의학박사 학위논문

건강보험심사평가원 자료를 활용한 안트라사이클린 표준 화학요법이 **50**대 유방암 생존자의 후기 심부전 발생에 미치는 영향 분석

Effect of standard low-dose anthracycline chemotherapy on late congestive heart failure in breast cancer survivors aged between 50 and 59 at diagnosis: A nationwide study

2021년 2월

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지도교수 노동영

이 논문을 의학박사 학위논문으로 제출함

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Abstract

Effect of standard low-dose anthracycline chemotherapy on late congestive heart failure in breast cancer survivors aged between 50 and 59 at diagnosis: A nationwide study

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Introduction

Although chemotherapy-induced congestive heart failure (CHF) is a critical adverse event in cancer survivors, there is no consensus regarding long-term monitoring of CHF among international guidelines. The incidence and risk factors of late CHF in real-world practice have not yet been thoroughly scrutinized. This study aimed to investigate the age groups vulnerable to chemotherapy-induced late CHF, assess the risk of late CHF following (neo)adjuvant chemotherapy regimens,

and define the long-term effects of standard low-dose anthracycline on late CHF in high-risk age groups among breast cancer survivors.

Methods

This nationwide retrospective cohort study analyzed the national insurance claims data for nearly 98% of Korean citizens. A total of 56,338 newly diagnosed female breast cancer survivors without a previous or recent history of CHF or other cancers were included (between Jan 2010 and Dec 2015). The main outcome was late CHF after 2 years following breast cancer diagnosis.

Results

The total number of person-years was 199,648 (mean follow-up, 66.8 months) and 713 survivors developed late CHF. The incidence rate of late CHF was 3.57 per 1,000 person-years. In multivariate analysis according to the subject's age at diagnosis, anthracycline-based [hazard ratio (HR) 1.765, 95% confidence interval (CI) 1.206-2.583] and taxane plus anthracycline-based regimens (HR 1.816, 95% CI 1.192-2.768) significantly increased the risk of late CHF only in the 50-59 age group. In this population, after adjustment for age, insurance, past medical history, and other adjuvant treatments, cyclophosphamide plus anthracycline (HR 1.672, 95% CI 1.095-2.555), fluorouracil plus anthracycline plus cyclophosphamide (HR 2.006, 95% CI 1.260-3.196) and anthracycline plus cyclophosphamide plus taxane

(HR 1.922, 95% CI 1.260-2.932) regimens were significant risk factors for late CHF. Among the 50-59 age group, standard low-dose anthracycline significantly increased the risk of late CHF (HR 1.627, CI 1.080-2.451) in the Cox proportional hazard regression models. In competing risk model, standard low-dose anthracycline was a significant risk factor for late CHF [subdistribution hazard ratio (SHR) 1.553, 95% CI 1.029–2.340].

Conclusions

This nationwide cohort study showed that standard low-dose anthracycline is a risk factor for late-onset CHF in breast cancer survivors who were in their 50s at breast cancer diagnosis. Tailored screening strategies should be considered for breast cancer survivors at different levels of risk for developing late CHF.

Keywords

Breast neoplasms, Chemotherapy, Anthracyclines, Adverse effects, Heart Failure, Cancer survivors, Screening

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Introduction

As the survival outcome of cancer treatment continues to improve, the importance of long-term survivorship care after cancer treatment has received greater attention (1, 2). Recently, the European Organization for Research and Treatment of Cancer Quality of Life Group has developed a comprehensive questionnaire which captures the full range of health-related issues such as physical, social and mental health issues in cancer survivors (3). The National Cancer Policy Forum reported that there are substantial problems which should be dealt with in cancer survivorship care (4). Some authors suggest that cancer survivorship should become a practical category with supported actionable care plans and a functional information system (5).

Cancer survivors can be influenced by various factors after cancer diagnosis. Some authors reported that eight topics should be taken care of including delay of treatment and survival outcome, sexual well-being, concerns about childbearing, tailored follow-up, presence of a family history of breast cancer, diet and physical activity for survivors and their families, qualitative approach toward understanding of breast cancer survivorship, and, mobile health care for breast cancer survivors (6). One retrospective cohort study showed that childhood, adolescent and young adult cancer survivors faced significantly lower income than non-cancer controls, which may subsequently affect their lives (7). A systematic review suggested that cancer survivors should receive

survivorship care plans which seem to be feasible and can improve health care professionals' survivorship care although future research should evaluate implementations and effectiveness (8).

The lives of cancer survivors can also be influenced by various long-term and late effects after cancer-directed treatments. Among them, cardiovascular diseases are important adverse effects. A population-based study using Finnish Cancer Registry and national hospital discharge registry showed that the long-term risks of cardiovascular diseases such as cardiomyopathy, cardiac insufficiency, atherosclerosis, brain vascular thrombosis, myocardial infarction, cardiac ischemia and cardiac arrhythmia were significantly higher in early-onset cancer survivors than healthy siblings (9). The cardiovascular care of cancer patients has been a new discipline in company with recent advances in cancer therapy, which cause unfavorable cardiovascular complications. Anthracyclines, radiation therapy and targeted cancer therapy have been recognized to have cardiovascular complications (10).

Chemotherapy-induced congestive heart failure (CHF) is one of the most important adverse effects. Although many international guidelines have been introduced to prevent this life-threatening problem, there is no consensus regarding long-term monitoring of survivors for CHF among these practice guidelines. The National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines do not recommend long-term screening beyond 1 year after finishing anthracycline or trastuzumab therapy (11, 12). However, the

European Society for Medical Oncology and Canadian Cardiovascular Society guidelines have suggested long-term monitoring for CHF (13, 14).

This disagreement can be due to the lack of comprehensiveness among existing studies. Although many studies have investigated chemotherapy-induced CHF in cancer survivors, these studies have limitations that are worth noting. Some studies were focused on high-dose anthracycline, which is no longer used as the standard adjuvant chemotherapy (15, 16). As the cardiotoxicity of anthracycline has been recognized, lower dose of anthracycline in standard adjuvant chemotherapy has been introduced and reduced dose of anthracycline has been used in patients at high risk for CHF (11, 12). Thus, the results of the previous studies cannot be generalized to cancer survivors in today's changing practice environment. Moreover, many of previous studies were limited to adolescent or old cancer survivors who are not majority of cancer survivors (17-24). The results of these studies need to be interpreted in the context of the study population.

Previously, authors have reported that breast cancer survivors younger than 66 years are at a high risk of late CHF (25). Among 91,227 cases and 273,681 controls, younger breast cancer survivors aged 50 or less showed a higher risk of late CHF than their younger counterparts. Although older age was a risk factor for late CHF, older breast cancer survivors aged 66 or more showed no increased risk of late CHF in comparison with controls. In addition, not only

anthracycline-based regimens but also taxane-based regimens were associated with a higher risk of late CHF. Although the reason can be anthracycline used in the taxane-based regimen or an additional risk of taxane, the risk of late CHF according to (neo)adjuvant chemotherapy regimens were not assessed and the age categories (≤50, 51-65, ≥66y) was broad. The incidence and risk factor of late CHF in "real-world" practice has not yet been thoroughly scrutinized.

Therefore, we conducted a large nationwide cohort study of 56,338 breast cancer survivors using data from the Health Insurance Review and Assessment Service (HIRA), which consists of data from nearly 98% of Korean citizens (26). The HIRA is a governmental institution in the Republic of Korea that collects all the medical claims data from hospitals around the nation and reviews healthcare services for reimbursement decisions. The HIRA data archives general information, diagnoses based on the 10th revision of the International Classification of Diseases (ICD-10), and healthcare services such as prescriptions, procedures, and treatments.

This study aimed to further investigate the age groups vulnerable to chemotherapy-induced late CHF, assess the risk of late CHF following (neo)adjuvant chemotherapy regimens, and define the long-term effects of standard anthracycline on late CHF in the high-risk age groups among breast cancer survivors.

Methods

Data source and extraction

From Jan 2010 to Dec 2015, 203,956 patients tagged with codes C50 (invasive breast cancer) and V193, which is indicative of cancer patients, for reimbursement were extracted from the HIRA database (27). Among them, 87,237 patients already tagged with code C50 between Jan 2008 and Dec 2009 were excluded to eliminate previous cases (Figure 1).

A total of 116,719 newly diagnosed breast cancer survivors were identified. We excluded 861 male patients, 6,535 patients previously diagnosed with ductal carcinoma in situ, 15,297 metastatic or recent (within 2 years after breast cancer diagnosis) recurrent cases, 17,676 patients who did not undergo breast cancer surgeries, 16,226 patients with a previous or recent claim with another cancer code (code C), 3,336 patients with a previous or recent (within 2 years following breast cancer diagnosis) history of CHF and 450 patients who had no follow-up after 2 years following breast cancer diagnosis.

Variables and operational definitions

Basic information including age and insurance was collected. The Charlson Comorbidity Index (CCI) was evaluated with ICD-10 codes. (28) Previous history of hypertension (HT), diabetes mellitus (DM), and

dyslipidemia was evaluated based on the ICD-10 codes [HT, I10-13, 15, 16; DM, E10-14; and dyslipidemia, E78] and prescribed medications (29). We defined the treatment groups based on claims data within 1 year after the breast cancer diagnosis. Surgery, adjuvant radiation therapy, (neo)adjuvant chemotherapy (cyclophosphamide, doxorubicin, epirubicin, fluorouracil, methotrexate, paclitaxel, docetaxel, carboplatin), (neo)adjuvant endocrine therapy (tamoxifen, toremifene, anastrozole, letrozole, exemestane), and trastuzumab treatment were reviewed (27). Patients were allocated into endocrine therapy groups based on the initially prescribed endocrine medication and toremifene use was considered as tamoxifen use.

CHF was defined as three or more claims with the codes I50 or I110 (25). In-hospital mortality was included in the analysis because the HIRA only archives mortality information from hospitals. Recurrence or metastasis was defined as breast cancer diagnosis with metastatic codes (C77.0, C77.1, C77.2, C77.4, C77.5, C77.6, C77.8, C78, C79), claims for second-line or more systemic treatments (vinorelbine, capecitabine, gemcitabine, albumin-bound paclitaxel, eribulin, everolimus, bevacizumab, lapatinib, ifosfamide or trastuzumab emtasine, palbociclib, cisplatin), or radiation therapy at distant metastatic sites.

(Neo)adjuvant chemotherapy was categorized in three ways. Category 1 included none, anthracycline-based, taxane plus anthracycline-based, taxane-based, and other chemotherapy regimen subgroups. Category 2 was divided into none, cyclophosphamide plus

anthracycline (AC), fluorouracil plus anthracycline plus cyclophosphamide (FAC), anthracycline plus taxane (AT), anthracycline plus cyclophosphamide plus taxane (ACT), taxane plus cyclophosphamide (TC), taxane plus carboplatin (TCab), and cyclophosphamide plus methotrexate plus fluorouracil (CMF). Category 3 was classified as no-chemotherapy and standard low-dose anthracycline groups. The standard low-dose anthracycline group was defined as patients treated with only four cycles of anthracycline during the entire study period because low-dose anthracycline is defined as doxorubicin less than 250 mg/m^2 or epirubicin less than 600 mg/m^2 in the ASCO guidelines (12).

For landmark analysis, the index date was defined as the date 2 years after breast cancer diagnosis for each patient. Late-onset CHF was defined as CHF which developed after 2 years following breast cancer diagnosis (25).

Selection of high-risk age group for late CHF

To identify the high-risk age groups for chemotherapy-induced late CHF, the patients were divided into subgroups (<40, 40-49, 50-59, and ≥60) according to their age at diagnosis. Cox proportional hazard regression analysis was performed for the entire population and the age subgroups, adjusted for (neo)adjuvant chemotherapy category 1, age at diagnosis, insurance (health insurance or medicare), CCI, previous DM, previous HT, previous dyslipidemia, radiation therapy, trastuzumab, and

endocrine therapy [tamoxifen, aromatase inhibitor (AI), none]. The age group that was most influenced by (neo)adjuvant chemotherapy with regard to late CHF was selected as the main study population.

Statistical analysis

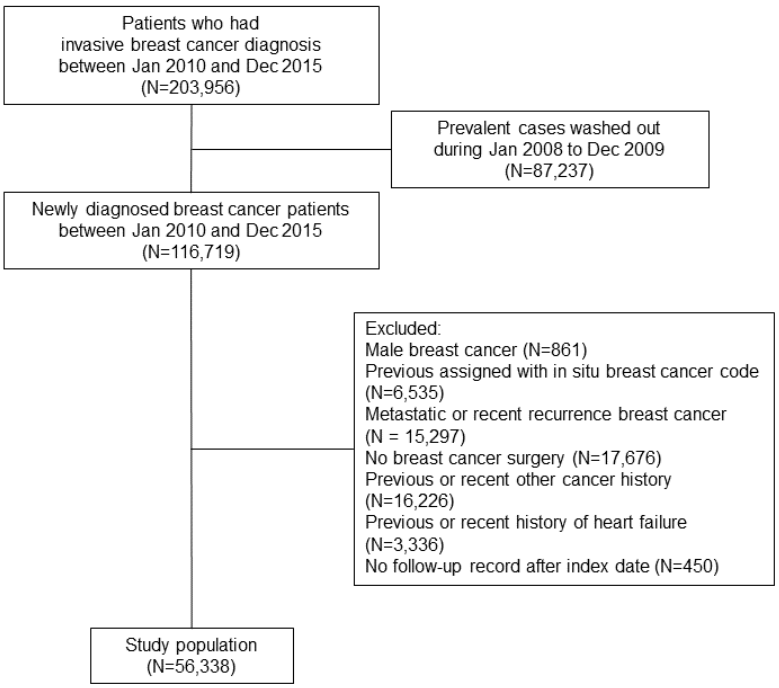
Descriptive statistics among the high-risk age groups for late CHF are summarized with absolute and relative frequencies. To assess the risk of late CHF according to the (neo)adjuvant chemotherapy regimen (category 2), Cox proportional hazards regression models were constructed. The models adjusted for age at diagnosis in Model 1, age at diagnosis, insurance and past medical history (CCI, DM, HT, and dyslipidemia) in Model 2, and age at diagnosis, insurance, past medical history, and adjuvant treatments (radiation therapy, trastuzumab, endocrine therapy) in Model 3. We created a Fine and Gray competing risk regression model with recurrence and in-hospital death as competing events with adjustments for the covariates used in Cox Model 3 (30, 31).

In the high-risk age group for late CHF, to investigate the long-term effects of standard low-dose anthracycline on late CHF, the group that received standard low-dose anthracycline was extracted and compared with patients who received no chemotherapy. A Kaplan–Meier analysis and log-rank test were used to assess the late CHF-free probability. We fit the Cox proportional hazards regression models with the same adjustments as above. The proportional hazards assumption

using the scaled Schoenfeld residuals test was analyzed. Cumulative incidence function and competing risk regression model were created with recurrence and in-hospital death as competing risks. Sensitivity analysis was also performed, excluding subjects with a previous history of DM, HT, or dyslipidemia, which are known risk factors for heart diseases (32-34).

Statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). All p values reported are two-sided. $p < .05$ was considered to indicate statistical significance. This study was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2019-0875).

Figure 1. Flowchart of study subjects.



Results

Basic characteristics

A total of 56,338 cases were included in this analysis (Table 1). The mean follow-up period was 66.8 months and the total number of person-years was 199,648 (Table 2). Late CHF and in-hospital mortality occurred in 713 (1.3%) and 1,048 patients (1.9%), respectively. The incidence rate for late CHF was 3.57 per 1,000 person-years.

Selection of high-risk age group

In multivariate analyses among the total population, the anthracycline-based [hazard ratio (HR) 1.245, 95% confidence interval (CI) 1.024-1.514] and taxane plus anthracycline-based regimen (HR 1.247, 95% CI 0.985-1.578) showed increased risks of late CHF in the fully adjusted Cox proportional hazards model (Table 2). In subgroup analysis based on age at diagnosis, the anthracycline-based (HR 1.765, 95% CI 1.206-2.583) and taxane plus anthracycline-based (HR 1.816, 95% CI 1.192-2.768) regimens significantly increased the risks of late CHF only in the 50-59 age group (Table 2 & Figure 2), which we selected as the main study subjects. Table 3 presents the basic characteristics of the 50-59 age group according to the (neo)adjuvant chemotherapy regimen category. The number of subjects in the age 50-59 subgroup was 16,985. The median follow-up period was 66.6 months, the total number of person-years was 59,841, and the incidence

rate of late CHF was 3.18 per 1,000 person-years. However, in the age ≥60 subgroup, anthracycline-based (HR 1.022, 95% CI 0.765-1.365) and taxane plus anthracycline-based (HR 0.889, 95% CI 0.602-1.314) regimens did not increase the risk of late CHF.

Chemotherapy regimen related to late CHF in breast cancer survivors aged between 50 and 59 at diagnosis

In the 50-59 age group, the AC, FAC, and ACT regimens were associated with an increased risk of late CHF in all adjusted models (Table 4 and Table 5). After adjustment for age, insurance, past medical history, and other adjuvant treatments, the associations were statistically significant (AC, HR 1.672, 95% CI 1.095-2.555; FAC, HR 2.006, 95% CI 1.260-3.196; ACT, HR 1.922, 95% CI 1.260-2.932) and they remained significant [AC, subdistribution hazard ratio (SHR) 1.720, CI 1.110-2.670; FAC, SHR 1.950, CI 1.190-3.190; ACT, SHR 1.700, CI 1.100-2.630] after competing risk analyses (Table 6). CMF and taxane without anthracycline regimens were not related to the risk of late CHF.

Standard low-dose anthracycline related to late CHF in breast cancer survivors aged between 50 and 59 at diagnosis

In the 50-59 age group, the number of patients treated with adjuvant anthracycline was 9,129. From this group, we selected 5,643 patients treated with standard low-dose anthracycline during the study period.

We chose 6220 subjects who never received chemotherapy during the study period as a control (Table 7). Kaplan–Meier analysis showed that the CHF-free probability was significantly lower ($p < 0.008$) in the standard low-dose anthracycline group than in the no-chemotherapy group (Figure 3). The risk of late CHF was significantly associated with standard low-dose anthracycline use (in Model 3, HR 1.627, CI 1.080-2.451) in all multivariate analyses (Table 8). After competing risk analyses, the results persisted (Gray's test, $p = 0.027$; SHR 1.553, CI 1.029-2.340, Figure 4 and Table 9). The scaled Schoenfeld residuals test showed no evidence that the proportional hazards assumption had been violated ($p = 0.266$, Figure 5). Lastly, in sensitivity analysis, although we excluded subjects with a previous history of DM, HT, or dyslipidemia, the results were essentially unchanged (Table 10).

Table 1. Characteristics of total subjects according to age at diagnosis

Parameters	Age < 40	Age 40-49	Age 50-59	Age ≥ 60	Total
	N (%)	N (%)	N (%)	N (%)	N (%)
Total	7,084	21,579	16,985	10,690	56,338
Age at diagnosis (years, mean±SD)	35.1±3.7	44.9±2.8	53.8±2.8	67.0±5.8	50.5±10.5
Insurance					
Health insurance	7,026 (99.20)	21,218 (98.3)	16,691 (98.3)	10,293 (96.3)	55,228 (98.0)
Medicare	58 (0.8)	361 (1.7)	294 (1.7)	397 (3.7)	1,110 (2.0)
Charlson Comorbidity Index (mean±SD)	1.2±1.2	1.4±1.3	2.0±1.7	3.1±2.1	1.9±1.7
Previous diabetes mellitus	57 (0.8)	569 (2.6)	1,281 (7.5)	2,342 (21.9)	4,249 (7.5)
Previous hypertension	197 (2.8)	1,992 (9.2)	4,418 (26.0)	6,240 (58.7)	12,847 (22.8)
Previous dyslipidemia	215 (3.0)	2,174 (10.1)	5,228 (30.8)	5,799 (54.2)	13,416 (23.8)
(Neo)adjuvant therapy					
None	677 (9.6)	1,596 (7.4)	1,471 (8.7)	1,139 (10.7)	4,883 (8.7)
CT	1,366 (19.3)	2,424 (11.2)	2,343 (13.8)	1,311 (12.3)	7,444 (13.2)
ET	1,496 (21.1)	6,527 (30.2)	4,681 (27.6)	4,440 (41.5)	17,144 (30.4)
CT + ET	2,574 (36.3)	8,444 (39.1)	5,594 (32.9)	2,595 (24.3)	19,207 (34.1)
CT + TZM	315 (4.4)	860 (4.0)	1,419 (8.4)	615 (5.8)	3,209 (5.7)
CT + ET + TZM	631 (8.9)	1,642 (7.6)	1,382 (8.1)	533 (5.0)	4,188 (7.4)

Other	25 (0.4)	86 (0.4)	95 (0.6)	57 (0.5)	263 (0.5)
(Neo)adjuvant chemotherapy					
None	2,198 (31.0)	8,209 (38.0)	6,247 (36.8)	5,636 (52.7)	22,290 (39.6)
Anthracycline-based	2,517 (35.5)	7,018 (32.5)	5,655 (33.3)	2,268 (21.2)	17,458 (31.0)
Taxane + Anthracycline-based	2,014 (28.4)	4,658 (21.6)	3,474 (20.5)	1,335 (12.5)	11,481 (20.4)
Taxane-based	113 1.6	389 (1.8)	348 (2.0)	205 (1.9)	1,055 (1.9)
Chemotherapy, others	242 (3.4)	1,305 (6.0)	1,261 (7.4)	1,246 (11.7)	4,054 (7.2)
(Neo)adjuvant endocrine therapy					
None	2,369 (33.4)	4,912 (22.8)	5,275 (31.1)	3,097 (29.0)	15,653 (27.8)
Tamoxifen	4,702 (66.4)	15,843 (73.4)	4,024 (23.7)	1,403 (57.9)	25,972 (46.1)
Aromatase inhibitor	13 (0.2)	824 (3.8)	7,686 (45.3)	6,190 (13.1)	14,713 (26.1)
Radiation	4,997 (70.5)	15,460 (71.6)	12,270 (72.2)	6,348 (59.4)	39,075 (69.4)
Trastuzumab	971 (13.7)	2,588 (12.0)	2,896 (17.1)	1,205 (11.3)	7,660 (13.6)
Incidence					
Late CHF diagnosis	25 (0.4)	101 (0.5)	190 (1.1)	397 (3.7)	713 (1.3)
In-hospital mortality	120 (1.7)	258 (1.2)	271 (1.6)	399 (3.7)	1,048 (1.9)
Duration after cohort entry (mean±SD, month)	68.3±20.5	66.9±20.3	66.6±20.1	66.2±20.5	66.8±20.3

SD, standard deviation; CT, chemotherapy; ET, endocrine therapy; TZM, trastuzumab; CHF, congestive heart failure

Table 2. Cox proportional hazards regression analysis of late congestive heart failure risk by (neo)adjuvant chemotherapy regimens according to age at diagnosis

Age at diagnosis	Regimen category	Cases, No.	Events, No.	Person-years	Late CHF IR per 1000 person-years	Model 1 (Crude)			Model 2[a](Adjusted)		
						HR	(95% CI)	*p*	HR	(95% CI)	*p*
All ages		56,338	713	199,648	3.57						
	None	22,290	321	75,885	4.23	1	(reference)		1	(reference)	
	Anthracycline-based	17,458	207	67,572	3.06	0.723	(0.607-0.861)	<.001	1.245	(1.024-1.514)	0.028
	Taxane+Anthracycline-based	11,481	112	38,376	2.92	0.690	(0.556-0.856)	<.001	1.247	(0.985-1.578)	0.066
	Taxane-based	1,055	2	1,686	1.19	0.280	(0.070-1.127)	0.073	0.323	(0.080-1.302)	0.112
	Chemotherapy, others	4,054	71	16,129	4.40	1.038	(0.803-1.343)	0.776	1.057	(0.814-1.372)	0.676
< 40y		7,084	25	26,123	0.96						
	None	2,198	7	7,939	0.88	1	(reference)		1	(reference)	
	Anthracycline-based	2,517	7	10,201	0.69	0.756	(0.265-2.156)	0.601	0.751	(0.250-2.255)	0.610
	Taxane+Anthracycline-based	2,014	9	6,788	1.33	1.525	(0.568-4.097)	0.403	1.663	(0.571-4.843)	0.351
	Taxane-based	113	0	176	0	NA	NA	NA	NA	NA	NA
	Chemotherapy, others	242	2	1,019	1.96	2.182	(0.453-10.514)	0.331	2.068	(0.405-10.570)	0.383
40-49y		21,579	101	76,952	1.31						
	None	8,209	29	27,710	1.05	1	(reference)		1	(reference)	
	Anthracycline-based	7,018	45	27,590	1.63	1.518	(0.951-2.422)	0.080	1.520	(0.937-2.467)	0.09
	Taxane+Anthracycline-based	4,658	22	15,726	1.40	1.343	(0.772-2.338)	0.297	1.379	(0.777-2.449)	0.272
	Taxane-based	389	0	596	0	NA	NA	NA	NA	NA	NA

	Chemotherapy, others	1,305	5	5,330	0.94	0.860	(0.333-2.224)	0.756	0.777	(0.299-2.019)	0.605
50-59y		16,985	190	59,841	3.18						
	None	6,247	46	21,192	2.17	1	(reference)		1	(reference)	
	Anthracycline-based	5,655	78	21,340	3.66	1.694	(1.177-2.439)	0.005	1.765	(1.206-2.583)	0.003
	Taxane+Anthracycline-based	3,474	47	11,530	4.08	1.876	(1.249-2.817)	0.002	1.816	(1.192-2.768)	0.006
	Taxane-based	348	1	554	1.81	0.765	(0.105-5.562)	0.791	0.679	(0.093-4.980)	0.703
	Chemotherapy, others	1,261	18	5,225	3.44	1.608	(0.932-2.775)	0.088	1.535	(0.887-2.655)	0.126
60y≤		10,690	397	36,730	10.81						
	None	5,636	239	19,043	12.60	1	(reference)		1	(reference)	
	Anthracycline-based	2,268	77	8,442	9.12	0.727	(0.562-0.940)	0.015	1.022	(0.765-1.365)	0.885
	Taxane+Anthracycline-based	1335	34	4,332	7.85	0.624	(0.436-0.894)	0.010	0.889	(0.602-1.314)	0.556
	Taxane-based	205	1	360	2.78	0.221	(0.031-1.580)	0.133	0.248	(0.035-1.776)	0.165
	Chemotherapy, others	1246	46	4,554	10.1	0.805	(0.587-1.103)	0.177	0.944	(0.681-1.309)	0.730

CHF, congestive heart failure; IR, incidence rate; HR, hazard ratio; CI, confidence interval;

[a]Model 2: adjusted for age at diagnosis (continuous), insurance (health insurance or medicare), Charlson Comorbidity Index (continuous), previous hypertension (yes or no), previous diabetes mellitus (yes or no), previous dyslipidemia (yes or no), radiotherapy (yes or no), trastuzumab (yes or no), endocrine therapy (tamoxifen, none, aromatase inhibitor)

Table 3. Basic characteristics of breast cancer survivors aged 50 to 59 years at diagnosis according to (neo)adjuvant chemotherapy regimens

Parameters	None	Anthracycline -based	Taxane + Anthracycline -based	Taxane-based	Chemotherapy, others
	N (%)	N (%)	N (%)	N (%)	N (%)
Total	6247	5655	3474	348	1261
Age at diagnosis (years, mean±SD)	53.8±2.9	53.8±2.8	53.8±2.8	54.2±2.8	53.9±2.8
Insurance					
Health insurance	6138 (98.3)	5578 (98.6)	3409 (98.1)	337 (96.8)	1229 (97.5)
Medicare	109 (1.7)	77 (1.4)	65 (1.9)	11 (3.2)	32 (2.5)
Charlson Comorbidity Index (mean±SD)	2.1±1.7	2.0±1.7	1.9±1.7	2.2±1.8	2.2±1.8
Previous diabetes mellitus	435 (7.0)	423 (7.5)	287 (8.3)	28 (8.0)	108 (8.6)
Previous hypertension	1580 (25.3)	1474 (26.1)	931 (0.3)	78 (22.4)	355 (28.2)
Previous dyslipidemia	1965 (31.5)	1726 (30.5)	1032 (0.3)	109 (31.3)	396 (31.4)
(Neo)adjuvant endocrine therapy					
None	1513 (24.2)	2169 (38.4)	1112 (32.0)	133 (38.2)	348 (27.6)

Tamoxifen	1855 (29.7)	1138 (20.1)	690 (19.9)	74 (21.3)	267 (21.2)
Aromatase inhibitor	2879 (46.1)	2348 (41.5)	1672 (48.1)	141 (40.5)	646 (51.2)
Radiation	4189 (67.1)	4167 (73.7)	2734 (78.7)	261 (75.0)	919 (72.9)
Trastuzumab	95 (1.5)	1518 (26.8)	993 (28.6)	125 (35.9)	165 (13.1)
Incidence					
Late CHF diagnosis	46 (0.7)	78 (1.4)	47 (1.4)	1 (0.3)	18 (1.4)
In-hospital mortality	55 (0.9)	89 (1.6)	102 (2.9)	1 (0.3)	24 (1.9)
Duration after cohort entry (mean±SD, month)	64.9±20.4	69.7±19.0	64.1±19.9	43.2±8.0	74.1±19.7

SD, standard deviation; CHF, congestive heart failure

Table 4. Cox proportional hazards regression analysis of late congestive heart failure risk according to (neo)adjuvant chemotherapy regimens in breast cancer survivors aged 50 to 59 years at diagnosis

Regimen	Cases, No.	Events, No.	Person-years	Late CHF IR per 1000 person-years	Model 1[a]			Model 2[b]			Model 3[c]		
					HR	(95% CI)	*p*	HR	(95% CI)	*p*	HR	(95% CI)	*p*
None	6,247	46	21,192	2.17	1	(reference)		1	(reference)		1	(reference)	
AC	3,584	46	13,109	3.51	1.631	(1.083-2.454)	0.019	1.660	(1.102-2.499)	0.015	1.672	(1.095-2.555)	0.017
FAC	2,071	32	8,232	3.89	1.822	(1.160-2.862)	0.009	1.910	(1.215-3.003)	0.005	2.006	(1.260-3.196)	0.003
AT	189	1	762	1.31	0.646	(0.089-4.685)	0.665	0.668	(0.092-4.856)	0.690	0.728	(0.100-5.315)	0.754
ACT	3,285	46	10,768	4.27	1.967	(1.307-2.960)	0.001	1.896	(1.259-2.854)	0.002	1.922	(1.260-2.932)	0.002
TC	287	0	421	0	NA	NA	NA	NA	NA	NA	NA	NA	NA
TCab	61	1	132	7.55	3.246	(0.447-23.571)	0.245	2.373	(0.326-17.270)	0.394	2.160	(0.287-16.253)	0.455
CMF	1,261	18	5,225	3.44	1.619	(0.938-2.794)	0.083	1.531	(0.887-2.641)	0.126	1.537	(0.888-2.658)	0.124

CHF, congestive heart failure; IR, incidence rate; HR, hazard ratio; CI, confidence interval; AC, cyclophosphamide plus

anthracycline; FAC, fluorouracil plus anthracycline plus cyclophosphamide; AT, anthracycline plus taxane; ACT, anthracycline plus cyclophosphamide plus taxane; TC, taxane plus cyclophosphamide; TCab, taxane plus carboplatin; CMF, cyclophosphamide plus methotrexate plus fluorouracil

[a]Model 1: adjusted for age at diagnosis (continuous)

[b]Model 2: adjusted for age at diagnosis (continuous), insurance (health insurance or medicare), Charlson Comorbidity Index (continuous), previous hypertension (yes or no), previous diabetes mellitus (yes or no), previous dyslipidemia (yes or no)

[c]Model 3: adjusted for age at diagnosis (continuous), insurance (health insurance or medicare), Charlson Comorbidity Index (continuous), previous hypertension (yes or no), previous diabetes mellitus (yes or no), previous dyslipidemia (yes or no), radiotherapy (yes or no), trastuzumab (yes or no), endocrine therapy (tamoxifen, none, aromatase inhibitor)

Table 5. (Neo)adjuvant chemotherapy regimens in breast cancer survivors aged 50 to 59 years at diagnosis

Regimen	None	Anthracycline-based	Taxane + Anthracycline-based	Taxane-based	Chemotherapy, others
	(n = 6,247)	(n = 5,655)	(n = 3,474)	(n = 348)	(n = 1,261)
	N (%)	N (%)	N (%)	N (%)	N (%)
None	6,247 (36.8)				
AC		3,584 (21.1)			
FAC		2,071 (12.2)			
AT			189 (1.1)		
ACT			3,285 (19.3)		
TC				287 (1.7)	
TCab				61 (0.4)	
CMF					1,261 (7.4)

AC, cyclophosphamide plus anthracycline; FAC, fluorouracil plus anthracycline plus cyclophosphamide; AT, anthracycline plus taxane; ACT, anthracycline plus cyclophosphamide plus taxane; TC, taxane plus cyclophosphamide; TCab, taxane plus carboplatin; CMF, cyclophosphamide plus methotrexate plus fluorouracil

Table 6. Competing risk analysis of late congestive heart failure risk by (neo)adjuvant chemotherapy regimens in breast cancer survivors aged 50 to 59 years at diagnosis

Chemotherapeutic regimen	Adjusted SHR (95% CI)[a]		
	SHR	(2.50-97.50%)	*p*
None	1	(reference)	
AC	1.720	(1.110-2.670)	0.015
FAC	1.950	(1.190-3.190)	0.008
AT	NA	NA	NA
ACT	1.700	(1.100-2.630)	0.016
TC	NA	NA	NA
TCab	NA	NA	NA
CMF	1.410	(0.784-2.550)	0.250

HR, subdistribution hazard ratio; CI, confidence interval; AC, cyclophosphamide plus anthracycline; FAC, fluorouracil plus anthracycline plus cyclophosphamide; AT, anthracycline plus taxane; ACT, anthracycline plus cyclophosphamide plus taxane; TC, taxane plus cyclophosphamide; TCab, taxane plus carboplatin; CMF, cyclophosphamide plus methotrexate plus fluorouracil

[a]The Fine and Gray proportional subdistribution hazards model with in-hospital mortality and recurrence as competing risks adjusted for age at diagnosis (continuous), insurance(health insurance, medicare), Charlson Comorbidity Index (continuous), previous hypertension (yes or no), previous diabetes mellitus (yes or no), previous dyslipidemia (yes or no), radiotherapy (yes or no), trastuzumab (yes or no), endocrine (tamoxifen, none, aromatase inhibitor) was used.

Table 7. Basic characteristics of no-chemotherapy group and standard low-dose anthracycline subgroup among breast cancer survivors aged 50 to 59 years

Parameters	No-chemotherapy	Low-dose anthracycline	Total
	N (%)	N (%)	N (%)
Total	6,220	5,643	11,863
Age at diagnosis (years, mean±SD)	53.8±2.9	53.8±2.8	53.8±2.8
Insurance			
Health insurance	6,111 (98.2)	5,559 (98.5)	11,670 (98.4)
Medicare	109 (1.8)	84 (1.5)	193 (1.6)
Charlson Comorbidity Index (mean±SD)	2.1±1.7	2.0±1.7	2.1±1.7
Previous diabetes	432 (6.9)	453 (8.0)	885 (7.5)
Previous hypertension	1,571 (25.3)	1,517 (26.9)	3,088 (26.0)
Previous dyslipidemia	1,961 (31.5)	1,752 (31.0)	3,713 (31.3)
(Neo)adjuvant chemotherapeutic regimens			
None	6,220 (100)	0 (0.0)	6,220 (52.4)

AC	0 (0.0)	2,966 (52.6)	2,966 (25.0)
ACT	0 (0.0)	2,677 (47.4)	2,677 (22.6)
(Neo)adjuvant endocrine therapy			
None	1,499 (24.1)	1,835 (32.5)	3,334 (28.1)
Tamoxifen	1,848 (29.7)	1,188 (21.1)	3,036 (25.6)
Aromatase inhibitor	2,873 (46.2)	2,620 (46.4)	5,493 (46.3)
Radiation	4,171 (67.1)	4,325 (76.6)	8,496 (71.2)
Trastuzumab	95 (1.5)	1,623 (28.8)	1,718 (14.5)
Incidence			
Late CHF diagnosis	45 (0.7)	67 (1.0)	112 (0.9)
In-hospital mortality	41 (0.7)	87 (1.5)	128 (1.1)
Duration after cohort entry (mean±SD, month)	64.8±20.4	64.0±18.2	64.4±19.4

SD, standard deviation; AC, cyclophosphamide plus anthracycline; ACT, anthracycline plus cyclophosphamide plus taxane; CHF, congestive heart failure

Table 8. Cox proportional hazards regression analysis of late congestive heart failure risk between no-chemotherapy group and standard low-dose anthracycline subgroup among breast cancer survivors aged 50 to 59 years at diagnosis

Regimen	Cases, No.	Events, No.	Person-years	Late CHF IR per 1000 person-years	Model 1[a]			Model 2[b]			Model 3[c]		
					HR	(95% CI)	*p*	HR	(95% CI)	*p*	HR	(95% CI)	*p*
None	6,220	45	21,085	2.13	1	(reference)		1	(reference)		1	(reference)	
Low-dose anthracycline	5,643	67	18,679	3.59	1.664	(1.140-2.429)	0.008	1.640	(1.123-2.396)	0.011	1.627	(1.080-2.451)	0.020

CHF, congestive heart failure; IR, incidence rate; HR, hazard ratio; CI, confidence interval

[a]Model 1: adjusted for age at diagnosis (continuous)

[b]Model 2: adjusted for age at diagnosis (continuous), insurance (health insurance or medicare), Charlson Comorbidity Index (continuous), previous hypertension (yes or no), previous diabetes mellitus (yes or no), previous dyslipidemia (yes or no)

[c]Model 3: adjusted for age at diagnosis (continuous), insurance (health insurance or medicare), Charlson Comorbidity Index (continuous), previous hypertension (yes or no), previous diabetes mellitus (yes or no), previous dyslipidemia (yes or no), radiotherapy (yes or no), trastuzumab (yes or no), endocrine therapy (tamoxifen, none, aromatase inhibitor)

Table 9. Competing risk analysis of late congestive heart failure risk between no-chemotherapy group and standard low-dose anthracycline subgroup among breast cancer survivors aged 50 to 59 years at diagnosis

Parameters	Adjusted SHR (95% CI)[a]		
	SHR	(2.50-97.50%)	*p*
Low-dose anthracycline (vs. no-chemotherapy)	1.553	(1.029-2.340)	0.036
Age at diagnosis	1.056	(0.984-1.130)	0.130
Insurance (medicare)	0.748	(0.198-2.820)	0.670
Charlson Comorbidity Index	1.097	(0.977-1.230)	0.120
Previous diabetes mellitus	1.749	(1.009-3.030)	0.047
Previous hypertension	3.747	(2.436-5.770)	0.000
Previous dyslipidemia	1.079	(0.701-1.660)	0.730
Endocrine therapy	1.162	(0.741-1.820)	0.510
Radiation	0.805	(0.526-1.230)	0.320
Trastuzumab	1.025	(0.587-1.790)	0.930

SHR, subdistribution hazard ratio; CI, confidence interval

[a]The Fine and Gray proportional subdistribution hazards model with in-hospital mortality and recurrence as competing risks adjusted for age at diagnosis (continuous), insurance (health insurance, medicare), Charlson Comorbidity Index (continuous), previous hypertension (yes or no), previous diabetes mellitus (yes or no), previous dyslipidemia (yes or no), radiotherapy (yes or no), trastuzumab (yes or no), endocrine (tamoxifen, none, aromatase inhibitor) was used.

Table 10. Sensitivity analysis

Regimen	Cases, No.	Events, No.	Person-years	Late CHF IR per 1000 person-years	Model 1[a]			Model 2[b]			Model 3[c]		
					HR	(95% CI)	*p*	HR	(95% CI)	*p*	HR	(95% CI)	*p*
None	3,505	10	11,816	0.85	1	(reference)		1	(reference)		1	(reference)	
Low-dose anthracycline	3,171	20	10,612	1.88	2.235	(1.045-4.784)	0.038	2.265	(1.058-4.850)	0.035	2.670	(1.216-5.863)	0.014

CHF, congestive heart failure; IR, incidence rate; HR, hazard ratio; CI, confidence interval

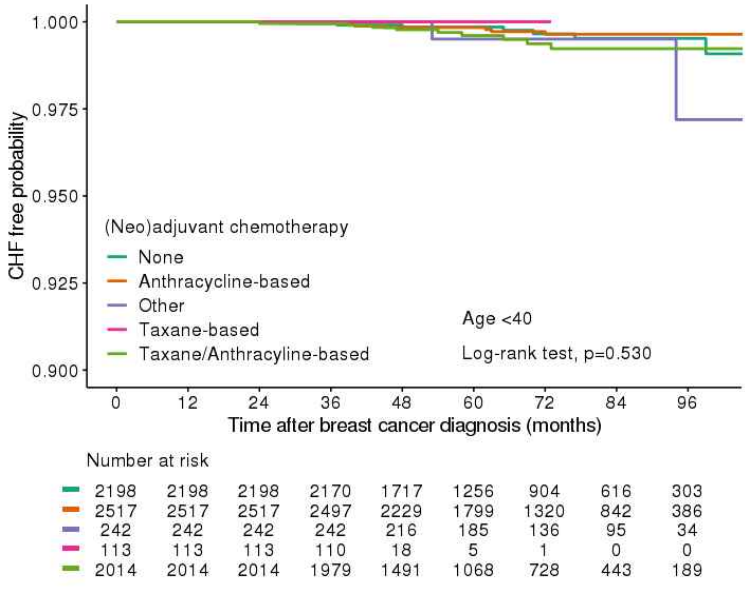
[a]adjusted for age at diagnosis (continuous)

[b]adjusted for age at diagnosis (continuous), insurance (health insurance, medicare), Charlson Comorbidity Index (continuous)

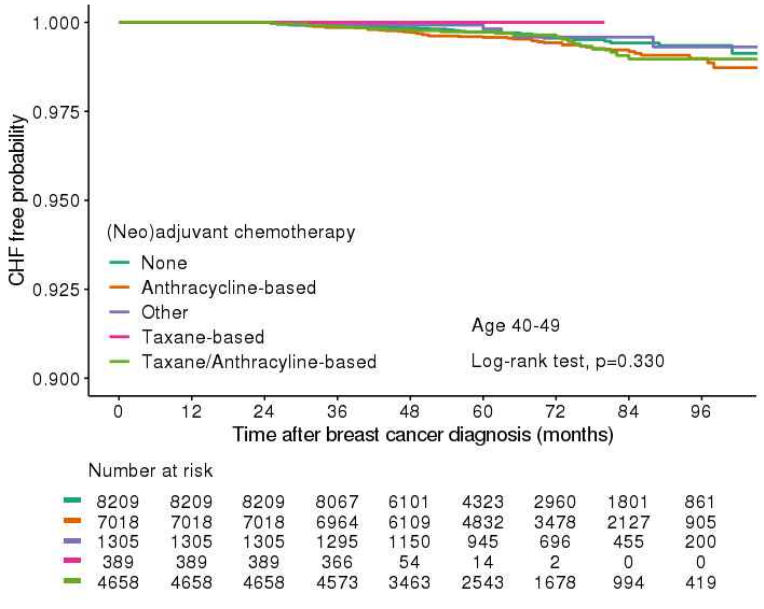
[c]adjusted for age at diagnosis (continuous), insurance (health insurance, medicare), Charlson Comorbidity Index (continuous), radiation (yes or no), trastuzumab (yes or no), endocrine (tamoxifen, none, aromatase inhibitor)

Figure 2. Kaplan–Meier curve of late congestive heart failure by (neo)adjuvant chemotherapy regimens and age at breast cancer diagnosis

A



B



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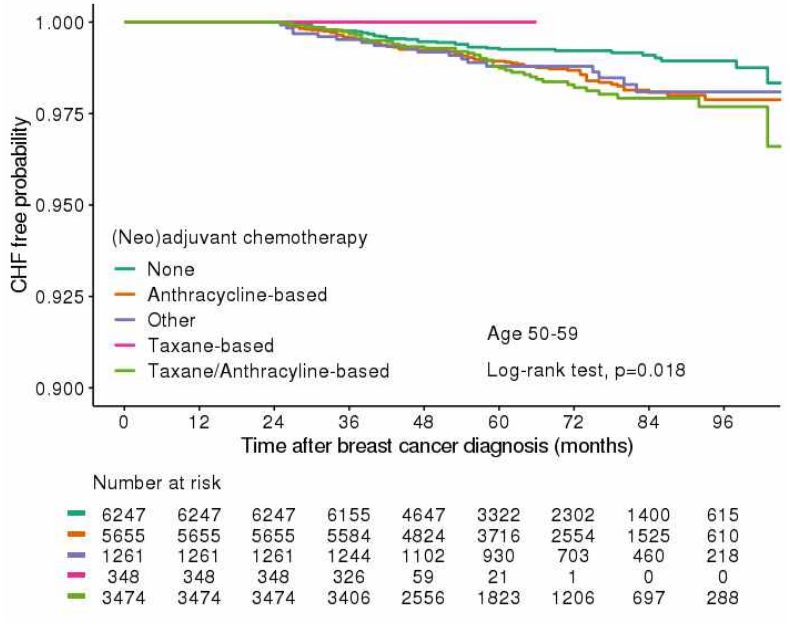
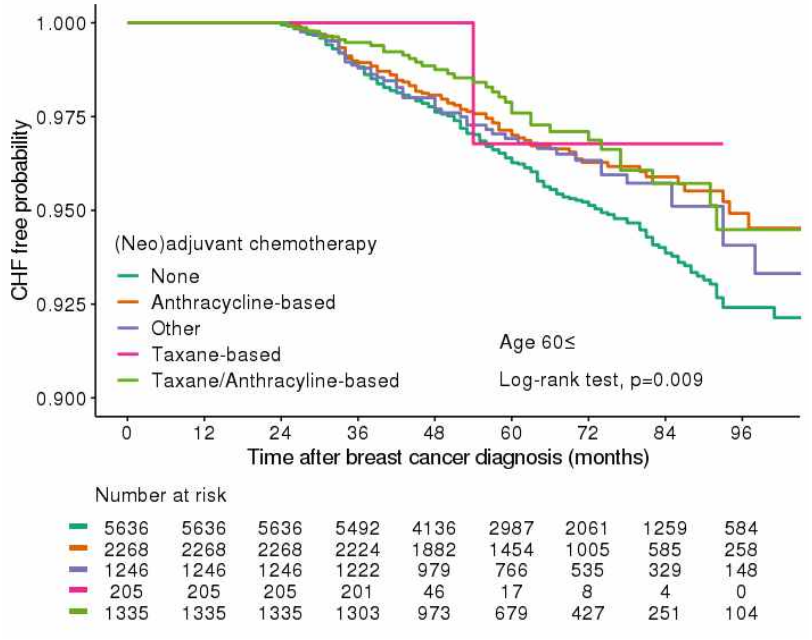


D



(A) <40y subgroup, (B) 40-49y subgroup, (C) 50-59y subgroup, (D) 60y≤ subgroup

Figure 3. Kaplan–Meier curve of late congestive heart failure between no-chemotherapy group and standard low-dose anthracycline subgroup among breast cancer survivors aged 50 to 59 years at diagnosis.

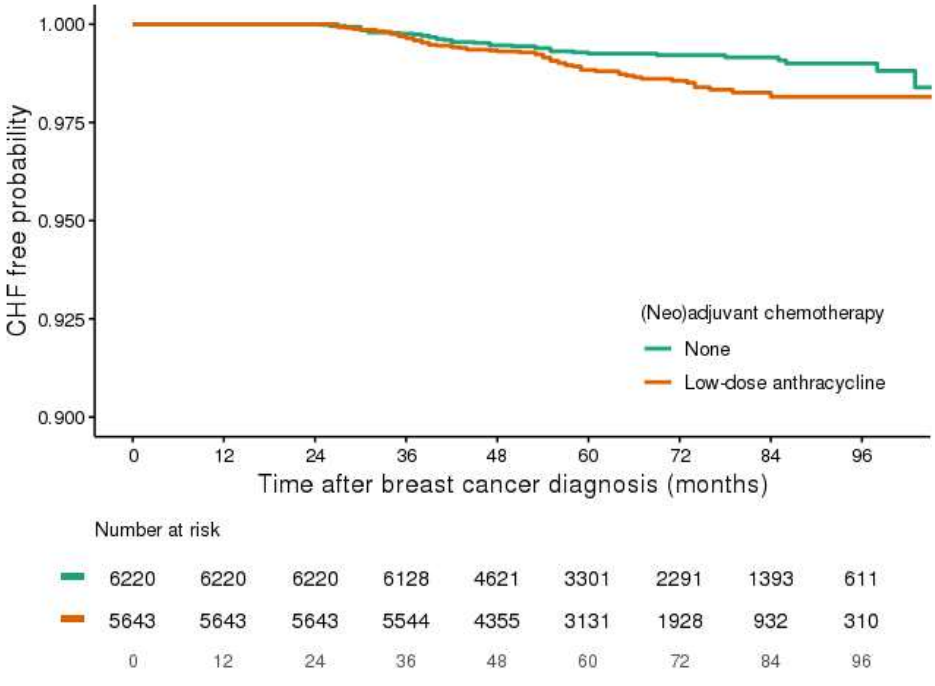


Figure 4. Cumulative incidence function of late congestive heart failure with competing risks between no-chemotherapy group and standard low-dose anthracycline subgroup among breast cancer survivors aged 50 to 59 years at diagnosis. (1, congestive heart failure; 2, in-hospital mortality and recurrence as competing risks)

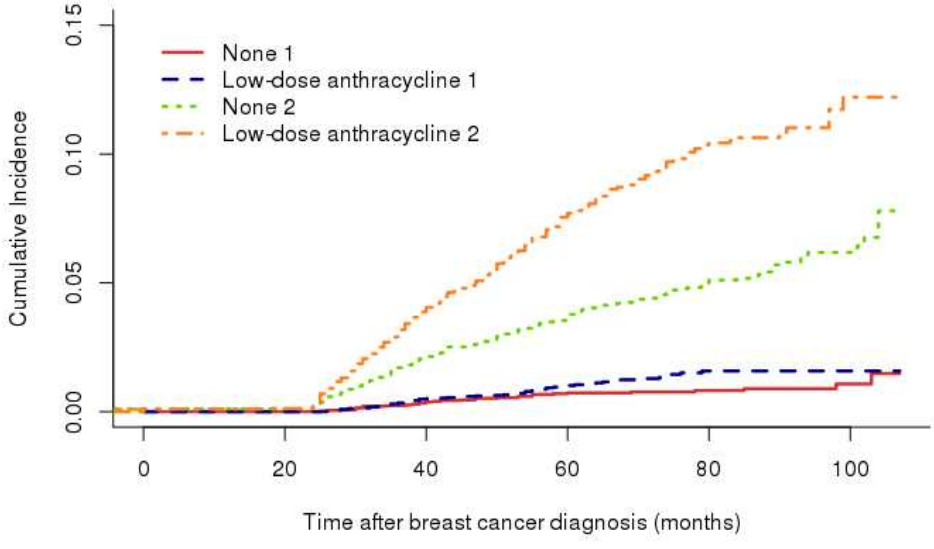
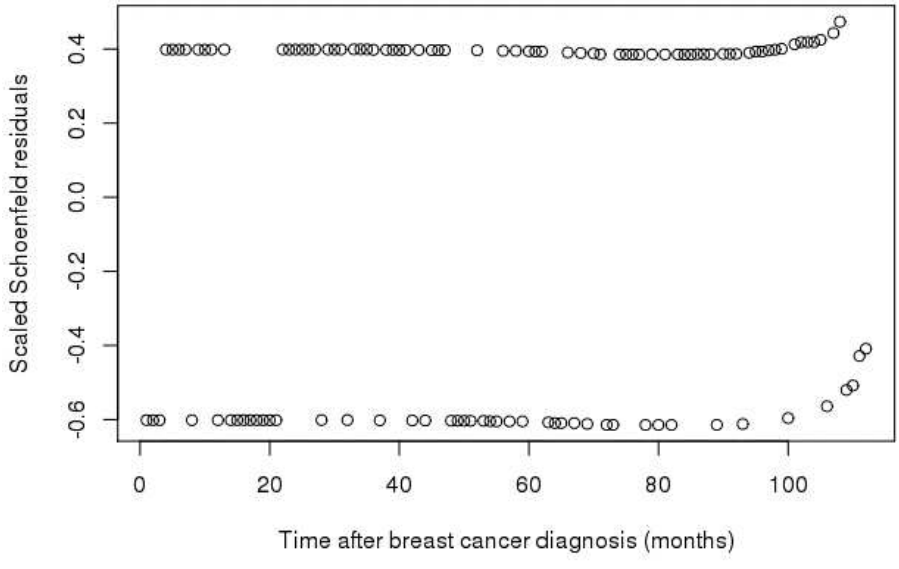


Figure 5. Scaled Schoenfeld residuals in univariate Cox proportional hazards model.



Discussion

This nationwide cohort study showed that breast cancer survivors aged between 50 and 59 at diagnosis were at a high risk for late CHF. In this age group, adjuvant anthracycline chemotherapy was associated with late CHF, and even standard low-dose anthracycline use significantly increased the risk of late CHF. Trastuzumab and adjuvant chemotherapy without anthracycline were not related to the risk of late CHF. Other age groups were not at high risk for late CHF.

This study provides a new perspective regarding the effect of standard low-dose anthracycline on the development of late CHF. There have been many studies about anthracycline-induced CHF. High-dose anthracycline (e.g., doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2) is a well-known risk factor for CHF (15, 16). Low-dose anthracycline (doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) in combination with other risk factors such as DM, HT, dyslipidemia, and old age ($\geq$ 60 years) is considered to increase the risk of CHF. Low-dose anthracycline alone has not yet been identified as a risk factor for CHF. The ASCO guidelines contain no recommendations regarding the risk of cardiac dysfunction in cancer survivors treated with low-dose anthracycline alone without any other risk factors (12). However, in this large cohort study, standard low-dose anthracycline increased the risk of late CHF in relatively young survivors aged 50 to 59 years at breast cancer diagnosis (35). Even in sensitivity analysis, standard low-dose anthracycline alone without DM, HT, dyslipidemia or old age significantly increased the risk of late CHF.

To our knowledge, this is the first study that revealed an association between standard low-dose anthracycline and late CHF in younger breast cancer survivors (36). Although the current international guidelines about chemotherapy-induced CHF provide useful and appropriate approaches in most cases (11, 12), there remains room for improvement (16). Based on our results, there is an unmet need for relatively young breast cancer survivors aged 50 to 59 years treated with standard low-dose anthracycline, which was not previously assumed to be a risk factor for CHF.

Several theories can be suggested to explain why only breast cancer survivors aged 50 to 59 years showed an increased risk of late CHF after standard anthracycline chemotherapy in this study. First, because older breast cancer patients aged 60 years and above are at a high risk for CHF, adjuvant anthracycline treatment can cause immediate or early-onset CHF; thus, the group was excluded from our study. Second, in practice, clinicians are usually reluctant to administer full standard doses of chemotherapy to older patients (37), which may lead to reduced effects of anthracycline on CHF. In contrast, younger breast cancer patients aged 50 to 59 years are assumed to be at a lower risk for CHF and consequently, standard doses of anthracycline are usually administered (12). Third, standard adjuvant anthracycline is a weak risk factor for CHF (38). Thus, although the effect of standard low-dose anthracycline is not evident in the early phases, it can cause late effects. Lastly, the likelihood of developing late CHF can vary according to age. Interestingly, anthracycline-based regimens showed an increased risk of late CHF (HR 1.520, CI 0.937-2.467, p = 0.090) in breast cancer survivors aged between 40 and 49, and were not associated with the

risk of late CHF in patients younger than 40 in this study (HR 0.751, CI 0.250-2.255, p = 0.610, Table 2).

Our study provides an explanation for the lack of consensus concerning the long-term risk of CHF (12, 13). Considering our results, the occurrence of late CHF can be attributed to the combined effects of a relatively young age at diagnosis and low-dose anthracycline chemotherapy in breast cancer survivors. In terms of the late effects, weak risk factors appear to have a greater impact than strong risk factors such as old age and high-dose anthracycline. This suggests that long-term monitoring of late CHF taking into account various weak risk factors should be considered.

In a previous study, we reported that taxane-based regimens were associated with an increased risk of late CHF in breast cancer survivors and suggested that this may be caused by anthracycline in taxane-based regimens or by taxane itself. Several studies have reported that anti-microtubule agents may cause chemotherapy-induced cardiotoxicity (39-41). However, in the current study, after subdividing taxane-based regimens into taxane plus anthracycline-based and taxane-based regimens, taxane itself was not associated with late CHF. Trastuzumab which is a known risk factor for early-onset CHF began to be covered by the national insurance from 2010 in South Korea (42-44), and we were able to analyze its long-term effects on late CHF. In our study, trastuzumab was not associated with late CHF, similar to the results in previous studies (Table 9) (23, 45-47).

Radiotherapy is a well-known risk factor for heart disease (48-50). A previous population-based case-control study showed that radiotherapy for

breast cancer increased the rate of ischemic heart disease (48). Subjects aged 60 years or more and with risk factors showed an increased risk of major coronary events after exposure to radiation. In our study, radiation therapy did not increase the rate of late CHF (SHR 0.805, CI 0.526-1.230). However, our results should be interpreted cautiously. We could not get information about the side (right or left) and field of radiation, the mean follow-up period was shorter than those of previous studies, and the outcome variable was CHF in our study, not ischemic heart disease. Thus, the effect of radiotherapy cannot be confirmed from this study.

There has been a controversy about the long-term effect of AI on cardiovascular disease risk. A retrospective cohort study of 13,273 postmenopausal breast cancer survivors showed that AI did not increase the risk of cardiac ischemia and stroke, but was associated with a significantly increased risk of other cardiovascular diseases such as pericarditis, dysrhythmia, and valvular dysfunction (51). In a recent population-based cohort study analyzing 17,922 breast cancer survivors, AI was significantly associated with an increased risk of CHF (HR 1.86, 95% CI, 1.14−3.03) and cardiovascular mortality (HR 1.50, 95% CI 1.11−2.04) compared with tamoxifen. AI showed trends toward increased risks of myocardial infarction and ischemic stroke (52). In this study, patients who were prescribed only with AI were not identified because we allocated patients into endocrine therapy groups based on initial prescriptions, and thus the effect of AI on late CHF risk was not investigated.

Cardio-oncology has emerged as a new sector of interest in cardiology

which tries to detect, monitor, and treat cardiovascular disease related to adverse effects of cardiotoxic treatments in oncology (53). Although there are limited studies about the effect of early treatment on CHF outcomes, several researches have shown the promising results of prompt initiation of CHF treatments. One study reported that when enalapril or carvedilol was promptly administered in patients with anthracycline-induced CHF, the proportion of responders progressively decreased as the time between the end of chemotherapy and the initiation of CHF treatment increased (54). Other study demonstrated that, in early-onset CHF, the prompt CHF therapy resulted in 11% of full recovery and 71% partial recovery (15). However, the previous studies were conducted in early-onset CHF settings. Further research is needed to study the effect of early detection and prompt treatment in late CHF on clinical outcomes.

Limitations

Several limitations of our study should be noted. First, although we conducted survival analysis with in-hospital mortality, it should not be interpreted as overall survival. Because the HIRA collects data only from hospitals, we were unable to include mortality data from patients who died outside hospitals. Second, the HIRA database does not archive information about stage, laboratory results, lifestyle factors such as diet, smoking, obesity, or physical activities, and details about radiation therapy. Third, although we developed algorithms which we used to define metastatic or recurred breast cancers, there remains a possibility that some recurrent or metastatic cases were included in the analysis. Finally, the exact doses of anthracycline administered to subjects were not evaluated. Instead, we analyzed the total frequency of anthracycline administration.

Conclusions

This nationwide cohort study showed that standard chemotherapy with low-dose anthracycline is a risk factor for late-onset CHF in breast cancer survivors who were in their 50s at breast cancer diagnosis. Tailored screening strategies for breast cancer survivors who are at different levels of risk for developing late CHF should be considered.

Competing interests

All of the authors declare that they have no conflicts of interest.

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국문초록

서론: 항암치료로 인하여 발생하는 심부전은 암생존자에 있어 중요한 부작용 중에 하나이다. 이러한 심부전은 암생존자의 생존율 및 삶의 질에 중대한 영향을 미칠 수 있다. 그러나 현재까지 국제 가이드라인에서는 이들 심부전에 대한 장기적 추적 관찰의 필요성에 대하여 논란이 있다.

방법: 본 후향적 코호트 연구는 2008년부터 2018년까지 건강보험심사평가원 자료를 활용하여 유방암 생존자에 있어 후기 심부전 발생의 빈도를 조사하였고, 후기 심부전과 관련된 인자들을 확인하였다. 한편, 표준 요법으로 사용되는 저용량 안트라사이클린이 후기 심부전에 미치는 영향을 분석하였다. 2010년 1월부터 2015년 12월까지 심부전의 과거력이 없는 총 56,338명의 새롭게 유방암으로 진단받은 환자를 추출하였다. 후기 심부전은 유방암 진단 후 2년 이후에 발생한 심부전으로 정의하였다.

결과: 중간 추적 기간 66.8개월 동안(총 199,648인년) 713명의 유방암 생존자에서 후기 심부전이 발생하였다. 후기 심부전의 발생률은 1,000인년당 3.57명이었다. 나이대 별 콕스 비례 위험 모형에서 다변량 분석에서 안트라사이클린 [hazard ratio (HR) 1.765, 95% confidence interval (CI) 1.206-2.583] 및 안트라사이틀린-탁산 병합요법 (HR 1.816, 95% CI 1.192-2.768) 은 유방암 진단 당시 50대 여성에서 통계적으로 의미있게 후기 심부전의 발생을 증가시켰다. 50대 여성에서는 나이, 보험, 과거력 및 다른 치료를 보정하였을 때에도 동일하게 안트라사이클린이 포함된 항암제가 후기 심부전의 발생을 의미있게 증가시켰다. 50대 유방암으로 진단받은 여성의 경우 표준 저용량 안트라사이클린이 후기 심부전을 의미있게 증가시켰다 (HR 1.627, CI 1.080-2.451).

결론: 본 국가 단위 코호트 연구에서 표준 저용량 안트라사이클린은 50대에 유방암으로 진단받았던 유방암 생존자에 있어 후기 심부전을 증가시켰다. 환자별로 후기 심부전의 발생 위험을 고려하여 맞춤형 심부전 관리가 고려되어야 한다.

주요어: 유방암, 항암치료, 안트라사이클린, 부작용, 심부전, 암생존자,
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