data sparsity due to evidence of overdispersion of the counts with respect to the Poisson model as well as spatial patterns demonstrating some dependence between the neighbouring areas (Torabi, 2019; Cramb *et al*., 2018; Richardson *et al*., 2004).

Overall, Bayesian disease mapping has become an important tool for epidemiology, public health, and environmental health. It provides a flexible and powerful framework for understanding the patterns and risk factors of diseases at a regional or local level and can be used to inform health policy and resource allocation decisions (Richardson *et al*., 2004).

1.4 Research aims

This thesis assesses relative risk of breast cancer incidence and mortality at national and sub-national levels in relation to key socioeconomic dimensions to understand the full extent of geographical and social inequalities in Iran associated with breast cancer morbidity and mortality.

Hence, the main objectives of the completed analyses were to:

1. Estimate relative risk of breast cancer incidence and mortality at the province level in Iran from 2000 to 2010
2. Assess the association between relative risk of breast cancer incidence and mortality and wealth quintiles at the province level
3. Estimate relative risk of breast cancer incidence trends at the district level in Iran between 2000 and 2010
4. Assess the correlation between relative risk of breast cancer incidence and female education quintiles at the district level

5. Estimate predicted relative risk of breast cancer incidence in Iran at the district level from 2011 to 2021
6. Assess the correlation between predicted relative risk of breast cancer incidence and health system components in 2020 at the province level

1.5 Research in context

In this study, MEDLINE (through PubMed) has been searched using the terms ("Breast Neoplasm*" [Title] OR "Breast Tumour*" [Title] OR "Human Mammary Carcinoma*" [Title] OR "Human Mammary Neoplasm*" [Title] OR "Breast Cancer*" [Title] OR "Cancer of the Breast" [Title]) AND ("Iran" [Mesh]) with publication date from 1999 to 2022. In total, 561 articles were identified in PubMed and then screened according to inclusion criteria related to estimates of breast cancer incidence and mortality in Iran using registry data sources at national and sub-national levels. Thirty-one articles met some of the inclusion/exclusion criteria by their titles only. Most research evidence on breast cancer incidence and mortality in Iran has focused on the overall national picture, and in a few cases, research has been conducted on specific provinces/regions (Nasrollahzadeh *et al.,* 2020; Bab *et al.,* 2019; Ahmadi *et al.,* 2018; Zahmatkesh *et al.,* 2016). Apart from my own paper, which is published from the current research (Rahimzadeh *et al.,* 2021), two of these have looked at the province-level estimations in Iran from 2004 to 2008 (Jafari-Koshki *et al.,* 2014) and from 1990 to 2016 (Ataeinia *et al.,* 2021). Still, no study has analysed levels and trends by smaller areas (districts) or looked into geospatial and social inequalities.

1.6 Novelty of study

1) This study is the first comprehensive sub-national level analysis of Iran's breast cancer incidence and mortality. It uses several administrative datasets simultaneously, providing invaluable information for the public health sector in Iran, particularly at the sub-regional level.

2) The study results do not only confirm that breast cancer incidence has increased over time, that wealthier provinces have higher relative risk of breast cancer incidence and this is likely due to higher rates of detection. The study also demonstrates that the downward trend in relative risk of breast cancer

mortality among provinces in the wealthiest quintile is larger than that observed in the poorest quintile, suggesting a likely reversal in coming years. This highlights the urgent need to improve access to diagnosis and treatment to contain breast cancer-associated mortality in the most deprived areas and to reduce existing inequalities. Also, this study provides detailed information about breast cancer incidence in 316 districts in Iran which is beneficial for health policy and resource allocation such as screening and treatment facilities.

3) The study emphasises the need for a comprehensive and practical plan to control breast cancer, considering sub-national variability.

4) The study also highlights the need for an improved cancer registry for breast cancer incidence monitoring to ensure actionable data.

1.7 Structure of the thesis

Background literature detailing the study's rationale has been provided in this chapter, ending with the aims and study novelty. Chapter 2 provides a review of the literature. This chapter discusses key gaps and further work needed to address the topic. Chapter 3 provides comprehensive information on the research strategies that have been used and details of statistical method specifications to achieve the objectives of this PhD work. The results obtained are presented in chapters 4 and 5 and visualised in several sections to address project objectives. Chapter 6 provides the overall discussion about the study outcome, comparison with published studies, conclusions and public health implications.

2 Literature Review

2.1 Overview

This chapter provides an extensive review of the literature specific to breast cancer at global, regional, and national levels. The chapter will describe Iran's sociodemographic and epidemiological profile to allow the reader to become familiar with the country.

2.2 Health system and the health status in Iran

2.2.1 Demographic profile of Iran

Figure 1. Map of Iran by province.

(Iran shapefiles in this thesis have been republished from http://www.openstreetmap.org/ under a CC BY license, authorised by http://www.openstreetmap.org/copyright).

Iran (Figure 1) is a Middle Eastern country, the second largest after Saudi Arabia and the third most populous country after Pakistan and Egypt. Based on archaeological findings, the history of civilisation in the Iranian plateau dates back more than 5000 years old (Lamberg-Karlovsky and Tosi, 1973), while the establishment of a sovereign state in Iran has a history of approximately 3000 years (Achaemenid Empire[1]) (Brosius, 2020; Danaei *et al.,* 2019). Iran is now a country with a population exceeding 80 million (based on the most recent 2016 census), distributed across 31 provinces and largely inhabiting urban regions (Statistical Centre of Iran, 2021). Table 1 illustrates the population of rural areas that decreased in the most recent census (2016), while the urban population increased compared to the 2011 census.

Over the past five decades, the Iranian population has increased nearly four times (from 24 million to 80 million), with an older-age structure (Vos *et al.,* 2016; Mohammadi *et al.,* 2017; Danaei *et al.,* 2019). Figure 2 shows that the life expectancy has increased from ~50 to 80 for both males and females in 45 years (1970 to 2015), while the adult mortality rate has significantly decreased in the same period (Danaei *et al.,* 2019). The capital, Tehran, in 2016 had more than 8.5 million people, more than 16 million if the wider metropolitan area is considered, making it one of the world's largest megacities (ranking 24th in the world). Other major cities such as Mashhad, Karaj, and Isfahan have more than 2 million population (Danaei *et al.,* 2019). Iran is an ethnically diverse country and is categorised as a higher-middle-income country by the World Bank, with a Gross Domestic Product (GDP) exceeding US$454 billion in 2017 and a GDP per capita of approximately $5593 (Danaei *et al.,* 2019).

[1] The Achaemenid Empire, also called the First Persian Empire, was an ancient Iranian empire that was based in Western Asia and founded by Cyrus the Great in 550 BC (Brosius, 2020) .

Table 1. Population changes: 2011 and 2016 (two recent censuses)[1].

Year	Population	Increase in period [2]		Average annual growth (%)
		Absolute	Relative (%)	
Total				
2011	75,149,669	4,653,887	6.6	1.3
2016	79,926,270	4,776,601	6.4	1.2
Urban areas				
2011	53,646,661	5,386,697	11.2	2.1
2016	59,146,847	5,500,186	10.3	2.0
Rural areas				
2011	21,446,783	-684,318	-3.1	-0.6
2016	20,730,625	-716,158	-3.3	-0.7

[1] The unsettled population has been included in the total population.
[2] The absolute and relative increase of the period in 2011 was related to 2006-2011 and in 2016 to the five years of 2011-2016 (Statistical Centre of Iran, 2021).

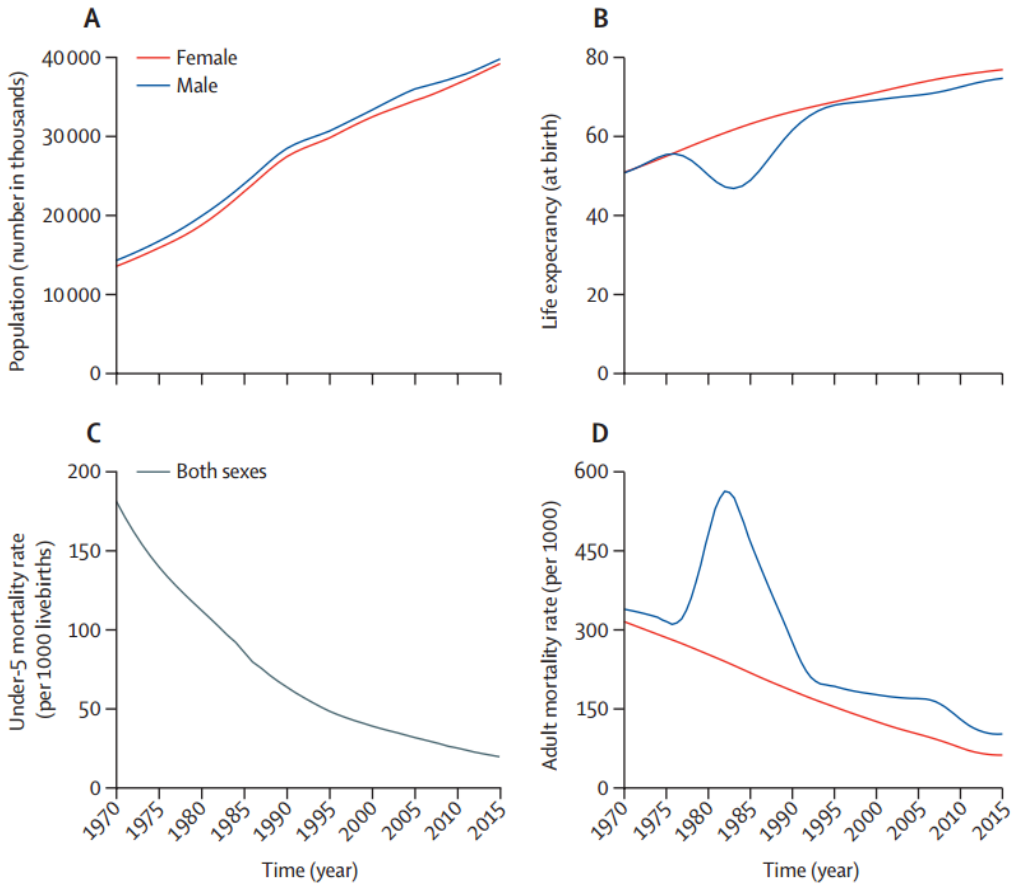


Figure 2. Trends in population size (A), life expectancy at birth (B), under-5 years' mortality (C), and adult mortality (D) in Iran from 1970 to 2015 (Danaei *et al.*, 2019).

2.2.2 Recent censuses

As required by the national legislation, the national population and housing censuses were conducted every ten years between 1956 and 2006 and then every five years until 2016. The department of general statistics undertook the first such census in 1956; the Statistical Centre of Iran took subsequent censuses in 1966, 1976, 1986, 1996, 2006 and 2011. The last census (2016) was the Eighth National Population and Housing Census, conducted on September 24, 2016 (Statistical Centre of Iran, 2021). By providing accurate statistics and information on Iran's population size, structure, and characteristics, this census is an appropriate tool and main source for the planners, policymakers, and officials to design and implement social, economic, and cultural programs. Furthermore, the Census is considered one of the fundamental activities in the national statistical system due to the provision of essential frames for implementing population and household surveys. The demographic structure of the population, the

population size (and annual growth rate) by province and the literacy rate of the population aged six and over for the 2011 and 2016 censuses are presented in Table 2 to Table 4.

Table 2. Population by age groups: 2011 and 2016, two recent censuses (Statistical Centre of Iran, 2021).

Age	**2011**		**2016**	
	Number	**Percent**	**Number**	**Percent**
Total	**75,149,669**	**100.0**	**79,926,270**	**100.0**
0-4	6,232,552	8.29	7,093,004	8.87
5-9	5,657,791	7.53	6,411,277	8.02
10-14	5,671,435	7.55	5,688,384	7.12
15-19	6,607,043	8.79	5,458,997	6.83
20-24	8,414,497	11.20	6,392,879	8.00
25-29	8,672,654	11.54	8,201,133	10.26
30-34	6,971,924	9.28	8,600,913	10.76
35-39	5,571,018	7.41	7,037,598	8.81
40-44	4,906,749	6.53	5,518,307	6.90
45-49	4,030,481	5.36	4,833,123	6.05
50-54	3,527,408	4.69	3,925,971	4.91
55-59	2,680,119	3.57	3,350,593	4.19
60-64	1,862,907	2.48	2,542,573	3.18
65-69	1,343,731	1.79	1,711,464	2.14
70-74	1,119,968	1.49	1,177,625	1.47
75-79	913,531	1.22	886,392	1.11
80 and over	919,539	1.22	1,096,037	1.37
Not stated	46,322	0.06	_	_

Table 3. Population and average annual growth rate by province: 2011 and 2016, two recent censuses (Statistical Centre of Iran, 2021).

Province [1]	2011	2016	Average annual growth rate (percent)
Total	**75,149,669**	**79,926,270**	**1.24**
Alborz	2,412,513	2,712,400	2.37
Ardabil	1,248,488	1,270,420	0.35
Azarbaijan, East	3,724,620	3,909,652	0.97
Azarbaijan, West	3,080,576	3,265,219	1.17
Bushehr	1,032,949	1,163,400	2.41
Chahar Mahal and Bakhtiari	895,263	947,763	1.15
Fars	4,596,658	4,851,274	1.08
Gilan	2,480,874	2,530,696	0.40
Golestan	1,777,014	1,868,819	1.01
Hamadan	1,758,268	1,738,234	-0.23
Hormozgan	1,578,183	1,776,415	2.39
Ilam	557,599	580,158	0.80
Isfahan	4,879,312	5,120,850	0.97
Kerman	2,938,988	3,164,718	1.49
Kermanshah	1,945,227	1,952,434	0.07
Khorasan, North	867,727	863,092	-0.11
Khorasan, Razavi	5,994,402	6,434,501	1.43
Khorasan, South	662,534	768,898	3.02
Khuzestan	4,531,720	4,710,509	0.78
Kohgiluyeh and Boyer-Ahmad	658,629	713,052	1.60
Kordestan	1,493,645	1,603,011	1.42
Lorestan	1,754,243	1,760,649	0.07
Markazi	1,413,959	1,429,475	0.22
Mazandaran	3,073,943	3,283,582	1.33
Qazvin	1,201,565	1,273,761	1.17
Qom	1,151,672	1,292,283	2.33
Semnan	631,218	702,360	2.16
Sistan and Baluchistan	2,534,327	2,775,014	1.83
Tehran	12,183,391	13,267,637	1.72
Yazd	1,074,428	1,138,533	1.17
Zanjan	1,015,734	1,057,461	0.81

[1] Provinces are alphabetically ordered.

Table 4. Literacy rate[1] of the population aged six and over in urban and rural areas and provinces in 2016 (Statistical Centre of Iran, 2021).

Province [2]	**Total**	**Urban**	**Rural**
Total	**87.64**	**90.79**	**78.5**
Alborz	92.23	92.80	85.02
Ardabil	83.06	87.27	74.07
Azarbaijan, East	84.70	88.13	75.78
Azarbaijan, West	82.04	86.20	74.03
Bushehr	89.21	90.77	85.34
Chahar Mahal and Bakhtiari	84.70	88.70	77.41
Fars	88.83	91.54	82.52
Gilan	87.32	92.48	78.46
Golestan	86.10	90.42	81.02
Hamadan	84.96	89.08	77.86
Hormozgan	87.84	92.39	82.33
Ilam	84.92	88.38	77.54
Isfahan	89.93	90.98	82.13
Kerman	85.44	89.26	79.93
Kermanshah	84.53	87.62	75.41
Khorasan, North	83.27	89.61	75.08
Khorasan, Razavi	89.08	91.98	81.05
Khorasan, South	86.79	92.16	79.08
Khuzestan	86.30	89.74	75.50
Kohgiluyeh and Boyer-Ahmad	84.35	89.95	77.37
Kordestan	81.51	85.33	72.27
Lorestan	82.98	86.95	75.73
Markazi	87.00	90.83	74.36
Mazandaran	88.69	92.11	84.00
Qazvin	88.65	91.36	80.61
Qom	88.73	89.20	79.59
Semnan	91.49	93.25	84.52
Sistan and Baluchistan	76.03	84.15	68.23
Tehran	92.91	93.46	84.32
Yazd	90.86	92.03	84.13
Zanjan	84.83	89.26	75.66

[1] Literacy rate is the number of literate people divided by the aged six and over population multiplied by 100. All individuals who can read and write a simple text in Farsi or any other language are considered literate whether they have a formal certificate. All students, including first-year primary school beginners and learners of the Adult Literacy Movement, are considered literate (Statistical Centre of Iran, 2021).

[2] Provinces are alphabetically ordered.

2.2.3 Non-communicable disease status in Iran

Iran is experiencing a demographic and epidemiological transitional period; its population is ageing, risk factors contributing to diseases are changing, and infectious diseases and the burden on the healthcare system are being replaced by emerging non-communicable diseases, including cardiovascular diseases, malignancies, and mental health disorders (Danaei *et al.,* 2019).

The risk factors affecting the Iranian population are changing partly due to the increasing trends of urbanisation, worsening air pollution in most Iranian large cities (Esfandeh *et al.,* 2021) and the rising prevalence of substance abuse among the youth (Danaei *et al.,* 2019). The growing burden of non-communicable diseases, along with ecological challenges, including air pollution and water crisis; the inadequate infrastructure of the health system in Iran, especially in preventive care to overcome these issues, should be the priorities of any program to address future health challenges in Iran (Danaei *et al.,* 2019).

The Iranian health system has accomplished significant achievements in providing health services during the past century, successfully controlling infectious diseases and decreasing child and adult mortality (Khosravi *et al.,* 2007). Considering political instability, war, sanctions, and natural disasters affecting the country during this period, the current achievements of the health system can be regarded as enormous (Danaei *et al.,* 2019) and have been obtained through the efforts of different governments and policymakers during the past decades, which have resulted in this impressive success (Danaei *et al.,* 2019).

Although there are registry systems for births, deaths, cancer, and many communicable and non-communicable diseases and immunisation, the lack of an integrated health information system represents an obstacle to conducting systematic analysis (Mehrdad, 2009). For example, apart from the analysis of processes and outcomes, no accurate data on patient's satisifaction is available, hindering the ability of to evaluate the health system performance and health policymaking processes in Iran (Mehrdad, 2009). Despite efforts to measure patients' satisfaction, the current information system is far

from optimum. The quality of services and efficiency of the health system are two major issues that need more attention (Mehrdad, 2009).

2.3 Clinical definition of breast cancer

There are many types of breast cancers, and correctly identifying each one is essential to determining the proper treatment (Johns Hopkins Medicine Pathology, 2021). Breast cancers can be classified into different subgroups based on similarities in the gene expression and molecular profiles (Makki, 2015), but in general, they are divided into two main overarching groups: carcinomas and sarcomas (Johns Hopkins Medicine Pathology, 2021). Carcinomas are cancers that arise from the epithelial component of the breast. The epithelial part consists of the cells that line the lobules and terminal ducts; under normal conditions, a specialised subgroup of epithelial cells, lactocytes, are responsible for producing breast milk. Carcinomas comprise most of all breast cancers and will be further discussed below. Sarcomas are rare cancers that arise from the breast's stromal (connective tissue) components. These stromal component cells include myofibroblasts and blood vessel cells, and cancers arising from these supportive cells include phyllodes tumours and angiosarcoma. Sarcomas account for less than 1% of primary breast cancers (Johns Hopkins Medicine Pathology, 2021).

Most breast malignancies arise from the epithelial component of the breast and are categorised as carcinomas. The in-situ breast carcinomas are either ductal (also known as intraductal carcinoma) or lobular. This distinction is primarily based on the lesion's growth pattern and cytologic features rather than their anatomic location within the mammary ductal-lobular system (Li *et al.,* 2005). Invasive ductal carcinoma is the most common form of breast cancer, accounting for 80% of all breast cancer diagnoses (Johns Hopkins Medicine Pathology, 2021).

Invasive breast carcinomas consist of several histologic subtypes; the estimated percentages from a contemporary population-based study of 135,157 women with breast cancer reported to the Surveillance, Epidemiology, and End Results database of the National Cancer Institute between 1992 and 2001 in the US show invasive ductal type, 76% and invasive lobular type, 8% (Li *et al.,* 2005). Although inflammatory breast cancer is an invasive ductal carcinoma, it is a rare and aggressive disease

with different symptoms, outlook, and treatment that accounts for almost 2–4% of all breast cancers. Despite its low incidence rate, inflammatory breast cancer is responsible for 7–10% of breast cancer-related mortality in western countries (Lim *et al.,* 2018).

2.3.1 Molecular subtypes of breast cancer

Breast cancer is categorised based on gene expression profiling, which can determine the underlying biology of the tumour. The diverse subtypes can be defined based on the expression level of four significant biomarkers by immunohistochemistry or other techniques of molecular biology: estrogen receptor (*ER*), progesterone receptor (*PR*), human epidermal growth factor receptor 2 (*HER2*), and *Ki-67* which is closely associated with cell proliferation, and higher levels of Ki-67 expression are generally indicative of faster cell proliferation rates (Timms *et al*., 2014). The most common subtypes include: *Luminal A* which is *ER* and *PR* positive and *HER2*-negative (with low expression of *Ki-67*) and is considered the least aggressive form of breast cancer. *Luminal B* which is also *ER* and *PR* positive and *HER2*-negative (with high expression of *Ki-67*) and tends to be more aggressive than *Luminal A*. *HER2-enriched* which is *HER2*-positive and *PR/ER* negative and is associated with a poor prognosis due to faster growth than luminal cancers. This subtype is characterised by overexpression of the *HER2* oncogene. *Triple-negative* which is *HER2*-negative and *PR/ER* negative, making it less responsive to hormone therapy and targeted therapies and is considered more aggressive than *Luminal A* or *B*. Lastly, *Basal-like* subtype which is characterised by a lack of expression of luminal genes and a high expression of genes associated with the basal cell layer of the breast and has a more aggressive course. *Basal-like* cancers (15% of all invasive breast cancers) predominate among *Triple-negative* cancers (Timms *et al*., 2014, Sørlie *et al*., 2001). Each category has exclusive molecular characteristics, so they can be an important tool in guiding personalised treatment for breast cancer patients (Timms *et al*., 2014, Pusztai *et al*., 2006).

2.4 Risk factors related to breast cancer

Understanding the extent of the cancer burden attributable to potentially modifiable risk factors is essential for developing effective prevention and mitigation policies (Brown *et al.,* 2018). Various non-

modifiable (e.g. age, gender and ethnicity) and modifiable (e.g. behavioural, social and cultural) risk factors have been identified for the progression of the main subcategories of non-communicable diseases, including cancers (Yarahmadi *et al.*, 2013, Afshin *et al.*, 2015, Azadnajafabad *et al.*, 2021). Risk factors associated with breast cancer can be classified into seven groups: demographic characteristics, reproductive factors, hormonal factors, hereditary factors, breast-related factors, lifestyle and others (Momenimovahed and Salehiniya, 2019) (Table 5). Identifying each modifiable factor may contribute to developing prevention strategies to decrease breast cancer incidence (Kamińska *et al.*, 2015).

Table 5. Risk factors related to breast cancer worldwide (Momenimovahed and Salehiniya, 2019).

Risk factors		Protective	Predisposing	Controversial
Demographic	Female gender		*	
	Age		*	
	Blood group			*
Reproductive	Age of menarche			*
	Late age of menopause		*	
	Full-term pregnancy	*		
	Abortion			*
	Ovulatory menstrual cycle	*		
	Pregnancy characteristics	*	*	
Hormonal	Hormonal contraceptive methods		*	
	Ovulation-stimulating drugs			*
	Postmenopausal hormone therapy		*	
Hereditary	Genetic factors		*	
	Positive family history of breast cancer		*	
Breast related	Lesser lactation duration	*		
	More breast density			*
	Benign breast disorders		*	
Lifestyle	Obesity and overweight		*	
	Alcohol consumption		*	
	Smoking		*	
	Coffee			*
	Diet		*	
	More physical activity	*		
	Vitamin D	*		
	Duration of sleep			*
Others	Air pollution		*	
	Night work		*	
	Socioeconomic status		*	
	Diabetes		*	
	Radiation		*	

2.4.1 Female gender

The analysis of the occurrence of breast cancer by sex shows a clear association with women predominantly diagnosed and men representing less than 1% of all diagnosed breast cancers (Dong *et al.,* 2020; Gnerlich *et al.,* 2011; Giordano *et al.,* 2002). A study on transgender people receiving hormone treatment in the Netherlands has also shown an increased breast cancer risk in trans women compared with cisgender men and lower risk in trans men compared with cisgender women (De Blok *et al.,* 2019). Although a higher incidence of breast cancer exists among women (Schwartz and Von Glascoe, 2021), epidemiological data have shown an apparent increase in the occurrence of breast cancer in men over the last three decades, especially in older adult males with hormonal imbalance, being exposed to radiation, and family history of breast cancer, with the most common risk factor for men identified in a mutation of the *BRCA2* gene (described in "Genetics" section) (Yousef, 2017; Speirs and Shaaban, 2009; Stang and Thomssen, 2008).

2.4.2 Age

Age is the most critical risk factor for breast cancer after gender (Thakur *et al.,* 2017). The breast cancer incident rate increases significantly with age, with the highest rate observed around menopause (45-55 years age group) and then gradually decreases or remains constant (Johansson *et al.,* 2021; Kim *et al.,* 2015). Worldwide, the breast cancer incidence rate in the 50-69 years age group was consistently the highest (among the three age groups 15-49 years, 50-69 years, and 70+ years) from 1990 to 2017 (Lin *et al.,* 2019; Li *et al.,* 2019). Nevertheless, breast tumours in younger women appear in larger, advanced stages with lower survival (Assi *et al.,* 2013).

2.4.3 Late age of menopause

The late age of menopause (over 50 years old) has been related to an increased risk of breast cancer (Kim *et al.,* 2015; Laamiri *et al.,* 2015). Review research indicated that early menopause notably protects against breast cancer (Olsson and Olsson, 2020), consistent with a case-control study that

confirmed the association between the late age of menopause and the higher breast cancer incidence rate (Thakur *et al.*, 2017).

2.4.4 Full-term pregnancy

The risk of breast cancer decreases with early age full-term pregnancies and an increasing number of childbirths (Husby *et al.,* 2018). A study indicated that every childbirth reduces the breast cancer risk by up to 10%, and women who were older at their first childbirth had a 27% increased risk of developing breast cancer (Ma *et al.,* 2006). However, another study showed having more than five full-term pregnancies is associated with an increased breast cancer risk (Mahouri *et al.,* 2007).

2.4.5 Hormonal therapies

Use of contraceptive pills (Beaber *et al.,* 2014; Kotsopoulos *et al.,* 2014) and Hormone Replacement Therapy (HRT) as the postmenopausal hormone therapy (Xu *et al.,* 2021) are associated with an increased risk of breast cancer, with different levels of risk by type of HRT, higher risks for combined treatments, and a longer duration of use (Vinogradova *et al.,* 2020). Users of HRT who started around the time of menopause were at higher risk of breast cancer than those who have never used HRT due to the higher estrogen levels (Collaborative Group on Hormonal Factors in Breast Cancer, 2019).

Concerns about the increased risk of breast cancer linked to HRT (Marjoribanks *et al.,* 2012) have resulted in a considerable decrease in HRT use over the past two decades (Xu *et al.,* 2021; Parkin, 2011). Nowadays, clinical guidelines advise using HRT for no longer than five years and have indicated the need for more information about the risks of breast cancer associated with different types of HRT (Chlebowski and Anderson, 2015; Sarri *et al.,* 2015). However, the association between HRT duration and breast cancer varied with no increased risks for less than one year of HRT but increasing risks for longer exposures to the medications (Vinogradova *et al.,* 2020).

2.4.6 Hereditary factors

Genetics

Approximately 20-25% of breast cancer risk is defined by known breast cancer susceptibility genes (Neamatzadeh *et al.,* 2015; Palacios *et al.,* 2008; Oldenburg *et al.,* 2007), among which almost 40% of hereditary breast cancer cases occur due to mutations in the *BRCA1* and *BRCA2* genes (Cobain *et al.,* 2016), with 55%–65% of individuals with the *BRCA1* mutation and 45% with the *BRCA2* mutation developing breast cancer by the age of 70 years old (Godet and Gilkes, 2017). Mutations in *BRACA1/2* genes can increase the chance of developing breast cancer by up to 70% (Kuchenbaecker *et al.,* 2017). *BRCA1* and *BRCA2* are two important genes in cells' DNA repair system and are tumour suppressor genes. When genes are not mutated, these genes help keep breast, ovarian, and other types of cells from growing and dividing too rapidly or in an uncontrolled way which is typical for cancer cells (Gorodetska *et al.,* 2019). The prevalence of *BRCA1/2* mutations is estimated at between 0.10% and 0.12% in the general population (Balmana *et al.,* 2011). The distribution of *BRCA1* and *BRCA2* mutations varies from 1.8 to 13.1% in high-income countries (Southey *et al.,* 1999; Bonadona *et al.,* 2005; Tommasi *et al.,* 2005) and from 0.8 to 8.6% in Asian countries (Liede and Narod, 2002; Zhi *et al.,* 2002; Choi *et al.,* 2004; Saxena *et al.,* 2006).

Beyond the well-known *BRCA* mutations, there are several genetic factors that have been implicated in the development of breast cancer. Some of these key factors include *HER2*, *P53*, *ER* and *PR*. The *HER2* is an oncogene which helps to control cell growth and division, while its over-expression has been linked to a more aggressive form of breast cancer that is often referred to as *HER2*-positive breast cancer. *P53* gene which is a tumour suppressor, helps to prevent the development of cancer by regulating cell division and cell death. Mutations in the *P53* gene have been related to an increased risk of breast cancer. *ER* and *PR* are proteins that are produced by the epithelial cells that line the lumen of the terminal duct lobular unit where most breast cancers arise and can be used as markers for the presence of hormone receptor-positive breast cancer (Neamatzadeh *et al.,* 2015; Palacios *et al.,* 2008). The presence or absence of these genetic factors can influence the aggressiveness of the cancer and also guide treatment decisions (Balmana *et al.,* 2011).

Family history of breast cancer

Family history of breast cancer is one of the significant risk factors for breast cancer (Jones *et al.,* 2017; Thakur *et al.,* 2017; Bravi *et al.,* 2018). First-degree families of breast cancer patients have an almost two-fold higher risk of developing breast cancer (Neamatzadeh *et al.,* 2015; Sadr-Nabavi *et al.,* 2014) and having a family history of breast cancer may candidate an individual for treatment or intensified breast screening with Magnetic Resonance Imaging (MRI) in Canada (Metcalfe *et al.,* 2009).

2.4.7 Benign breast disorders

Benign breast diseases, which refer to a non-cancerous lump, cyst, or nipple discharge (fluid) of the breast, are among the most significant risk factors for breast cancer (Zendehdel *et al.,* 2018, Román *et al.,* 2017). A cohort study indicated that benign breast diseases are associated with an increased risk of invasive breast cancer, which varies at different ages (Kerlikowske *et al.,* 2017). However, the risk of breast cancer decreases in postmenopausal women with benign breast disease (Arthur *et al.,* 2017). The association between benign breast disorders and breast cancer also depends on the histological sorting of the disease and family history of breast cancer (Hartmann *et al.,* 2005).

2.4.8 Lifestyle-related factors

The association of modifiable risk factors with the risk of breast cancer has indicated that having a healthy lifestyle can lead to postmenopausal breast cancer prevention (Arthur *et al.,* 2018). Another study confirms that an overall healthy lifestyle may reduce breast cancer risk among females with breast cancer genetic risk factors (Arthur *et al.,* 2020). Therefore, it is essential to emphasise the necessity of a healthy lifestyle to the public to minimise breast cancer's burden (Xu *et al.,* 2021).

Body-Mass Index (BMI)

Higher BMI has been associated with a higher risk of breast cancer incidence (12–13% increase in risk per 5 kg/m²) (Babu *et al.,* 2018; Simmonds *et al.,* 2014; Renehan *et al.,* 2008). Since adipose tissue characterises the source of estrogen (Renehan *et al.,* 2008; Cleary and Grossmann, 2009),

postmenopausal overweight or obesity can increase the breast cancer risk, especially among Asian women, compared with North American and European women (Li *et al.,* 2019). Additionally, women with higher BMI tend to have higher blood insulin levels linked to some cancers, including breast cancer (Li *et al.,* 2019; Chlebowski, 2021).

Smoking

Evidence shows that smoking, which has been the subject of many studies for more than three decades, increases the risk of breast cancer by 21% in people who have smoked for more than ten years (Jones *et al.,* 2017). A population-based prospective study found that smoking before or after a breast cancer diagnosis is associated with worse breast cancer survival (Passarelli *et al.,* 2016). Although no significant association between smoking and developing breast cancer has been seen in pre-and postmenopausal women in a case-control study (Ghosn *et al.,* 2020), another meta-analysis of the cohort studies concluded that current smoking is associated with worse breast cancer-specific survival than never smoking in breast cancer patients (Duan *et al.,* 2017).

Alcohol

Drinking alcohol is also associated with a higher risk of breast cancer. Women who have 2 to 3 units of alcohol a day have about a 20% increased risk of developing breast cancer than non-drinkers (Chlebowski, 2021). This risk grows progressively with increasing amounts of alcoholic beverage intake (Newman and Pearlman, 2022). The GBD 2017 study showed alcohol use was among significant contributors to breast cancer DALY and death in most regions (Li *et al.,* 2019). In addition, populations living in low and middle-income countries have been adopting westernised lifestyles, including rising rates of alcohol consumption that can affect the risk of breast cancer in these regions (Newman and Pearlman, 2022). Breast cancer represents a crucial socioeconomic burden of disease and disability globally which will continue unless the critical risk factors such as alcohol use and high BMI get reduced (Xu *et al.,* 2021).

Diet

An unhealthy diet has been a risk factor for breast cancer (Chlebowski, 2021). A low-fat dietary pattern that includes increased vegetable, fruit, and grain consumption meaningfully decreases the risk of death due to breast cancer (Chlebowski *et al.*, 2020; Chang *et al.*, 2017). A case-control study has also indicated a strong association between a nonvegetarian diet and breast cancer risk in India (Thakur *et al.*, 2017). The lower risk of postmenopausal breast cancer among vegetarian women than meat-eaters may be explained by their lower BMI (Watling *et al.*, 2022). A systematic review and meta-analysis reported that consumption of soft drinks could significantly increase the odds of breast cancer due to increased BMI and insulin resistance (Brennan *et al.*, 2010).

Physical activity

A systematic review and meta-analysis in 2019 showed that post-diagnosis physical activity was associated with lower breast cancer mortality (Spei *et al.*, 2019). The results of a cohort study also showed that increased physical activity is associated with a reduction in the breast cancer risk in postmenopausal women (McTiernan *et al.*, 2003), consistent with another observational study (Holmes *et al.*, 2005). It has been stated that the greatest benefit of exercise was seen among women who had three to five hours of walking per week at an average speed (Holmes *et al.*, 2005).

2.4.9 Other factors

Several other factors are associated with increased breast cancer incidence, including environmental factors such as air pollution (Andersen *et al.*, 2017; Wei *et al.*, 2012) and occupation factors such as overnight work (Benabu *et al.*, 2015, Megdal *et al.*, 2005). Long-term exposure to air pollution has increased the incidence of postmenopausal breast cancer in European women (Andersen *et al.*, 2017). Night/shift work is also associated with an increased risk of breast cancer, especially in women who have worked for over 20 years (Benabu *et al.*, 2015). The role of socioeconomic status in breast cancer incidence rate has also been discussed in recent studies, with high socioeconomic status increasing the breast cancer incidence (Orsini *et al.*, 2016; Lundqvist *et al.*, 2016; Thakur *et al.*, 2017). Diabetes is

associated with a higher risk of breast cancer among postmenopausal women and those with higher BMI (Tabassum *et al.,* 2016). Researchers suggest that blood glucose and insulin levels are associated with an increased risk of breast cancer in women with a BMI > 26 kg/m2 (Muti *et al.,* 2002). In addition, data from the GBD 2019 showed a rising contribution of high blood glucose to the risk of developing breast cancer while recognising high blood glucose as the top rank cause of global breast cancer deaths in 2019 (Xu *et al.,* 2021). A large population-based case-control study found that the risk of breast cancer incidence is two to three times higher in women with a history of radiation in previous cancer treatment, screening or other disease treatment (John *et al.,* 2007).

It is worth noting several reasons why various risk factors like diabetes and obesity are associated with breast cancer. Firstly, obesity and insulin resistance, which is often associated with diabetes, can lead to hormonal imbalances, including an increase in circulating insulin levels, which have been linked to an increased risk of breast cancer (Wolf *et al*., 2005, Endogenous Hormones and Breast Cancer Collaborative Group, 2002). Secondly, the mentioned risks can also lead to a state of chronic low-grade inflammation, which has been implicated in the development and progression of breast cancer. Thirdly, obesity is associated with changes in the levels of estrogen and other hormones, which can affect the growth of breast tissue and increase the risk of breast cancer (Friedenreich, 2001). Fourthly, obesity and insulin resistance can change cellular signalling pathways that control cell growth and division, leading to an increased risk of breast cancer (Wolf *et al*., 2005, Sachdev and Yee, 2001). Lastly, these risk factors have been linked to changes in DNA stability and repair, which can increase the risk of genetic mutations and development of cancer (Wolf *et al*., 2005). These associations are complex and may involve multiple interrelated mechanisms, and that not all individuals with these risk factors will develop breast cancer. Addressing modifiable risk factors, such as maintaining a healthy weight and engaging in regular physical activity, can reduce the risk of breast cancer and improve overall health (Daly *et al*., 2021).

2.5 Risk factor status in Iran

A systematic review and meta-analysis in 2020 in Iran suggested that family history, HRT, passive smoking, late full-term pregnancy and genetic mutations might increase the risk of breast cancer incidence. In contrast, daily exercise and vegetable consumption had an inverse association with breast cancer incidence (Shamshirian *et al.,* 2020). Another study has also reported that inadequate consumption of vegetables and soft drinks, industrially produced juices, fried foods, and sweets increase the breast cancer risk among Iranian women (Marzbani *et al.,* 2019). The overall *BRCA1* mutation rate in Iranian breast cancer patients with various levels of family history is estimated to be 31.8% (Neamatzadeh *et al.,* 2015). This is comparable to Algerian and Tunisian estimations for families' *BRCA1* mutation frequency, reported at 36.4% and 37.5%, respectively (Uhrhammer *et al.,* 2008; Troudi *et al.,* 2007). However, the prevalence of *BRCA1* mutations reported in research on French hereditary breast cancer and/or ovarian cancer families (10.3%) is approximately three times less than estimated for Iran (Laraqui *et al.,* 2013). Detection of *BRCA* mutations in a considerable proportion of Iranian patients indicates that these genes play an essential role in breast cancer incidence in this population (Neamatzadeh *et al.,* 2015). Since breast cancer onset for individuals with a *BRCA1* or *BRCA2* mutation is happening typically before age 50 (Neamatzadeh *et al.,* 2015), the high prevalence of these mutations in Iran can somehow explain that breast cancer incidence among Iranian females occurs at least one decade earlier than western countries (Nafissi *et al.,* 2018). In addition, several studies have illustrated the relationship between low levels of physical activity, being overweight or obese and higher breast cancer incidence (Maleki *et al.,* 2020; Marzbani *et al.,* 2019; Fararouei *et al.,* 2019). In response to these findings, it is necessary to raise awareness and educate about healthy diets and the need to change unhealthy dietary patterns in Iran (Marzbani *et al.,* 2019).

2.6 Breast cancer screening

2.6.1 Screening types

Based on the American Cancer Society (ACS) guideline, there are three main methods for breast cancer screening, including Breast Self-Examination (BSE), which is regular physical breast exams done by women themselves, Clinical Breast Examination (CBE), which is regular physical breast exams done by a health professional and Mammography which is the gold standard approach for ages above 40 years old in most western countries but not all (American Cancer Society, 2020; Zubor *et al*., 2019; Geisel *et al*., 2018). MRI is also recommended for high-risk individuals with a strong family history of breast cancer (American Cancer Society, 2020).

ACS and other guidelines state that the most significant benefit of screening mammograms occurs in women aged 50 to 74. There is insufficient data to support the utility of annual mammograms in women older than 75 years old (American Cancer Society, 2020). There remains uncertainty about the appropriate age to start screening, specifically about whether to screen women younger than 50 (Lauby-Secretan *et al.,* 2015) due to radiological and public health terms (Duffy *et al.,* 2020). The typical composition of the breast is more radiologically dense in younger women, reducing the sensitivity of mammography (Checka *et al.,* 2012). Also, breast cancer incidence and mortality are lower in women younger than 50 years than in older women, so screening at younger ages becomes controversial (Lauby-Secretan *et al.,* 2015). These variations reflect the different interpretations of the evidence and trade-offs between the benefits and potential harms of mammography, such as overdiagnosis and false positive results. In addition, access to mammography and other screening tools, as well as the prevalence of breast cancer, may also influence the recommendations (Zubor *et al*., 2019). Guidlines suggest that it is important for women to discuss their individual risk factors and screening options with their healthcare provider, who can help them make an informed decision about the best screening strategy for their needs (American Cancer Society, 2020). It is recommended that women receive regular breast cancer screening and early detection through a combination of self-examination, clinical

examination, and appropriate imaging tests, such as mammography, based on their age, risk factors, and overall health (Sood *et al*., 2019).

2.6.2 The public health implication and impact on mortality

BSE is easy to perform, has no associated costs and does not require any equipment or trained personnel (Safizadeh *et al.,* 2018; Kataoka *et al.,* 2015; Taif, 2014), so it can be done regularly, especially in low and middle-income countries with a lack of resources, as a helpful approach (Ahmed *et al.,* 2018). Furthermore, performing BSE frequently makes women familiar with their breasts' normal appearance and feel, and they can notice any changes in their breasts as soon as they present (American Cancer Society, 2020). Although BSE might not be proper as a general strategy, mainly because it is not possible to ensure women perform it well (Mittra *et al.,* 2021) and earlier meta-analysis and randomised studies showed that regular BSE is not an effective method of reducing breast cancer mortality (Hackshaw and Paul, 2003; Thomas *et al.,* 2002), the WHO suggests BSE as a valuable method for decreasing the mortality rate by early detection of breast cancer (World Health Organization, 2009), especially in regions where mammography and regular clinical examinations are not feasible.

Therefore, the effectiveness of BSE has been controversial in detecting breast cancer and reducing mortality (Allen *et al*., 2010). In spite of the advantages mentioned above regarding BSE, the use of this technique has some disadvantages including increased number of healthcare visits and twice the number of benign biopsy results, leading to increased healthcare costs (Kösters and Gøtzsche, 2003; Nelson *et al*., 2009). Another disadvantage is that increased biopsies lead to a higher risk of breast cancer (Paley, 2001) and higher levels of anxiety that require counselling or treatment (Thomas *et al.,* 2002). Overall, the controversy surrounding the effectiveness of BSE in reducing mortality highlights the need for continued research to better understand its impact on breast cancer outcomes and the best ways to promote early detection and treatment of the disease. Actually, the main BSE goal is to empower women with the information they need to make informed decisions about their health (Allen *et al*., 2010).

A recent study indicated that CBE led to a significant mortality reduction of nearly 30% in women aged 50 and older. Despite successful downstaging in women younger than 50, no mortality reduction was observed (Mittra *et al.*, 2021). They suggest that CBE in low and middle-income countries is feasible, provided that adequate training of screening providers, careful monitoring, and performance quality are assured (Mittra *et al.*, 2021; Costa Vieira *et al.*, 2017). However, whether CBE in low and middle-income countries at the community level can reduce breast cancer mortality is still unknown. Its success can only be determined several years after implementing CBE as a public health programme (Mittra *et al.*, 2021).

Mammography, widely practised in Western countries, might not be suitable for low and middle-income countries because of its cost and complexity (Black and Richmond, 2019). Furthermore, most women in low and middle-income countries are younger than 50, and mammography is less effective in this age group (Moss *et al.*, 2015). A systematic review and meta-analysis of the Incidence-Based Mortality (IBM)[1] studies estimated that the risk of death from breast cancer in women invited for mammography screening is reduced by 22% compared to women not invited (Dibden *et al.*, 2020). This result is consistent with earlier overviews of cohort studies (Beau *et al.*, 2018; Marmot *et al.*, 2013; Broeders *et al.*, 2012; Gabe and Duffy, 2005) which suggest an invitation to screening reduces mortality by approximately 20%. Another meta-analysis of eight clinical trial studies on the effect of mammography screening on breast cancer mortality showed 13–16% reductions in mortality with an invitation to screening in women aged 40–49 years (Duffy *et al.*, 2020). There was also a substantial reduction in mortality in the intervention group from grade 1 and 2 breast cancers, but no difference in mortality from grade 3 breast cancers (Duffy *et al.*, 2020). Participating in mammography screening is substantial and saves lives through early detection that otherwise would have been lost under the dominant therapy at the time of diagnosis (Duffy *et al.*, 2020).

[1] IBM studies denote to those where mortality from breast cancer are only included in women diagnosed after screening has been introduced (Broeders *et al.*, 2012).

2.6.3 Challenges of screening effect

Throughout the same period that screening was introduced, breast cancer treatment improved, making it difficult to separate the effect of screening from treatment (Beau *et al.*, 2018). Incidence of late-stage breast cancer can be used to address this problem. If a decrease in late-stage breast cancer incidence is not observed, a decline in the breast cancer mortality rate would be attributable to treatment and not screening (Beau *et al.*, 2018). A study in the USA concluded that the reduction in breast cancer mortality after the implementation of screening was predominantly the result of improved systemic therapy (Welch *et al.*, 2016), and another study, using Dutch data, indicated that the screening program would have had little influence on the decrease in breast cancer mortality (Autier *et al.*, 2017). There is a need for research to clarify whether substantial progress in both early-detection technology and breast cancer treatment might reduce breast cancer mortality (Duffy *et al.*, 2020). A further difficulty in determining the impact of screening is the absence of a general control population (Broeders *et al.*, 2012) which can be addressed using individual data in IBM studies (Broeders *et al.*, 2012). In addition, during the pandemic, COVID-19 affected health and economies and timely access to cancer control services causing a big concern globally. The public health burden of disturbances to breast cancer screening and other efforts to diagnose breast cancers early due to pandemic has been a global challenge impacting breast cancer treatment and survival (Figueroa *et al.*, 2021).

2.7 Breast cancer treatment

Breast cancer subtypes have different risk profiles and treatment strategies. The choice of treatment depends on several factors, including the stage and the molecular subtype of the cancer, as well as the patient's age, overall health, and personal preferences. More than 90% of breast cancers are nonmetastatic at the time of diagnosis for which therapeutic goals are tumour eradication and preventing recurrence (Waks and Winer, 2019). Breast cancer treatment typically involves a combination of surgical intervention, radiation therapy, chemotherapy, and hormonal or targeted therapy. Surgery is the most common treatment for breast cancer and can involve removal of the tumour (lumpectomy) or the entire breast (mastectomy). Radiation therapy is often used after surgery to destroy any remaining cancer cells and reduce the risk of recurrence. Chemotherapy which is often used in combination with

surgery and/or radiation therapy, is a systemic treatment that uses drugs (e.g. Paclitaxel, Docetaxel, Epirubicin and Capecitabine) to abolish cancer cells throughout the body. Hormonal therapy (e.g. Tamoxifen, Aromatase inhibitors, Fulvestrant and Selective estrogen receptor degraders (SERDs)) blocks the effects of hormones, such as estrogen, that can help the growth of certain types of breast cancer (*ER* and *PR* positive). Targeted therapy as a type of treatment, targets specific proteins or mutated variants of genes that drive the growth of cancer cells (Waks and Winer, 2019). Immunotherapy is another type of cancer treatment still being studied for breast cancer, and not all patients will be eligible for this treatment. Immunotherapy like Pembrolizumab is immune checkpoint inhibitor that strengthen the power of the immune system to fight cancer and stimulate the immune system to recognise and attack cancer cells. It is still an emerging field in breast cancer and is currently mostly used in the treatment of certain subtypes of breast cancer, such as *Triple-negative* breast cancer (Adams *et al*., 2019). Lastly, the development of olaparib PARP inhibitors represents a significant advance in the treatment of *BRCA1/2*-related breast cancer, offering new hope for patients with this challenging disease (Miglietta *et al*., 2022).

The success of these treatments can differ depending on the subtype and stage of the cancer. For example, hormone therapy is most effective for hormone receptor-positive breast cancers, while chemotherapy, which is more often toxic, can be effective for all subtypes. Targeted therapies have shown potential of treating *HER2*-positive breast cancers, but their effectiveness can vary based on the specific mutation (Burguin *et al*., 2021, Waks and Winer, 2019). It is important to note that the efficacy of these treatments also depends on individual patient factors, such as overall health and response to treatment. Working closely with a healthcare team experienced in treating breast cancer can help determine the most effective treatment plan for each patient (Waks and Winer, 2019).

2.8 Global studies

2.8.1 The global burden of breast cancer

Globally, in 2017 the most common types of cancer incidence among women were Non-Melanoma Skin Cancer, breast cancer, cervical cancer and liver cancer (Figure 3). This figure shows the

international importance of breast cancer, while the burden of breast cancer is still increasing globally (Fitzmaurice *et al*., 2019). In addition, Figure 4 and Figure 5 showed the age-standardised female breast cancer incidence and mortality rates worldwide in 2019. The incidence and mortality rates are spatially varying in the world. Comparing Figure 4 and Figure 5 shows that those countries with higher incidence rates do not necessarily have the higher mortality rates, which could be due to early diagnosis or treatment at an early stage. Both figures also indicate the importance of breast cancer worldwide and the need for prompt action to prevent, control, and treat this disease (Xu *et al.*, 2021).

Globally, 1 in 18 women develops breast cancer over a lifetime (Fitzmaurice *et al.,* 2019). Approximately 645,000 premenopausal and 1.4 million postmenopausal breast cancer cases were diagnosed worldwide in 2018, with more than 130,000 and 490,000 deaths occurring in each menopausal group, respectively (Heer *et al.,* 2020).

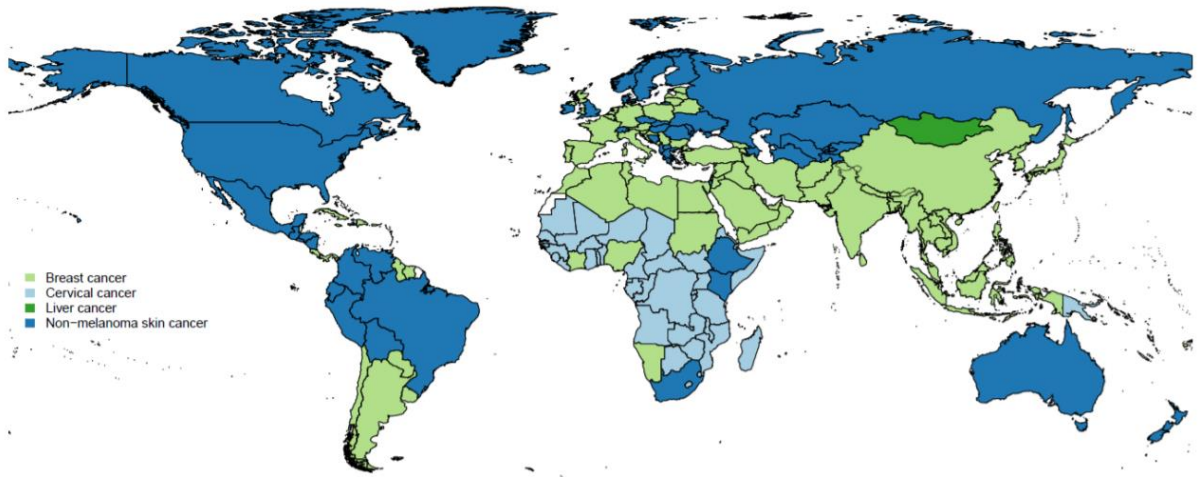


Figure 3. Top-ranked cancers by the absolute number of new cases for all ages in females, 2017 (Fitzmaurice *et al.,* 2019).

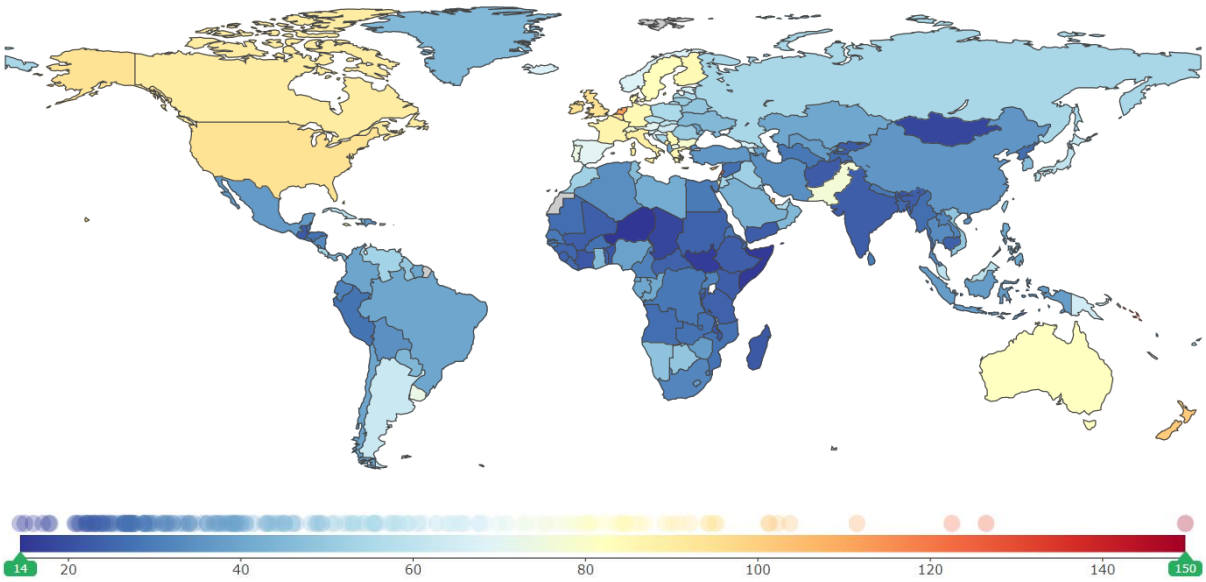


Figure 4. Female age-standardised breast cancer new cases diagnosed per 100,000 in 2019 (Global Burden of Disease, 2019).

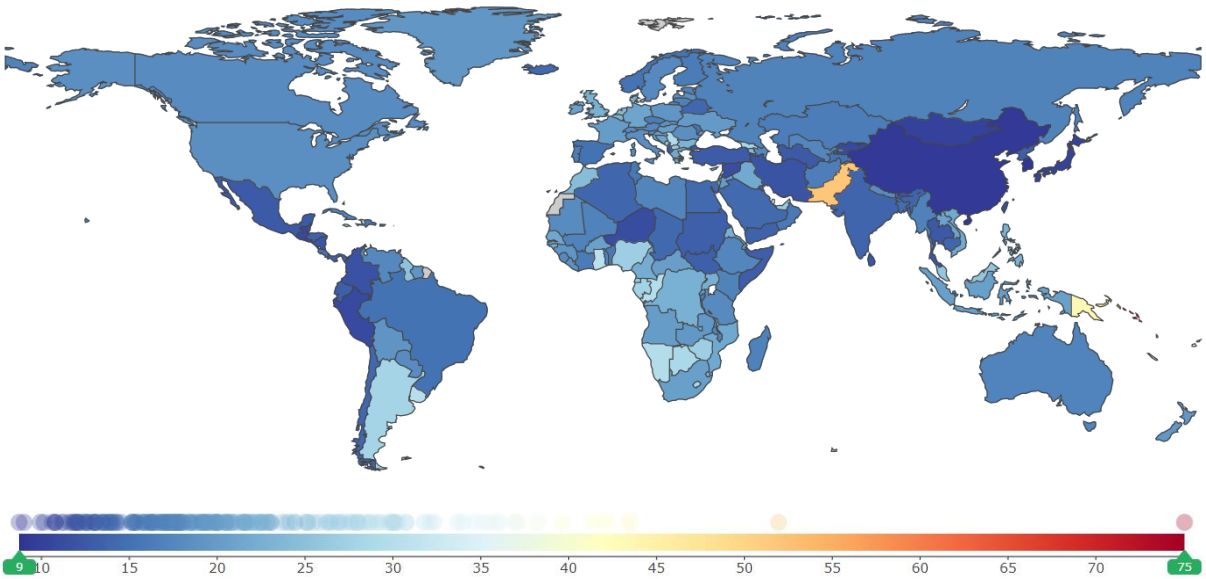


Figure 5. Female age-standardised breast cancer mortality rates per 100,000 in 2019 (Global Burden of Disease, 2019).

2.8.2 The regional burden of breast cancer

Historically, breast cancer incidence has been highest in Northern America, Western and Northern Europe, and Australia/New Zealand. However, it has been increasing sharply in Asia (Kim *et al.,* 2015), probably attributable to economic development and lifestyle-related changes toward westernisation (Forouzanfar *et al.,* 2011; Bhoo-Pathy *et al.,* 2013). Breast cancer mortality has also increased among Asian women (Kim *et al.,* 2015). However, Asian regions (western, south-central, south-eastern and eastern) and countries vary in the types and extent of changes in breast cancer risk factors and cannot be considered a single homogeneous group (Kim *et al.,* 2015). Based on GBD 2019 results, the European region among WHO regions had the highest breast cancer incidence rate, while the Eastern Mediterranean region had the highest mortality rate (Table 6), which was greater than the global average (Global Burden of Disease, 2019).

Table 6. Female age-standardised breast cancer incidence and mortality rates by WHO regions in 2019 (Global Burden of Disease, 2019).

WHO regions	**Incidence per 100,000**	**Mortality per 100,000**
European Region	68.3 (61.2, 76.8)	19.1 (17.6, 20.3)
Region of the Americas	65.2 (57.1, 74.3)	17.2 (16.1, 18.1)
Eastern Mediterranean Region	47.6 (41.0, 55.6)	25.2 (21.4, 30.2)
Western Pacific Region	40.2 (33.7, 47.3)	10.6 (9.1, 12.2)
African Region	30.0 (25.8, 34.6)	20.9 (17.9, 24.1)
South-East Asia Region	26.0 (22.0, 30.4)	14.7 (12.3, 17.4)

An ecological study (Ghoncheh *et al.,* 2015) explored the incidence and mortality of breast cancer in association with Human Development Index (HDI)[1] components, including life expectancy at birth, average years of education and Gross National Income (GNI) per capita in Asia in 2012 (Figure 6).

The study showed a statistically significant positive correlation of 0.56 (p-value < 0.001) between the Age-Standardised Incidence Rate (ASIR) of breast cancer and HDI. A positive correlation was also observed between the ASIR and components of HDI [0.44 (p-value= 0.002) between ASIR and life expectancy at birth, 0.50 (p-value < 0.001) between ASIR and the average years of education, and 0.37

[1] HDI is a summary composite measure of a country's average achievements in three basic aspects of human development: health, knowledge and standard of living.

(p-value= 0.013) between ASIR and the level of income for each one of the countrys' population] (Figure 7) (Ghoncheh *et al.*, 2015).

On the other hand, there was a negative and not statistically significant correlation of -0.05 between the Age-Standardised Mortality Rate (ASMR) of breast cancer and HDI (p-value= 0.74), including HDI's components [-0.01 (p-value= 0.51) between ASMR and life expectancy at birth, -0.02 (p-value= 0.87) between ASMR and the average years of education, and -0.06 (p-value= 0.67) between ASMR and the level of income for each one of the countrys' population] (Figure 8) (Ghoncheh *et al.*, 2015).

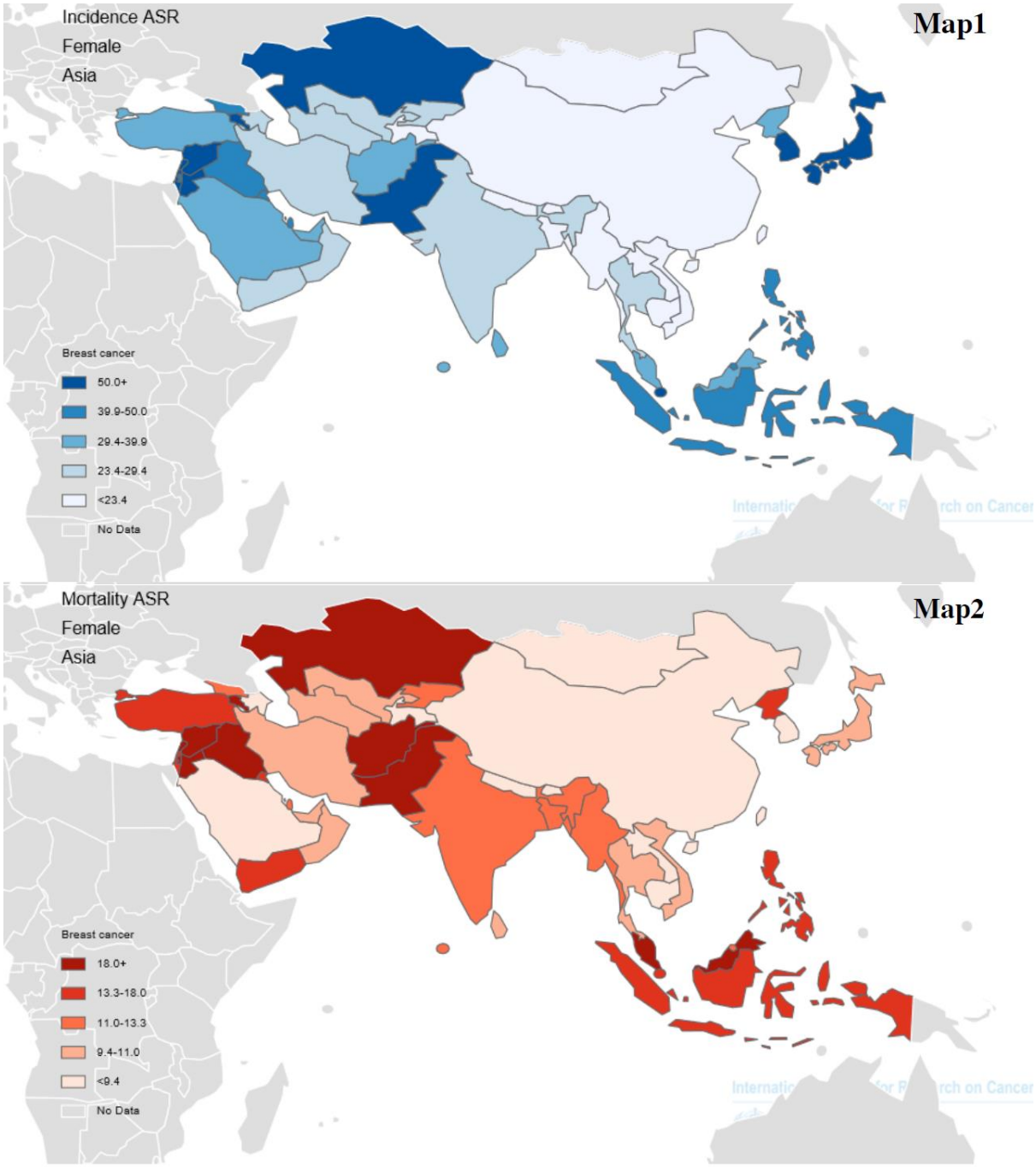


Figure 6. Map 1: Distribution of the age-standardised breast cancer incidence rates per 100,000 in Asia in 2012; Map 2: Distribution of age-standardised breast cancer mortality rates per 100,000 in Asia in 2012 (Ghoncheh *et al.*, 2015).

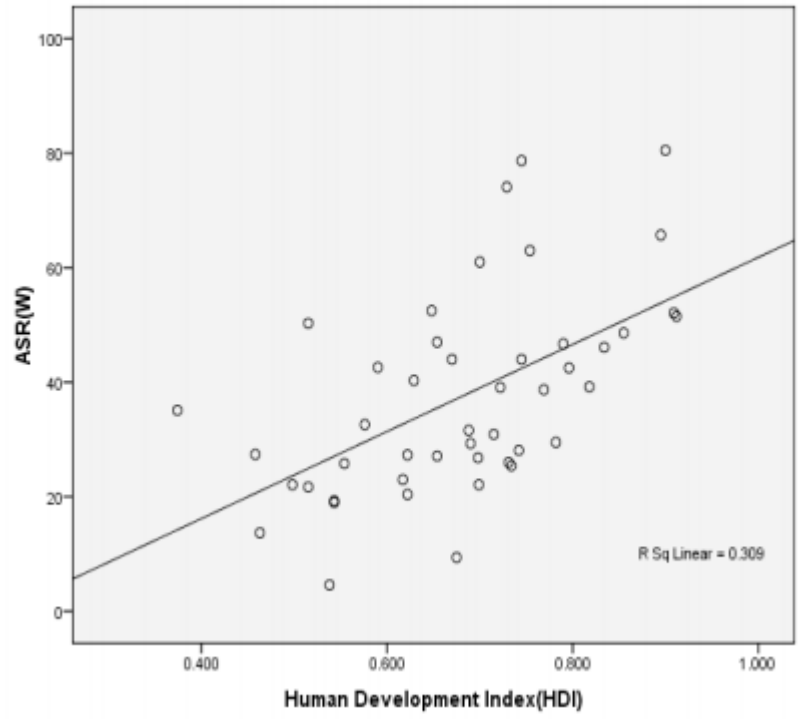


Figure 7. Correlation between HDI and age-standardised breast cancer incidence rates per 100,000 in Asia in 2012. Each dot represents an Asian country (Ghoncheh *et al.*, 2015).

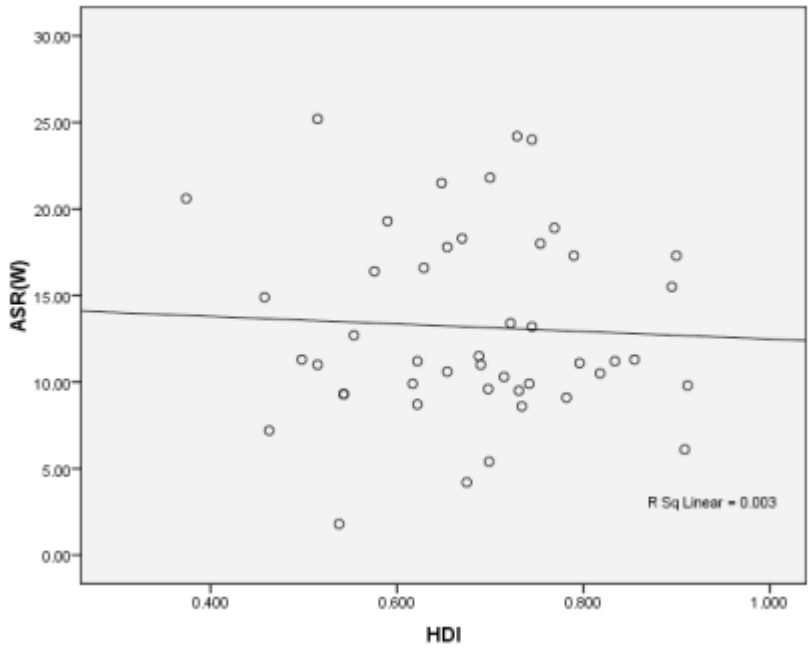


Figure 8. Correlation between HDI and age-standardised breast cancer mortality rates per 100,000 in Asia in 2012. Each dot represents an Asian country (Ghoncheh *et al.*, 2015).

With increasing knowledge, education, and employment as components of HDI, women are more likely to look for diagnostic methods which cause higher reported incidence (Ceber *et al.*, 2013). In addition, the lack of public access to screening and treatment services in regions with a lower level of HDI could probably lead to increase mortality rates (Ghoncheh *et al.*, 2015).

2.9 Breast cancer status in Iran

The age-standardised breast cancer incidence rate in Iran over time has been presented in Figure 9, compared to the global trend. Although the trend of ASMR in Iran is consistent with international rates from 1990, the increasing rate of ASIR in Iran has been much higher than the global rate (Global Burden of Disease, 2019).

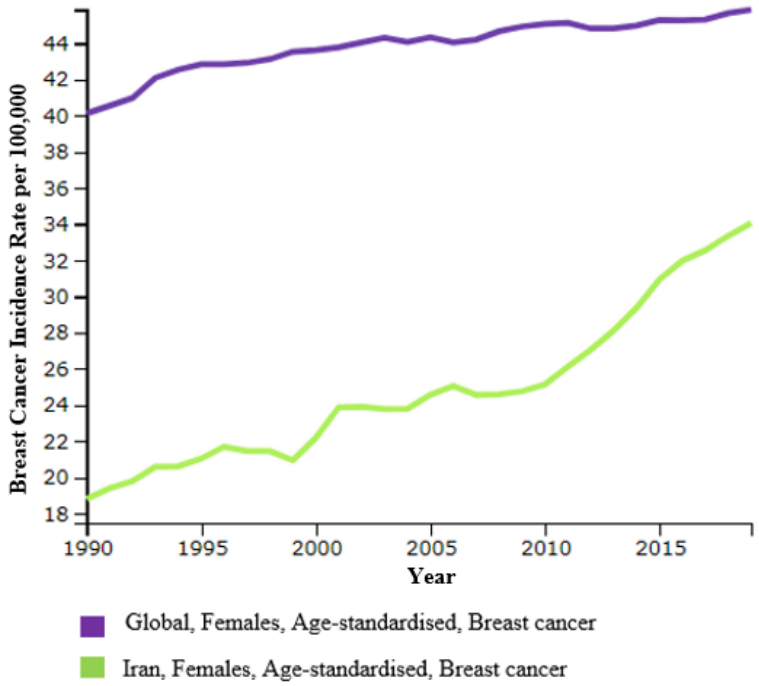


Figure 9. Iran vs Global estimation of breast cancer incidence rate per 100,000 by time from 1990 to 2019 (Global Burden of Disease, 2019).

Based on the national and sub-national burden of disease study (Farzadfar *et al.*, 2014), breast cancer was second only to digestive organs cancer new cases compared to other cancers. In 2016, among Iranian women aged 40-44, 22.9% of diagnoses were cancers specific to the digestive organs, followed

by breast cancer (22.6%) (Figure 10). These results can be accessed online using data visualisation tools at www.vizit.report website.

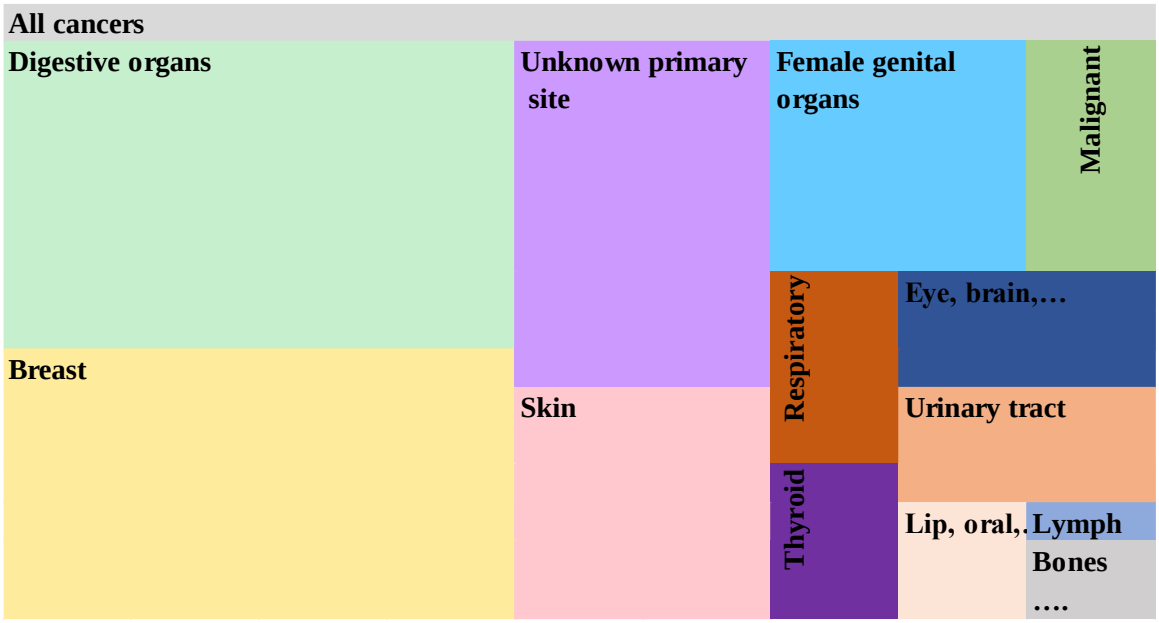


Figure 10. Distribution of all cancer new cases percentage in Iran in 2016 among women aged 40-44 years old (www.vizit.report).

National-level estimates usually give a summary overview of the disease status in the country while they conceal essential information on sub-national heterogeneity (Betrán *et al.*, 2016). Jafari-Koshki *et al.* (2014) analysed breast cancer incidence data in Iran from 2004 to 2008 at the province level. Estimated provincial trends for seven provinces with the highest increasing patterns indicated that Khorasan, North, Khorasan, South, Khorasan, Razavi, Tehran, Golestan, Khuzestan and Azarbaijan, East (see Appendix Table 1 for the geographical information) had a trend significantly steeper than the country trend (Jafari-Koshki *et al.*, 2014). Ataeinia *et al.* (2021) showed a threefold increase in age-specific breast cancer incidence rate at national and sub-national levels and a twofold increase in breast cancer provincial disparity in Iran from 1990 to 2015. Looking at Mortality to Incidence Ratio (MIR) trend for breast cancer in Iran presents a significant declining pattern of MIR due to decreased mortality, despite the high level of breast cancer incidence (Figure 11).

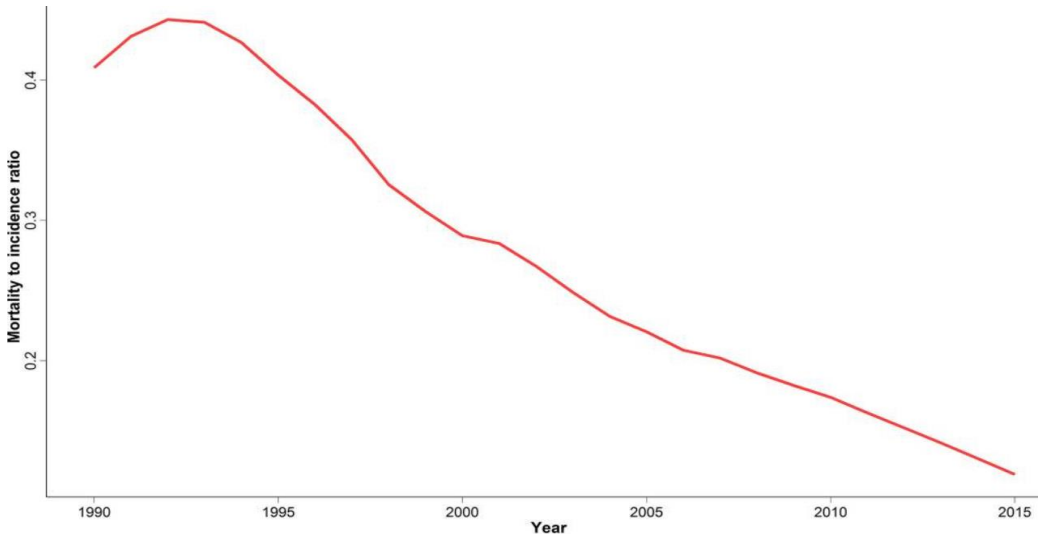


Figure 11. National time trend of mortality to incidence ratio for breast cancer in Iran; 1990 to 2015 (Ataeinia *et al.*, 2021).

2.10 Summary

This chapter provided a detailed review of studies that reported global, regional, and national breast cancer incidence and mortality trends. The literature review showed geographical differences in levels and trends of breast cancer, while there has been a consistent rise in breast cancer incidence rate worldwide. Also, information about the health status in Iran, breast cancer-related risk factors and types of breast cancer screening were discussed. Considering the breast cancer-related risks and health profile in Iran, this chapter could suggest a rationale behind the current research in Iran for zooming in on breast cancer estimations in smaller areas (districts) to proper health services allocation where there are limited resources. In the next chapter, I thoroughly described the datasets and statistical methods that have been used in this study.

3 Research methods for breast cancer estimations

3.1 Overview

The current thesis involves developing and applying a diverse range of quantitative research methods and integrating methodologies used for the disease mapping, which is suitable for spotting high-risk areas and planning proper interventions (Boulieri *et al.,* 2020). This section included available information on the data sources used for this thesis and the approaches used to check the validity of statistical methods.

3.2 Datasets

3.2.1 Breast cancer incidence data

Cancer incidence data were collected between 2000 and 2010 by the Iranian Ministry of Health and Medical Education through Iran's National Cancer Registry (NCR) to monitor cancer incidence. The NCR includes information on sex, age at diagnosis, province and district of residence at diagnosis, in addition to the cancer code based on the International Classification of Diseases for Oncology (World Health Organization, 2013), as described in other studies (Mohagheghi and Mosavi-Jarrahi, 2010; Etemadi *et al.,* 2008). The first report on all-cancer data, which referred to the various pathology departments in Iran since 1930, dates back to 1960 (Habibi, 1962; Habibi, 1965). Even though this information has been valued among epidemiologists in Iran and the region for following changes in cancer incidence (Etemadi *et al.,* 2008), it was not designed according to cancer register standards. Hence its activities were stopped in 1980 and resumed in early 2000 using more advanced technology and logistics (Mohagheghi and Mosavi-Jarrahi, 2010) in collecting, entering and cleaning the data.

The coverage rate for the NCR of 18% in 2000 (only based on pathology data) (Mohagheghi and Mosavi-Jarrahi, 2010) increased to 86% in 2009 (based on both pathology and population data) (Modirian *et al.,* 2014). This study has used data on 48,108 registered breast cancer cases in women aged 30 and above between 2000 and 2010 (excluding 2006, when data is unavailable). Missing data in cancer registry data were initially imputed through the Amelia package in R (Honaker *et al.,* 2010;

Ataeinia *et al.*, 2021; Shabani *et al.*, 2020). In addition, an investigation for duplicated data was done by the text mining algorithm in Python software (version 2.7.4) (Shabani *et al.*, 2020; Ataeinia *et al.*, 2021). Data for new cases were summarised by age-sex-province-district-year.

3.2.2 Breast cancer mortality data

Mortality data by cause of death at the province level were extracted from the Death Registry System (DRS). An efficient DRS is crucial for the health policy system to get reliable information (Mohammadi *et al.*, 2014). However, DRSs usually face a degree of misclassification and incompleteness in many low and middle-income countries. Therefore, addressing those challenges could prevent misleading results. Thus, data were cleaned and adjusted for inconsistency in DRS administration, duplicates, misalignment, misclassification, missing values and incompleteness (Mohammadi *et al.*, 2014). Detailed descriptions of DRS and cleaning methods can be found elsewhere (Sheidaei *et al.*, 2017). The national DRS consists of five sub-datasets, including DRS data from 1995-2001 and 2001-2004, collected by the Deputy for Research and Technology and the Deputy for Public Health at the provincial level, respectively; DRS data from 2006-2010, managed by the Deputy for Public Health at provincial and district levels; Behesht-e-Zahra cemetery data from 1995-2010 (Tehran data) and Bagh-e-Rezvan cemetery data from 2007-2010 (Isfahan data) (Sheidaei *et al.*, 2017). This study used data on 17,441 breast cancer deaths in women aged 30 years old and above, registered in the DRS between 2000 and 2010. Data for mortality were summarised by age-sex-province-year.

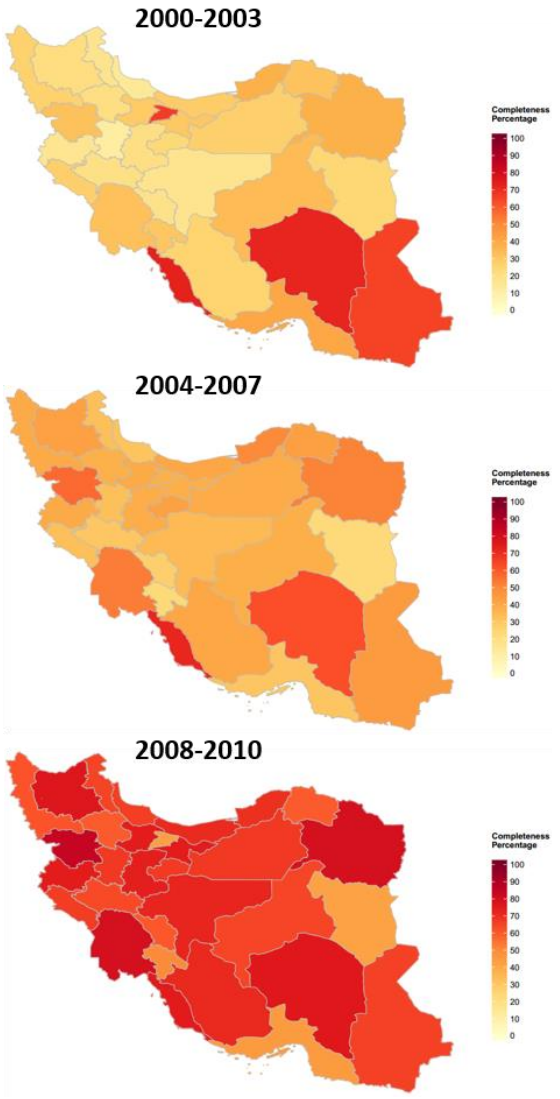
3.2.3 Covariates and population data

To account for variables that may explain the primary variable of interest distribution, population-level data has been included through several covariates in the analytical model. All covariates were available from 2000 to 2010. Population data were extracted from 1996, 2006 and 2011 censuses for each age-sex-province (Statistical Centre of Iran, 2021), with estimates for the years between censuses calculated using the population growth formula (Preston *et al.*, 2001). In addition, for each year, province and district, the following covariates were included: female urbanisation rate, calculated as the proportion of the female population living in urban areas divided by the total female population; female mean Years of Schooling (YOS), which is calculated from data on the distribution of the female population

by the highest level of education attained in a given year and official duration of each level of education, and Wealth Index (WI), calculated as the summary measure of 22 household assets, was extracted from the Household Expenditure and Income Survey (HEIS) (Figure 12, Table 7). Data on the household's ownership of some selected assets (e.g. television and car), materials used for housing construction, and having some facilities (e.g. water access type) have been used. Twenty-four asset indicators have been implemented for each family as input data in a Principal Components Analysis (PCA). The first component of PCA has been extracted, which explained 22.4% of all variance as the wealth index. Then the family level data was aggregated using appropriate weights to obtain the average wealth index by province-district-year (www.vizit.report).

Due to the high correlation between YOS and WI and based on the model response, I used YOS as a covariate in the models along with urbanisation and cancer registry coverage. I used quintiles of WI to see how relative risk of breast cancer incidence and mortality change by each quintile at the province level (the results have been displayed in chapter 4) and district level (the results have been displayed in chapter 5). A quintile is a fifth (20%) of the population, and since I had WI scores as a continuous measure, I could categorise the data with the lowest scores as the 'poorest quintile' or Q1 and the highest scores as the 'richest quintile' or Q5. I also specified YOS as a continuous measure and separately computed quintiles of YOS (Q1 means the lowest mean of YOS, and Q5 represents the highest mean of YOS). Then I used quintiles of YOS to see how the relative risk of breast cancer incidence changes by each quintile at the district level (the results have been displayed in chapter 5).

The Social Security Insurance (SSI) organisation registry was used to calculate the completeness of the cancer registry as an additional covariate in the model. As treatment for cancer patients is sufficiently expensive, insurance organisations have almost 100% coverage for registered cancer patients. With nearly 40% coverage of the population in Iran, SSI has a comprehensive registry of financial insurance services for registered cancer patients. Assuming the cancer registry has worked in the same way for other insurance organisations, similar completeness rates have been considered for all cancer patients, with quantities of 22% completeness in 2000 and 75% completeness in 2010 (Shabani *et al.*, 2020).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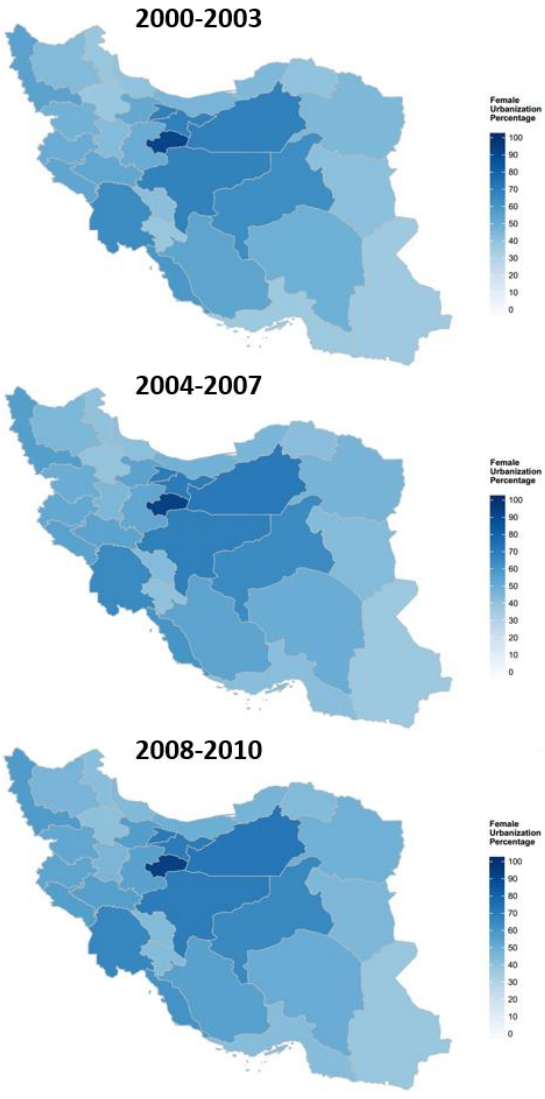
2000-2003
Female Urbanization Percentage
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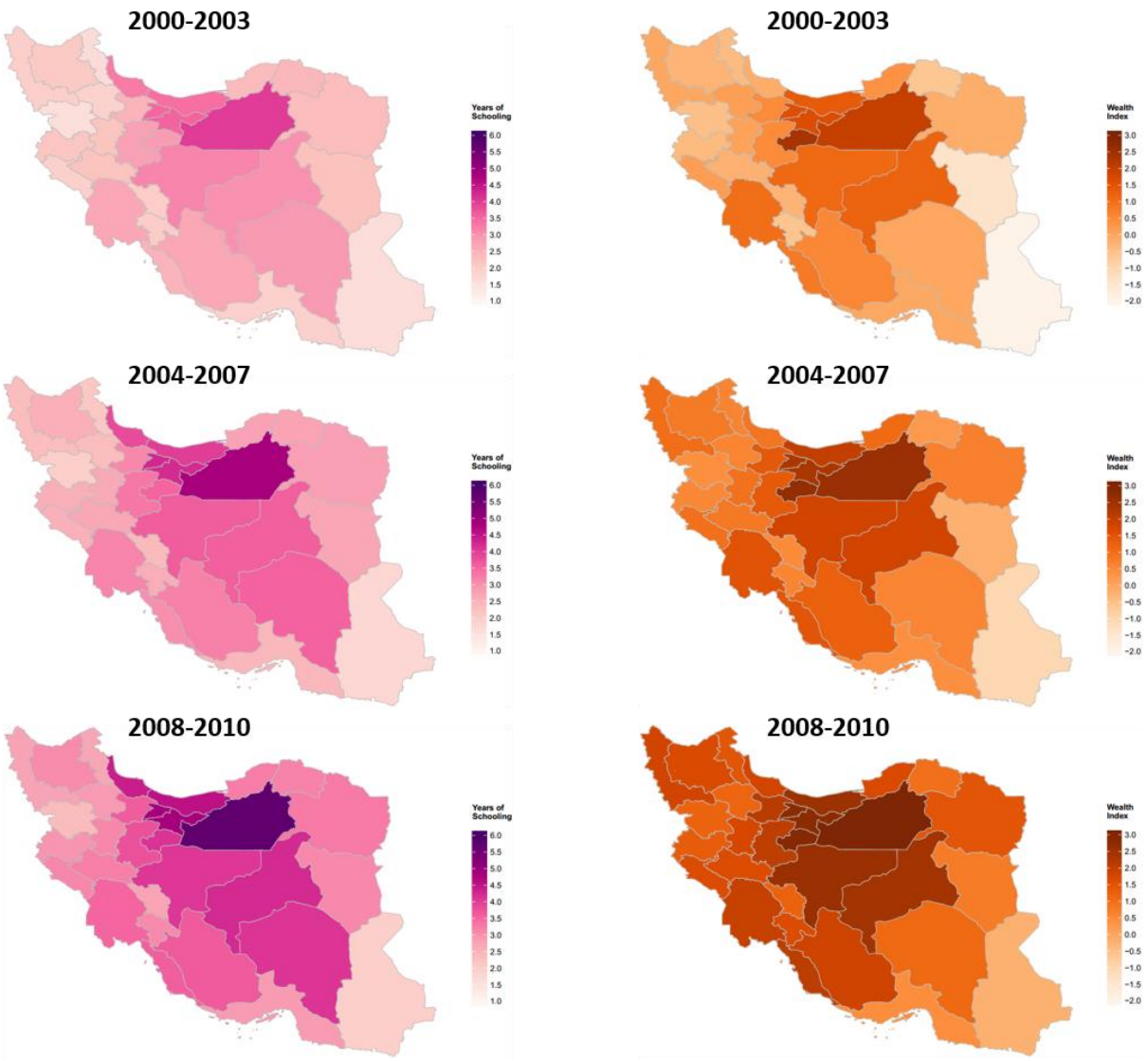


c **d**

Figure 12. Covariates distribution over provinces by three time-intervals in Iran: a) cancer registry completeness percentage, b) female urbanisation percentage, c) mean female years of schooling, d) and wealth index.

Table 7. Summary table of covariates

	Mean	Std. Dev.	Min	Max
year: 2000				
Female mean years of schooling	2.37	0.54	1.32	3.89
Wealth Index	-0.04	0.84	-2.52	2.21
Female urbanization percentage	50.14	20.60	4.20	99.63
Cancer registry completeness percentage	0.27	0.19	0.05	0.89
year: 2002				
Female mean years of schooling	2.61	0.58	1.44	4.19
Wealth Index	0.36	0.76	-1.90	2.27
Female urbanization percentage	50.84	20.56	4.53	99.63
Cancer registry completeness percentage	0.47	0.18	0.13	0.89
year: 2004				
Female mean years of schooling	2.83	0.61	1.63	4.60
Wealth Index	0.76	0.70	-1.40	2.50
Female urbanization percentage	51.54	20.50	4.85	99.62
Cancer registry completeness percentage	0.51	0.17	0.19	0.89
year: 2006				
Female mean years of schooling	3.10	0.64	1.69	4.98
Wealth Index	1.15	0.66	-1.00	2.78
Female urbanization percentage	52.37	20.59	5.45	99.62
Cancer registry completeness percentage	0.37	0.16	0.19	0.89
year: 2008				
Female mean years of schooling	3.36	0.67	1.82	5.42
Wealth Index	1.54	0.63	-0.46	2.93
Female urbanization percentage	53.11	20.53	6.03	99.61
Cancer registry completeness percentage	0.66	0.11	0.34	0.89
year: 2010				
Female mean years of schooling	3.64	0.71	2.00	5.96
Wealth Index	1.91	0.62	-0.08	3.17
Female urbanization percentage	53.85	20.47	6.77	99.60
Cancer registry completeness percentage	0.73	0.10	0.47	0.89

3.2.4 Health system data

During this research, I have been granted access to other health system-related covariates, including the number of health centres/units, number of specialist physicians (consultants), number of General Physicians (GPs), number of pharmacies, number of beds in hospitals, number of Intensive Care Units (ICU), number of nurses and number of community health workers (Behvarzes), per 100,000 population. This dataset has been available only for 2020 as health system components at the province level. Pearson correlation has been calculated to assess the correlation between the predicted relative risk of breast cancer incidence in 2020 and Iran's mentioned health system components (the results have been displayed in chapter 5). P-values less than 0.05 were considered significant.

3.3 Data preparation

I prepared four datasets for my analysis, including province level at three time-intervals (breast cancer incidence and mortality), district level at three time-intervals (breast cancer incidence), province level (breast cancer incidence and mortality) and district level (breast cancer incidence) by each year. First, to analyse geographical inequalities, age-standardised breast cancer incidence and mortality have been estimated for the 31 provinces and three time-intervals 2000-2003, 2004-2007 and 2008-2010. For this purpose, I used an indirect age-standardisation technique. The mean national rate for Iran in 2010 in each province-district-age group was multiplied by age-specific population and then combined to estimate the expected incidence and mortality cases. Second, district incidence dataset was prepared in the same way as the province in the three time-intervals 2000-2003, 2004-2007 and 2008-2010. Note that no mortality data existed at the district level. Therefore, I focused on the analysis of the incidence dataset. Third, the relative risk of breast cancer incidence and mortality for 31 provinces and the relative risk of breast cancer incidence for 316 districts for 11 years from 2000 to 2010 has been estimated. Finally, to visualise the results of spatio-temporal model, Standardised Morbidity (Mortality) Ratio (SMRs) have been mapped versus relative risk (Lambda) of breast cancer incidence and mortality, respectively. SMRs are defined as the observed number of cases divided by the expected number of cases (Yu *et al.*, 2010).

The relative rank position, and the associated credible interval of each province was calculated using the posterior samples resulting from the spatio-temporal model (Marshall *et al*., 1998). The 20,000 posterior samples obtained after running the spatio-temporal model, were ranked for each province. A distribution of probable ranks for each province was estimated and then credible intervals derived. Mean, median rank and a 95% credible interval were calculated. All draws-based approach was also used to estimate the national breast cancer relative risks and projection for 2011 onwards.

In addition, to calculate the posterior probability of relative risk for each district being greater than the national relative risk, the posterior samples of each district relative risk were compared to the national relative risk. In this study, I've had 20,000 posterior samples for each district. The relative risk of a district in an iteration (MCMC iteration) was compared to the national lambda in that iteration to see whether it is greater or not. This has been repeated for all iterations (20,000). The probability was calculated based on a proportion of district lambda being greater than the national lambda out of 20,000.

3.4 Model Background

The critical key in health studies is using a suitable method to analyse them (Lawson, 2018). Disease mapping using Bayesian inference can be a beneficial method for counting rare events in small-population regions. In addition, Bayesian methods enable researchers to have a sensible interpretation of statistical concepts, directly quantifying the uncertainty, and incorporate complex issues (Lawson, 2018; Gelman *et al*., 2013).

Hierarchical models, also known as multi-level models or mixed-effects models, allow for the modelling of relationships between variables at different levels of hierarchy like geographical regions and are useful in this context as a degree of dependence across areas can be exploited (Waller and Carlin, 2010). Bayesian spatial hierarchical models extend the general hierarchical modelling framework to account for the spatial relationships between the neighbouring areas (Richardson *et al*., 2004). The use of spatial hierarchical models in public health provides a flexible framework for modelling the complex relationships between health outcomes, environmental factors, and population characteristics in different geographical regions (Waller and Carlin, 2010). These models provide some

spatial smoothing of the raw relative risk estimates that otherwise would be calculated separately in each area. Such smoothing delivers a more stable estimate of relative risk pattern than that provided by the raw estimates which are strongly influenced by the size of the population at risk and lead to a noisy picture of the unobserved risks (Richardson *et al*., 2004).

Besag's Intrinsic Conditional Auto-Regressive (ICAR) model (Besag, 1974) can account for the spatial correlation by considering information from adjacent areas (Rao and Molina, 2015). Typically, more flexibility is needed to explain the geographical variability in risk estimates; therefore, ICAR is coupled with a Normal random effect (Waller and Carlin, 2010). The Besag, York and Mollié (BYM) model combines spatial and non-spatial random effects components to consider all variations in data (Besag *et al*., 1991). Spatial modelling can also be extended to a spatio-temporal model by adding a temporal term in small areas to quantify the temporal trends in data. This allows to investigate temporal trends at the small area level, aiming at detecting unusual behaviours or trends diverging from the national/regional ones, which might impact on the local health policies (DiMaggio, 2015).

3.4.1 Frequentist vs Bayesian approach

Two ways of thinking essentially lead to the stochastic models for spatial or spatio-temporal data: frequentist, which refers to the classical approach and Bayesian, which have been more recently intensively considered (Python, 2017). The Bayesian approach, in which all inference is based on posterior probability with no p-values, closely approximates our natural thought processes (Johnson *et al.*, 2009; Diggle and Kenward, 1994). This approach provides substantial advantages over conventional frequentist methods, particularly for sparse data that often results in inflated estimates (Greenland *et al.*, 2000). For instance, the use of prior distributions in the Bayesian approach allows the formal inclusion of information found through previous studies or from the expert opinion, which provides more details than fixed unknown parameters in frequentist statistics. The posterior probability in the Bayesian approach, in which a parameter does not exceed a certain threshold (credible interval), provides a more intuitive and interpretable quantity than a frequentist p-value and invalidly narrow confidence intervals that are non-intuitive (Blangiardo *et al.*, 2013; Rothman *et al.*, 2008). In addition,

it is easy to specify a hierarchical structure on the data and/or parameters in the Bayesian approach, which presents the added benefit of making predictions for new observations and missing data imputations relatively straightforward. At the same time, there are still some difficulties in high-dimensional inference in frequentist statistics (Blangiardo *et al.,* 2013). Despite the advantages of the Bayesian approach, the use of conventional tests is still common everywhere, especially in medical research (Vijayaragunathan *et al.,* 2022).

3.5 Statistical analysis

Even with the large sample size and geographical information available in the cancer registry dataset, there will not be sufficient information to estimate the relative risks at the province and district level using simple summary statistics. Districts in the same provinces usually have similar trends and levels of breast cancer incidence. This spatial correlational structure allowed estimates for each district and year to be informed by its data, if available, and by data from other years in the same district and other districts, especially those in the same province with data for similar periods and covariates simultaneously. The spatial or spatio-temporal structure shared information to a greater degree when data were non-existent or weakly informative (e.g., had a small sample size) and to a lesser extent for data-rich districts and provinces. The statistical model included covariates that help make estimates, including female mean YOS, female urbanisation, WI and completeness percentage of cancer registry. The details of model components are introduced in section 3.6 (Model definition).

When some populations at risk are small or the disease is rather rare, relative risks may produce very unreliable maps (Knorr-Held and Besag, 1998). Spatio-temporal modelling allows the borrowing of information from neighbouring areas and years, allowing estimation for locations and years with little or no data (Blangiardo *et al.,* 2013). The reason for using Poisson distribution was the nature of the data. The breast cancer incidence case is a discrete variable, and usually, the breast incidence probability (a portion of patients in the population) is minimal. So, the binomial distribution (mean np $\cong$ standard deviation np (1-p)) can be approximated by the Poisson with the same mean and standard deviation value. Based on this assumption, binomial and Poisson distributions can provide similar results.

Therefore, I decided to go ahead with the Poisson model and then the log-risk estimates were modelled using a combination of spatially atructured and non-structured random effects (Lawson, 2018). In this study, I fitted a Bayesian Poisson spatial model (with 30,000 iterations, 3000 burn-in[1] and 2 chains) and then a spatio-temporal model at province and district level (with 15,000 iterations, 5000 burn-in and 2 chains) with covariates, giving more precise results in each province and district.

This model was developed in open-source software OpenBUGS version 3.2.3 using the Markov chain Monte Carlo (MCMC) algorithm, R2OpenBUGS package in R for Windows version 4.2.1 (http://www.r-project.org/) and STATA software (version 11.0). This allowed me to estimate relative risks of breast cancer incidence and mortality by province and incidence by district and year, including the 2.5th and 97.5th percentiles of this distribution as estimates of the lower and upper credible intervals (CrI).

[1] The burn-in period shows the early phase of the simulations in which the sequences get closer to the mass of the distribution (Plummer *et al*., 2006). It is actually a term that describes the practice of throwing away some iterations at the beginning of an MCMC run. Burn-in is intended to give the Markov Chain time to reach its equilibrium distribution, particularly if it has started from a lousy starting point, via discarding the first n samples (Plummer *et al*., 2006) in the hope that the remaining samples are representative of the target distribution of interest (Cowles *et al*., 1999).

3.6 Model definition

I developed the three following models to analyse the datasets. The OpenBUGS models (model 1 which is spatial and model 2 which is spatio-temporal) including all the specific priors for U_i, X_t, epsilon and hyperpriors are provided in Appendix Text 1 and Appendix Text 2, respectively.

3.6.1 Spatial model

The spatial model was applied to three time-intervals at the province/district levels. This model fits the data spatially and has no time component. Also, in this model, I used WI quintiles to see how relative risk of breast cancer incidence and mortality change by different quintiles. The final results are included in chapter 4.

$$Y_i \sim Poisson\,(E_i\lambda_i)$$

$$log\,(\lambda_i) = \alpha + \beta_{yos}YOS_i + \beta_{urb}URB_i + \beta_{comp}COMP_i + U_i + \varepsilon_i$$

i: province/district, 31/316

Y_i : breast Cancer Count (incidence/mortality)

E_i: the expected number of cases

λ_i: relative risk parameters

α : intercept

YOS_i : mean female years of Schooling

URB_i : female urbanisation percentage

$COMP_i$: cancer registry completeness percentage

U_i : spatially structured random term

ε_i : residual

3.6.2 Spatio-temporal model

The spatio-temporal model was applied to the province and district data, separately. Compared to the previous model, this model considers the effect of time. The adjacent year information is evaluated for estimation of the current year. The final results are included in chapter 4 and 5.

$$Y_{i,t} \sim Poisson\left(E_{i,t}\lambda_{i,t}\right)$$

$$log\left(\lambda_{i,t}\right) = \alpha + \beta_{yos}YOS_{i,t} + \beta_{urb}URB_{i,t} + \beta_{comp}COMP_{i,t} + U_i + X_t + \varepsilon_{i,t}$$

i: province, 31; district, 316

t: year, 11

$Y_{i,t}$: breast Cancer Count (incidence or mortality)

$E_{i,t}$: the expected number of cases

$\lambda_{i,t}$: relative risk parameters

α : intercept

$YOS_{i,t}$: mean female years of Schooling

$URB_{i,t}$: female urbanisation percentage

$COMP_{i,t}$: cancer registry completeness percentage

U_i : spatially structured random term

X_t : temporal random term

$\varepsilon_{i,t}$: residual

3.6.3 Prediction model

Since there was no available data for years 2011 onward, to project relative risk, the uncertainty from the Bayesian spatio-temporal model was propagated into the projection by taking a sample of 20,000 values from 2 chains from the posterior distribution of relative risk for each district. Then the projection model was run on each value of the sample and the summary statistics were calculated for the combined projection models. The final results are included in chapter 5.

$$R_{ij} = b_{0_{ij}} + b_{1_{ij}} X$$

$$i = 1,2,\dots,316\ (districts)\ \&\ j = 1,\dots,20000\ (N\ of\ posterior\ samples\ out\ of\ MCMC)$$

Here R_{ij} is each posterior sample of relative risk of breast cancer incidence for each district, X is the year variable, and b is a vector of regression coefficients.

3.7 Model convergence and goodness of model fit

Various metrics are used to show the quality of model convergence and the quality of model fitting. In addition, these measurements can provide some quantitative values to check whether the convergence and fitting process are acceptable or not.

The model's convergence was assessed informally via visual checks of density and trace plots and formally using the Brooks-Gelman-Rubin (BGR) index. The BGR statistic is an ANOVA[1]-type diagnostic that compares within- and among-chain variance. Values around one can indicate convergence, with 1.1 considered an acceptable limit (Gelman and Hill, 2006). I examined plots of the value of the BGR statistic to check that it was reliably converging toward its final value for each model. I also examined values of R-hat, which is simply the ratio of the between and within chain variance and provides an index for the full set of parameters together. Therefore, the R-hat value delivers information on the convergence of the algorithm (at convergence, R-hat = 1). If R-hat is significantly larger than 1

[1] Analysis of variance

(i.e., > 1.1), the model has not yet converged and it is essential to run more iterations (Bürkner, 2017). The results of R-hat are provided below (Table 8).

Table 8. R-hat index for each model specific parameters to check model convergence.

Spatio-temporal (incidence at province)

Parameter	R-hat
alpha	1.00
Bcomp	1.00
Burban	1.00
Byos	1.01
deviance	1.00
frac.spatial	1.00
lambda	1.00
sd.spatial	1.00
sigma2u	1.00
sigma2v	1.00
var.spatial	1.00
ypred	1.00

Spatio-temporal (mortality at province)

Parameter	R-hat
alpha	1.13
Bcomp	1.18
Burban	1.08
Byos	1.09
deviance	1.03
frac.spatial	1.09
lambda	1.08
sd.spatial	1.12
sigma2u	1.08
sigma2v	1.06
var.spatial	1.12
ypred	1.03

Spatio-temporal (incidence at district)

Parameter	R-hat
alpha	1.03
Bcomp	1.00
Burban	1.00
Byos	1.03
deviance	1.00
frac.spatial	1.00
lambda	1.00
sd.spatial	1.00
sigma2u	1.00
sigma2v	1.00
var.spatial	1.00
ypred	1.00

The model's goodness of fit was assessed using the Deviance Information Criterion (DIC), Moran's I test and cross-validation method which is described in the next section (3.8). The DIC is a hierarchical modelling generalisation of the Akaike Information Criterion (AIC), a quality estimator for evaluating statistical models and comparing them (Cain and Zhang, 2019). It is used in Bayesian model selection problems where the posterior distributions of the models have been obtained by MCMC simulation (Ando, 2007). Many other researchers have also successfully used this approach in health monitoring applications (Asaria *et al.,* 2012; Di Cesare *et al.,* 2015). Although the minimum DIC estimates the model with the best predictions, it is difficult to say definitively what would establish a significant difference in DIC. Differences of more than ten might undoubtedly rule out the model with the higher DIC. Still, if the difference is less than five, and the models provide very different results, it could be misleading only to report the model with the lowest DIC (El-Basyouny and Sayed, 2009). Since the model also borrows strength via covariates, I checked the improvement of model fitting according to the DIC, using different covariates. A sensitivity analysis has also been done by fitting a model including the province-level prevalence of female obesity. Based on the DIC, the quality of this

model fit was worse than the model I have selected. Including an inappropriately large number of covariates would lead to a model driven by the covariates more than the outcome data themselves, so I have included standard covariates in these models. The model residuals have also been calculated, and Moran's I test (Moran, 1950) has been performed to check no spatial correlation among residuals. The Moran's I test computes the fitted line slope between the actual residual for each province/district and the mean residual calculated, including the neighbouring areas. The obtained Moran's I coefficient (close to zero) and the associated p-value ($p > 0.05$) indicated that there was no evidence to reject the null hypothesis of no spatial correlation. I then concluded that the model allows for spatial patterns appropriately. The Moran's I test results for the province-level estimates are presented in Appendix Figure 1.

3.8 Cross-validation

The validity of the model estimates was verified by cross-validation. A 10% subset of the data was withheld from the model and predicted values for these provinces-districts-years were compared to the heldout original data. I did cross-validation for two main models: the spatial model for provinces (incidence and mortality for three time-intervals) and the spatio-temporal model for provinces and districts (incidence and mortality for 2000 to 2010). The areas whose data were withheld were randomly selected, creating the appearance of provinces/districts with no data where data were available. In the spatial and spatio-temporal models for province, I had 31 provinces per time which means I held out three provinces randomly by each time for incidence and mortality models (results are presented in sections 4.5 and 4.7). In the spatio-temporal model for district, I had 3160 data points (316 districts and 10 years) from which I held out 320 data points that were randomly selected (32 districts per year) (results are presented in section 5.6). This test was designed to check how well the statistical model predicts relative risks of breast cancer incidence and mortality in provinces, districts and years without data. The test was repeated five times, with a different subset of withheld data in each repetition. The model was then fitted to the data from the remaining 90% of provinces/districts, and prediction of the heldout observations were made. Then, I compared the differences between the heldout data (observed)

and the estimates (model output), and reported median relative error ((Model - Observed)/ Observed), median absolute relative error (|(Model - Observed)/ Observed|), median error (Model - Observed) and median absolute error (|Model - Observed|). I also calculated the Bayesian Wilcoxon rank test which is a statistical hypothesis test to combine the ideas of the classical Wilcoxon signed-rank test with Bayesian inference. It is used to compare two related samples and determine if their means are significantly different. The Bayesian Wilcoxon test starts by defining a prior distribution for the difference in population means between the two samples and then calculating the posterior distribution of the difference in means. If the distribution does not include zero, this suggests evidence for a difference between the two groups being compared (Chechile, 2018). In addition, I checked the coverage of the 95% CrIs of the estimates. In a model with a good external predictive validity, this coverage would consist of 95% of heldout values.

3.9 Ethics

The Ethics Committee of the National Institute for Medical Research Development in Iran (IR.NIMAD.REC.1396.192) and the Ethics Committee of the Middlesex University in the UK (14142.2020) approved the study protocol.

3.10 Summary

This chapter highlighted the development of Bayesian Poisson spatial and spatio-temporal models to estimate female relative risk of breast cancer incidence and mortality for 31 provinces and 316 districts in Iran from 2000 to 2010, the prediction method for the years 2011 to 2021 and explained the validation of statistical models. In addition, I described the main components of the models and the Bayesian framework that has been proved to be a suitable approach to tackle issues due to complex spatial and temporal dependence structures. The analysis of breast cancer by geographical levels and time has provided valuable insight into understanding its patterns in Iran. The obtained results are described in further detail in Chapters 4 and 5.

4 Geographical and socioeconomic inequalities in female breast cancer incidence and mortality in Iranian provinces

4.1 Overview

In this chapter, I addressed the following research objectives: Estimate breast cancer incidence and mortality rates at the province level in Iran from 2000 to 2010 using spatial model and assess the association between breast cancer incidence and mortality rates with wealth quintiles at the province level, in addition estimate the relative risk of breast cancer incidence and mortality by province and year using spatio-temporal model.

This chapter presents the results of provincial estimates of breast cancer incidence and mortality and its socioeconomic inequalities in Iranian provinces. Also, the cross-validation results for the province-level models have been provided for both spatial and spatio-temporal model. The part of results presented in this chapter have been already published (Rahimzadeh *et al.,* 2021).

4.2 National breast cancer incidence and mortality rates

The national average of breast cancer incidence rates (per 100,000 people) in 2000-2003, 2004-2007 and 2008-2010 were respectively 15.0, 22.8 and 39.6, while breast cancer mortality rates (per 100,000) were 10.9, 10.3 and 9.9, respectively. The national incidence rate increased by 52% from 2000-2003 to 2004-2007 and almost 75% between 2004-2007 and 2008-2010. The percentage reduction in the mean national mortality rate was consistently around 5% between these periods (Figure 13, Figure 14).

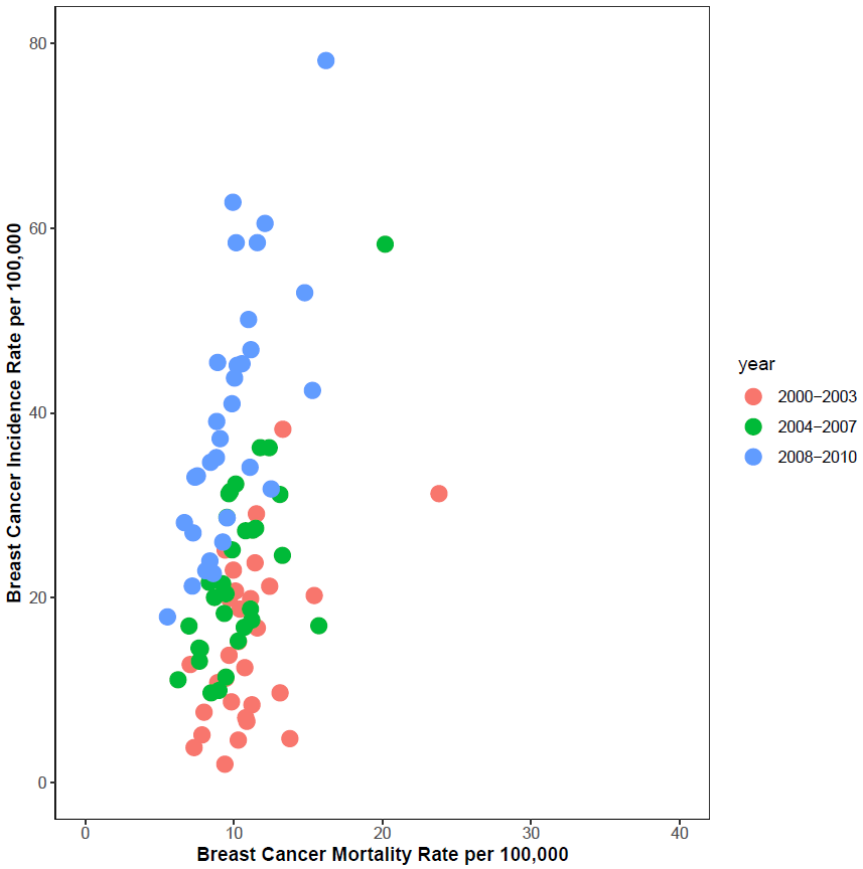
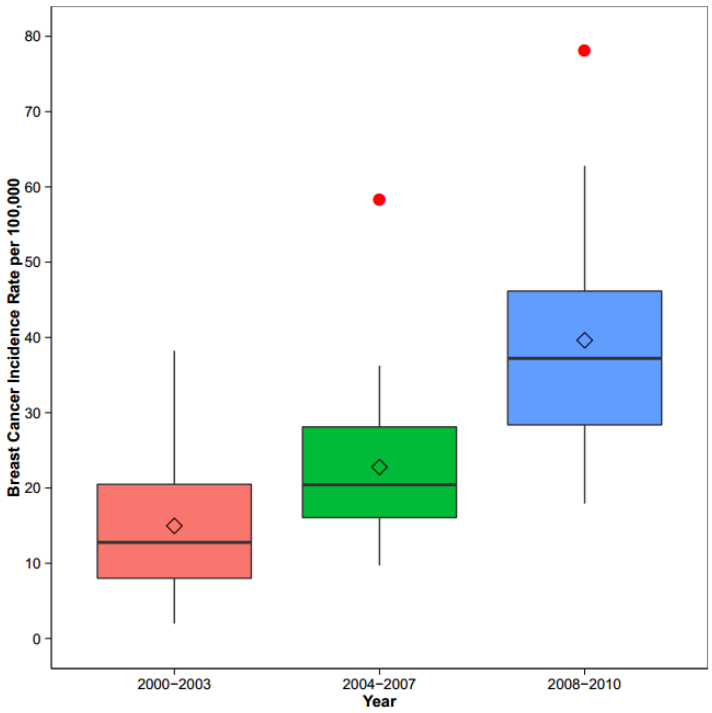


Figure 13. Breast cancer incidence versus mortality rates per 100,000 by three time-intervals (each dot shows a province).

a



b

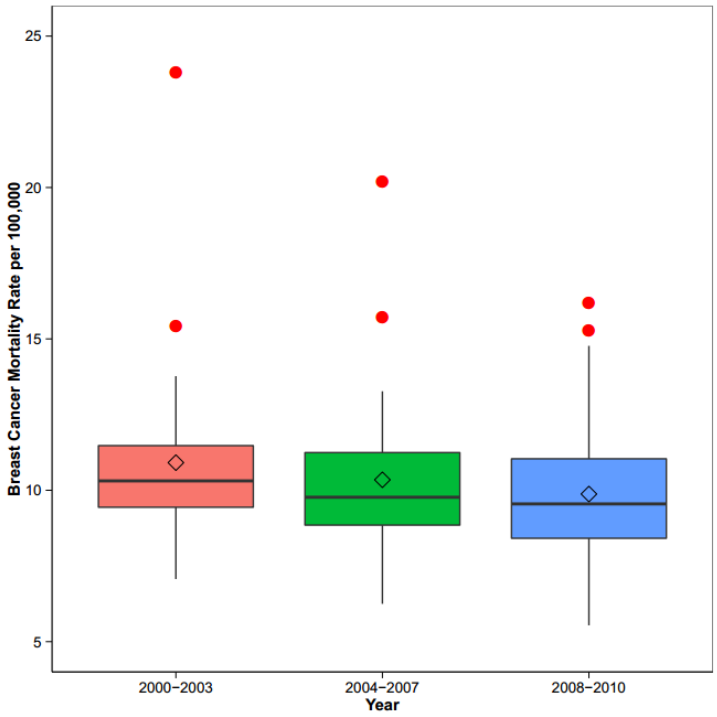


Figure 14. Box plots of breast cancer incidence rates per 100,000 (a) and breast cancer mortality rates per 100,000 (b) (the diamond symbol shows the mean value, and red dots show outliers).

4.3 Breast cancer incidence and mortality rates across provinces

The incidence rate for breast cancer was highest in Tehran (78.2 [95% CrI: 75.5, 80.9]), Khuzestan (62.8 [58.4, 67.3]), and Yazd (60.5 [52.2, 69.3]) in 2008-2010. In contrast, Sistan and Baluchistan (17.9 [14.5, 21.6]), Zanjan (21.3 [16.5, 26.4]), and Ardabil (22.6 [18.1, 27.5]) were found to have the lowest rates in the same time-interval (Figure 15a, Appendix Table 2). The breast cancer mortality rate was highest in Tehran (16.2 [15.0, 17.4]), Alborz (15.3 [12.6, 18.2]), and Semnan (14.8 [10.2, 19.9]) in 2008-2010. Meanwhile, Sistan and Baluchistan (5.5 [3.8, 7.4]), Hormozgan (6.7 [4.4, 9.1]), Zanjan (7.2 [4.8, 9.9]) reported the lowest rates (Figure 15b, Appendix Table 3).

Relative changes have been calculated for breast cancer incidence and mortality rates between 2000-2003 and 2008-2010. Provinces with the highest relative percentage change of incidence rates between 2000-2003 and 2008-2010 were Khorasan, North (1111.1% [673.1%, 3013.6%]), Alborz (793.5% [620.8%, 1082.8%]), and Ilam (524% [342.9%, 994.8%]). In contrast, Qazvin (43.5% [38.2%, 50.7%]), Qom (57.0% [49.4%, 66.5%]) and Yazd (58.3% [52.4%, 65.2%]) had the lowest relative percentage change of incident rates. While the mortality relative changes have been decreased for most of the provinces maximum at Tehran (-31.9% [-31.2%, -32.7%]), Sistan and Baluchistan (-24.7% [-23.7%, -26.9%]), and Zanjan (-24.2% [-22.0%, -27.3%]), relative changes show a different pattern for Semnan (19.4% [15.7%, 24.4%]), Alborz (10.9% [9.0%, 14.5%]), and Kermanshah (5.3% [4.5%, 6.4%]) with the greatest increasing trends in mortality rates (Table 9).

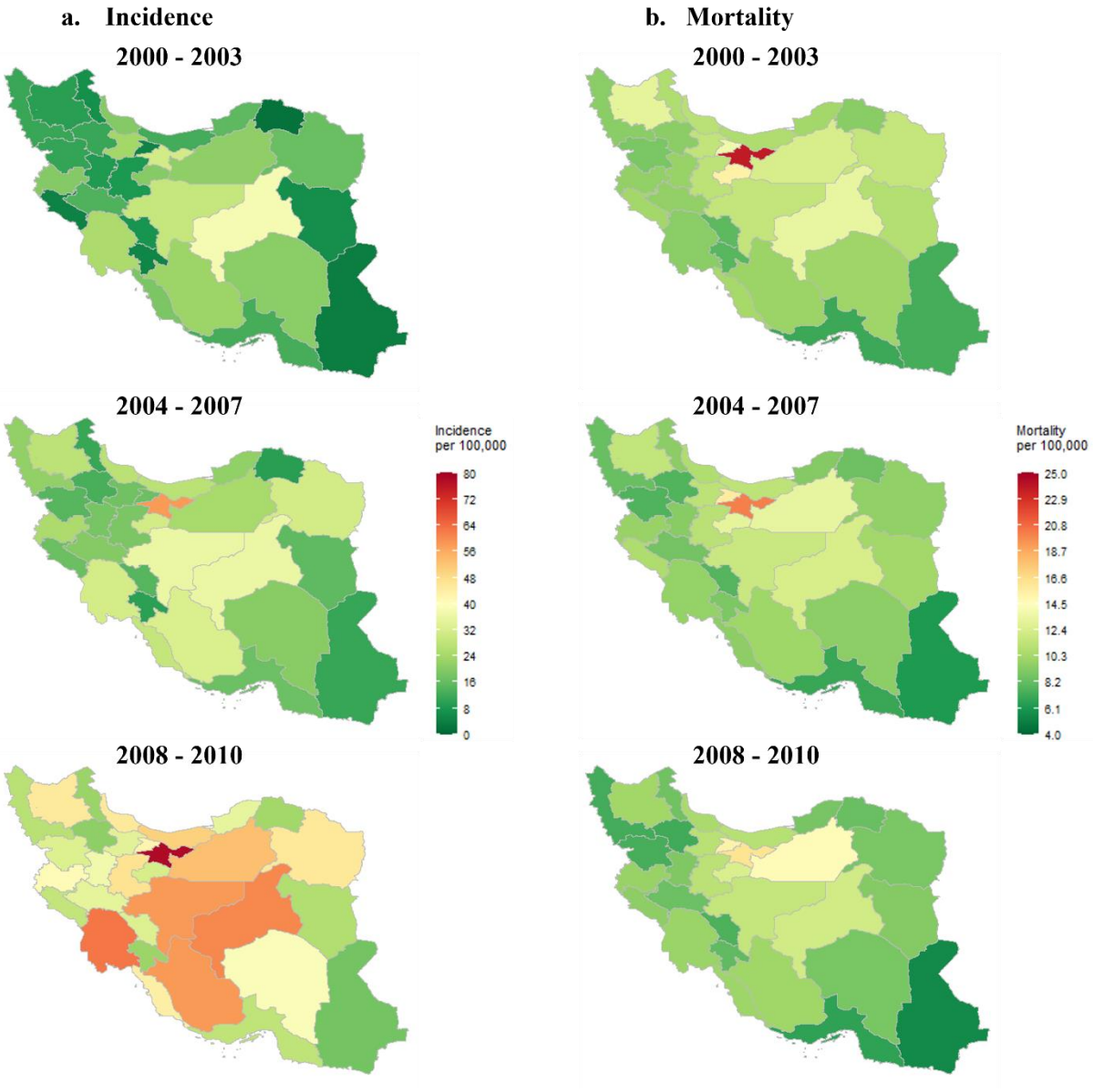
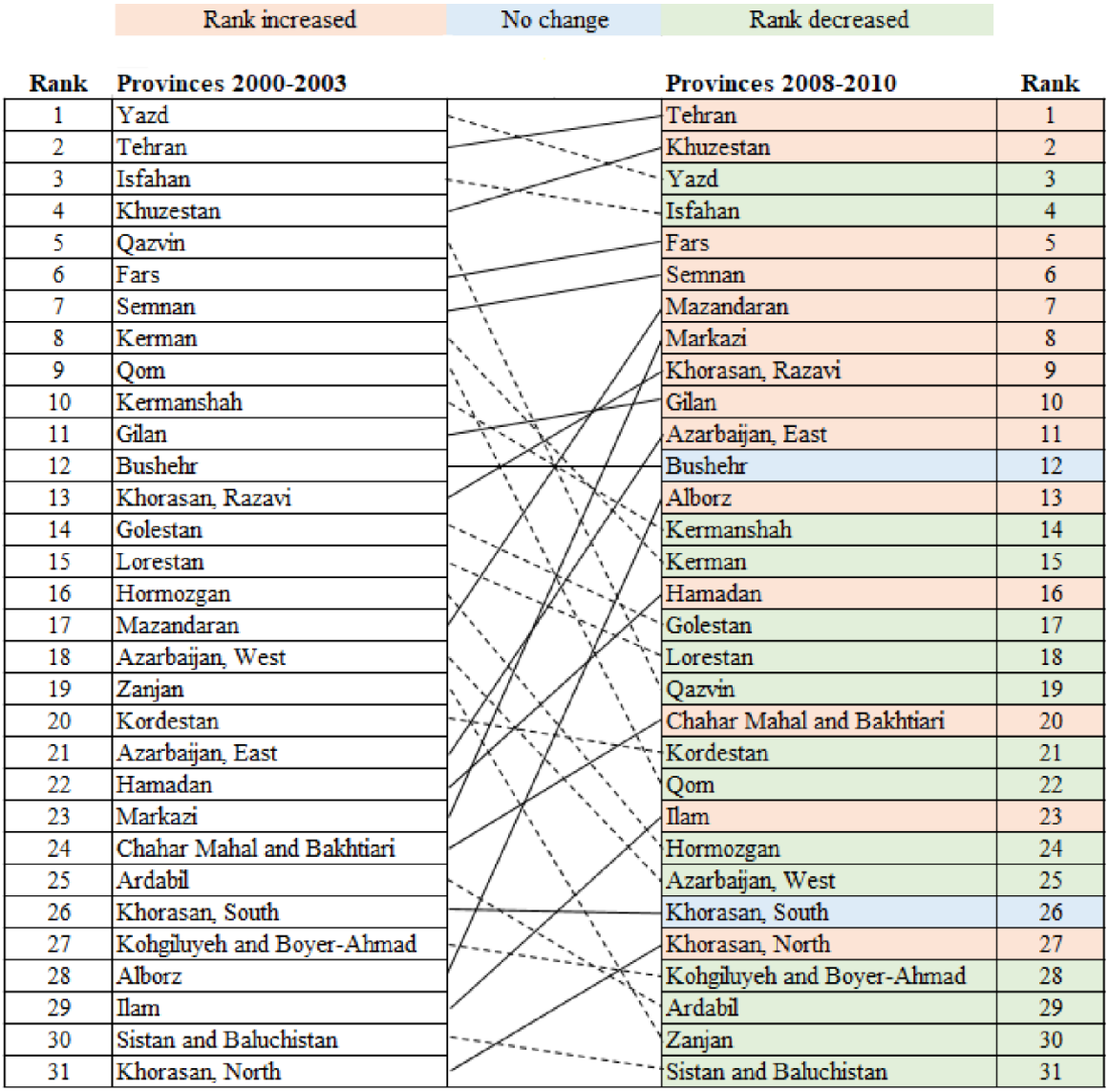


Figure 15. (a) Posterior breast cancer incidence rates per 100,000 by the province level for 2000-2003, 2004-2007 and 2008-2010; (b) Posterior breast cancer mortality rates per 100,000 by the province level for 2000-2003, 2004-2007 and 2008-2010.

Table 9. Relative percentage change of rates (per 100,000) for female breast cancer incidence and mortality by province (alphabetically sorted by provinces name).

	Incidence	**Mortality**
	Relative percentage change between 2000-03 and 2008-10 (95% CrI)	**Relative percentage change between 2000-03 and 2008-10 (95% CrI)**
Alborz	793.5 (620.8, 1082.8)	10.9 (9.0, 14.5)
Ardabil	223.0 (183.1, 288.7)	-20.4 (-22.8, -18.6)
Azarbaijan, East	365.6 (328.1, 414.4)	-22.1 (-23.2, -20.5)
Azarbaijan, West	138.9 (124.7, 157.9)	-22.3 (-26.3, -21.7)
Bushehr	133.2 (112.3, 163.4)	-2.9 (-4.9, -2.8)
Chahar Mahal and Bakhtiari	336.1 (258.8, 496.0)	-5.0 (-5.3, -4.0)
Fars	154.2 (144.8, 165.5)	2.0 (1.7, 2.4)
Gilan	127.8 (118.7, 139.1)	-4.5 (-6.5, -4.5)
Golestan	130.6 (115.7, 152.6)	-12.9 (-12.9, -12.5)
Hamadan	326.3 (275.6, 397.7)	-7.1 (-7.9, -7.3)
Hormozgan	120.3 (101.5, 148.0)	-5.6 (-6.4, -6.2)
Ilam	524.0 (342.9, 994.8)	-6.8 (-7.3, -3.3)
Isfahan	101.0 (95.9, 106.8)	0.9 (0.0, 1.0)
Kerman	88.6 (81.0, 98.6)	-14.6 (-14.5, -14.1)
Kermanshah	105.9 (96.3, 118.3)	5.3 (4.5, 6.4)
Khorasan, North	1111.1 (673.1, 3013.6)	-13.4 (-13.7, -12.2)
Khorasan, Razavi	171.8 (160.7, 184.4)	-23.3 (-24.8, -22.0)
Khorasan, South	293.2 (220.1, 483.4)	-14.7 (-15.7, -12.5)
Khuzestan	149.6 (139.7, 160.8)	2.1 (1.7, 2.7)
Kohgiluyeh and Boyer-Ahmad	345.0 (234.6, 684.2)	2.5 (0.0, 6.7)
Kordestan	205.7 (173.6, 253.7)	-16.9 (-20.0, -16.4)
Lorestan	151.7 (132.6, 177.6)	-10.6 (-12.9, -11.5)
Markazi	457.1 (375.9, 575.7)	0.0 (-2.1, 1.2)
Mazandaran	303.2 (272.6, 341.8)	2.8 (1.6, 2.2)
Qazvin	43.5 (38.2, 50.7)	-2.6 (-2.7, -2.4)
Qom	57.0 (49.4, 66.5)	-18.8 (-19.3, -18.1)
Semnan	149.6 (127.7, 180.3)	19.4 (15.7, 24.4)
Sistan and Baluchistan	374.3 (286.7, 563.9)	-24.7 (-26.9, -23.7)
Tehran	149.9 (145.0, 155.2)	-31.9 (-32.7, -31.2)
Yazd	58.3 (52.4, 65.2)	-9.0 (-9.3, -8.2)
Zanjan	88.3 (75.2, 110.7)	-24.2 (-27.3, -22.0)

The relative ranking position of provinces has changed over time (Figure 16). Yazd had the highest incidence rate in 2000-2003, replaced by Tehran in 2008-2010. Tehran - the most populous province in Iran, with almost 10% of the total Iranian population living there - had the highest mortality rates from 2000 to 2003 and 2008 to 2010 (Figure 17). Looking at changes in rank of provinces regarding breast cancer incidence and mortality may inform appropriate changes in policies or programmes, and highlight the locations where additional resources should be focused. Some provinces experienced a more significant change over time probably due to particular factors (coverage, screening, risk factors, etc.), while for others, the ranking has essentially not changed.



Rank	Provinces 2000-2003	Provinces 2008-2010	Rank
1	Yazd	Tehran	1
2	Tehran	Khuzestan	2
3	Isfahan	Yazd	3
4	Khuzestan	Isfahan	4
5	Qazvin	Fars	5
6	Fars	Semnan	6
7	Semnan	Mazandaran	7
8	Kerman	Markazi	8
9	Qom	Khorasan, Razavi	9
10	Kermanshah	Gilan	10
11	Gilan	Azarbaijan, East	11
12	Bushehr	Bushehr	12
13	Khorasan, Razavi	Alborz	13
14	Golestan	Kermanshah	14
15	Lorestan	Kerman	15
16	Hormozgan	Hamadan	16
17	Mazandaran	Golestan	17
18	Azarbaijan, West	Lorestan	18
19	Zanjan	Qazvin	19
20	Kordestan	Chahar Mahal and Bakhtiari	20
21	Azarbaijan, East	Kordestan	21
22	Hamadan	Qom	22
23	Markazi	Ilam	23
24	Chahar Mahal and Bakhtiari	Hormozgan	24
25	Ardabil	Azarbaijan, West	25
26	Khorasan, South	Khorasan, South	26
27	Kohgiluyeh and Boyer-Ahmad	Khorasan, North	27
28	Alborz	Kohgiluyeh and Boyer-Ahmad	28
29	Ilam	Ardabil	29
30	Sistan and Baluchistan	Zanjan	30
31	Khorasan, North	Sistan and Baluchistan	31

Figure 16. Provinces ranked by incidence rates per 100,000 for 2000-2003 and 2008-2010. Dotted and solid lines show a decrease and increase in rank, respectively.

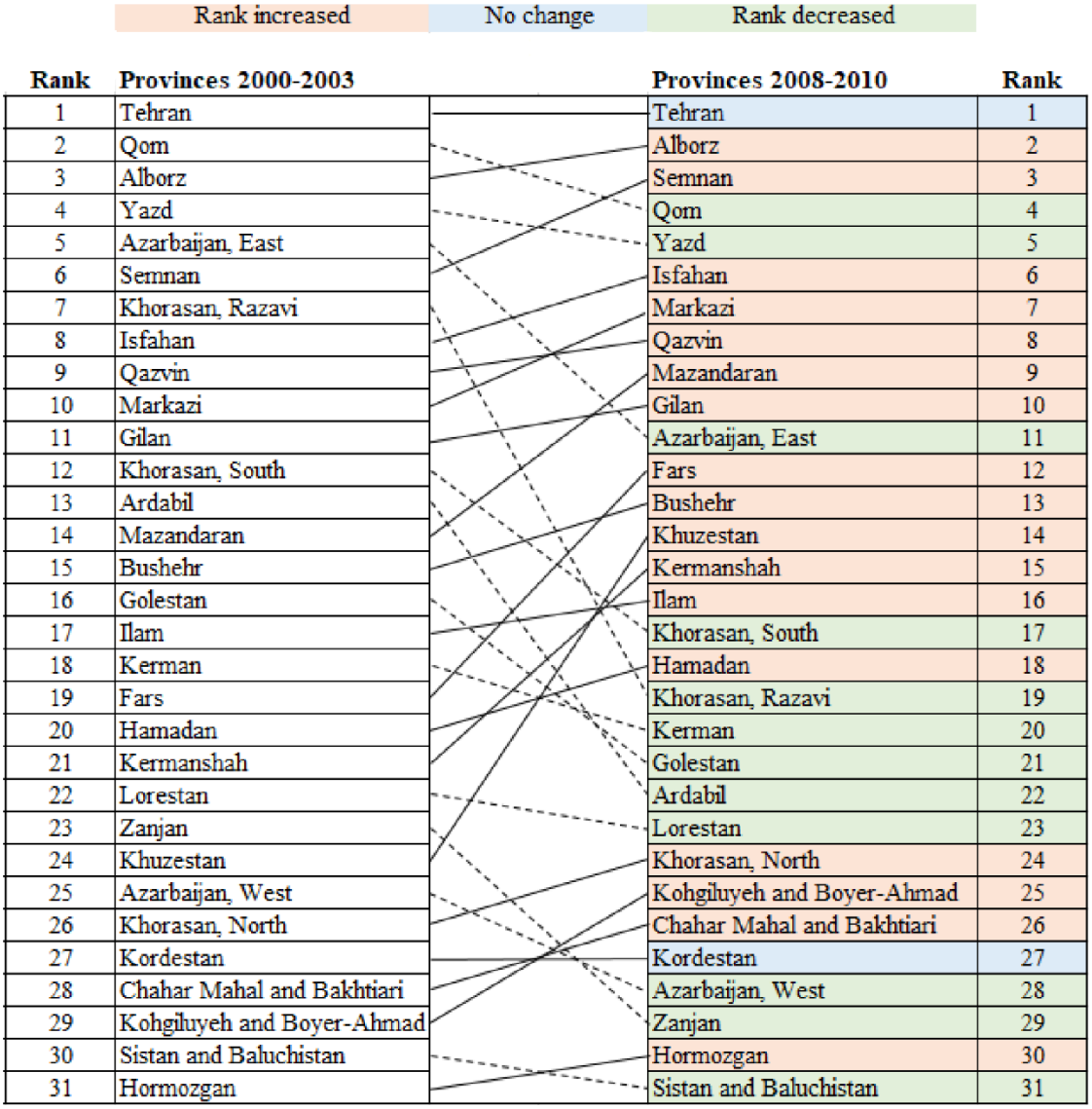


Figure 17. Provinces ranked by mortality rates per 100,000 for 2000-2003 and 2008-2010. Dotted and solid lines show a decrease and increase in rank, respectively.

4.4 Breast cancer estimations in relation to deprivation at sub-national levels

The province-level deprivation was associated with breast cancer incidence and mortality rates over three time-intervals. When grouped by wealth index quintiles (Figure 18, Table 10), results showed that the wealthiest provinces (highest quintile) had higher levels of breast cancer incidence in 2000-2003 (average from 7.0 per 100,000 people in the lowest quintile (Q1) to 24.1 per 100,000 people in the highest quintile (Q5)), 2004-2007 (Q1:15.7, Q5:32.0) and 2008-2010 (Q1:30.7, Q5:48.8). Similarly, the wealthiest provinces had higher levels of breast cancer mortality in 2000-2003 (Q1:9.3, Q5:15.0), 2004-2007 (Q1:8.6, Q5:13.5) and 2008-2010 (Q1:8.3, Q5:12.5). Thus, while the national mortality rate is decreasing, the reduction in mortality rate observed in the wealthier provinces is larger than the one observed in the most deprived provinces.

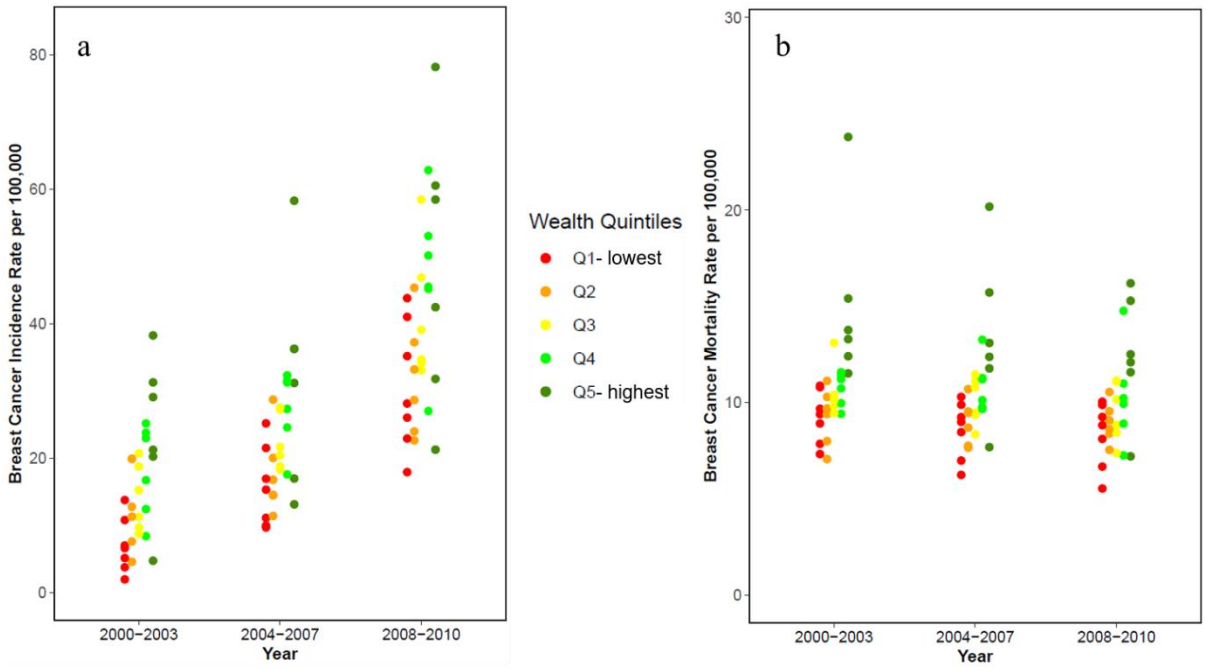


Figure 18. Breast cancer incidence (a) and mortality (b) rates per 100,000 by province arranged by quintiles of provinces wealth. Each dot represents the posterior incidence and mortality rates for one province. Dark green colour shows the wealthiest quintile and the red colour shows the most-deprived quintile.

Table 10. Breast cancer incidence and mortality rates (per 100,000) by wealth index quintiles in Iran over time.

		Most deprived	Q2	Q3	Q4	Least deprived
Incidence	2000-2003	7.0 (4.5, 9.9)	12.7 (9.8, 16.0)	14.1 (10.9, 17.5)	18.3 (15.5, 21.2)	24.1 (20.3, 28.3)
	2004-2007	15.7 (12.1, 19.6)	17.7 (13.6, 22.2)	22.3 (19.4, 25.5)	27.4 (24.0, 31.0)	32.0 (28.2, 36.0)
	2008-2010	30.7 (25.2, 36.7)	31.8 (26.3, 37.8)	41.0 (36.1, 46.2)	47.3 (42.6, 52.2)	48.8 (43.8, 54.0)
Mortality	2000-2003	9.3 (6.4, 12.5)	9.3 (6.7, 12.1)	10.5 (8.1, 13.3)	10.7 (8.7, 12.9)	15.0 (12.1, 18.2)
	2004-2007	8.6 (6.1, 11.4)	9.0 (6.3, 12.0)	10.1 (8.2, 12.2)	10.9 (8.7, 13.2)	13.5 (11.1, 16.1)
	2008-2010	8.3 (5.7, 11.3)	9.0 (6.3, 11.9)	9.5 (7.3, 11.9)	10.4 (8.2, 12.6)	12.5 (10.1, 15.1)

In addition, when breast cancer incidence data were grouped by district-level deprivation through the spatial model at three time-intervals (Figure 19), similarly, the results showed that the wealthiest districts (highest quintile) had higher levels of breast cancer incidence in 2000-2003 (average from 8.1 in Q1 to 16.7 in Q5), 2004-2007 (Q1:12.4, Q5:22.4) and 2008-2010 (Q1:21.9, Q5:39.1).

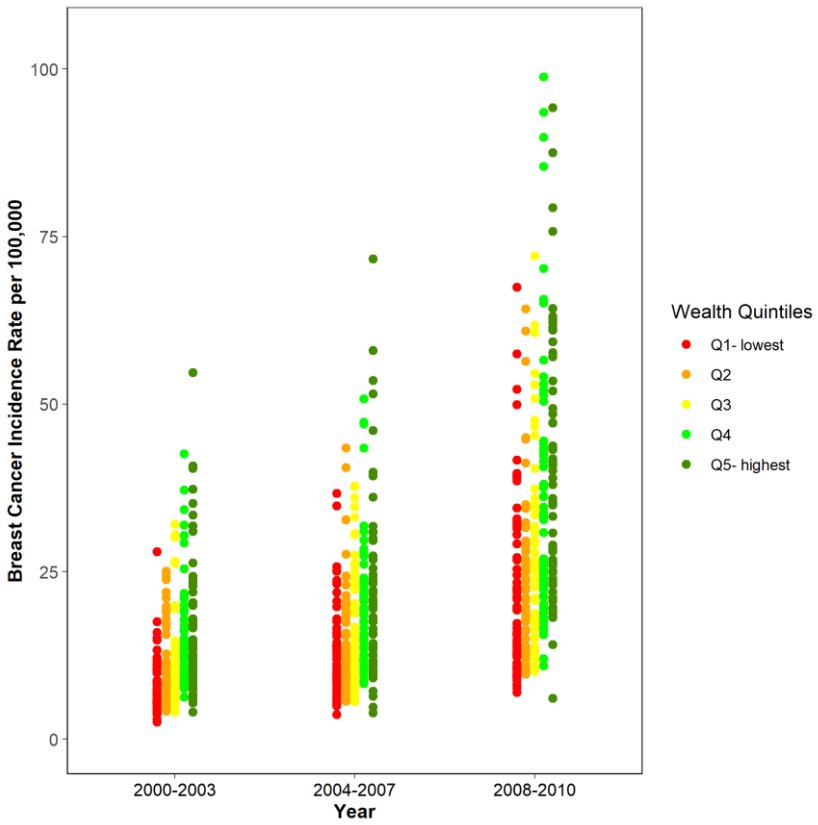


Figure 19. Breast cancer incidence rates per 100,000 by district arranged by quintiles of district wealth. Each dot represents the posterior incidence rate for one district. Dark green colour shows the wealthiest quintile and the red colour shows the most-deprived quintile.

4.5 Cross-validation results for the spatial model at the province level

Results of the cross-validation for each time-interval are presented in Table 11. The estimates of breast cancer incidence rate were unbiased as evidenced by median relative errors very close to zero overall (-0.02 in 2000-2003, 0.24 in 2004-2007 and 0.005 in 2008-2010). The p-values computed by the classic Wilcoxon test were all over 0.05, suggesting no significant difference between estimated versus heldout observed values. The 95% CrIs of estimated rates covered 100% observed values in 2000-2003, 86.7% in 2004-2007 and 93.3% in 2008-2010.

The median relative errors were also very close to zero for mortality data (0.04 in 2000-2003, 0.06 in 2004-2007 and 0.005 in 2008-2010), with all three p-values over 0.05. Similarly, the 95% CrIs of estimated rates covered 100% observed values in 2000-2003, 86.7% in 2004-2007 and 86.7% in 2008-2010. The cross-validitation findings confirmed that the statistical models applied to estimate the breast cancer incidence and mortality rates at the province level fitted well.

Table 11. Results of cross-validation for the spatial model at the province level (p-values < 0.05 show a significant difference between estimated values and heldout values).

Data		No. of held out observations	Relative error*			Absolute relative error			Error•			Absolute error			(P*)	95% CrI Coverage
			Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3		
Incidence	2000-2003	3	-0.02	-0.43	0.89	0.48	0.34	0.91	-0.28	-9.93	5.52	6.23	5.52	9.35	0.28	100%
	2004-2007	3	0.24	-0.08	0.57	0.29	0.24	0.57	4.16	-2.87	9.99	7.75	4.26	15.12	0.28	86.67%
	2008-2010	3	0.005	-0.2	0.14	0.19	0.11	0.29	0.14	-7.97	4.31	7.07	3.54	13.31	0.8	93.33%
Mortality	2000-2003	3	0.04	-0.01	0.12	0.07	0.04	0.14	0.37	-0.19	1.09	0.8	0.4	1.19	0.2	100%
	2004-2007	3	0.06	-0.09	0.1	0.1	0.06	0.27	0.71	-1.47	0.99	1.2	0.74	3.17	0.71	86.67%
	2008-2010	3	0.005	-0.14	0.25	0.19	0.11	0.34	0.05	-1.34	1.78	1.8	0.96	2.53	0.68	86.67%

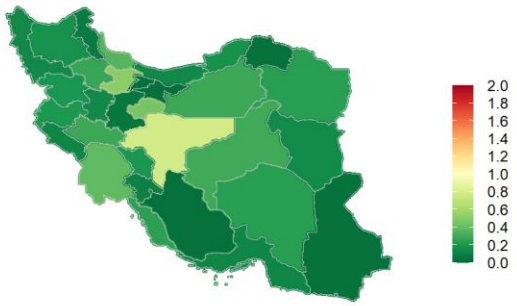
*(Estimated values minus heldout values) / heldout values

•Estimated values minus heldout values

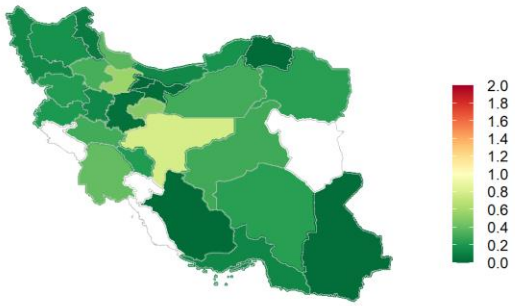
4.6 Relative risk of breast cancer incidence and mortality across provinces over 11 years (spatio-temporal model)

The relative risk of breast cancer incidence was highest in Tehran (1.58 [95% CrI: 1.51, 1.64]), Fars (1.29 [1.19, 1.39]), and Yazd (1.28 [1.07, 1.50]) in 2010. In contrast, Khorasan, North (0.42 [0.30, 0.57]), Zanjan (0.43 [0.32, 0.56]), and Sistan and Baluchistan (0.46 [0.36, 0.56]) were found to have the lowest relative risks in the same time-interval. Relative risk of breast cancer incidence was highest in Tehran (1.71 [1.64, 1.79]), Isfahan (1.11 [1.01, 1.21]), and Yazd (1.07 [0.88, 1.30]) in 2005. Meanwhile, Khorasan, North (0.20 [0.12, 0.30]), Kohgiluyeh and Boyer-Ahmad (0.23 [0.13, 0.37]) and Alborz (0.35 [0.27, 0.44]) reported the lowest relative risk of breast cancer incidence in 2005. In 2000, Isfahan (0.78 [0.69, 0.87]), Qazvin (0.52 [0.38, 0.68]) and Qom (0.46 [0.32, 0.62]) had the highest relative risk of breast cancer incidence while Fars (0.04 [0.03, 0.07]), Tehran (0.041 [0.03, 0.05]) and Alborz (0.04 [0.02, 0.07]) had the lowest relative risks (Figure 20, Table 12). The province-level deprivation was also associated with relative risk of breast cancer incidence over the years from 2000 to 2010. When grouped by wealth index quintiles (Appendix Figure 2), results showed that the wealthiest provinces (highest quintile) had higher levels of breast cancer incidence.

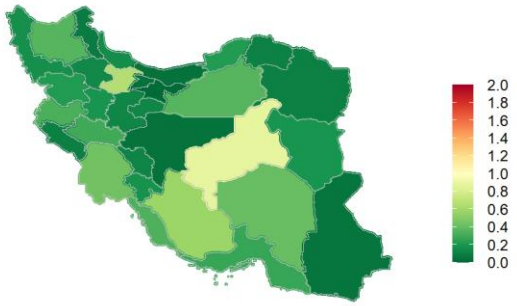
Relative Risk, year 2000



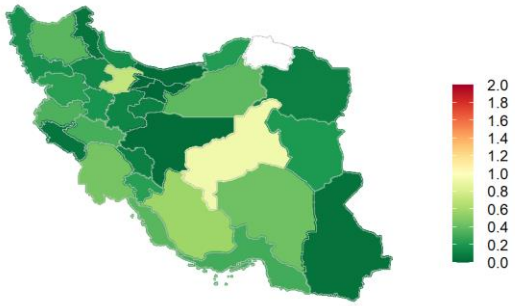
SMR, year 2000



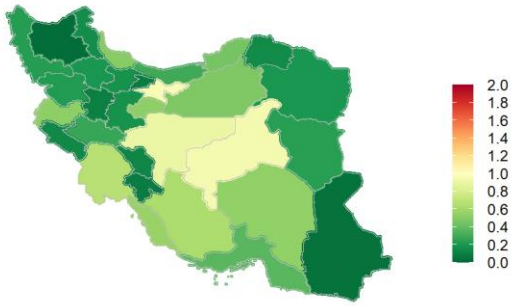
Relative Risk, year 2001



SMR, year 2001



Relative Risk, year 2002



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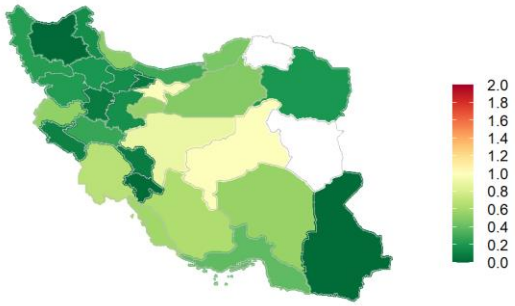
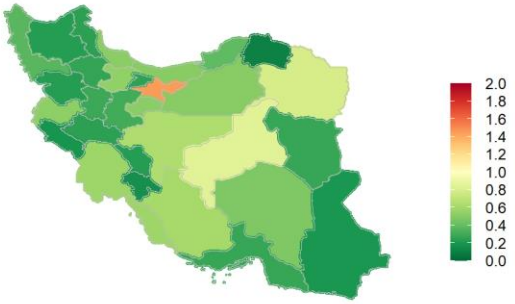
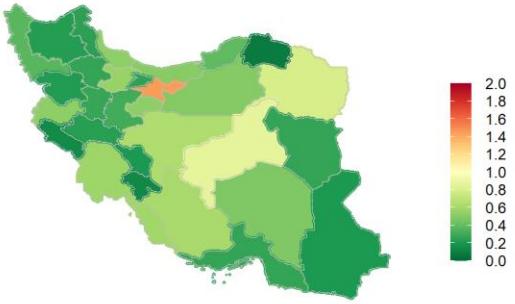


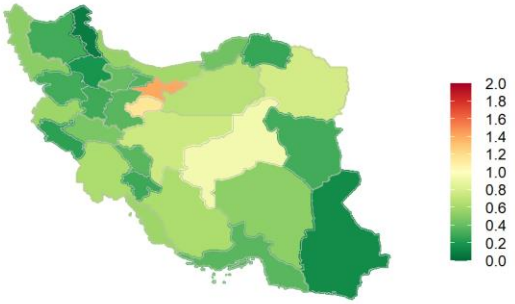
Relative Risk, year 2003



SMR, year 2003



Relative Risk, year 2004



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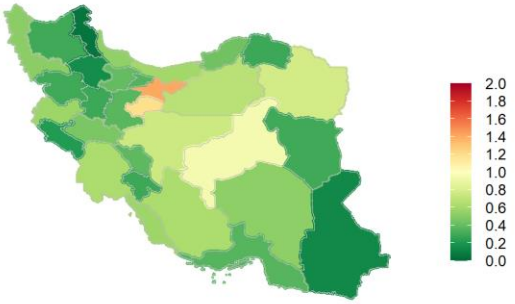
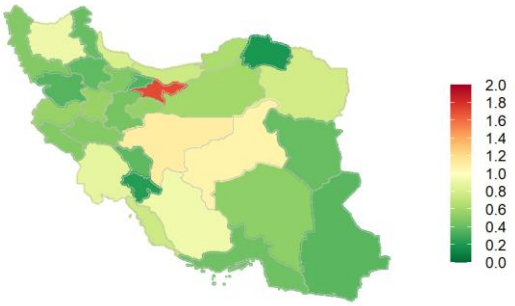
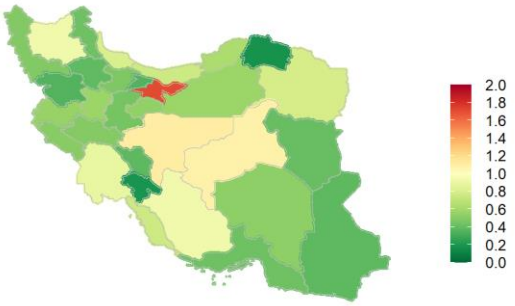


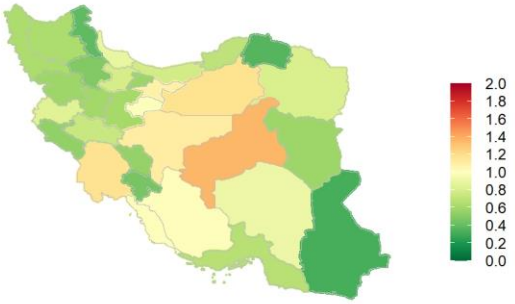
Relative Risk, year 2005



SMR, year 2005

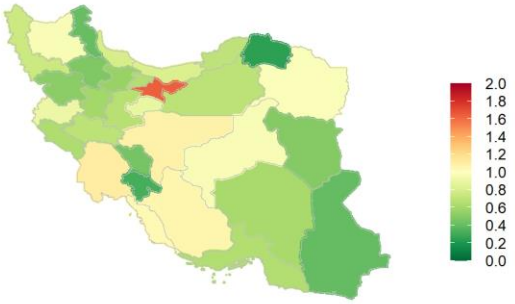


Relative Risk, year 2006

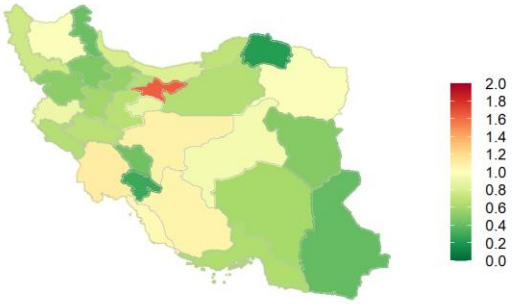


SMR, year 2006

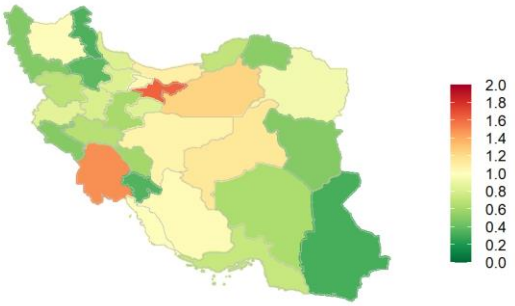
Relative Risk, year 2007



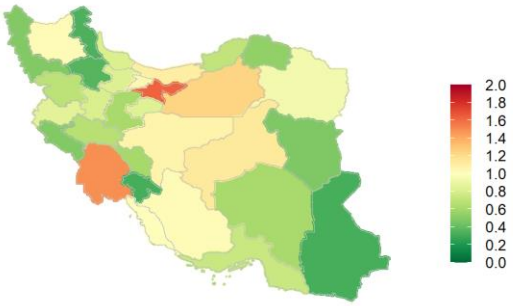
SMR, year 2007



Relative Risk, year 2008



SMR, year 2008



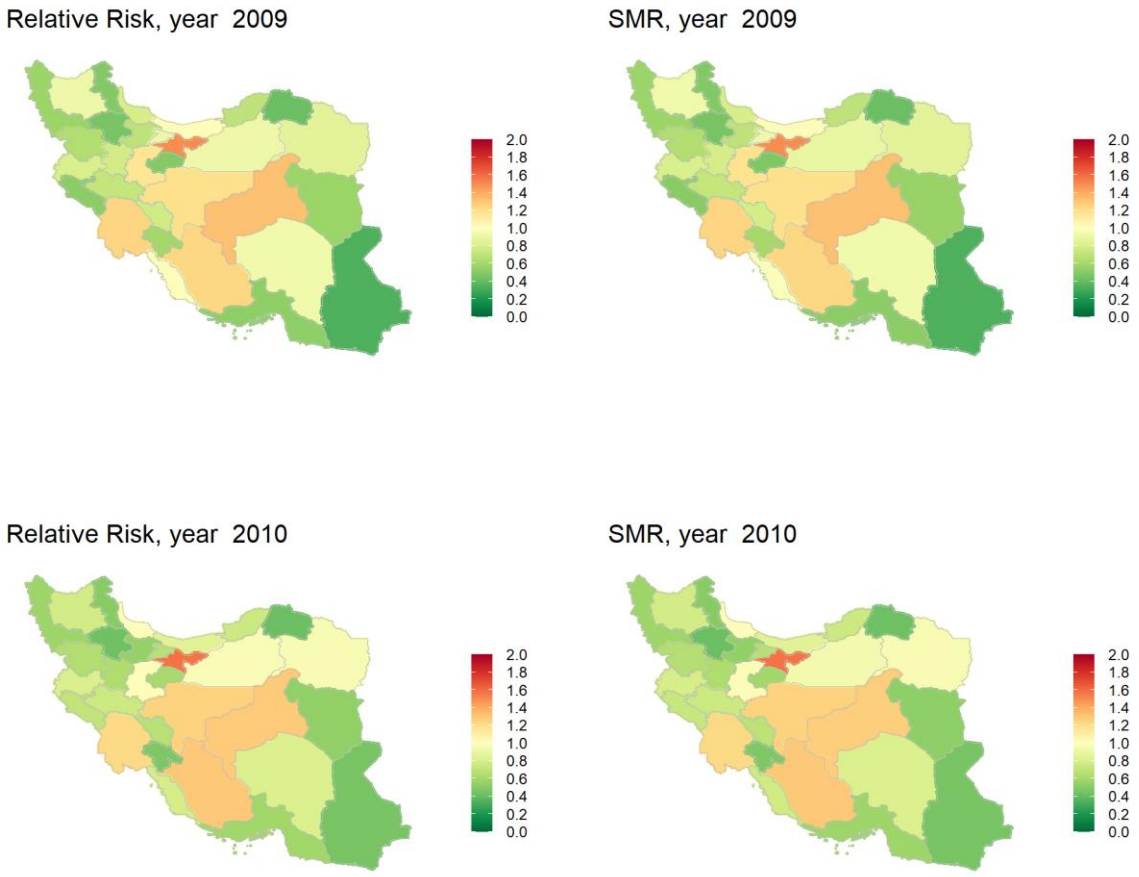


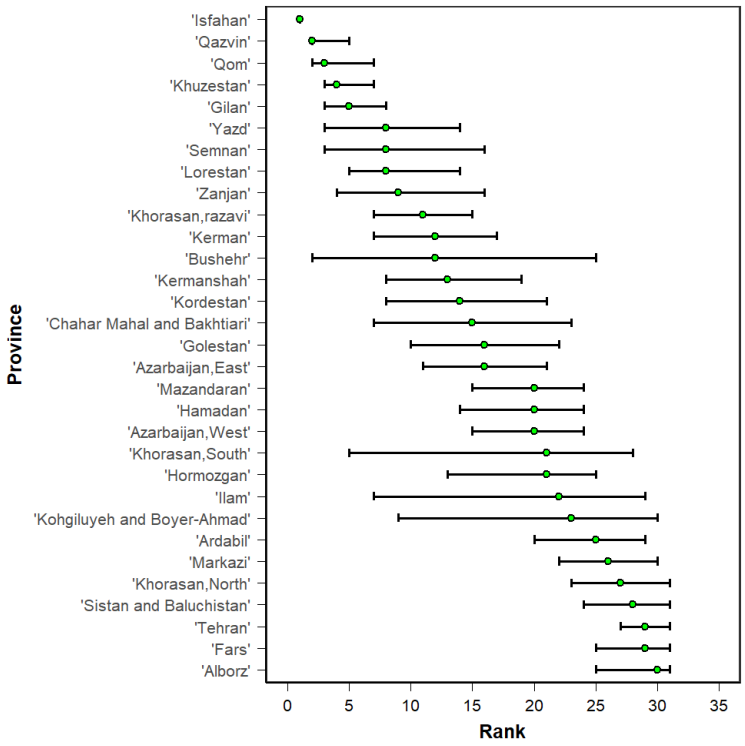
Figure 20. Estimated relative risk of breast cancer incidence (left side) versus standardised morbidity ratio (SMR) (right side) by province level from 2000 to 2010. Cancer registry data was not available in 2006, so SMR map for 2006 is empty.

Table 12. Posterior mean and 95% credible interval for the relative risk of breast cancer incidence by province level (sorted by mean values in 2010).

	Relative risk of breast cancer incidence (CrI)		
Provinces	**2000**	**2005**	**2010**
Tehran	0.04 (0.03, 0.05)	1.71 (1.64, 1.79)	1.58 (1.51, 1.64)
Fars	0.04 (0.03, 0.07)	0.93 (0.84, 1.03)	1.29 (1.19, 1.39)
Yazd	0.30 (0.20, 0.43)	1.07 (0.88, 1.30)	1.28 (1.07, 1.50)
Isfahan	0.78 (0.69, 0.87)	1.11 (1.01, 1.21)	1.25 (1.16, 1.35)
Khuzestan	0.39 (0.32, 0.47)	0.88 (0.78, 0.98)	1.22 (1.12, 1.33)
Markazi	0.07 (0.04, 0.12)	0.45 (0.35, 0.57)	1.01 (0.86, 1.16)
Gilan	0.36 (0.29, 0.44)	0.81 (0.71, 0.92)	1.01 (0.91, 1.12)
Semnan	0.29 (0.17, 0.45)	0.60 (0.42, 0.81)	0.97 (0.76, 1.20)
Khorasan, razavi	0.24 (0.20, 0.29)	0.78 (0.71, 0.86)	0.96 (0.89, 1.04)
Mazandaran	0.14 (0.10, 0.19)	0.76 (0.67, 0.86)	0.85 (0.76, 0.95)
Kerman	0.24 (0.17, 0.31)	0.53 (0.44, 0.63)	0.82 (0.72, 0.94)
Kermanshah	0.21 (0.15, 0.29)	0.56 (0.46, 0.67)	0.81 (0.69, 0.93)
Bushehr	0.25 (0.08, 0.63)	0.76 (0.58, 0.97)	0.79 (0.62, 0.98)
Azarbaijan, East	0.18 (0.14, 0.23)	0.92 (0.82, 1.02)	0.78 (0.70, 0.86)
Lorestan	0.29 (0.20, 0.39)	0.50 (0.39, 0.62)	0.75 (0.63, 0.88)
Golestan	0.18 (0.12, 0.26)	0.63 (0.51, 0.76)	0.75 (0.63, 0.88)
Ilam	0.13 (0.04, 0.32)	0.49 (0.32, 0.70)	0.71 (0.51, 0.94)
Chahar Mahal and Bakhtiari	0.20 (0.11, 0.31)	0.38 (0.26, 0.53)	0.68 (0.52, 0.85)
Alborz	0.04 (0.02, 0.07)	0.35 (0.27, 0.44)	0.68 (0.58, 0.78)
Kordestan	0.20 (0.13, 0.29)	0.36 (0.26, 0.46)	0.65 (0.53, 0.79)
Hamadan	0.14 (0.09, 0.20)	0.56 (0.46, 0.68)	0.64 (0.54, 0.76)
Qom	0.46 (0.32, 0.62)	0.55 (0.41, 0.71)	0.62 (0.49, 0.77)
Hormozgan	0.13 (0.07, 0.21)	0.43 (0.32, 0.57)	0.59 (0.47, 0.73)
Azarbaijan, West	0.14 (0.10, 0.19)	0.49 (0.41, 0.58)	0.58 (0.50, 0.66)
Qazvin	0.52 (0.38, 0.68)	0.49 (0.37, 0.63)	0.55 (0.43, 0.69)
Khorasan, South	0.15 (0.05, 0.37)	0.41 (0.28, 0.59)	0.54 (0.39, 0.72)
Ardabil	0.08 (0.04, 0.14)	0.41 (0.31, 0.54)	0.51 (0.40, 0.63)
Kohgiluyeh and Boyer_Ahmad	0.11 (0.03, 0.28)	0.23 (0.13, 0.37)	0.48 (0.33, 0.66)
Sistan and Baluchistan	0.05 (0.02, 0.09)	0.37 (0.28, 0.47)	0.46 (0.36, 0.56)
Zanjan	0.28 (0.18, 0.40)	0.39 (0.28, 0.53)	0.43 (0.32, 0.56)
Khorasan, North	0.05 (0.02, 0.10)	0.20 (0.12, 0.30)	0.42 (0.30, 0.57)

Figure 21 shows the point estimates (median) and 95% credible intervals for the ranks of provinces based on the relative risk of breast cancer incidence in 2000 and 2010 (the higher the rank the higher relative risk). The relative ranking position of provinces has changed over time. Isfahan and Qazvin had the highest relative risk of breast cancer incidence in 2000, replaced by Tehran and Yazd in 2010. The intervals are wide especially for some provinces, illustrating the great uncertainty associated with the ranks. For instance, Bushehr in 2000 is ranked twelveth which can be placed in top (second rank) and in the bottom (twenty-fifth rank). Simillarly, Khorasan, South is ranked twenty-first which can be changed between rank fifth in top and twenty-eighth in bottom.

2000



2010

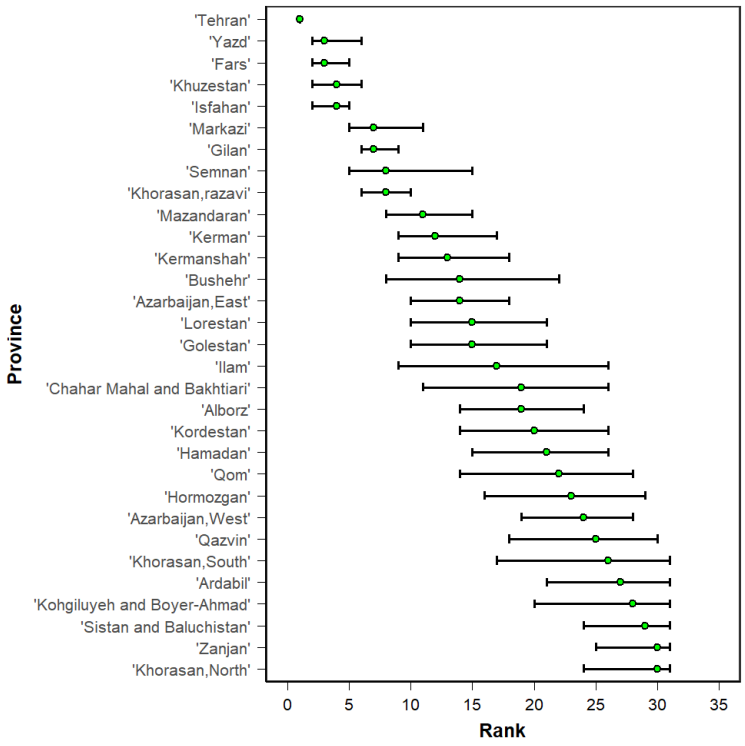
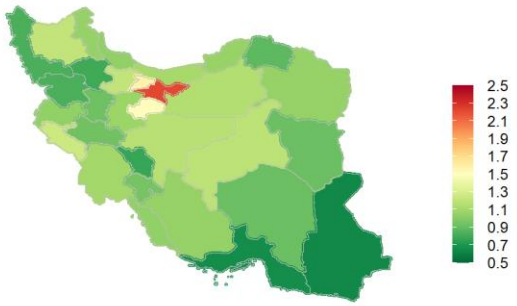


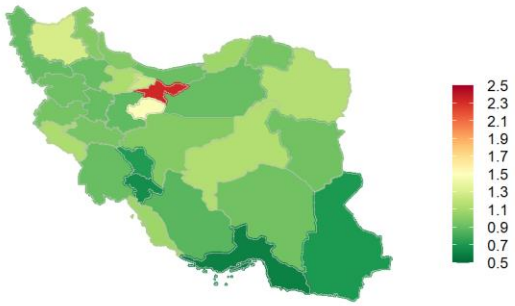
Figure 21. Median and 95% credible intervals for incidence rank of each province which has been calculated from all posterior samples for 2000 (upper figure) and 2010 (lower figure).

The relative risk of breast cancer mortality was highest in Tehran (1.61 [95% CrI: 1.50, 1.72]), Alborz (1.51 [1.35, 1.69]), and Qom (1.17 [1.00, 1.34]) in 2010. In contrast, Sistan and Baluchistan (0.62 [0.54, 0.72]), Hormozgan (0.63 [0.53, 0.75]), and Chahar Mahal and Bakhtiari (0.64 [0.52, 0.77]) were found to have the lowest mortality in the same time-interval. Relative risk of breast cancer mortality was highest in Tehran (2.03 [95% CrI: 1.91, 2.15]), Alborz (1.62 [1.48, 1.75]), and Qom (1.36 [1.16, 1.56]) in 2005. Meanwhile, Hormozgan (0.65 [0.55, 0.79]), Sistan and Baluchistan (0.67 [0.58, 0.77]), and Zanjan (0.73 [0.62, 0.85]) reported the lowest relative risk of breast cancer mortality in 2005. In 2000, Tehran (2.22 [95% CrI: 2.08, 2.37]), Alborz (1.57 [1.35, 1.81]), and Qom (1.51 [1.29, 1.74]) had the highest relative risk of breast cancer mortality while Sistan and Baluchistan (0.64 [0.55, 0.75]), Hormozgan (0.66 [0.55, 0.81]), and Chahar Mahal and Bakhtiari (0.78 [0.64, 0.95]) had the lowest mortality (Figure 22, Table 13). The province-level deprivation was also associated with relative risk of breast cancer mortality over the years from 2000 to 2010. When grouped by wealth index quintiles (Appendix Figure 3), the wealthiest provinces had higher levels of breast cancer mortality. While the national relative risk of breast cancer mortality is decreasing, the reduction in mortality observed in the wealthier provinces is larger than the one observed in the most deprived provinces.

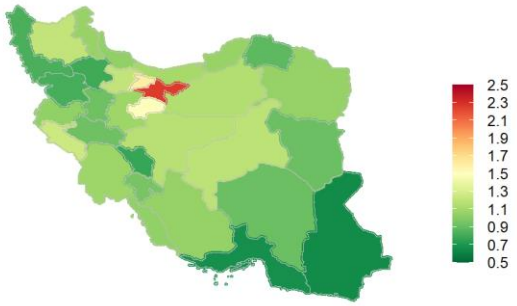
Relative Risk, year 2000



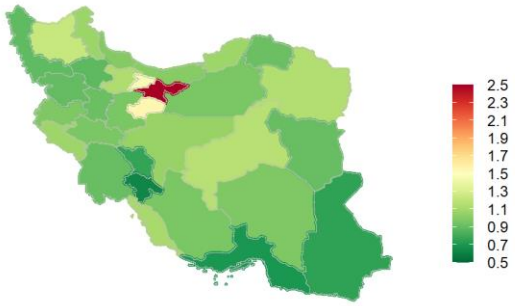
SMR, year 2000



Relative Risk, year 2001



SMR, year 2001



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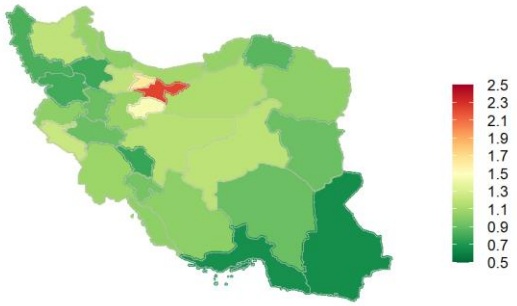

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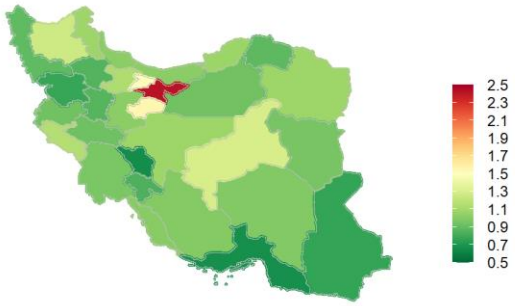

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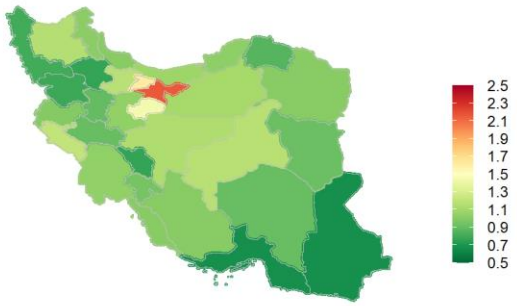
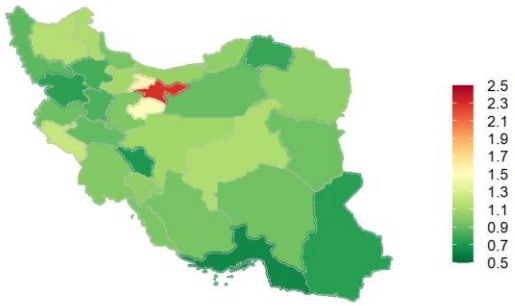
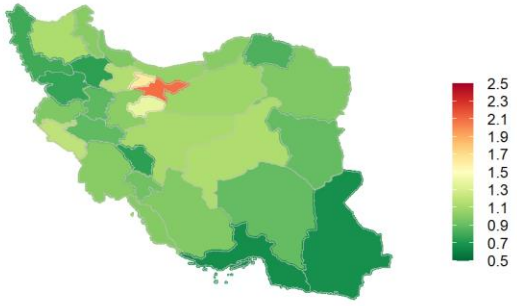


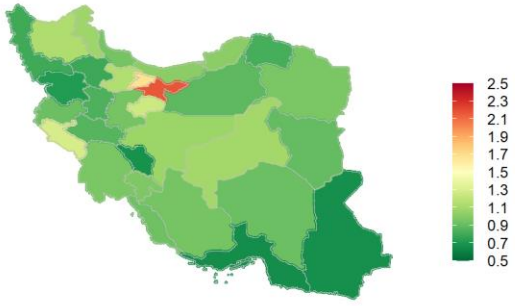
SMR, year 2003



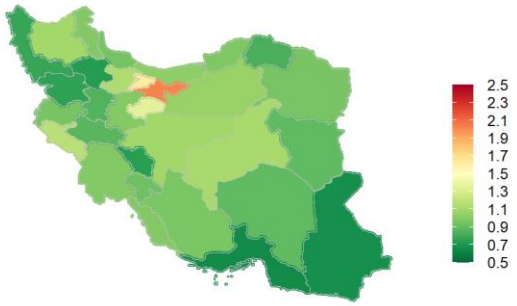
Relative Risk, year 2004



SMR, year 2004



Relative Risk, year 2005



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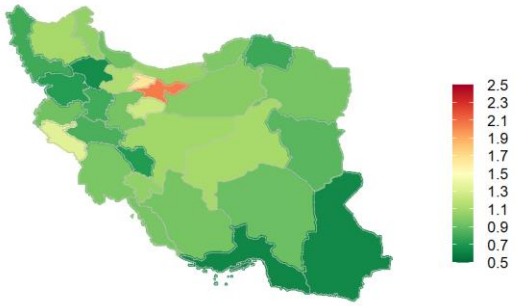
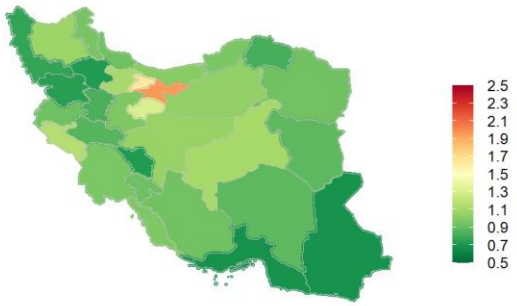


Relative Risk, year 2006



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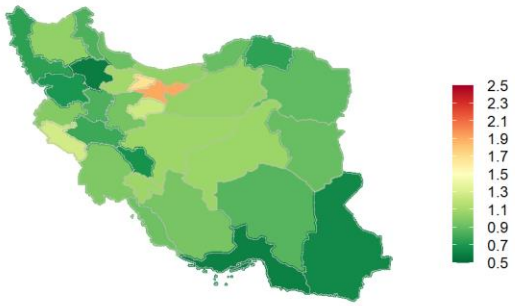
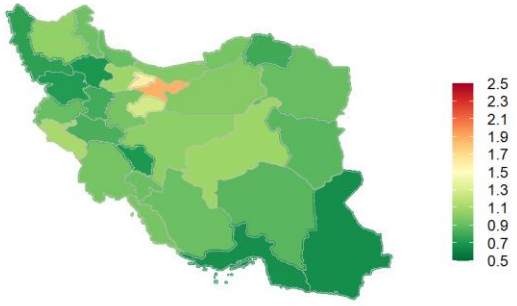


Relative Risk, year 2007



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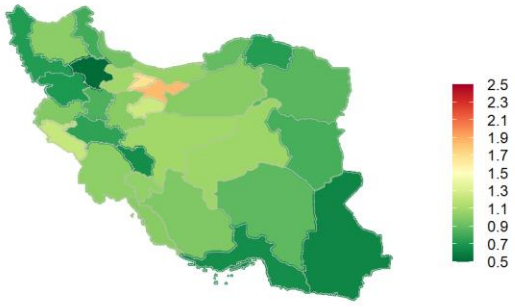
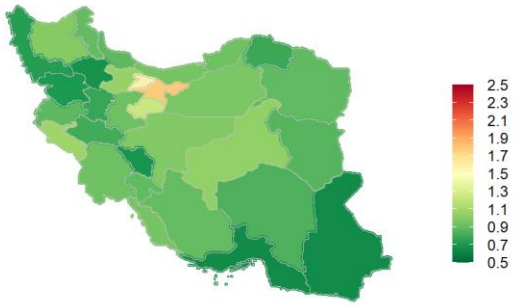
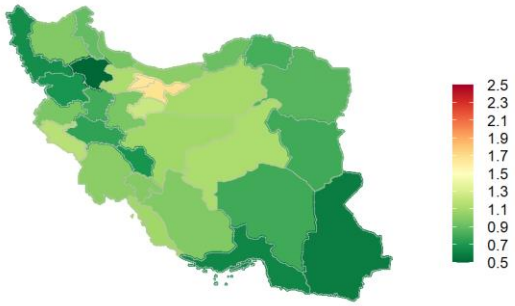


Relative Risk, year 2008



SMR, year 2008



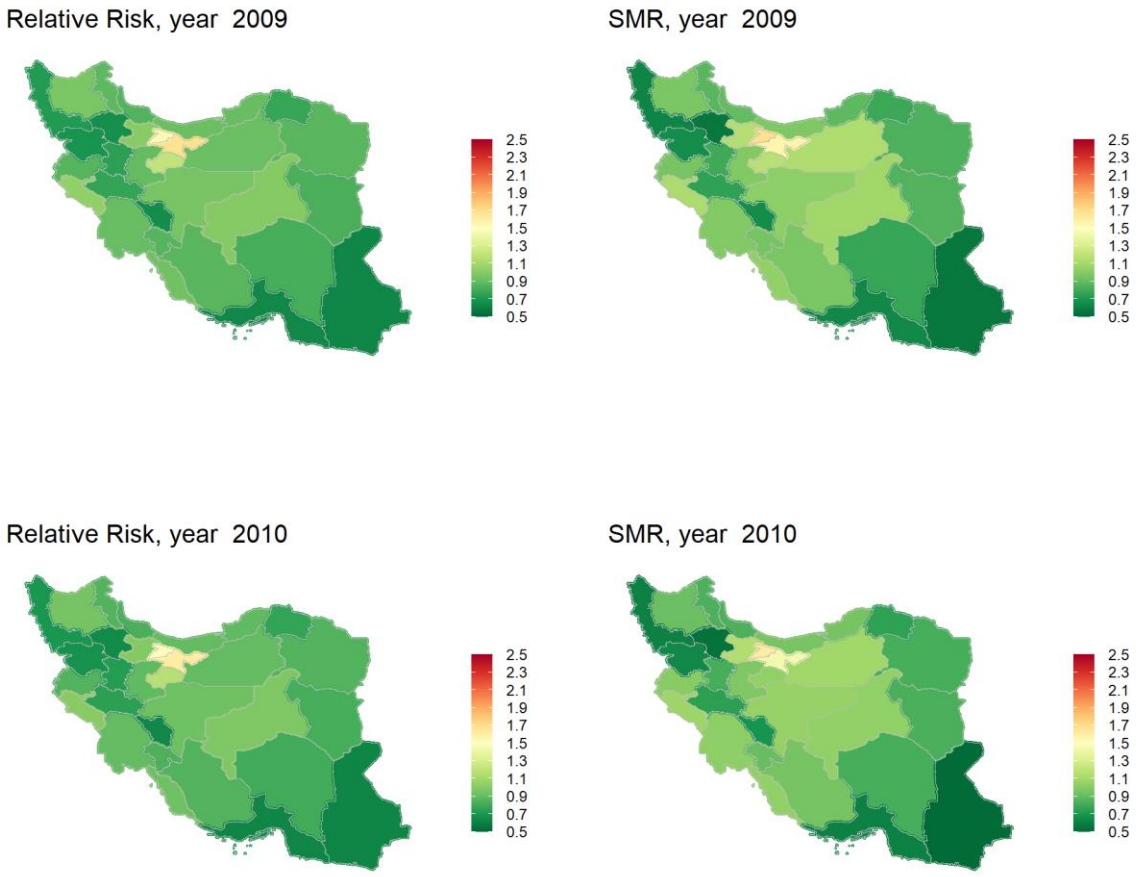


Figure 22. Estimated relative risk of breast cancer mortality (left side) versus standardised mortality ratio (SMR) (right side) by province level from 2000 to 2010.

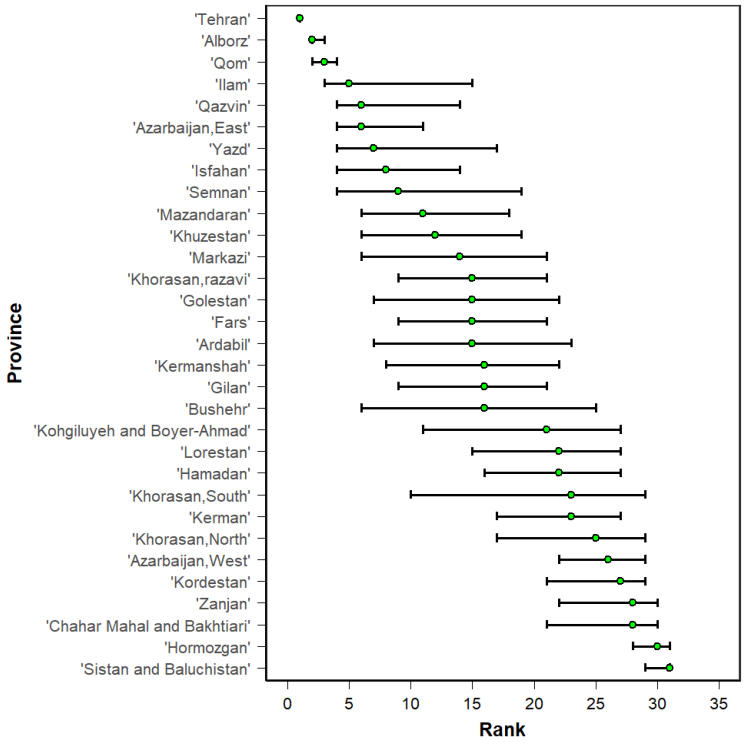
Table 13. Posterior mean and 95% credible interval for the relative risk of breast cancer mortality by province level (sorted by mean values in 2010).

	Relative risk of breast cancer mortality (CrI)		
Provinces	**2000**	**2005**	**2010**
Tehran	2.22 (2.08, 2.37)	2.03 (1.91, 2.15)	1.61 (1.50, 1.72)
Alborz	1.57 (1.35, 1.81)	1.62 (1.48, 1.78)	1.51 (1.35, 1.69)
Qom	1.51 (1.29, 1.74)	1.36 (1.16, 1.56)	1.17 (1.00, 1.34)
Ilam	1.25 (1.04, 1.47)	1.18 (0.99, 1.38)	1.01 (0.85, 1.19)
Qazvin	1.21 (1.05, 1.36)	1.14 (1.00, 1.28)	1.00 (0.88, 1.14)
Yazd	1.19 (1.03, 1.37)	1.12 (0.97, 1.28)	0.98 (0.83, 1.12)
Azarbaijan, East	1.21 (1.10, 1.33)	1.10 (1.00, 1.20)	0.95 (0.86, 1.04)
Isfahan	1.17 (1.06, 1.27)	1.09 (1.00, 1.18)	0.93 (0.85, 1.03)
Bushehr	1.04 (0.84, 1.26)	0.99 (0.83, 1.17)	0.93 (0.80, 1.08)
Mazandaran	1.11 (1.00, 1.22)	1.03 (0.94, 1.13)	0.90 (0.82, 1.00)
Khuzestan	1.10 (0.98, 1.22)	0.99 (0.90, 1.09)	0.90 (0.82, 0.98)
Semnan	1.15 (0.98, 1.35)	1.06 (0.90, 1.24)	0.90 (0.74, 1.09)
Markazi	1.07 (0.94, 1.21)	1.00 (0.88, 1.12)	0.89 (0.78, 1.00)
Golestan	1.06 (0.93, 1.19)	0.98 (0.87, 1.10)	0.89 (0.79, 1.00)
Kermanshah	1.04 (0.93, 1.18)	0.96 (0.85, 1.08)	0.85 (0.73, 0.96)
Fars	1.05 (0.96, 1.15)	0.97 (0.89, 1.05)	0.85 (0.77, 0.94)
Khorasan, razavi	1.05 (0.96, 1.14)	0.96 (0.88, 1.05)	0.85 (0.78, 0.93)
Ardabil	1.05 (0.91, 1.20)	0.99 (0.86, 1.13)	0.85 (0.74, 0.97)
Kohgiluyeh and Boyer_Ahmad	0.95 (0.80, 1.11)	0.93 (0.80, 1.09)	0.84 (0.72, 0.99)
Gilan	1.04 (0.94, 1.15)	0.95 (0.86, 1.04)	0.83 (0.75, 0.92)
Khorasan, South	0.92 (0.78, 1.13)	0.89 (0.77, 1.09)	0.82 (0.69, 1.00)
Kerman	0.92 (0.81, 1.03)	0.89 (0.80, 0.99)	0.81 (0.72, 0.91)
Khorasan, North	0.88 (0.73, 1.03)	0.83 (0.70, 0.97)	0.77 (0.64, 0.90)
Lorestan	0.94 (0.81, 1.05)	0.87 (0.77, 0.98)	0.75 (0.66, 0.85)
Hamadan	0.93 (0.82, 1.05)	0.85 (0.76, 0.96)	0.73 (0.65, 0.83)
Azarbaijan, West	0.83 (0.74, 0.93)	0.78 (0.70, 0.87)	0.70 (0.63, 0.78)
Kordestan	0.83 (0.72, 0.94)	0.76 (0.66, 0.85)	0.68 (0.60, 0.77)
Zanjan	0.80 (0.69, 0.92)	0.73 (0.62, 0.85)	0.65 (0.57, 0.75)
Chahar Mahal and Bakhtiari	0.78 (0.64, 0.95)	0.74 (0.62, 0.89)	0.64 (0.52, 0.77)
Hormozgan	0.66 (0.55, 0.81)	0.65 (0.55, 0.79)	0.63 (0.53, 0.75)
Sistan and Baluchistan	0.64 (0.55, 0.75)	0.67 (0.58, 0.77)	0.62 (0.54, 0.72)

Figure 23 shows the point estimates and 95% credible intervals for the ranks of provinces based on relative risk of breast cancer mortality in 2000 and 2010 (the higher the rank the higher relative risk). The relative ranking position of provinces has changed over time. Tehran - the most populous province in Iran, with almost 10% of the total Iranian population living there - and Alborz had the highest relative risk in 2000 and 2010 (Figure 23). However, the intervals are wide for some provinces, demonstrating the great uncertainty associated with the ranks.

Looking at changes in rank of provinces regarding relative risk of breast cacner incidence and mortality may inform appropriate changes in policies or programmes, and highlight the locations where additional resources should be focused. Some provinces experienced a more significant change over time probably due to specific factors such as coverage, screening, risk factors, while for others, the ranking has not changed.

2000



2010

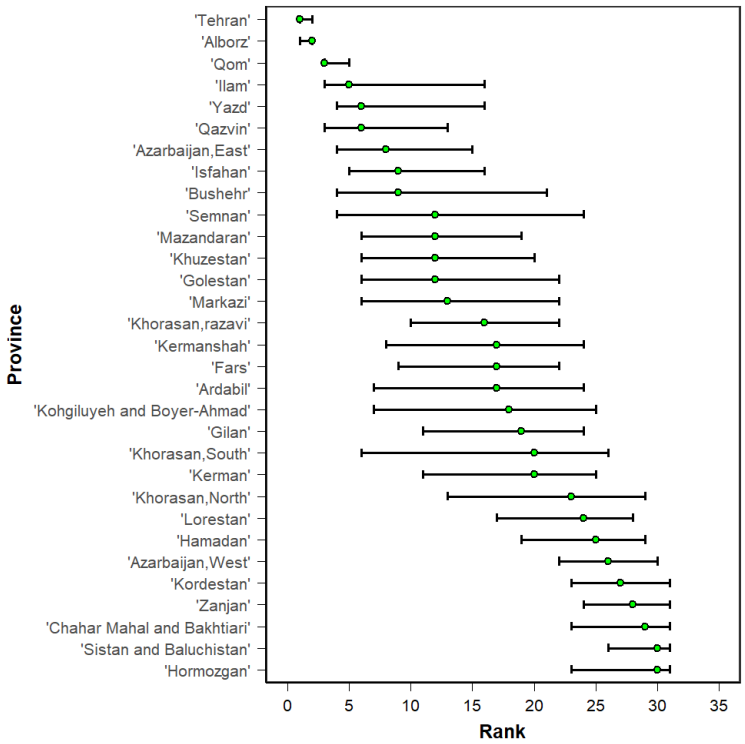


Figure 23. Median and 95% credible intervals for mortality rank of each province which has been calculated from all posterior samples for 2000 (upper figure) and 2010 (lower figure).

4.7 Cross-validation results for the spatio-temporal model at the province level

Results of the spatio-temporal models' cross-validation for incidence and mortality by years are presented in Table 14 and Table 15, respectively. The estimates of relative risks for breast cancer incidence were unbiased as evidenced by median relative errors very close to zero overall. The mean difference of heldout values and estimates assessed by the Bayesian Wilcoxon rank test and their corresponding credible intervals were all acceptable (the distributions include zero) suggesting good model fitting. The 95% CrIs of estimated relative risks covered more than 86% of observed values in 2000, 2001 and 2002 and 100% in 2003 onwards.

The median relative errors were also very close to zero for mortality data. Similarly, the 95% CrIs of estimated rates covered more than 86% to 100% observed values in 2000-2010. The cross-validitation findings confirmed that the spatio-temporal models applied to estimate the relative risks of breast cancer incidence and mortality at the province level fitted well.

Table 14. Results of cross-validation for the spatio-temporal model at the province level for the relative risks of breast cancer incidence.

Data	No. of held out observations	Relative error*			Absolute relative error			Error•			Absolute error			Mean (95% CrI) Ω	95% CrI Coverage
		Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3		
2000	3	0.04	-0.24	0.25	0.26	0.12	0.62	0.01	-0.05	0.05	0.08	0.02	0.15	-0.15 (-0.71, 0.39)	86.66%
2001	3	0.23	-0.41	1.45	0.75	0.41	1.45	0.04	-0.13	0.14	0.15	0.08	0.23	0.18 (-0.49, 0.29)	86.66%
2002	3	0.26	-0.19	5.10	0.41	0.29	5.10	0.06	-0.10	0.19	0.19	0.07	0.20	0.54 (-0.05, 1.16)	93.33%
2003	3	0.24	0.03	0.27	0.24	0.06	0.27	0.07	0.01	0.13	0.07	0.03	0.13	0.65 (-0.32, 0.98)	100%
2004	3	0.18	0.01	0.38	0.18	0.08	0.38	0.07	0.01	0.12	0.08	0.05	0.12	0.71 (-0.29, 1.12)	100%
2005	3	0.24	-0.07	0.33	0.25	0.13	0.33	0.11	-0.05	0.15	0.11	0.10	0.15	0.60 (-0.21, 1.01)	100%
2007	3	0.17	0.02	0.28	0.17	0.05	0.28	0.13	0.01	0.16	0.13	0.05	0.16	0.37 (-0.06, 0.68)	100%
2008	3	0.23	0.05	0.43	0.23	0.12	0.43	0.14	0.02	0.27	0.14	0.04	0.27	0.51 (-0.23, 0.79)	100%
2009	3	0.32	-0.01	0.38	0.32	0.13	0.38	0.18	-0.02	0.36	0.19	0.14	0.36	0.60 (-0.22, 0.99)	100%
2010	3	0.11	0.03	0.40	0.19	0.07	0.40	0.10	0.02	0.29	0.13	0.05	0.33	0.39 (-0.002, 0.75)	100%

* (Estimated values minus heldout values) / heldout values

• Estimated values minus heldout values

Ω Bayesian Wilcoxon rank test (mean difference and its posterior distribution)

Table 15. Results of cross-validation for the spatio-temporal model at the province level for relative risk of breast cancer mortality.

Data	No. of held out observations	Relative error*			Absolute relative error			Error•			Absolute error			Mean (95% CrI) Ω	95% CrI Coverage
		Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3		
2000	3	0.05	0.00	0.13	0.08	0.04	0.13	0.06	0.00	0.10	0.07	0.04	0.13	0.33 (-0.02, 0.67)	86.66%
2001	3	0.02	-0.07	0.09	0.08	0.07	0.11	0.02	-0.07	0.09	0.08	0.07	0.13	0.03 (-0.37, 0.47)	86.66%
2002	3	-0.04	-0.07	0.05	0.07	0.05	0.09	-0.05	-0.07	0.05	0.07	0.05	0.08	-0.04 (-0.34, 0.23)	100%
2003	3	0.05	-0.01	0.08	0.07	0.03	0.08	0.05	-0.01	0.07	0.05	0.03	0.07	0.33 (-0.16, 0.83)	86.66%
2004	3	0.008	-0.01	0.05	0.03	0.01	0.06	0.01	-0.01	0.05	0.03	0.01	0.05	0.14 (-0.13, 0.41)	100%
2005	3	0.009	-0.04	0.01	0.02	0.01	0.08	0.01	-0.05	0.02	0.03	0.01	14.75	-0.004 (-0.28, 0.26)	100%
2006	3	0.05	-0.01	0.08	0.07	0.02	0.09	0.06	-0.02	0.07	0.07	0.03	0.08	-0.003 (-0.18, 0.24)	93.33%
2007	3	0.04	-0.04	0.08	0.06	0.04	0.08	0.04	-0.04	0.06	0.06	0.04	0.07	0.162 (-0.14, 0.48)	93.33%
2008	3	0.008	-0.06	0.04	0.06	0.03	0.09	0.01	-0.07	0.03	0.05	0.03	0.08	0.14 (-0.15, 0.45)	93.33%
2009	3	-0.08	-0.10	0.03	0.10	0.08	0.13	-0.09	-0.12	0.03	0.09	0.08	0.14	-0.09 (-0.41, 0.22)	93.33%
2010	3	-0.05	-0.10	0.006	0.09	0.05	0.10	-0.06	-0.09	0.005	0.09	0.04	0.10	-0.20 (-0.49, 0.09)	93.33%

*(Estimated values minus heldout values) / heldout values

•Estimated values minus heldout values

Ω Bayesian Wilcoxon rank test (mean difference and its posterior distribution)

4.8 Summary

This chapter proposed a Bayesian spatial and spatio-temporal framework to estimate female relative risk of breast cancer incidence and mortality for 31 provinces in Iran and to assess the related inequality over three time-intervals and over 11 years. The findings suggested an evident increase in breast cancer incidence and decreased breast cancer mortality in Iran. Economically developed provinces provide a high relative risk of breast cancer incidence and mortality, while it seems the relative risk of breast cancer mortality will decrease among least deprived provinces in the future. Mentioned results can inform appropriate changes in policies or programmes and highlight the locations where additional resources should be focused. Spatial attention to estimation of breast cancer risk factors and supporting plans for screening and prevention policies to tackle breast cancer incidence and mortality would help reduce inequality.

5 District changes in breast cancer incidence from 2000 to 2021

5.1 Overview

I applied the Bayesian spatio-temporal model to the breast cancer incidence data, as described in Chapter 3, to estimate female relative risks of breast cancer incidence for 316 districts in Iran from 2000 to 2021. In this chapter, I addressed the following research objectives: estimate the relative risk of breast cancer incidence at the district level in Iran between 2000 and 2010, assessing the correlation between relative risk of breast cancer incidence with female education quintiles and wealth index quintiles at district level, predicting relative risk of breast cancer incidence in Iran at district level from 2011 to 2021 and assessing the correlation between predicted breast cancer incidence with health system components in 2020 at province level.

5.2 Bayesian spatio-temporal findings for relative risk of breast cancer incidence

Among the 316 districts, there were 1095 breast cancer new cases in 2000, with the most in Isfahan (16.8% of all new cases) and 7960 new cases in 2010, with the most in Tehran (25.4%). The national average of breast cancer relative risk increased from 0.21 (95% CrI: 0.19, 0.22) in 2000 to 0.52 (0.49, 0.54) in 2005 and 0.66 (0.63, 0.68) in 2010 (Figure 24, Table 16). The analysis at district level implied having more sparse data and geographical areas with no available data, especially in 2000. In Figure 25, estimated relative risk of breast cancer incidence resulting from the spatio-temporal model (left side) were compared with the raw data (right side) for all years. The comparison shows how the model can smoothly interpolate for districts with missing data. In addition, since there were no data available in 2006, the model could estimate all districts for 2006, consistent with earlier and later years.

The three leading districts with the highest relative risk of breast cancer incidence in 2000 were Isfahan (1.14 [0.98, 1.31]), Kashan (1.02 [0.71, 1.40]) and Ahvaz (0.74 [0.57, 0.92]). However, Savojbolagh (0.05 [0.02, 0.11]), Tehran (0.06 [0.04, 0.08]) and Saravan (0.08 [0.03, 0.16]) had the lowest relative risk in 2000. The relative risk of breast cancer incidence was highest in Yazd (1.96 [1.63, 2.33]), Shiraz (1.90 [1.72, 2.09]) and Shemiranat (1.90 [1.12, 2.91]) in 2010. In contrast, Savojbolagh (0.11 [0.05, 0.20]), Saravan (0.17 [0.08, 0.30]) and Nikshahr (0.20 [0.09, 0.36]) were found to have the lowest

relative risk in 2010 (Appendix Table 4). The trend of relative risk for each district is presented in Appendix Figure 4, separately.

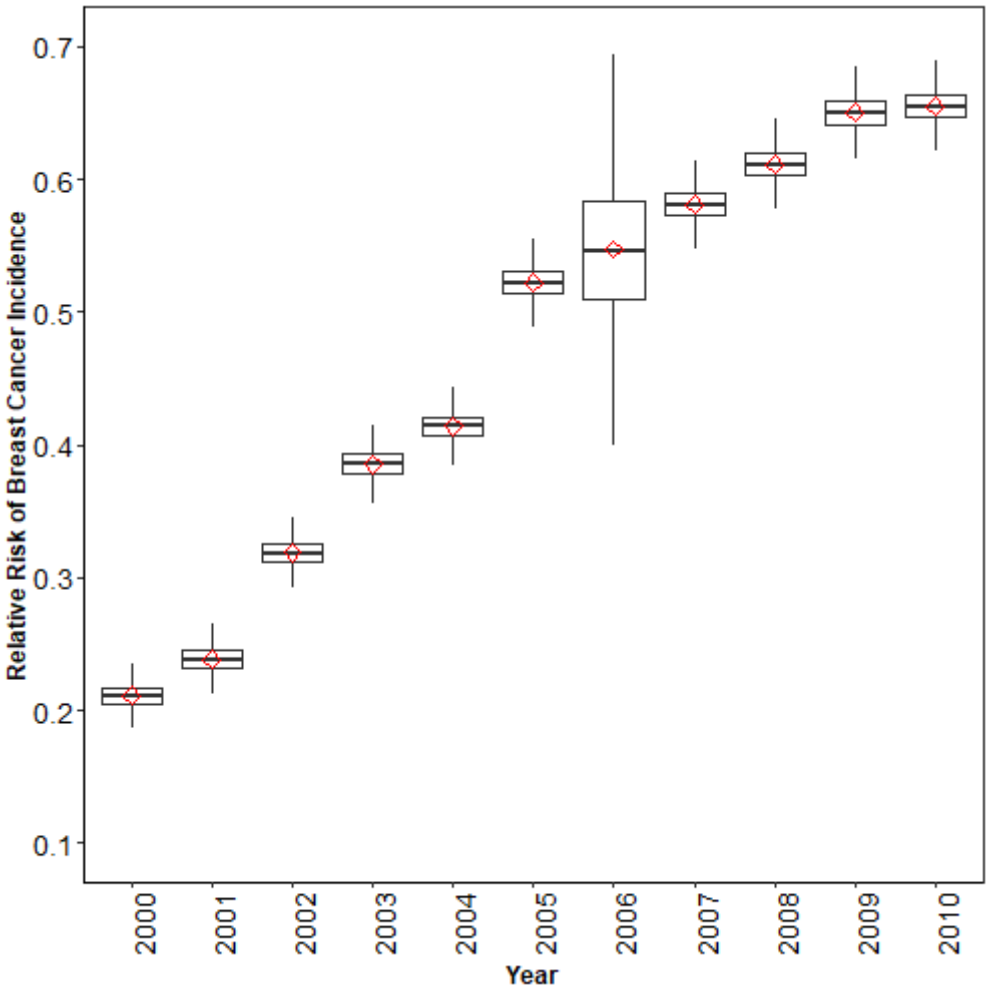
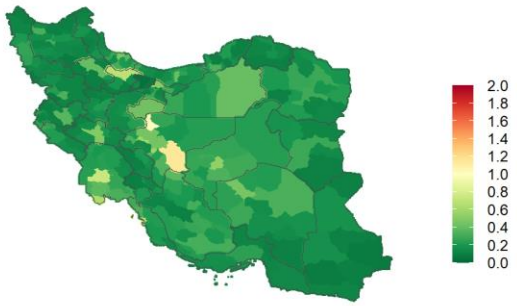
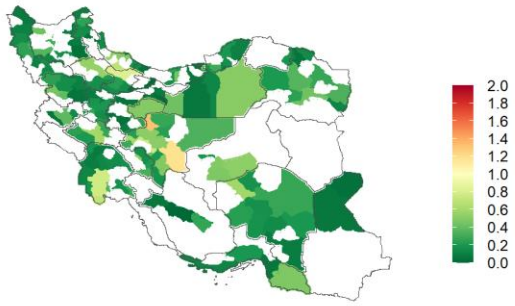


Figure 24. National average for relative risk of breast cancer incidence by year out of all posterior samples (red diamonds show the mean value).

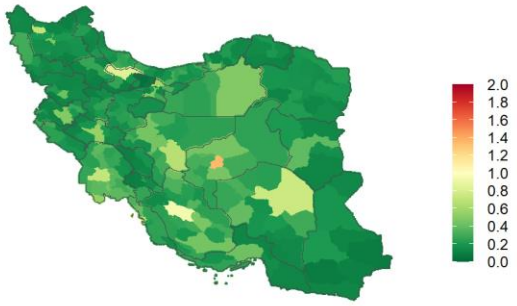
Relative Risk, year 2000



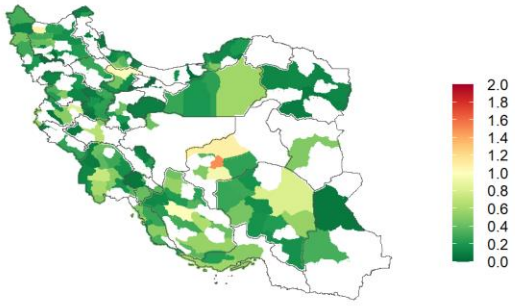
SMR, year 2000



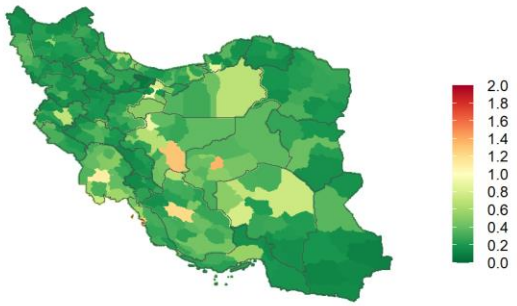
Relative Risk, year 2001



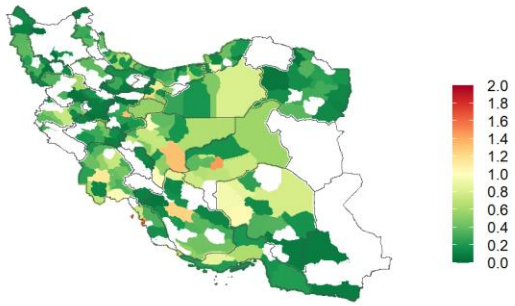
SMR, year 2001



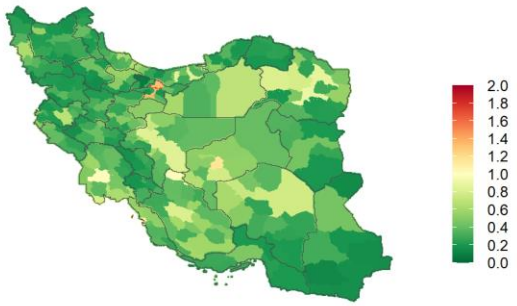
Relative Risk, year 2002



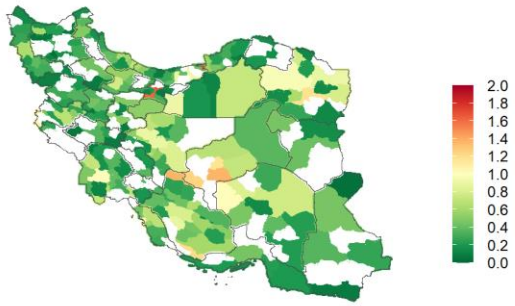
SMR, year 2002



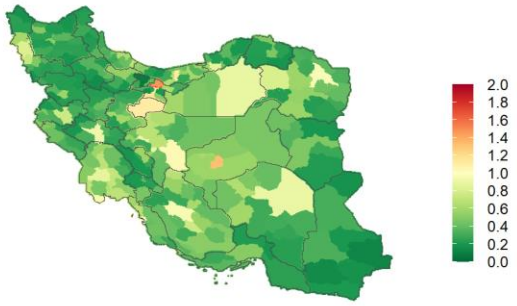
Relative Risk, year 2003



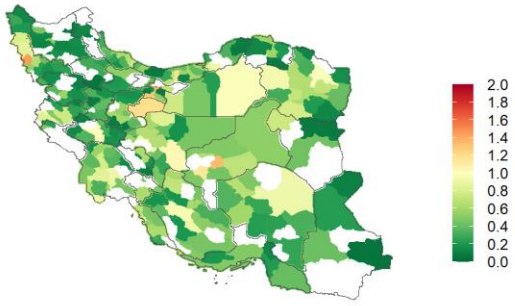
SMR, year 2003



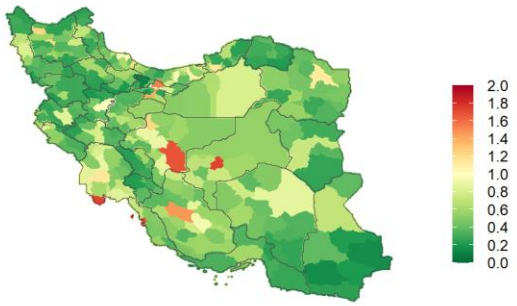
Relative Risk, year 2004



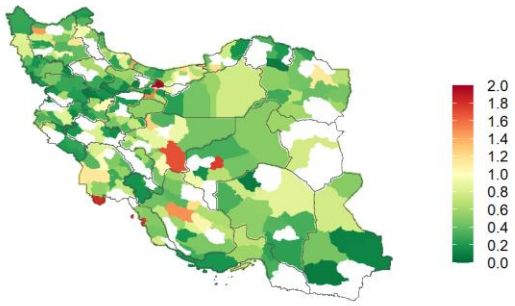
SMR, year 2004



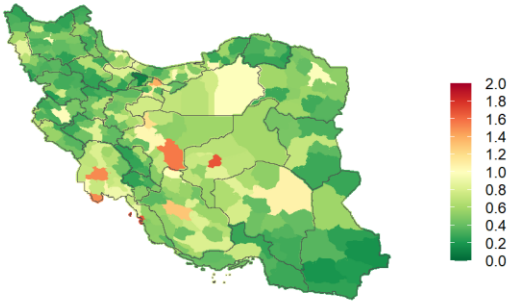
Relative Risk, year 2005



SMR, year 2005

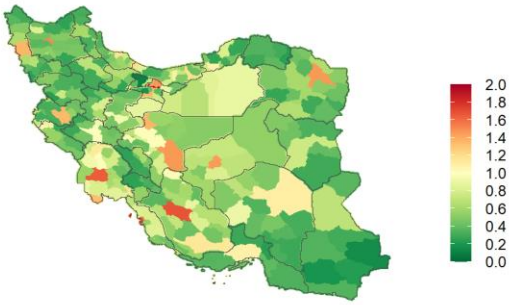


Relative Risk, year 2006

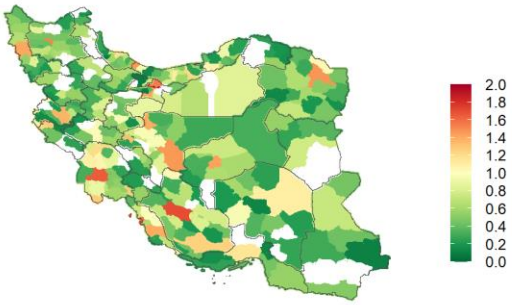


SMR, year 2006

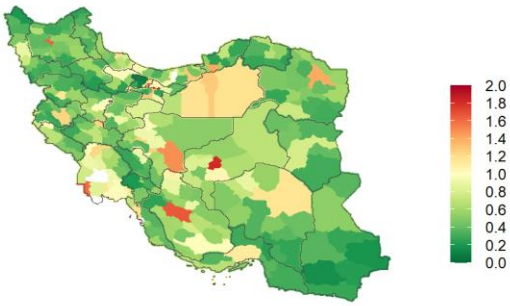
Relative Risk, year 2007



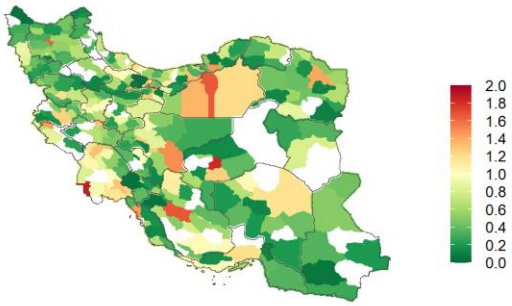
SMR, year 2007



Relative Risk, year 2008



SMR, year 2008



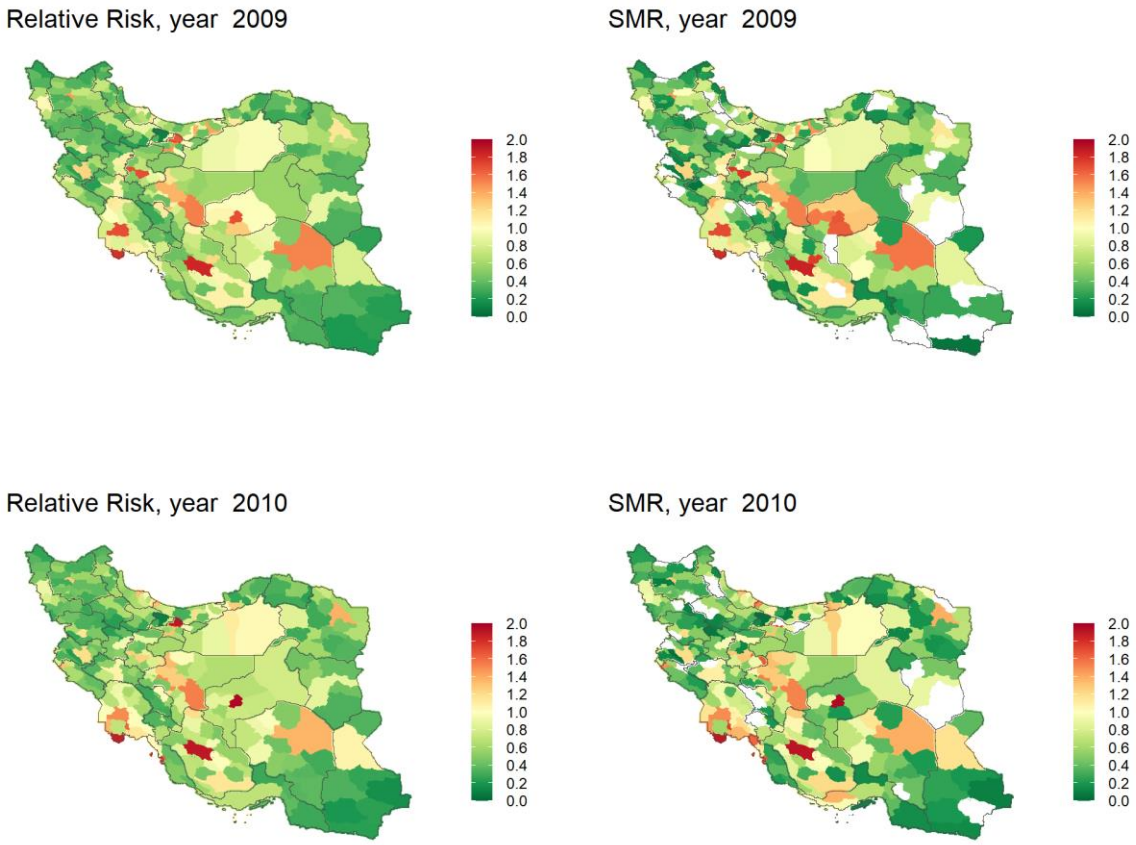
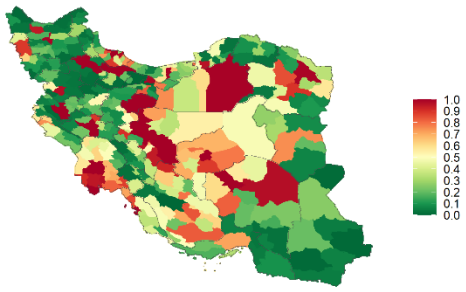


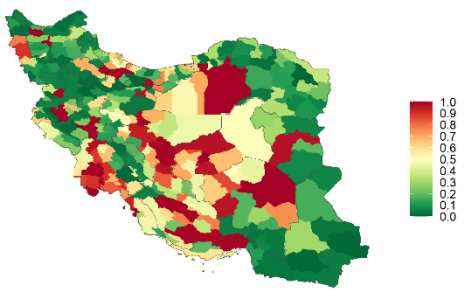
Figure 25. Estimated relative risk of breast cancer incidence (left side) versus SMR (right side) by district level from 2000 to 2010. Cancer registry data was not available in 2006, so SMR map for 2006 is empty.

In addition, the posterior probability with values between 0 and 1 were plotted on the map of districts by year (Figure 26). In 2000, with the national mean of 0.21 (0.95% CrI: 0.19, 0.22), there were 94 districts out of 316 in which the posterior probability was more than 50% compared to 121 districts in 2010 with the national mean of 0.66 (0.63, 0.68).

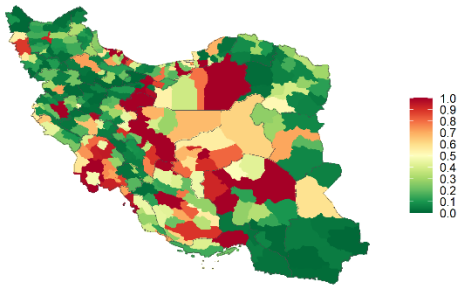
Posterior Probability, year 2000



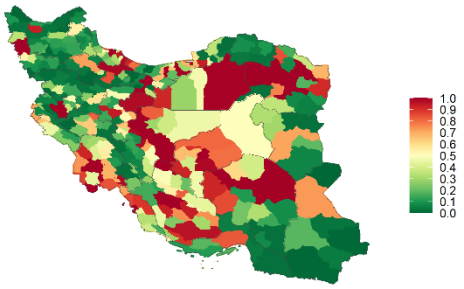
Posterior Probability, year 2001



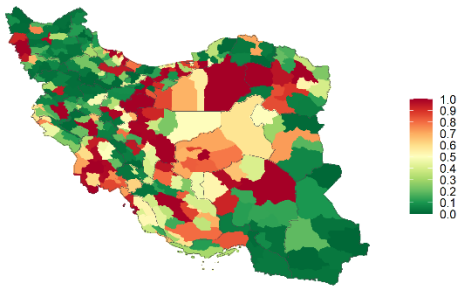
Posterior Probability, year 2002



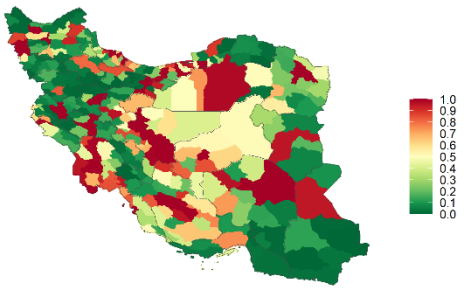
Posterior Probability, year 2003



Posterior Probability, year 2004



Posterior Probability, year 2005



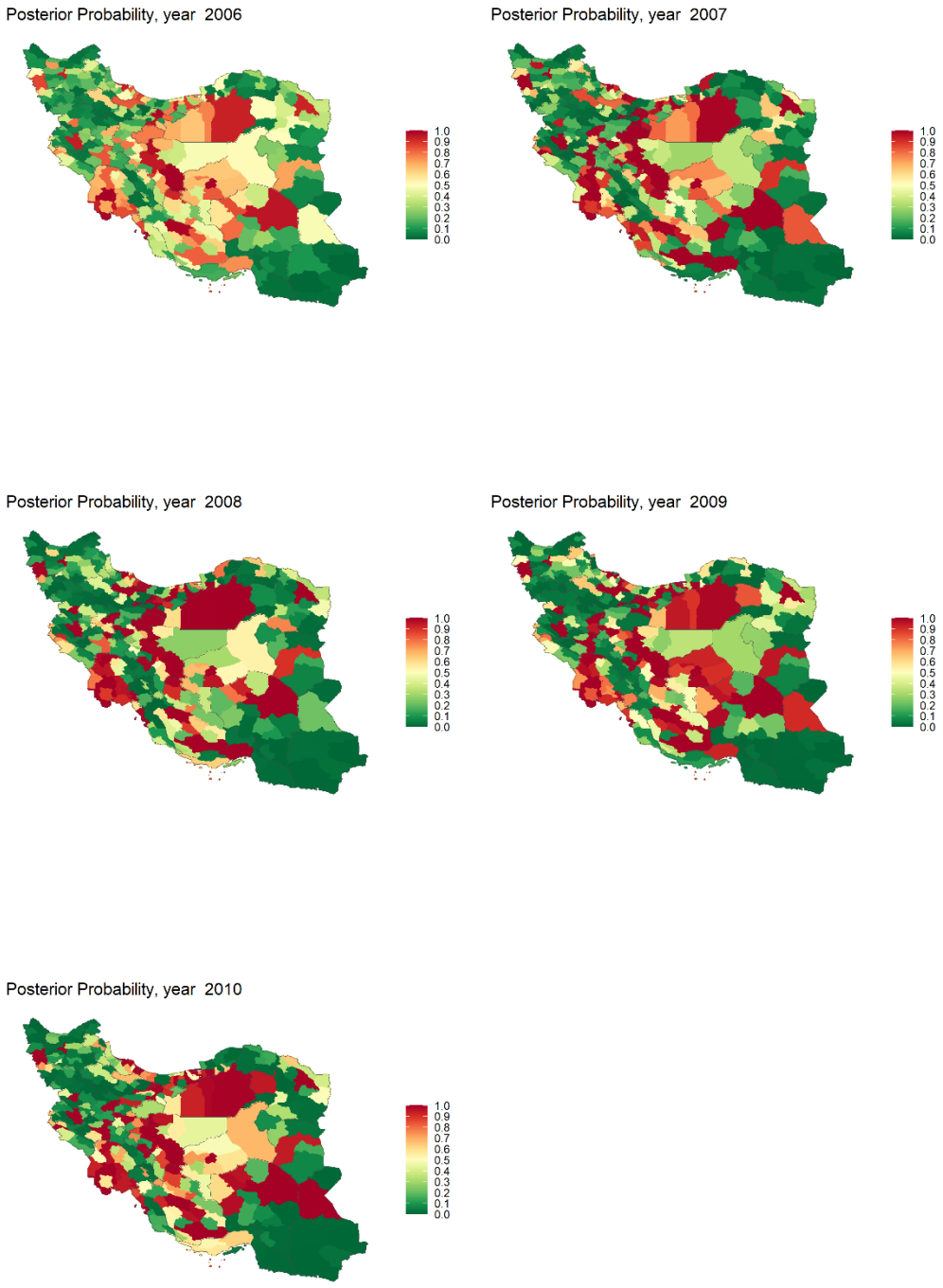


Figure 26. Maps of the posterior probability for each district in which the relative risk exceeds the national relative risk, by year from 2000 to 2010**.**

5.3 Breast cancer estimations in relation to years of schooling and wealth index

The average relative risk of breast cancer incidence increased with the YOS quintiles, ranging from 0.15 in the lowest quintile to 0.24 in the highest quintile for the year 2000 and from 0.48 to 0.79 for the year 2010. The relative risk of breast cancer incidence was 60% higher across districts in the highest YOS quintile (average years of schooling: 3.9) than those in the lowest YOS quintile (average years of schooling: 2.2; relative index of inequality: 1.6). Figure 27 shows that while the breast cancer relative risk increases over time, it is also rising by YOS quintiles. The districts in the highest quintile had a higher relative risk than districts in the lower quintiles. In addition, Figure 28 confirms that the relative risk of breast cancer incidence increased faster by mean YOS in the most recent years than in the earlier years and also by early quintiles. However, the relative risk slightly changed with increasing mean YOS over Q4 (Figure 28). The same results were also seen for WI quintiles so that the districts in the highest WI quintiles had higher relative risk of breast cancer incidence over time (Appendix Figure 5).

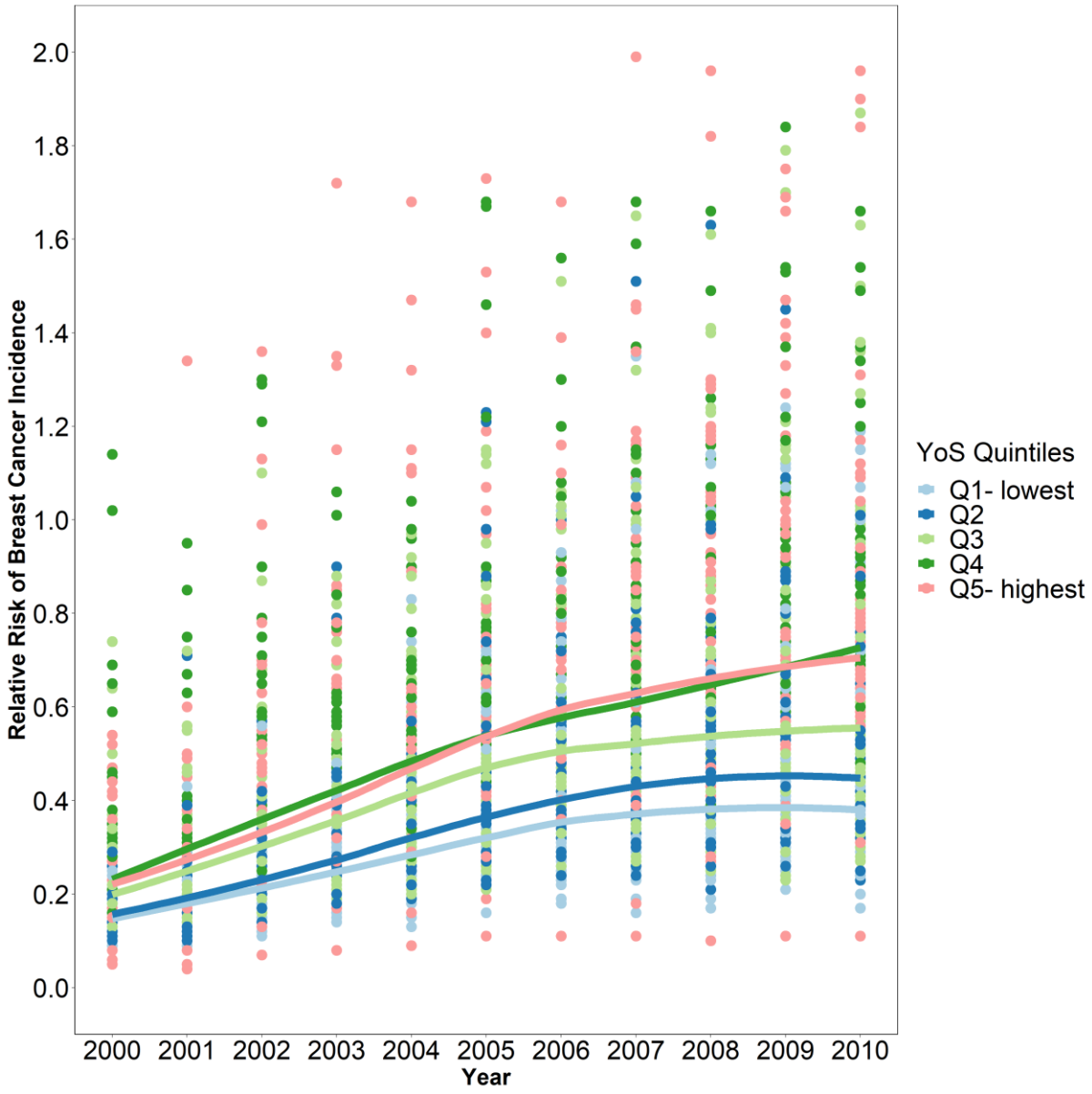


Figure 27. Relative risk of breast cancer incidence categorised by YOS quintiles over time (each point represents a district. Light blue colour shows the lowest YOS quintile, and the pink colour shows the highest YOS quintile).

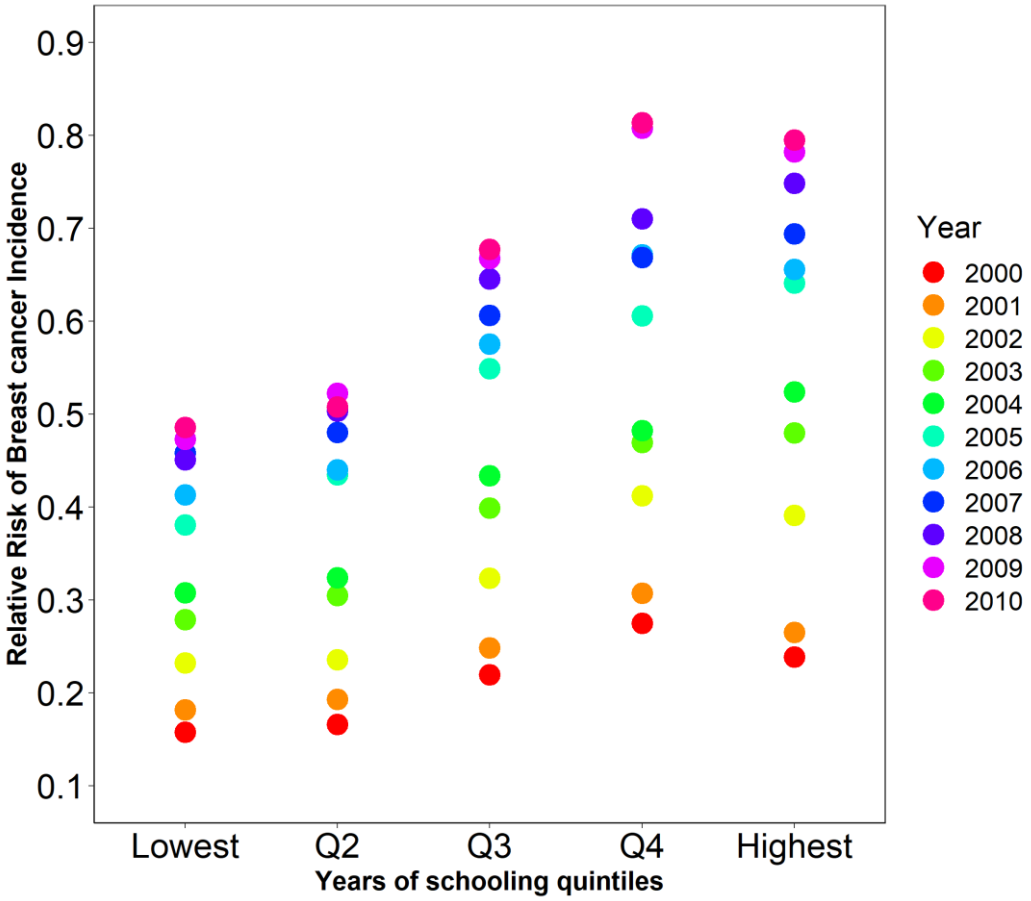


Figure 28. National average for relative risk of breast cancer incidence categorised by year and YOS quintiles (each point represents a year).

5.4 Projections for 2011 to 2021

If post-2010 trends continue, relative risk of breast cancer incidence will reach a value of 1.23 in 2021, almost two times greater than the 2010 level (0.66) (Figure 29, Table 16). Figure 30 shows how posterior predictive distribution change for the years from 2011 to 2021 based on the posterior values and uncertainty resulted from previous years spatio-temporal model. The trend results for each district are also presented in Appendix Figure 4, separately.

The three leading districts with the highest relative risk were Tehran (3.99 [95%CrI: 3.86, 4.33]), Bushehr (3.89 [3.07, 4.77]) and Abadan (3.67 [2.99, 4.39]) in 2021. In contrast, Savojbolagh (0.19 [0.10, 0.33]), Saravan (0.34 [0.18, 0.54]) and Nikshahr (0.35 [0.17, 0.62]) had the lowest relative risk in 2021 (Appendix Table 5).

Table 16. National average of relative risk of breast cancer incidence from 2000 to 2021 (based on the all posterior samples).

Year	National Relative Risk (95% CrI)
2000	0.21 (0.19, 0.22)
2001	0.23 (0.21, 0.25)
2002	0.31 (0.30, 0.33)
2003	0.38 (0.36, 0.40)
2004	0.41 (0.39, 0.43)
2005	0.52 (0.49, 0.54)
2006	0.55 (0.47, 0.65)
2007	0.58 (0.55, 0.60)
2008	0.61 (0.58, 0.63)
2009	0.65 (0.62, 0.67)
2010	0.66 (0.63, 0.68)
2011	0.75 (0.73, 0.78)
2012	0.80 (0.77, 0.83)
2013	0.85 (0.82, 0.88)
2014	0.89 (0.86, 0.93)
2015	0.94 (0.91, 0.98)
2016	0.99 (0.95, 1.03)
2017	1.04 (1.00, 1.08)
2018	1.09 (1.05, 1.13)
2019	1.13 (1.10, 1.18)
2020	1.18 (1.14, 1.23)
2021	1.23 (1.18, 1.28)

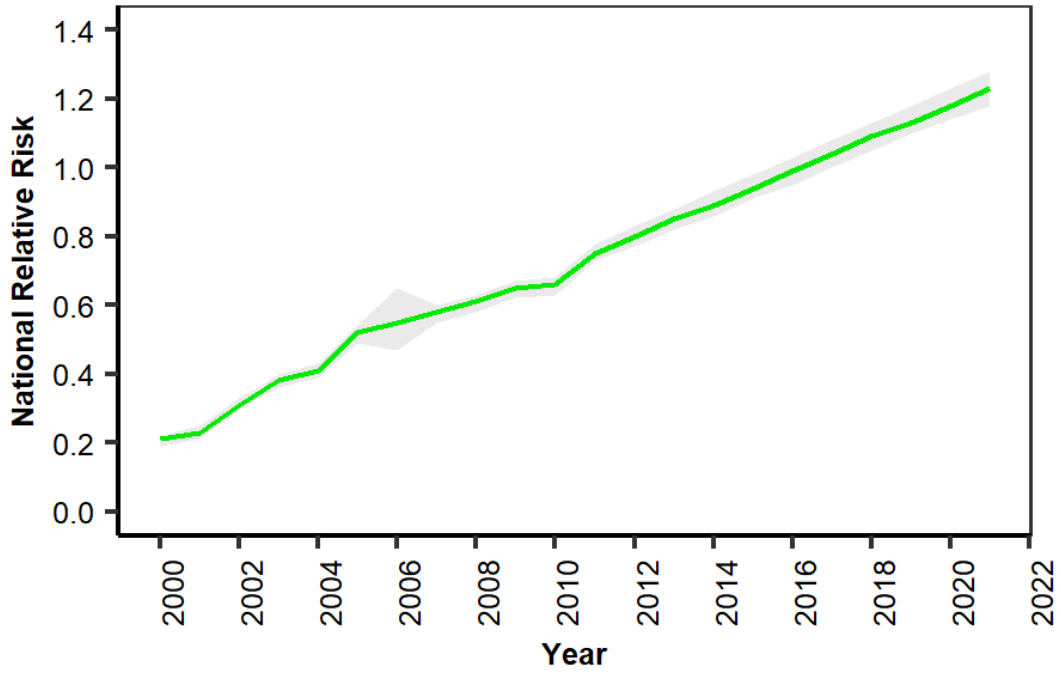
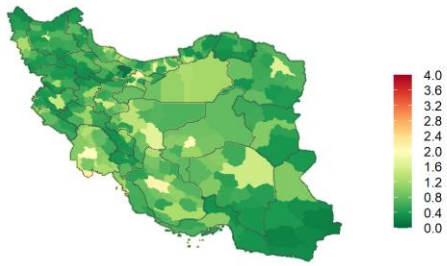
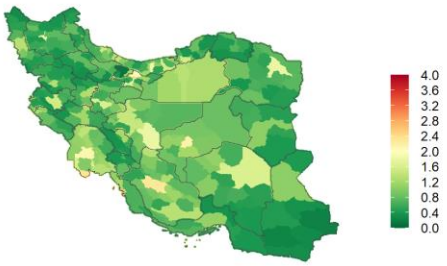


Figure 29. The trend of national relative risk of breast cancer incidence by year from 2000 to 2021 (Grey shadow shows a 95% credible interval).

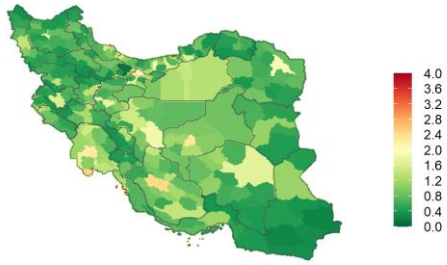
Relative Risk, year 2011



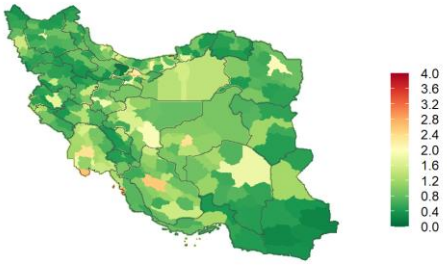
Relative Risk, year 2012



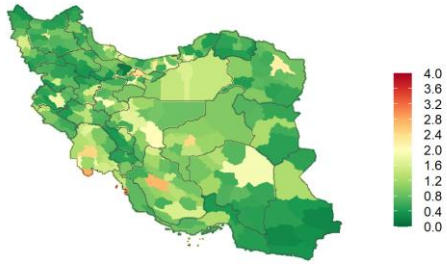
Relative Risk, year 2013



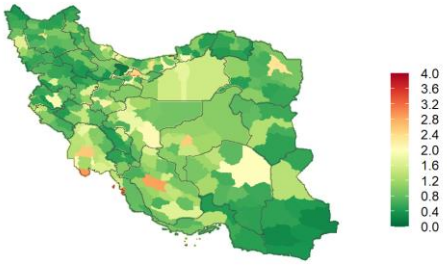
Relative Risk, year 2014



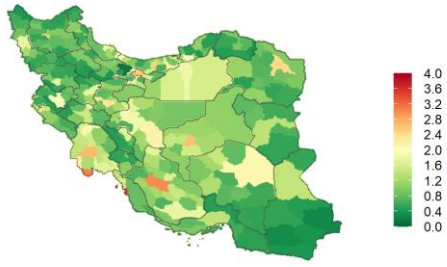
Relative Risk, year 2015



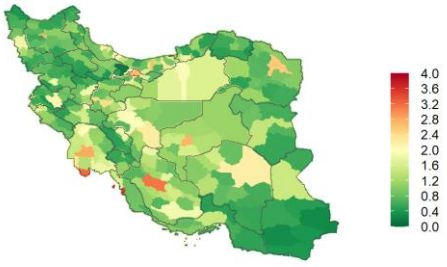
Relative Risk, year 2016



Relative Risk, year 2017



Relative Risk, year 2018



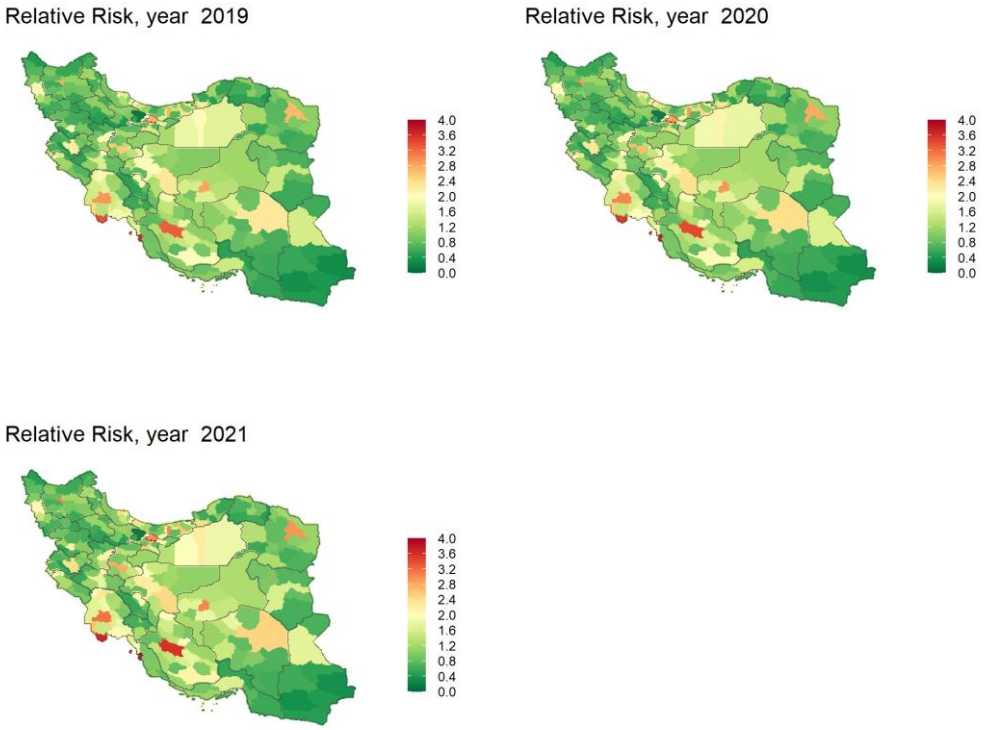


Figure 30. Projected relative risk of breast cancer incidence by district level from 2011 to 2021.

5.5 Correlation of relative risk of breast cancer incidence with health system components in 2020

The relative risk of breast cancer incidence was associated with multiple components of the health system. The 2020 projected breast cancer relative risk showed a significant positive correlation with the total number of GPs (r^1= 0.43, p-value= 0.01), the total number of pharmacies (r= 0.42, p-value= 0.01), the total number of ICUs (r= 0.44, p-value= 0.01) and the total number of nurses (r= 0.43, p-value= 0.01). While there was also a significant positive correlation between breast cancer relative risk with the total number of specialists (r= 0.50, p-value= 0.001) and the number of beds in hospitals of medical universities (r= 0.48, p-value= 0.001), no significant correlation was seen for the number of health centres (r= 0.03, p-value > 0.05) and number of community health workers (Behvarzes) (r= 0.06, p-value > 0.05). The obtained results confirm that higher number of health system components most likely leads to higher probability of breast cancer detection and the increased number of breast cancer incidence.

5.6 Cross-validation results for the spatio-temporal model at the district level

Results of the cross-validation are presented in Table 17. The estimates of relative risk of breast cancer incidence were unbiased, as evidenced by the median relative errors being very close to zero overall (ranging from -0.10 to 0.24). Median errors for estimated relative risks were also small and ranged between -0.24 (the year 2001) and 0.22 (the year 2010). The mean difference of heldout values and estimates computed by the Bayesian Wilcoxon rank test and their correspondence credible intervals were all non-significant (the distributions include zero) suggesting reasonable difference and credible intervals. The cross-validation confirmed that the statistical model used to estimate the relative risk of breast cancer incidence at the district level fitted well. The 95% CrIs of estimated relative risks covered more than 86% to 100% observed values in 2000-2010.

[1] Pearson correlation coefficient

Table 17. Results of cross-validation for the spatio-temporal model at the district level for relative risk of breast cancer incidence.

Data	No. of held out observations	Relative error*			Absolute relative error			Error•			Absolute error			Mean (95% CrI) Ω	95% CrI Coverage
		Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3	Median	Q1	Q3		
2000	32	0.07	-0.37	0.81	0.35	0.20	0.64	0.10	-0.15	0.20	0.20	0.01	0.30	-0.13 (-0.60, 0.33)	86.66%
2001	32	-0.01	-0.25	0.62	0.39	0.21	0.66	-0.24	-0.30	0.36	0.19	0.04	0.29	-0.15 (-0.39, 0.25)	86.66%
2002	32	0.23	-0.16	0.93	0.51	0.11	0.86	0.12	-0.22	0.19	0.18	0.10	0.34	0.34 (-0.04, 1.01)	93.33%
2003	32	0.14	-0.27	0.80	0.42	0.18	0.88	0.07	-0.09	0.13	0.10	0.05	0.21	0.54 (-0.12, 0.88)	100%
2004	32	0.06	-0.10	0.72	0.33	0.12	0.72	0.14	-0.25	0.38	0.19	0.09	0.28	0.70 (-0.19, 0.85)	93.33%
2005	32	0.13	-0.20	0.39	0.29	0.10	0.41	0.17	-0.19	0.27	0.21	0.15	0.30	0.43 (-0.12, 1.05)	93.33%
2007	32	0.24	-0.21	0.59	0.27	0.19	0.59	0.06	-0.14	0.18	0.15	0.02	0.26	0.17 (-0.10, 0.40)	100%
2008	32	-0.07	-0.15	0.45	0.22	0.15	0.45	-0.03	-0.15	0.26	0.13	0.04	0.24	0.31 (-0.15, 0.50)	100%
2009	32	-0.10	-0.24	0.64	0.22	0.14	0.67	-0.09	-0.12	0.17	0.15	0.08	0.30	0.52 (-0.14, 0.70)	100%
2010	32	0.21	-0.19	0.45	0.29	0.13	0.61	0.22	-0.26	0.53	0.16	0.04	0.35	0.30 (-0.01, 0.65)	100%

*(Estimated values minus heldout values) / heldout values

•Estimated values minus heldout values

Ω Bayesian Wilcoxon rank test (mean difference and its posterior distribution)

5.7 Summary

Using Iran's most comprehensive breast cancer database, this chapter estimated spatial and temporal trends in relative risk of breast cancer incidence from 2000 to 2021 over 316 districts. The national relative risk of breast cancer incidence has almost doubled during the two decades. There also seems to be an increasing trend in breast cancer incidence in districts with a higher level of female education in Iran. I then checked the validity of the model using specific approaches described in chapter 3, and I concluded that the model estimations are reliable and the final results could be trusted. These results contribute to the body of evidence about health inequalities in breast cancer by providing robust estimates of spatial and temporal breast cancer distribution in Iran.

6 Discussion and conclusions

6.1 Breast cancer disparity in Iran and comparison with published literature

I have used the most comprehensive breast cancer database and several covariates to estimate relative risk of breast cancer incidence and mortality trends in Iran at national and sub-national level over the past two decades. I have applied a Bayesian spatio-temporal model, which incorporated epidemiological features, to make estimates for all provinces and districts in the country.

The current study analyses the relative risk of breast cancer incidence and mortality across 31 provinces from 2000 to 2010 and relative risk of breast cancer incidence across 316 districts in Iran from 2000 to 2021. Results showed a substantial rise in the incidence nationally, while the relative risk of breast cancer mortality had a decreasing trend. The results of sub-national level analysis reflect the genuinely high level of heterogeneity of breast cancer incidence and mortality in Iran.

When attempting to compare the results with previous studies; no studies were found to directly compare the relative risk of breast cancer incidence at year-district levels. This work found that all the provinces and districts had increasing trends in relative risk of breast cancer incidence from 2000 to 2021. The corresponding estimates from this study were in line to those of Ataeinia *et al.* (2021) study for province-level estimations using the same data sources. However, I estimated the breast cancer relative risk by district levels for the first time in Iran. Based on available studies (Rezaei *et al.*, 2019; Taheri *et al.*, 2012) on breast cancer incidence across the thirty Iranian provinces between 2004 and 2009, Gilan and Azerbaijan, East had the highest and Kohgiluyeh and Boyer-Ahmad had the lowest breast cancer incidence. However, Tehran, Yazd, Fars and Isfahan had the highest relative risk of breast cancer incidence and Khorasan, North had the lowest relative risk among 31 provinces in 2010 in the current study. Among 316 districts, Tehran, Bushehr and Abadan had the highest relative risk of breast cancer incidence, while Nikshahr, Saravan and Savojbolagh had the lowest relative risk in 2021 in the current study. Khorasan, Razavi and Golestan experienced the steepest increase in breast cancer incidence from 2004 to 2008 among 30 provinces (Jafari-Koshki *et al.*, 2014). My findings show that Khorasan, North, Alborz and Ilam have the most significant percentage change in incidence rate

between 2000-2003 and 2008-2010. Jafari-Koshki *et al.* (2014) study showed a steady decline in breast cancer incidence rates in Iran between 2004 and 2008 using a Bayesian space-time model. They used data from Iranian cancer registry at the province level but there were no details on cleaning process of cancer registry data to consider data incompleteness and duplications, as was performed in this study. Their analysis had also no covariates to better estimate the breast cancer incidence as was done here.

On the one hand, a part of a rising pattern in incidence could be attributable to improvements in the national cancer registry system and an increase in the number of patients registered (Ataeinia *et al.*, 2021). Upgrading diagnostic tools, more extensive healthcare coverage, awareness of the general population on breast cancer symptoms, and greater readiness to undertake screening despite cultural barriers were all possible factors of increase in breast cancer incidence rate (Ataeinia *et al.*, 2021). On the other hand, potential lifestyle risk factors, including higher fat intake, smoking and low physical activity (especially in post-menopausal women), could explain the increase in breast cancer incidence observed among Iranian women (Fararouei *et al.*, 2019; Vahid *et al.*, 2018; Mobarakeh *et al.*, 2014). In addition, changes in cultural habits such as increased age at childbearing and in particular older age at first pregnancy can partly explain the observed trends (Namiranian *et al.*, 2014; Hosseinzadeh *et al.*, 2014; Akbari *et al.*, 2011). However, the specific effect of the factors mentioned above on breast cancer incidence is still controversial and needs further investigation (Ataeinia *et al.*, 2021).

Although several studies have shown that trends in age-standardised breast cancer mortality rates have increased in Iran from 1995 to 2004 (Taghavi *et al.*, 2012) and 2006 to 2010 (Enayatrad *et al.*, 2015), my findings show a declining trend in relative risk of breast cancer mortality between 2000 and 2010. This finding can reflect early detection and improved treatment strategies during the study period (Ataeinia *et al.*, 2021; Yedjou *et al.*, 2019). This study also shows a lower relative risk of breast cancer mortality in the most deprived provinces, with wealthier provinces having higher relative risks of breast cancer incidence and mortality. However, the change in breast cancer mortality among the wealthiest provinces is larger than the one observed among the most deprived, suggesting a possible reverse association in the coming years, in line with other existing studies (Ghoncheh *et al.*, 2016; Downing *et al.*, 2007). Consistent with current results, in a previous study of female breast cancer in the United

States, the analysis by county-level depriviation indicated that the highest breast cancer death rates shifted from the wealthier areas to the poorer areas in the early 1990s (DeSantis *et al*., 2011). It is also noteworthy that before 1990, breast cancer mortality was lower in women living in most deprived areas compared with those living in least deprived areas, by as much as 7% in 1975 to 1977. Then, by 2003 to 2007, this situation had reversed, with women in poor areas had a 7% higher relative risk of breast cancer mortality than those in wealthy areas (DeSantis *et al*., 2011). Higher breast cancer mortality in higher socioeconomic groups can be due to several reasons, including: increased number of cases resulted from better screening and early detection (Singh, 2003), lifestyle factors (women in higher socioeconomic groups may engage in behaviours, such as drinking alcohol and using hormone replacement therapy, that have been linked to an increased relative risk of breast cancer incidence and mortality) and higher stress levels which has been linked to an increased risk of cancer and other health problems (Bowen *et al*., 2021). It is important to note that these discrepancies are complex and influenced by a wide range of social, economic, and environmental factors. Addressing the underlying causes of these disparities, such as improving access to quality healthcare and addressing social and economic inequalities, can help to reduce disparities in breast cancer mortality (Ghoncheh *et al*., 2016; Downing *et al*., 2007). Globally, the age-standardised mortality declined from 1990 to 2019, especially in high and high-middle income countries (Xu *et al*., 2021), which may be due to an increase in survival resulting from improved management and treatment of breast cancer (Siegel *et al*., 2021). Another global study (Azamjah *et al*., 2019) however indicated an increasing trend in breast cancer mortality over the past 25 years, probably due to an increase in the number of new cases, which is an alarming sign for health policymakers, especially in low and middle-income countries which have experienced sharp increases in breast cancer mortality rate (Azamjah *et al.*, 2019).

My results suggest high levels of geographical heterogeneity in breast cancer incidence and mortality across Iranian provinces and districts. Previous research shows that cancer incidence and mortality in Asian countries have a positive and a negative correlation with the country's level of development measured by HDI, respectively (Ghoncheh *et al.*, 2015). More advanced financial development and comprehensive cancer prevention policies are associated with lower mortality (Bellanger *et al.*, 2018).

In Iran, a direct and substantial association was also found between the incidence of breast cancer and HDI (Rezaei *et al.,* 2019). These findings align with current results in which higher levels of breast cancer incidence are observed across provinces with a higher level of wealth and districts with higher levels of female education and wealth. This could be explained by increasing life expectancy, urbanisation, higher exposure to risk factors, delayed childbearing, and a higher rate of screening resulting from higher socioeconomic status (Coccia, 2013).

6.2 Breast cancer screening in Iran

A large proportion of breast cancer is curable if diagnosed early (Abolfotouh *et al.,* 2015; Hajian *et al.,* 2011), therefore detecting early signs of breast cancer, particularly at the early stage, plays a crucial role in identifying appropriate treatment (Kwok *et al.,* 2015). Most Middle East countries lack a nationally organised cancer screening program since all face numerous cultural and socioeconomic barriers to screening (Bray *et al.,* 2018; Shabani *et al.,* 2020). Despite the potential benefits of screening, previous findings demonstrate that the breast cancer screening usage rate among Iranian women remains low (1.3% to 30.5%) (Hatefnia *et al.,* 2010; Charkazi *et al.,* 2013), resulting in breast cancer to be mostly diagnosed at an advanced stage (stage III and IV) (Naghibi *et al.,* 2013). For instance, the screening rate in the north of Iran varied from 21.7% in Mazandaran in 2016 (Kardan-Souraki *et al.,* 2019) to only 15.7% in Gilan in 2017-2018 (Nasrollahzadeh *et al.,* 2020). In the south of Iran, only 1.3% of women have had a mammography screening at any point in their lifetime (Heydari *et al.,* 2008). Many Iranian women are diagnosed with advanced stages of breast cancer when no treatment can be provided, indicating the importance of giving continued attention to early detection (Hajian *et al.,* 2011; Mousavi *et al.,* 2007). Several studies suggest that the most critical barriers to adopting breast cancer screening behaviour by Iranian women are fear, prioritising their family above their own health, the tendency to live in the moment and avoid bad thoughts and cultural values (Noori and Schouten, 2018; Rastad *et al.,* 2012; Lamyian *et al.,* 2007). Giving priority to family members seems to be rooted in the culture and societal expectations in Iran, possibly to the detriment of the women's own health (Noori and Schouten, 2018). Living in a socially, politically and economically unstable country has changed the coping mechanism of living in the moment into a cultural value upon which Iranians base their

everyday behaviour on (Noori and Schouten, 2018). These cultural values threaten preventive behaviour because they replace preventive behaviour with treatment, discouraging Iranian women from preventing illnesses in advance (Noori and Schouten, 2018). This suggests that taking full advantage of female screening participation in our community must be considered a fundamental priority. Women require information about the impact of regularly attending the screening on breast cancer mortality and overdiagnosis to make informed decisions (Jacklyn *et al.,* 2016).

6.3 Quality of life in patients with breast cancer

In oncology, patients' Quality of Life (QoL) has become a significant objective of cancer care. Understanding the components of QoL support a better understanding of the cancer patient's health to manage the problems (Sosnowski *et al.,* 2017). QoL is one of the most important psychological factors affecting breast cancer patients (Bouya *et al.,* 2018). As the survival rate of breast cancer increases, many breast cancer patients are opposed to cancer-related side effects, with severe impact on physical, psychological, social, and spiritual aspects of QoL (Noal *et al.,* 2011). Evaluation of QoL is essential for preventive intervention and provides information to clinicians about patient illness and treatment that influence the QoL of patients (Getu *et al.,* 2021).

Since anxiety, depression and chemotherapy side effects such as nausea, vomiting and fatigue are significantly associated with an impaired QoL, the whole caregivers' team must get involved in the management of psychological issues in breast cancer patients (Williams *et al.,* 2021; Daldoul *et al.,* 2018).

Cognitive-Behavioural Therapy (CBT), with its three major components - coping skills therapy, problem-solving therapy, and cognitive restructuring methods - effectively improves the QoL of breast cancer patients (Getu *et al.,* 2021). Systematic review and meta-analysis of clinical trials reported the effectiveness of CBT in improving sleep, fatigue, anxiety and depression, pain, and QoL in female breast cancer patients (Ye *et al.,* 2018; Getu *et al.,* 2021; Aricò *et al.,* 2016; Taso *et al.,* 2014). These review studies could help physicians, nurses, and patients make informed choices about the importance

of including CBT as part of the standard care practice to enhance breast cancer patient's mental, physical, and social health outcomes (Getu *et al.,* 2021).

Another systematic review of randomised controlled trials has shown that exercise is a safe and effective method of improving the QoL in patients with breast cancer (Zhang *et al.,* 2019). Courneya *et al.* (2003) reported that significant self-esteem and QoL changes in breast cancer patients resulted from increased social interaction or a sense of accomplishment in completing the exercise program. A beneficial effect on total mood disturbance has been seen in breast cancer patients attending the sessions with the exercise specialists as the most helpful intervention component (Zhang *et al.,* 2019). Still, more high-quality, multicentre trials evaluating the effect of exercise in breast cancer patients are needed (Zhang *et al.,* 2019). In addition, assessments of the comparative value for money of interventions will be required to impact breast cancer patients' QoL (Ngan *et al.,* 2022).

6.4 Breast cancer association with the health system components

A health system is made of all the organisations, institutions, resources and people whose main purpose is to improve health (Ahmad *et al.,* 2003). The health system delivers preventive, curative and rehabilitative interventions through a combination of public health actions and health care facilities that should be responsive and financially fair while treating people respectfully (World Health Organization, 2010). WHO describes the health systems in six essential components: service delivery, health workforce, health information systems, access to essential medicines, financing, and leadership/governance (World Health Organization, 2007). These components contribute to the strengthening of the health systems in different ways. Some components, such as leadership/governance and health information systems, provide the basis for the overall policy and regulation of all the other health system units. Crucial input components to the health system are financing as well as the health workforce. The last group, namely medical products and technologies and service delivery, reflects the immediate outputs of the health system, i.e. the availability and distribution of care (World Health Organization, 2007). Focusing on these separate components helps put boundaries around this complex construct and permits the identification of indicators and measurement strategies for monitoring progress (World Health Organization, 2010).

Considering the importance of the health system, research has shown a strong association between health system delay with a higher probability of breast cancer patients diagnosed at advanced stage (Unger-Saldaña *et al.,* 2015; Poum *et al.,* 2014). To overcome this issue, possible solutions should consist of strategies directed to the population, the health professionals and the health system that may improve the time at diagnosis hence the clinical stages at diagnosis (Unger-Saldaña *et al.,* 2015).

Disparities in breast cancer outcomes can result from modifiable social and health system determinants, such as poor access to care, also lack of health education, lack of financial resources, challenging patient-provider interactions, and structural barriers within the health system itself (Wheeler *et al.,* 2013), which warn policymakers in identifying strategies to more equally distribute clinical expertise and health infrastructure across populations (Wheeler *et al.,* 2013). My results similarly showed a significant positive association between breast cancer incidence and health workforce (the number of nurses, GPs, and consultants), and also between breast cancer incidence and service delivery (the number of beds in hospitals, the number of pharmacies and the number of ICUs) as components of the health system. The higher quality health system ensures better detection, leading to an increased number of cases and better consequences for breast cancer patients (Hu *et al.,* 2016).

6.5 Conclusions

To the best of my knowledge, this study is the first sub-national level analysis for relative risk of breast cancer incidence and mortality in Iran which focuses on the district level over time, simultaneously using several administrative datasets and Bayesian spatio-temporal modelling to obtain province and district-level estimations between 2000 and 2021 and addressing the incompleteness of the cancer registry. At the same time, with incidence increasing, mortality has decreased, but with lower incidence in the most deprived provinces, possibly due to underdiagnosis or late-stage diagnosis. Although the relative risk of breast cancer mortality is still higher in wealthier provinces, the larger reduction observed over time in these provinces suggests a possible reversal in coming years, whereas the poorest provinces will still have higher mortality levels. On the other hand, breast cancer incidence was much

higher across districts with higher levels of female education than those with the lowest level of female education.

Most of the cancer registry data in Iran has been pathology-based, which regularly provides beneficial information to improve the cancer care systems, especially in low and middle-income settings where there are no comprehensive population-based cancer registries (Jedy-Agba *et al.*, 2012). The population-based data have been gathered in some provinces from 2009 in Iran, so there are just a few population-based data in all parts of the country (Modirian *et al.*, 2014). Despite using national cancer registry data, looking just at the raw data confirms available data is sparse and sparse data usually provides biased estimations (Shioda *et al.*, 2019). Therefore, any surveillance approach using these raw data might fail to deliver reasonable estimates. In this regard, I developed a Bayesian Poisson model to impute the gaps in data and better estimate where data were available. This model considered spatial and temporal correlations in data to yield stronger estimations. The increase in the coverage rate of the cancer registry throughout the analysis may impact the interpretation of the time trends. However, I have addressed this issue by including coverage rate as a covariate in the model. This allows any bias caused by differences in coverage rate to be estimated empirically and the model to borrow strength based on this covariate.

6.5.1 Public health implications

My results emphasised the high heterogeneity across provinces and districts in the relative risk of breast cancer incidence and mortality in Iran, confirming the need for a comprehensive and practical plan to control breast cancer that considers sub-national variability and a call to improve data collection for breast cancer surveillance in the country. These differences emphasise the crucial need to improve access to diagnosis and treatment facilities to contain breast cancer-associated mortality in the most deprived areas and reduce inequalities through a stratified resource allocation approach. The observed heterogeneity can reflect lower access, knowledge and acceptance toward screening in underprivileged and smaller areas compared to large cities, like Tehran, that have multiple diagnostic facilities, cancer specialists, and healthcare coverage in addition to higher educational levels of patients, leading to

increased screening participation (Trewin *et al.*, 2017). The methods and findings presented in this thesis could be used in other settings with similar sociodemographic characteristics for policymaking.

In Iran's health system, policies were considered in the several domains of primary and secondary care, training healthcare professionals, and research to reach universal health coverage (Sajadi *et al.*, 2019); however, international sanctions against Iran from 2011 forced some restrictions on all these efforts (Kokabisaghi, 2018) affecting all aspects of the health system in monitoring morbidity and mortality. Policymakers should be informed that sanctions indirectly had critical adverse effects on the Iranian population's health by diminishing access to diagnostic and treatment facilities, specifically for those with cancers (Farzadfar *et al.*, 2022). Eventually, the COVID-19 pandemic and its convergence with socioeconomic challenges, economic burden, and the heavy burden of non-communicable disease in Iran could, directly and indirectly, affect the health system for major diseases, especially in the most deprived areas (Maani *et al.*, 2021).

6.6 Future work

Firstly, one of the main strengths of my thesis is the number of reliable data used to estimate spatial and time trends of breast cancer in Iran. This provides a good platform for further modelling. However, effort should go into keeping the cancer registry and death registry databases up-to-date by stakeholders in the Ministry of Health, Treatment and Medical Education and National Universities of Medical Sciences with improvement in consistency in reporting across provinces and districts. Recommended future studies should include the most recent breast cancer incidence data (i.e. 2010 forward), which were not available during this project, both population- and pathology-based. In addition, the future investigation should ensure to provide more accurate predictions for those years in which no data were available, using district-level covariates (if become available) to allow predictions based on covariate-based models. In addition, here, I presented estimates at the district level for breast cancer incidence only since no mortality data were available at the district level. Being able to model mortality data at a smaller spatial level could yield detailed information regarding mortality trends in the country and critical information to prioritise resource allocation.

Secondly, a Pearson correlation test was used to examine the association of breast cancer incidence with some health system components. During this project, these components such as the number of health centres/units, number of consultants, number of GPs, etc. were only available for one year (2020) at the province level. A multivariate analysis using more comprehensive data for the health system over the years and possibly smaller areas (i.e. district level) is warranted to provide further insight into the associations.

Thirdly, this approach can be used to identify and provide a more accurate understanding of breast cancer risk factors at sub-national levels. Since breast cancer risk factors vary across geographical areas, their considerations should guide the development of control strategies for breast cancer, and more appropriate interventions based on province and district characteristics. This evidence will optimise resource allocation.

Finally, the results of my dissertation provide the motivation and plausible support to conduct further analysis on the field of inequalities in breast cancer and other chronic diseases across the province and district levels. For example, a better understanding of differences in diagnosis and access to treatment would allow identifying where additional investments are needed. The methods used here can provide critical information to understand health inequalities in the country.

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Appendix

Appendix Table 1. List of provinces and districts in Iran.

Province (total: 31)	Districts (total: 316)
Markazi (10) *	Arak, Ashtiyan, Tafresh, Khomeyn, Delijan, Saveh, Shazand, Mahalat, Zarandiyeh, Komijan
Gilan (16)	Astara, Astanehye Ashrafiyeh, Bandar Anzali, Tavalesh, Rasht, Rudbar, Rudsar, Sumehsara, Fuman, Langrud, Lahijan, Shaft, Amlash, Rezvanshahr, Siyahkal, Masal
Mazandaran (15)	Amol, Babol, Behshahr, Tonekabon, Ramsar, Sari, Savadkuh, Qaemshahr, Nur, Noshahr, Babolsar, Mahmudabad, Neka, Chalus, Juybar
Azerbaijan, East (19)	Ahar, Tabriz, Sarab, Maragheh, Marand, Miyaneh, Hashtrud, Bonab, Bostanabad, Shabestar, Kalibar, Haris, Jolfa, Malekan, Azarshahr, Osku, Charoymaq, Varzaqan, Ajabshir
Azerbaijan, West (14)	Orumiyeh, Piranshahr, Khoy, Sardasht, Salmas, Maku, Mahabad, Miyandoab, Naqadeh, Bukan, Shahindezh, Takab, Oshnaviyeh, Chaldoran
Kermanshah (12)	Eslamabade Gharb, Kermanshah, Paveh, Sarpole Zahab, Sonqor, Qasreshirin, Kangavar, Gilanegharb, Javanrud, Sahneh, Harsin, Salas-e-Babajani
Khuzestan (18)	Abadan, Andimeshk, Ahvaz, Izeh, Bandar-e-Mahshahr, Behbahan, Khorramshahr, Dezful, Dashte Azadegan, Ramhormoz, Shadegan, Shushtar, Masjedsoleyman, Shush, Baghmalek, Omidiyeh, Lali, Hendijan
Fars (22)	Abadeh, Estahban, Eqlid, Jahrom, Darab, Sepidan, Shiraz, Fasa, Firuzabad, Kazerun, Lar (Larestan), Marvdasht, Mamasany, Neyriz, Lamard, Bovanat, Arsanjan, Khorrambid, Zarrindasht, Qirokarzin, Mohr, Farashband
Kerman (13)	Baft, Bam, Jiroft, Rafsanjan, Zarand, Sirjan, Shahrebabak, Kerman, Kahnuj, Bardsir, Ravar, Anbarabad, Manujan
Khorasan, Razavi (17)	Taybad,Torbate Heydarieh, Torbate Jam, Darrehgaz, Sabzevar, Quchan, Kashmar, Gonabad, Mashhad, Neyshabur, Chenaran, Khaf, Sarakhs, Fariman, Bardeskan, Rashtkhar, Kalat
Isfahan (20)	Ardestan, Isfahan, Khomeynishahr, Khansar, Semirom, Faridan, Fereydunshahr, Falavarjan, Shahreza, Kashan, Golpayegan, Lanjan, Nayin, Najafabad, Natanz, Shahinshahr va Meyme, Mobarakeh, Aran va Bidgol, Tiran va Karvan, Chadegan
Sistan and Baluchistan (8)	Iranshahr, Chah Bahar, Khash, Zabol, Zahedan, Saravan, Nikshahr, Sarbaz
Kordestan (9)	Baneh, Bijar, Saqqez, Sanandaj, Qorveh, Marivan, Divandarreh, Kamyaran, Sarvabad
Hamadan (8)	Tuyserkan, Malayer, Nahavand, Hamadan, Kabudarahang, Asadabad, Bahar, Razan
Chahar Mahaal and Bakhtiari (6)	Borujen, Shahrekord, Farsan, Lordakan, Ardal, Kuhrang
Lorestan (9)	Aligudarz, Borujerd, Khorramabad, Dalfan, Dorud, Kuhdasht, Azna, Poldokhtar, Selseleh

Ilam (7)	Ilam, Darrehshahr, Dehloran, Shirvan va Chardavol, Mehran, Abdanan, Eyvan
Kohgiluyeh and Boyer-Ahmad (4)	Boyerahmad, Kohgiluyeh, Gachsaran, Dena
Bushehr (9)	Bushehr, Tangestan, Dashtestan, Dashti, Dayyer, Kangan, Genaveh, Deylam, Jam
Zanjan (7)	Abhar, Khodabandeh, Zanjan, Ijrud, Khorramdarreh, Tarom, Mahneshan
Semnan (4)	Semnan, Damghan, Semnan, Shahrud
Yazd (10)	Ardakan, Bafq, Taft, Mehriz, Yazd, Meybod, Abarkuh, Sadugh, Khatam, Tabas
Hormozgan (9)	Abumusa, Bandarabbas, Bandar-e Lengeh, Qeshm, Minab, Bandar-e-Jask, Rudan, Hajiabad, Bastak
Tehran (10)	Tehran, Damavand, Rey, Shemiranat, Varamin, Shahriyar, Eslamshahr, Robatkarim, Pakdasht, Firuzkuh
Ardabil (9)	Ardebil, Bilehsowar, Khalkhal, Meshginshahr, Germi, Parsabad, Kowsar, Namin, Neer
Qom (1)	Qom
Qazvin (4)	Bueenzahra, Takestan, Qazvin, Abyek
Golestan (11)	Bandare Gaz, Torkman, Aliabad, Kordkuy, Gorgan, Gonbade Kavus, Minudasht, Aqqala, Kalaleh, Azadshahr, Ramyan
Khorasan, North (6)	Esfarayen, Bojnurd, Jajarm, Shirvan, Faruj, Maneh va Semelqan
Khorasan, South (6)	Birjand, Sarbisheh, Qaenat, Nehbandan, Sarayan, Ferdows
Alborz (3)	Karaj, Savojbolagh, Nazarabad

*The number in the bracket shows the total number of districts in each province

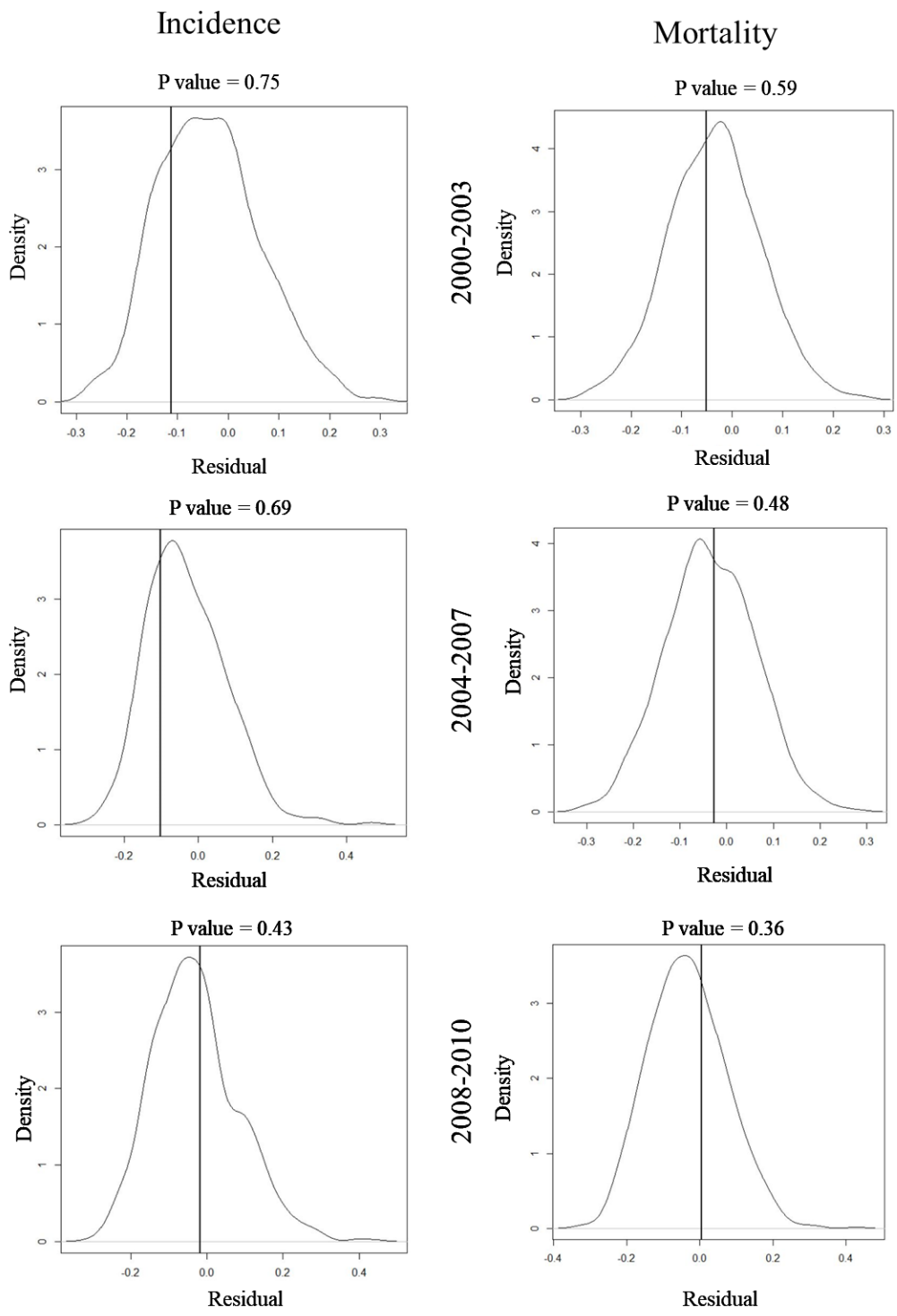
Appendix Text 1. Spatial model in OpenBUGS

```
# Y = Breast cancer count (incidence/mortality)
# i = province (31)
# Y~ Poisson(lambda*Exp)
#Nprov = 31

model {
for (i in 1: Nprov) {

Y[i] ~ dpois(mu[i])
mu[i] <- lambda[i]*E[i]
log(lambda[i]) <- v[i]
v[i]~dnorm(mu2[i], precv)                    #precv = tau. v = 1/variance. v
mu2[i] <- alpha +u[i] +Byos*predyos[i]+Burban*urbanizationf[i]+Bcomp*median_com[i]
ypred[i] ~ dpois(mu[i])
}

Byos ~ dnorm (0, 0.0001)
Burban ~ dnorm (0, 0.0001)
Bcomp ~ dnorm (0, 0.0001)

# put a hyperprior on U
U [1: Nprov] ~ car. normal (adj [], weights [], num [], precu)     # spatial model
for (k in 1: sumNumNeigh) {weights[k]<-1}

# other priors

precu ~ dgamma (0.5,0.0005)
precv ~ dgamma (0.5,0.0005)
alpha ~ dflat ()
sigma2u<-1/precu
sigma2v<-1/precv
sd. spatial<-sd (u [1: Nprov])
var. spatial<- sd. spatial*sd. spatial
frac. spatial<-var. spatial/ (var. spatial+sigma2v)
}
```

Appendix Text 2. Spatio-temporal model in OpenBUGS

```
# Y = Breast cancer count (incidence/mortality)
# i = districts (316) or province (31)
# t = year (T=11, from 2000(1)-2010(11))
# Y~ Poisson(lambda*Exp)
#Ndist = 316/ #Nprov = 31

model {
for (i in 1: Ndist) {
for (t in 1: T) {

Y [i, t] ~ dpois (mu [i, t])
mu [i, t] <- lambda [i, t] *E [i, t]
log (lambda [i, t]) <- v [i, t]
v [i, t] ~dnorm (mu2[i, t], precv)                    #precv = tau. v = 1/variance. v
mu2 [i, t] <- alpha +u[i] +Byos*predyos [i, t] + Burban*urbanization [i, t] +Bcomp*median_com [i, t] + xi[t]
ypred [i, t] ~ dpois (mu [i, t])

}
}

Byos ~ dnorm (0, 0.0001)
Burban ~ dnorm (0, 0.0001)
Bcomp ~ dnorm (0, 0.0001)

#put a hyperprior on U
u [1: Ndist] ~ car. normal (adj [], weights [], num [], precu)       # spatial model
for (k in 1: sumNumNeigh) {weights[k]<-1}

#Temporal random effects - Random Walk order 1
xi [1: T] ~ car. Normal (adj. time [], weights. time [], num. time [], precxi)
for (n in 1: sumNumNeigh.time) {weights. time[n] <- 1}

# other priors
precu ~ dgamma (0.5,0.0005)
precv ~ dgamma (0.5,0.0005)
precxi ~ dgamma (0.5,0.0005)
alpha ~ dflat ()
sigma2u<-1/precu
sigma2v<-1/precv
sigma2xi<-1/precxi
sd. spatial<-sd (u [1: Ndist])
var. spatial<- sd. spatial*sd. spatial
frac. spatial<-var. spatial/ (var. spatial+sigma2v)
}
```

Appendix Figure 1. The Moran's I test results for the province-level estimates at three time-intervals (p-values > 0.05 indicated that there was no evidence of residual's spatial correlation).



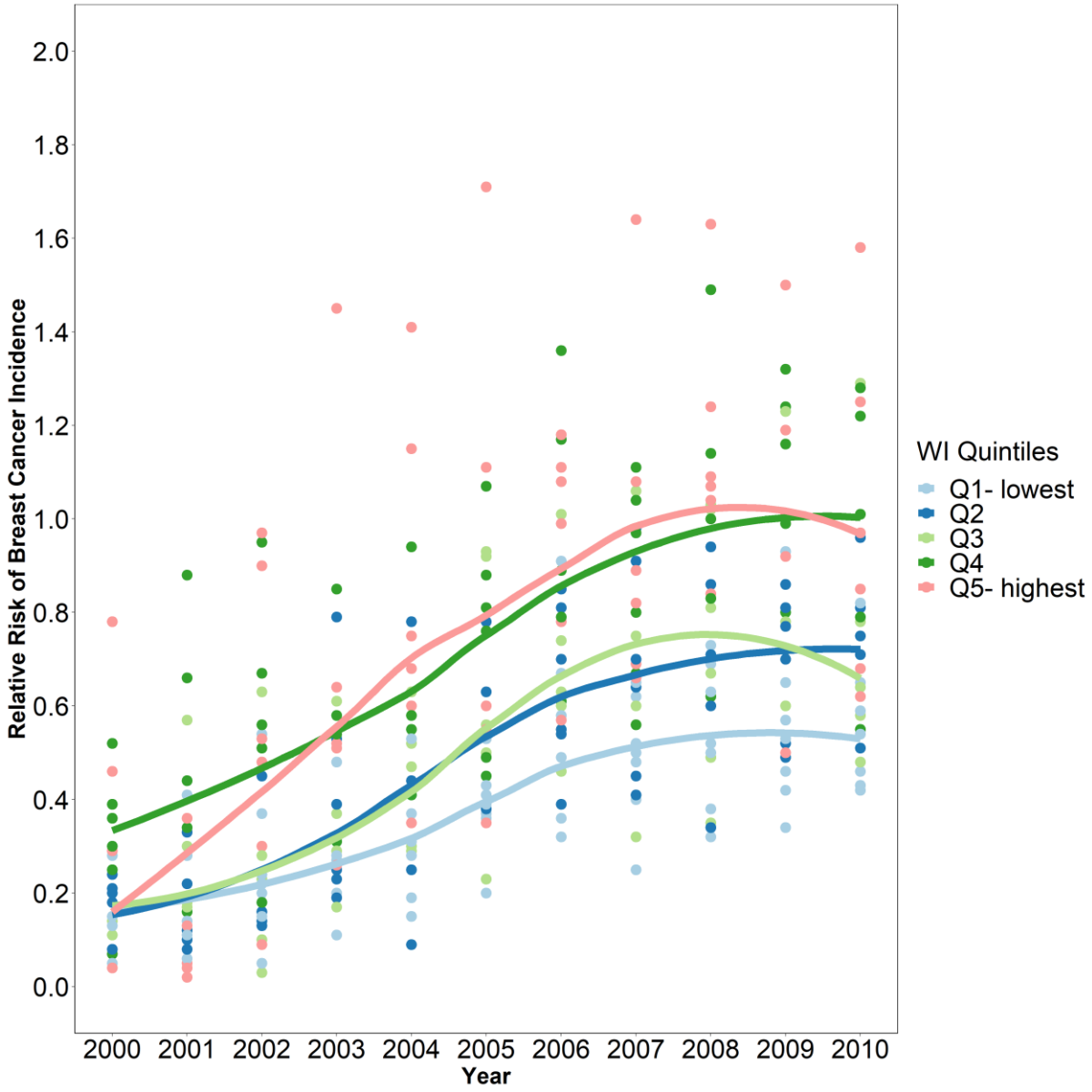
Appendix Table 2. Breast cancer incidence rates per 100,000 for females by province and time-intervals (sorted by mean values in 2008-2010).

	Breast cancer Incidence rate (95% CrI)		
Provinces	**2000-2003**	**2004-2007**	**2008-2010**
Tehran	31.3 (29.6, 33.0)	58.3 (56.1, 60.5)	78.2 (75.5, 80.9)
Khuzestan	25.2 (22.4, 28.1)	31.5 (28.6, 34.5)	62.8 (58.4, 67.3)
Yazd	38.2 (31.6, 45.4)	36.2 (30.3, 42.6)	60.5 (52.2, 69.3)
Isfahan	29.1 (26.5, 31.8)	36.3 (33.6, 39.0)	58.4 (54.7, 62.3)
Fars	23.0 (20.5, 25.5)	32.3 (29.6, 35.1)	58.4 (54.5, 62.5)
Semnan	21.2 (15.5, 27.8)	24.6 (18.6, 31.1)	53.0 (43.3, 63.3)
Mazandaran	12.4 (10.4, 14.6)	27.3 (24.5, 30.2)	50.1 (46.0, 54.4)
Markazi	8.4 (6.1, 11.2)	18.8 (15.4, 22.5)	46.9 (40.9, 53.1)
Khorasan, Razavi	16.7 (14.9, 18.7)	31.3 (28.9, 33.7)	45.5 (42.4, 48.7)
Gilan	19.9 (17.2, 22.7)	27.3 (24.3, 30.4)	45.3 (41.1, 49.7)
Azarbaijan, East	9.7 (8.1, 11.4)	27.5 (24.9, 30.3)	45.2 (41.5, 48.9)
Bushehr	18.8 (13.7, 24.5)	28.7 (22.9, 35.1)	43.8 (36.1, 51.9)
Alborz	4.8 (3.2, 6.6)	17.0 (14.2, 19.9)	42.4 (37.9, 47.2)
Kermanshah	19.9 (16.5, 23.5)	25.2 (21.7, 28.9)	41.0 (36.1, 46.1)
Kerman	20.7 (17.5, 24.1)	20.4 (17.5, 23.5)	39.1 (34.8, 43.6)
Hamadan	8.7 (6.5, 11.3)	18.3 (15.2, 21.6)	37.2 (32.4, 42.3)
Golestan	15.3 (12.0, 18.7)	21.5 (18.0, 25.3)	35.2 (30.3, 40.3)
Lorestan	13.8 (10.7, 17.1)	20.0 (16.6, 23.7)	34.7 (29.8, 39.8)
Qazvin	23.8 (18.9, 29.1)	17.6 (13.9, 21.7)	34.1 (28.5, 40.2)
Chahar Mahal and Bakhtiari	7.6 (4.5, 11.3)	14.5 (10.6, 18.9)	33.2 (26.6, 40.4)
Kordestan	10.8 (7.9, 14.0)	14.6 (11.5, 17.9)	33.1 (28.0, 38.3)
Qom	20.2 (15.6, 25.4)	31.2 (25.7, 37.1)	31.8 (25.9, 38.0)
Ilam	4.6 (1.9, 8.4)	16.8 (11.5, 22.8)	28.6 (21.1, 37.0)
Hormozgan	12.8 (9.3, 16.6)	16.9 (13.3, 21.0)	28.1 (23.1, 33.5)
Azarbaijan, West	11.3 (9.2, 13.5)	21.7 (18.9, 24.5)	27.0 (23.8, 30.4)
Khorasan, South	6.6 (3.4, 10.4)	15.3 (10.8, 20.5)	26.0 (19.7, 33.2)
Khorasan, North	2.0 (.6, 3.9)	9.7 (6.5, 13.4)	24.0 (18.4, 30.2)
Kohgiluyeh and Boyer-Ahmad	5.2 (2.1, 9.0)	10.0 (6.2, 14.3)	22.9 (16.4, 30.0)
Ardabil	7.0 (4.7, 9.7)	11.4 (8.5, 14.6)	22.6 (18.2, 27.5)
Zanjan	11.3 (7.9, 15.1)	13.1 (9.7, 17.0)	21.3 (16.5, 26.4)
Sistan and Baluchistan	3.8 (2.2, 5.6)	11.1 (8.7, 13.8)	17.9 (14.5, 21.6)

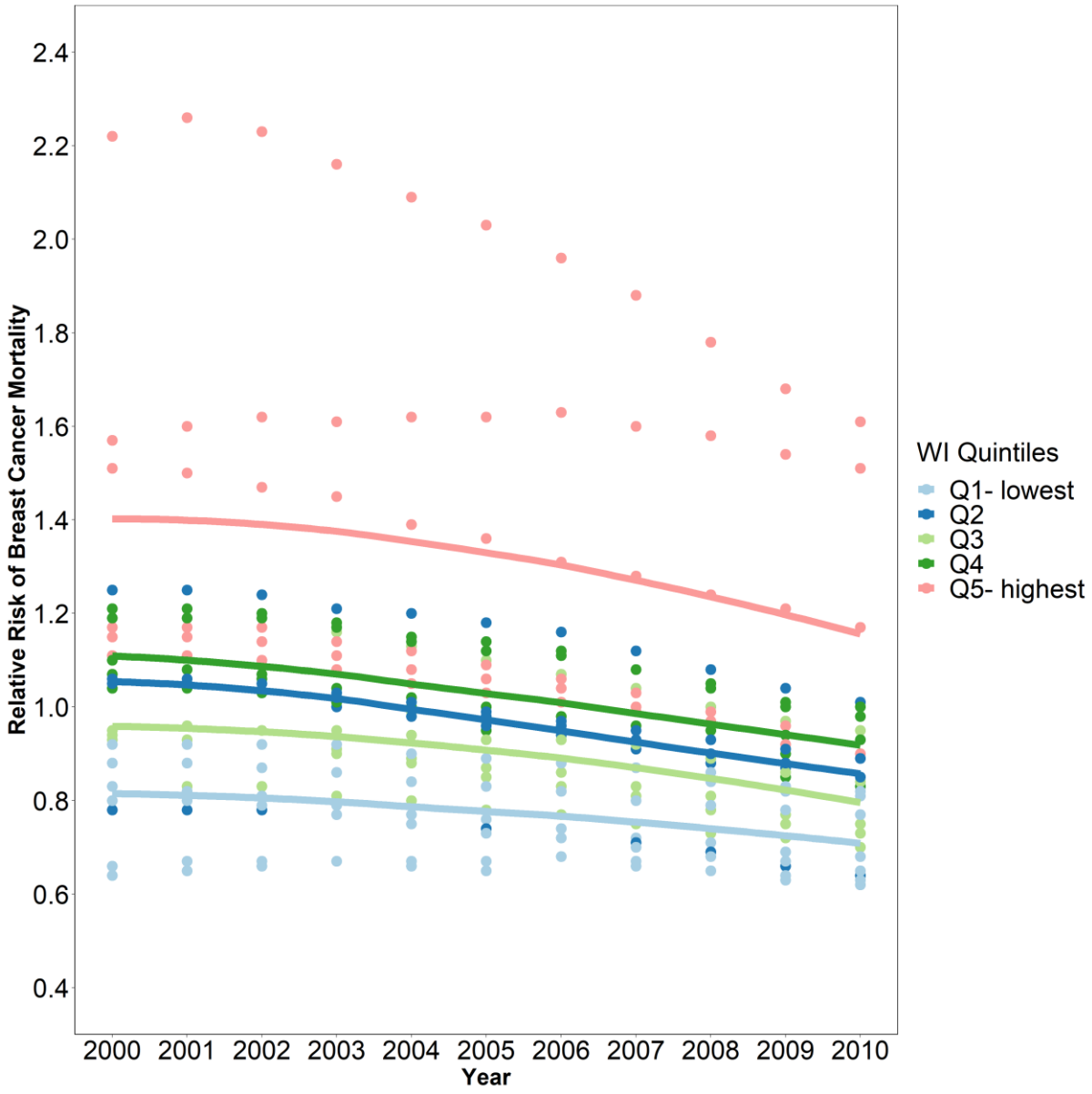
Appendix Table 3. Breast cancer mortality rates per 100,000 for females by province and time-intervals (sorted by mean values in 2008-2010).

	Breast cancer Mortality rate (95% CrI)		
Provinces	**2000-2003**	**2004-2007**	**2008-2010**
Tehran	23.8 (22.3, 25.3)	20.2 (18.9, 21.5)	16.2 (15.0, 17.4)
Alborz	13.8 (11.0, 16.7)	15.7 (13.1, 18.5)	15.3 (12.6, 18.2)
Semnan	12.4 (8.2, 17.2)	13.3 (9.1, 17.8)	14.8 (10.2, 19.9)
Qom	15.4 (11.4, 19.9)	13.1 (9.8, 16.9)	12.5 (9.2, 16.3)
Yazd	13.3 (9.7, 17.2)	12.4 (9.2, 15.8)	12.1 (8.9, 15.6)
Isfahan	11.5 (9.9, 13.2)	11.8 (10.3, 13.4)	11.6 (10.0, 13.2)
Markazi	11.2 (8.6, 14.2)	11.1 (8.7, 13.8)	11.2 (8.5, 14.0)
Qazvin	11.4 (8.4, 14.7)	11.2 (8.4, 14.3)	11.1 (8.2, 14.3)
Mazandaran	10.7 (8.9, 12.7)	11.3 (9.6, 13.1)	11.0 (9.1, 12.9)
Gilan	11.1 (9.2, 13.2)	10.8 (9.0, 12.7)	10.6 (8.6, 12.6)
Azarbaijan, East	13.1 (11.2, 15.1)	11.5 (9.8, 13.2)	10.2 (8.6, 12.0)
Fars	10.0 (8.4, 11.6)	10.1 (8.7, 11.7)	10.2 (8.6, 11.8)
Bushehr	10.4 (7.1, 14.3)	9.5 (6.6, 13.0)	10.1 (6.9, 13.6)
Khuzestan	9.4 (7.8, 11.2)	9.8 (8.2, 11.4)	9.9 (8.3, 11.7)
Kermanshah	9.7 (7.5, 12.1)	9.9 (7.8, 12.2)	9.9 (7.7, 12.3)
Ilam	10.3 (6.1, 15.1)	10.7 (6.7, 15.3)	9.6 (5.9, 14.0)
Khorasan, South	10.9 (7.0, 15.2)	10.3 (7.0, 14.2)	9.3 (5.9, 13.3)
Hamadan	9.8 (7.6, 12.3)	9.4 (7.3, 11.7)	9.1 (7.0, 11.4)
Khorasan, Razavi	11.6 (10.1, 13.2)	9.7 (8.4, 11.0)	8.9 (7.6, 10.3)
Kerman	10.1 (8.0, 12.4)	9.5 (7.6, 11.5)	8.9 (7.0, 10.8)
Golestan	10.3 (7.9, 13.1)	9.3 (7.0, 11.6)	8.8 (6.7, 11.2)
Ardabil	10.8 (7.9, 14.0)	9.5 (7.0, 12.3)	8.6 (6.1, 11.4)
Lorestan	9.7 (7.3, 12.3)	8.7 (6.6, 10.9)	8.4 (6.3, 10.8)
Khorasan, North	9.4 (6.2, 13.1)	8.5 (5.8, 11.6)	8.4 (5.4, 11.6)
Kohgiluyeh and Boyer-Ahmad	7.9 (4.5, 11.9)	9.0 (5.7, 12.9)	8.1 (4.8, 11.9)
Chahar Mahal and Bakhtiari	8.0 (5.0, 11.3)	7.8 (5.1, 10.8)	7.6 (4.9, 10.7)
Kordestan	8.9 (6.5, 11.6)	7.7 (5.6, 9.9)	7.4 (5.2, 9.7)
Azarbaijan, West	9.4 (7.6, 11.5)	8.4 (6.7, 10.1)	7.3 (5.6, 9.0)
Zanjan	9.5 (6.6, 12.7)	7.7 (5.3, 10.3)	7.2 (4.8, 9.9)
Hormozgan	7.1 (4.7, 9.7)	7.0 (4.8, 9.4)	6.7 (4.4, 9.1)
Sistan and Baluchistan	7.3 (5.2, 9.7)	6.3 (4.5, 8.2)	5.5 (3.8, 7.4)

Appendix Figure 2. Relative risk of breast cancer incidence categorised by wealth index quintiles over time (each point represents a province). Light blue colour shows the lowest WI quintile and the pink colour shows the highest WI quintile.



Appendix Figure 3. Relative risk of breast cancer mortality categorised by wealth index quintiles over time (each point represents a province). Light blue colour shows the lowest WI quintile and the pink colour shows the highest WI quintile.



Appendix Table 4. Posterior mean and 95% credible interval for the relative risk of breast cancer incidence by district and year (sorted by mean values in 2010).

District	2000	2005	2010
Yazd	0.54 (0.35, 0.76)	1.73 (1.38, 2.12)	1.96 (1.63, 2.33)
Shiraz	0.11 (0.07, 0.16)	1.46 (1.29, 1.66)	1.9 (1.72, 2.09)
Shemiranat	0.52 (0.23, 1.03)	1.53 (0.84, 2.49)	1.9 (1.12, 2.91)
Abadan	0.64 (0.4, 0.95)	1.73 (1.28, 2.25)	1.87 (1.44, 2.37)
Tehran	0.06 (0.04, 0.08)	2.05 (1.95, 2.14)	1.84 (1.76, 1.92)
Bushehr	0.65 (0.29, 1.26)	1.67 (1.18, 2.27)	1.66 (1.2, 2.2)
Bandar-e-Mahshahr	0.37 (0.2, 0.62)	0.74 (0.46, 1.11)	1.63 (1.2, 2.14)
Isfahan	1.14 (0.98, 1.31)	1.68 (1.5, 1.86)	1.54 (1.4, 1.69)
Ahvaz	0.74 (0.57, 0.92)	1.14 (0.95, 1.35)	1.5 (1.3, 1.72)
Najafabad	0.59 (0.37, 0.88)	0.66 (0.43, 0.96)	1.49 (1.12, 1.91)
Mashhad	0.29 (0.22, 0.37)	1.12 (0.99, 1.25)	1.38 (1.25, 1.51)
Kerman	0.33 (0.21, 0.47)	0.88 (0.67, 1.11)	1.37 (1.12, 1.64)
Khorramshahr	0.33 (0.17, 0.57)	0.86 (0.52, 1.3)	1.36 (0.91, 1.93)
Kashan	1.02 (0.71, 1.4)	1.22 (0.89, 1.61)	1.34 (1.02, 1.72)
Rasht	0.47 (0.34, 0.62)	0.97 (0.79, 1.17)	1.31 (1.12, 1.52)
Ramsar	0.29 (0.14, 0.52)	0.67 (0.37, 1.11)	1.31 (0.81, 1.97)
Ilam	0.29 (0.13, 0.56)	0.88 (0.56, 1.31)	1.31 (0.91, 1.81)
Rey	0.29 (0.15, 0.49)	1.4 (0.99, 1.87)	1.31 (0.96, 1.72)
Tabriz	0.31 (0.23, 0.4)	1.21 (1.05, 1.39)	1.27 (1.12, 1.43)
Shahinshahr va Meyme	0.45 (0.27, 0.7)	0.9 (0.62, 1.24)	1.27 (0.95, 1.64)
Gorgan	0.34 (0.2, 0.52)	1.15 (0.86, 1.49)	1.27 (0.99, 1.58)
Arak	0.15 (0.09, 0.24)	0.69 (0.5, 0.9)	1.25 (1.03, 1.51)
Babol	0.42 (0.28, 0.6)	0.98 (0.74, 1.25)	1.2 (0.96, 1.47)
Abadeh	0.38 (0.17, 0.72)	0.76 (0.43, 1.2)	1.2 (0.76, 1.78)
Delijan	0.25 (0.11, 0.48)	0.56 (0.27, 1.01)	1.19 (0.64, 1.95)
Kermanshah	0.37 (0.26, 0.51)	0.86 (0.69, 1.05)	1.19 (1.01, 1.39)
Lanjan	0.36 (0.2, 0.58)	0.58 (0.36, 0.87)	1.17 (0.82, 1.58)
Hendijan	0.33 (0.13, 0.69)	0.86 (0.35, 1.76)	1.15 (0.57, 2.01)
Lar (Larestan)	0.32 (0.14, 0.61)	0.58 (0.36, 0.86)	1.15 (0.83, 1.52)
Sanandaj	0.34 (0.21, 0.52)	0.63 (0.43, 0.87)	1.15 (0.88, 1.46)
Damghan	0.24 (0.12, 0.44)	0.65 (0.35, 1.06)	1.12 (0.67, 1.69)
Bandar Anzali	0.47 (0.26, 0.76)	0.9 (0.57, 1.31)	1.1 (0.75, 1.53)
Rudsar	0.26 (0.14, 0.44)	1.19 (0.81, 1.66)	1.09 (0.75, 1.51)
Zahedan	0.18 (0.1, 0.3)	0.71 (0.49, 0.98)	1.07 (0.8, 1.37)
Khorramabad	0.5 (0.32, 0.72)	0.8 (0.59, 1.06)	1.07 (0.83, 1.35)
Abumusa	0.24 (0.09, 0.54)	0.56 (0.21, 1.24)	1.07 (0.4, 2.4)
Lahijan	0.38 (0.21, 0.62)	1.02 (0.69, 1.43)	1.04 (0.72, 1.43)
Behshahr	0.2 (0.1, 0.34)	0.78 (0.51, 1.14)	1.04 (0.72, 1.42)
Shahrud	0.41 (0.24, 0.65)	0.81 (0.53, 1.15)	1.04 (0.73, 1.4)
Aran va Bidgol	0.27 (0.13, 0.49)	0.54 (0.29, 0.91)	1.03 (0.61, 1.58)
Genaveh	0.34 (0.15, 0.67)	0.72 (0.38, 1.19)	1.03 (0.6, 1.6)
Deylam	0.3 (0.11, 0.65)	0.74 (0.29, 1.6)	1.03 (0.47, 1.88)
Omidiyeh	0.27 (0.13, 0.49)	0.72 (0.38, 1.2)	1.02 (0.59, 1.59)

Kordkuy	0.22 (0.11, 0.4)	0.56 (0.29, 0.95)	1.01 (0.58, 1.58)
Shahrekord	0.21 (0.12, 0.34)	0.59 (0.39, 0.82)	1 (0.75, 1.29)
Astanehye Ashrafiyeh	0.19 (0.09, 0.33)	0.57 (0.32, 0.91)	0.99 (0.63, 1.45)
Sari	0.18 (0.1, 0.29)	1.07 (0.82, 1.35)	0.99 (0.78, 1.23)
Behbahan	0.31 (0.17, 0.53)	0.78 (0.48, 1.16)	0.99 (0.65, 1.41)
Ramhormoz	0.27 (0.12, 0.52)	0.49 (0.27, 0.79)	0.99 (0.64, 1.45)
Fasa	0.29 (0.16, 0.48)	0.95 (0.61, 1.36)	0.99 (0.66, 1.39)
Dashte Azadegan	0.24 (0.11, 0.43)	0.86 (0.48, 1.36)	0.98 (0.58, 1.51)
Zarand	0.23 (0.11, 0.41)	0.38 (0.21, 0.64)	0.98 (0.62, 1.44)
Arsanjan	0.32 (0.13, 0.65)	0.87 (0.41, 1.59)	0.96 (0.47, 1.68)
Borujerd	0.3 (0.17, 0.46)	0.86 (0.61, 1.17)	0.95 (0.69, 1.24)
Shushtar	0.24 (0.12, 0.41)	0.89 (0.57, 1.3)	0.94 (0.63, 1.32)
Khomeynishahr	0.33 (0.19, 0.53)	0.56 (0.35, 0.83)	0.94 (0.67, 1.26)
Hamadan	0.22 (0.13, 0.33)	0.98 (0.76, 1.23)	0.94 (0.75, 1.16)
Damavand	0.3 (0.13, 0.59)	0.82 (0.45, 1.32)	0.94 (0.55, 1.47)
Jahrom	0.28 (0.12, 0.54)	0.77 (0.49, 1.14)	0.93 (0.62, 1.31)
Sirjan	0.29 (0.15, 0.48)	0.61 (0.38, 0.92)	0.93 (0.65, 1.29)
Dezful	0.2 (0.11, 0.34)	0.81 (0.56, 1.11)	0.92 (0.67, 1.22)
Rafsanjan	0.46 (0.27, 0.71)	0.77 (0.5, 1.08)	0.92 (0.65, 1.25)
Orumiyeh	0.27 (0.18, 0.39)	0.82 (0.64, 1.01)	0.91 (0.74, 1.1)
Eqlid	0.26 (0.11, 0.51)	0.55 (0.3, 0.91)	0.9 (0.53, 1.41)
Saveh	0.15 (0.07, 0.26)	0.34 (0.19, 0.54)	0.89 (0.6, 1.25)
Golpayegan	0.22 (0.11, 0.4)	0.54 (0.29, 0.88)	0.89 (0.52, 1.38)
Semnan	0.2 (0.1, 0.35)	0.53 (0.32, 0.82)	0.89 (0.59, 1.25)
Birjand	0.29 (0.13, 0.56)	0.74 (0.49, 1.05)	0.88 (0.61, 1.2)
Ashtiyan	0.23 (0.09, 0.49)	0.58 (0.22, 1.23)	0.87 (0.37, 1.69)
Sadugh	0.28 (0.1, 0.63)	0.7 (0.25, 1.54)	0.87 (0.38, 1.66)
Kazerun	0.22 (0.1, 0.42)	0.65 (0.42, 0.95)	0.86 (0.59, 1.19)
Sabzevar	0.21 (0.12, 0.33)	0.53 (0.36, 0.74)	0.84 (0.62, 1.08)
Shahreza	0.35 (0.19, 0.57)	0.88 (0.57, 1.28)	0.84 (0.54, 1.2)
Langrud	0.27 (0.14, 0.45)	0.66 (0.4, 1)	0.83 (0.53, 1.21)
Mahalat	0.23 (0.1, 0.46)	0.62 (0.3, 1.08)	0.82 (0.43, 1.36)
Qasreshirin	0.25 (0.1, 0.51)	0.61 (0.26, 1.19)	0.82 (0.36, 1.57)
Bandare Gaz	0.3 (0.14, 0.55)	0.83 (0.43, 1.41)	0.82 (0.44, 1.36)
Chalus	0.16 (0.07, 0.31)	0.35 (0.19, 0.6)	0.81 (0.49, 1.22)
Oshnaviyeh	0.26 (0.11, 0.52)	0.57 (0.28, 1.02)	0.81 (0.42, 1.36)
Faridan	0.34 (0.17, 0.61)	0.73 (0.4, 1.18)	0.81 (0.46, 1.3)
Amol	0.23 (0.13, 0.36)	0.78 (0.55, 1.06)	0.8 (0.58, 1.06)
Qaemshahr	0.26 (0.12, 0.51)	0.6 (0.4, 0.85)	0.8 (0.57, 1.07)
Siyahkal	0.21 (0.09, 0.42)	0.62 (0.31, 1.05)	0.79 (0.43, 1.31)
Tabas	0.23 (0.09, 0.45)	0.55 (0.27, 0.97)	0.78 (0.41, 1.3)
Andimeshk	0.24 (0.12, 0.42)	0.71 (0.42, 1.11)	0.77 (0.47, 1.15)
Falavarjan	0.25 (0.13, 0.41)	0.5 (0.3, 0.76)	0.77 (0.51, 1.1)
Karaj	0.08 (0.05, 0.12)	0.41 (0.32, 0.51)	0.77 (0.66, 0.89)
Masjedsoleyman	0.22 (0.11, 0.38)	0.55 (0.31, 0.87)	0.76 (0.46, 1.15)
Boyerahmad	0.19 (0.08, 0.37)	0.39 (0.21, 0.65)	0.76 (0.47, 1.11)

Tonekabon	0.18 (0.09, 0.31)	0.58 (0.37, 0.87)	0.75 (0.5, 1.05)
Darrehgaz	0.18 (0.08, 0.33)	0.4 (0.2, 0.71)	0.75 (0.41, 1.2)
Eyvan	0.26 (0.11, 0.53)	0.66 (0.31, 1.18)	0.75 (0.38, 1.33)
Mehriz	0.34 (0.16, 0.62)	0.75 (0.39, 1.3)	0.75 (0.38, 1.29)
Azadshahr	0.18 (0.08, 0.35)	0.45 (0.19, 0.89)	0.75 (0.41, 1.22)
Astara	0.17 (0.07, 0.33)	0.36 (0.17, 0.65)	0.74 (0.4, 1.21)
Estahban	0.25 (0.11, 0.47)	0.68 (0.35, 1.17)	0.73 (0.39, 1.25)
Marvdasht	0.2 (0.09, 0.39)	0.42 (0.25, 0.64)	0.73 (0.5, 1.01)
Poldokhtar	0.17 (0.07, 0.33)	0.42 (0.17, 0.85)	0.73 (0.38, 1.22)
Bafq	0.3 (0.14, 0.56)	0.6 (0.3, 1.08)	0.73 (0.38, 1.23)
Aliabad	0.2 (0.1, 0.36)	0.54 (0.29, 0.9)	0.73 (0.43, 1.13)
Naqadeh	0.18 (0.09, 0.34)	0.38 (0.2, 0.64)	0.72 (0.42, 1.11)
Sepidan	0.15 (0.06, 0.3)	0.38 (0.19, 0.69)	0.72 (0.4, 1.18)
Lamard	0.23 (0.1, 0.45)	0.5 (0.25, 0.87)	0.72 (0.39, 1.18)
Shahrebabak	0.25 (0.11, 0.49)	0.5 (0.26, 0.85)	0.72 (0.4, 1.16)
Ardestan	0.19 (0.08, 0.39)	0.59 (0.29, 1.06)	0.72 (0.36, 1.25)
Abarkuh	0.28 (0.12, 0.56)	0.74 (0.35, 1.31)	0.72 (0.37, 1.24)
Ardebil	0.13 (0.07, 0.21)	0.47 (0.31, 0.65)	0.72 (0.53, 0.94)
Shadegan	0.38 (0.19, 0.66)	0.62 (0.34, 1.02)	0.71 (0.41, 1.12)
Farashband	0.22 (0.09, 0.46)	0.52 (0.22, 1.07)	0.71 (0.34, 1.26)
Garmsar	0.28 (0.13, 0.49)	0.51 (0.27, 0.86)	0.71 (0.39, 1.13)
Meybod	0.3 (0.14, 0.55)	0.62 (0.32, 1.06)	0.71 (0.39, 1.18)
Bandarabbas	0.25 (0.14, 0.4)	0.6 (0.41, 0.83)	0.7 (0.5, 0.92)
Bandar-e Lengeh	0.16 (0.08, 0.29)	0.33 (0.18, 0.56)	0.7 (0.42, 1.07)
Bastak	0.17 (0.07, 0.34)	0.34 (0.15, 0.65)	0.7 (0.35, 1.19)
Qazvin	0.69 (0.49, 0.91)	0.61 (0.45, 0.8)	0.7 (0.54, 0.88)
Darab	0.25 (0.11, 0.49)	0.64 (0.37, 0.98)	0.69 (0.42, 1.04)
Firuzabad	0.24 (0.1, 0.46)	0.58 (0.32, 0.95)	0.69 (0.4, 1.08)
Neka	0.18 (0.08, 0.37)	0.53 (0.28, 0.88)	0.68 (0.38, 1.06)
Shush	0.22 (0.11, 0.39)	0.51 (0.29, 0.82)	0.68 (0.41, 1.03)
Shahriyar	0.17 (0.08, 0.33)	0.38 (0.27, 0.52)	0.68 (0.54, 0.83)
Amlash	0.19 (0.08, 0.39)	0.44 (0.21, 0.81)	0.67 (0.34, 1.15)
Babolsar	0.23 (0.12, 0.39)	0.69 (0.43, 1.05)	0.67 (0.42, 0.97)
Gachsaran	0.21 (0.09, 0.4)	0.38 (0.2, 0.63)	0.67 (0.39, 1.04)
Ardakan	0.27 (0.12, 0.52)	0.55 (0.28, 0.96)	0.67 (0.36, 1.12)
Khatam	0.23 (0.09, 0.48)	0.54 (0.21, 1.14)	0.67 (0.29, 1.27)
Torbate Jam	0.23 (0.12, 0.41)	0.47 (0.27, 0.73)	0.66 (0.42, 0.97)
Mobarakeh	0.23 (0.11, 0.41)	0.61 (0.35, 0.97)	0.66 (0.39, 1.02)
Varamin	0.15 (0.09, 0.25)	0.68 (0.48, 0.92)	0.66 (0.48, 0.86)
Shazand	0.15 (0.06, 0.29)	0.41 (0.21, 0.69)	0.65 (0.38, 1.02)
Bonab	0.17 (0.08, 0.31)	0.6 (0.34, 0.95)	0.65 (0.37, 1.01)
Kashmar	0.21 (0.11, 0.36)	0.6 (0.36, 0.91)	0.65 (0.41, 0.95)
Nayin	0.23 (0.11, 0.45)	0.51 (0.26, 0.89)	0.65 (0.33, 1.09)
Khorramdarreh	0.2 (0.09, 0.39)	0.42 (0.2, 0.77)	0.65 (0.33, 1.1)
Marivan	0.23 (0.11, 0.42)	0.37 (0.19, 0.63)	0.64 (0.38, 1)
Eslamshahr	0.18 (0.08, 0.35)	0.33 (0.2, 0.49)	0.64 (0.46, 0.86)

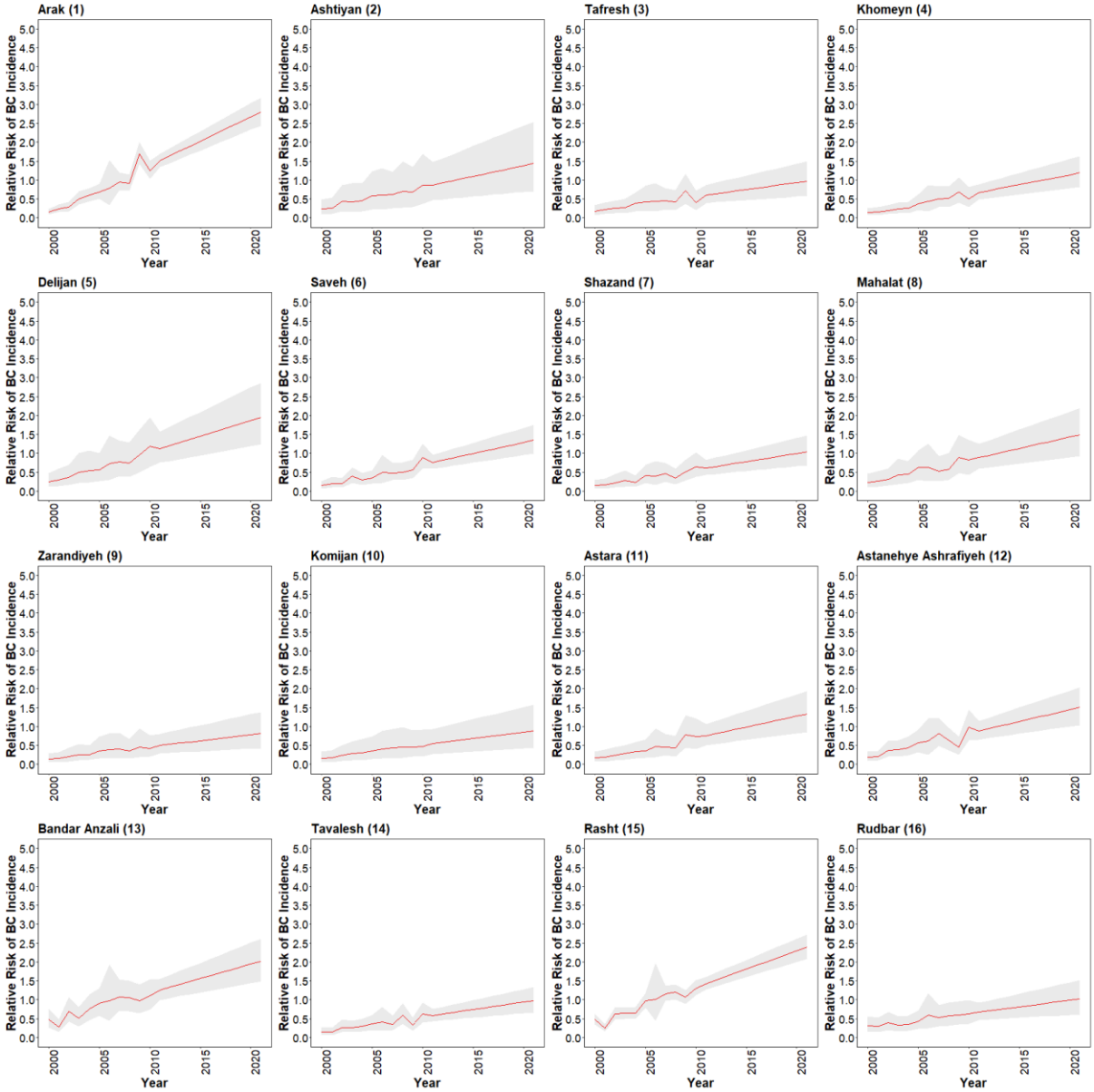
Tavalesh	0.14 (0.07, 0.26)	0.36 (0.2, 0.59)	0.63 (0.39, 0.93)
Rudbar	0.32 (0.16, 0.56)	0.43 (0.23, 0.71)	0.63 (0.36, 0.99)
Sarakhs	0.19 (0.08, 0.39)	0.54 (0.27, 0.95)	0.63 (0.32, 1.07)
Mehran	0.22 (0.09, 0.45)	0.54 (0.22, 1.11)	0.63 (0.29, 1.15)
Kangan	0.23 (0.1, 0.48)	0.48 (0.23, 0.88)	0.63 (0.32, 1.08)
Zanjan	0.41 (0.26, 0.6)	0.62 (0.43, 0.85)	0.63 (0.45, 0.84)
Meshginshahr	0.19 (0.09, 0.33)	0.72 (0.43, 1.1)	0.63 (0.37, 0.95)
Shaft	0.16 (0.07, 0.32)	0.35 (0.17, 0.63)	0.62 (0.32, 1.05)
Juybar	0.22 (0.09, 0.44)	0.77 (0.41, 1.29)	0.62 (0.33, 1.06)
Izeh	0.15 (0.07, 0.28)	0.38 (0.2, 0.62)	0.62 (0.37, 0.94)
Kalat	0.2 (0.07, 0.43)	0.5 (0.18, 1.09)	0.62 (0.23, 1.35)
Khalkhal	0.19 (0.07, 0.43)	0.47 (0.17, 1.08)	0.62 (0.22, 1.41)
Qom	0.44 (0.31, 0.59)	0.56 (0.42, 0.71)	0.62 (0.49, 0.77)
Lali	0.22 (0.08, 0.48)	0.56 (0.2, 1.22)	0.61 (0.25, 1.21)
Quchan	0.15 (0.07, 0.26)	0.41 (0.23, 0.66)	0.61 (0.37, 0.91)
Baghmalek	0.16 (0.07, 0.32)	0.44 (0.22, 0.78)	0.6 (0.32, 1.02)
Gonabad	0.22 (0.1, 0.44)	0.56 (0.31, 0.9)	0.6 (0.34, 0.95)
Natanz	0.2 (0.09, 0.39)	0.51 (0.21, 1.01)	0.6 (0.29, 1.05)
Rezvanshahr	0.17 (0.07, 0.35)	0.52 (0.25, 0.91)	0.59 (0.3, 1.01)
Mahmudabad	0.21 (0.1, 0.38)	0.51 (0.27, 0.86)	0.59 (0.33, 0.95)
Kangavar	0.19 (0.09, 0.34)	0.39 (0.2, 0.68)	0.59 (0.32, 0.98)
Khorrambid	0.21 (0.08, 0.43)	0.52 (0.21, 1.08)	0.59 (0.28, 1.06)
Semirom	0.2 (0.09, 0.38)	0.47 (0.23, 0.84)	0.59 (0.3, 1.02)
Marand	0.33 (0.19, 0.53)	1.23 (0.86, 1.65)	0.58 (0.37, 0.83)
Haris	0.19 (0.08, 0.38)	0.46 (0.23, 0.81)	0.58 (0.3, 1.01)
Sonqor	0.17 (0.07, 0.33)	0.39 (0.2, 0.66)	0.58 (0.32, 0.95)
Taft	0.2 (0.09, 0.41)	0.42 (0.2, 0.74)	0.58 (0.3, 0.99)
Sumehsara	0.3 (0.16, 0.51)	0.72 (0.44, 1.1)	0.57 (0.34, 0.88)
Mohr	0.18 (0.07, 0.38)	0.45 (0.18, 0.95)	0.57 (0.27, 1.03)
Azna	0.15 (0.06, 0.3)	0.32 (0.15, 0.59)	0.57 (0.29, 0.98)
Neyriz	0.22 (0.1, 0.42)	0.57 (0.31, 0.94)	0.56 (0.31, 0.9)
Robatkarim	0.11 (0.05, 0.21)	0.19 (0.1, 0.3)	0.56 (0.4, 0.75)
Fuman	0.27 (0.13, 0.47)	0.51 (0.28, 0.82)	0.55 (0.31, 0.89)
Sarab	0.15 (0.07, 0.27)	0.77 (0.45, 1.18)	0.55 (0.31, 0.86)
Miyandoab	0.15 (0.08, 0.27)	0.32 (0.18, 0.5)	0.55 (0.35, 0.81)
Borujen	0.17 (0.08, 0.33)	0.38 (0.2, 0.65)	0.55 (0.31, 0.88)
Sarayan	0.19 (0.07, 0.41)	0.43 (0.16, 0.95)	0.55 (0.2, 1.2)
Harsin	0.17 (0.08, 0.32)	0.35 (0.17, 0.61)	0.54 (0.28, 0.92)
Selseleh	0.16 (0.05, 0.38)	0.41 (0.14, 0.95)	0.54 (0.18, 1.26)
Masal	0.18 (0.07, 0.36)	0.45 (0.21, 0.81)	0.53 (0.26, 0.93)
Azarshahr	0.15 (0.06, 0.3)	0.39 (0.2, 0.68)	0.53 (0.29, 0.87)
Khansar	0.2 (0.09, 0.38)	0.44 (0.21, 0.8)	0.53 (0.26, 0.94)
Malayer	0.17 (0.09, 0.29)	0.39 (0.24, 0.58)	0.53 (0.35, 0.75)
Bojnurd	0.18 (0.08, 0.36)	0.38 (0.23, 0.58)	0.53 (0.35, 0.77)
Baft	0.17 (0.08, 0.31)	0.45 (0.25, 0.74)	0.52 (0.3, 0.82)
Shirvan	0.14 (0.06, 0.28)	0.29 (0.15, 0.5)	0.52 (0.3, 0.81)

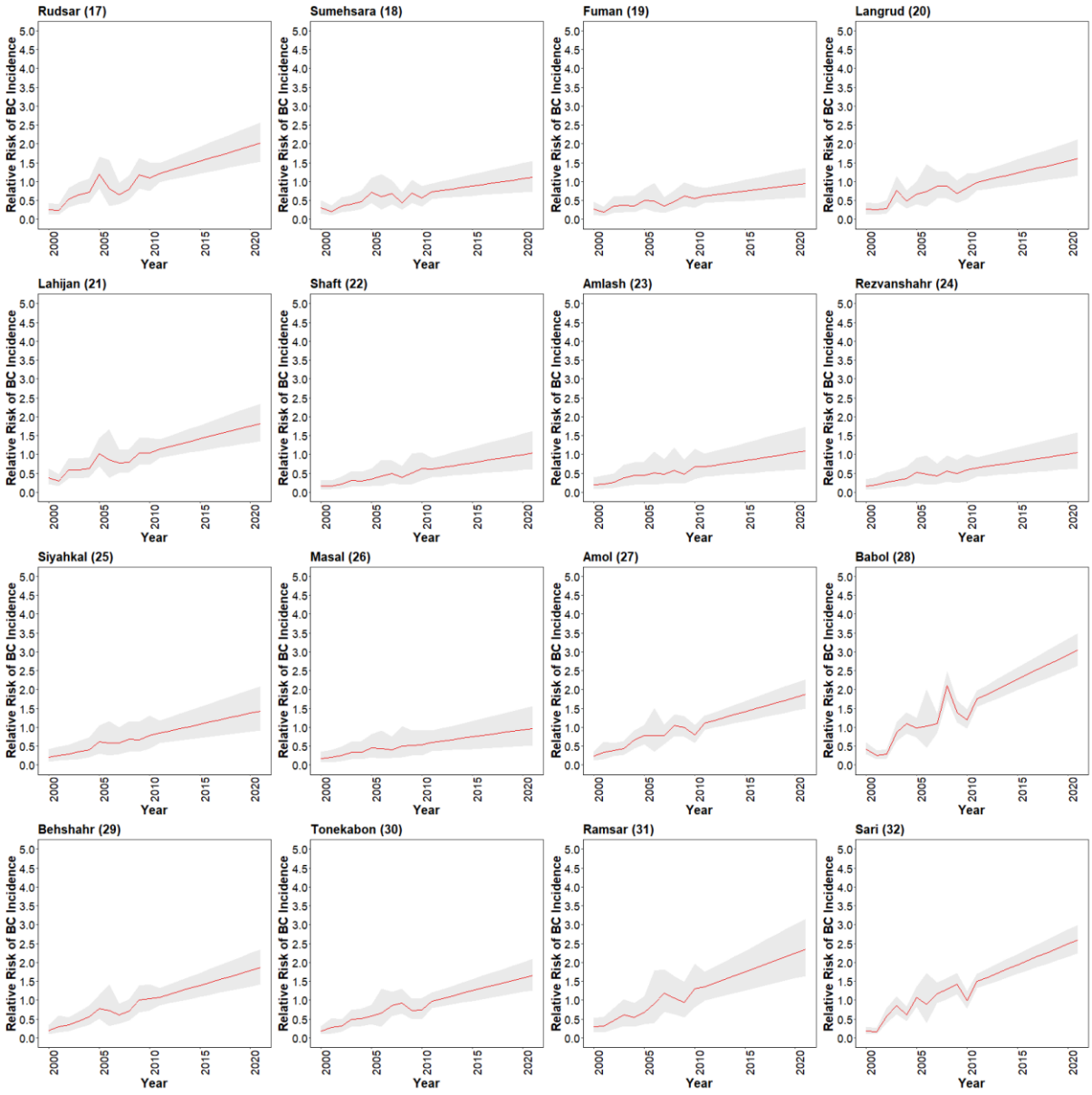
Khomeyn	0.14 (0.07, 0.26)	0.37 (0.2, 0.61)	0.51 (0.28, 0.81)
Mamasany	0.12 (0.06, 0.22)	0.38 (0.2, 0.61)	0.51 (0.3, 0.8)
Baneh	0.14 (0.06, 0.28)	0.32 (0.16, 0.57)	0.51 (0.27, 0.84)
Pakdasht	0.12 (0.06, 0.23)	0.27 (0.14, 0.46)	0.51 (0.31, 0.77)
Firuzkuh	0.15 (0.06, 0.32)	0.38 (0.15, 0.8)	0.51 (0.2, 1.08)
Torkman	0.2 (0.09, 0.4)	0.47 (0.25, 0.77)	0.51 (0.29, 0.82)
Jolfa	0.15 (0.06, 0.31)	0.37 (0.17, 0.7)	0.5 (0.2, 1.05)
Paveh	0.16 (0.07, 0.34)	0.36 (0.16, 0.67)	0.5 (0.24, 0.88)
Ravar	0.22 (0.08, 0.46)	0.5 (0.2, 1.06)	0.5 (0.21, 0.93)
Nahavand	0.14 (0.06, 0.27)	0.29 (0.16, 0.48)	0.5 (0.3, 0.77)
Dashti	0.2 (0.08, 0.39)	0.47 (0.23, 0.83)	0.5 (0.25, 0.87)
Dayyer	0.21 (0.09, 0.43)	0.56 (0.26, 1.01)	0.5 (0.24, 0.9)
Takestan	0.19 (0.09, 0.34)	0.41 (0.23, 0.66)	0.5 (0.29, 0.78)
Sarpole Zahab	0.16 (0.07, 0.33)	0.45 (0.22, 0.8)	0.49 (0.24, 0.85)
Jiroft	0.17 (0.09, 0.32)	0.4 (0.22, 0.65)	0.49 (0.29, 0.74)
Fariman	0.19 (0.08, 0.37)	0.44 (0.22, 0.78)	0.49 (0.25, 0.84)
Dorud	0.2 (0.1, 0.35)	0.36 (0.19, 0.6)	0.49 (0.28, 0.78)
Dehloran	0.17 (0.07, 0.35)	0.38 (0.16, 0.75)	0.49 (0.22, 0.91)
Tiran va Karvan	0.15 (0.06, 0.3)	0.38 (0.15, 0.78)	0.48 (0.23, 0.85)
Qorveh	0.12 (0.06, 0.22)	0.29 (0.16, 0.48)	0.48 (0.28, 0.74)
Bahar	0.16 (0.08, 0.3)	0.47 (0.25, 0.76)	0.48 (0.26, 0.78)
Abyek	0.16 (0.07, 0.33)	0.45 (0.22, 0.79)	0.48 (0.25, 0.82)
Komijan	0.15 (0.06, 0.34)	0.36 (0.14, 0.73)	0.47 (0.2, 0.91)
Hashtrud	0.15 (0.06, 0.28)	0.51 (0.25, 0.91)	0.47 (0.23, 0.84)
Salmas	0.21 (0.1, 0.37)	0.7 (0.42, 1.06)	0.47 (0.27, 0.75)
Bovanat	0.16 (0.07, 0.34)	0.41 (0.17, 0.84)	0.47 (0.22, 0.87)
Zarrindasht	0.2 (0.07, 0.43)	0.48 (0.18, 1.03)	0.47 (0.21, 0.87)
Tuyserkan	0.17 (0.08, 0.31)	0.36 (0.19, 0.61)	0.47 (0.26, 0.76)
Asadabad	0.15 (0.07, 0.3)	0.33 (0.17, 0.58)	0.47 (0.25, 0.77)
Gonbade Kavus	0.22 (0.12, 0.36)	0.68 (0.44, 0.98)	0.47 (0.3, 0.69)
Qirokarzin	0.17 (0.07, 0.35)	0.36 (0.16, 0.68)	0.46 (0.22, 0.84)
Fereydunshahr	0.16 (0.07, 0.33)	0.42 (0.19, 0.79)	0.46 (0.21, 0.88)
Aligudarz	0.14 (0.06, 0.29)	0.36 (0.16, 0.73)	0.46 (0.25, 0.75)
Tangestan	0.2 (0.08, 0.41)	0.47 (0.22, 0.84)	0.46 (0.22, 0.82)
Ajabshir	0.17 (0.07, 0.33)	0.39 (0.16, 0.78)	0.45 (0.22, 0.8)
Maragheh	0.16 (0.07, 0.32)	0.59 (0.37, 0.88)	0.44 (0.27, 0.67)
Shahindezh	0.14 (0.06, 0.29)	0.37 (0.18, 0.67)	0.44 (0.18, 0.92)
Javanrud	0.13 (0.05, 0.26)	0.33 (0.14, 0.67)	0.44 (0.22, 0.75)
Bardsir	0.16 (0.07, 0.31)	0.42 (0.2, 0.74)	0.44 (0.21, 0.78)
Farsan	0.19 (0.09, 0.36)	0.35 (0.17, 0.64)	0.44 (0.22, 0.76)
Minudasht	0.14 (0.06, 0.26)	0.33 (0.16, 0.57)	0.44 (0.23, 0.72)
Sarbisheh	0.15 (0.04, 0.4)	0.37 (0.11, 0.94)	0.44 (0.13, 1.13)
Ferdows	0.18 (0.08, 0.36)	0.47 (0.23, 0.81)	0.44 (0.22, 0.77)
Sahneh	0.16 (0.07, 0.32)	0.37 (0.18, 0.66)	0.43 (0.22, 0.74)
Chadegan	0.15 (0.06, 0.32)	0.37 (0.14, 0.78)	0.43 (0.18, 0.81)
Saqqez	0.17 (0.08, 0.3)	0.42 (0.24, 0.66)	0.43 (0.26, 0.66)

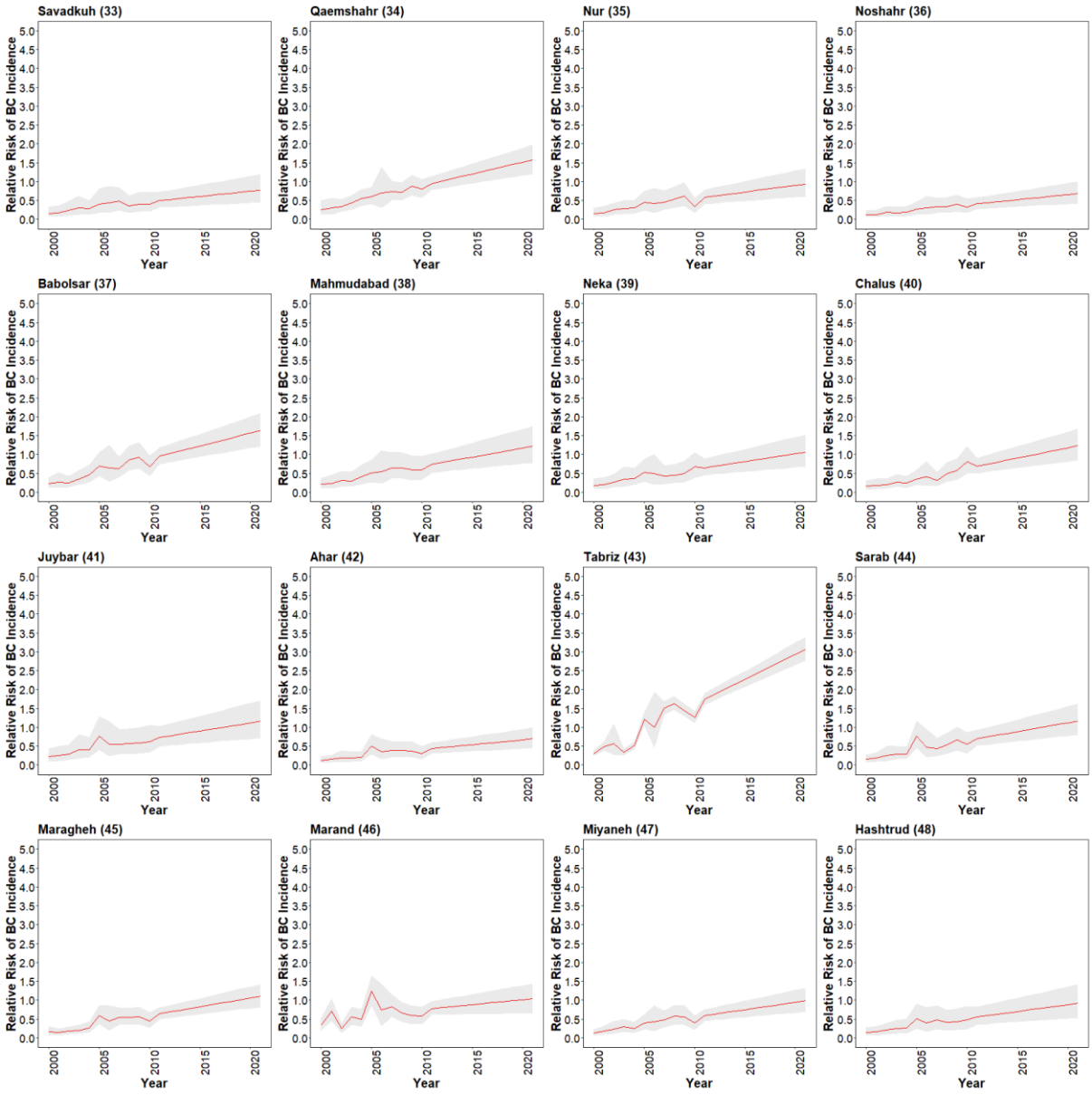
Zarandiyeh	0.14 (0.06, 0.29)	0.36 (0.15, 0.74)	0.42 (0.2, 0.77)
Torbate Heydarieh	0.3 (0.17, 0.48)	0.45 (0.28, 0.67)	0.42 (0.27, 0.62)
Tafresh	0.17 (0.07, 0.34)	0.42 (0.18, 0.85)	0.41 (0.2, 0.72)
Savadkuh	0.16 (0.07, 0.33)	0.4 (0.17, 0.82)	0.41 (0.2, 0.72)
Khoy	0.13 (0.06, 0.21)	0.29 (0.18, 0.45)	0.41 (0.26, 0.59)
Bukan	0.13 (0.06, 0.23)	0.37 (0.2, 0.6)	0.41 (0.24, 0.65)
Chenaran	0.14 (0.06, 0.28)	0.37 (0.16, 0.75)	0.41 (0.22, 0.69)
Germi	0.13 (0.06, 0.26)	0.31 (0.15, 0.56)	0.41 (0.2, 0.71)
Qaenat	0.13 (0.06, 0.26)	0.31 (0.14, 0.63)	0.41 (0.22, 0.67)
Bostanabad	0.14 (0.06, 0.28)	0.35 (0.17, 0.61)	0.4 (0.2, 0.69)
Piranshahr	0.14 (0.06, 0.28)	0.33 (0.16, 0.6)	0.4 (0.2, 0.68)
Razan	0.12 (0.05, 0.25)	0.27 (0.13, 0.48)	0.4 (0.21, 0.67)
Abdanan	0.14 (0.06, 0.29)	0.33 (0.15, 0.64)	0.4 (0.19, 0.75)
Dashtestan	0.22 (0.1, 0.43)	0.5 (0.3, 0.78)	0.4 (0.24, 0.62)
Miyaneh	0.13 (0.06, 0.23)	0.39 (0.23, 0.62)	0.39 (0.22, 0.6)
Jam	0.14 (0.05, 0.31)	0.35 (0.13, 0.77)	0.39 (0.16, 0.78)
Qeshm	0.19 (0.08, 0.38)	0.51 (0.25, 0.9)	0.39 (0.19, 0.68)
Minab	0.13 (0.06, 0.23)	0.32 (0.18, 0.53)	0.39 (0.23, 0.61)
Mahabad	0.14 (0.06, 0.28)	0.34 (0.18, 0.55)	0.38 (0.22, 0.6)
Kahnuj	0.11 (0.05, 0.21)	0.27 (0.14, 0.46)	0.38 (0.21, 0.59)
Kowsar	0.12 (0.04, 0.29)	0.29 (0.09, 0.71)	0.38 (0.11, 0.95)
Shabestar	0.16 (0.07, 0.31)	0.57 (0.33, 0.9)	0.37 (0.2, 0.62)
Malekan	0.12 (0.05, 0.24)	0.3 (0.15, 0.54)	0.37 (0.19, 0.65)
Salas-e-Babajani	0.1 (0.03, 0.25)	0.27 (0.09, 0.62)	0.37 (0.12, 0.86)
Taybad	0.13 (0.06, 0.25)	0.41 (0.21, 0.71)	0.37 (0.19, 0.63)
Shirvan va Chardavol	0.11 (0.04, 0.23)	0.26 (0.11, 0.49)	0.37 (0.15, 0.77)
Abhar	0.14 (0.07, 0.25)	0.32 (0.16, 0.54)	0.37 (0.2, 0.6)
Bilehsowar	0.12 (0.05, 0.25)	0.28 (0.12, 0.55)	0.37 (0.16, 0.71)
Neer	0.11 (0.04, 0.26)	0.28 (0.1, 0.64)	0.37 (0.13, 0.83)
Chaldoran	0.13 (0.04, 0.29)	0.31 (0.12, 0.63)	0.36 (0.14, 0.71)
Anbarabad	0.15 (0.05, 0.33)	0.34 (0.12, 0.77)	0.36 (0.15, 0.71)
Manujan	0.11 (0.04, 0.25)	0.29 (0.11, 0.59)	0.36 (0.13, 0.8)
Kuhdasht	0.13 (0.06, 0.24)	0.25 (0.13, 0.43)	0.36 (0.2, 0.58)
Khaf	0.14 (0.06, 0.28)	0.35 (0.15, 0.7)	0.35 (0.17, 0.62)
Zabol	0.11 (0.05, 0.19)	0.39 (0.24, 0.6)	0.35 (0.21, 0.55)
Kohgiluyeh	0.1 (0.04, 0.21)	0.23 (0.11, 0.4)	0.35 (0.14, 0.71)
Tarom	0.11 (0.04, 0.26)	0.28 (0.1, 0.63)	0.35 (0.14, 0.71)
Mahneshan	0.11 (0.04, 0.24)	0.28 (0.1, 0.63)	0.35 (0.12, 0.78)
Rudan	0.11 (0.04, 0.22)	0.25 (0.11, 0.47)	0.35 (0.17, 0.62)
Namin	0.12 (0.05, 0.25)	0.35 (0.16, 0.64)	0.35 (0.16, 0.65)
Iranshahr	0.17 (0.07, 0.33)	0.39 (0.21, 0.65)	0.34 (0.18, 0.55)
Divandarreh	0.12 (0.05, 0.23)	0.29 (0.13, 0.53)	0.34 (0.17, 0.62)
Kamyaran	0.12 (0.05, 0.24)	0.3 (0.12, 0.61)	0.34 (0.17, 0.6)
Dena	0.13 (0.05, 0.26)	0.31 (0.13, 0.62)	0.34 (0.15, 0.64)
Parsabad	0.11 (0.05, 0.21)	0.26 (0.13, 0.45)	0.34 (0.18, 0.57)
Kalaleh	0.11 (0.05, 0.22)	0.25 (0.12, 0.45)	0.34 (0.17, 0.57)

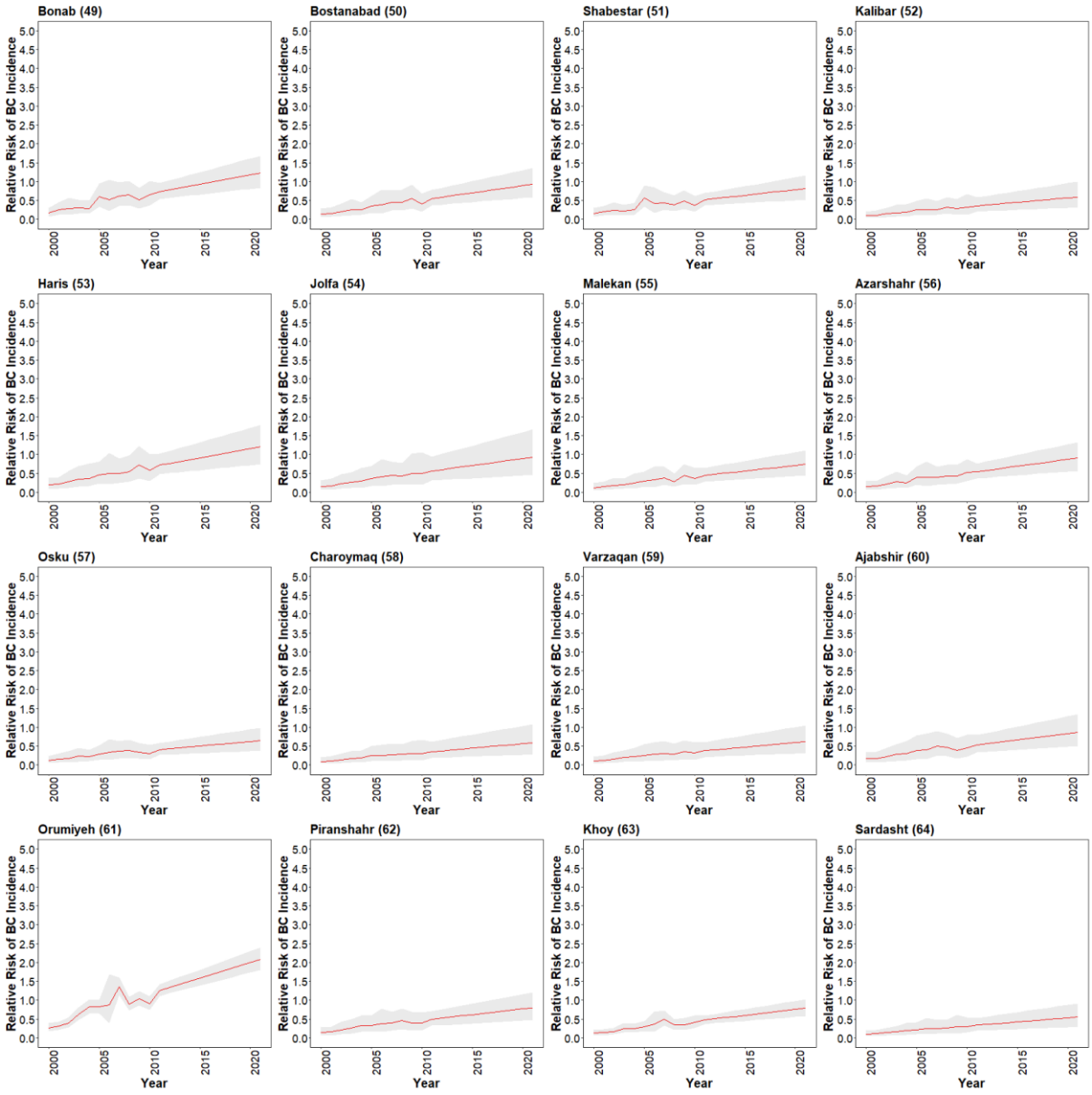
Nehbandan	0.11 (0.04, 0.26)	0.27 (0.09, 0.65)	0.34 (0.11, 0.82)
Nur	0.16 (0.07, 0.31)	0.45 (0.24, 0.75)	0.33 (0.17, 0.57)
Gilanegharb	0.12 (0.05, 0.25)	0.31 (0.14, 0.58)	0.33 (0.15, 0.62)
Ardal	0.11 (0.04, 0.25)	0.26 (0.09, 0.62)	0.33 (0.11, 0.77)
Dalfan	0.12 (0.05, 0.24)	0.29 (0.12, 0.58)	0.33 (0.17, 0.58)
Maneh va Semelqan	0.13 (0.05, 0.27)	0.31 (0.12, 0.68)	0.33 (0.15, 0.62)
Noshahr	0.12 (0.05, 0.23)	0.27 (0.13, 0.47)	0.32 (0.17, 0.55)
Kalibar	0.1 (0.04, 0.2)	0.26 (0.12, 0.49)	0.32 (0.13, 0.67)
Varzaqan	0.11 (0.04, 0.22)	0.26 (0.11, 0.55)	0.32 (0.14, 0.6)
Rashtkhar	0.12 (0.04, 0.27)	0.29 (0.1, 0.66)	0.32 (0.13, 0.65)
Ijrud	0.1 (0.04, 0.22)	0.27 (0.1, 0.57)	0.32 (0.13, 0.7)
Osku	0.12 (0.05, 0.24)	0.29 (0.14, 0.52)	0.31 (0.15, 0.54)
Charoymaq	0.09 (0.04, 0.2)	0.25 (0.1, 0.51)	0.31 (0.12, 0.66)
Bam	0.18 (0.09, 0.31)	0.35 (0.19, 0.56)	0.31 (0.18, 0.49)
Bijar	0.12 (0.05, 0.22)	0.3 (0.15, 0.53)	0.31 (0.16, 0.54)
Darrehshahr	0.11 (0.04, 0.23)	0.27 (0.1, 0.59)	0.31 (0.13, 0.62)
Esfarayen	0.11 (0.05, 0.22)	0.22 (0.1, 0.4)	0.31 (0.16, 0.53)
Nazarabad	0.15 (0.06, 0.32)	0.28 (0.13, 0.5)	0.31 (0.15, 0.55)
Ahar	0.12 (0.06, 0.23)	0.5 (0.28, 0.82)	0.3 (0.16, 0.5)
Neyshabur	0.28 (0.17, 0.42)	0.46 (0.31, 0.66)	0.3 (0.19, 0.44)
Bardeskan	0.11 (0.04, 0.23)	0.28 (0.13, 0.53)	0.3 (0.14, 0.55)
Lordakan	0.14 (0.06, 0.26)	0.29 (0.13, 0.58)	0.3 (0.16, 0.51)
Jajarm	0.11 (0.04, 0.25)	0.27 (0.1, 0.6)	0.3 (0.12, 0.59)
Sardasht	0.09 (0.04, 0.19)	0.22 (0.1, 0.41)	0.29 (0.14, 0.54)
Kuhrang	0.1 (0.04, 0.21)	0.24 (0.09, 0.51)	0.29 (0.11, 0.62)
Bandar-e-Jask	0.14 (0.07, 0.26)	0.28 (0.13, 0.52)	0.29 (0.15, 0.51)
Hajiabad	0.12 (0.05, 0.25)	0.35 (0.15, 0.67)	0.29 (0.13, 0.57)
Takab	0.11 (0.05, 0.23)	0.25 (0.11, 0.47)	0.28 (0.13, 0.52)
Sarvabad	0.09 (0.03, 0.19)	0.22 (0.09, 0.47)	0.28 (0.11, 0.59)
Bueenzahra	0.1 (0.05, 0.19)	0.21 (0.1, 0.37)	0.28 (0.14, 0.48)
Aqqala	0.11 (0.05, 0.22)	0.28 (0.11, 0.56)	0.28 (0.13, 0.51)
Maku	0.1 (0.04, 0.18)	0.25 (0.13, 0.44)	0.27 (0.14, 0.46)
Khash	0.11 (0.04, 0.24)	0.22 (0.1, 0.41)	0.27 (0.13, 0.5)
Ramyan	0.11 (0.05, 0.22)	0.26 (0.1, 0.54)	0.27 (0.12, 0.5)
Sarbaz	0.1 (0.03, 0.26)	0.21 (0.06, 0.54)	0.25 (0.07, 0.64)
Faruj	0.1 (0.04, 0.21)	0.23 (0.09, 0.51)	0.25 (0.11, 0.5)
Chah Bahar	0.12 (0.05, 0.24)	0.25 (0.11, 0.51)	0.24 (0.12, 0.41)
Kabudarahang	0.1 (0.05, 0.19)	0.21 (0.1, 0.37)	0.24 (0.12, 0.43)
Khodabandeh	0.1 (0.05, 0.2)	0.25 (0.13, 0.44)	0.24 (0.12, 0.42)
Eslamabade Gharb	0.11 (0.05, 0.19)	0.28 (0.15, 0.46)	0.23 (0.12, 0.39)
Nikshahr	0.09 (0.03, 0.18)	0.16 (0.07, 0.3)	0.2 (0.09, 0.36)
Saravan	0.08 (0.03, 0.16)	0.16 (0.08, 0.29)	0.17 (0.08, 0.3)
Savojbolagh	0.05 (0.02, 0.11)	0.11 (0.04, 0.23)	0.11 (0.05, 0.2)

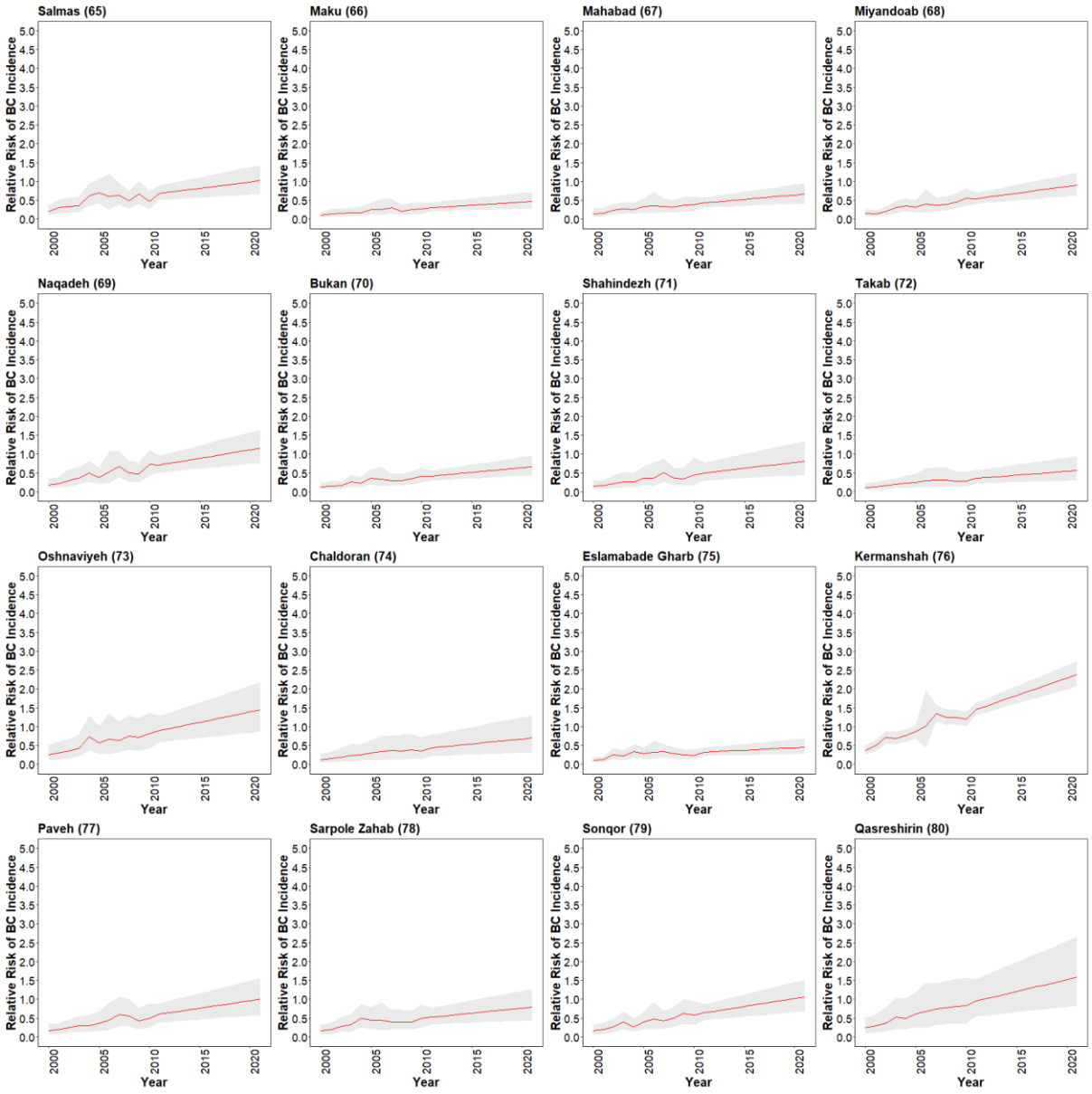
Appendix Figure 4. Trend of relative risk of breast cancer incidence for each district from 2000-2021 in Iran (spatio-temporal model for 2000-2010 and projection for 2011-2021). Grey shadow shows 95% credible interval.

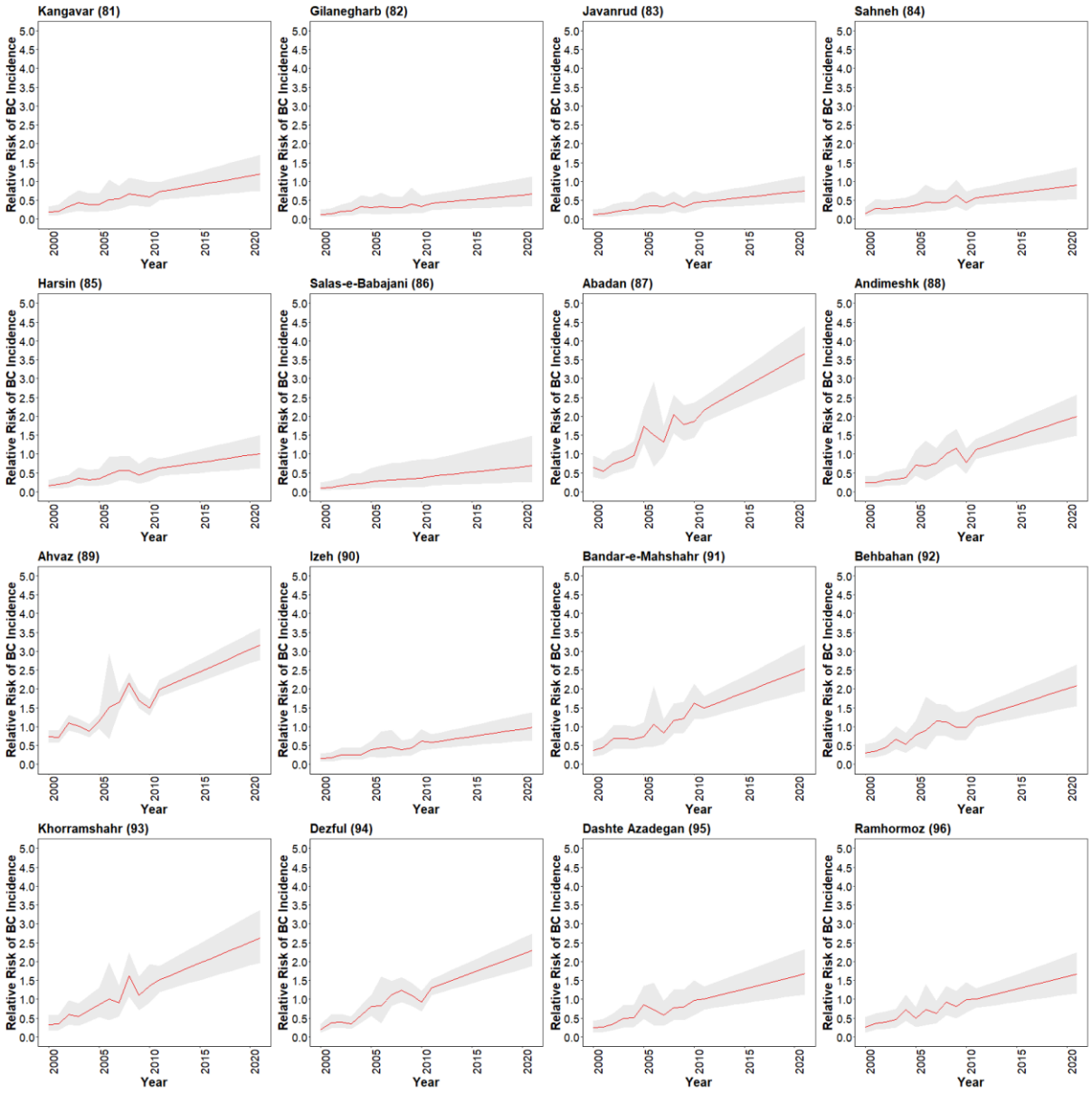


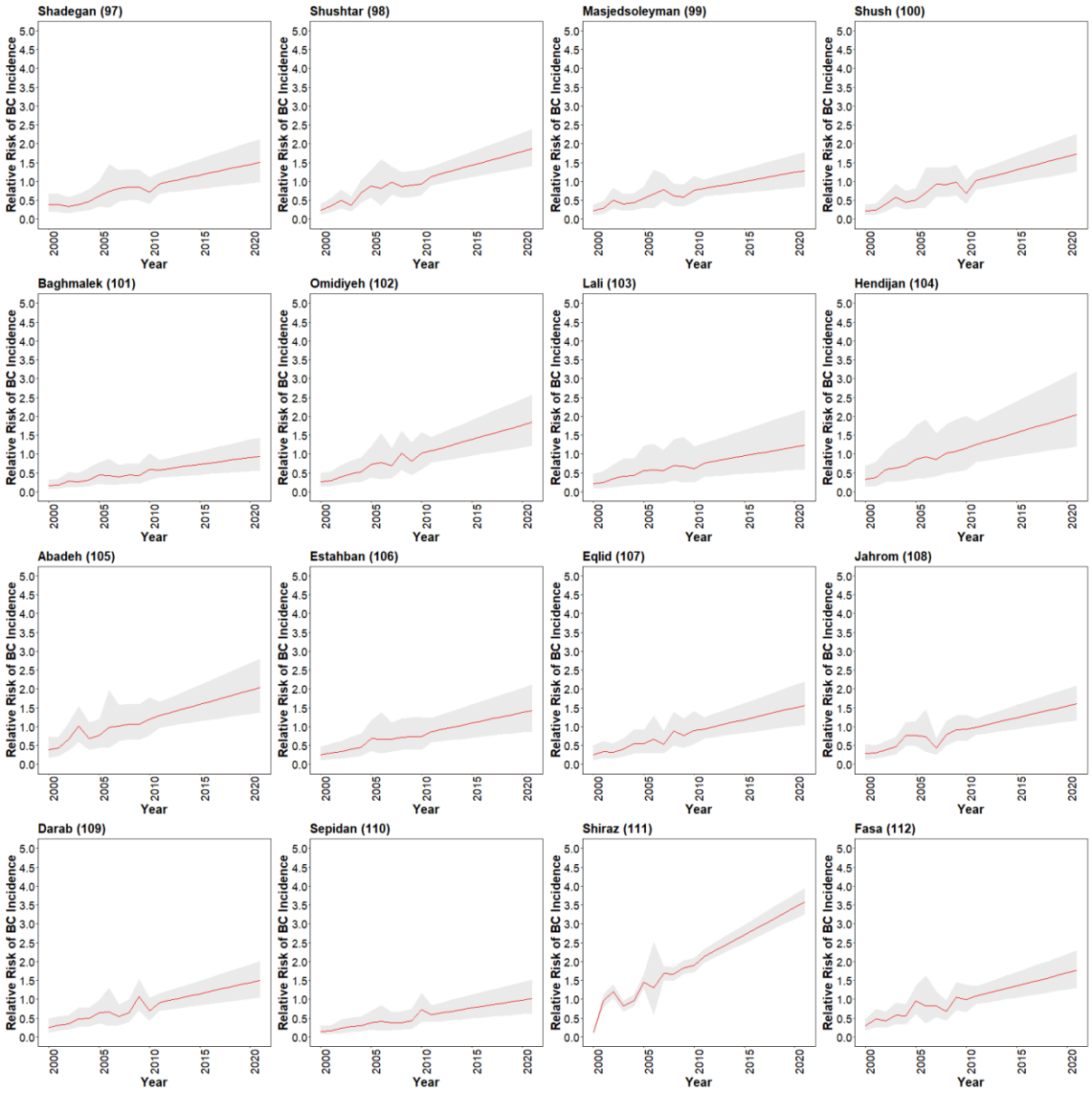

Rudsar (17)
Sumehsara (18)
Fuman (19)
Langrud (20)
Lahijan (21)
Shaft (22)
Amlash (23)
Rezvanshahr (24)
Siyahkal (25)
Masal (26)
Amol (27)
Babol (28)
Behshahr (29)
Tonekabon (30)
Ramsar (31)
Sari (32)
Relative Risk of BC Incidence
Year

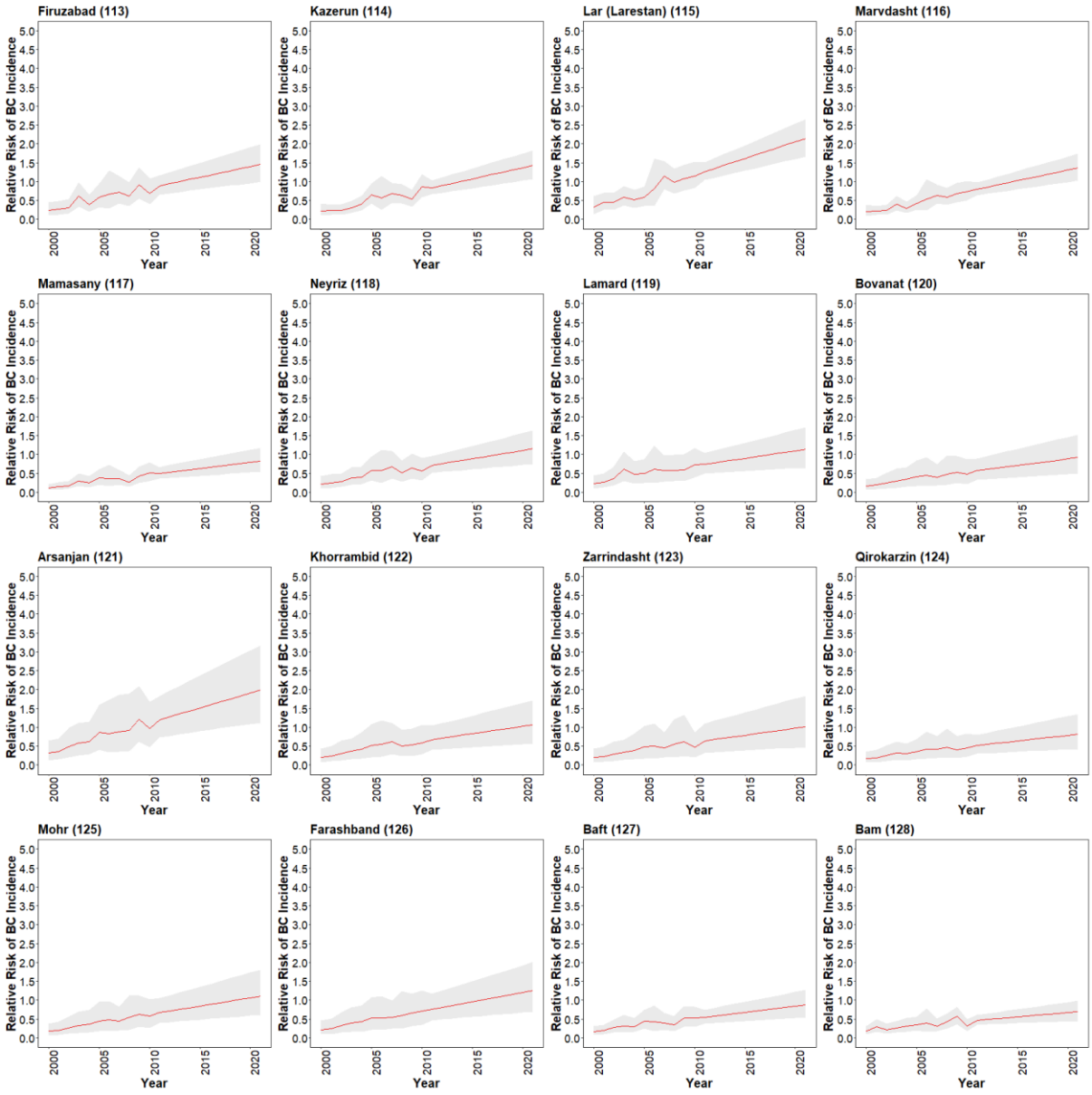

Savadkuh (33)
Qaemshahr (34)
Nur (35)
Noshahr (36)
Babolsar (37)
Mahmudabad (38)
Neka (39)
Chalus (40)
Juybar (41)
Ahar (42)
Tabriz (43)
Sarab (44)
Maragheh (45)
Marand (46)
Miyaneh (47)
Hashtrud (48)
Relative Risk of BC Incidence
Year

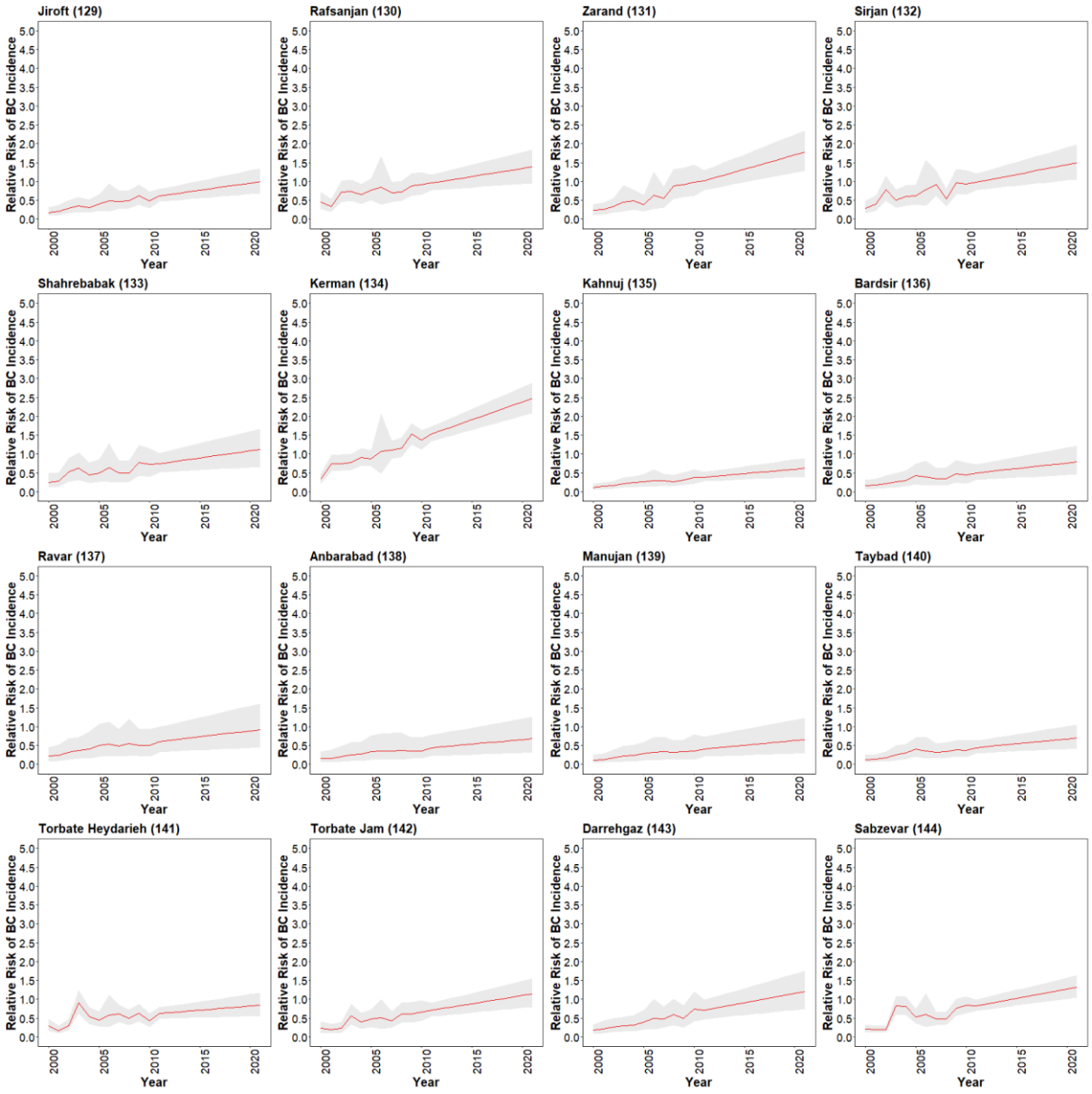

Bonab (49)
Bostanabad (50)
Shabestar (51)
Kalibar (52)
Haris (53)
Jolfa (54)
Malekan (55)
Azarshahr (56)
Osku (57)
Charoymaq (58)
Varzaqan (59)
Ajabshir (60)
Orumiyeh (61)
Piranshahr (62)
Khoy (63)
Sardasht (64)
Relative Risk of BC Incidence
Year

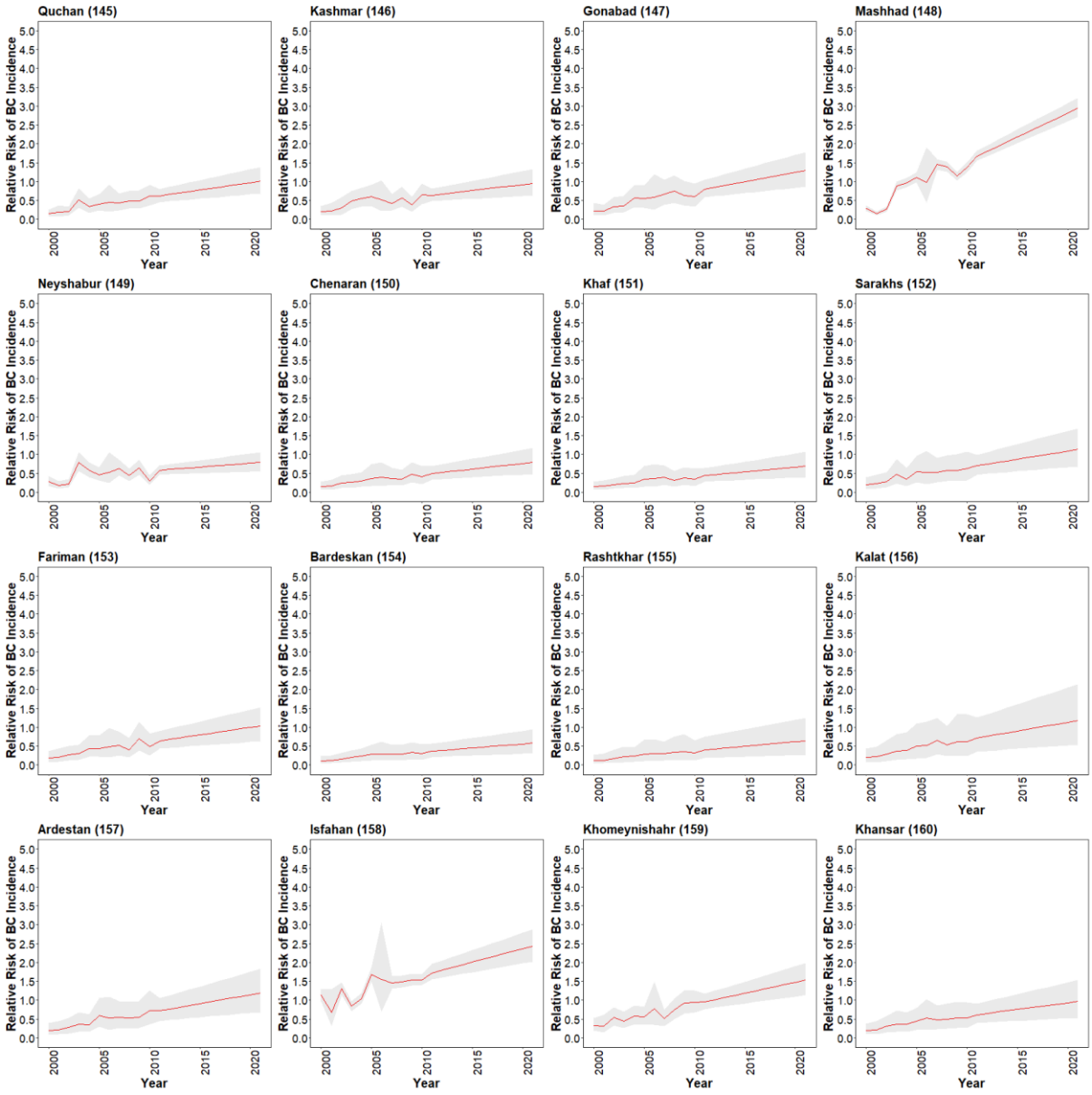

Salmas (65)
Maku (66)
Mahabad (67)
Miyandoab (68)
Naqadeh (69)
Bukan (70)
Shahindezh (71)
Takab (72)
Oshnaviyeh (73)
Chaldoran (74)
Eslamabade Gharb (75)
Kermanshah (76)
Paveh (77)
Sarpole Zahab (78)
Sonqor (79)
Qasreshirin (80)
Relative Risk of BC Incidence
Year

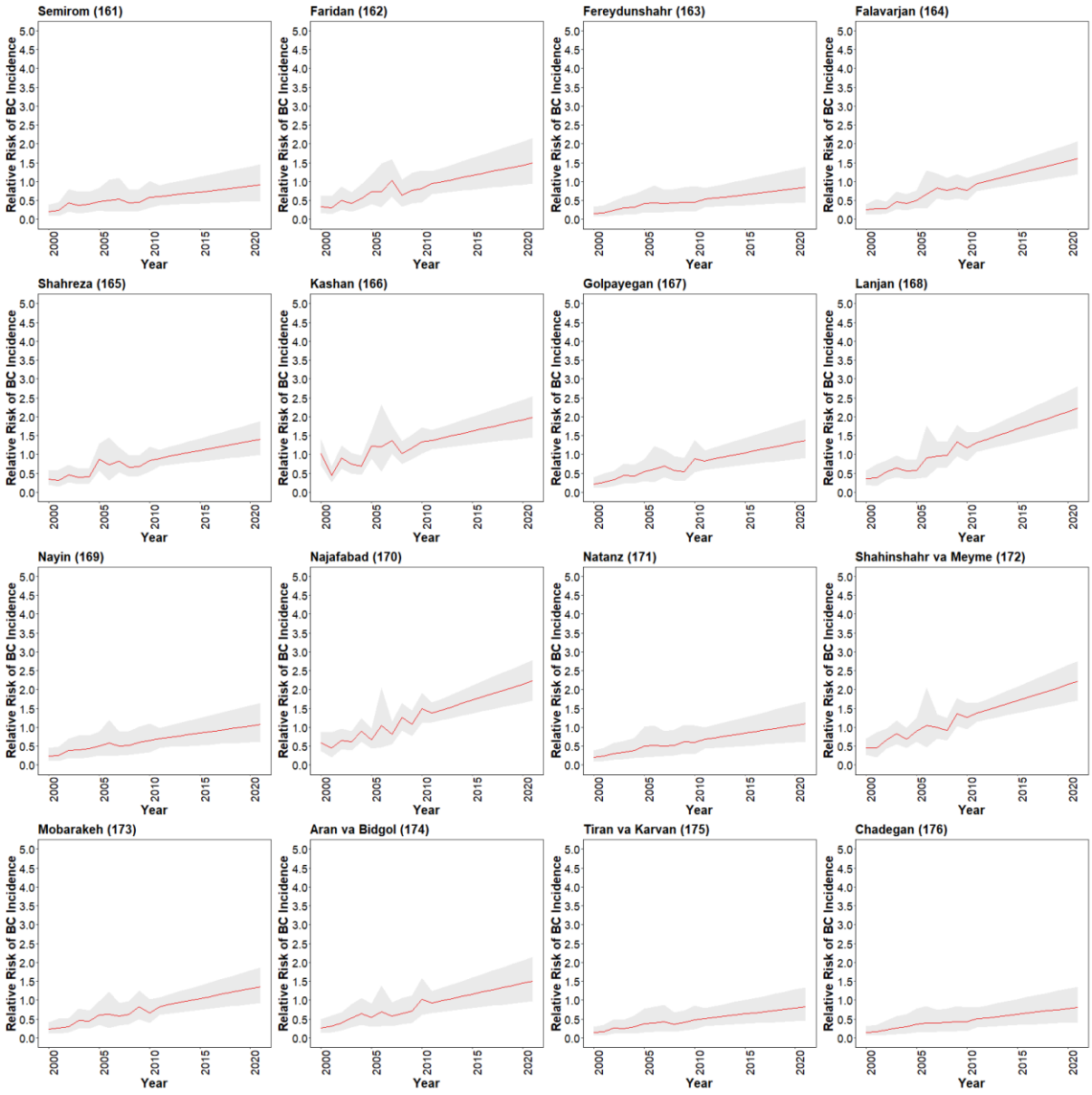

Kangavar (81)
Gilanegharb (82)
Javanrud (83)
Sahneh (84)
Harsin (85)
Salas-e-Babajani (86)
Abadan (87)
Andimeshk (88)
Ahvaz (89)
Izeh (90)
Bandar-e-Mahshahr (91)
Behbahan (92)
Khorramshahr (93)
Dezful (94)
Dashte Azadegan (95)
Ramhormoz (96)
Relative Risk of BC Incidence
Year

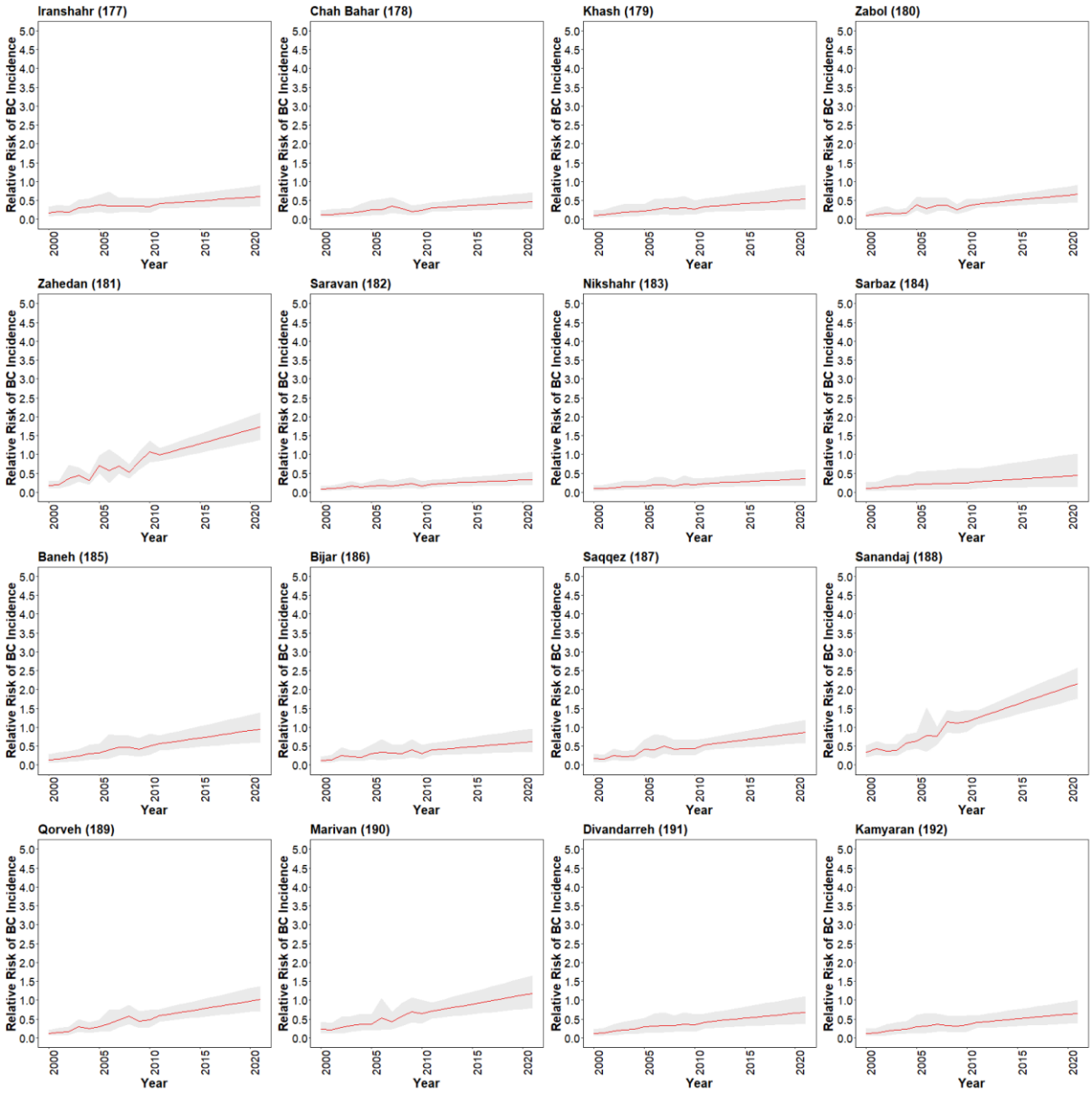

Shadegan (97)
Shushtar (98)
Masjedsoleyman (99)
Shush (100)
Baghmalek (101)
Omidiyeh (102)
Lali (103)
Hendijan (104)
Abadeh (105)
Estahban (106)
Eqlid (107)
Jahrom (108)
Darab (109)
Sepidan (110)
Shiraz (111)
Fasa (112)
Relative Risk of BC Incidence
Year

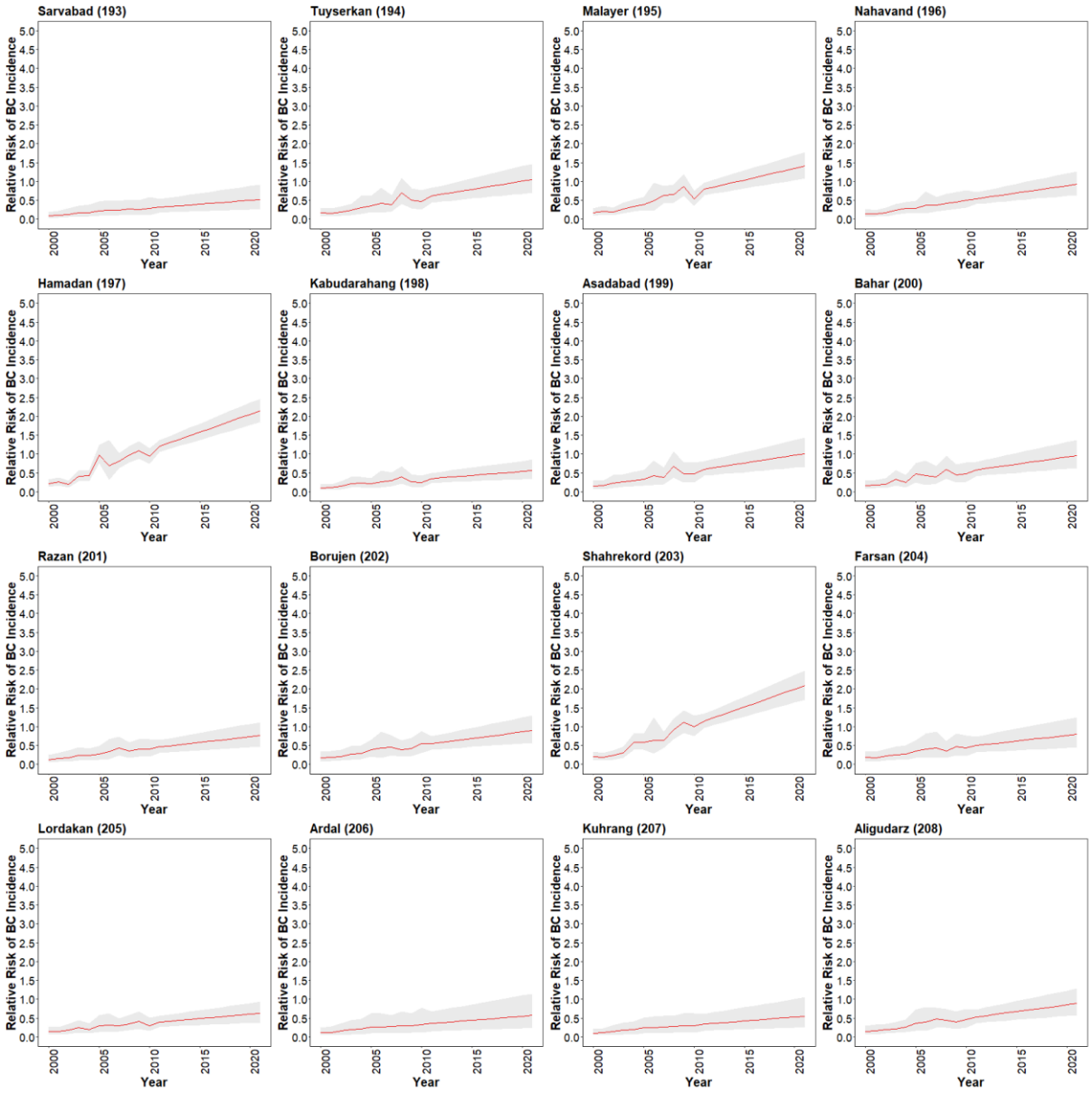

Firuzabad (113)
Kazerun (114)
Lar (Larestan) (115)
Marvdasht (116)
Mamasany (117)
Neyriz (118)
Lamard (119)
Bovanat (120)
Arsanjan (121)
Khorrambid (122)
Zarrindasht (123)
Qirokarzin (124)
Mohr (125)
Farashband (126)
Baft (127)
Bam (128)
Relative Risk of BC Incidence
Year

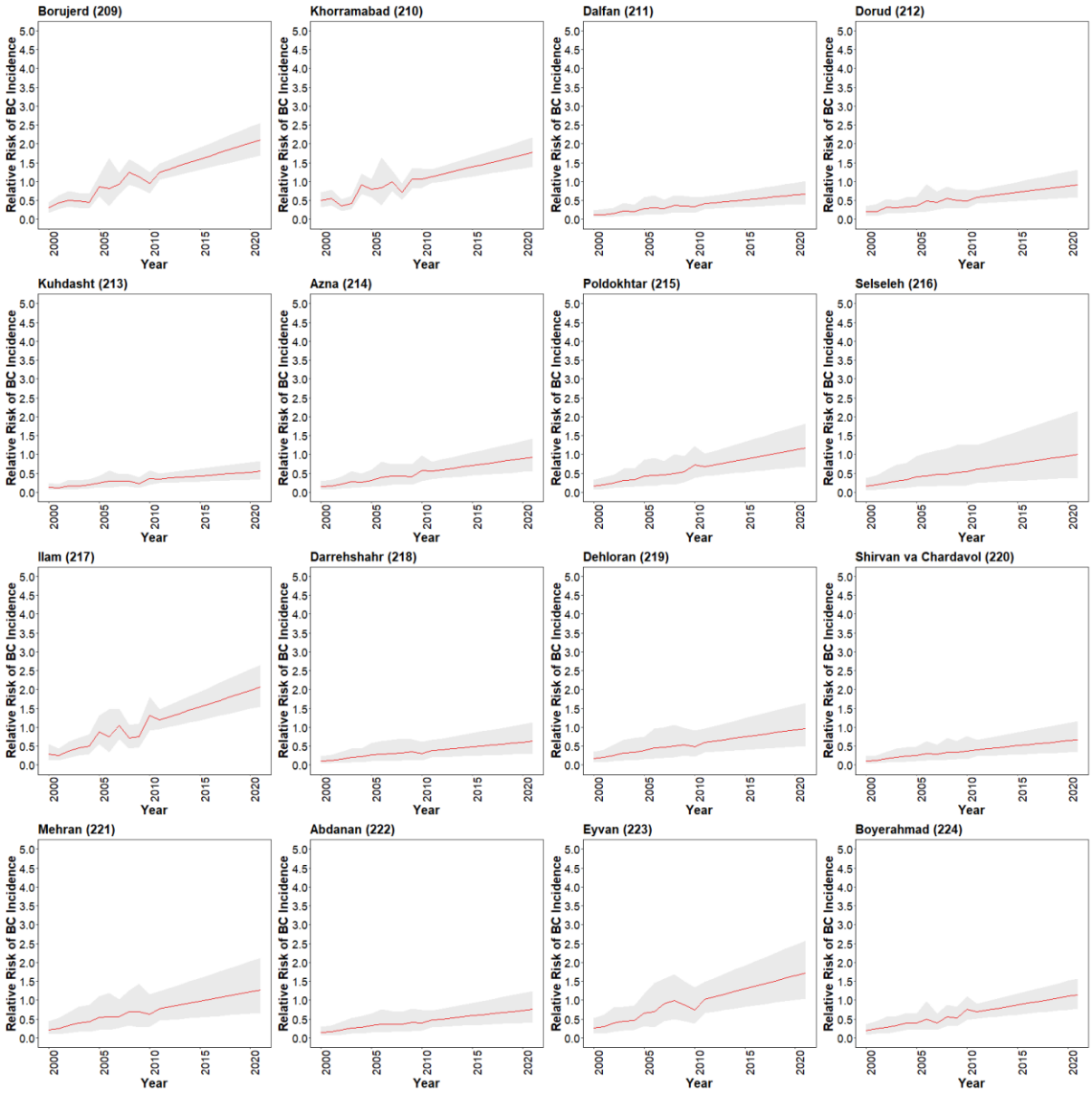

Jiroft (129)
Rafsanjan (130)
Zarand (131)
Sirjan (132)
Shahrebabak (133)
Kerman (134)
Kahnuj (135)
Bardsir (136)
Ravar (137)
Anbarabad (138)
Manujan (139)
Taybad (140)
Torbate Heydarieh (141)
Torbate Jam (142)
Darrehgaz (143)
Sabzevar (144)
Relative Risk of BC Incidence
Year

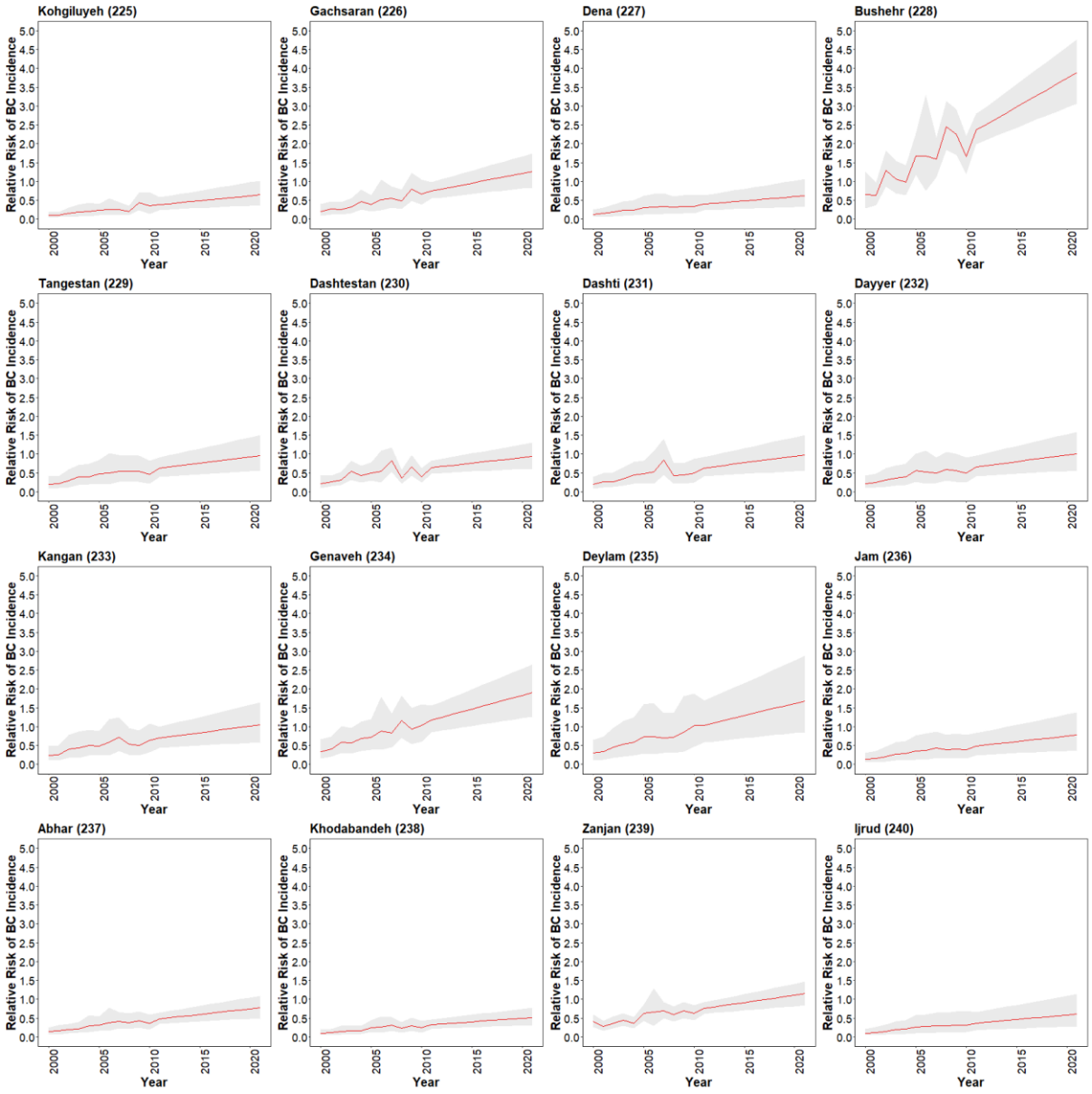

Quchan (145)
Kashmar (146)
Gonabad (147)
Mashhad (148)
Neyshabur (149)
Chenaran (150)
Khaf (151)
Sarakhs (152)
Fariman (153)
Bardeskan (154)
Rashtkhar (155)
Kalat (156)
Ardestan (157)
Isfahan (158)
Khomeynishahr (159)
Khansar (160)
Relative Risk of BC Incidence
Year

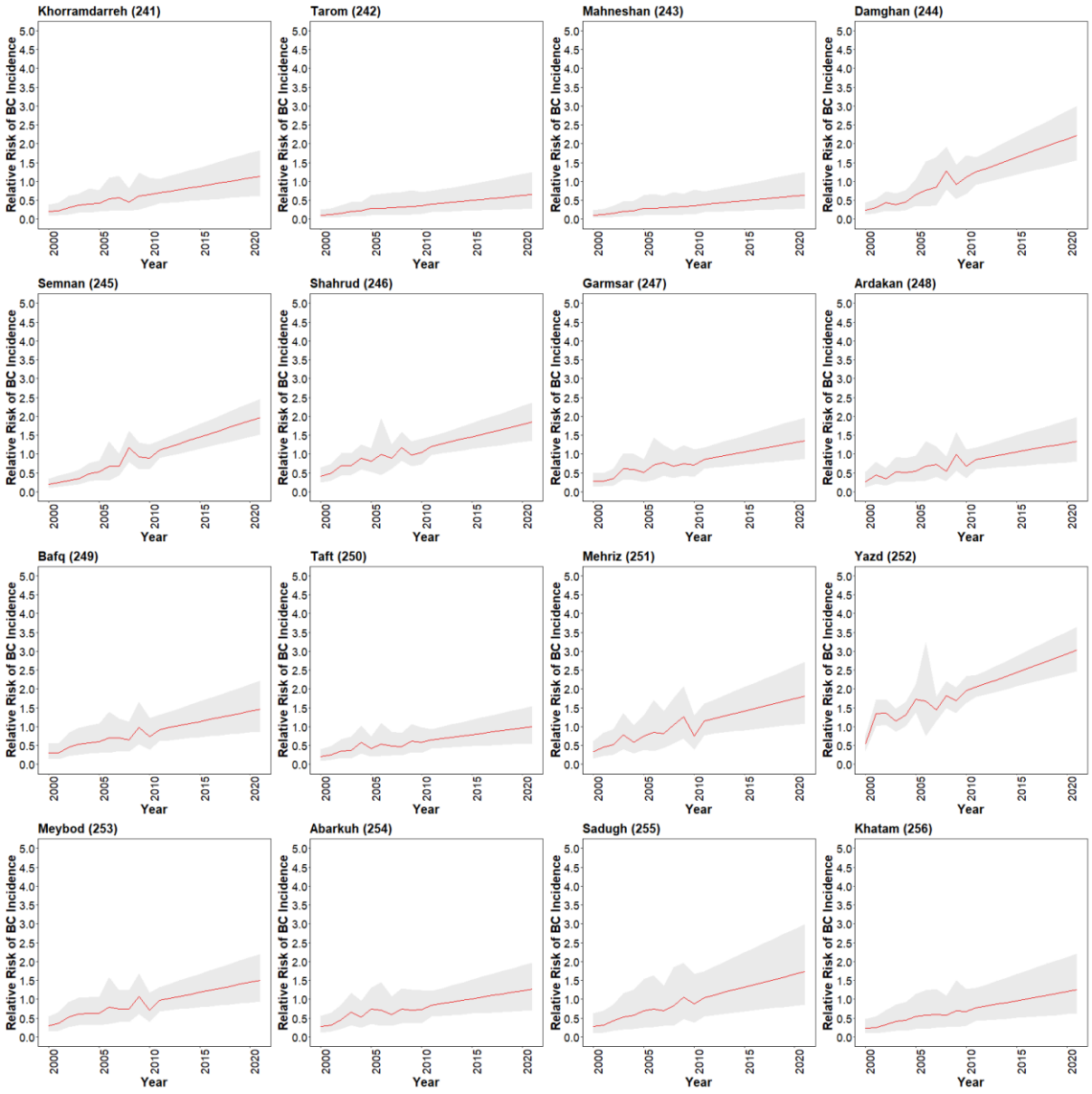

Semirom (161)
Faridan (162)
Fereydunshahr (163)
Falavarjan (164)
Shahreza (165)
Kashan (166)
Golpayegan (167)
Lanjan (168)
Nayin (169)
Najafabad (170)
Natanz (171)
Shahinshahr va Meyme (172)
Mobarakeh (173)
Aran va Bidgol (174)
Tiran va Karvan (175)
Chadegan (176)
Relative Risk of BC Incidence
Year

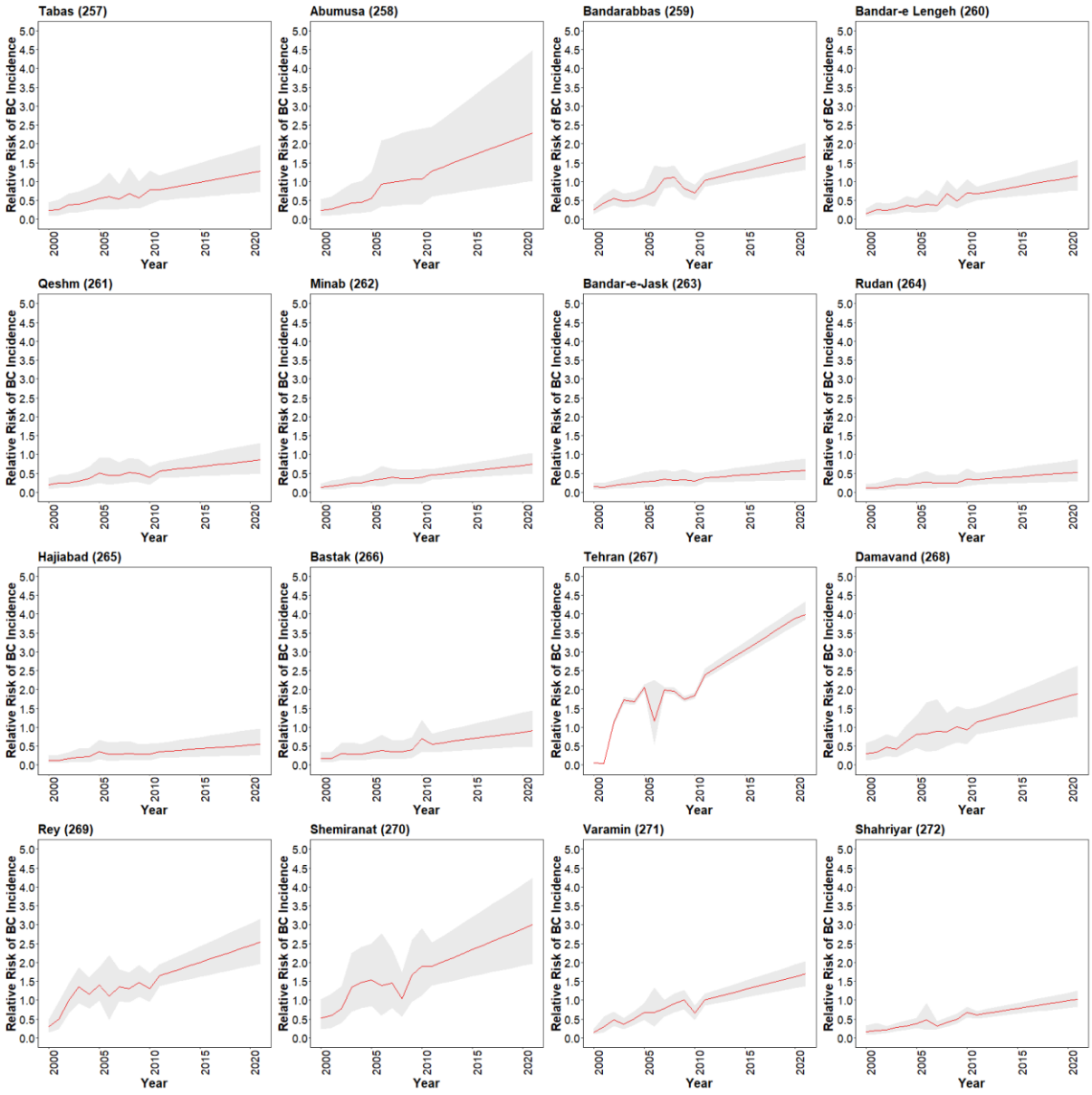

Iranshahr (177)
Chah Bahar (178)
Khash (179)
Zabol (180)
Zahedan (181)
Saravan (182)
Nikshahr (183)
Sarbaz (184)
Baneh (185)
Bijar (186)
Saqqez (187)
Sanandaj (188)
Qorveh (189)
Marivan (190)
Divandarreh (191)
Kamyaran (192)
Relative Risk of BC Incidence
Year

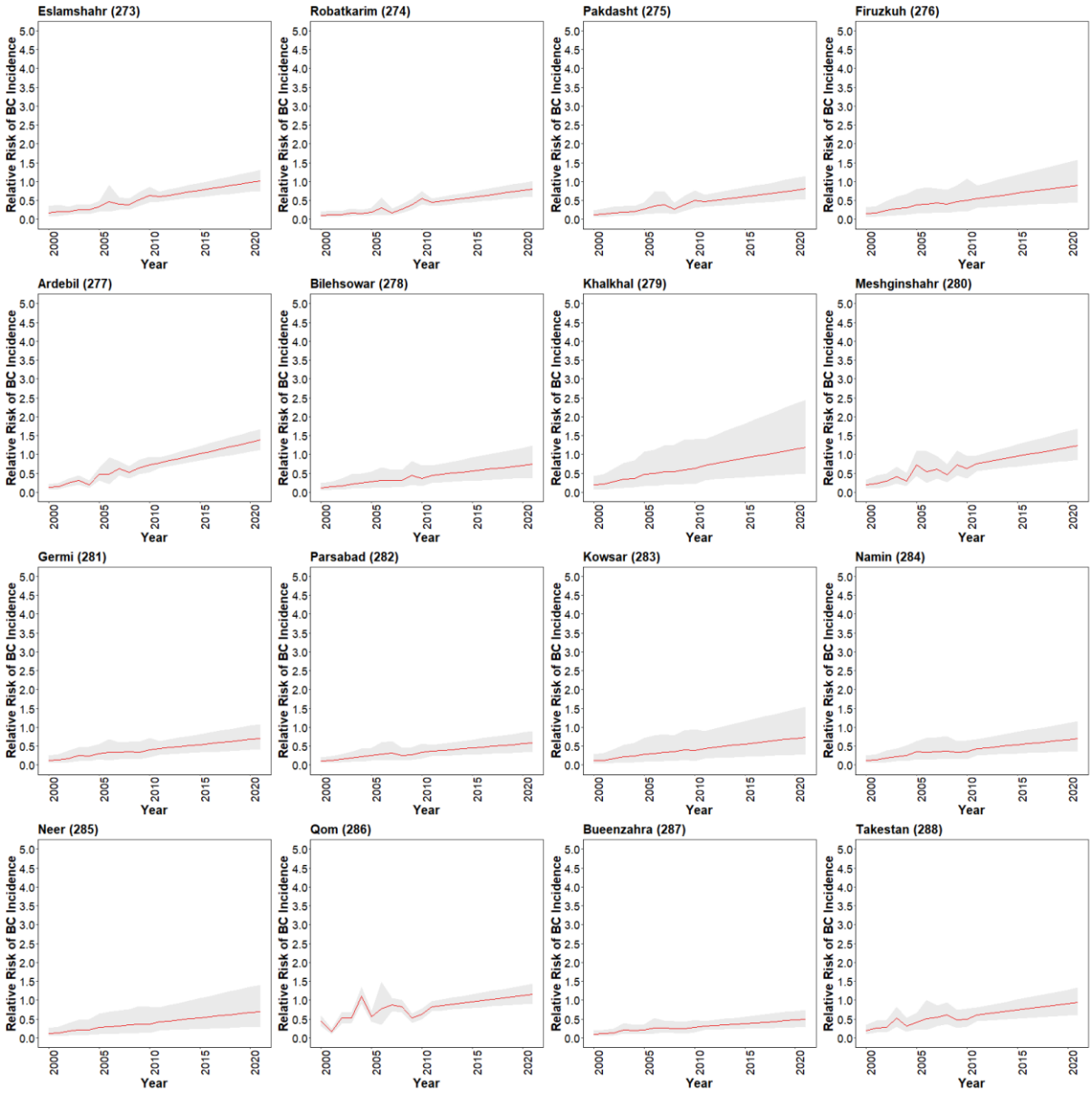

Sarvabad (193)
Tuyserkan (194)
Malayer (195)
Nahavand (196)
Hamadan (197)
Kabudarahang (198)
Asadabad (199)
Bahar (200)
Razan (201)
Borujen (202)
Shahrekord (203)
Farsan (204)
Lordakan (205)
Ardal (206)
Kuhrang (207)
Aligudarz (208)
Relative Risk of BC Incidence
Year

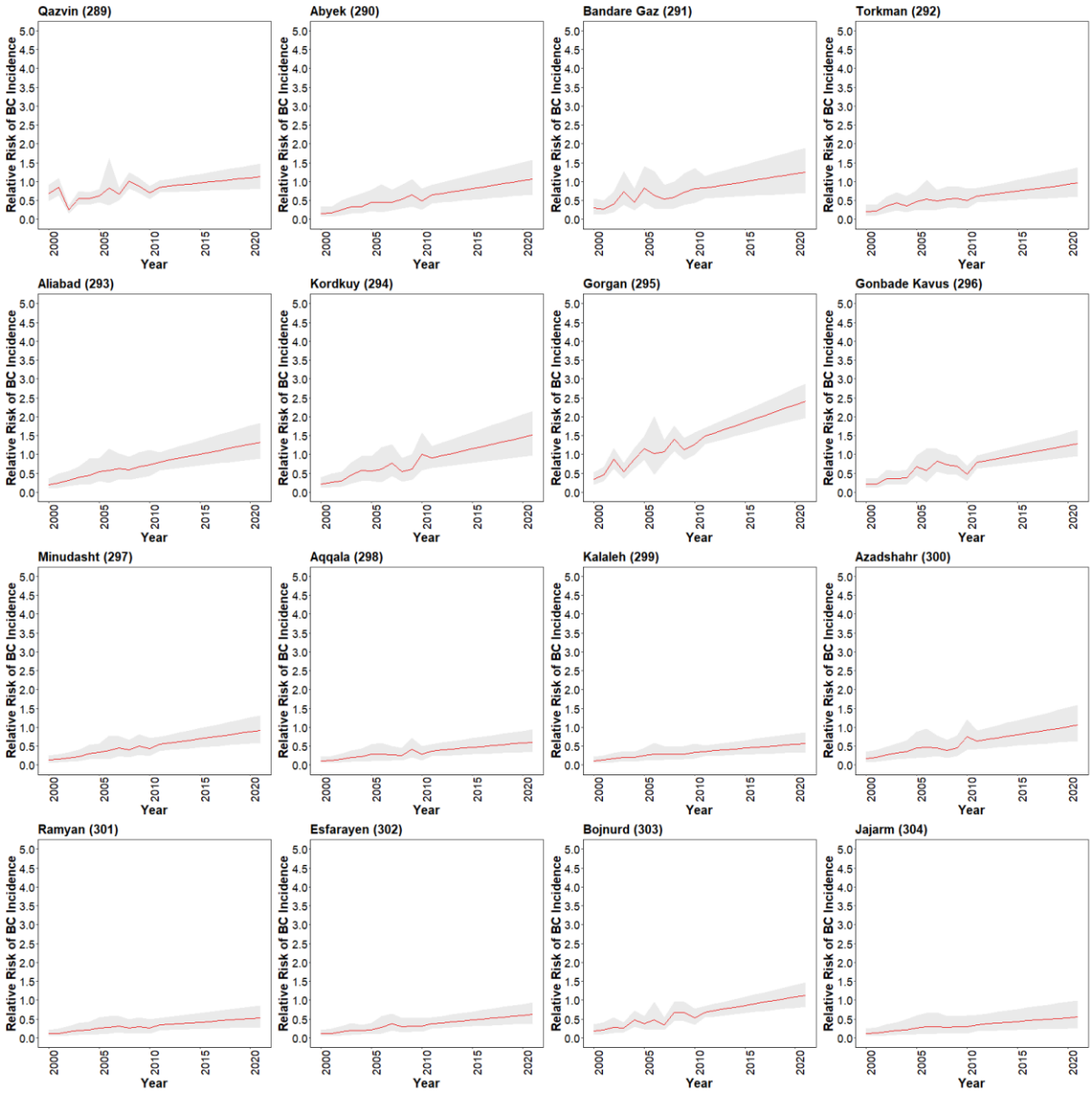

Borujerd (209)
Khorramabad (210)
Dalfan (211)
Dorud (212)
Kuhdasht (213)
Azna (214)
Poldokhtar (215)
Selseleh (216)
Ilam (217)
Darrehshahr (218)
Dehloran (219)
Shirvan va Chardavol (220)
Mehran (221)
Abdanan (222)
Eyvan (223)
Boyerahmad (224)
Relative Risk of BC Incidence
Year

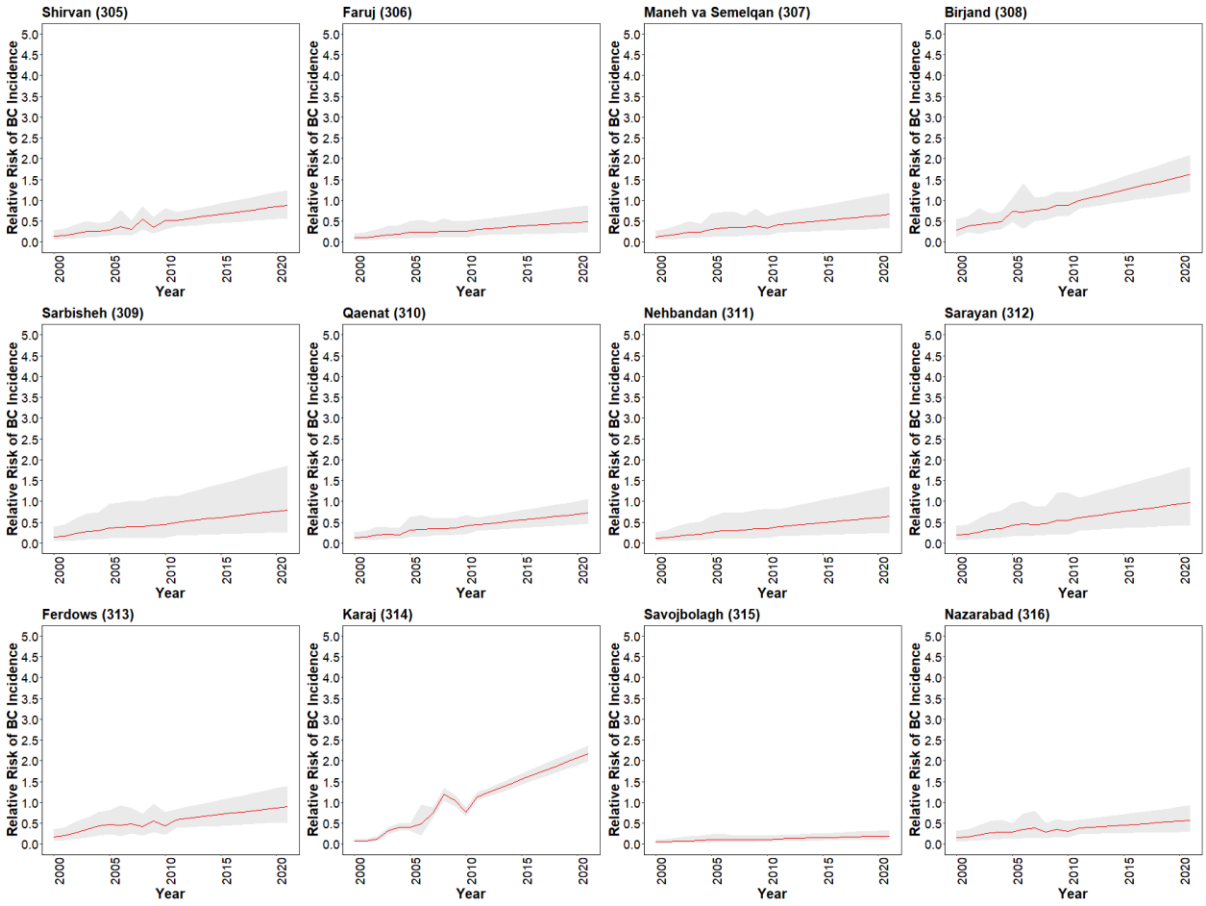

Kohgiluyeh (225)
Gachsaran (226)
Dena (227)
Bushehr (228)
Tangestan (229)
Dashtestan (230)
Dashti (231)
Dayyer (232)
Kangan (233)
Genaveh (234)
Deylam (235)
Jam (236)
Abhar (237)
Khodabandeh (238)
Zanjan (239)
Ijrud (240)
Relative Risk of BC Incidence
Year


Khorramdarreh (241)
Tarom (242)
Mahneshan (243)
Damghan (244)
Semnan (245)
Shahrud (246)
Garmsar (247)
Ardakan (248)
Bafq (249)
Taft (250)
Mehriz (251)
Yazd (252)
Meybod (253)
Abarkuh (254)
Sadugh (255)
Khatam (256)
Relative Risk of BC Incidence
Year

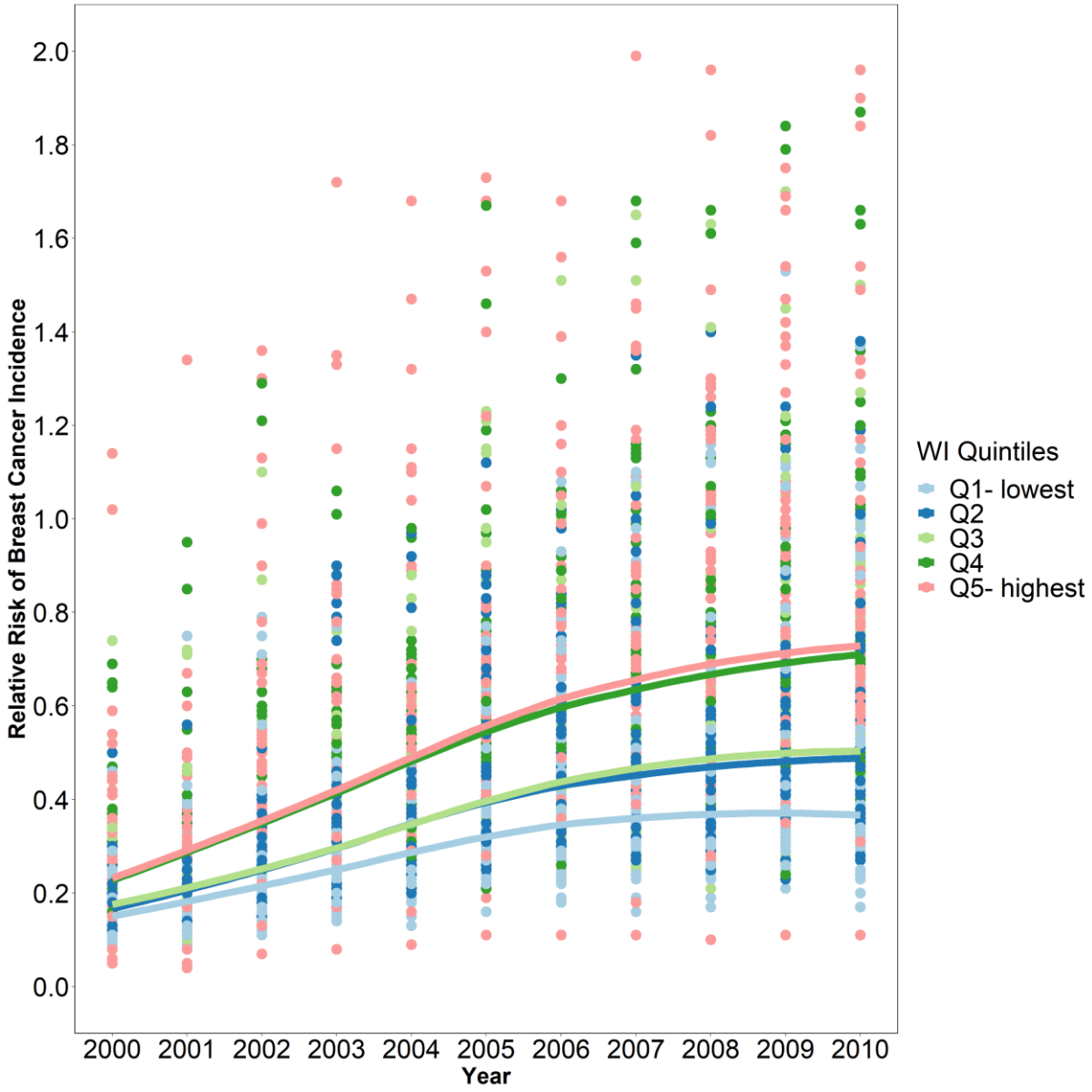

Tabas (257)
Abumusa (258)
Bandarabbas (259)
Bandar-e Lengeh (260)
Qeshm (261)
Minab (262)
Bandar-e-Jask (263)
Rudan (264)
Hajiabad (265)
Bastak (266)
Tehran (267)
Damavand (268)
Rey (269)
Shemiranat (270)
Varamin (271)
Shahriyar (272)
Relative Risk of BC Incidence
Year


Eslamshahr (273)
Robatkarim (274)
Pakdasht (275)
Firuzkuh (276)
Ardebil (277)
Bilehsowar (278)
Khalkhal (279)
Meshginshahr (280)
Germi (281)
Parsabad (282)
Kowsar (283)
Namin (284)
Neer (285)
Qom (286)
Bueenzahra (287)
Takestan (288)
Relative Risk of BC Incidence
Year


Qazvin (289)
Abyek (290)
Bandare Gaz (291)
Torkman (292)
Aliabad (293)
Kordkuy (294)
Gorgan (295)
Gonbade Kavus (296)
Minudasht (297)
Aqqala (298)
Kalaleh (299)
Azadshahr (300)
Ramyan (301)
Esfarayen (302)
Bojnurd (303)
Jajarm (304)
Relative Risk of BC Incidence
Year


Shirvan (305)
Faruj (306)
Maneh va Semelqan (307)
Birjand (308)
Sarbisheh (309)
Qaenat (310)
Nehbandan (311)
Sarayan (312)
Ferdows (313)
Karaj (314)
Savojbolagh (315)
Nazarabad (316)
Relative Risk of BC Incidence
Year

Appendix Figure 5. Relative risk of breast cancer incidence categorised by wealth index quintiles over time (each point represents a district. Light blue colour shows the lowest WI quintile and the pink colour shows the highest WI quintile).



Appendix Table 5. Predicted posterior mean and 95% credible interval for the relative risk of breast cancer incidence by district and year (sorted by mean values in 2021).

District	2011	2016	2021
Tehran	2.39 (2.28, 2.56)	3.22 (3.07, 3.44)	3.99 (3.86, 4.33)
Bushehr	2.37 (1.99, 2.79)	3.13 (2.54, 3.77)	3.89 (3.07, 4.77)
Abadan	2.17 (1.85, 2.53)	2.92 (2.42, 3.46)	3.67 (2.99, 4.39)
Shiraz	2.13 (1.97, 2.34)	2.85 (2.62, 3.14)	3.58 (3.26, 3.95)
Ahvaz	1.99 (1.8, 2.23)	2.57 (2.29, 2.92)	3.16 (2.77, 3.61)
Tabriz	1.74 (1.6, 1.91)	2.4 (2.18, 2.64)	3.07 (2.76, 3.39)
Babol	1.75 (1.55, 1.98)	2.4 (2.09, 2.74)	3.05 (2.63, 3.5)
Yazd	2.05 (1.79, 2.37)	2.54 (2.13, 3)	3.03 (2.47, 3.65)
Shemiranat	1.9 (1.38, 2.53)	2.45 (1.69, 3.37)	3 (1.96, 4.24)
Mashhad	1.67 (1.56, 1.83)	2.31 (2.14, 2.52)	2.94 (2.72, 3.22)
Arak	1.51 (1.34, 1.69)	2.16 (1.89, 2.43)	2.8 (2.44, 3.18)
Khorramshahr	1.52 (1.2, 1.89)	2.07 (1.59, 2.63)	2.62 (1.97, 3.37)
Sari	1.5 (1.32, 1.7)	2.05 (1.78, 2.35)	2.6 (2.24, 3)
Rey	1.64 (1.38, 1.95)	2.09 (1.67, 2.54)	2.54 (1.96, 3.15)
Bandar-e-Mahshahr	1.49 (1.21, 1.8)	2.01 (1.58, 2.48)	2.53 (1.94, 3.17)
Kerman	1.53 (1.34, 1.74)	2.01 (1.72, 2.32)	2.48 (2.08, 2.9)
Isfahan	1.72 (1.55, 1.96)	2.08 (1.79, 2.41)	2.44 (2.02, 2.88)
Gorgan	1.48 (1.27, 1.71)	1.94 (1.62, 2.28)	2.41 (1.97, 2.87)
Rasht	1.43 (1.28, 1.61)	1.91 (1.68, 2.16)	2.39 (2.08, 2.73)
Kermanshah	1.46 (1.31, 1.64)	1.92 (1.69, 2.19)	2.38 (2.07, 2.74)
Ramsar	1.35 (1, 1.75)	1.84 (1.32, 2.44)	2.34 (1.64, 3.15)
Dezful	1.31 (1.11, 1.54)	1.8 (1.5, 2.14)	2.3 (1.88, 2.74)
Abumusa	1.29 (0.6, 2.45)	1.79 (0.81, 3.46)	2.29 (1.02, 4.48)
Najafabad	1.38 (1.13, 1.65)	1.81 (1.42, 2.22)	2.23 (1.7, 2.79)
Damghan	1.26 (0.92, 1.64)	1.74 (1.24, 2.32)	2.23 (1.56, 3)
Lanjan	1.31 (1.07, 1.58)	1.77 (1.39, 2.19)	2.22 (1.71, 2.8)
Shahinshahr va Meyme	1.38 (1.15, 1.64)	1.8 (1.44, 2.19)	2.21 (1.71, 2.76)
Karaj	1.14 (1.05, 1.24)	1.66 (1.52, 1.81)	2.18 (1.99, 2.37)
Sanandaj	1.25 (1.06, 1.45)	1.71 (1.41, 2.02)	2.16 (1.75, 2.59)
Hamadan	1.2 (1.05, 1.37)	1.67 (1.45, 1.92)	2.15 (1.85, 2.47)
Lar (Larestan)	1.26 (1.04, 1.51)	1.7 (1.35, 2.07)	2.14 (1.66, 2.65)
Borujerd	1.25 (1.05, 1.47)	1.68 (1.37, 2.01)	2.11 (1.69, 2.56)
Shahrekord	1.15 (0.97, 1.34)	1.62 (1.34, 1.91)	2.09 (1.71, 2.49)
Orumiyeh	1.25 (1.11, 1.41)	1.67 (1.46, 1.9)	2.08 (1.8, 2.39)
Behbahan	1.25 (0.99, 1.53)	1.67 (1.27, 2.08)	2.08 (1.55, 2.65)
Ilam	1.19 (0.94, 1.48)	1.63 (1.25, 2.06)	2.07 (1.55, 2.65)
Hendijan	1.25 (0.79, 1.87)	1.65 (1, 2.53)	2.05 (1.21, 3.19)
Abadeh	1.29 (0.97, 1.66)	1.66 (1.18, 2.22)	2.04 (1.37, 2.8)
Bandar Anzali	1.26 (1, 1.55)	1.64 (1.24, 2.08)	2.02 (1.48, 2.61)
Rudsar	1.22 (0.98, 1.49)	1.62 (1.26, 2.03)	2.02 (1.53, 2.56)
Andimeshk	1.12 (0.87, 1.41)	1.56 (1.19, 1.99)	2 (1.49, 2.57)
Arsanjan	1.2 (0.73, 1.83)	1.59 (0.93, 2.5)	1.99 (1.12, 3.17)
Kashan	1.38 (1.14, 1.65)	1.68 (1.3, 2.09)	1.98 (1.46, 2.54)

Semnan	1.1 (0.89, 1.35)	1.54 (1.2, 1.9)	1.97 (1.52, 2.47)
Delijan	1.12 (0.75, 1.57)	1.54 (0.99, 2.22)	1.95 (1.23, 2.86)
Genaveh	1.18 (0.85, 1.56)	1.54 (1.06, 2.1)	1.91 (1.27, 2.65)
Damavand	1.14 (0.82, 1.52)	1.52 (1.06, 2.08)	1.9 (1.28, 2.64)
Amol	1.11 (0.94, 1.31)	1.49 (1.22, 1.79)	1.87 (1.5, 2.28)
Shushtar	1.13 (0.9, 1.39)	1.5 (1.16, 1.89)	1.87 (1.41, 2.39)
Behshahr	1.08 (0.86, 1.32)	1.47 (1.14, 1.83)	1.86 (1.42, 2.34)
Omidiyeh	1.09 (0.78, 1.45)	1.47 (1, 2.01)	1.84 (1.22, 2.58)
Shahrud	1.21 (0.98, 1.46)	1.52 (1.17, 1.91)	1.84 (1.36, 2.36)
Lahijan	1.14 (0.92, 1.4)	1.48 (1.14, 1.87)	1.82 (1.35, 2.34)
Mehriz	1.15 (0.77, 1.6)	1.48 (0.94, 2.16)	1.81 (1.09, 2.71)
Zarand	1.02 (0.77, 1.3)	1.4 (1.03, 1.82)	1.78 (1.28, 2.35)
Khorramabad	1.13 (0.96, 1.33)	1.45 (1.18, 1.75)	1.77 (1.39, 2.17)
Fasa	1.09 (0.87, 1.35)	1.43 (1.09, 1.82)	1.76 (1.3, 2.29)
Shush	1.02 (0.79, 1.29)	1.38 (1.03, 1.78)	1.73 (1.26, 2.26)
Zahedan	0.98 (0.82, 1.17)	1.36 (1.1, 1.63)	1.73 (1.38, 2.11)
Sadugh	1.04 (0.54, 1.74)	1.39 (0.7, 2.36)	1.73 (0.86, 2.99)
Eyvan	1.02 (0.66, 1.48)	1.37 (0.86, 2.03)	1.72 (1.04, 2.58)
Varamin	1 (0.85, 1.17)	1.35 (1.12, 1.6)	1.69 (1.38, 2.03)
Dashte Azadegan	1 (0.73, 1.34)	1.34 (0.94, 1.83)	1.68 (1.13, 2.33)
Deylam	1.03 (0.58, 1.7)	1.36 (0.73, 2.27)	1.68 (0.86, 2.88)
Ramhormoz	1.01 (0.77, 1.29)	1.34 (0.97, 1.76)	1.66 (1.16, 2.24)
Bandarabbas	1.04 (0.87, 1.21)	1.35 (1.09, 1.62)	1.66 (1.31, 2.02)
Tonekabon	0.98 (0.79, 1.2)	1.32 (1.03, 1.65)	1.65 (1.26, 2.09)
Babolsar	0.95 (0.75, 1.18)	1.29 (0.98, 1.63)	1.63 (1.21, 2.09)
Birjand	0.99 (0.8, 1.22)	1.31 (1.01, 1.66)	1.62 (1.21, 2.09)
Jahrom	0.99 (0.78, 1.22)	1.3 (0.97, 1.66)	1.61 (1.16, 2.1)
Falavarjan	0.95 (0.75, 1.18)	1.28 (0.97, 1.62)	1.61 (1.2, 2.07)
Langrud	0.98 (0.76, 1.23)	1.29 (0.96, 1.67)	1.6 (1.16, 2.11)
Qaemshahr	0.95 (0.78, 1.15)	1.27 (1, 1.56)	1.58 (1.2, 1.98)
Qasreshirin	0.96 (0.54, 1.54)	1.27 (0.69, 2.1)	1.58 (0.83, 2.66)
Eqlid	0.93 (0.69, 1.24)	1.25 (0.87, 1.72)	1.57 (1.05, 2.19)
Khomeynishahr	0.95 (0.77, 1.17)	1.24 (0.95, 1.57)	1.53 (1.13, 1.98)
Shadegan	0.94 (0.67, 1.24)	1.22 (0.83, 1.69)	1.51 (0.98, 2.13)
Meybod	0.97 (0.68, 1.33)	1.24 (0.81, 1.76)	1.51 (0.93, 2.2)
Kordkuy	0.9 (0.64, 1.22)	1.21 (0.81, 1.68)	1.51 (0.98, 2.15)
Astanehye Ashrafiyeh	0.89 (0.66, 1.15)	1.19 (0.85, 1.59)	1.5 (1.04, 2.03)
Darab	0.91 (0.69, 1.16)	1.21 (0.87, 1.58)	1.5 (1.05, 2.01)
Sirjan	0.98 (0.77, 1.21)	1.24 (0.92, 1.59)	1.5 (1.05, 1.98)
Aran va Bidgol	0.92 (0.66, 1.24)	1.21 (0.82, 1.69)	1.5 (0.97, 2.14)
Mahalat	0.89 (0.6, 1.25)	1.19 (0.76, 1.72)	1.49 (0.93, 2.19)
Faridan	0.95 (0.67, 1.28)	1.22 (0.82, 1.71)	1.49 (0.95, 2.15)
Firuzabad	0.89 (0.65, 1.16)	1.17 (0.82, 1.58)	1.46 (0.99, 1.99)
Bafq	0.92 (0.61, 1.31)	1.19 (0.75, 1.76)	1.46 (0.87, 2.22)
Ashtiyan	0.87 (0.46, 1.47)	1.16 (0.59, 2.01)	1.44 (0.71, 2.54)
Oshnaviyeh	0.9 (0.59, 1.28)	1.17 (0.73, 1.72)	1.44 (0.86, 2.18)

Siyahkal	0.85 (0.59, 1.18)	1.14 (0.75, 1.63)	1.43 (0.91, 2.09)
Estahban	0.87 (0.59, 1.23)	1.15 (0.73, 1.68)	1.43 (0.87, 2.12)
Kazerun	0.84 (0.66, 1.03)	1.13 (0.87, 1.43)	1.42 (1.06, 1.83)
Shahreza	0.9 (0.7, 1.13)	1.15 (0.84, 1.5)	1.41 (0.99, 1.88)
Malayer	0.8 (0.64, 0.97)	1.1 (0.86, 1.37)	1.4 (1.08, 1.77)
Rafsanjan	0.96 (0.76, 1.18)	1.17 (0.86, 1.51)	1.39 (0.96, 1.84)
Ardebil	0.77 (0.65, 0.92)	1.08 (0.89, 1.3)	1.38 (1.12, 1.68)
Marvdasht	0.8 (0.64, 0.98)	1.08 (0.83, 1.35)	1.37 (1.03, 1.74)
Golpayegan	0.83 (0.6, 1.11)	1.1 (0.76, 1.52)	1.37 (0.91, 1.93)
Mobarakeh	0.83 (0.61, 1.08)	1.1 (0.77, 1.47)	1.36 (0.92, 1.86)
Garmsar	0.86 (0.61, 1.17)	1.11 (0.74, 1.57)	1.36 (0.87, 1.97)
Saveh	0.76 (0.59, 0.96)	1.05 (0.79, 1.35)	1.35 (0.99, 1.75)
Ardakan	0.86 (0.59, 1.18)	1.1 (0.7, 1.58)	1.34 (0.81, 1.98)
Astara	0.75 (0.51, 1.06)	1.04 (0.68, 1.5)	1.33 (0.85, 1.93)
Sabzevar	0.83 (0.7, 0.99)	1.08 (0.87, 1.31)	1.32 (1.04, 1.64)
Aliabad	0.8 (0.58, 1.06)	1.06 (0.74, 1.45)	1.32 (0.89, 1.84)
Masjedsoleyman	0.81 (0.6, 1.05)	1.05 (0.73, 1.42)	1.29 (0.86, 1.78)
Gonabad	0.8 (0.58, 1.05)	1.05 (0.72, 1.41)	1.29 (0.86, 1.78)
Gonbade Kavus	0.79 (0.63, 0.98)	1.04 (0.79, 1.31)	1.28 (0.95, 1.65)
Abarkuh	0.84 (0.54, 1.22)	1.06 (0.63, 1.6)	1.27 (0.71, 1.97)
Tabas	0.79 (0.5, 1.16)	1.03 (0.61, 1.57)	1.27 (0.73, 1.98)
Mehran	0.77 (0.46, 1.24)	1.02 (0.56, 1.67)	1.26 (0.67, 2.12)
Gachsaran	0.75 (0.55, 0.99)	1.01 (0.7, 1.36)	1.26 (0.84, 1.74)
Farashband	0.77 (0.46, 1.18)	1.01 (0.58, 1.59)	1.25 (0.69, 2.01)
Khatam	0.77 (0.42, 1.3)	1.01 (0.53, 1.76)	1.25 (0.62, 2.21)
Bandare Gaz	0.83 (0.55, 1.15)	1.04 (0.63, 1.52)	1.25 (0.7, 1.9)
Lali	0.76 (0.39, 1.29)	1 (0.5, 1.73)	1.24 (0.59, 2.18)
Meshginshahr	0.76 (0.57, 0.98)	1 (0.71, 1.33)	1.24 (0.86, 1.69)
Chalus	0.69 (0.5, 0.91)	0.96 (0.68, 1.29)	1.23 (0.85, 1.68)
Bonab	0.74 (0.54, 0.96)	0.98 (0.69, 1.32)	1.23 (0.84, 1.68)
Mahmudabad	0.74 (0.52, 1.02)	0.98 (0.65, 1.38)	1.21 (0.78, 1.75)
Haris	0.72 (0.48, 1.02)	0.96 (0.61, 1.4)	1.2 (0.74, 1.78)
Darrehgaz	0.7 (0.47, 0.98)	0.95 (0.61, 1.37)	1.2 (0.74, 1.75)
Khomeyn	0.67 (0.49, 0.89)	0.93 (0.66, 1.26)	1.19 (0.82, 1.63)
Kangavar	0.73 (0.51, 0.99)	0.96 (0.63, 1.34)	1.19 (0.76, 1.71)
Ardestan	0.72 (0.45, 1.05)	0.95 (0.57, 1.44)	1.19 (0.68, 1.83)
Khalkhal	0.71 (0.32, 1.41)	0.95 (0.41, 1.93)	1.19 (0.49, 2.45)
Kalat	0.72 (0.35, 1.26)	0.95 (0.45, 1.7)	1.18 (0.54, 2.14)
Marivan	0.71 (0.52, 0.94)	0.94 (0.66, 1.29)	1.18 (0.79, 1.66)
Sarab	0.7 (0.51, 0.93)	0.93 (0.66, 1.27)	1.17 (0.8, 1.62)
Poldokhtar	0.68 (0.42, 1.02)	0.93 (0.56, 1.41)	1.17 (0.68, 1.82)
Juybar	0.73 (0.49, 1.03)	0.94 (0.6, 1.37)	1.16 (0.71, 1.71)
Naqadeh	0.71 (0.51, 0.96)	0.93 (0.64, 1.3)	1.16 (0.76, 1.64)
Qom	0.83 (0.71, 0.97)	0.99 (0.81, 1.2)	1.16 (0.91, 1.44)
Neyriz	0.72 (0.51, 0.96)	0.93 (0.63, 1.29)	1.15 (0.74, 1.63)
Zanjan	0.76 (0.62, 0.92)	0.95 (0.73, 1.19)	1.15 (0.84, 1.47)

Bandar-e Lengeh	0.68 (0.51, 0.87)	0.91 (0.64, 1.22)	1.15 (0.77, 1.57)
Lamard	0.74 (0.49, 1.04)	0.94 (0.58, 1.37)	1.14 (0.65, 1.71)
Torbate Jam	0.71 (0.54, 0.91)	0.93 (0.67, 1.23)	1.14 (0.8, 1.55)
Boyerahmad	0.69 (0.51, 0.9)	0.92 (0.64, 1.24)	1.14 (0.77, 1.58)
Sarakhs	0.7 (0.46, 0.99)	0.92 (0.58, 1.34)	1.13 (0.68, 1.69)
Khorramdarreh	0.7 (0.42, 1.06)	0.91 (0.52, 1.45)	1.13 (0.62, 1.83)
Qazvin	0.86 (0.71, 1.02)	0.99 (0.76, 1.25)	1.13 (0.8, 1.48)
Bojnurd	0.68 (0.54, 0.84)	0.9 (0.68, 1.15)	1.13 (0.83, 1.46)
Sumehsara	0.73 (0.54, 0.95)	0.92 (0.64, 1.25)	1.12 (0.74, 1.55)
Shahrebabak	0.75 (0.52, 1.03)	0.93 (0.59, 1.35)	1.12 (0.65, 1.67)
Mohr	0.67 (0.39, 1.05)	0.89 (0.5, 1.42)	1.11 (0.61, 1.81)
Maragheh	0.64 (0.5, 0.8)	0.87 (0.66, 1.11)	1.1 (0.81, 1.42)
Amlash	0.67 (0.41, 1.02)	0.88 (0.52, 1.37)	1.09 (0.61, 1.73)
Natanz	0.68 (0.43, 0.99)	0.88 (0.53, 1.33)	1.09 (0.62, 1.68)
Nayin	0.69 (0.46, 0.99)	0.89 (0.54, 1.32)	1.08 (0.62, 1.65)
Khorrambid	0.68 (0.4, 1.04)	0.87 (0.49, 1.37)	1.07 (0.57, 1.71)
Abyek	0.64 (0.42, 0.91)	0.86 (0.54, 1.24)	1.07 (0.66, 1.57)
Neka	0.65 (0.45, 0.89)	0.86 (0.57, 1.21)	1.06 (0.68, 1.53)
Sonqor	0.64 (0.45, 0.87)	0.85 (0.56, 1.19)	1.06 (0.68, 1.51)
Azadshahr	0.64 (0.42, 0.92)	0.85 (0.53, 1.25)	1.06 (0.64, 1.59)
Rezvanshahr	0.64 (0.41, 0.92)	0.85 (0.52, 1.25)	1.05 (0.63, 1.58)
Tuyserkan	0.62 (0.44, 0.83)	0.83 (0.57, 1.15)	1.05 (0.7, 1.47)
Kangan	0.69 (0.44, 1)	0.87 (0.52, 1.31)	1.05 (0.58, 1.64)
Shazand	0.6 (0.42, 0.82)	0.82 (0.55, 1.14)	1.04 (0.68, 1.47)
Shaft	0.61 (0.39, 0.91)	0.83 (0.5, 1.26)	1.04 (0.61, 1.62)
Fariman	0.64 (0.43, 0.9)	0.84 (0.54, 1.21)	1.04 (0.63, 1.53)
Marand	0.78 (0.6, 0.98)	0.91 (0.63, 1.21)	1.03 (0.65, 1.44)
Shahriyar	0.61 (0.52, 0.72)	0.82 (0.67, 0.98)	1.03 (0.82, 1.25)
Rudbar	0.67 (0.47, 0.92)	0.85 (0.54, 1.22)	1.02 (0.6, 1.52)
Salmas	0.69 (0.51, 0.89)	0.86 (0.59, 1.16)	1.02 (0.66, 1.43)
Sepidan	0.6 (0.39, 0.85)	0.81 (0.52, 1.18)	1.02 (0.63, 1.52)
Qorveh	0.59 (0.44, 0.76)	0.8 (0.58, 1.07)	1.02 (0.72, 1.37)
Eslamshahr	0.6 (0.48, 0.74)	0.81 (0.62, 1.02)	1.02 (0.76, 1.31)
Harsin	0.62 (0.42, 0.87)	0.82 (0.52, 1.19)	1.01 (0.62, 1.5)
Zarrindasht	0.64 (0.33, 1.1)	0.83 (0.4, 1.47)	1.01 (0.47, 1.83)
Quchan	0.62 (0.46, 0.81)	0.82 (0.57, 1.09)	1.01 (0.68, 1.38)
Asadabad	0.6 (0.42, 0.81)	0.8 (0.54, 1.11)	1.01 (0.66, 1.43)
Dayyer	0.65 (0.41, 0.96)	0.83 (0.49, 1.28)	1.01 (0.56, 1.59)
Paveh	0.6 (0.38, 0.89)	0.8 (0.48, 1.22)	1 (0.58, 1.55)
Selseleh	0.61 (0.25, 1.25)	0.8 (0.32, 1.7)	1 (0.38, 2.15)
Taft	0.65 (0.42, 0.94)	0.82 (0.49, 1.24)	1 (0.56, 1.54)
Jiroft	0.62 (0.46, 0.79)	0.8 (0.57, 1.07)	0.99 (0.68, 1.35)
Tavalesh	0.58 (0.43, 0.76)	0.78 (0.55, 1.04)	0.98 (0.67, 1.34)
Miyaneh	0.59 (0.45, 0.76)	0.79 (0.57, 1.04)	0.98 (0.69, 1.32)
Izeh	0.58 (0.41, 0.8)	0.78 (0.53, 1.09)	0.98 (0.64, 1.38)
Tafresh	0.6 (0.39, 0.87)	0.78 (0.49, 1.18)	0.97 (0.58, 1.49)

Masal	0.6 (0.36, 0.91)	0.78 (0.44, 1.23)	0.97 (0.52, 1.55)
Khansar	0.62 (0.39, 0.91)	0.79 (0.47, 1.22)	0.97 (0.53, 1.53)
Dehloran	0.6 (0.33, 0.97)	0.78 (0.42, 1.31)	0.97 (0.5, 1.64)
Dashti	0.63 (0.41, 0.92)	0.8 (0.49, 1.21)	0.97 (0.55, 1.5)
Sarayan	0.61 (0.3, 1.08)	0.79 (0.37, 1.46)	0.97 (0.43, 1.84)
Bahar	0.58 (0.42, 0.79)	0.77 (0.52, 1.09)	0.96 (0.63, 1.37)
Tangestan	0.62 (0.39, 0.91)	0.79 (0.48, 1.2)	0.96 (0.55, 1.5)
Torkman	0.62 (0.45, 0.83)	0.79 (0.53, 1.1)	0.96 (0.6, 1.37)
Fuman	0.61 (0.43, 0.83)	0.78 (0.51, 1.1)	0.95 (0.58, 1.37)
Baghmalek	0.58 (0.37, 0.84)	0.76 (0.47, 1.14)	0.95 (0.57, 1.44)
Kashmar	0.63 (0.48, 0.82)	0.79 (0.56, 1.07)	0.95 (0.63, 1.32)
Baneh	0.56 (0.39, 0.79)	0.76 (0.5, 1.09)	0.95 (0.61, 1.39)
Nur	0.58 (0.41, 0.79)	0.76 (0.51, 1.07)	0.94 (0.6, 1.35)
Dashtestan	0.64 (0.48, 0.83)	0.79 (0.55, 1.06)	0.94 (0.61, 1.3)
Takestan	0.61 (0.45, 0.81)	0.78 (0.53, 1.07)	0.94 (0.6, 1.33)
Bostanabad	0.55 (0.37, 0.78)	0.74 (0.48, 1.07)	0.93 (0.59, 1.36)
Jolfa	0.56 (0.31, 0.94)	0.75 (0.38, 1.3)	0.93 (0.46, 1.67)
Nahavand	0.54 (0.4, 0.71)	0.73 (0.52, 0.99)	0.93 (0.64, 1.27)
Azna	0.56 (0.35, 0.81)	0.74 (0.46, 1.11)	0.93 (0.56, 1.42)
Hashtrud	0.56 (0.35, 0.83)	0.74 (0.44, 1.12)	0.92 (0.53, 1.42)
Bovanat	0.57 (0.33, 0.89)	0.74 (0.41, 1.21)	0.92 (0.49, 1.53)
Ravar	0.61 (0.32, 1)	0.76 (0.39, 1.3)	0.92 (0.44, 1.61)
Dorud	0.58 (0.42, 0.77)	0.75 (0.5, 1.04)	0.92 (0.59, 1.32)
Minudasht	0.55 (0.37, 0.75)	0.73 (0.48, 1.03)	0.92 (0.59, 1.31)
Azarshahr	0.54 (0.36, 0.76)	0.73 (0.47, 1.04)	0.91 (0.57, 1.32)
Miyandoab	0.54 (0.41, 0.7)	0.72 (0.52, 0.96)	0.91 (0.63, 1.23)
Sahneh	0.57 (0.38, 0.81)	0.74 (0.46, 1.09)	0.91 (0.53, 1.37)
Semirom	0.6 (0.37, 0.9)	0.76 (0.43, 1.18)	0.91 (0.49, 1.46)
Bastak	0.56 (0.34, 0.84)	0.73 (0.42, 1.14)	0.91 (0.49, 1.45)
Firuzkuh	0.55 (0.3, 0.91)	0.73 (0.38, 1.24)	0.91 (0.45, 1.57)
Ferdows	0.58 (0.38, 0.84)	0.74 (0.46, 1.12)	0.9 (0.52, 1.4)
Komijan	0.54 (0.28, 0.93)	0.72 (0.36, 1.26)	0.89 (0.43, 1.58)
Borujen	0.55 (0.39, 0.75)	0.72 (0.48, 1.02)	0.89 (0.57, 1.3)
Aligudarz	0.53 (0.37, 0.73)	0.71 (0.48, 1.01)	0.89 (0.58, 1.28)
Baft	0.55 (0.38, 0.75)	0.72 (0.47, 1.01)	0.88 (0.55, 1.27)
Shirvan	0.52 (0.37, 0.71)	0.7 (0.47, 0.98)	0.88 (0.57, 1.25)
Ajabshir	0.54 (0.34, 0.8)	0.7 (0.42, 1.07)	0.87 (0.5, 1.34)
Saqqez	0.53 (0.39, 0.71)	0.7 (0.49, 0.95)	0.87 (0.59, 1.2)
Qeshm	0.56 (0.37, 0.8)	0.71 (0.43, 1.05)	0.85 (0.49, 1.3)
Torbate Heydarieh	0.62 (0.48, 0.78)	0.73 (0.52, 0.97)	0.84 (0.55, 1.17)
Fereydunshahr	0.53 (0.32, 0.83)	0.69 (0.39, 1.11)	0.84 (0.45, 1.39)
Shabestar	0.52 (0.37, 0.7)	0.67 (0.45, 0.92)	0.82 (0.52, 1.16)
Mamasany	0.5 (0.36, 0.67)	0.66 (0.45, 0.92)	0.82 (0.54, 1.17)
Qirokarzin	0.52 (0.3, 0.81)	0.67 (0.36, 1.07)	0.82 (0.42, 1.35)
Tiran va Karvan	0.51 (0.31, 0.79)	0.67 (0.39, 1.06)	0.82 (0.46, 1.33)
Zarandiyeh	0.5 (0.28, 0.8)	0.66 (0.35, 1.09)	0.81 (0.42, 1.38)

Shahindezh	0.5 (0.3, 0.78)	0.65 (0.38, 1.06)	0.81 (0.44, 1.34)
Chadegan	0.5 (0.28, 0.81)	0.66 (0.35, 1.08)	0.81 (0.42, 1.36)
Pakdasht	0.47 (0.33, 0.65)	0.64 (0.44, 0.89)	0.81 (0.53, 1.14)
Piranshahr	0.5 (0.32, 0.72)	0.65 (0.4, 0.96)	0.8 (0.47, 1.21)
Farsan	0.5 (0.32, 0.74)	0.65 (0.38, 0.99)	0.8 (0.44, 1.25)
Robatkarim	0.45 (0.35, 0.55)	0.62 (0.48, 0.78)	0.8 (0.6, 1.02)
Sarbisheh	0.5 (0.18, 1.13)	0.65 (0.22, 1.49)	0.8 (0.26, 1.86)
Khoy	0.47 (0.37, 0.59)	0.63 (0.47, 0.81)	0.79 (0.57, 1.02)
Sarpole Zahab	0.52 (0.34, 0.78)	0.66 (0.39, 1.02)	0.79 (0.44, 1.27)
Bardsir	0.5 (0.32, 0.73)	0.64 (0.39, 0.97)	0.79 (0.45, 1.23)
Neyshabur	0.58 (0.47, 0.72)	0.69 (0.51, 0.88)	0.79 (0.55, 1.05)
Chenaran	0.5 (0.33, 0.69)	0.64 (0.41, 0.93)	0.79 (0.48, 1.18)
Jam	0.49 (0.25, 0.83)	0.63 (0.31, 1.1)	0.78 (0.37, 1.38)
Savadkuh	0.5 (0.31, 0.73)	0.63 (0.38, 0.96)	0.77 (0.44, 1.19)
Abhar	0.48 (0.34, 0.64)	0.63 (0.42, 0.87)	0.77 (0.5, 1.09)
Razan	0.46 (0.31, 0.65)	0.61 (0.39, 0.88)	0.76 (0.47, 1.12)
Abdanan	0.47 (0.28, 0.73)	0.62 (0.35, 0.98)	0.76 (0.41, 1.24)
Javanrud	0.46 (0.3, 0.67)	0.61 (0.37, 0.9)	0.75 (0.44, 1.15)
Malekan	0.45 (0.28, 0.64)	0.59 (0.37, 0.88)	0.74 (0.44, 1.11)
Minab	0.46 (0.33, 0.61)	0.6 (0.41, 0.82)	0.74 (0.49, 1.04)
Bilehsowar	0.45 (0.24, 0.71)	0.59 (0.32, 0.97)	0.74 (0.38, 1.23)
Kowsar	0.44 (0.18, 0.91)	0.59 (0.23, 1.22)	0.74 (0.28, 1.55)
Qaenat	0.44 (0.3, 0.61)	0.58 (0.38, 0.83)	0.72 (0.45, 1.05)
Chaldoran	0.44 (0.21, 0.78)	0.57 (0.27, 1.04)	0.7 (0.32, 1.3)
Taybad	0.44 (0.29, 0.63)	0.57 (0.36, 0.84)	0.7 (0.42, 1.05)
Germi	0.44 (0.27, 0.64)	0.57 (0.34, 0.86)	0.7 (0.41, 1.09)
Namin	0.43 (0.26, 0.69)	0.57 (0.32, 0.93)	0.7 (0.37, 1.16)
Neer	0.42 (0.2, 0.81)	0.56 (0.25, 1.11)	0.7 (0.29, 1.41)
Ahar	0.44 (0.31, 0.6)	0.57 (0.38, 0.79)	0.69 (0.44, 0.99)
Salas-e-Babajani	0.41 (0.17, 0.85)	0.55 (0.21, 1.17)	0.69 (0.26, 1.49)
Bam	0.47 (0.35, 0.61)	0.58 (0.4, 0.79)	0.69 (0.44, 0.99)
Khaf	0.44 (0.28, 0.64)	0.56 (0.34, 0.85)	0.69 (0.39, 1.07)
Noshahr	0.41 (0.27, 0.58)	0.55 (0.35, 0.79)	0.68 (0.42, 1.01)
Anbarabad	0.44 (0.22, 0.78)	0.56 (0.26, 1.02)	0.68 (0.31, 1.26)
Divandarreh	0.42 (0.25, 0.64)	0.55 (0.32, 0.87)	0.68 (0.38, 1.1)
Bukan	0.42 (0.3, 0.57)	0.54 (0.37, 0.76)	0.67 (0.43, 0.96)
Zabol	0.41 (0.3, 0.53)	0.54 (0.38, 0.72)	0.67 (0.46, 0.91)
Dalfan	0.41 (0.27, 0.59)	0.54 (0.34, 0.8)	0.67 (0.41, 1.01)
Shirvan va Chardavol	0.41 (0.23, 0.67)	0.54 (0.29, 0.91)	0.67 (0.34, 1.16)
Maneh va Semelqan	0.42 (0.22, 0.7)	0.54 (0.27, 0.94)	0.67 (0.33, 1.18)
Mahabad	0.43 (0.31, 0.58)	0.55 (0.36, 0.76)	0.66 (0.42, 0.95)
Gilanegharb	0.42 (0.24, 0.67)	0.54 (0.3, 0.9)	0.66 (0.34, 1.13)
Manujan	0.41 (0.2, 0.73)	0.53 (0.25, 0.98)	0.66 (0.3, 1.23)
Osku	0.41 (0.26, 0.59)	0.53 (0.32, 0.79)	0.65 (0.38, 0.99)
Kamyaran	0.41 (0.26, 0.6)	0.53 (0.32, 0.8)	0.65 (0.38, 1)
Kohgiluyeh	0.38 (0.24, 0.58)	0.51 (0.31, 0.8)	0.65 (0.37, 1.02)

Tarom	0.4 (0.18, 0.74)	0.53 (0.23, 0.98)	0.65 (0.28, 1.24)
Rashtkhar	0.4 (0.18, 0.74)	0.52 (0.23, 1)	0.64 (0.27, 1.25)
Mahneshan	0.39 (0.18, 0.73)	0.51 (0.23, 0.99)	0.64 (0.28, 1.25)
Nehbandan	0.39 (0.16, 0.81)	0.51 (0.2, 1.08)	0.64 (0.24, 1.37)
Lordakan	0.39 (0.27, 0.55)	0.51 (0.32, 0.74)	0.63 (0.38, 0.93)
Darrehshahr	0.39 (0.2, 0.67)	0.51 (0.25, 0.89)	0.63 (0.3, 1.12)
Varzaqan	0.38 (0.21, 0.61)	0.5 (0.26, 0.83)	0.62 (0.31, 1.04)
Kahnuj	0.39 (0.27, 0.52)	0.5 (0.34, 0.71)	0.62 (0.4, 0.89)
Bijar	0.4 (0.26, 0.58)	0.51 (0.3, 0.78)	0.62 (0.35, 0.97)
Dena	0.4 (0.23, 0.64)	0.51 (0.28, 0.85)	0.62 (0.33, 1.06)
Esfarayen	0.38 (0.25, 0.54)	0.5 (0.32, 0.74)	0.62 (0.38, 0.94)
Aqqala	0.38 (0.23, 0.56)	0.49 (0.29, 0.75)	0.61 (0.34, 0.94)
Iranshahr	0.42 (0.29, 0.57)	0.51 (0.32, 0.74)	0.6 (0.34, 0.91)
Ijrud	0.37 (0.19, 0.66)	0.49 (0.23, 0.89)	0.6 (0.27, 1.13)
Kalibar	0.36 (0.21, 0.58)	0.48 (0.26, 0.79)	0.59 (0.31, 1)
Charoymaq	0.35 (0.19, 0.62)	0.47 (0.23, 0.85)	0.59 (0.28, 1.08)
Bardeskan	0.37 (0.21, 0.57)	0.47 (0.26, 0.75)	0.58 (0.31, 0.94)
Bandar-e-Jask	0.37 (0.26, 0.52)	0.48 (0.29, 0.71)	0.58 (0.32, 0.9)
Parsabad	0.36 (0.23, 0.53)	0.47 (0.29, 0.71)	0.58 (0.34, 0.9)
Ardal	0.36 (0.15, 0.68)	0.46 (0.19, 0.91)	0.57 (0.23, 1.14)
Kalaleh	0.36 (0.23, 0.51)	0.47 (0.29, 0.69)	0.57 (0.33, 0.87)
Nazarabad	0.39 (0.24, 0.59)	0.48 (0.27, 0.75)	0.57 (0.29, 0.93)
Takab	0.36 (0.21, 0.57)	0.46 (0.26, 0.76)	0.56 (0.3, 0.94)
Kabudarahang	0.35 (0.24, 0.5)	0.45 (0.29, 0.67)	0.56 (0.34, 0.85)
Kuhdasht	0.35 (0.24, 0.49)	0.45 (0.29, 0.66)	0.56 (0.33, 0.83)
Jajarm	0.35 (0.17, 0.61)	0.45 (0.21, 0.8)	0.56 (0.25, 1)
Sardasht	0.34 (0.19, 0.53)	0.45 (0.24, 0.72)	0.55 (0.29, 0.91)
Kuhrang	0.34 (0.17, 0.61)	0.44 (0.21, 0.83)	0.55 (0.25, 1.05)
Hajiabad	0.36 (0.19, 0.59)	0.45 (0.22, 0.78)	0.55 (0.26, 0.97)
Khash	0.34 (0.19, 0.55)	0.44 (0.23, 0.74)	0.53 (0.26, 0.92)
Rudan	0.33 (0.2, 0.51)	0.43 (0.24, 0.69)	0.53 (0.29, 0.87)
Ramyan	0.34 (0.2, 0.52)	0.43 (0.24, 0.69)	0.53 (0.28, 0.86)
Sarvabad	0.32 (0.17, 0.53)	0.42 (0.21, 0.72)	0.52 (0.26, 0.92)
Khodabandeh	0.32 (0.21, 0.46)	0.42 (0.26, 0.62)	0.52 (0.31, 0.78)
Bueenzahra	0.31 (0.21, 0.45)	0.4 (0.25, 0.59)	0.49 (0.28, 0.74)
Faruj	0.31 (0.16, 0.53)	0.4 (0.19, 0.7)	0.49 (0.22, 0.89)
Maku	0.31 (0.2, 0.44)	0.39 (0.24, 0.58)	0.48 (0.28, 0.73)
Chah Bahar	0.31 (0.2, 0.45)	0.39 (0.24, 0.58)	0.47 (0.27, 0.72)
Eslamabade Gharb	0.33 (0.23, 0.45)	0.39 (0.25, 0.56)	0.46 (0.27, 0.69)
Sarbaz	0.29 (0.1, 0.63)	0.37 (0.12, 0.83)	0.44 (0.14, 1.03)
Nikshahr	0.23 (0.13, 0.38)	0.29 (0.15, 0.5)	0.35 (0.17, 0.62)
Saravan	0.22 (0.14, 0.33)	0.28 (0.16, 0.43)	0.34 (0.18, 0.54)
Savojbolagh	0.13 (0.07, 0.21)	0.16 (0.09, 0.27)	0.19 (0.1, 0.33)

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RESEARCH ARTICLE

Geographical and socioeconomic inequalities in female breast cancer incidence and mortality in Iran: A Bayesian spatial analysis of registry data

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Data Availability Statement: Individual level data for breast cancer incidence and mortality belong to third parties namely "Iranian National Cancer and Death Registry at Ministry of Health and Medical Education". In the present study, we used aggregated level data which are freely accessible through https://vizit.report/en/index.html. Raw and estimated data by provinces have also been included in the supplementary material.

Abstract

Background

In Iran, trends in breast cancer incidence and mortality have generally been monitored at national level. The purpose of this study is to examine province-level disparities in age-standardised breast cancer incidence versus mortality from 2000 to 2010 and their association with socioeconomic status.

Methods

In this study, data from Iran's national cancer and death registry systems, and covariates from census and household expenditure surveys were used. We estimated the age-standardised incidence and mortality rates in women aged more than 30 years for all 31 provinces in the consecutive time intervals 2000–2003, 2004–2007 and 2008–2010 using a Bayesian spatial model.

Results

Mean age-standardised breast cancer incidence across provinces increased over time from 15.0 per 100,000 people (95% credible interval 12.0,18.3) in 2000–2003 to 39.6 (34.5,45.1) in 2008–2010. The mean breast cancer mortality rate declined from 10.9 (8.3,13.8) to 9.9 (7.5,12.5) deaths per 100,000 people in the same period. When grouped by wealth index quintiles, provinces in the highest quintile had higher levels of incidence and mortality. In the wealthiest quintile, reductions in mortality over time were larger than those observed among provinces in the poorest quintile. Relative breast cancer mortality decreased by 16.7% in the highest quintile compared to 10.8% in the lowest quintile.

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Conclusions

Breast cancer incidence has increased over time, with lower incidence in the poorest provinces likely driven by underdiagnoses or late-stage diagnosis. Although the reported mortality rate is still higher in wealthier provinces, the larger decline over time in these provinces indicates a possible future reversal, with the most deprived provinces having higher mortality rates. Ongoing analysis of incidence and mortality at sub-national level is crucial in addressing inequalities in healthcare systems and public health both in Iran and elsewhere.

Introduction

The second main cause of death globally is cancer which accounts for 25 million new cases and almost 9.6 million deaths (17.1% of total deaths) in 2017 [1]. Estimates suggest that the number of new cancer cases is expected to increase by 20 million annually by 2025 [2], and to double by 2035 [3]. Breast cancer represents approximately 25% of all cancer incidence and about 15% of all cancer deaths among women [4], and it is the most diagnosed cause of cancer death in women worldwide [5, 6]. Globally, breast cancer resulted in almost two million new cases and over 600,000 deaths (2.4% of total female deaths) in 2017 [5].

Several studies have considered the geographical distribution of breast cancer incidence and mortality [7–11]. A large proportion of new female breast cancer cases are now taking place in low-and-middle income countries, with 60% of incidence and 75% of deaths occurring in deprived societies [12]. Moreover, while the age-standardised female breast cancer mortality rate has declined in many high-income countries [4, 13] it is increasing in low- and low-middle income regions [1].

In spite of advances in early detection and treatment for numerous cancers, socioeconomic inequalities persist in cancer incidence and mortality [14]. Although many developed populations have a higher incidence rate of breast cancer [12, 15, 16], this is likely due to better detection [17], with women in poor countries having a higher burden of breast cancer mortality as they are less likely to be screened [18, 19]. This suggests that the high levels of geographical heterogeneity in breast cancer incidence and mortality [20, 21] are partly explained by inequalities in implementation and access to screening or treatment [21].

In Iran, cancer is the third most common cause of death after cardiovascular diseases and motor vehicle accidents [9, 22]. Breast cancer is the most common cancer in women [23], with median age at diagnosis a decade earlier (40 to 50 years old) than in high income countries (over 50 years) [24, 25]. In 2017, the age-standardised incidence rate from breast cancer was 39.8 per 100,000 females (95% UI 31.0,43.4) while the age-standardised death rate was 11.3 deaths per 100,000 females (8.9,11.9), with a percentage change of 128.3 (61.3,189.5) and 38.2 (-0.5,67.8) respectively between 1990 and 2017 [1].

Despite earlier research [9, 26–28], there are no comprehensive studies with reliable data on breast cancer incidence and mortality at subnational level in Iran. Although geographical and subnational disparities are typically ignored in national investigations, they are essential for analysing inequalities and imbalance interventions in healthcare systems [29]. As part of the NASBOD (National and Subnational Burden of Disease, Injuries, and Risk Factors) project in Iran [30], here, we used national cancer registry and death registry data to assess levels of breast cancer incidence and mortality and their association with socioeconomic status (SES) across the 31 Iranian provinces for the period from 2000 to 2010.

Methods

Cancer incidence data

Cancer incidence data were collected between 2000 and 2010 by the Iranian Ministry of Health through the National Cancer Registry of Iran, which monitors cancer incidence and includes information on sex, age at diagnosis, province, and district of residence at diagnosis, in addition to the cancer code from the International Classification of Diseases for Oncology [31], as described previously [32, 33]. The first report on all-cancer data, which referred to the various pathology departments in Iran since 1930, dates back to 1960 [34, 35]. Even though this information has been valued among epidemiologists in Iran and in the region [32], it was not designed following cancer register gold standards, hence, its activities were stopped in 1980 and were then resumed in early 2000 using more advanced technology and logistics [33].

The coverage rate for cancer registry was 18% in 2000 (only based on pathology data) [33] but increased to 86% in 2009 (based on pathology and population data) [36]. In this study, we have used data on 48,108 new cases of breast cancer in women aged 30 years old and above, registered in the country between 2000 and 2010 (although data were missing in 2006).

Mortality data

Mortality data by cause of death at province level were available from the Death Registry System (DRS). Detailed descriptions of the DRS and cleaning methods can be found elsewhere [37]. In addition, all mortality rates have been adjusted by applying the previously calculated completeness rate of registration [38]. The national DRS consists of five sub-datasets, including: DRS data from 1995–2001 and 2001–2004, collected by the Deputy for Research and Technology at provincial level and the Deputy for Public Health at provincial level, respectively; DRS data from 2006–2010, collected by the Deputy for Public Health at provincial and district levels; Behesht-e-Zahra cemetery data from 1995–2010 (Tehran data) and Bagh-e-Rezvan cemetery data from 2007–2010 (Isfahan data) [37]. In this study, we have used data on 17,441 breast cancer deaths in women aged 30 years old and above, registered in the DRS between 2000 and 2010.

Covariates and populations

Data for incidence and mortality were summarised by age-sex-province-year units. Population data were extracted from the 1996, 2006, and 2011 censuses for each age-sex-province unit [39], with estimates for years between censuses calculated using the population growth formula [40]. In addition, for each year and province the following covariates were included: female urbanisation rate, calculated as the proportion of the female population living in urban areas divided by the total female population; female mean years of schooling (YOS); and wealth index (WI), calculated as the summary measure of 22 household assets extracted from the Household Expenditure and Income Survey (HEIS) (S1 Table and S1 Fig) [39].

The Social Security Insurance (SSI) organisation registry was used to calculate the completeness of the cancer registry as an additional covariate in the model (S1 Table). As treatment for cancer patients is above cost thresholds, insurance organisations have almost 100% coverage for registered cancer patients. Amongst these, SSI with nearly 40% coverage of population in Iran has a comprehensive registry of the financial insurance services for registered cancer patients. Since we assumed that the cancer registry has worked in the same way for other insurance organisations, similar completeness rates have been assumed for all cancer patients, with 22% completeness in 2000 and 75% completeness in 2010, based on the SSI registry [41]. All data were fully anonymized before we accessed them.

Ethics

The Ethics Committee of the National Institute for Medical Research Development in Iran (IR.NIMAD.REC.1396.192) and the Ethics Committee of the Middlesex University in UK (14142.2020) approved the study protocol.

Statistical analysis

To analyse geographical inequalities, we estimated age-standardised breast cancer incidence and mortality for the 31 provinces (Fig 1) and three time intervals: 2000–2003, 2004–2007 and 2008–2010. We used the mean national rate for Iran in 2010 in each age group and then multiplied by the population in each province-age group to estimate the expected incidence and deaths. In this study, we applied a Bayesian Poisson spatial model using covariates, which prevented unbalanced estimates and gave proper results in each province. Spatial modelling

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Fig 1. Map of Iran by province.

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allows borrowing of information from neighbouring areas, which allows estimation for areas with little or no data [29, 42] (S1 Appendix). The dependence of estimates on data for neighbouring provinces is determined by how stable or unreliable the estimated effects are in each province, and on observed similarities between neighbouring provinces. Applying the Besag, York, and Mollie model, cross-province variance is empirically divided into a spatial component, fitted using a conditional autoregressive prior, and a non-spatial component fitted using a prior with a Gaussian distribution [43, 44]. The model also borrows strength via covariates, which included the incompleteness of the cancer registry, proportion of the province's population living in urban areas, female mean years of schooling. Household wealth index is used as proxy of the socioeconomic at province level and used as a stratifier for the health outcomes.

In addition, the residuals have been calculated and Moran's I test [45] has been performed to check that there is no spatial autocorrelation among residuals. The Moran's I test computes the fitted line slope between the actual residual for each province and the mean residual computed including the neighbouring areas. The obtained Moran's I coefficient (close to zero) and the associated p-value ($p>0.05$) indicated that there was no evidence to reject the null hypothesis of no spatial autocorrelation. We therefore conclude that the model allows for spatial patterns appropriately. The inclusion of the three covariates leads to improved model specification according to the Deviance Information Criterion [46].

Our model was fitted in open-source software OpenBUGS version 3.2.3 using the Markov chain Monte Carlo algorithm and R version 3.0.2. This allowed us to make draws from the posterior distribution of the model parameters and to estimate incidence and mortality rates by province and by quintiles of wealth in each province, including the 2.5th and 97.5th percentiles of this distribution as estimates of the lower and upper bounds of credible intervals (CrI), respectively.

Results

The national age-standardised breast cancer incidence rates (per 100,000 people) in 2000–2003, 2004–2007 and 2008–2010 were respectively 15.0 (95% CrI 12.0,18.3), 22.8 (95% CrI 19.2,26.6) and 39.6 (95% CrI 34.5,45.1), while the mortality rates (per 100,000) were 10.9 (95% CrI 8.3,13.8), 10.3 (95% CrI 8.0,12.9) and 9.9 (95% CrI 7.5,12.5) respectively. The national incidence rate increased by 52% from 2000–2003 to 2004–2007 and by almost 75% between 2004–2007 and 2008–2010. Meanwhile, the percentage reduction in the mean national mortality rate was consistently around 5% between these time periods (S2 and S3 Figs).

The age-standardised incidence rate for breast cancer was highest in Tehran (78.2 [95% CrI: 75.5,80.9]), Khuzestan (62.8 [95% CrI: 58.4,67.3]), and Yazd (60.5 [95% CrI: 52.2,69.3]) in 2008–2010. In contrast, Sistan and Baluchistan (17.9 [95% CrI: 14.5,21.6]), Zanjan (21.3 [95% CrI: 16.5,26.4]), and Ardabil (22.6 [95% CrI: 18.1,27.5]) were found to have the lowest rates in the same time interval (Fig 2A and Table 1). The breast cancer age-standardised death rate was highest in Tehran (16.2 [95% CrI: 15.0,17.4]), Alborz (15.3 [95% CrI: 12.6,18.2]), and Semnan (14.8 [95% CrI: 10.2,19.9]) in 2008–2010. Meanwhile, Sistan and Baluchistan (5.5 [95% CrI: 3.8,7.4]), Hormozgan (6.7 [95% CrI: 4.4,9.1]), Zanjan (7.2 [95% CrI: 4.8,9.9]) reported the lowest rates (Fig 2B and Table 2).

Provinces with the highest percentage of age-standardised incidence rates between 2000–2003 and 2008–2010 were Khorasan, North (1111.1% [95% CrI: 673.1,3013.6]), Alborz (793.5% [95% CrI: 620.8,1082.8]), and Ilam (524% [95% CrI: 342.9,994.8]). In contrast, Qazvin (43.5% [95% CrI: 38.2,50.7]), Qom (57.0% [95% CrI: 49.4,66.5]) and Yazd (58.3% [95% CrI: 52.4,65.2]) had the lowest percentage of incident rates. Provinces with the greatest significant increasing trends in age-standardised death rates were Semnan (19.4% [95% CrI: 15.7,24.4]), Alborz (10.9% [95% CrI: 9.0,14.5]), and Khuzestan (5.3% [95% CrI: 4.5,6.4]). Meanwhile,

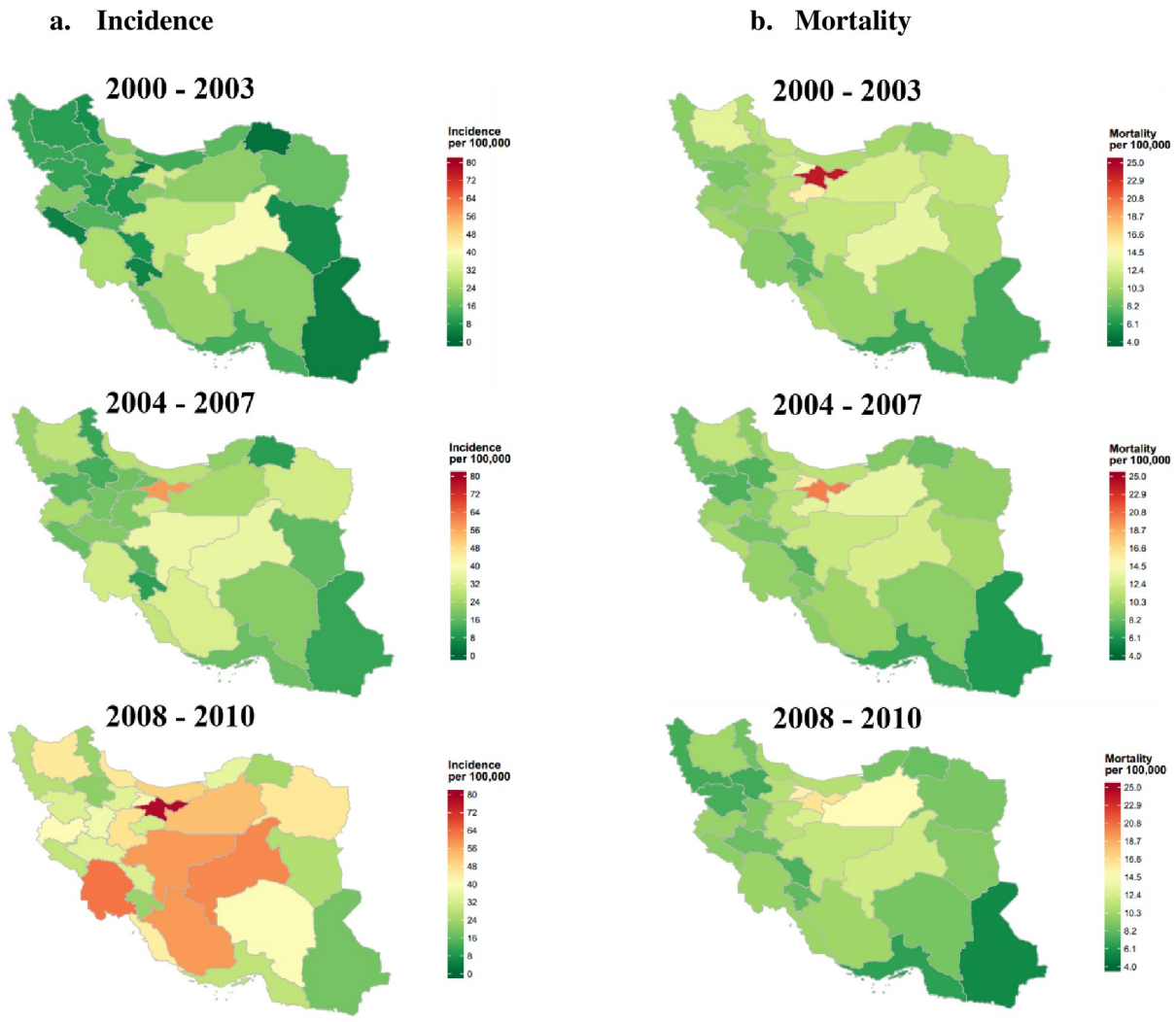

Fig 2. a. Map of posterior age-standardised breast cancer incidence rate by province level for 2000–2003, 2004–2007 and 2008–2010; b. Map of posterior age-standardised breast cancer mortality rate by province level for 2000–2003, 2004–2007 and 2008–2010.

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Tehran (-31.9% [95% CrI: -31.2 to -32.7]), Sistan and Baluchistan (-24.7% [95% CrI: -23.7 to -26.9]), and Zanjan (-24.2% [95% CrI: -22.0 to -27.3]) experienced the highest decreasing trend in death rate from 2000–2003 to 2008–2010 (Tables 1 and 2).

Arrow diagrams (Fig 3) indicate that Yazd province had the highest incidence rate in 2000–2003 while in 2008–2010 Tehran was in the upper level. However, Tehran as the most populous city in Iran, had the highest mortality rates in 2000–2003 and 2008–2010 (Fig 4).

When grouped by wealth index quintiles (Fig 5 and Table 3), provinces in the highest quintile had higher levels of breast cancer incidence in 2000–2003 (average from 7.0 per 100,000 people in the lowest quintile to 24.1 per 100,000 people in the highest quintile), 2004–2007 (15.7,32.0) and 2008–2010 (30.7,48.8). Similarly, provinces in the highest quintile had greater levels of breast cancer mortality in 2000–2003 (mean from 9.3 per 100,000 people in the lowest quintile to 15.0 per 100,000 people in the highest quintile), 2004–2007 (8.6,13.5) and 2008–2010 (8.3,12.5). While the national mortality rate is decreasing, the reduction in wealthier provinces is much greater than in less wealthy provinces.

Table 1. Age-standardised breast cancer incidence rates (per 100,000) for females by province and time intervals and percentage change of age-standardised rates (sorted by values in 2008–2010).

	Breast cancer Incidence rate (CrI)			
	2000–2003	2004–2007	2008–2010	Percentage change between 2000–03 and 2008–10 (%)
Tehran	31.3 (29.6,33.0)	58.3 (56.1,60.5)	78.2 (75.5,80.9)	149.9 (145.0,155.2)
Khuzestan	25.2 (22.4,28.1)	31.5 (28.6,34.5)	62.8 (58.4,67.3)	149.6 (139.7,160.8)
Yazd	38.2 (31.6,45.4)	36.2 (30.3,42.6)	60.5 (52.2,69.3)	58.3 (52.4,65.2)
Isfahan	29.1 (26.5,31.8)	36.3 (33.6,39.0)	58.4 (54.7,62.3)	101.0 (95.9,106.8)
Fars	23.0 (20.5,25.5)	32.3 (29.6,35.1)	58.4 (54.5,62.5)	154.2 (144.8,165.5)
Semnan	21.2 (15.5,27.8)	24.6 (18.6,31.1)	53.0 (43.3,63.3)	149.6 (127.7,180.3)
Mazandaran	12.4 (10.4,14.6)	27.3 (24.5,30.2)	50.1 (46.0,54.4)	303.2 (272.6,341.8)
Markazi	8.4 (6.1,11.2)	18.8 (15.4,22.5)	46.9 (40.9,53.1)	457.1 (375.9,575.7)
Khorasan, Razavi	16.7 (14.9,18.7)	31.3 (28.9,33.7)	45.5 (42.4,48.7)	171.8 (160.7,184.4)
Gilan	19.9 (17.2,22.7)	27.3 (24.3,30.4)	45.3 (41.1,49.7)	127.8 (118.7,139.1)
Azarbaijan, East	9.7 (8.1,11.4)	27.5 (24.9,30.3)	45.2 (41.5,48.9)	365.6 (328.1,414.4)
Bushehr	18.8 (13.7,24.5)	28.7 (22.9,35.1)	43.8 (36.1,51.9)	133.2 (112.3,163.4)
Alborz	4.8 (3.2,6.6)	17.0 (14.2,19.9)	42.4 (37.9,47.2)	793.5 (620.8,1082.8)
Kermanshah	19.9 (16.5,23.5)	25.2 (21.7,28.9)	41.0 (36.1,46.1)	105.9 (96.3,118.3)
Kerman	20.7 (17.5,24.1)	20.4 (17.5,23.5)	39.1 (34.8,43.6)	88.6 (81.0,98.6)
Hamadan	8.7 (6.5,11.3)	18.3 (15.2,21.6)	37.2 (32.4,42.3)	326.3 (275.6,397.7)
Golestan	15.3 (12.0,18.7)	21.5 (18.0,25.3)	35.2 (30.3,40.3)	130.6 (115.7,152.6)
Lorestan	13.8 (10.7,17.1)	20.0 (16.6,23.7)	34.7 (29.8,39.8)	151.7 (132.6,177.6)
Qazvin	23.8 (18.9,29.1)	17.6 (13.9,21.7)	34.1 (28.5,40.2)	43.5 (38.2,50.7)
Chahar Mahal and Bakhtiari	7.6 (4.5,11.3)	14.5 (10.6,18.9)	33.2 (26.6,40.4)	336.1 (258.8,496.0)
Kordestan	10.8 (7.9,14.0)	14.6 (11.5,17.9)	33.1 (28.0,38.3)	205.7 (173.6,253.7)
Qom	20.2 (15.6,25.4)	31.2 (25.7,37.1)	31.8 (25.9,38.0)	57.0 (49.4,66.5)
Ilam	4.6 (1.9,8.4)	16.8 (11.5,22.8)	28.6 (21.1,37.0)	524.0 (342.9,994.8)
Hormozgan	12.8 (9.3,16.6)	16.9 (13.3,21.0)	28.1 (23.1,33.5)	120.3 (101.5,148.0)
Azarbaijan, West	11.3 (9.2,13.5)	21.7 (18.9,24.5)	27.0 (23.8,30.4)	138.9 (124.7,157.9)
Khorasan, South	6.6 (3.4,10.4)	15.3 (10.8,20.5)	26.0 (19.7,33.2)	293.2 (220.1,483.4)
Khorasan, North	2.0 (.6,3.9)	9.7 (6.5,13.4)	24.0 (18.4,30.2)	1111.1 (673.1,3013.6)
Kohgiluyeh and Boyer-Ahmad	5.2 (2.1,9.0)	10.0 (6.2,14.3)	22.9 (16.4,30.0)	345.0 (234.6,684.2)
Ardabil	7.0 (4.7,9.7)	11.4 (8.5,14.6)	22.6 (18.2,27.5)	223.0 (183.1,288.7)
Zanjan	11.3 (7.9,15.1)	13.1 (9.7,17.0)	21.3 (16.5,26.4)	88.3 (75.2,110.7)
Sistan and Baluchistan	3.8 (2.2,5.6)	11.1 (8.7,13.8)	17.9 (14.5,21.6)	374.3 (286.7,563.9)

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Discussion

The current study reports the age-standardised breast cancer incidence and death rates across 31 provinces in Iran between 2000 and 2010. Nationally, there was a substantial rise in age-standardised incidence rates, while age-standardised death rates were identified to have a decreasing trend. Several provinces, such as Semnan, Alborz, Khuzestan, Mazandaran, Kohgiluyeh and Boyer-Ahmad, Kermanshah, Fars, and Isfahan showed different patterns with substantial increase in death age-standardised rates.

We tried to compare our results with previous studies; however, no studies were found for a direct comparison at the year-province-specific level of incidence and mortality rates. While our study found that all the aforementioned provinces had increasing trends in age-standardised incidence rate during 2000–2010, a previous study showed estimated overall incidence rate of breast cancer had a smooth decreasing pattern in Iran in 2004–2008 [28]. Although the trend of age-standardised mortality rate of breast cancer increased dramatically during 1995 to

Table 2. Age-standardised breast cancer mortality rates (per 100,000) for females by province and time intervals and percentage change of age-standardised rates (sorted by values in 2008–2010).

	Breast cancer Mortality rate (CrI)			
	2000–2003	2004–2007	2008–2010	Percentage change between 2000–03 and 2008–10 (%)
Tehran	23.8 (22.3,25.3)	20.2 (18.9,21.5)	16.2 (15.0,17.4)	-31.9 (-32.7,-31.2)
Alborz	13.8 (11.0,16.7)	15.7 (13.1,18.5)	15.3 (12.6,18.2)	10.9 (9.0,14.5)
Semnan	12.4 (8.2,17.2)	13.3 (9.1,17.8)	14.8 (10.2,19.9)	19.4 (15.7,24.4)
Qom	15.4 (11.4,19.9)	13.1 (9.8,16.9)	12.5 (9.2,16.3)	-18.8 (-19.3,-18.1)
Yazd	13.3 (9.7,17.2)	12.4 (9.2,15.8)	12.1 (8.9,15.6)	-9.0 (-9.3,-8.2)
Isfahan	11.5 (9.9,13.2)	11.8 (10.3,13.4)	11.6 (10.0,13.2)	.9 (.0,1.0)
Markazi	11.2 (8.6,14.2)	11.1 (8.7,13.8)	11.2 (8.5,14.0)	.0 (-2.1,-1.2)
Qazvin	11.4 (8.4,14.7)	11.2 (8.4,14.3)	11.1 (8.2,14.3)	-2.6 (-2.7,-2.4)
Mazandaran	10.7 (8.9,12.7)	11.3 (9.6,13.1)	11.0 (9.1,12.9)	2.8 (1.6,2.2)
Gilan	11.1 (9.2,13.2)	10.8 (9.0,12.7)	10.6 (8.6,12.6)	-4.5 (-6.5,-4.5)
Azarbaijan, East	13.1 (11.2,15.1)	11.5 (9.8,13.2)	10.2 (8.6,12.0)	-22.1 (-23.2,-20.5)
Fars	10.0 (8.4,11.6)	10.1 (8.7,11.7)	10.2 (8.6,11.8)	2.0 (1.7,2.4)
Bushehr	10.4 (7.1,14.3)	9.5 (6.6,13.0)	10.1 (6.9,13.6)	-2.9 (-4.9,-2.8)
Khuzestan	9.4 (7.8,11.2)	9.8 (8.2,11.4)	9.9 (8.3,11.7)	2.1 (1.7,2.7)
Kermanshah	9.7 (7.5,12.1)	9.9 (7.8,12.2)	9.9 (7.7,12.3)	5.3 (4.5,6.4)
Ilam	10.3 (6.1,15.1)	10.7 (6.7,15.3)	9.6 (5.9,14.0)	-6.8 (-7.3,-3.3)
Khorasan, South	10.9 (7.0,15.2)	10.3 (7.0,14.2)	9.3 (5.9,13.3)	-14.7 (-15.7,-12.5)
Hamadan	9.8 (7.6,12.3)	9.4 (7.3,11.7)	9.1 (7.0,11.4)	-7.1 (-7.9,-7.3)
Khorasan, Razavi	11.6 (10.1,13.2)	9.7 (8.4,11.0)	8.9 (7.6,10.3)	-23.3 (-24.8,-22.0)
Kerman	10.1 (8.0,12.4)	9.5 (7.6,11.5)	8.9 (7.0,10.8)	-14.6 (-14.5,-14.1)
Golestan	10.3 (7.9,13.1)	9.3 (7.0,11.6)	8.8 (6.7,11.2)	-12.9 (-12.9,-12.5)
Ardabil	10.8 (7.9,14.0)	9.5 (7.0,12.3)	8.6 (6.1,11.4)	-20.4 (-22.8,-18.6)
Lorestan	9.7 (7.3,12.3)	8.7 (6.6,10.9)	8.4 (6.3,10.8)	-10.6 (-12.9,-11.5)
Khorasan, North	9.4 (6.2,13.1)	8.5 (5.8,11.6)	8.4 (5.4,11.6)	-13.4 (-13.7,-12.2)
Kohgiluyeh and Boyer-Ahmad	7.9 (4.5,11.9)	9.0 (5.7,12.9)	8.1 (4.8,11.9)	2.5 (.0,6.7)
Chahar Mahal and Bakhtiari	8.0 (5.0,11.3)	7.8 (5.1,10.8)	7.6 (4.9,10.7)	-5.0 (-5.3,-4.0)
Kordestan	8.9 (6.5,11.6)	7.7 (5.6,9.9)	7.4 (5.2,9.7)	-16.9 (-20.0,-16.4)
Azarbaijan, West	9.4 (7.6,11.5)	8.4 (6.7,10.1)	7.3 (5.6,9.0)	-22.3 (-26.3,-21.7)
Zanjan	9.5 (6.6,12.7)	7.7 (5.3,10.3)	7.2 (4.8,9.9)	-24.2 (-27.3,-22.0)
Hormozgan	7.1 (4.7,9.7)	7.0 (4.8,9.4)	6.7 (4.4,9.1)	-5.6 (-6.4,-6.2)
Sistan and Baluchistan	7.3 (5.2,9.7)	6.3 (4.5,8.2)	5.5 (3.8,7.4)	-24.7 (-26.9,-23.7)

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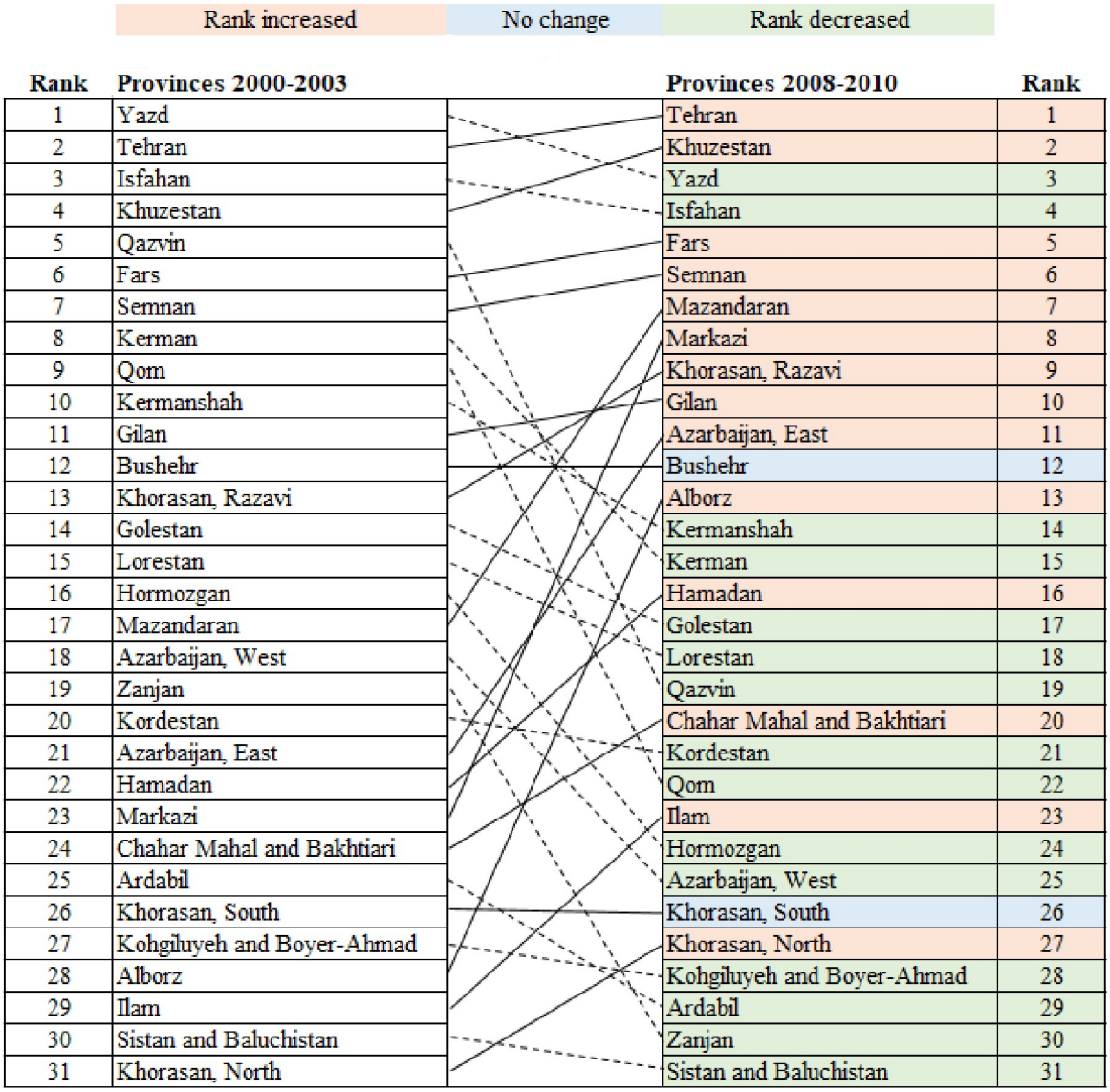
2004 [47] and 2006–2010 [48], our findings show a declining trend in mortality rate between 2000 and 2010.

Based on available studies [26, 49] for 30 provinces from 2004 to 2009, Gilan and Azerbaijan, East had the highest risk and Kohgiluyeh and Boyer-Ahmad had the lowest risk of breast cancer incidence. Likewise, another study [50] reported that the age-standardised rate of breast cancer in Azerbaijan, East was higher in 2006–2007, compared to that of Ardabil, which had the lowest rate. However, we found Tehran, Yazd, Khuzestan and Isfahan have the highest age-standardised breast cancer incidence rate and Sistan and Baluchistan has the lowest rate. Khorasan, Razavi and Golestan notably experienced the steepest increasing trend in breast cancer incidence from 2004 to 2008 among 30 provinces [28], while our findings show Khorasan, North; Alborz and Ilam have the greatest percentage change of incidence rate from 2000–2010.

Our results suggest high levels of geographical heterogeneity in breast cancer incidence and mortality across Iranian provinces. All provinces in our study have age-standardised incidence



Rank	Provinces 2000-2003	Provinces 2008-2010	Rank
1	Yazd	Tehran	1
2	Tehran	Khuzestan	2
3	Isfahan	Yazd	3
4	Khuzestan	Isfahan	4
5	Qazvin	Fars	5
6	Fars	Semnan	6
7	Semnan	Mazandaran	7
8	Kerman	Markazi	8
9	Qom	Khorasan, Razavi	9
10	Kermanshah	Gilan	10
11	Gilan	Azarbaijan, East	11
12	Bushehr	Bushehr	12
13	Khorasan, Razavi	Alborz	13
14	Golestan	Kermanshah	14
15	Lorestan	Kerman	15
16	Hormozgan	Hamadan	16
17	Mazandaran	Golestan	17
18	Azarbaijan, West	Lorestan	18
19	Zanjan	Qazvin	19
20	Kordestan	Chahar Mahal and Bakhtiari	20
21	Azarbaijan, East	Kordestan	21
22	Hamadan	Qom	22
23	Markazi	Ilam	23
24	Chahar Mahal and Bakhtiari	Hormozgan	24
25	Ardabil	Azarbaijan, West	25
26	Khorasan, South	Khorasan, South	26
27	Kohgiluyeh and Boyer-Ahmad	Khorasan, North	27
28	Alborz	Kohgiluyeh and Boyer-Ahmad	28
29	Ilam	Ardabil	29
30	Sistan and Baluchistan	Zanjan	30
31	Khorasan, North	Sistan and Baluchistan	31

Fig 3. Provinces ranked by age-standardised incidence rate for 2000–2003 and 2008–2010. Dotted and solid lines show decrease and increase of rank, respectively.

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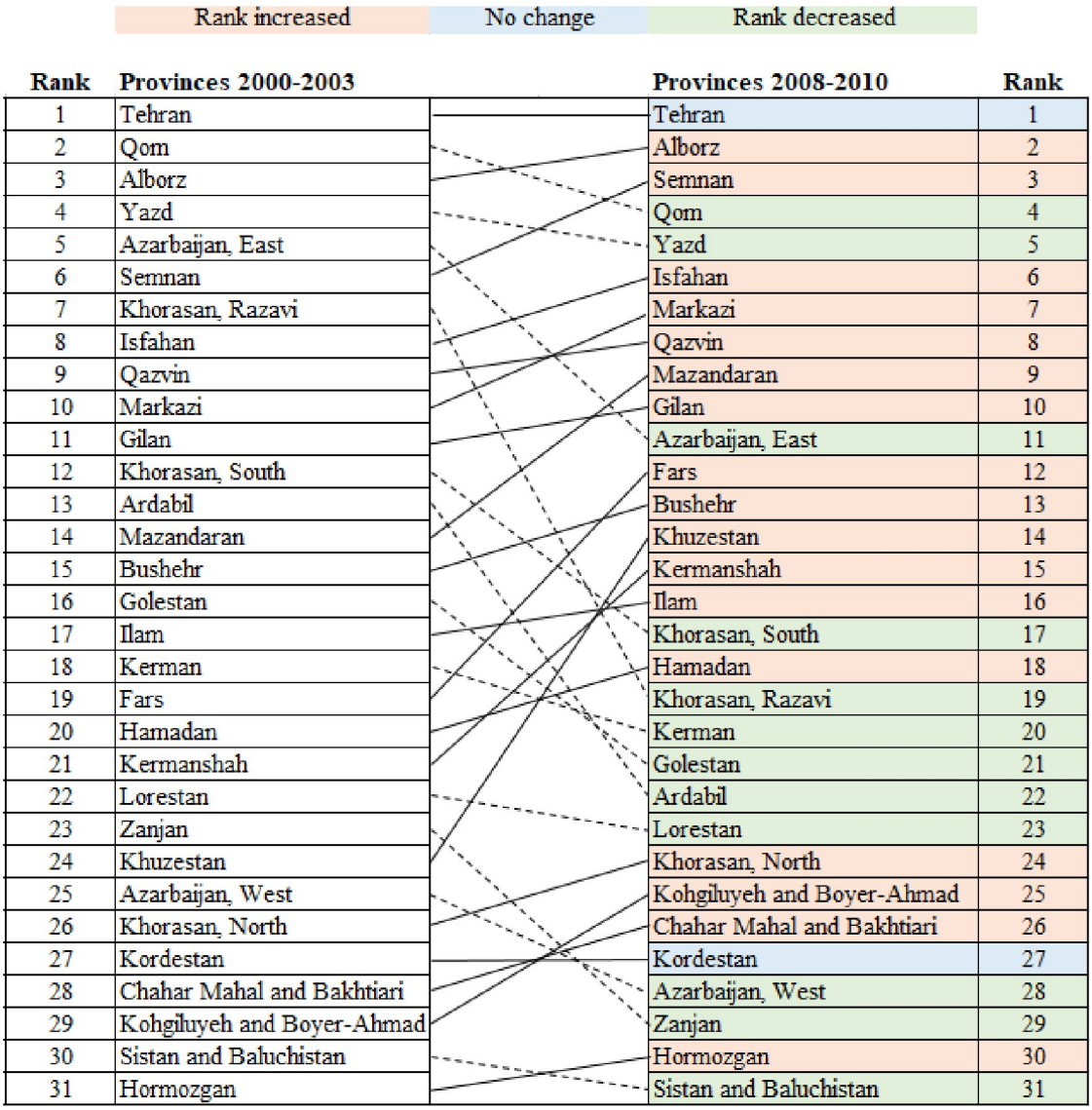
and mortality rates well above the cumulative probability of breast cancer incidence and death for individuals aged 15–79 years at the national level in Iran in 2000 (2.4 per 100,000 women and 0.7, respectively) and 2010 (2.8 and 0.7, respectively) estimated by the Global Burden of Disease study [10].

Previous research shows that cancer incidence and mortality in Asian countries have respectively a positive and a negative correlation with the country's level of development measured by the Human Development Index [7]. In particular, greater financial development and larger and more complex cancer prevention policies are associated with lower mortality within each major income level [18]. Moreover, female age-standardised incidence rate decreased in high socio-demographic index (SDI) countries but increased in the other SDI quintiles from 2007 to 2017 [5]. In Iran, a direct and substantial association was also found between the



Rank	Provinces 2000-2003	Provinces 2008-2010	Rank
1	Tehran	Tehran	1
2	Qom	Alborz	2
3	Alborz	Semnan	3
4	Yazd	Qom	4
5	Azarbaijan, East	Yazd	5
6	Semnan	Isfahan	6
7	Khorasan, Razavi	Markazi	7
8	Isfahan	Qazvin	8
9	Qazvin	Mazandaran	9
10	Markazi	Gilan	10
11	Gilan	Azarbaijan, East	11
12	Khorasan, South	Fars	12
13	Ardabil	Bushehr	13
14	Mazandaran	Khuzestan	14
15	Bushehr	Kermanshah	15
16	Golestan	Ilam	16
17	Ilam	Khorasan, South	17
18	Kerman	Hamadan	18
19	Fars	Khorasan, Razavi	19
20	Hamadan	Kerman	20
21	Kermanshah	Golestan	21
22	Lorestan	Ardabil	22
23	Zanjan	Lorestan	23
24	Khuzestan	Khorasan, North	24
25	Azarbaijan, West	Kohgiluyeh and Boyer-Ahmad	25
26	Khorasan, North	Chahar Mahal and Bakhtiari	26
27	Kordestan	Kordestan	27
28	Chahar Mahal and Bakhtiari	Azarbaijan, West	28
29	Kohgiluyeh and Boyer-Ahmad	Zanjan	29
30	Sistan and Baluchistan	Hormozgan	30
31	Hormozgan	Sistan and Baluchistan	31

Fig 4. Provinces ranked by age-standardised mortality rate for 2000–2003 and 2008–2010. Dotted and solid lines show decrease and increase of rank, respectively.

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incidence of breast cancer and the Human Development Index [26]. These findings are similar to our results in which higher levels of breast cancer incidence are observed across provinces with higher level of wealth index. This could be explained by increasing life expectancy, urbanisation, higher exposure to risk factors, delayed childbearing, a higher rate of screening, and better cancer registries [15]. Furthermore, high-income countries are characterised by diets higher in fats and also by higher levels of obesity, with both factors associated with higher risk of postmenopausal breast cancer (12–13% increase in risk per 5 kg/m^2) [51, 52].

Although we anticipated observing a lower mortality rate in the least deprived provinces in our study, most provinces with higher rates of incidence and mortality were in higher quintiles of the wealth index. However, the slope of mortality reduction over time among provinces in the wealthiest quintile is larger than that observed in the poorest quintile, which suggests a possible reverse association in coming years, agreeing with other existing studies [53, 54].

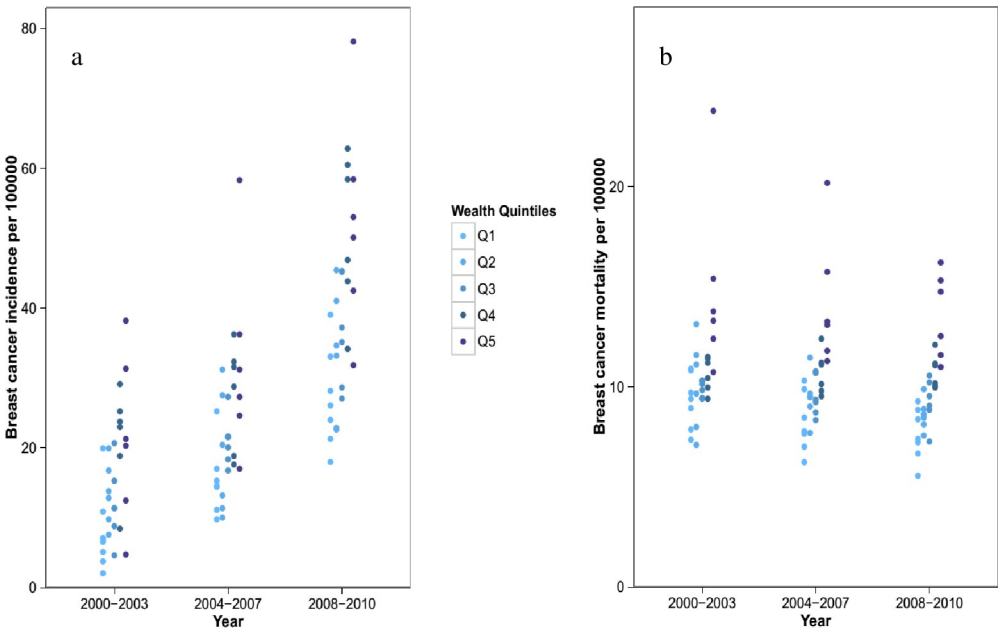

Fig 5. Breast cancer incidence (a) and mortality (b) rate by province arranged by quintiles of province wealth. Each dot represents the posterior mean of incidence and mortality for one province. The darkest colour show the wealthiest quintile and the lightest colour the most-deprived quintile.

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It appears that the high incidence rates observed in our study are likely owing to higher breast screening in the last time interval of study (2008–2010) compared to the first time interval (2000–2003) especially among those groups who were in wealthier areas [55, 56]. The increasing completeness percentage of cancer registry over time in Iran (S1 Table) may also have played an important role in the increases in reported numbers of new cases. Nevertheless, despite the potential benefits of screening, previous findings demonstrate that breast cancer screening usage rate among Iranian women is low (1.3% to 30.5%) [57]. For instance, screening rate in the North of Iran varied from 21.7% of women in Mazandaran to only 15.7% of women in Gilan [58, 59]. Also, in the South of Iran, only 1.3% of the women had a mammography screening at any point in their lifetime [60]. This suggests that taking full advantage of female screening participation in our community must be considered as a fundamental priority.

These efforts have some limitations. Firstly, the increase in coverage rate of the cancer registry over the period of analysis may impact on the interpretation of the time trends. However, we have addressed this issue by including coverage rate as a covariate in the model. This allows any bias caused by differences in coverage rate to be estimated empirically and for the model

Table 3. Age-standardised breast cancer incidence and mortality rates (per 100,000) by province wealth index quintile.

		Poorest quintile	Q2	Q3	Q4	Q5
Incidence	2000–2003	7.0 (4.5,9.9)	12.7 (9.8,16.0)	14.1 (10.9,17.5)	18.3 (15.5,21.2)	24.1 (20.3,28.3)
	2004–2007	15.7 (12.1,19.6)	17.7 (13.6,22.2)	22.3 (19.4,25.5)	27.4 (24.0,31.0)	32.0 (28.2,36.0)
	2008–2010	30.7 (25.2,36.7)	31.8 (26.3,37.8)	41.0 (36.1,46.2)	47.3 (42.6,52.2)	48.8 (43.8,54.0)
Mortality	2000–2003	9.3 (6.4,12.5)	9.3 (6.7,12.1)	10.5 (8.1,13.3)	10.7 (8.7,12.9)	15.0 (12.1,18.2)
	2004–2007	8.6 (6.1,11.4)	9.0 (6.3,12.0)	10.1 (8.2,12.2)	10.9 (8.7,13.2)	13.5 (11.1,16.1)
	2008–2010	8.3 (5.7,11.3)	9.0 (6.3,11.9)	9.5 (7.3,11.9)	10.4 (8.2,12.6)	12.5 (10.1,15.1)

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to borrow strength based on this covariate. Secondly, the cancer registry in Iran is conducted mostly via a pathology-based system, which is less efficient than population-based registration. Thirdly, although we have considered the completeness of cancer registry by SSI registry, information on a small proportion of patients not supported by SSI is still absent in our models. Fourthly, the most recent data source is from 2010; this underlines the need for publication of more detailed and up-to-date information.

To our knowledge, this study is the first subnational level analysis of breast cancer incidence and mortality in Iran, simultaneously using several administrative datasets and Bayesian spatial modelling to obtain province-level estimates between 2000 and 2010 and also addressing the incompleteness of the cancer registry. Our results highlight the high levels of heterogeneity across provinces in the levels of incidence and mortality rates of breast cancer in Iran and the need for a comprehensive and effective plan to control breast cancer which takes into account subnational variability. These differences emphasise the urgent need to improve not only access to diagnosis but also access to treatment to contain breast cancer associated mortality in the most deprived areas and reduce inequalities.

Conclusions

In conclusion, our findings showed that breast cancer incidence has increased over time in Iran, while mortality has decreased, but with lower incidence in the most deprived provinces possibly due to underdiagnosis or late-stage diagnosis. Although the mortality rate is still higher in wealthier provinces, the larger reduction observed over time in these provinces suggests a possible reversal in coming years, with the poorest provinces having higher levels of mortality. Improvements in prevention, access, and quality of screening procedures are needed to improve early diagnosis in the most deprived areas. The study also highlights the need for an improved cancer registry for breast cancer incidence monitoring to ensure the data can be actionable.

Supporting information

S1 Appendix. Bayesian Poisson spatial model.
(DOCX)

S1 Table. Summary table of covariates.
(DOCX)

S1 Fig. Map of covariates by time: cancer registry completeness percentage (a), female urbanization percentage (b), female mean years of schooling (c), and wealth index (d) (the last one is not used as covariate in the model but its correlation is checked with incidence and mortality rates).
(DOCX)

S2 Fig. Age-standardised breast cancer incidence versus age-standardised mortality rate per 100,000 by three time intervals.
(DOCX)

S3 Fig. Box plots of age-standardised breast cancer incidence rate (a) and age-standardised breast cancer mortality rate (b). Diamond symbol shows the mean value.
(DOCX)

S1 Data.
(PDF)

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