Moderation Effect of Mammography Screening Among Women with Multiple Chronic Conditions

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Research Article

Keywords: Breast cancer screening, comorbidity, mammography participation, health policy, women health.

Posted Date: October 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-962596/v1>

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Version of Record: A version of this preprint was published at Scientific Reports on February 10th, 2022. See the published version at <https://doi.org/10.1038/s41598-022-06187-7>.

Abstract

Purpose: To investigate the moderation effects of mammography screening on early stage breast cancer and all-cause mortality among women aged 50-69 years with chronic conditions in Taiwan.

Method: We used a matched cohort design with four nationwide population databases, and an exact matching approach to match groups with different chronic conditions. Women population aged 50-69 years in 2010 in Taiwan were studied. A generic Charlson comorbidity index (CCI) measure was used to identify chronic illness burden. The sample sizes of each paired matched group with CCI scores of 0, 1, 2, or 3+ were 170,979 using a 1-to-1 exact matching. Conditional logistic regressions with interaction terms were used to test moderation effect, and adjusted predicted probabilities and marginal effects to quantify average and incremental chronic conditions associated with outcome measures. Statistical analyses were conducted in 2020-2021.

Results: Women with more chronic conditions were less likely to participate in mammography screening or to receive early breast cancer diagnoses, but were at greater risk of mortality. However, mammography participation increased the likelihood of early breast cancer diagnosis (OR=1.48, 95%CI=1.36-1.60) and decreased risk of all-cause mortality (OR=0.63, 95%CI=0.60-0.66). The interaction terms of CCI and mammography participation indicated significantly increased benefits of early breast cancer diagnosis and decreased risk of all-cause mortality as chronic illness increased.

Conclusions: Mammography participation significantly moderated the link between comorbidity and outcome measures among women with chronic conditions. Hence, it is important for public health policy to promote mammography participation for women with multiple chronic conditions.

Key Message

1. Comorbidity substantially affects breast cancer risk and cancer stage at diagnosis. However, most existing studies suggest that women with chronic conditions are less likely to participate in breast cancer screening.
2. This study found mammography participation significantly moderated the link between comorbidity and outcome measures among women with chronic conditions.
3. Hence, it is important for public health policy to promote mammography participation for women with multiple chronic conditions.

Introduction

Female breast cancer is the leading cause of global cancer incidence, with an estimated 2.3 million new cases, and the fifth leading cause of cancer mortality worldwide.¹ In 2020, the global cancer project (GLOBOCAN 2020) estimated increasing age-specific standardized incidence of 47.8 per million and mortality rates of 13.6 per million.¹ In Taiwan, female breast cancer is also the leading cause of cancer. Age-standardized incidence rates increased from 28.4 per million in 1995 to 78.9 per million in 2018, and age-standardized mortality rates from 9.7 per million to 12.5 per million.² To improve early diagnosis and survival outcomes, mammography has been suggested as an effective screening tool. The American Cancer Society recommends that average-risk women aged 45-54 years undergo mammography annually, and women aged 55 years or older biannually. A report from the 2013 National Health Interview Survey of America found that 69.1% of women aged 50 years or older are adherent to breast cancer screening guidelines every 2 years, while but mammography screening rates remain much lower in Asian countries.³

Cancer and chronic conditions may share common risk factors, including demographics (age, sex, ethnicity), and genetic and lifestyle-related factors (obesity, diet, physical activity, tobacco or alcohol consumption).⁴⁻⁶ Studies have shown that comorbidity substantially affects breast cancer risk and cancer stage at diagnosis.^{4,7-9} Therefore, chronic conditions play an important role in adherence to breast cancer screening guidelines for prevention and control. However, most existing studies suggest that women with chronic conditions are less likely to participate in breast cancer screening.^{10,11} Several plausible explanations address the negative association between comorbidity and mammography. For example, women with comorbid conditions may be deterred by physical barriers (pain, limited mobility), or by competing demands and health priorities given limited resources (time, money, energy).^{7,9,10}

Furthermore, unclear potential benefits of mammography among women with different health statuses, especially those aged 50-69 years, may affect health providers' referral decisions or individuals' willingness to undergo mammography.¹²⁻¹⁵ Most existing studies focus on benefits of mammography screening among older women and were conducted in the United States or Europe.^{16,17} For example, a systematic review by Braithwaite et al. (2016) considered seven studies regarding the benefit or harm of mammography screening in

women aged 65 years or older in relation to comorbidity, all conducted in the United States. Their findings suggested that these women may have longer life expectancy due to screening.¹⁵ Another recent study by Demb et al. (2020) examined the effects of continuous mammography on risk of incident breast cancer and mortality among 222,088 screened women ages 66-94 years in the United States, and found higher risk of other cause of death among women with comorbidity than among those without, but similar risk of incident breast cancer in women with different comorbidity levels. Their findings suggest that older women with increasing comorbidity may have diminished benefit from continuous screening.¹² Very few studies younger women with chronic conditions. There was a recent study by Beau et al. (2020) investigated the effect of chronic diseases on risk of breast cancer mortality among women aged 50-69 years in screened and non-screened regions in Denmark, and found marginal effect of mammography on breast cancer mortality in women with chronic diseases.¹⁸

Given that few studies examine the potential benefit of mammography screening among women aged 50-69 years with chronic conditions in Asian countries, we sought to use a population-based matched cohort study design to examine the potential benefit and moderation effect of mammography screening among women aged 50-69 years at various health statuses in Taiwan. Breast cancer screening policy in Taiwan is a key national cancer prevention policy. Since 2004, after passage of the National Cancer Prevention Law of 2003, Taiwan's Ministry of Health Promotion Administration initiated an organized breast cancer screening strategy covering free biannual mammography services for the entire population of women aged 50-69 years.¹⁹ The current study identified entire female population aged 50-69 years in 2010 and used an exact matching approach to match women at different chronic illness levels. A generic comorbidity measure was used to characterize total chronic illness burden. We then compared the effect of mammographic screening on early diagnosis of breast cancer and all-cause mortality among matched cohorts at various health statuses.

Methods

Study Design and Data Source

We used a matched cohort study design with at least 4-year follow-up using four nationwide population databases in Taiwan. The first was the National Health Insurance (NHI) administrative claims database, which includes more than 99% of Taiwan's 23 million enrollees.²⁰ The NHI database provides information including enrollment status, comorbid conditions, preventive care use, and primary health providers for chronic conditions. The second database was a national breast cancer screening registry, 2004-2014, which collected accurate mammography dates for participants. The third was a national cancer registry, from which accurate diagnoses of overall cancer and breast cancer could be derived, 1979-2014.^{21,22} The fourth was a national death registry, 2004-2014, which provides accurate death dates. We linked and analyzed these four population-based datasets with encrypted identifiers for the study population during 2020-2021 in the Health and Welfare Data Science Center of the Ministry of Health and Welfare, a government-operated national data warehouse.

Ethical aspects

The study followed the ethical standards of the Institutional Review Board of the Kaohsiung Medical University Hospital (IRB number: KMHIRB-E(I)-20190177) and the Helsinki Declaration of the World Medical Association. Consent to Participate: Given this research was retrospective study using secondary health administrative database, patients' informed consent was waived.

Study Population

We first identified all women aged 50-69 years in 2010 (n=2,564,252) eligible for free mammography screening in the national breast cancer screening program using the national NHI enrollment data. The study index date was defined as January 1, 2010, and the study end date as December 31, 2014. Each study cohort was followed from the index date to the first of study end date, or death. To avoid potential problems due to existing cancer disease or erroneous records, we excluded women with any record of cancer diagnosis (n=143,619) or death (n=487) before the index date. We then excluded women with any record of breast cancer screening services before the index date (n=510,808) to ensure that all study subjects were new to mammography. To reduce potential bias due to missing data when measuring an individual's health status, we further excluded women without medical records during follow-up (n=33,536). A total of 1,867,802 women aged 50-69 years were included in this study.

To identify levels of overall chronic illness severity in the study sample, we used the Deyo-Charlson Comorbidity Index (CCI), weighting comorbid conditions from the index date to the date of mammography, incident breast cancer, death, or study end date, whichever came first.^{23,24} This index is an ICD-9-CM coding adaption and has been widely used by health researchers to measure general disease severity and case mix in health administrative claims databases, with low scores representing lowest risk.^{23,24} The study sample was classified into four groups with CCI scores of 0, 1, 2, or 3+. As older age is concurrent with increased risk of chronic conditions and mortality, leading to

selection bias and incomparable samples, we used a 1-to-1 exact matching approach to match groups with different overall chronic illness severity levels based on index age in years and baseline income status (<new Taiwanese dollar [NTD] 20,000, dependent, NTD 20,000-40,000, and NTD 40,001+) to create four pairs of exactly balanced groups.²⁵ The sample sizes of each paired matched group with CCI scores of 0, 1, 2, or 3+ were 170,979. Figure 1 shows study inclusion and exclusion criteria.

Measurements and Variable Definitions

Outcome of Interest

We aimed to examine the effect of mammography on early breast cancer diagnosis and all-cause mortality among women with various comorbid conditions. The first diagnosis in the Taiwan cancer registry after the index date with ICD-9-CM diagnosis code 174 or ICD-10-CM code C50 was identified as incident breast cancer. Based on the Tumor–Nodes–Metastasis staging system of the American Joint Committee on Cancer version 7 in the National Cancer Registry, incident breast cancer stages were categorized as 0–IV and early stage (0–II) or advanced stage (III, IV). We also linked data with the National Death Registry and defined all-cause mortality as any death record after the index date. In addition, we included a set of binary variables for mammography participation, and mammography access through in-reach in a hospital or out-reach in a community.

Other Confounding Baseline Covariates

In addition to covariates such as the CCI and income status categories, we included two variables to identify health behavior characteristics (participation in any population-based pap smear cervical cancer screening program or adult physical examination program within the follow-up period). In Taiwan, the Health Promotion Administration, Ministry of Health and Welfare, provides government-initiated national population-based health promotion programs, including the two mentioned.²⁶ Women aged older than 30 years are eligible to participate in free annual pap smear screening under the national population-based cervical cancer screening program. Adults aged 40–65 years are eligible to participate in free physical examinations to receive routine blood tests and basic physical examination every 3 years, and those older than 65 years every year.²⁶ To address the issue of patients with multiple outpatient visits to different health care providers, we used a plurality provider algorithm to assign the most frequently visited hospitals or clinics based on administrative billing for the greatest numbers of care visits during follow-up.²⁷ Health care institution characteristics included accreditation level (medical center, regional hospital, local hospital, clinic), certification status for mammography screening (yes/no), and geographic location (Taipei, northern, central, southern, Kao-Ping, and eastern regions).

Statistical Analysis

Descriptive analyses using chi-square tests for categorical variables and t-tests for continuous variables. The Cochran–Armitage test for trend was used to test linear trends in frequencies of outcome measures among different chronic condition levels.²⁸ Individual-level conditional logistic regression models were used to compare outcome measures among exactly matched women with different chronic conditions. Conditional logistic regression was a proper method for matched data to address the sparse data problem and provide robust results.²⁹ Interaction terms for mammography and CCI were generalized to test the moderation effects of mammography on early breast cancer diagnosis and mortality.³⁰ If an effect exists, the moderating variable may change the direction or magnitude of the relationship between CCI and outcome measures and the interaction term will be statistically significant.³⁰ In addition, to contextualize the magnitude of the mammography moderation effect, we generated adjusted predicted probabilities (APPs) and marginal effects (MEs) of the probabilities.³¹ These are used to quantify the average and incremental level of chronic illness associated with outcome measures.^{31,32} Specifically, we generated APPs and MEs of each chronic illness severity level on early breast cancer diagnosis and mortality among women who did or did not undergo mammography. For each chronic illness level, we also generated MEs to compare the likelihood of severe chronic illness on outcome measures among women who did or did not undergo mammography. Data analysis was generated using SAS® software, version 9.4 of the SAS System for Windows. Copyright©2020. SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. A p value <0.05 was considered statistically significant.

Results

Table 1 summaries baseline demographic, health behavior, and health care institution characteristics among women aged 50–69 years at different chronic illness levels in 2010. Before matching, cohorts with higher CCIs were older. Mean age among women with CCI 0, 1, 2, 3+ in 2010 was 56.25, 57.87, 58.87, and 60.38 years, respectively. After exact matching based on index age and income status, demographic characteristics among women at different CCI levels were comparable.

Table1. Study cohort demographic and clinical characteristics and primary health care providers' organizational characteristics among study women with different levels of chronic illness

Variables	Pre-Matching Cohort				p-value ^b	Matched Cohort ^a				p-value ^b
	CCI=0	CCI=1	CCI=2	CCI =3+		CCI=0	CCI=1	CCI=2	CCI =3+	
N	1,053,018	424,072	184,014	206,698		170,979	170,979	170,979	170,979	
Women' demographic characteristics										
Age in years (Mean±STD) ^a	56.25 (±5.14)	57.87 (±5.53)	58.87 (±5.68)	60.38 (±5.70)	<0.001	59.36 (±5.56)	59.36 (±5.56)	59.36 (±5.56)	59.36 (±5.56)	1.000
Age categories (N, %)										
50-54	476,831 (45.28%)	142,370 (33.57%)	50,495 (27.44%)	40,133 (19.42%)	<0.001	40,133 (23.47%)	40,133 (23.47%)	40,133 (23.47%)	40,133 (23.47%)	1.000
55-59	310,812 (29.52%)	125,694 (29.64%)	52,010 (28.26%)	52,004 (25.16%)		49,522 (28.96%)	49,522 (28.96%)	49,522 (28.96%)	49,522 (28.96%)	
60-64	168,161 (15.97%)	89,201 (21.03%)	43,237 (23.50%)	53,414 (25.84%)		43,052 (25.18%)	43,052 (25.18%)	43,052 (25.18%)	43,052 (25.18%)	
65-69	97,214 (9.23%)	66,807 (15.75%)	38,272 (20.80%)	61,147 (29.58%)		38,272 (22.38%)	38,272 (22.38%)	38,272 (22.38%)	38,272 (22.38%)	
Income status (N, %) ^{a,c}										
<NTD 20,000	150,843 (14.32%)	58,005 (13.68%)	26,069 (14.17%)	31,646 (15.31%)	<0.001	25,205 (14.74%)	25,205 (14.74%)	25,205 (14.74%)	25,205 (14.74%)	1.000
Dependent	280,440 (26.63%)	132,443 (31.23%)	63,314 (34.41%)	82,820 (40.07%)		62,576 (36.60%)	62,576 (36.60%)	62,576 (36.60%)	62,576 (36.60%)	
NTD 20,000-40,000	468,303 (44.47%)	180,911 (42.66%)	74,892 (40.70%)	76,528 (37.02%)		67,897 (39.71%)	67,897 (39.71%)	67,897 (39.71%)	67,897 (39.71%)	
NTD 40,001+	153,432 (14.57%)	52,713 (12.43%)	19,739 (10.73%)	15,704 (7.60%)		15,301 (8.95%)	15,301 (8.95%)	15,301 (8.95%)	15,301 (8.95%)	
Women' health behavioral characteristics (N, %)										
Receiving population-based pap smear screening within follow up period (N, %)										
No	448,375 (42.58%)	177,792 (41.92%)	79,555 (43.23%)	108,514 (52.50%)	<0.001	78,619 (45.98%)	75,486 (44.15%)	75,122 (43.94%)	87,535 (51.20%)	<0.001
Yes	604,643 (57.42%)	246,280 (58.08%)	104,459 (56.77%)	98,184 (47.50%)		92,360 (54.02%)	95,493 (55.85%)	95,857 (56.06%)	83,444 (48.80%)	

Note: CCI=modified Charlson comorbidity index, NHI= National Health Insurance Administration, NTD=New Taiwanese Dollar.

^a Exact matching approach was used to 1-to-1 match groups of samples with different level of overall chronic illness severity based on their index age in years and baseline income status.

^b P-value for comparison of patients' and health care providers' characteristics between screened and non-screened women, chi-square tests were used for categorical variables and t-tests for continuous variables.

^c Income status was presented in New Taiwanese Dollar (NTD). The exchange rate between NTD and US Dollar is about 30:1 in this study.

Receiving population-based adult physical examinations within follow up period (N, %)										
No	503,333 (47.80%)	166,320 (39.22%)	69,744 (37.90%)	88,006 (42.58%)	<0.001	78,177 (45.72%)	66,243 (38.74%)	64,350 (37.64%)	73,608 (43.05%)	<0.001
Yes	549,685 (52.20%)	257,752 (60.78%)	114,270 (62.10%)	118,692 (57.42%)		92,802 (54.28%)	104,736 (61.26%)	106,629 (62.36%)	97,371 (56.95%)	
Primary Health Care Providers' Characteristics										
Accreditation level (N, %)										
Medical Center	105,313 (10.00%)	60,118 (14.18%)	30,565 (16.61%)	38,403 (18.58%)	<0.001	17,997 (10.53%)	24,519 (14.34%)	28,264 (16.53%)	31,687 (18.53%)	<0.001
Regional Hospital	134,006 (12.73%)	71,877 (16.95%)	35,982 (19.55%)	48,697 (23.56%)		22,169 (12.97%)	29,101 (17.02%)	33,523 (19.61%)	40,144 (23.48%)	
Local Hospital	95,131 (9.03%)	47,445 (11.19%)	22,546 (12.25%)	29,415 (14.23%)		15,974 (9.34%)	19,405 (11.35%)	21,014 (12.29%)	24,152 (14.13%)	
Clinics	718,568 (68.24%)	244,632 (57.69%)	94,921 (51.58%)	90,183 (43.63%)		114,839 (67.17%)	97,954 (57.29%)	88,178 (51.57%)	74,996 (43.86%)	
Mammography certification (N, %)										
No	780,993 (74.17%)	277,076 (65.34%)	110,768 (60.20%)	111,189 (53.79%)	<0.001	125,451 (73.37%)	111,359 (65.13%)	103,045 (60.27%)	92,184 (53.92%)	<0.001
Yes	272,025 (25.83%)	146,996 (34.66%)	73,246 (39.80%)	95,509 (46.21%)		45,528 (26.63%)	59,620 (34.87%)	67,934 (39.73%)	78,795 (46.08%)	
NHI branch (N, %)										
Taipei	371,797 (35.31%)	148,509 (35.02%)	62,989 (34.23%)	64,526 (31.22%)	<0.001	59,305 (34.69%)	59,623 (34.87%)	58,171 (34.02%)	53,419 (31.24%)	1.000
Northern	146,004 (13.87%)	58,190 (13.72%)	24,402 (13.26%)	27,358 (13.24%)		23,801 (13.92%)	23,336 (13.65%)	22,828 (13.35%)	22,401 (13.10%)	
Central	191,240 (18.16%)	74,823 (17.64%)	32,048 (17.42%)	38,248 (18.50%)		30,933 (18.09%)	30,583 (17.89%)	29,905 (17.49%)	31,599 (18.48%)	
Southern	138,465 (13.15%)	60,606 (14.29%)	28,523 (15.50%)	32,241 (15.60%)		22,928 (13.41%)	24,322 (14.23%)	26,469 (15.48%)	26,695 (15.61%)	
Kao-Ping	184,951 (17.56%)	71,427 (16.84%)	30,499 (16.57%)	37,690 (18.23%)		30,641 (17.92%)	28,985 (16.95%)	28,454 (16.64%)	31,432 (18.38%)	
Eastern	20,561 (1.95%)	10,517 (2.48%)	5,553 (3.02%)	6,635 (3.21%)		3,371 (1.97%)	4,130 (2.42%)	5,152 (3.01%)	5,433 (3.18%)	

Note: CCI=modified Charlson comorbidity index, NHI= National Health Insurance Administration, NTD=New Taiwanese Dollar.

^a Exact matching approach was used to 1-to-1 match groups of samples with different level of overall chronic illness severity based on their index age in years and baseline income status.

^b P-value for comparison of patients' and health care providers' characteristics between screened and non-screened women, chi-square tests were used for categorical variables and t-tests for continuous variables.

^c Income status was presented in New Taiwanese Dollar (NTD). The exchange rate between NTD and US Dollar is about 30:1 in this study.

Table 2 compares mammography participation, newly diagnosed breast cancer stages, and all-cause mortality among women at different levels of chronic illness severity. The Cochran–Armitage test for trend was used to compare frequencies of outcome measures across chronic illness levels. Mammography rates and repeat participation rates decreased as chronic illness levels increased ($p < 0.001$). Approximately 0.92–1.25% of matched cohorts at each CCI level were newly diagnosed with breast cancer. The proportion of early breast cancer diagnosis decreased as the chronic illness level increased ($p < 0.001$), while the all-cause mortality rate increased ($p < 0.001$).

Table 2
Associations between different levels of chronic illness and outcomes of interest among matched cohorts

Matched Cohort					
Variables	CCI=0	CCI=1	CCI=2	CCI=3+	p-value ^a
N	170,979	170,979	170,979	170,979	
Mammography Utilization					
Mammography participation during follow-up period (N, %)					
No	90,925 (53.18%)	99,169 (58.00%)	107,156 (62.67%)	125,604 (73.46%)	<0.001
Yes	80,054 (46.82%)	71,810 (42.00%)	63,823 (37.33%)	45,375 (26.54%)	
Repeated Mammography during follow-up period (N, %)					
No repeated mammography	138,191 (80.82%)	145,830 (85.29%)	151,285 (88.48%)	159,979 (93.57%)	<0.001
Repeated mammography (at least twice during the observation period)	32,788 (19.18%)	25,149 (14.71%)	19,694 (11.52%)	11,000 (6.43%)	
Repeated Mammography during follow-up period among those received mammography (N, %)					
No repeated mammography	47,266 (59.04%)	46,661 (64.98%)	44,129 (69.14%)	34,375 (75.76%)	<0.001
Repeated mammography (at least twice during the observation period)	32,788 (40.96%)	25,149 (35.02%)	19,694 (30.86%)	11,000 (24.24%)	
Assess of mammography services among those received mammography (N, %)					
Inreach (through in-hospital examination)	43,739 (54.64%)	41,720 (58.10%)	38,861 (60.89%)	28,355 (62.49%)	<0.001
Outreach (through mammography car)	36,315 (45.36%)	30,090 (41.90%)	24,962 (39.11%)	17,020 (37.51%)	
Breast Cancer Diagnoses					
Newly diagnosed as breast cancer (N, %)					
No	168,834 (98.75%)	169,301 (99.02%)	169,211 (98.97%)	169,404 (99.08%)	<0.001
Yes	2,145 (1.25%)	1,678 (0.98%)	1,768 (1.03%)	1,575 (0.92%)	
Breast cancer stage (N, %) ^c					
Stage 0	284 (13.24%)	267 (15.91%)	235 (13.29%)	152 (9.65%)	<0.001
Stage I	650 (30.30%)	562 (33.49%)	511 (28.90%)	394 (25.02%)	
Stage II	688 (32.07%)	514 (30.63%)	569 (32.18%)	432 (27.43%)	

Note: CCI=modified Charlson comorbidity index.

^a P-value was generated by using Cochran-Armitage tests for trend.

^b Misclassification were those TNM classifications in the national cancer registry, which were not missing, but with codes like "999/99" (unclear or physicians did not code), "888/88" (non-applicable), "BBB/BB/B" or "X" (TX, NX, MX, occult carcinoma, found cancer cell but may not a specific tumor).

^c Only those with newly diagnosed as breast cancer were analyzed.

Matched Cohort					
Stage III	284 (13.24%)	188 (11.20%)	251 (14.20%)	227 (14.41%)	
Stage IV	136 (6.34%)	80 (4.77%)	110 (6.22%)	278 (17.65%)	
Missing values/ or misclassification ^b	103 (4.80%)	67 (3.99%)	92 (5.20%)	92 (5.84%)	
Breast cancer early/late stage (exclude missing) during follow-up period (N, %) ^c					
Early Stage (0,1,2)	1,622 (79.43%)	1,343 (83.36%)	1,315 (78.46%)	978 (65.95%)	<0.001
Late Stage (3,4)	420 (20.57%)	268 (16.64%)	361 (21.54%)	505 (34.05%)	
All-cause mortality (N, %)					
No	168,979 (98.83%)	168,028 (98.27%)	165,805 (96.97%)	155,997 (91.24%)	<0.001
Yes	2,000 (1.17%)	2,951 (1.73%)	5,174 (3.03%)	14,982 (8.76%)	
Note: CCI=modified Charlson comorbidity index.					
^a P-value was generated by using Cochran-Armitage tests for trend.					
^b Misclassification were those TNM classifications in the national cancer registry, which were not missing, but with codes like “999/99” (unclear or physicians did not code), “888/88” (non-applicable), “BBB/BB/B” or “X” (TX, NX, MX, occult carcinoma, found cancer cell but may not a specific tumor).					
^c Only those with newly diagnosed as breast cancer were analyzed.					

Table 3 provides results from five conditional logistic regression models, which examined the effects of chronic illness on mammography participation (Model 1); and early diagnosis of breast cancer (Model 2); the interaction of CCI and mammography on early diagnosis of breast cancer (Model 3); all-cause mortality (Model 4); and the interaction effect on all-cause mortality (Model 5). Compared with CCI score 0, women with more severe chronic conditions were less likely to participate in mammography screening, less likely to be diagnosed at an early stage of breast cancer, and at higher risk of all-cause mortality. Mammography participation increased the likelihood of early breast cancer diagnosis (OR=1.48, 95%CI=1.36-1.60) and decreased risk of all-cause mortality (OR=0.63, 95%CI=0.60-0.66). The interaction terms of CCI and mammography participation indicated statistically significantly increased benefits of early breast cancer diagnosis and decreased risk of all-cause mortality as chronic illness increased.

Table 3

Conditional logistic regression model results for the effect of mammography uptake on early diagnosis of breast cancer and mortality prevention among women with different levels of chronic illness

Covariates/ Models	Model 1: Mammography participation		Model 2: Early diagnosis of breast cancer		Model 3: Early detection of breast cancer (Interaction)		Model 4: All-cause mortality		Model 5: All-cause mortality (Interaction)	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Mammography participation (ref.= No)										
Yes			1.48 (1.36, 1.60)	<.0001	1.03 (0.90,1.18)	0.672	0.63 (0.60, 0.66)	<.0001	0.95 (0.86, 1.06)	0.353
Women' chronic illness characteristics										
CCI categories (Ref.: CCI=0)										
1	0.66 (0.65, 0.67)	<0.001	0.80 (0.74, 0.87)	<0.001	0.61 (0.53, 0.69)	<0.001	1.44 (1.35, 1.53)	<0.001	1.57 (1.46, 1.69)	<0.001
2	0.48 (0.47, 0.49)	<0.001	0.79 (0.73, 0.85)	<0.001	0.66 (0.58, 0.75)	<0.001	2.40 (2.27, 2.53)	<0.001	2.72 (2.54, 2.91)	<0.001
3+	0.29 (0.29, 0.30)	<0.001	0.60 (0.55, 0.65)	<0.001	0.41 (0.36, 0.47)	<0.001	6.38 (6.07, 6.72)	<0.001	7.71 (7.24, 8.22)	<0.001
Interaction of mammography participation and levels of chronic illness burden										
CCI: 1 * mammography participation					1.62 (1.34, 1.96)	<.0001			0.78 (0.68, 0.89)	0.0002
CCI: 2 * mammography participation					1.35 (1.12, 1.62)	0.002			0.68 (0.60, 0.77)	<0.001
CCI: 3+ * mammography participation					2.08 (1.70, 2.54)	<0.001			0.47 (0.41, 0.53)	<0.001
Women' health behavioral characteristics										
Receiving population-based pap smear screening within follow up period (Ref.: No)										
Yes	11.05 (10.87, 11.25)	<0.001	2.22 (2.04, 2.41)	<0.001	2.24 (2.06, 2.44)	<0.001	0.62 (0.59, 0.64)	<0.001	0.61 (0.59, 0.64)	<0.001
Receiving population-based adult physical examinations within follow up period (Ref.: No)										

Note: Ref.=Reference group; OR=odds ratio; CI=confidence interval. NHI= National Health Insurance Administration; CCI=modified Charlson comorbidity index.

Covariates/ Models	Model 1: Mammography participation		Model 2: Early diagnosis of breast cancer		Model 3: Early detection of breast cancer (Interaction)		Model 4: All-cause mortality		Model 5: All-cause mortality (Interaction)	
Yes	1.80 (1.78, 1.83)	<0.001	0.88 (0.82, 0.95)	0.001	0.89 (0.83, 0.96)	0.003	0.47 (0.45, 0.49)	<0.001	0.46 (0.44, 0.48)	<0.001
Primary health care providers' characteristics										
Accreditation level (Ref.: Medical Center)										
Regional Hospital	1.10 (1.08, 1.13)	<0.001	0.72 (0.66, 0.80)	<0.001	0.72 (0.65, 0.79)	<0.001	0.83 (0.78, 0.87)	<0.001	0.83 (0.78, 0.88)	<0.001
Local Hospital	1.04 (1.01, 1.08)	0.011	0.40 (0.35, 0.47)	<0.001	0.40 (0.35, 0.46)	<0.001	0.63 (0.59, 0.68)	<0.001	0.63 (0.59, 0.68)	<0.001
Clinics	0.86 (0.83, 0.89)	<0.001	0.32 (0.27, 0.38)	<0.001	0.32 (0.27, 0.38)	<0.001	0.38 (0.35, 0.42)	<0.001	0.39 (0.36, 0.42)	<0.001
Mammography certification (Ref.: No)										
Yes	1.59 (1.54, 1.64)	<0.001	1.44 (1.25, 1.66)	<0.001	1.44 (1.25, 1.66)	<0.001	0.95 (0.88, 1.01)	0.1066	0.94 (0.88, 1.01)	0.096
NHI branch (Ref.: Taipei)										
Northern	1.12 (1.09, 1.15)	<0.001	0.89 (0.79, 0.99)	0.040	0.89 (0.79, 1.00)	0.043	1.44 (1.36, 1.53)	<0.001	1.44 (1.36, 1.53)	<0.001
Central	0.99 (0.97, 1.02)	0.613	0.94 (0.85, 1.04)	0.214	0.94 (0.85, 1.04)	0.243	1.50 (1.42, 1.58)	<0.001	1.49 (1.42, 1.58)	<0.001
Southern	1.17 (1.14, 1.20)	<0.001	0.97 (0.87, 1.09)	0.609	0.97 (0.87, 1.09)	0.595	1.59 (1.50, 1.68)	<0.001	1.59 (1.50, 1.69)	<0.001
Kao-Ping	1.09 (1.07, 1.11)	<0.001	0.98 (0.88, 1.08)	0.678	0.98 (0.88, 1.08)	0.676	1.63 (1.54, 1.71)	<0.001	1.62 (1.54, 1.71)	<0.001
Eastern	1.17 (1.12, 1.22)	<0.001	0.88 (0.70, 1.10)	0.250	0.88 (0.70, 1.10)	0.267	1.97 (1.77, 2.19)	<0.001	1.98 (1.77, 2.20)	<0.001
Note: Ref.=Reference group; OR=odds ratio; CI=confidence interval. NHI= National Health Insurance Administration; CCI=modified Charlson comorbidity index.										

Table 4 shows results of mean APPs for the probability of early breast cancer diagnosis and all-cause mortality among different chronic illness levels, and MEs of predicted probability between women who did and did not undergo mammography. The APPs of early diagnosis decreased for CCI scores 0, 1, 2, 3+ among both women with and without participating in mammography screening. Positive MEs of early breast cancer diagnosis between women who did and did not participate indicated the magnitude of benefit of mammography across chronic illness levels. The APPs of all-cause mortality increased for CCI scores 0, 1, 2, 3+ among women with and without participating in mammography screening. The MEs of all-cause mortality between women who did and did not participate at each chronic severity level indicated that mammography reduced the risk of mortality as chronic illness severity levels increased.

Table 4

Results of adjusted predicted probabilities and marginal effects of the levels of chronic illness and probabilities of outcome of interests among matched cohorts with and without mammography participation

Outcomes	Mammography Participation (Yes)	Mammography Participation (No)	ME of chronic illness among women with mammography (Yes)	ME of chronic illness among women without mammography (No)	ME of mammography by different levels of chronic illness (Ref.: with mammography participation versus without)
	APP (% , 95%CI)	APP (% , 95%CI)			
Early diagnosis of breast cancer					
CCI					
0	1.23 (1.17, 1.30)	0.88 (0.82, 0.93)	Ref.	Ref.	0.35 (0.29, 0.42)
1	0.92 (0.87, 0.98)	0.65 (0.61, 0.70)	-0.31 (-0.39, -0.23)	-0.22 (-0.28, -0.17)	0.27 (0.21, 0.32)
2	0.86 (0.80, 0.91)	0.61 (0.57, 0.65)	-0.37 (-0.45, -0.30)	-0.27 (-0.32, -0.21)	0.25 (0.20, 0.30)
3+	0.65 (0.60, 0.70)	0.46 (0.43, 0.49)	-0.58 (-0.65, -0.51)	-0.41 (-0.47, -0.36)	0.19 (0.15, 0.23)
All-cause mortality					
CCI					
0	0.81 (0.77, 0.85)	1.52 (1.45, 1.59)	Ref.	Ref.	-0.71 (-0.76, -0.66)
1	1.16 (1.10, 1.21)	2.17 (2.09, 2.24)	0.35 (0.29, 0.41)	0.65 (0.55, 0.75)	-1.01 (-1.07, -0.94)
2	1.93 (1.85, 2.01)	3.57 (3.48, 3.67)	1.12 (1.05, 1.19)	2.06 (1.94, 2.17)	-1.64 (-1.74, -1.55)
3+	4.77 (4.61, 4.94)	8.55 (8.41, 8.70)	3.97 (3.82, 4.12)	7.04 (6.88, 7.19)	-3.78 (-3.98, -3.58)
Note: CCI=modified Charlson comorbidity index; Ref.=reference group; ME= marginal effects; APP=adjusted predicted probabilities					

Discussion

This study examined potential benefits and moderation effects of mammography screening on early breast cancer diagnosis and mortality among women aged 50-69 years at various health statuses. A generic CCI measure was used to identify women at different levels of overall chronic illness burden. Consistent with previous literature, our findings indicate that women at higher chronic illness levels were less likely to participate in mammography screening and to have breast cancer newly diagnosed at early stages, and were at greater risk of all-cause mortality.^{4,7-9} Our findings further provide empirical evidence that mammography may moderate the association between chronic illness burden and early breast cancer diagnosis and mortality.

Comorbidity may present barriers to breast cancer screening and complicate diagnostic decision-making.^{7,10} Similar to findings from a systematic review and meta-analysis study based on few high-quality studies in Europe or in the United States by Diaz et al. (2017) and a recently study conducted in Taiwan by Hsieh (2021),^{10,11} our study findings indicate that women aged 50-69 years at higher chronic illness levels were less likely to participate in mammography screening in Taiwan. As Fleming et al. (2005) indicated, comorbidity as a predictor of newly diagnosed breast cancer stage may relate to several hypotheses: the interaction between comorbid conditions and cancers at the cellular level may increase risks of metastasis, or comorbid conditions may constitute a competing demand against use of preventive services. Additionally, as observed in clinical settings, physicians are more likely to request mammography for women at higher general risk

of breast cancer (e.g., family history), but less likely to request it for average-risk women with chronic illnesses.⁷ These all may exacerbate the odds of late-stage breast cancer diagnosis and prognosis among women with chronic illness.

Existing studies suggest that mammography screening and reducing barriers to health system access may decrease the risks of late-stage diagnosis and mortality among women with chronic illness. Most of these existing studies focus on older women and were conducted in Europe and the United States.^{7,12,15,18,33} To the best of our knowledge, no studies specifically examined potential benefits of mammography screening for stage at diagnosis or mortality among younger women at different health statuses in Asian countries. In general, our findings confirm the benefit of mammography screening, which increased the likelihood of early stage breast cancer diagnosis by 48% and decreased odds of all-cause mortality by 37%. Mammography screening significantly moderated the link between chronic illness burden and late-stage diagnosis and risk of all-cause mortality.

Our study has several strengths. It used four longitudinal nationwide population-based datasets linking NHI administrative claims, national cancer registry, death registry, and breast cancer screening registry in Taiwan. These included all women aged 50-69 years in 2010, or approximately 2.5 million population, and provided accurate screening attendance information for identifying screened and non-screened groups. In addition, the study database allowed us to generate a generic composite measure of total chronic illness burden from NHI administrative data, reducing potential recall bias from self-reported health status,¹⁰ or missing information due to using data from regional hospital-based electronic medical records.¹⁸ In addition, Czwikla et al. (2018) addressed methodology concern of selection bias issue as the results of mammography screening participants and nonparticipants are not comparable regarding various health statuses.³³ To avoid potential selection bias as Czwikla et al. (2018) point out, we used an exact matching approach to generate balanced groups with different burdens of chronic conditions based on birth years and income status and compared outcomes of interest at the same chronic condition levels between screened and non-screened groups.

Nevertheless, this study also has several limitations. First, to compare results with existing studies,^{12,18} we used the CCI to measure overall burden of chronic conditions. Future studies may use other types of comorbidity measures to investigate benefits of mammography among women at different health statuses. Second, some unobservable confounders are unavailable when investigating research questions using secondary administrative data, such as lifestyle factors and habits or breast cancer awareness. Finally, the data were from women aged 50-69 years in Taiwan. Results may not generalize to other health systems in other countries.

In conclusion, analyzing national population-based data in Taiwan, this study provides empirical evidence with respect to the moderation effect of mammography screening, which increased likelihood of early stage breast cancer diagnosis and decreased odds of all-cause mortality. Public health policy and strategies may be necessary to improve mammography participation and early detection efforts for women with comorbid conditions.

Declarations

Funding Source: This study was supported by the Ministry of Science and Technology grant (MOST105-2314-B-037-063, MOST106-2314-B-037-036, MOST 108-2410-H-037-007, MOST 109-2423-H-037-001-SS3). This study is supported partially by the Kaohsiung Medical University Research Foundation (KMU-M108007), the Kaohsiung Medical University Research Center Grant (KMU-KMU-TC109B08), the Research Center for Environmental Medicine from the Featured Area Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan, and Kaohsiung Medical University Research Center Grant (KMU-TC109A01-1). I am also grateful to Kaohsiung Medical University for providing administrative and funding support. The author thanks the help from the Division of Medical Statistics and Bioinformatics, Department of Medical Research, Kaohsiung Medical University Hospital, and Center for Big Data Research (KMU-KMU-TC109B08), Kaohsiung Medical University for providing administrative support. None of which had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest/Ethical approval: We assure that each author meets authorship requirements. We declare that none of the authors has a conflict of interest with regard to this manuscript.

Financial Disclosure: The authors declare that they have no conflict of interest.

(For Original Research Only) Specific contributions:

Conception or design of the work, the acquisition, analysis: HMH

Interpretation of data for the work: HMH, CTS, FMC

Revising it critically: HMH, CTS, FMC

Final approval: HMH, CTS, FMC

Availability of Data and Materials: Not applicable

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Figures

Figure 1

Inclusion and exclusion criteria in this study