

동반질환 중증도가 유방암 환자의 사망 위험에 미치는 요인

서화정

가천대학교 사회과학대학 의료경영학과

Factors of Specific Comorbidities Severity on the Risk of Mortality among Breast Cancer Survivors

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Background: For cancer patients, comorbidities affect the risk, progression, and process of treatment. They negatively affect prognoses by increasing mortality. It is therefore necessary to predict prognoses accurately for cancer survivors by measuring comorbidities and their severity.

Methods: In this study, the frequency of comorbidities was analyzed on the basis of the Charlson comorbidity index (CCI) in breast cancer patients drawn from the National Health Insurance Service-National Sample Cohort data. This study examined the relative effects of certain factors (age, diagnosis period, and CCI) between deaths and cancer survivors with logistic regression analysis. We applied Cox's proportional hazard regression analysis to predict the risk of mortality according to CCI as a survival predictor of breast cancer patients using three models with correction for age, including the body mass index (BMI), smoking status, alcohol intake, and childbirth history.

Results: The frequency analysis based on CCI found that the most frequent type of condition was pulmonary disease (2,262; 21.5%), followed by peptic ulcer (2,019; 19.2%), and metastatic cancer (1,821; 17.3%). The older one gets, the greater one's risk of mortality with more severe comorbidities. Age and BMI led to greater risk of mortality, with correction for the variables (age, BMI, smoking status, alcohol intake and childbirth history) that could cause confounding.

Conclusions: Severity of comorbidities significantly increased the risk of mortality for breast cancer patients. In particular, those cancer survivors who are aged ≥ 60 years, who have high BMI, and who once smoked need to get continuous care due to poor prognoses.

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INTRODUCTION

On the basis of the most recent data from the National Cancer Registration and Statistics System, one out of three persons is expected to have cancer during their lifetime of 82 years on average. Two hundred fourteen thousand and seven hundred one persons were diagnosed with cancer for 2015 alone and 59.5% up for a decade from 134,591 in 2004.

In addition to cancer incidence, the cancer survival rate has been on a constant increase. For the past 5 years (2006-2010), the 5-year relative cancer survival rate was 64.1%; that is, at least six out of 10 cancer patients survived at least 5 years after their first diagnosis with cancer.¹⁾

In South Korea, the 5-year relative breast cancer survival rate was 92.3% as of 2011-2015, and the rate has been on a constant rise. The perfect cure for cancer is being realized for more and more patients. For this reason, a tumor, which had been categorized as a fatal component, is being conceptualized as a chronic disease.²⁾ It is therefore essential to make an intervention for cancer survivors who have completed treatment.

Although the cancer survival rate is over 60% and long-term cancer survivors may die of diseases other than cancer, no systematic healthcare service model has been built for cancer survivors. For this reason, it is necessary to determine the healthcare outcomes for cancer patients at the early stage and accumulate relevant knowledge.

A number of countries, including South Korea, statistical data are produced regarding cancer incidence and mortality in certain populations.³⁾ While there has been research on relations among such factors as socioeconomic position, income class, mortality, and risk of mortality, there has been little research on risks of mortality depending on cancer patients' comorbidity.^{4,5)} After cancer diagnosis, cancer-related health risk factors, hypertension due to sequelae from cancer, diabetes, heart disease, and other comorbid diseases appear to be higher than those of the general population.⁶⁾ Nonetheless, relatively little care is given to other diseases than cancer, and thus some patients died not out of cancer but out of comorbidity.⁷⁾

Comorbidities are known to affect risk, detection, progression, and treatment of cancer.⁸⁾ In particular, elderly cancer patients (aged ≥ 70) have an average of ≥ 3 comorbidities,⁹⁾ which can reportedly have negative effects on prognoses, for example, by increasing the mortality rate.¹⁰⁾ The variation in the fatality rate among cancer types also affects the causes of mortality for cancer; reportedly, 24.0% of those cancer patients who had survived for 5 years after the diagnosis with cancer died of conditions other than cancer.¹¹⁾ Diabetes, metabolic syndrome, and obesity reportedly affect the prognoses for cancer patients.¹²⁾ These symptoms are also closely associated with the presence of comorbidities.

This study aimed to use data from a large cohort to meas-

ure the prognoses for cancer survivors more accurately on the basis of principal comorbidities and their severity (a weighted score was assigned to each comorbidities) during their survival. It intended to improve the prognoses for cancer survivors by measuring comorbidities and their severity accurately.

METHODS

1. Study design

The National Health Insurance Service-National Sample Cohort (NHIS-NSC) is a population-based retrospective cohort based on 9 years from 2002 to 2010 in a sample of approximately 1 million people or 2.2% of the whole nation in South Korea.¹³⁾

After entering the cohort, the comorbidity measuring period was defined as 1 year prior to breast cancer occurrence. Since subjects with comorbidity before the breast cancer diagnosis were included, the effect of death risk factors as of the reference year examined. The study model was designed as shown in Figure 1.

2. Criteria and definitions

1) Breast cancer patients

The variables of main symptom in the treatment data were used to identify those diagnosed with breast cancer. The data with C50 for main symptom were drawn. Those diagnosed with breast cancer are manipulatively defined as those with ≥ 3 C50 codes for main symptom and sub symptom.¹⁴⁾

2) Specific comorbidity and Charlson comorbidity index (CCI)

Comorbidities are some of the components that determine individuals' health status and need to be differentiated from complications. In other words, comorbidities refer to those

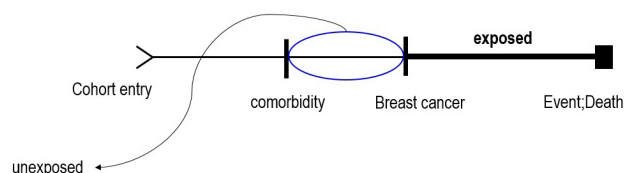


Figure 1. Study design associated follow-up from cohort entry to event occurrence.

conditions not causally related to the main condition, whereas complications refer to those conditions occurring in causal relation to the main condition.¹⁵⁾ It was determined that comorbidities other than the primary cancer occurred among patients; that is, information about disease classi-

fication codes in addition to that of C50 was identified.

Feinstein¹⁶⁾ defined comorbidities as conditions that additionally coexisted or occurred separately in addition to the main diagnosis or disease for patients. To actually measure comorbidities, it is necessary to apply implicit or explicit weight to each condition, giving consideration to the importance of each condition in all of the comorbidities.

Charlson et al.¹⁷⁾ defined numerous clinical conditions through reviewing hospital charts and assessed their relevance in the prediction of 1-year mortality. A weighted score was assigned to each of 17 comorbidities, based on the relative risk of 1-year mortality.¹⁸⁾ These studies consistently demonstrate that the Charlson index is a valid prognostic indicator.

3) Operation definition of variables used

In this study, the socio-demographic variables, survivorship-related variables and indicator-specific variables were analyzed. As for the socio-demographic variables, age at diagnosis were categorized into 10-year-olds (<40, 40-49, 50-59, 60-69, and ≥70). Childbirth history used (never, ever). Smoking status used the 'smoking status' variable and alcohol intake used the 'drinking habit' variable in the health check-up database of NHIS-NSC (never, ever).

Table 1. Characteristics of the study population

Variable	Value
Socio-demographic	
Age at diagnosis, y	
<40	656 (24.3)
40-49	1,062 (39.4)
50-59	579 (21.5)
60-69	296 (11.0)
≥70	103 (3.8)
Health history	
Childbirth history	
Never	2,583 (95.8)
Ever	113 (4.2)
Smoking status	
Never	1,587 (58.9)
Ever	69 (2.6)
Missing	1,040 (38.6)
Alcohol intake	
Never	1,199 (44.5)
Ever	386 (14.3)
Missing	1,111 (41.2)
Survivorship	
Survivor status	
Deaths	286 (10.6)
Survivors	2,410 (89.4)
Survival duration	
<1 year	503 (18.7)
1 to <3 years	712 (26.4)
3 to <5 years	600 (22.3)
≥5 years	881 (32.7)
Indicator	
Charlson comorbidity index	
0	768 (28.5)
1-2	135 (5.0)
≥3	1,793 (66.5)
Body mass index	
<23	1,185 (44.0)
≥23	498 (18.5)
Missing	1,013 (37.6)

Values are presented as number (%).

Table 2. Charlson comorbidity index scoring and prevalence of comorbid conditions

Comorbidity clinical condition	Weights	Value
Acute myocardial infarction	1	138 (1.31)
Congestive heart failure	1	68 (0.65)
Peripheral vascular disease	1	122 (1.16)
Cerebral vascular accident	1	379 (3.60)
Dementia	1	38 (0.36)
Pulmonary disease	1	2,262 (21.51)
Connective tissue disorder	1	452 (4.30)
Peptic ulcer	1	2,019 (19.20)
Liver disease	1	195 (1.85)
Diabetes	1	824 (7.84)
Diabetes complications	2	824 (7.84)
Paraplegia	2	32 (0.30)
Renal disease	2	65 (0.62)
Any cancer	2	632 (6.01)
Metastatic cancer	3	1,821 (17.32)
Severe liver disease	3	644 (6.12)
Human immunodeficiency virus	6	1 (0.01)

Values are presented as number (%).

Table 3. Risk of mortality according to age, survival duration and CCI score of survivors

	Survivorship		OR (95% CI) ^a	<i>P</i>
	Deaths	Survivors		
Age at diagnosis, y				
<40	49 (17.1)	607 (25.2)	1 (reference)	
40-49	76 (26.6)	986 (40.9)	0.95 (0.65-1.39)	0.791
50-59	64 (22.4)	515 (21.4)	1.50 (1.01-2.24)	0.046
60-69	58 (20.3)	238 (9.9)	2.81 (1.85-4.29)	<0.001
≥70	39 (13.6)	64 (2.7)	7.78 (4.62-13.10)	<0.001
Time after cancer diagnosis				
<1	47 (16.4)	456 (18.9)	1 (reference)	
1 to <3	111 (38.8)	601 (24.9)	1.45 (0.99-2.12)	0.057
3 to <5	73 (25.5)	527 (21.9)	1.11 (0.74-1.66)	0.617
≥5	55 (19.2)	826 (34.3)	0.46 (0.30-0.71)	<0.001
Charlson comorbidity index				
0	90 (31.5)	678 (28.1)	1 (reference)	
1-2	10 (3.5)	125 (5.2)	2.29 (1.09-4.79)	0.028
≥3	192 (67.1)	1,601 (66.4)	5.10 (3.31-7.86)	<0.001

Values are presented as number (%) unless otherwise indicated.

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; OR, odds ratio.

^aLogistic regression.

As for the survivorship-related variables, survivor status divided to survivors and deaths based on the variable of 'date of death' in the table of births and deaths during the follow-up period of cohort observation (9 years). Diagnosis periods (survival duration) were classified less than 1 year, 1 to 3 years, 3 to 5 years, and 5 or more years from the initial diagnosis during the follow-up period of cohort observation.

The indicator-specific variables were body mass index (BMI; <23 kg/m² and ≥23 kg/m²), and CCI (0, 1-2, and ≥3). The BMI was calculated based on the BMI data (body weight [kg]/(height×height [m])); rounding to the two decimal places) from the health examination database.

3. Statistical analysis

Descriptive statistics were used to report age, survivorship as like survival status and duration, indicator as like CCI, and checkup data as like BMI, smoking status and child birth. We have identified the incidence of specific comorbidities in cancer survivors. Logistic regression analysis was performed to measure the relative effects of age, diagnosis period, and CCI between deaths and cancer survivors. We applied Cox's proportional hazard regression analysis to

predict the risk of mortality according to CCI as a survival predictor of breast cancer patients. We used three models to account the factors that could cause confounding in the baseline. Model 1 was adjusted for age (<40, 40-49, 50-59, 60-69, and ≥70). Model 2 was further adjusted for BMI (continuous). Model 3 was further adjusted for smoking status (never or ever), alcohol intake (never or ever) and child birth (never or ever). All analyses were conducted using R statistical software (R Foundation, Vienna, Austria).

RESULTS

1. Participant characteristics

Descriptive data on breast cancer patients are summarized in Table 1. The majority of participants were in the age group 40-49 years (39.4%), 113 (4.2%) had childbirth history, 69 (2.6%) had smoking status, 386 (14.3%) had alcohol intake. Eleven percent was identified as deaths (286 persons) and 89% were cancer survivors (2,410 persons): of these, 503 (18.7%) survived for <1 year, 712 (26.4%) for 1 to <3 years, 600 (22.3%) for 3 to <5 years, and 881 (32.7%) for ≥5 years. CCI was estimated to have an average of 5.71

Table 4. Hazard ratio estimates of death from Cox's proportional hazards model for CCI

Parameter	Case	Model 1		Model 2		Model 3	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
CCI							
0	768 (28.49)	1 (reference)		1 (reference)		1 (reference)	
≥1	1,928 (71.51)	2.73 (1.81-4.13)	>0.001	4.27 (1.72-10.60)	0.002	4.02 (1.61-10.01)	0.003

Model 1: adjusted for age (<40, 40-49, 50-59, 60-69, and ≥70); model 2: further adjusted for body mass index (continuous); model 3: further adjusted for smoking status (never or ever), alcohol intake (never or ever), and childbirth (never or ever).

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio.

(ranging from 0 to 29). BMI was estimated at 23.65 on average; 1,683 patients (62.4%) had the results identified and 1,013 (37.6%) had missing data (Table 1).

2. Prevalence of comorbid

The frequency analysis based on CCI found that the most frequent type of condition was pulmonary disease (2,262; 21.5%), followed by peptic ulcer (2,019; 19.2%), metastatic cancer (1,821; 17.3%), and diabetes (824; 7.8%) (Table 2).

3. Factors influencing on survivorship

1) Odds ratio death based on CCI

Logistic regression analysis was performed to measure the relative impact of the variables that predicted morbidity for breast cancer patients. The impact of age, survival duration, and the scores for CCI on mortality for breast cancer patients was analyzed.

Compared with those aged <40 (reference), the odds ratio was 1.50 times higher for those aged 50-59 ($P<0.05$), 2.81 times higher for those aged 60-69 ($P<0.001$) and 7.78 times higher for those aged ≥70 ($P<0.001$). As for survival duration, the patients surviving ≥5 years had a 0.46 time higher odds ratio ($P<0.001$) compared with those surviving <1 year. Compared with a CCI of 0 (reference), a CCI of 1-2 had a 2.29 times stronger impact on mortality ($P<0.05$) and that of ≥3 had a 5.10 times stronger impact on mortality ($P<0.001$) (Table 3).

2) Factors associated with death in breast survivors

The age-adjusted hazard ratio (HR) (model 1) for diabetes associated with the development of cancer was 2.73 (95% confidence interval [CI], 1.81-4.13). The age and BMI-adjusted HR (model 2) was 4.27 (95% CI, 1.72-10.60). The

fully adjusted HR (model 3) was 4.02 (95% CI, 1.61-10.01) (Table 4).

DISCUSSION

In this study, the risk of mortality for cancer survivors was analyzed on the basis of CCI among breast cancer patients as drawn from NHIS-NSC data. In the research using the data regarding health insurance claims, correction for patients' health status and severity of the condition is important.¹⁹⁾ The analysis obtained the following results: first, the frequency analysis based on CCI found that the most frequent type of condition was pulmonary disease (2,262; 21.5%), followed by peptic ulcer (2,019; 19.2%), metastatic cancer (1,821; 17.3%), and diabetes (824; 7.8%). Yancik et al.²⁰⁾ reported that principal comorbidities of breast cancer included hypertension and arthritis. They also reported that renal disease increased the risk of mortality. Thomsen found that the highest hazard ratio was identified for pulmonary circulation (1.51), followed by heart failure (1.29).²¹⁾ In the Shanghai breast cancer survivor cohort, the main comorbidities were reported as follows: hypertension (22.4%), chronic gastritis (14.3%), diabetes mellitus (6.2%), chronic bronchitis/asthma (5.8%), coronary heart disease (5.0%), and stroke (2.2). Diabetes and rheumatoid arthritis were associated with increased risk of total mortality.²²⁾ In the study of Woo et al.²³⁾ where the CCI index was applied as a long-term survival prediction factor after the breast cancer operation, it turned out that comorbidity factors common among breast cancer patients included peptic ulcer (19.7%), chronic pulmonary disease (4.3%), diabetes without complication (4.3%), any cancer (1.71%), and mild liver disease (1.27%) in order. In one study that analyzed comorbidity among 89,953 breast cancer patients, at least 30% of the patients had metabolic diseases such as hyper-

cholesterolemia, hypertension, and diabetes.²⁴⁾

Second, the older one gets, the greater one's risk of mortality with more severe comorbidities. Older age and presence of certain specific comorbidities are associated with a higher risk of dying.²⁰⁾ The Annual Report to the Nation on the Status of Cancer (1975-2010) indicated that the most frequent type of comorbidity was diabetes, followed by chronic disease and heart disease for patients aged ≥ 65 .²⁵⁾ Among women aged 35, compared to the menopausal age group (50 years or older), breast cancer showed a higher level of biological malignancy and worse convalescence than others.²⁶⁾ However, it needs to be noted that cancer survivors were aged 60 on average, in an age group involving various complications. In one study that analyzed comorbidity among 89,953 breast cancer patients, at least 30% of the patients had metabolic diseases such as hypercholesterolemia, hypertension, and diabetes.²⁴⁾

Third, age and BMI led to greater risk of mortality, with correction for the variables that could cause confounding. Reportedly, the higher the BMI the higher the risk of mortality.²⁷⁾ There is a finding that postmenopausal women who had gained about ≥ 30 kg in adulthood were at more than twice higher risk of breast cancer than ordinary women.²⁸⁾ The measurement of comorbidities has been improved to predict the mortality rate, length of stay in hospital, costs, treatment planning, and so on. The evaluation of comorbidities is important because variation of patients' characteristics can also have negative effects on the prognoses. Obesity is not only a risk factor for breast cancer, but it is also reported to be more difficult to treat. In the study of Kang et al.²⁹⁾ where the correlation between obesity and breast cancer incidence among 28,631 objects between 2009 and 2013 was analyzed, the group of breast cancer patients whose BMI was less than 23 showed statistically significant difference from the and non-breast cancer controls. The odds ratio of breast cancer incidence was 1.87 times higher than those of less than 23. In addition, obese breast cancer patients have poor prognoses for treatment such as metastasis, recurrence, and death, and a high mortality rate. According to Caan et al.³⁰⁾ among women with breast cancer in stage 2 to 3, the group with the highest level of body fat showed 35% higher mortality than the group with the lowest level of body fat. The group of breast cancer patients with a high level of body fat and with the smallest amount of muscle showed 89% higher mortality than the other

group.

In this large prospective cohort of breast cancer survivors, one could confirm that CCI increased the risk of mortality. In particular, those cancer survivors who were aged ≥ 60 years, who had high BMI, needed to get continuous care due to poor prognoses.

Despite implications stated above, this study involves the following limitations: first, this study refers to claim data of the National Health Insurance Service, and it was unable to utilize clinical information of breast cancer survival prediction factors such as stage, hormone receptor. Second, this study does not utilize socioeconomic variables such as income and occupation as confounding variables in this study. This requires caution in generalizing the findings of the study. Third, the childbirth history could not be clearly identified because more than 75% of the subjects analyzed based on the sample cohort data followed for 9 years were 40s or older. Despite such limitations, however, this study is of significance in that it examines breast cancer survivors' comorbidity as a risk factor of mortality in relation to the severity of each disease.

요 약

연구배경: 암 환자의 동반질환은 사망 위험, 진행 및 치료 과정에 영향을 미친다. 따라서 동반질환과 그 중증도를 측정하여 암 생존자에 대한 예후를 정확하게 예측할 필요가 있다.

방법: 본 연구는 국민건강보험공단의 표본 코호트 데이터베이스에서 추출한 유방암 환자에서 Charlson 동반질환지수(CCI)를 기준으로 주요 동반질환의 빈도를 분석하였다. 사망자와 암 생존자 간 연령, 진단 기간 및 CCI의 상대적인 영향을 측정하기 위해 로지스틱 회귀분석을 수행하였다. 유방암 환자의 생존 예측인자로서 CCI에 따른 사망위험률을 확인하기 위하여 콕스의 비례위험 회귀분석을 적용하였다.

결과: 첫째, Charlson 동반질환지수에 기초한 빈도 분석에서 주요 동반질환은 폐질환에 이어 소화성 궤양 및 전이성 암의 순이었다. 둘째, 나이가 들수록 동반질환 중증도가 높고 사망 위험이 높다. 셋째, 교란을 유발할 수 있는 변수(나이, BMI, 흡연력, 음주력 및 출산력)를 보정한 모형에서 연령과 BMI는 사망 위험을 높였다.

결론: 동반질환의 중증도는 유방암 환자의 사망 위험을 크게 증가시켰다. 특히 60세 이상, BMI가 높고 흡연경력이 있는 암 생존자들은 예후가 좋지 않아 지속적인 치료 및 사후관리가 요구된다.

중심 단어: 유방암, 코호트 연구, 암 생존자, 동반질환, 사망률

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