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Investigating Regional Income-Based Shared Frailty among Women with Breast Cancer

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Abstract

Breast cancer is the most commonly occurring cancer among women globally and also the most common cancer overall, with around 2.3 million new cases of breast cancer and around 685,000 deaths related to breast cancer reported globally in 2020. However, there are significant variations in the incidence and mortality rates across and within countries. Some studies have argued the role of neighbourhood socioeconomic status, family support mechanisms (marital status) and access to health care in explaining survival disparities.

The objective of this study is to identify and evaluate possible role of regional socioeconomic status in determining disparities in survival of women with breast cancer, while adjusting for other demographic and biomedical factors. Individual-level data of women in the US with breast cancer diagnosis between 1975 and 2019 was retrieved from the well-known Surveillance, Epidemiology, and End Results (SEER) Program submission 2021.

We hypothesized that individuals from counties in the US with similar socioeconomic status share unmeasured vulnerabilities towards survival from breast cancer. To validate this hypothesis, we have fitted semiparametric survival models with shared frailty defined for different categories of the county-level median household income.

Our modeling results show significant unmeasured heterogeneity between the clusters of individuals based on economic status of their counties. Individuals residing in counties with lower annual median household income share a higher risk of death due to breast cancer as compared to those from counties with higher median household incomes.

Key words: Breast cancer; Gamma frailty; Survival; Socioeconomic Determinants of Health; SEER; Healthcare disparity.

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1. Introduction

Breast cancer is the most commonly occurring cancer among women globally and also the most common cancer overall (WHO (2023a), WCRF (2023)). In the year 2020, approximately 2.3 million new cases of breast cancer were diagnosed, and around 685,000 deaths related to breast cancer were reported globally. There are significant variations in breast cancer incidence and mortality rates across different regions. As per the 2020 global data, breast cancer incidences were higher in developed countries whereas breast cancer deaths were higher in developing countries (WCRF (2023)). This may be due to systematic early detection programmes in developed countries, thereby underscoring the importance of economic and biomedical resources in ensuring adequate health programmes to facilitate awareness, early detection and treatment. Late diagnoses, inadequate health services and low universal health coverage are some of the important factors leading to global disparities in the outcomes of breast cancer (WHO (2023a)). Consider that breast cancer five-year survival rates are above 90% in high-income countries, as compared to 66% in India and 40% in South Africa (WHO (2023a)).

Centers of Disease Control and Prevention (CDC) have reported breast cancer as the second most common cancer among women (CDC (2023)). Breast cancer incidence is attributed to physical, hormonal, environmental, and genetic factors, including obesity, immunity, and the tumor environment. Interestingly, race, socioeconomic status and geography have also been found to determine patterns of breast cancer incidence. Incidence rates are the highest among non-Hispanic (NH) whites (130.8 per 100,000), followed closely by NH blacks (126.7 per 100,000). Yet, NH black women have the highest breast cancer death rate among all races in the US (28.4 deaths per 100,000). In fact, for every stage at diagnosis, NH black women have the lowest 5-year rate of survival (ACS (2019)).

Social Determinants of Health (SDH) have emerged in the recent years as a key issue alongside the traditional roles of genetic and demographic factors affecting survival of individuals with breast cancer. Disparities in access to and quality of healthcare could lead to disparities in health outcomes. WHO defines SDH as the "conditions in which people are born, grow, work, live and age, and the wider set of forces and systems shaping the conditions of daily life" (WHO (2023b)). The 2017 NIMHD Research Framework identified the domains of influence (Biological, Behavioral, Physical/Built Environment, Sociocultural Environment, Healthcare System) as well as different levels of influence (Individual, Interpersonal, Community, Societal) within those domains (NIMHD-NIH (2022)).

Among different SDH, geographical or physical/built environment health disparities are thought to be due – not only to limited physical access to health care – but also to differences in demography, attitudes, lifestyle factors, and cultural practices in regional and rural settings. A report by the US National Academies of Medicine stipulated that reducing geographical disparities in quality of care will benefit all its citizens but is likely to yield greater benefits to minority individuals (NRC (2004)). In the past few years, multilevel research on the local social context known as 'neighbourhood effects' and health led to findings about large racial/ethnic differences on mortality and morbidity (Chandra and Skinner (2004)). Neighbourhood as a SDH can be viewed through its components of the built environment, services, and the people within the neighbourhood (Bharmal *et al.* (2015)). Higher rates of obesity in neighbourhoods with poor walkability, access to healthy foods, health care facilities, are some of the mechanisms by which built environments can influence breast cancer outcomes (Obeng-Gyasi *et al.* (2022)). Neighbourhoods are in turn impacted by the socioeconomic conditions, *i.e.*, poorer neighbourhoods may have lower access to green spaces, healthy food markets, healthcare services, *etc.*, compared to richer neighbourhoods. Over time, such disparities may accrue and lead to unhealthy behaviours such as sedentary lifestyles, use of addictive substances, *etc.*, thereby perpetuating a cycle of poor health outcomes and worsening neighbourhood and socioeconomic conditions.

Disparities in breast cancer outcomes is currently an active area of research in epidemiology. A population-based cancer-specific survival study of patients diagnosed with breast, prostate, colorectal, or lung cancer between 2000 and 2013 in California, USA, by Ellis *et al.* (2018) estimated that the stage of diagnosis of cancer accounted for merely 24% of disparities in the survival of breast cancer patients. They found significant racial/ethnic survival disparities, with an overall reduction in survivability of black patients as compared to white patients. Their findings also suggested a significant role of neighbourhood socioeconomic status, family support mechanisms (marital status) and access to health care in explaining survival disparities. Hastert *et al.* (2021) used data from a regional cohort of African-American survivors of breast, colorectal, lung, and prostate cancer, to study the association between social needs of survivors and their health-related quality of life (HRQoL). They found a significant reduction in Functional Assessment of Cancer Therapy–General score, a measurement of HRQoL, for not getting care due to lack of transportation, for housing instability, for food insecurity, and for feeling unsafe in their neighbourhood.

In this direction, the present study aims to identify and evaluate the possible role(s) of regional socioeconomic status towards characterizing disparities in survival of women with breast cancer, while adjusting for other demographic and biomedical factors. Individual-level data of women in the US with breast cancer diagnosis between 1975 and 2019 was retrieved from the well-known Surveillance, Epidemiology, and End Results (SEER) Program submission 2021. In particular, we consider the location information of these individuals at the level of counties within the US states at which they reside. A county in the US provides a reasonably consistent environment for the local historic, geographic, and socioeconomic conditions that are commonly shared by the residents therein.

We hypothesized that individuals from counties with similar socioeconomic status share unmeasured vulnerabilities towards survival from breast cancer. To validate this hypothesis, we fitted semiparametric survival models with shared frailty defined for different categories of the county-level median household income. That is, individuals were clustered into different groups based on the median household income level of their county. Each of these clusters of individuals with breast cancer was expected to share some common unmeasured (or unaccounted for) risk of death due to breast cancer that was different from other clusters. This shared unmeasured risk could be due to various factors not directly included in the model, but those related to the local economic conditions of the individuals. For example, a county with lower median household income may imply less accessibility to healthcare services, higher risk of job loss, inadequate transportation, *etc.* Other relevant demographic and clinical factors available in the dataset, like age, cancer stage at diagnosis, breast cancer sub-type, and race are also included in the analysis. Posterior estimates of the random effects (frailty coefficients) corresponding to all clusters have been obtained. These estimates are a measure of unaccounted disparity between the clusters in the mortality risks from breast cancer.

The rest of the paper is organized in four sections. Description of the data and the shared frailty survival model has been provided in the next section on methodology. Section 3 contains descriptive summary of the data and the results of the fitted frailty survival models. A thorough discussion on the results is presented in section 4, and concluding remarks from the findings are provided in section 5.

2. Methodology

2.1. Data

SEER program of the National Cancer Institute (NCI) of the National Institutes of Health (NIH), USA, provides information on cancer statistics (SRP) [https://seer.cancer.gov/]. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48 percent of the US population.

In this study, we have used the SEER research data on individuals who are women with breast cancer diagnosed between 1975 and 2019, based on the November 2021 submission of the SEER (SEER (2022)). The individual-level data is compiled from 8 cancer registries which are linked to county-specific attributes such as median household income, rurality, *etc.* The dataset covers a total of 465,908 individuals from eight US geographic areas, *viz.*, San Francisco-Oakland SMSA, Connecticut, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, and Atlanta (Metropolitan). A list of variables used in the study and their description are provided in Table 1. Cases with complete information on these variables were included in the modeling exercise. A descriptive summary of the resulting dataset of 83,344 individuals is presented in Table 2.

2.2. Shared frailty survival model

The term *frailty* was used by Clayton (1978) to refer to any unobservable random effect shared by individuals with similar (unmeasured) risks in the analysis of mortality rates. Heterogeneity in unaccounted risks can be either defined for individuals experiencing recurrent events, or for clusters of individuals sharing common risks of an event (shared frailty). Shared frailty reflects excess risk for distinct groups of individuals sharing certain characteristics, over and above the risk explained by the measured covariates. In survival models, frailty is introduced as a random effect that acts multiplicatively on the hazard. The variance of the frailty measures the degree of heterogeneity in the hazard of different clusters of individuals- the case of shared frailty (Balan and Putter (2019)).

As a general structure for the shared frailty survival model, the conditional hazard function given the shared frailty can be written as

$$h_{ij}(t|Z_i) = h_0(t) Z_i exp(\beta^T x_{ij}(t)) \tag{1}$$

where, Z_i is an unobserved random effect common to all observations from cluster i, *i.e.*, the shared frailty of cluster i, β is a vector of unknown regression coefficients, $x_{ij}(t)$ are the observed covariates (which could also be time-dependent), and $h_0(t)$ is the baseline hazard function (Balan and Putter (2019), Hanagal (2019)). Z_i, being latent random terms having multiplicative effect on the hazard, are assumed to be iid random variables with a non-negative distribution, referred to as Z. We have used the R package "frailtyEM" by Balan and Putter (2019) to fit the model defined in (1). They have assumed that the distribution of the unobservable random variable Z is defined by the Laplace transform

$$L_Z(c;\alpha,\gamma) \equiv E[exp(-Zc)] = exp(-\alpha\psi(c,\gamma)) \tag{2}$$

With $\alpha > 0$ and $\gamma > 0$, this formulation for the frailty distribution includes several distributions such as gamma, positive stable, inverse Gaussian, and compound Poisson, which belong to the Power Variance Function (PVF) family. Since these distributions are a part of the same family, likelihood values of models fitted with different frailty distributions are comparable.

3. Results

Semiparametric shared frailty survival models were fitted using the *emfrail* function of the R package frailtyEM. Shared frailty was defined with respect to clusters based on median household income of the counties. The frailty parameter was assumed to follow Gamma distribution. Models were fitted with various baseline hazard distributions such as Breslow, Exponential, Weibull, Lognormal; and the best model was chosen based on the highest log-likelihood value. The resulting model, adjusted for the factors – age category, race, breast cancer stage, and breast cancer subtype – had a Gamma frailty with Weibull baseline hazard. A summary of results of the selected model is shown in Table 3.

From Table 3, we observed that both the Commenges-Andersen test and the likelihood-ratio test conclude that the random effect (shared frailty) is highly significant. This is further validated by the non-zero variance of the frailty parameter, Var(Z), the confidence interval of which does not contain zero. This variation in frailty can be visualized from the histogram of the frailty estimates (Figure 1). Values of the posterior frailty estimates corresponding to each category of county-level median household income is provided in Table 4.

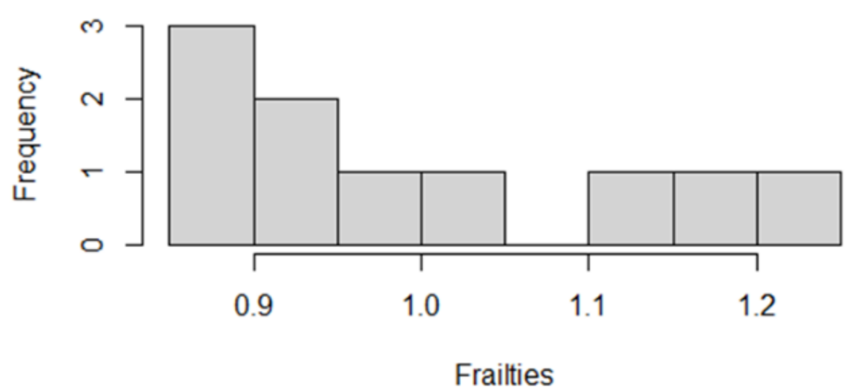

Figure 1: Histogram of posterior frailty estimates of the selected model

We can see from Table 4 that, in general, the frailty estimates decrease as the median household income level increases. That is, the additional unaccounted risk of an individual of dying due to breast cancer increases as the median household income level of their county decreases. The lower risk for the \$35,000 - \$39,999 income category could be a result of inappropriate representation of the cluster due to the relatively low number of individuals that belong to it (see Table 2).

The coefficient estimates of the selected survival model given in Table 3 provide a comprehensive insight into the impact of the factors on survival of women with breast cancer after adjusting for the unmeasured random effects (shared frailty) in the clusters. All the estimates were highly significant. Among the individuals with breast cancer, those belonging to white or other races are at significantly lower risk (around 30% lower) of dying due to breast cancer as compared to their black counterparts. As expected, risk of death increases by almost 10 times for individuals getting diagnosed in a late stage (stage III and higher) as compared to those diagnosed early. Among the four-breast cancer sub-types, risk of death is significantly higher for the HR−/HER2− category, also known as Triple-negative breast cancer (TNBC), as compared to each of the other three categories, namely Luminal A, Luminal B, and HER2. In other words, the risk of death associated with the other three sub-types is lower by around 54% – 62% than that for the TNBC sub-type. Compared to women with breast cancer who are lower than 50 years of age, the hazard of dying increases by 45% among those over 50 years of age.

4. Discussion

Factors considered in our study including age, breast cancer sub-type, race, and cancer stage, have been reported as significant risk factors by various previous studies (Ellis *et al.* (2018), Narod *et al.* (2018), Wadsten *et al.* (2017), CDC (2022)). Results from our modelling exercise reiterated the significant role of these risk factors in survival of women with breast cancer. In addition, as our results also show that black women with breast cancer are at significantly higher risk of death which has been previously reported by Ellis *et al.* (2018). This racial disparity can be partly because of genetic factors, and partly because of the socioeconomic disparities as well as disparities in accessibility to screening, treatment, and relevant resources across races.

The primary objective of this study was to investigate the possible role of unmeasured impact of regional socioeconomic status on survival of individuals with breast cancer in the US, while adjusting for other factors that have been previously shown to be associated with survival risk. Our findings validate the hypothesis that there is a significant unmeasured heterogeneity among clusters of individuals based on economic status of their respective counties. Individuals residing in counties with lower annual median household income share a higher risk of death due to breast cancer as compared to those from counties with higher median household incomes. The higher unmeasured risk for such individuals can be attributed to lack of adequate healthcare facilities, insecurity of jobs, less adherence to clinical follow-up due to potential loss of wages, lack of resources (which could include transportation, time and/or paid leave), poor diet and exercise, among other factors interdependent with the economic status of a county. This inference is concurrent with the findings of some previous studies that have explored the socioeconomic determinants of disparities in survival of individuals with cancer (Hastert *et al.* (2021), Merletti *et al.* (2011)).

5. Conclusion

Our findings indicate that economic vulnerabilities of women with breast cancer present added risks of mortality beyond the identified risks due to other common covariates. Socioeconomic and external environmental factors can play a significant role in cancer survival. Apart from efforts to improve healthcare practices such as early clinical interventions, detection programmes and screening, community education, *etc.*, there is a need to address the socioeconomic disparities to improve cancer survivability. Efforts in this direction begin with development of new policies aimed to reduce disparities and mitigate risks arising from the various SDH for individuals with breast cancer.

Our study has certain limitations. Due to constraints of data availability, we could not include additional factors such as treatment type or appropriateness, education level, *etc.* in the analysis. Additionally, since the data obtained pertains to only 8 registries associated with SEER, future studies could benefit from including additional registries to gain further insights into the effects of regional SDH on breast cancer outcomes.

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Table 1: List of variables and their description

Name	Description	Categories
surv_months	Survival time in months (since diagnosis). It is right censored for individuals who remained alive till the end of follow-up.	
event	Survival status of the individual	1: Died 0: Alive (censored)
age	Baseline age of the individual (15 years and above)	
age_cat1	Factor variable derived from the baseline age.	less than 50 50 or more
sub_type	Breast cancer subtype. For more information, see https://seer.cancer.gov/seerstat/ databases/ssf/breast-subtype.html.	HR+/HER2− (Luminal A) HR−/HER2− (TNBC) HR+/HER2+ (Luminal B) HR−/HER2+ (HER2)
race_1	Race recode of individuals. This recode is independent of Hispanic ethnicity of the individuals.	1: White 2: Black 3: Other (American Indian, AK Native, Asian/Pacific Islander)
AJCC6_stage	AJCC 6TH STAGE classification of breast cancer. Refer http://seer.cancer.gov/ seerstat/variables/seer/ajcc-stage/6th	0, I, IIA, IIB, IIIA, IIIB, IIIC, IIINOS, IV
grade1	A broader classification of stage of breast cancer of the individual at baseline, based on the AJCC6_stage variable.	early: 0, I, IIA, IIB, IIA late: IIIA, IIIB, IIIC, IIINOS, IV
Median_HI	Median annual household income of the county where the individual resides.	less than $35,000 $35,000 - $39,999 $40,000 - $44,999 $45,000 - $49,999 $50,000 - $54,999 $55,000 - $59,999 $60,000 - $64,999 $65,000 - $69,999 $70,000 - $74,999 $75,000 and more

Table 2: Factor-wise summary of the dataset from SEER

Variable	Overall distribution/ summary [Total cases = 83344]	Survival status-wise distribution/ summary	
		Died [8109]	Censored [75235]
age_cat1	<50: n = 16084 50+: n =67260	<50: n = 1502 50+: n = 6607	<50: n = 14582 50+: n = 60653
race_1	1: White: n= 67123 2: Black: n= 3972 3: Other: n =11901 4: Unknown: n = 348	1: White: n= 6450 2: Black: n= 616 3: Other: n = 1033 4: Unknown: n = 10	1: White: n= 60673 2: Black: n= 3356 3: Other: n = 10868 4: Unknown: n = 338
Median_HI	< $35,000: n = 500 $35,000 - $39,999: n = 355 $40,000 - $44,999: n = 1524 $45,000 - $49,999: n = 2266 $50,000 - $54,999: n = 6703 $55,000 - $59,999: n = 5590 $60,000 - $64,999: n = 6943 $65,000 - $69,999: n = 9919 $70,000 - $74,999: n = 6949 $75,000+: n = 42595	< $35,000: n = 76 $35,000 - $39,999: n = 38 $40,000 - $44,999: n = 223 $45,000 - $49,999: n = 289 $50,000 - $54,999: n = 746 $55,000 - $59,999: n = 580 $60,000 - $64,999: n = 667 $65,000 - $69,999: n = 924 $70,000 - $74,999: n = 654 $75,000+: n = 3912	< $35,000: n = 424 $35,000 - $39,999: n = 317 $40,000 - $44,999: n = 1301 $45,000 - $49,999: n = 1977 $50,000 - $54,999: n = 5957 $55,000 - $59,999: n = 5010 $60,000 - $64,999: n = 6276 $65,000 - $69,999: n = 8995 $70,000 - $74,999: n = 6295 $75,000+: n = 38683
sub_type	HR+/HER2-: n = 63379 HR-/HER2-: n = 8350 HR+/HER2+: n = 8123 HR-/HER2+: n = 3492	HR+/HER2-: n = 5030 HR-/HER2-: n = 1743 HR+/HER2+: n = 836 HR-/HER2+: n = 500	HR+/HER2-: n = 58349 HR-/HER2-: n = 6607 HR+/HER2+: n = 7287 HR-/HER2+: n = 2992
grade	Early: n = 71433 Late: n = 11911	Early: n = 3580 Late: n = 4529	Early: n = 67853 Late: n = 7382

Table 3: Results of the fitted semiparametric shared frailty survival model with gamma frailty and Weibull baseline hazard

Regression coefficients	Coef.	Exp(Coef.)	SE(Coef.)	p-value
age_cat1 (50+) [base category: <50]	0.3727	1.4517	0.0289	<0.0001
race_1 (other) [base category: Black]	-0.3731	0.6886	0.0514	<0.0001
race_1 (White) [base category: Black]	-0.3114	0.7324	0.043	<0.0001
grade1 (late) [base category: early]	2.2813	9.7892	0.0228	<0.0001
sub_type (HR-/HER2+) [base category: HR-/HER2-]	-0.7899	0.4539	0.051	<0.0001
sub_type (HR+/HER2-) [base category: HR-/HER2-]	-0.9708	0.3788	0.0281	<0.0001
sub_type (HR+/HER2+) [base category: HR-/HER2-]	-0.9738	0.3777	0.0422	<0.0001
Commenges- Andersen test for heterogeneity: p-value = 0.0165				
Likelihood ratio test for heterogeneity: **No-frailty log-likelihood = -84378.39** **With-frailty log-likelihood = -84363.04** **LRT p-value = 1.51e-08**				
Frailty variance: 95% confidence intervals in the ( ) **Var[Z] = 0.018 (0.006 – 0.061)**				

Table 4: Posterior frailty estimate for each category of county-level median household income

less than \$35,000	\$35,000 - \$39,999	\$40,000 - \$44,999	\$45,000 - \$49,999	\$50,000 - \$54,999
1.1899	0.9941	1.2126	1.137	1.004

\$55,000 - \$59,999	\$60,000 - \$64,999	\$65,000 - \$69,999	\$70,000 - \$74,999	\$75,000 and above
0.9244	0.9133	0.8821	0.8740	0.8838