ONLINE EXCLUSIVE

Anthracycline Chemotherapy–Induced Cardiotoxicity in Breast Cancer Survivors: A Systematic Review

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PROBLEM IDENTIFICATION: This review identifies specific cardiotoxicity related to anthracycline chemotherapy, specific risk factors related to increased anthracycline chemotherapy–induced cardiotoxicity, and underlying mechanisms of action of anthracycline chemotherapy–induced cardiotoxicity.

LITERATURE SEARCH: PubMed®, CINAHL®, Embase®, and Web of Science were searched in May 2018 using keywords related to heart diseases, anthracycline chemotherapy, and breast cancer.

DATA EVALUATION: Data were extracted, and study quality was assessed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

SYNTHESIS: 1,117 articles were identified through the literature search. After a review of the abstracts and articles, 15 clinical studies were identified for the final analysis by using exclusion and inclusion criteria.

IMPLICATIONS FOR PRACTICE: Nurses should recognize the critical elements for prevention and early detection of anthracycline chemotherapy–induced cardiotoxicity.

Anthracycline chemotherapy is commonly indicated for the treatment of breast cancer. These agents include doxorubicin, epirubicin, daunorubicin, and idarubicin (Smith et al., 2010). They are used singularly or in combination with other chemotherapy agents to increase the overall survival rate of breast cancer survivors (BCSs) (Gianni et al., 2009; Menna, Salvatorelli, Gianni, & Minotti, 2008). Anthracyclines are the most frequently used chemotherapy regimen in breast cancer and may reduce mortality from breast cancer by about 33% (Early Breast Cancer Trialists' Collaborative Group, 2012). Research shows that the adoption of anthracycline-based chemotherapy regimens not only increases long-term breast cancer survival rates, but also reduces the risk of relapse and death for people with early-stage breast cancer after surgery (Smith et al., 2010). Because all chemotherapy agents may cause some adverse reactions among BCSs, cardiotoxicity is a concern. The cytotoxic effects of anthracycline agents are from the generation of oxygen-derived free radicals, which can cause myocyte apoptosis. The loss of cardiac myocytes results in cardiomyopathy and cardiac failure (Ewer & Lippman, 2005). The use of anthracyclines among BCSs is restricted because of the severe cardiac side effects.

Although anthracycline chemotherapy–induced cardiotoxicity in people with breast cancer has been identified as a major health concern (Brower, 2013; Smith et al., 2010), a need remains for information about what is known and what is not. Studies have shown that anthracycline chemotherapy may cause a decrease in left and right ventricular systolic and diastolic functioning (Abdar Esfahani, Mokarian, & Karimipanah, 2017; Appel, Jensen, Nielsen, Ryberg, & Zerahn, 2010; Boyd et al., 2017; Narayan et al., 2017; Sawaya et al., 2012; Schneeweiss et al., 2018; Serrano et al., 2015), impaired myocardial contraction measured

by strain imaging (Cheng et al., 2017; Khouri et al., 2014; Stoodley et al., 2013), impaired left atrial electrical conduction (Yaylali, Saricopur, Yurtdas, Senol, & Gokoz-Dogu, 2016), and cardiac myopathy and cardiac failure (Bowles et al., 2012). The relationships between anthracycline chemotherapy–induced cardiotoxicity and type or stage of breast cancer, patient age, specific drug dosage, previous cardiovascular status, and risk factors prior to chemotherapy still need to be examined.

The major aim of this systematic review was to identify specific cardiac problems after treatment related to use of anthracycline chemotherapy among early- and late-stage BCSs. The review also identified specific risk factors that increase the risk and the underlying mechanism of anthracycline chemotherapy–induced cardiotoxicity, as well as the clinical implications of anthracycline chemotherapy–induced cardiotoxicity for BCSs.

Methods

Search Strategies

The search included studies published from January 2008 to June 2018 using PubMed®, CINAHL®, Embase®, and Web of Science. The authors used specified MeSH (Medical Subject Headings) terms and keywords related to anthracycline chemotherapy–induced cardiotoxicity in patients with breast cancer. Combination terms associated with heart disease or heart diseases, anthracycline or drug therapy or chemotherapy, and breast cancer or breast neoplasm or breast neoplasms were used. All publications were cross-checked to retrieve the articles using the selection criteria. The final search strategy used for PubMed was also used for each electronic health journal database. Additional publications were also identified by reviewing the reference lists from eligible articles.

Inclusion and Exclusion Criteria

Citations from all search results were downloaded and merged by using the reference management software package EndNote X7. This was followed by screening study titles and abstracts for potential inclusion and then reviewing full-text articles to determine the eligibility for inclusion. Reported studies met the following inclusion criteria:

- Clinical trial research focused on anthracycline chemotherapy–induced cardiac issues among BCSs aged 18 years or older
- Original article publications
- Published in peer-reviewed journals

- Published in English
- Published from January 2008 to June 2018

Studies were excluded if they were not clinical trial research, research on chemotherapy drugs used for a cancer other than breast cancer, not focused on anthracycline chemotherapy–induced cardiotoxicity, focused on chemotherapy drugs other than anthracycline among BCSs, or published before January 1, 2008. For the purpose of this review, cardiotoxicity is defined as left ventricular ejection fraction (LVEF) decreased by 10% or greater, acute or chronic cardiac failure, and other cardiac problems caused by anthracycline chemotherapy (Boyd et al., 2017; Finkelman et al., 2017; Grover et al., 2015; Narayan et al., 2017; Sawaya et al., 2012; Serrano et al., 2015).

Study designs included randomized controlled trials (RCTs), cohort studies (prospective observational studies), cross-sectional studies, and retrospective analytical studies. Study participants were restricted to patients with breast cancer who were prescribed, were undergoing, or had completed anthracycline chemotherapy.

Search Outcome

After applying inclusion and exclusion criteria to the titles and abstracts of the initial search, 27 publications met the criteria. Upon review of each of the 27 articles, 15 fulfilled all inclusion criteria and were included in the systematic review. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the selection process is presented in Figure 1. A standard spreadsheet was used to extract data related to authors, setting, design, intervention, sample characteristics, outcome measures, and results (see Table 1).

Data Evaluation

Table 2 summarizes the methodologic quality assessment of the 15 articles included in this systematic review. The Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project was used as the assessment tool (National Collaborating Centre for Methods and Tools, 2017). This instrument provides a standardized means to assess study quality for review of articles related to public health. It also provides an overall methodologic quality rating of evidence using a scale of strong, moderate, or weak rating in eight areas (i.e., selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis) (National Collaborating Centre for Methods and Tools, 2017). Thirteen of the

15 studies received a moderate global quality rating (Abdar Esfahani et al., 2017; Appel et al., 2010; Cheng et al., 2017; Finkelman et al., 2017; Grover et al., 2015; Ho et al., 2010; Khouri et al., 2014; Kotwinski et al., 2016; Narayan et al., 2017; Sawaya et al., 2012; Serrano et al., 2015; Stoodley et al., 2013; Yaylali et al., 2016). Two studies received a strong global rating (Bowles et al., 2012; Boyd et al., 2017). None of the studies received a weak global quality rating. Overall, the quality rating for the 15 reviewed studies was moderate (Zeng et al., 2015).

Results

Study Characteristics

The 15 clinical studies consisted of three retrospective studies, four cross-sectional studies, and eight prospective studies. For the eight prospective studies, six studies assessed echocardiograms to measure left ventricular longitudinal systolic and diastolic myocardial strain, early and subsequent changes in left ventricular ejection, and symptoms of cardiac failure (Boyd et al., 2017; Cheng et al., 2017; Narayan et al., 2017; Sawaya et al., 2012; Serrano et al., 2015; Stoodley et al., 2013). One study used cardiovascular magnetic resonance to measure the changes of LVEF before and after anthracycline-based chemotherapy (Kotwinski et al., 2016). One study used a blood sample to measure early changes in arginine-nitric oxide metabolite levels and the association with cancer therapeutics–related cardiac dysfunction (Finkelman et al., 2017).
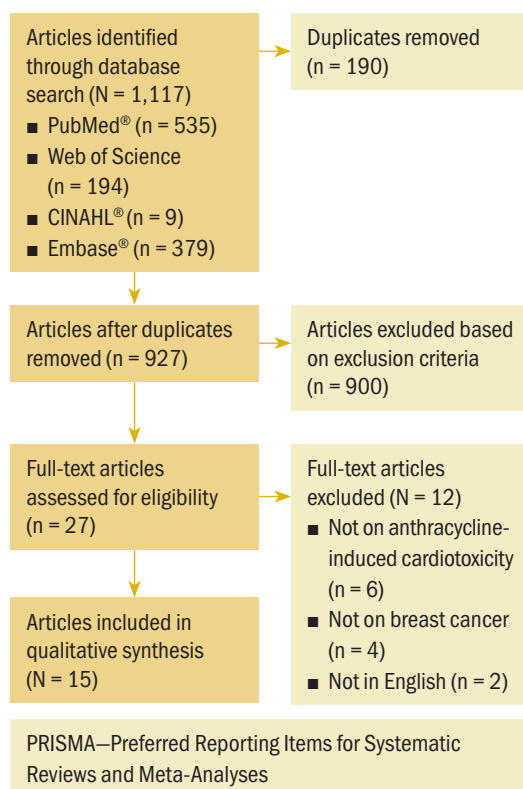
Participant Characteristics

The number of participants ranged from 27 to 12,500 BCSs. The mean age of participants was 60 years (range = 18–99). The total population was 13,781 BCSs, with the majority having advanced-stage breast cancer. All were prescribed anthracycline or anthracycline plus other chemotherapy. Studies were made up of BCSs who completed their anthracycline chemotherapy within seven days to eight years after anthracycline treatment. Most of the BCSs (n = 12,956) were from the United States; the remaining participants were from Denmark, Iran, Australia, Canada, Ireland, the United Kingdom, Spain, China, and Turkey. BCSs with preexisting cardiovascular diseases were excluded from the clinical studies (Bowles et al., 2012; Serrano et al., 2015; Yaylali et al., 2016).

Post-Treatment Cardiac Issues
After Anthracycline Chemotherapy

This review identified specific post-treatment cardiac issues related to anthracycline chemotherapy among BCSs. The type of acute and chronic cardiotoxicity

FIGURE 1. PRISMA Flowchart of Selected Studies

Articles identified through database search (N = 1,117)
- PubMed® (n = 535)
- Web of Science (n = 194)
- CINAHL® (n = 9)
- Embase® (n = 379)

→ Duplicates removed (n = 190)

Articles after duplicates removed (n = 927)

→ Articles excluded based on exclusion criteria (n = 900)

Full-text articles assessed for eligibility (n = 27)

→ Full-text articles excluded (N = 12)
- Not on anthracycline-induced cardiotoxicity (n = 6)
- Not on breast cancer (n = 4)
- Not in English (n = 2)

Articles included in qualitative synthesis (N = 15)

PRISMA—Preferred Reporting Items for Systematic Reviews and Meta-Analyses

caused by anthracycline chemotherapy (ranging from months to years after treatment) in patients with breast cancer included the following:

- Risk of developing chronic or acute cardiac failure and decreased LVEF (Appel et al., 2010; Boyd et al., 2017; Kotwinski et al., 2016; Narayan et al., 2017; Sawaya et al., 2012; Stoodley et al., 2013)
- Decreased myocardial function and impaired global longitudinal strain, a parameter assessed by 2D speckle-tracking echocardiography (2DSTE) to evaluate left ventricular function (Bowles et al., 2012; Khouri et al., 2014)
- Moderately elevated baseline blood pressure (Kotwinski et al., 2016)
- Atrial electromechanical delay and impaired atrial electronic conduction and aortic function (Grover et al., 2015; Yaylali et al., 2016)
- Risk of decreased right ventricular systolic and diastolic function (Abdar Esfahani et al., 2017; Serrano et al., 2015)
- Increase in the duration of contraction mainly by increasing the isovolumic contraction time (Cheng et al., 2017)

TABLE 1. Summary of Studies Related to Anthracycline Chemotherapy–Induced Cardiotoxicity Selected for Systematic Review

Study and Setting	Sample, Design, and Intervention	Outcome Measures	Results
Abdar Esfahani et al., 2017 (Iran)	Cross-sectional study of 67 women with newly diagnosed breast cancer who were scheduled to receive anthracycline for the first time ($\overline{X}$ age = 40.75 years, SD = 7.14); physical examination and echocardiography were performed before administration of anthracycline for the first time and 6 months later.	Variables included right heart measures (RV end-diastolic dimensions and right atrium length and diameter), RV fractional area change, index of myocardial performance, tricuspid annular plane systolic excursion, pulmonary artery systolic pressure, lateral tricuspid annular early and late diastolic velocities, and tissue Doppler diastolic and systolic velocities.	A significant decrease was found in RV systolic and diastolic function during anthracycline chemotherapy. Altered RV echocardiographic indexes can be considered as early indicators of anthracycline chemotherapy–induced cardiotoxicity.
Appel et al., 2010 (Denmark)	Retrospective study of 34 women with advanced metastatic breast cancer receiving high-dose epirubicin within a time interval of 2 years ($\overline{X}$ age = 57 years, SD = 6.9); MUGA examination was done prior to and after treatment, and patients were observed for the development of heart failure.	A change in diastolic filling variables was measured by MUGA scan for individuals at risk for developing heart failure.	Epirubicin treatment induces a considerable decrease in LVEF and a high risk of developing congestive heart failure even when the accepted maximum limit for the cumulated dose is not exceeded. The risk of developing heart failure is significantly higher if LVEF is reduced less than 50% after ending epirubicin treatment.
Bowles et al., 2012 (United States)	Retrospective cohort study of 12,500 patients with stage I invasive breast cancer ($\overline{X}$ age = 60 years, range = 22–99) who received anthracycline alone (30%), trastuzumab alone (1%), anthracycline plus trastuzumab (4%), other chemotherapy (20%), or no chemotherapy (47%); 86% of participants were White, 10% were Black, 4% were Asian, and 0.3% were Native American or Alaskan Native.	Incidence of heart failure/CM was identified following chemotherapy initiation, and risk of heart failure/CM with time-varying chemotherapy exposures versus no chemotherapy was assessed.	For patients receiving anthracycline alone, the risk of heart failure/CM was higher compared to patients who received no chemotherapy.
Boyd et al., 2017 (Australia)	Prospective study of 151 patients with histologically confirmed breast cancer ($\overline{X}$ age = 52 years, SD = 9) who were administered anthracycline chemotherapy (i.e., doxorubicin or epirubicin) in 4–6 cycles; no patients were receiving trastuzumab therapy at the time of the study, and follow-up echocardiograms were performed within 7 days of chemotherapy completion. 26% of patients had more than one cardiac risk factor.	LVEF, GLS, strain rate, and radial and circumferential strain were assessed. In addition, left atrial volumes and LV diastolic parameters were evaluated by echocardiography.	Longitudinal and circumferential strain were significantly reduced after anthracycline therapy despite clinically insignificant changes in LVEF. LV subclinical dysfunction, defined as a greater than 11% reduction in GLS, occurred in 22% of the cohort. Reductions in GLS were induced equally by doxorubicin and epirubicin. In patients with greater than 11% reduction in GLS, greater segmental strain reduction was evident. Increased occurrence of diastolic dysfunction occurred with subclinical systolic dysfunction.

TABLE 1. Summary of Studies Related to Anthracycline Chemotherapy–Induced Cardiotoxicity Selected for Systematic Review *(Continued)*

Study and Setting	Sample, Design, and Intervention	Outcome Measures	Results
Cheng et al., 2017 (United States and Canada)	Prospective multicenter study of 41 patients with HER2-positive breast cancer ($\overline{X}$ age = 50 years, SD = 11) who received 240 mg/m^2 doxorubicin (60 mg/m^2 every 3 weeks) without radiation therapy; patients underwent an echocardiogram before and after chemotherapy. 11% of patients had hypertension, 8% had hyperlipidemia, and 5% were smokers.	Peak longitudinal myocardial systolic strain was measured on the apical 4- and 2-chamber view. The time to peak systolic longitudinal strain, ejection time, isovolumic contraction time, systolic time, and diastolic time were measured using strain curves and Doppler tracings and compared before and after anthracycline therapy. The heterogeneity of contraction (dyssynchrony) was measured by the SD of the systolic longitudinal strain of all segments.	Anthracycline treatment induces an increase in the duration of contraction, mainly by increasing the isovolumic contraction time. This increase is correlated to the decrease in strain and may indicate cardiac dysfunction.
Finkelman et al., 2017 (United States)	Ongoing prospective longitudinal cohort study of 170 patients with stage I (17%), II (55%), III (27%), or IV (1%) breast cancer ($\overline{X}$ age = 48 years, range = 41–56) who received (a) doxorubicin 240 mg/m^2 and cyclophosphamide every 2 weeks for 4 cycles followed by paclitaxel every 2 weeks for 4 cycles or weekly for 12 weeks or (b) doxorubicin 240 mg/m^2 and cyclophosphamide every 2 weeks for 4 cycles followed by paclitaxel and trastuzumab; 41% of patients were smokers, 28% had hypertension, 24% had hyperlipidemia, and 8% had diabetes mellitus. 60% of patients were White, 29% were Black, and 11% were other or unknown.	Plasma levels of arginine, citrulline ornithine, asymmetric dimethylarginine, symmetric dimethylarginine, and N-monomethylarginine were quantified at baseline and 1 and 2 months after doxorubicin initiation.	18% of participants receiving doxorubicin alone experienced CTRCD. For patients with breast cancer undergoing doxorubicin therapy, CTRCD rate is associated with early changes in arginine-nitric oxide metabolites, specifically arginine, asymmetric dimethylarginine, and N-monomethylarginine. These findings suggest a plausible mechanistic pathway involving endothelial dysfunction and increased oxidative and nitrosative stress. Biomarkers of arginine-nitric oxide metabolism could have the potential to identify patients at high risk for cardiac dysfunction from these therapies.
Grover et al., 2015 (Australia)	Cross-sectional study of 27 patients with early-stage (n = 25) or metastatic (n = 2) breast cancer ($\overline{X}$ age = 54 years, SD = 11) who received either 3–6 cycles of doxorubicin 50 mg/m^2 and/or trastuzumab in combination with taxanes or on its own with a loading dose of 8 mg/kg followed by 6 mg/kg every 21 days for 12 months as prescribed (not concurrently); 48% of patients were smokers, 37% had hypercholesterolemia, 26% had a family history of coronary artery disease, 19% had hypertension, and 15% had diabetes.	Patients underwent clinical evaluation and cardiovascular magnetic resonance imaging at baseline and 1, 4, and 14 months post-treatment, including functional assessment, measurement of aortic pulse wave velocity using velocity encoded imaging, and distensibility at ascending aorta and proximal descending aorta.	Compared to patients receiving trastuzumab, patients receiving anthracycline chemotherapy had a greater reduction in aortic distensibility in the ascending aorta with time. Lasting elevations in aortic stiffness and a decrease in aortic compliance suggested persistent negative arterial remodeling at least 6 months after anthracycline chemotherapy.

TABLE 1. Summary of Studies Related to Anthracycline Chemotherapy–Induced Cardiotoxicity Selected for Systematic Review *(Continued)*

Study and Setting	Sample, Design, and Intervention	Outcome Measures	Results
Ho et al., 2010 (Ireland)	Cross-sectional study of 75 patients with breast cancer ($\overline{X}$ age = 54 years, SD = 8) who received anthracycline chemotherapy with or without adjuvant trastuzumab; 13% of patients were smokers, and 8% had hypertension.	LVEF, peak systolic myocardial excursion, diastolic peak mitral E and A velocities, 6-point average of mitral annular E velocities function, 2D global and regional longitudinal, and radial strain were determined using standard 2D Doppler and tissue Doppler echocardiographic methods and speckle-tracking software.	Despite a normal LVEF, subtle abnormalities in myocardial diastolic and systolic function were present in patients with asymptomatic breast cancer previously exposed to anthracycline treatment. Regional reductions in longitudinal strain in the septal, lateral, anterior, and posterior walls were found in the anthracycline group.
Khouri et al., 2014 (United States)	Cross-sectional study of 57 patients with estrogen receptor–positive and HER2-negative (stages IA–IIIC) breast cancer ($\overline{X}$ age = 52 years, SD = 10) who were treated with standard-dose doxorubicin chemotherapy (median cumulative dose of 240 mg/m^2 without HER2-directed therapies); 28% of patients had hypertension, 21% were obese, 11% had hyperlipidemia, 5% were smokers, and 2% had diabetes.	Resting LV function was assessed by LVEF using 2D and 3D echocardiography and by GLS using 2DSTE.	Despite preserved LVEF, resting GLS detected reduced myocardial systolic performance, with 20% of patients demonstrating evidence of impaired GLS (i.e., greater than or equal to –17%). These results are consistent with those reported by other small studies in early-stage breast cancer showing GLS impairments in the absence of LVEF decline during and within 1 year of doxorubicin-containing adjuvant therapy.
Kotwinski et al., 2016 (United Kingdom)	Prospective gene environment interaction study of 196 patients with early-stage breast cancer ($\overline{X}$ age = 48 years) who were treated with planned adjuvant or neoadjuvant anthracycline chemotherapy (99% epirubicin 400 [range = 300–450] mg/m^2 and 1% doxorubicin 240 mg/m^2 for a median of 4 [range = 4–6] cycles)	LVEF was measured using cardiovascular magnetic resonance before and greater than 12 months after anthracycline chemotherapy.	Subclinical cardiotoxicity is common even within this low-risk cohort. Risk of cardiotoxicity was associated with modestly elevated baseline blood pressure, indicating that close attention should be paid to blood pressure in patients considered for anthracycline chemotherapy. By using cardiovascular magnetic resonance, the authors found that 1 in 5 patients experienced a decrease in LVEF of at least 5% following anthracycline chemotherapy.
Narayan et al., 2017 (United States)	Ongoing prospective longitudinal cohort study of 277 patients with breast cancer aged 18 years or older who received doxorubicin 240 mg/m^2 with concurrent cyclophosphamide followed by paclitaxel (64%), trastuzumab with docetaxel and cyclophosphamide or carboplatin (18%), or both (18%)	LV structure, diastolic and contractile function, and VA coupling measures were quantified by echocardiograms. Changes in echocardiographic parameters were evaluated over time.	For 64% of participants treated with doxorubicin, there was a sustained modest decrease in LVEF during follow-up at 1 and 3 years. Changes in volumes, strain, and ventricular-arterial coupling were consistently associated with concurrent and subsequent LVEF declines and recovery across therapies.

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TABLE 1. Summary of Studies Related to Anthracycline Chemotherapy–Induced Cardiotoxicity Selected for Systematic Review *(Continued)*

Study and Setting	Sample, Design, and Intervention	Outcome Measures	Results
Sawaya et al., 2012 (United States)	Prospective multicenter study of 81 patients with HER2-positive breast cancer ($\bar{X}$ age = 50 years, SD = 10) who were treated with either doxorubicin (cumulative dose of 240 mg/m^2) or epirubicin (cumulative dose of 300 mg/m^2) for 3 months, followed by weekly paclitaxel (80 mg/m^2) and trastuzumab (2 mg/kg) for 3 months, and then trastuzumab only (6 mg/kg) every 3 weeks for 9 months; 32% of patients had hypertension, 22% had hyperlipidemia, 7% were smokers, and 1% had diabetes.	LVEF, peak systolic longitudinal, radial, and circumferential myocardial strain were evaluated every 3 months by using echocardiograms. Ultrasensitive troponin I, N-terminal pro-B-type natriuretic peptide, and the interleukin family member (ST2) were also evaluated every 3 months using blood samples.	A significant decrease of LVEF (8% or more) was detected at the completion of anthracycline chemotherapy in 15% of patients who developed cardiotoxicity during follow-up. Changes in troponin or strain were detected at completion of anthracycline chemotherapy in 78% of patients developing subsequent cardiotoxicity. Longitudinal strain of less than 19% was present in all patients who later developed symptoms of heart failure.
Serrano et al., 2015 (Spain)	Analytical observational prospective cohort study of 100 patients with breast cancer ($\bar{X}$ age = 49.7 years, SD = 9) who received anthracycline chemotherapy (epirubicin or doxorubicin) or anthracycline chemotherapy plus trastuzumab for 2 years; 35% of patients were smokers, 22% had hypertension, 11% had hypercholesterolemia, and 7% had diabetes.	All patients underwent clinical evaluation, echocardiogram, and measurement of cardiac biomarkers at baseline, at end of anthracycline chemotherapy, and at 3 and 9 months after anthracycline chemotherapy was completed.	Development of diastolic dysfunction after treatment with anthracycline or anthracycline plus trastuzumab chemotherapy was common. The incidence of diastolic dysfunction during follow-up was 57% and persisted at the last follow-up visit in 73% of patients.
Stoodley et al., 2013 (Australia)	Prospective study of 52 patients with breast cancer ($\bar{X}$ age = 49 years, SD = 9) who received anthracycline chemotherapy (77% received doxorubicin and 23% received epirubicin); 26% of patients had hypertension, 22% had hypercholesterolemia, 12% were smokers, 6% had a history of ischemic heart disease, and 4% had diabetes.	Echocardiograms were performed 1 week prior to and 1 week following chemotherapy. Conventional Doppler, tissue velocity imaging, and 2DSTE were used to measure diastolic function. 2DSTE measurements included longitudinal diastolic strain and early and late myocardial strain rate. 2DSTE and LVEF were used to measure longitudinal systolic function.	Altered LV diastolic function was observed immediately after the administration of therapeutic doses of anthracycline chemotherapy. Analysis indicates that the changes in diastolic function were associated with reduced systolic function.
Yaylali et al., 2016 (Turkey)	Retrospective study of 53 patients with breast cancer ($\bar{X}$ age = 48 years, SD = 8) who received doxorubicin 240 mg/m^2, cyclophosphamide 2,400 mg/m^2, and paclitaxel 960 mg/m^2	Echocardiographic measurements were performed 11 months (SD =7, median = 9) after treatment with anthracycline chemotherapy.	In patients with breast cancer after anthracycline chemotherapy, left intra-atrial electromechanical intervals were prolonged, and LV diastolic function was impaired. Impaired left ventricular relaxation and left atrial electrical conduction could contribute to the development of atrial arrhythmias.

2DSTE—2D speckle-tracking echocardiography; CM—cardiomyopathy; CTRCD— cancer therapeutics–related cardiac dysfunction; GLS—global longitudinal strain; LV—left ventricular; LVEF—LV ejection fraction; MUGA—multigated acquisition; RV—right ventricular; VA—ventricular–arterial

Note. Specific cardiac issues post-treatment are related to aim 1 of the current study, specific cardiovascular risk factors are related to aim 2 of the current study, and clinical implications of anthracycline chemotherapy–induced cardiotoxicity are related to aim 3 of the current study.

■ Early alterations in arginine-nitric oxide metabolite levels (Finkelman et al., 2017).

When monitoring anthracycline chemotherapy–induced cardiotoxicity, evaluation was typically focused on measuring the left ventricular systolic function by using 2DSTE (Stoodley et al., 2013). The most common cardiotoxicity after anthracycline treatment is left ventricular systolic dysfunction and possible arrhythmias (Yaylali et al., 2016). Chronic and acute cardiac failure is the major concern of anthracycline chemotherapy–induced cardiotoxicity, and the risk of cardiac failure is high if patient's LVEF is less than 50% (Appel et al., 2007).

Significant Risk Factors for Cardiotoxicity

Results of this review identified significant risk factors related to anthracycline chemotherapy–induced cardiotoxicity. Cumulative anthracycline dose, prior trastuzumab therapy, elevated blood pressure, increased height, high body mass index (BMI), and high body surface area (BSA) are all associated with increased chronic progressive anthracycline cardiotoxicity (Guenancia et al., 2016; Kotwinski et al., 2016). The risk of cardiac failure and/or cardiomyopathy was significantly increased among BCSs treated with trastuzumab alone or anthracycline plus trastuzumab as compared to BCSs treated with anthracycline alone (Bowles et al., 2012; Finkelman et al., 2017; Guglin, Cutro, & Mishkin, 2008). A five-year cumulative incidence rate for cardiac failure and/or cardiomyopathy was associated with anthracycline use in late-stage breast cancer and with older age (Bowles et al., 2012). Risk factors for anthracycline chemotherapy–induced diastolic dysfunction include blood pressure, BMI, and age (Yaylali et al., 2016). Jordan et al. (2016) found that risk factors for anthracycline chemotherapy–induced cardiovascular events and myocardial fibrosis included increased body weight, high heart rate, and high systolic blood pressure, as well as history of coronary artery disease, diabetes mellitus, hyperlipidemia, or hypertension. In addition, myocardial fibrosis increased with age and was higher among women (Jordan et al., 2016).

Underlying Mechanisms of Cardiotoxicity

Results of this review identified the proposed underlying mechanisms of anthracycline chemotherapy–induced cardiotoxicity. Although the exact mechanism for anthracycline chemotherapy–induced myocardial dysfunction is unclear, there are several hypotheses. Anthracycline chemotherapy–induced cardiotoxicity is identified as a type I

cardiotoxicity and reported to be irreversible because of myocardial damage (Kotwinski et al., 2016). Because of the multiple toxic effects of anthracycline, mitochondrial dysfunction (DNA damage and impaired bioenergetics), possible cellular senescence (shortening of telomere length and loss of cardiac progenitor cells) may play a role in cardiac dysfunction and cardiac failure (Kotwinski et al., 2016). Intracellular oxidative stress resulting in mitochondrial dysfunction, cell apoptosis, and myocyte necrosis is thought to be associated with myocardial damage (Stoodley et al., 2013). The majority of research on anthracycline chemotherapy–induced cardiotoxicity focused on myocellular injury. Jordan et al. (2016) found that anthracycline treatment can cause chronic and persistent elevated extracellular volume, which is associated with subclinical development of diffuse myocardial fibrosis with the fibrotic tissue lowering left ventricular myocellular mass. The elevated extracellular volume reflects the interstitial process that may influence changes in myocellular composition (intramyocellular edema or deposition of protein, lipids, or iron); it also may change myocardial oxygenation or perfusion. Increased subclinical interstitial myocardial fibrosis coincides with decreased LVEF and myocardial mass among BCSs treated with anthracycline chemotherapy (Jordan et al., 2016). To assess the atrial mechanical alteration and prolonged left intra- and interatrial electromechanical features by anthracycline therapy, Yaylali et al. (2016) suggested that the change of cardiac function after anthracycline treatment is the result of the ventricular proarrhythmogenic mechanism. The left ventricular diastolic dysfunction and delayed electrical conduction creates an arrhythmogenic substrate, which leads to a decrease in intracardiac conduction and a heterogeneous dispersion of repolarization. Cardiac arrhythmias are caused by these two effects. Prolonged electromechanical intervals in the left intra- and interatrial are because of anthracycline chemotherapy–induced oxidative stress, which may cause autonomic dysfunction (Yaylali et al., 2016).

Discussion

Among all chemotherapy drugs, anthracyclines are the most common and effective antineoplastic agents (Patel, Balakrishnan, Kumar, Naswa, & Malhotra, 2010). Anthracyclines are recommended in the majority of triple-negative, HER2-positive and high-risk luminal HER2-negative tumors (Early Breast Cancer Trialists' Collaborative Group, 2012). Anthracyclines are not routinely recommended for use concomitant with endocrine therapy for estrogen receptor–positive

TABLE 2. Component and Global Assessment of Study Quality by Using the Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies

Study	Selection Bias	Study Design	Confounders	Blinding	DCM	Withdrawals/ Dropouts	Global Rating
Abdar Esfahani et al., 2017	2	2	2	1	1	2	2
Appel et al., 2010	2	2	2	1	1	1	2
Bowles et al., 2012	1	2	1	1	1	1	1
Boyd et al., 2017	2	1	1	1	1	1	1
Cheng et al., 2017	2	1	1	3	2	1	2
Finkelman et al., 2017	2	1	1	2	1	1	2
Grover et al., 2015	2	2	1	1	1	1	2
Ho et al., 2010	2	2	1	1	1	1	2
Khouri et al., 2014	2	2	1	2	1	1	2
Kotwinski et al., 2016	2	1	1	1	1	1	2
Narayan et al., 2017	2	1	3	1	1	1	2
Sawaya et al., 2012	2	1	1	1	1	1	2
Serrano et al., 2015	2	2	1	3	1	1	2
Stoodley et al., 2013	2	1	1	1	1	1	2
Yaylali et al., 2016	2	2	3	3	1	1	2

DCM—data collection methods
Note. A rating of 1 is strong, 2 is moderate, and 3 is weak.

breast cancer (Albain et al., 2009). The benefit of anthracyclines is undermined by potential cardiotoxicities that could be life-threatening (Stoodley et al., 2013). Therefore, healthcare providers should be vigilant to diagnose anthracycline chemotherapy–induced cardiotoxicity early so that actions or interventions can be implemented to prevent irreversible damage to the patient's heart (Abdar Esfahani et al., 2017). If anthracyclines remain as one of the cornerstones of chemotherapy for breast cancer, a need exists for cardio-oncology expertise to balance the use of anthracycline chemotherapy with the risk for cardiotoxicity (Groarke & Nohria, 2015).

Traditionally, hypertension, diabetes mellitus, hyperlipidemia, family history of premature coronary artery disease, and history of smoking are included as risk factors for cardiovascular disease (Negishi et al., 2013). Research also indicates that age is an established risk factor for anthracycline chemotherapy–induced cardiotoxicity among BCSs (Jordan et al., 2016).

Evidence shows that a BMI of more than 27 kg/m^2 was significantly associated with left ventricular dysfunction after anthracycline therapy in BCSs (Fumoleau et al., 2006). Body weight of more than 70 kg is identified as another risk factor of anthracycline chemotherapy–induced cardiotoxicity in patients with breast cancer (Dranitsaris et al., 2008). Among anthracycline agents, doxorubicin and epirubicin are most frequently used for BCSs (Khasraw, Bell, & Dang, 2012). Doxorubicin-containing chemotherapy causes dose-dependent myocardial injury for people with early-stage breast cancer (McGowan et al., 2017).

The mechanisms of anthracycline chemotherapy–induced cardiotoxicity in breast cancer are complex (Mele et al., 2016). According to a study by Cardinale et al. (2015), anthracycline chemotherapy–induced cardiotoxicity represents a continuum that begins with subclinical myocardial cell injury, followed by an early asymptomatic LVEF reduction, and then progresses to symptomatic cardiac failure if untreated.

Oxidative stress has been identified as a central mechanism in anthracycline-related myocardial cell injury (Xu, Tang, Qian, & Ashraf, 2001). Because the heart is susceptible to oxidative stress, anthracycline therapy can cause toxic free radicals that increase oxidative stress and lead to cardiovascular injury (Grover et al., 2015). Nitric oxide synthase–dependent endothelial dysfunction is identified as the primary mechanism for doxorubicin-induced cardiotoxicity (Deng et al., 2009). The arginine-nitric oxide metabolism pathway in anthracycline chemotherapy–induced cardiotoxicity causes endothelial dysfunction and edema secondary to increased oxidative stress in the vascular wall (Wolf & Baynes, 2006). Doxorubicin is reported to suppress endothelin production, which makes the myocytes susceptible to death. Structural changes of the vascular matrix can be caused by interference of the vascular tone regulated by endothelin, increasing aortic stiffness and the risk of cardiovascular disease (Keltai et al., 2010).

Implications for Practice and Research

No generally accepted method exists to provide protection for cardiac damage induced by anthracyclines, often leading to symptomatic cardiac failure and death during or after chemotherapy treatment. Clinical guidelines are needed for better surveillance and management of significant complications of anthracycline chemotherapy–induced cardiotoxicity among BCSs (Groarke & Nohria, 2015).

Research shows that the timing of detection rather than the timing of occurrence is reflected in late-onset anthracycline chemotherapy–induced cardiotoxicity in patients with cancer (Groarke & Nohria, 2015). Once LVEF reduction is detected or clinical symptoms are noted in the patient, anthracycline chemotherapy–induced cardiotoxicity is not reversible, and the prognosis is very poor (Felker et al., 2000; Jensen, Skovsgaard, & Nielsen, 2002). Doppler-based myocardial deformation imaging, such as 2DSTE, should be used to monitor patients' cardiac function during anthracycline chemotherapy and in long-term follow-up to prevent potential cardiac failure (Jurcut et al., 2008; Stoodley et al., 2013). Because early changes in global longitudinal strain are associated with subsequent declination in LVEF, this finding supports using global longitudinal strain detected by 2DSTE as an early indicator for anthracycline chemotherapy–induced cardiotoxicity in clinical practice (Narayan et al., 2017). Cardinale et al. (2015) found that anthracycline chemotherapy–induced cardiotoxicity in patients with cancer occurs almost exclusively within the first year

after treatment; therefore, cardiac surveillance during this high-risk period is critical (Groarke & Nohria, 2015). Early initiation of cardioprotective agents in patients with breast cancer following anthracycline chemotherapy has been found to be beneficial (Boyd et al., 2017). Dexrazoxane can reduce the incidence of contractile dysfunction in patients with breast cancer treated with anthracycline (Sun, Shi, & Geng, 2016). The American Society of Clinical Oncology Chemotherapy and Radiotherapy Expert Panel offers a guideline to support the use of dexrazoxane in patients with breast cancer who received high-dose doxorubicin (Sawyer, Peng, Chen, Pentassuglia, & Lim, 2010). The American Heart Association/American College of Cardiology guidelines recommend the use of cardioprotective drugs, such as angiotensin-converting enzyme (ACE) inhibitors or beta blockers, in asymptomatic patients with abnormal LVEF after chemotherapy (Sawaya et al., 2012). Initiation of cardioprotective drugs after the early detection of anthracycline chemotherapy–induced cardiotoxicity has been found to be associated with an 82% recovery rate in a mean period of eight months (SD = 5) (Cardinale et al., 2015). The concept of type I cardiotoxicity was challenged by these data, indicating a significant potential for reversibility of anthracycline chemotherapy–induced cardiotoxicity if early detection and treatment occurs (Groarke & Nohria, 2015).

Assessment of resting LVEF for patients before administration of anthracyclines as a standard of care for people with breast cancer is recommended by the European Society of Cardiology and the 2013 American College of Cardiology Foundation/American Heart Association guidelines for management of heart failure (Eschenhagen et al., 2011; Yancy et al., 2013). Late development of chronic cardiac failure is reported to be related to epirubicin dose and patient entry-level blood pressure and inversely related to post-epirubicin LVEF. Therefore, maximum cumulated doses of doxorubicin (550 mg/m²) and epirubicin (900 mg/m²) are recommended for use (Appel et al., 2010; Ryberg et al., 1998). Recognition of hypertension and initiation of hypertension therapy before patients

start anthracycline therapy is suggested. BSA indexing of anthracycline dose may be causal because of the association between increasing BSA and subclinical chronic progressive anthracycline chemotherapy–induced cardiotoxicity (Kotwinski et al., 2016). The 2012 American Society of Clinical Oncology practice guideline recommends adjusting anthracycline dosing based on patient's BSA (Griggs, Mangu, Temin, & Lyman, 2012). Because of post-treatment cardiotoxicity, non–anthracycline-based regimens may be used as an alternative treatment for patients with breast cancer who are at risk of cardiac complications (Jones et al., 2009). Trastuzumab is not routinely recommended for concomitant administration with anthracyclines because of its cardiotoxicity (Perez et al., 2014). Anthracyclines and taxanes are recommended to be sequentially administered rather than used concomitantly (Shao et al., 2012).

Evidence from this review identifies the importance for nurses to recognize the critical elements for prevention and early detection of anthracycline chemotherapy–induced cardiotoxicity. Early detection and assessment may affect long-term patient outcomes related to cardiac symptoms. BCSs who are at high risk, particularly those receiving anthracycline and trastuzumab, will need close monitoring through a cardio-oncology program during and after treatment. In addition, careful cardiology management and use of preventive medications may be vital for prevention of adverse outcomes. Larger, long-term, multicenter prospective trials are needed to validate the relationships of specific risk factors and determine if they may be causal in nature.

Conclusion

Anthracycline chemotherapy may cause acute and chronic cardiotoxicity among BCSs. The major concerns of anthracycline chemotherapy–induced cardiotoxicity include myocardial dysfunction and cardiac failure. Risk factors associated with anthracycline chemotherapy–induced cardiotoxicity include age, gender, obesity, BSA, cumulative anthracycline dose, and preexisting patient cardiovascular conditions. Monitoring anthracycline chemotherapy–induced cardiotoxicity and early identification of risk factors are essential for treatment management. Developing and testing new programs to enhance the quality of life of BCSs is critical.

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