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The Impact of Fertility Rate Changes on Breast Cancer Incidence at the Subnational Level

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An inverse association between fertility rates and breast cancer incidence has been observed at the national and global levels. However, few studies have examined this relationship using subnational data. We aimed to determine the correlation between total fertility rates (TFR) and breast cancer incidence across cities in Iran's Razavi Khorasan province between 2014 and 2019.

This ecological study utilized age-standardized breast cancer incidence rates and TFRs for 28 regions of Razavi Khorasan province from 2014 to 2019. Pearson correlation coefficients assessed the TFR-incidence correlation annually. Annual percent changes (APCs) in incidence rates were estimated using linear mixed models, unadjusted and adjusted for region-level TFRs.

TFR declined province-wide, with the steepest decreases in Bakharz (-45%), Torbat Jaam (-39%), and Torghab & Shandiz (-35%). Breast cancer incidence patterns were heterogeneous across cities, with significantly declining APCs in 7 regions, including Bajestan (-9.8%), Gonabad (-8.1%), and Torghab & Shandiz (-8.3%). Fertility adjustment had minimal impact on APCs. No significant correlation was observed between TFRs and incidence rates from 2014 to 2019 (correlation coefficients -0.193 to 0.193, p>0.05).

In contrast to national and global trends, declining fertility rates did not correlate with increasing breast cancer incidence across Razavi Khorasan cities from 2014 to 2019. Regional differences may modify the impacts of changing fertility patterns on breast cancer occurrence. Further investigations into this relationship are warranted using robust analytical methods.

INTRODUCTION

In 2018, breast cancer was the most commonly diagnosed cancer in women, globally representing 24.2% of all cancers in women and the most common cause of cancer-related mortality in women 1. Breast cancer is accounting for 12.5 percent of all cancers in

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Iran. It is the sixth leading cause of death in the country. According to the Iranian National Cancer Registry (INCR), the annual ASIR for primary breast cancer is 27.4 (per 100,000), with a crude incidence of 22.6 (per 100,000) [2]. This rising burden of breast cancer in Iran necessitates identifying modifiable risk factors that may impact population incidence rates. Reproductive factors, including menarche age, parity, age at first delivery, and menopause age, and lifestyle factors, such as smoking, are widely known as important considerations in the assessment of breast cancer risk [3]. In particular, an inverse relationship between parity and breast cancer has been consistently observed across studies, whereby multiparous women have a lower breast cancer risk than nulliparous women 4. Postmenopausal women with one child have a 13% reduced risk of breast cancer compared to women without children. Women with two and three children had a 19% and 29% reduced risk, respectively [5].

At the population level, a decline in fertility rates, as measured by the total fertility rate (TFR), has been correlated with increased breast cancer incidence in several countries [6, 7]. However, the association between national fertility trends and breast cancer occurrence may not necessarily apply at the subnational level. Evaluating this relationship using regional data can identify heterogeneity across smaller geographic units.

Razavi Khorasan province in northeastern Iran has experienced steep fertility declines over the past three decades, with the TFR dropping from around 7 in 1986 to 1.6 by 2011 [8]. Concurrent trends in breast cancer incidence have not been characterized. Examining the correlation between changing fertility rates and breast cancer occurrence at the city level in Razavi Khorasan province can elucidate whether regional patterns are consistent with the inverse association observed nationally and globally.

Therefore, the ecological study aimed to determine the correlation between total fertility rates and breast cancer incidence across cities in Razavi Khorasan province between 2014 and 2019. We hypothesized that age-standardized breast cancer incidence rates have increased over time in parallel with declining fertility rates. Findings from this analysis could shed light on the impact of demographic transitions on the emerging breast cancer burden in this region.

MATERIALS AND METHODS

This analysis utilized region-level data on age-standardized breast cancer incidence rates and total fertility rates in Khorasan Razavi province between 2014 and 2019. Annual age-standardized breast cancer incidence rates per 100,000 women were calculated for each of the 28 regions using population-based cancer registry data. We used data from the National Cancer Registry Center for Khorasan Razavi province. Age-standardized incidence rates (ASIRs) per 100,000 women were calculated for each city in Khorasan Razavi province. We employed the direct age-standardization method based on the WHO standard population. The study period of 2014-2019 was selected based on data availability. 2014 represents the first year of complete, validated data from the National Cancer Registry for all regions of Razavi Khorasan province, while 2019 was the most recent year with finalized data available at the time of analysis

TFR for each city was calculated using the Spectrum software, which incorporates demographic components affecting population changes. Population data were sourced from the National Statistics Office, Civil Registration Office, and SinaEHR system census. We used the DemProj module in Spectrum to project TFR for five years based on 5-year age groups. Calculations were performed separately for each city under Mashhad University of Medical Sciences.

We employed several statistical approaches to compare trends between total fertility rates (TFR) and age-standardized breast cancer incidence rates (ASR). Pearson correlation coefficients were calculated to assess the correlation between TFR and ASR for each year from 2014 to 2019. To evaluate temporal trends in both TFR and ASR, we used linear mixed-effects models with a random intercept for the region and fixed effect for the year, allowing us to estimate annual percent changes (APCs) for each variable while accounting for the hierarchical structure of the data. To directly compare trends between TFR and ASR, we used a bivariate linear mixed effects model,

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including both TFR and ASR as dependent variables, with year as a fixed effect and region as a random effect. We tested for a significant slope difference between TFR and ASR using a likelihood ratio test comparing models with and without an interaction term between year and variable type (TFR vs ASR).

Additionally, we conducted a time-series analysis using vector autoregression (VAR) models to examine the dynamic relationship between TFR and ASR over time, accounting for potential lagged effects. All statistical analyses were performed using Stata version 16.0 (StataCorp, College Station, TX, USA). P values less than 0.05 were considered statistically significant.

Ethical considerations in this study included obtaining permission from the Ethics Committee of Mashhad University of Medical Sciences. (Ethical Code: IR.MUMS.FHMPM.REC.1402.145.

RESULTS

Overall, age-standardized breast cancer incidence rates decreased from 2014 to 2019 in most regions, with the most significant declines seen in Bakharz (-61%), Torbat Heydarieh (-53%), and Torghab & Shandiz (-47%). More modest decreases were observed in Bajestan (-17%), Joghaty (-11%), and Jovain (-11%). Rates increased in a few regions, including Roshtkhar (+130%), Chenaran (+8%), and Khalil Abad (+21%) (Table 1).

Region-level total fertility rates also tended to decline between 2014 and 2019. The most significant percent decreases in TFR were seen in Bakharz (-45%), Torbat jaam (-39%), and Torghab & Shandiz (-35%). More modest TFR reductions occurred in most other regions, ranging from -15% (Kashmar) to -3% (Firizeh and Ghoochan). Only one region (Roshtkhar) had an increasing TFR (+12%) (Table 1).

The correlation between TFR and ASR was evaluated from 2014 to 2019. No statistically significant correlation was observed in any year, with Pearson correlation coefficients ranging from -0.193 to 0.193 (all p>0.05) (Table 2).

TFR declined over the 6 years, from 3.1 in 2014 to 1.8 in 2019. In contrast, ASR did not demonstrate a clear linear trend, fluctuating between 28.53 and 45.9 over the years analyzed (Table 2).

Figure 1 displays the temporal trends in age-standardized breast cancer incidence rates (ASR) and total fertility rates (TFR) in Khorasan Razavi province from 2014 to 2019. Overall, there was a declining trend in TFR over the 6 years, from 3.1 in 2014 to 1.8 in 2019. In contrast, ASR did not demonstrate a clear linear trend over time, fluctuating between 28.5 and 45.9 during the period examined.

Overall, breast cancer incidence rates decreased from 2014 to 2019 in most regions, with more significant declines generally observed in the unadjusted versus fertility-adjusted models. The unadjusted annual percent change (APC) ranged from -22.4% (Faiz abad) to 17.5% (Roshtkhar), while the fertility-adjusted APC ranged from -21.7% (Faiz abad) to 18.2% (Roshtkhar). (Table 3)

Statistically significant decreasing trends were observed in the unadjusted models for Bajestan (-9.8%), Joghaty (-7.6%), Jovain (-7.6%), Sabzevar (-7.6%), Torbat Heydarieh (-7.5%), Gonabad (-8.1%), and Torghab & Shandiz (-8.3%). After adjusting for region-level fertility rates, statistically significant declines remained for these regions, though effect sizes were slightly attenuated (Table 3).

Non-significant changes were found in both unadjusted and adjusted models for most other regions, including Bardaskan, Taibad, Torbat Jaam, Takhte Jolgeh, Chenaran, Khalil abad, Khaaf, Daregaz, Roshtkhar, Zaveh, Sarakhs, Fariman, Faiz abad, Firizeh, Ghoochan, Kashmar, Kalat, Mahvelat, and Neyshaboor.

In summary, breast cancer incidence trended downward in most regions from 2014-2019, with statistically significant decreases observed in 7 areas.

DISCUSSION

In this ecological study examining region-level data in Razavi Khorasan province from 2014-2019, we did not find evidence of a statistically significant inverse correlation between total fertility rates (TFR) and breast cancer incidence over time. While TFR declined across most cities during the period analyzed, breast cancer rates fluctuated over time and showed heterogeneous patterns across regions. To contextualize our regional findings, it's important to

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Table 1. Trends in Age-Standardized Breast Cancer Incidence Rates and Total Fertility Rates by Region, 2014-2019.

Region	Total Fertility Rate						Age-Standardized Rate					
	2014	2015	2016	2017	2018	2019	2014	2015	2016	2017	2018	2019
Bakharz	3.3	3.5	3	2.7	2.6	2.2	14.21	8.06	50.19	27.8	4.98	13.35
Bajestan	2.7	2.8	2.4	1.9	1.8	1.5	11.09	28.59	26.81	11.87	32.54	12.27
Bardaskan	3.3	3.3	3	2.3	2	1.9	16.18	9.89	28.37	5.51	16.03	13.12
Taibad	4.4	4.3	3.8	3.3	3.2	3.3	14.21	8.06	15.95	9.05	14.93	14.39
Torbat jaam	3.9	3.7	3	2.7	2.5	2.3	23.23	7.68	15.91	19.54	19.84	18.47
Torbat heydarieh	3.3	3.3	2.8	2.2	1.9	1.6	44.58	28.12	20.57	22.65	30.28	30.77
Takhte jolgeh	3.1	3.1	2.7	2.3	2.2	1.8	0	3.66	0	4.1	0	0
Joghaty	3.3	3.2	2.9	2.5	2.3	2.1	33.62	23.32	24.32	22.51	32.31	30.02
Jovain	3	3.2	2.8	2.3	2.3	2	33.62	23.32	24.32	22.51	32.31	30.02
Chenaran	1.9	2.4	2	1.2	2	1.8	10.63	7.63	15.54	17.52	23.13	23.14
Khalil abad	3.2	3	2.7	2.3	1.8	1.6	21.9	5.53	24.81	20.41	13.76	7.41
Khaaf	4.5	4.6	4	3.5	3	3	14.14	8.94	20.39	18.83	12.63	17.19
Daregaz	2.6	2.7	2	1.8	1.7	1.5	25.83	7.46	25.41	16.006	18.69	7.46
Roshtkhar	2.9	3.1	2.7	2.5	2	1.9	8.45	7.08	3.5	36.89	9.42	10.79
Zaveh	3.4	3.7	3.5	3.4	3.1	2.6	6.88	16.56	15.11	0	8.7	15.81
Sabzevar	2.9	2.8	2.3	1.9	1.7	1.5	33.62	22.32	24.32	22.54	32.31	30.02
Sarakhs	3.5	3.3	2.9	2.1	2.2	1.8	24.39	23.55	32.25	24.82	22.98	24.2
Torghab &shandiz	3	3.2	2.9	2.3	2	1.2	51.37	10.71	21.01	21.05	18.06	41.83
Fariman	2.3	2.4	2	1.9	2	1.8	17.68	7.32	18.39	14.03	22.25	22.83
Faiz abad	2.8	3	2.7	2.1	1.9	1.8	0	4.22	0	7.19	0	9.25
Firizeh	3.6	3.5	3	2.6	2.3	2.1	37.17	29.21	35.07	24.67	35.03	30.34
Ghoochan	2.9	2.9	2.7	2.3	2.2	1.8	23.59	13.23	25.82	22.54	23.86	20.6
Kashmar	3.3	3.3	3	2.3	1.9	1.7	35.02	17.23	22.12	20.71	19.92	27.61
Kalat	1.1	1.2	1.8	2.3	2	1.8	6.29	14.23	11.46	5.62	5.62	25.13
Gonabad	3.9	3.5	3	2.7	2.5	2.3	38.79	32.23	36.15	26.62	36.41	44.57
Mahvelat	2.8	3	2.7	2.1	1.9	1.8	7.66	4.22	16.3	15.85	7.97	12.15
Mashhad	3	3.2	2.9	2.3	2	1.2	67.14	40.18	44.69	45.47	45.61	39.78
Neyshaboor	3.1	3.1	2.7	2.3	2	1.8	37.17	29.21	35.07	24.67	35.03	30.34

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Table 2. Association Between Total Fertility Rates and Breast Cancer Incidence Rates, 2014-2019.

year	ASR	TFR	Correlation coefficient	P-Value
2014	45.9	3.1	0.193	0.325
2015	28.53	3.2	0.044	0.824
2016	34.36	2.7	0.126	0.522
2017	33.42	2.3	-0.080	0.686
2018	37.24	2.1	-0.174	0.376
2019	36.21	1.8	-0.193	0.326

consider the national trends in Iran during the same period (2014-2019). According to the World Bank, Iran's national TFR decreased slightly from 1.75 in 2014 to 1.71 in 2019 [15]. Concurrently, data from the Iranian National Cancer Registry indicate that the age-standardized incidence rate of breast cancer in Iran increased from 33.21 per 100,000 in 2014 to 34.6 per 100,000 in 2019 [16]. This national pattern of decreasing TFR and increasing breast cancer incidence contrasts with the heterogeneous trends we observed across Razavi Khorasan cities.

These findings contradict our original hypothesis that breast cancer incidence would mirror declining fertility trends at the city level. The results are also inconsistent with prior ecological analyses showing an inverse association between TFRs and breast cancer occurrence nationally and globally [1-6]. Specifically, studies from Iran, China, and the United States have reported increasing breast cancer incidence accompanying falling fertility rates [5,9,10]. However, our results align with other ecological analyses in Italy and Colombia that found no correlation between provincial-level fertility trends and breast cancer rates [11,12]. Reproductive patterns likely have a complex, multifactorial relationship with breast cancer incidence, and associations may be setting-specific. Evaluating correlations using small, subnational units can illuminate heterogeneous patterns not discernible from national-level data.

While our analysis revealed a negative correlation between TFR and breast cancer incidence (correlation coefficients ranging from -0.193 to 0.193), this association was not statistically significant (all $p>0.05$). This finding, though not reaching statistical significance, aligns with the general trend observed in other studies. For instance, a study by Lim et al. across Asian countries found an inverse relationship between TFR and breast cancer incidence [10]. However, the strength of this relationship varied considerably between countries, suggesting that regional factors may modify this association. Our study's lack of a significant correlation could be attributed to several factors. Firstly, the relatively short time frame (6 years) may not have been sufficient to capture the full impact of fertility changes on breast cancer incidence, given that such effects may manifest over decades. Secondly, the ecological nature of our study means that individual-level risk factors could not be accounted for, potentially masking the true relationship between fertility and breast cancer risk.

It's crucial to note that breast cancer incidence is

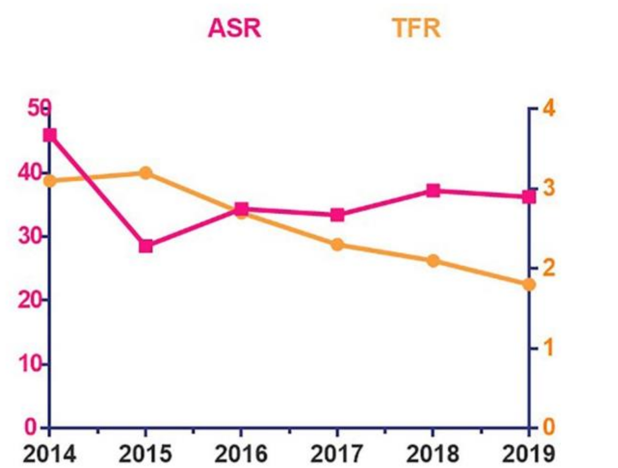

Figure 1. Temporal trends in breast cancer incidence and Total fertility rate.

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Table 3. Annual percent change in breast cancer incidence rates by region, 2014 to 2019, unadjusted and adjusted for region-level fertility rates.

Region	Overall APC (95% C.I) unadjusted for region-level fertility rates	Overall APC (95% C.I) adjusted for region-level fertility rates
Bakharz	-25.5% (-39.4% to -9.9%)	-24.1% (-38.3% to -8.4%)
Bajestan	-9.8% (-15.7% to -3.6%)	-9.3% (-15.2% to -3.1%)
Bardaskan	-4.3% (-10.8% to 2.5%)	-3.6% (-10.3% to 3.5%)
Taibad	-2.8% (-8.9% to 3.5%	-2.5% (-8.8% to 4.1%)
Torbat Jaam	-6.1% (-12.2% to 0.2%)	-5.7% (-11.9% to 0.8%)
Torbat Heydarieh	-7.5% (-13.5% to -1.3%)	-7.2% (-13.4% to -0.8%)
Takhte jolgeh	-1.2% (-11.4% to 9.8%)	-0.9% (-11.5% to 10.5%)
Joghaty	-7.6%(-13.4% to -1.5%)	-7.3% (-13.2% to -1.2%)
Jovain	-7.6% (-13.4% to -1.5%)	-7.3% (-13.2% to -1.2%)
Chenaran	0.4% (-6.9% to 8.1%)	1.0% (-6.2% to 8.5%)
Khalil abad	-5.4% (-11.7% to 1.2%)	-5.0% (-11.5% to 1.8%)
Khaaf	-1.7% (-8.5% to 5.5%)	-1.3% (-8.3% to 6.0%)
Daregaz	-5.5% (-11.7% to 0.9%)	-5.2% (-11.6% to 1.5%)
Roshtkhar	17.5% (-7.1% to 48.9%)	18.2% (-6.7% to 50.1%)
Zaveh	-0.2% (-9.6% to 10.1%)	0.4% (-9.3% to 10.6%)
Sabzevar	-7.6% (-13.4% to -1.5%)	-7.3% (-13.2% to -1.2%)
Sarakhs	-1.4% (-7.8% to 5.3%)	-1.0% (-7.7% to 6.0%)
Torghab &shandiz	-8.3% (-14.2% to -2.1%)	-7.9% (-13.9% to -1.6%)
Fariman	5.0% (-2.3% to 12.7%)	5.5% (-1.5% to 13.0%)
Faiz abad	-22.4% (-53.5% to 30.0%)	-21.7% (-53.1% to 31.1%)
Firizeh	-1.3% (-7.8% to 5.5%)	-0.9% (-7.6% to 6.1%)
Ghoochan	-0.3% (-6.9% to 6.7%)	0.2% (6.7% to 7.4%)
Kashmar	-6.1% (-12.3% to 0.5%)	-5.7% (-12.1% to 1.0%)
Kalat	-1.7% (-13.4% to 11.2%)	-1.3% (-13.2% to 11.8%)
Gonabad	-8.1% (-14.0% to -2.0%)	-7.7% (-13.8% to -1.4%)
Mahvelat	0.3% (-9.5% to 11.0%)	0.8% (-9.1% to 11.3%)
Mashhad	-6.6% (-12.3% to -0.6%)	-6.2% (-12.1% to -0.1%)
Neyshaboor	-1.3% (-7.8% to 5.5%)	-0.9% (-7.6% to 6.1%)

Notes: Annual percent change (APC) and 95% confidence interval (CI) were estimated from a linear mixed model with a random intercept and fixed linear time.

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factors beyond fertility rates. These include genetic factors, such as mutations in BRCA1 and BRCA2 genes, which are known to increase breast cancer risk significantly. A study by Khoramdad et al. found that Iranian women with a family history of breast cancer had 2.47 times higher odds of developing the disease [9]. Lifestyle factors, including diet, physical activity, and alcohol consumption, play important roles. The westernization of dietary patterns in Iran, characterized by increased consumption of processed foods and decreased intake of traditional, plant-based foods, may contribute to increasing breast cancer risk [14]. Reproductive factors beyond fertility, such as age at first birth, breastfeeding duration, and use of hormonal contraceptives, all influence breast cancer risk. While our study focused on TFR, our ecological data did not capture these nuanced aspects of reproductive history [3,4]. Environmental exposures, including endocrine-disrupting chemicals and other pollutants, may contribute to breast cancer risk, with urban areas potentially seeing different trends compared to rural regions [13, 14]. Additionally, improved access to mammography screening can lead to increased detection of breast cancer, potentially explaining some of the observed increases in incidence rates. Variations in healthcare access across different regions of Razavi Khorasan could contribute to the heterogeneous patterns we observed [13, 14].

The discordance between our regional findings and national trends, as well as findings from some other countries, highlights the complexity of the relationship between fertility transitions and breast cancer epidemiology. Several factors could explain these differences, including regional variations in risk factor prevalence, differences in healthcare systems and screening programs, socioeconomic factors, and cultural norms related to childbearing and healthcare-seeking behaviors [8, 13, 14].

Our analysis revealed that fertility adjustment had minimal impact on the effect sizes of annual percent changes in breast cancer incidence across regions. This suggests that while fertility rates declined during the study period, these changes did not substantially alter the observed trends in breast cancer incidence. This finding underscores the complexity of population-level trends and the potential influence of other factors, such as screening practices, environmental exposures, or lifestyle changes occurring concurrently with fertility transitions.

Key strengths of this analysis include the use of recent city-level data and mixed effects modeling to estimate region-specific trends. However, limitations include the aggregate nature of ecological data and the inability to make causal inferences. Individual-level information on known breast cancer risk factors was unavailable, which could have provided more nuanced insights into the relationship between fertility and breast cancer risk.

CONCLUSION

In conclusion, while our study did not find a significant inverse correlation between declining TFR and breast cancer incidence in Razavi Khorasan province, it highlights the complex and multifaceted nature of breast cancer epidemiology. The heterogeneous patterns observed across regions underscore the importance of considering local contexts when studying the impacts of demographic transitions on health outcomes. Further investigations using long-term data, robust analytical techniques, and individual-level risk factor information are warranted to clarify the effects of fertility declines on breast cancer epidemiology across different regional settings in Iran.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

Ethical considerations in this study included obtaining permission from the Ethics Committee of Mashhad University of Medical Sciences (Ethical Code: IR.MUMS.FHMPM.REC.1402.145).

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