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Assessing Cardiovascular Disease Risk In Women Newly Diagnosed With Breast Cancer

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ASSESSING CARDIOVASCULAR DISEASE RISK
IN WOMEN NEWLY DIAGNOSED WITH BREAST CANCER

Thesis
Submitted to the Faculty
Yale University School of Nursing

In Partial Fulfillment
of the Requirements for the Degree
Master of Science in Nursing

Ashleigh Kristina Smith, RN BSN OCN

May 21, 2012

The thesis is accepted in partial fulfillment of the requirements for the degree Master of Science in Nursing.

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 May 16, 2012
[Date]

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May 16, 2012
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Abstract

ASSESSING CARDIOVASCULAR DISEASE RISK

IN WOMEN NEWLY DIAGNOSED WITH BREAST CANCER

This prospective, descriptive study was designed to explore the baseline cardiovascular disease (CVD) risk factors of women newly diagnosed with breast cancer prior to receiving treatment with anthracyclines and/or trastuzumab. Women diagnosed with breast cancer are at risk for developing CVD and may experience increased risk factors related to breast cancer diagnoses and treatments. The specific aim was to determine baseline cardiovascular risk through the use of the Framingham General Cardiovascular Risk Assessment Score (FGCVRAS) calculation and heart/vascular age calculation. Subjects included 30 women (mean age 49.97). Mean FGCVRAS was 5.58% (SD 5.68), and mean heart/vascular age was 49.62 years (SD 18.33) with 9 women having heart/vascular ages that exceeded their actual ages. At a cardiovascular risk of approximately 5.3%, vascular age began to exceed actual age. At baseline, only 3 of the 30 women had ever had a cardiovascular risk assessment, 14 women had at least two CVD risk factors, and 6 women met diagnostic criteria for metabolic syndrome. Multiple regression showed that HDL, glucose, waist circumference, and mean systolic blood pressure most contributed to CVD risk as calculated by the FGCVRAS. At baseline, women diagnosed with breast cancer demonstrate a significant risk burden for CVD that needs to be assessed and addressed prior to beginning potentially cardiotoxic treatments.

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Statement of the Problem

Overall survival and quality of life are key treatment outcomes for breast cancer survivors. Breast cancer remains the most common cancer among women in the United States, with 2,591,855 having reported diagnoses of breast cancer.[1] Risk increases in women ages 40-49 and continues to increase with age.[1] With current therapies, the five-year survival rate for breast cancer is 89% overall, and 100% for carcinoma in situ.[1] The American Cancer Society estimates that there are 2.5 million breast cancer survivors in the United States alone.[2] With improving breast cancer survival rates, competing causes of death have emerged and contributed to increased mortality, including cardiovascular disease.[3] CVD risk increases after age 40,[4] correlating closely with the age that breast cancer risk also increases.[1]

As the length of survival after breast cancer therapy continues to increase, the potential impact of cardiovascular risk (CVR) becomes an important consideration for clinicians, especially in combination with the cardiotoxic side effects of breast cancer therapy. Cardiotoxicity as both a short- and long-term effect of cancer therapy results in decreased quality of survival.[5] It has been well documented in women with breast cancer as a result of treatment with anthracyclines,[6-13] trastuzumab,[8-91011, 13-18] and radiation therapy,[10, 11, 19-24] with risks including cardiac dysfunction, weight gain, and increased waist circumference.[7, 14, 17, 18, 25] Endocrine therapy, resulting in marked decreases in estrogen levels, also raises concern about potential cardiovascular risks.[26-34] Consequently, not only are women faced with a high lifetime risk of developing CVD, but they may also be at an increased risk because of their breast cancer diagnoses and treatments.

<center>1</center>

In the United States, CVD is the number one cause of death, accounting for one out of every 2.9 deaths.[4] Furthermore, one in three adults in the United States has CVD, and the risk of having CVD increases after age 40; women who are free of CVD at age 40 still have a greater than 50% lifetime risk for developing it, and women who are free of CVD at age 50 continue to have a high lifetime risk of 39.2%.[4] Non-breast cancer-related health issues, and specifically CVD, continue to be a common cause of death among breast cancer survivors,[34-40] demonstrating the importance of screening for, preventing, and treating CVD in this at-risk population, even in asymptomatic patients.[4, 41-43]

Despite this evidence, there are significant barriers to reducing cardiovascular morbidity and mortality related to cancer treatment. Patients must be screened for cardiac risk factors, and pre-existing cardiac disease must be treated in a manner that complements cancer treatment.[44] Standard tests utilized to detect cardiac damage have low sensitivity,[39] new targeted therapies also have cardiovascular side effects,[39, 40] and there is currently no known way to evaluate subclinical disease.[39, 44-48] Furthermore, even with guidelines recommending screening and risk assessments, healthcare provider compliance has been inconsistent.[49, 50] Providers describe barriers to addressing CVD risk, including insurance coverage regarding lifestyle interventions, lack of time, and the patients themselves.[49, 50] Also, despite similar calculated risk for female and male patients, providers were more likely to describe their female patients as at lower risk for cardiac disease.[50] Consequently, women newly diagnosed with breast cancer may begin treatment without ever having cardiovascular risk assessed by a primary care provider. Furthermore, although there are national guidelines in place for cardiovascular risk assessments in the general population, there are no standards for risk assessments before or after breast cancer treatment, despite evidence that they are needed.[41, 44]

In summary, women diagnosed with breast cancer continue to be at risk for developing CVD and may experience increased risk factors related to their breast cancer diagnoses and treatment with anthracyclines and/or trastuzumab. This study was designed to determine the cardiovascular risk of women newly diagnosed with breast cancer prior to receiving treatment with anthracyclines and/or trastuzumab. The following research questions guided the study:

1. What is the Framingham General Cardiovascular Risk Assessment Score of women newly diagnosed with breast cancer?

2. What is the heart/vascular age calculation of women newly diagnosed with breast cancer?

Review of the Literature

   Cardiovascular risks.

Cardiovascular risks factors were first developed by the Framingham Heart Study, which sought to determine factors that predict cardiac disease based on mathematical models.[51] The Framingham Heart Study developed risk scores by which risk of coronary heart disease (CHD) events could be predicted mathematically based on major CHD risk factors; these included sex, age, blood pressure, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), smoking, and diabetes. This resulted in the development of the Framingham Risk Assessment for Coronary Heart Disease (FRACHD), a multivariate assessment utilized to estimate risk of atherosclerotic CVD. Blood pressure and cholesterol categories were ultimately added to this assessment score in accordance with Fifth Joint National Committee on Hypertension (JNC-V) and the National Cholesterol Education Program Adult Treatment Panel II recommendations.[52, 53] Original assessments have changed over time, and now include age, total cholesterol, HDL, systolic blood pressure, use of anti-hypertensive medications, smoking, and diabetes. Other risk factors, including abdominal obesity, left ventricular hypertrophy,

insulin resistance, high triglycerides, and family history have been identified, as well.[52, 53] As medical understanding of the processes underlying atherosclerosis became apparent, it was recognized that, while useful in predicting high risk, a low score on the FRACHD was insufficient to define low risk, especially in women.[43] This resulted in the development of the Framingham General Cardiovascular Risk Assessment Score (FGCVRAS), which is a broader multivariate risk assessment of general 10-year CVD risk and the risk of individual CVD events, as well as a method for describing vascular age.[43] It encompasses more than atherosclerotic CVD, and includes risk of CHD, cerebral vascular events, peripheral artery disease, and heart failure.[52, 53]

Metabolic syndrome.

Metabolic syndrome refers to a group of metabolic risk factors – known CVD risk factors, including obesity, hyperglycemia, dyslipidemia, and hypertension – as well as the underlying risk factors that promote the development of metabolic syndrome, including obesity.[54, 55] Metabolic syndrome has been associated with increased risk of CVD, especially in men aged 45 years and older and women aged 55 years and older.[56] The FRACHD provides a superior prediction of CVD, although a diagnosis of metabolic syndrome may convey additional risk factors, and thus complement the FRACHD.[56]

Several organizations have statements defining metabolic syndrome with specific diagnostic criteria, including the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), and the International Diabetes Federation (IDF). There is no true consensus on the components that define metabolic syndrome; while the definitions put forth by each of these groups differ slightly, they all include glucose intolerance or insulin resistance,

obesity, hypertension, and dyslipidemia.[55, 57, 58] They all predict increased risk of CVD

independent of age, sex, ethnicity, history of CVD or type 2 diabetes mellitus (T2DM), non-HDL

cholesterol, smoking status, and family history with similar odds ratios but different sensitivities

and levels of false positive.[56]

The common characteristics of metabolic syndrome often create prothrombotic and

proinflammatory states that serve as increased risks for CVD, as well.[54] The largest underlying

risk factors of metabolic syndrome are abdominal obesity and insulin resistance; other non-

traditional risk factors of metabolic syndrome include markers of inflammation (including

elevated C-reactive protein levels), thrombophilia, and endothelial dysfunction.[54, 57]

While each of the components of metabolic syndrome is a known cardiovascular risk

factor, the presence of metabolic syndrome itself is also an important independent indicator of

cardiovascular risk. Metabolic syndrome allows for the identification of patients at increased risk

for CVD, and, depending on the diagnostic criteria utilized, is associated with two to four times

the risk of CVD, a risk that is higher in women than men and is of increasing concern in persons

with diabetes, pre-existing CVD, or chronic inflammation.[55, 57] Wilson et al. reported a baseline

prevalence of 12.5% in women aged 51 years, with an increase to 30.6% over eight years.[59] This

corresponded with relative risks of 2.25 for CVD (95% CI 1.31-3.88), and 1.54 for total coronary

heart disease (95% CI 0.68-3.53).[59] This study shows that prevalence of metabolic syndrome

increases with age and corresponds with CVD. It is important to note, however, that even in

persons with a low short-term (ten years, for example) risk of CVD or T2DM, their lifetime risks

remain high.[54]

CVD risk factors show an additive effect on cardiovascular risk; metabolic syndrome and

risk for CVD also exhibit these additive properties.[59] Furthermore, the components of metabolic

syndrome are interrelated, and ultimately linked to endothelial dysfunction.[55] Metabolic syndrome provides a framework for these relationships and for the understanding of increased risks associated with them. However, in terms of cardiovascular risk, the American Heart Association and National Heart, Lung, and Blood Institute continue to recognize metabolic syndrome as a secondary target for reduction of cardiovascular events, while maintaining that other well-established factors, such as smoking cessation, lowering LDL cholesterol levels, and managing blood pressure, should continue to be the primary targets of interventions.[54]

Hypertension.

Increases in blood pressure are related to increased risks in cardiovascular events.[54, 57] Increased blood pressure results in damage to vascular walls and endothelial dysfunction; these results have been seen even in small increases in blood pressure.[57] Overt hypertension should be treated to a goal of <140/90 mmHg; in the presence of other chronic conditions, such as diabetes or chronic kidney disease, blood pressure goals should be lower at <130/80 mmHg.[54]

Diabetes mellitus.

Diabetes is a major risk factor for atherosclerosis, increasing the risk of myocardial infarction roughly two-fold in men and four-fold in women.[57] Furthermore, the presence of diabetes increases the probability of a poorer outcome after a cardiovascular event.[57] Even pre-diabetic conditions, such as impaired fasting glucose, impaired glucose tolerance, and insulin resistance are associated with increases in cardiovascular risk.[57] The continuum – from insulin resistance, to impaired glucose tolerance, to impaired fasting glucose, and ultimately to T2DM – is important to recognize, not only to prevent the ultimate progression to diabetes, but also to mitigate the responses that cause increased cardiovascular risks.[60] The closer the individuals are

to diabetes on this continuum, the greater their cardiovascular risks.[60] Metabolic syndrome is a good predictor of diabetes, even apart from glucose intolerance.[56]

Hyperglycemia results in changes in endothelial, macrophage, and smooth muscle function, which ultimately results in atherosclerosis, decreases vascular production of nitric oxide necessary for vasodilation and endothelial function, contributes to hypertension, and increases plasminogen activator inhibitor-1 to impair thrombolysis.[60] Insulin resistance results in movement of free fatty acids from adipose tissue to the liver, promoting dyslipidemia of hypertriglyceridemia, low HDL, and small, dense LDL.[60] HDL levels are lowered in insulin resistant states as a hypercatabolic state of HDL is produced.[60] Build-up of lipid metabolites in liver cells can cause hepatic insulin resistance, as well.[60] Insulin resistance is also a proinflammatory state, which serves to increase cardiovascular risk.[60] Compensatory hyperinsulinemia has been linked to insulin resistance, and insulin levels can be a useful diagnostic tool.[54] Additionally, hyperinsulinemia may play a role in identifying persons with metabolic syndrome who may be at increased risk for CVD.[59]

Obesity, body mass index, and waist circumference.

Obesity also increases risk for CVD.[57, 60] It is associated with other cardiovascular risk factors, including the presence of diabetes, dyslipidemia, and hypertension, but research has shown that it is also an independent risk factor.[57] Research has also focused on weight distribution as an important indicator of cardiovascular risk. Upper body obesity, as measured by high waist-to-hip ratio and central (abdominal) fat distribution, is associated strongly with insulin resistance and metabolic syndrome.[54, 57] This may be related to the higher release of fatty acids from adipose tissue in upper body obesity, which can result in lipid accumulation in other tissue types, and may ultimately contribute to insulin resistance and dyslipidemia.[54] Visceral abdominal

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obesity, in particular, contributes to insulin resistance.[60] Waist measurement has been utilized as a reliable alternative measure of visceral adipose tissue, which conveys a higher risk of metabolic disturbance and cardiovascular events.[57] However, Gami et al. performed a systematic review of longitudinal studies on metabolic syndrome and cardiovascular risks and determined that substituting body mass index (BMI) for waist circumference measurements or waist-to-hip ratio did not affect outcomes.[58] While waist circumference can be a useful measurement, it must be noted that lesser degrees of abdominal width can be associated with other diagnostic criteria, and cutoffs can even vary according to ethnicity.[54]

Obesity has also been studied because of its link to breast cancer. Studies have linked elevations in BMI to breast cancer, with a relative risk of 1.26 to 2.52.[61] This risk appears to be present primarily in post-menopausal women; the relationship in premenopausal women is not clearly understood, and obesity may actually be protective in this population.[61] However, this relationship is not clear-cut. BMI is dependent on height, which is also a risk factor for breast cancer; weight gain itself has been a much stronger predictor of breast cancer risk, with a stronger association seen in weight gained after age 30-40.[61] This may be a result of weight gain related to increases in peripheral and central adipose tissue, as opposed to the gain of lean body weight seen in other age groups.[61]

Dyslipidemia.

As previously mentioned, insulin resistant states are associated with a dyslipidemia marked by hypertriglyceridemia, low HDL, and small, dense LDL.[54, 60] Dyslipidemia can exacerbate hepatic insulin resistance, and insulin resistance can also create these lipid abnormalities.[60] Hypertriglyceridemia results in higher risk of myocardial infarction and stroke that is increased in the presence of concurrent hypercholesterolemia.[57] Low HDL levels pose an

independent risk for cardiovascular events, and are a lipid abnormality frequently found in persons with central obesity or T2DM.[54, 57] HDL exerts positive effects by drawing cholesterol from peripheral tissues to the liver and exerting both anti-inflammatory and anti-oxidant vascular effects.[57] Because of the high risk conferred by elevated LDL, the primary goal in treatment is reduction in LDL cholesterol, even in metabolic syndrome.[54] Increasing HDL cholesterol is the secondary treatment goal.[54] Triglycerides greater than 150mg/dL are cause for concern, with lifestyle changes recommended. Levels of 500 or greater place the patient at risk for pancreatitis, and therefore should be treated more aggressively with medications.[54, 71]

Lipoprotein(a).

Lipoprotein(a) (Lp(a)) is a lipoprotein consisting of apolipoprotein(a), apolipoprotein B100, and LDL bound together.[62] Lp(a) levels are largely determined genetically based on variations in the apolipoprotein(a) gene, and are fairly resistant to lifestyle and medication changes.[62] Lp(a) is known to be both thrombogenic and atherogenic; increased blood levels have thus been positively associated with cardiovascular risk.[62, 63] This relationship exists independent of other CVD risk factors, and is now known to be a causal relationship whereby increased Lp(a) levels result in premature atherosclerosis and coronary artery disease.[62] The mechanisms of this effect are incompletely understood. Lp(a) has prothrombotic and anti-fibrinolytic properties, and Lp(a) deposits in the vascular intima may increase the rate of atherogenesis.[62] Also, Lp(a) levels are inversely related to vascular endothelial cell growth factor levels and coronary collateral circulation in patients with coronary artery disease.[63]

The relationship between Lp(a) and cancer is also incompletely understood. However, it is believed that Lp(a) may be involved in tumor angiogenesis. In a prospective study of males with lung cancer as compared to controls, Lp(a) levels were correlated with both presence and

stage of lung cancer.[63] A review of long-term prospective studies performed by The Emerging

Risk Factors Collaboration, however, found an independent, modest association between Lp(a)

level and risk of CHD and stroke, but that appeared to be exclusive to vascular outcomes only;

no association between Lp(a) level and cancer was found, although the population with cancer

was small and thus unable to be studied based on cancer type.[64]

High sensitivity C-reactive protein.

With the recent studies revealing the inflammatory nature of atherosclerosis, studies have

shown that markers, including C-reactive protein (CRP) can be used to predict both

atherosclerosis and cardiovascular events.[54, 57] Metabolic syndrome has also been linked to a

state of chronic, low-grade inflammation, as manifested by elevated cytokines and acute-phase

reactants, including CRP.[54] Inflammation can exacerbate metabolic syndrome. Inflammatory

cytokines can induce insulin resistance, and, in obese populations, these cytokines are produced

in larger amounts.[54] CRP levels may also help to identify persons at increased risk for T2DM.[59]

Elevated CRP levels are indicative of an elevated risk that requires lifestyle changes.[54]

However, it is important to note that CRP, as a marker of inflammation, can be elevated

for other reasons, as well. Inflammatory diseases, such as rheumatoid arthritis and lupus, for

example, and other conditions, such as recent infections or recent surgery, can also result in

elevated CRP.[65] Furthermore, studies have shown that breast cancer itself is associated with an

elevation in CRP.[66] Chronic inflammation may play a role in both the development and

progression of breast cancer, although no associations have been noted between elevations in

CRP and specific types of breast cancer.[67]

The emergence of cardiovascular disease risk and breast cancer.

In their study of five-year breast cancer survivors, Chapman et al. showed that non-breast cancer-related deaths were more common than cancer-related deaths, accounting for 60% of known deaths (72% in subjects aged 70 years or older and 48% for those younger than 70 years).[3] Patients may be at risk for non-breast cancer-related illnesses before, during, or after breast cancer treatment.[3] It is important to note again that most women are diagnosed with breast cancer after the age of 40,[1] which correlates with the increased lifetime risk of developing CVD noted in this age group.[4] Risks of developing both breast cancer and CVD increase with age. Furthermore, increasing age is associated with increased risk of non-breast cancer-related death, and, in a study of five-year breast cancer survivors, the presence of CVD at baseline was linked to mortality.[3] Consequently, not only are these women already faced with a high lifetime risk of developing CVD, but they may also be at an increased risk because of their breast cancer diagnoses and treatments.

Treatment-induced cardiotoxicity.

As the number of breast cancer survivors and the length of survival after therapy increase, the long-term side effects of cancer therapy become apparent. Treatment with anthracyclines is known to increase risk of cardiac dysfunction manifested by a decrease in left ventricular ejection fraction (LVEF).[6-7,8,9,10,11,12,13, 17] This cardiotoxicity can be defined as: mild, with a decrease in LVEF of 10% from baseline with a final value of at least 50%; moderate, with a decrease of at least 10% with a final value below 50% but no signs or symptoms of heart failure; or severe, with a decrease of at least 10% with a final value below 50% and signs or symptoms of heart failure or any decrease resulting in a value below 40%.[68] The risk of a cardiotoxic decrease in LVEF with anthracyclines is dose-dependent and irreversible.[69]

Treatment with anthracyclines and trastuzumab has resulted in increased risk individually and in combination.[8-9][10][11], [13-14][15][16][17][18]

Furthermore, risk factors including older age, lower baseline LVEF, and use of antihypertensive medications are correlated with increased risk of cardiac dysfunction in patients receiving both an anthracycline and trastuzumab,[13] suggesting that the presence of CVD risk factors prior to therapy can be an independent predictor of treatment-related cardiotoxicity.[9] In addition, a study of women with breast cancer treated with adjuvant chemotherapy containing taxanes and anthracyclines revealed more CVD risk factors as a result of their treatment than their age-matched healthy controls.[8] The "multiple-hit" hypothesis encompasses these findings, and describes CVD risk in women diagnosed with breast cancer as additive. Study results demonstrated baseline CVD risk factors, combined with therapy-induced risk factors and lifestyle changes during treatment, all contributed to the development of clinical or sub-clinical CVD.[9]

Screening and surveillance for cardiac risk.

The American Heart Association recommends that primary care providers begin assessing cardiovascular risks when clients reach age 20.[70] This risk assessment should include family history, smoking, alcohol, diet, physical activity, blood pressure, BMI, waist circumference, pulse, fasting serum lipid profile, and fasting blood glucose.[70] If risk factors are present, a complete assessment should be done every 2 years; if none are present, it is recommended every 5 years.[70] NCEP-ATP III guidelines concur with these recommendations.[71] Ten-year risk of CHD with a multiple risk score is also recommended.[70] This can be calculated through the FRACHD,[71] or, more broadly, through the FGCVRAS, as described above (see also Appendix A).

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Operational Definitions

CVD risk was measured by the Framingham General Cardiovascular Risk Assessment Score (FGCVRAS) and the heart/vascular age calculation. D'Agostino et al. developed an updated 10-year risk assessment for general CVD that includes age, total cholesterol, HDL, systolic blood pressure, use of antihypertensive medications, smoking, and diabetes, calculating both a risk score and an estimated vascular age, as previously described.[52] The tool was reviewed by Marma and Lloyd-Jones (2009), who determined that the inclusion of noncoronary endpoints expanded predicted risk, but younger individuals with high risk burdens could have a low 10-year risk, thus accentuating the importance of including the vascular age component in communicating risk.[72] The heart/vascular age calculation begins with measured CVD risk in an individual, and, given the population characteristics, translates this risk into the age at which another person would experience this risk level given no other risk factors.[53, 73]

Chapter II

Methods

Design

This study is part of a larger, prospective longitudinal study describing cardiovascular risk factors of women newly diagnosed with breast cancer before and after adjuvant treatments with therapies known to result in cardiac toxicity (anthracyclines and/or trastuzumab). This portion is a descriptive correlational study that describes the cardiovascular health of women newly diagnosed with breast cancer prior to beginning adjuvant chemotherapy with anthracyclines and/or trastuzumab as measured by the FGCVRAS and heart/vascular age calculation. In this section, the setting, sample, instruments, procedure for data collection, and data analysis will be discussed.

Setting

Subjects were from the Yale Cancer Center Breast Service, an outpatient healthcare setting in New Haven, CT.

Sample

Medical oncologists, nurses, and nurse practitioners working in the Breast Service identified potential subjects; a research assistant contacted those subjects who expressed interest. The principal investigator or research assistant explained the study and obtained informed consent. A convenience sample of 30 women receiving evaluation and treatment at the Yale Cancer Center Breast Service was studied. Inclusion criteria included a diagnosis of invasive breast cancer, scheduled adjuvant treatment with anthracyclines and/or trastuzumab, and ability to communicate in English. Exclusion criteria included serious cognitive impairment.

Data Collection Instruments

The FGCVRAS was conducted at baseline. This score, recently updated by D'Agostino et al., now encompasses risk for CVD as a whole; this multivariate, gender-specific assessment is interpreted based on the Cox Hazard Mathematical Model, and assigns point values to the aforementioned risk factors to obtain an absolute 10-year risk.[53] This instrument has been documented as effective in measuring CVD risk in both men and women.[53, 72]

The heart/vascular age calculation was also conducted at baseline (please see Appendix B). The heart/vascular age calculation begins with measured CVD risk in an individual, and given population characteristics, translates this risk into the age at which another person would experience this risk, level given no other risk factors.[53, 73]

Data Collection Procedures

Approval for the parent study was obtained from the Yale University Institutional Review Board. Data collection for the parent study began in October 2010, with baseline data collection completed in February 2012. Medical oncologists and nurse practitioners working with the Breast Service approached eligible subjects. The principal investigator or research assistant contacted those interested in participating, described the study, answered any questions, and obtained informed consent. Prior to the first chemotherapy, fasting blood samples were obtained, including glucose and lipid panel (total cholesterol, LDL, HDL, triglycerides). High-sensitivity C-reactive protein (hs-CRP), lipoprotein (a), and insulin levels were also obtained as fasting blood samples. Other baseline data included weight, height, calculated BMI, waist circumference, and mean systolic and diastolic blood pressure. These values were utilized to calculate the FGCVRAS (see Appendix A) and the heart/vascular age calculation (see Appendix B).

Chapter III

Results

Using the Statistical Package for the Social Sciences (SPSS for Windows, version 19)

computer program, measures of central tendency and descriptive statistics were used to interpret

the data obtained from the FGCVRAS and heart/vascular age calculation.

Sample Characteristics

Demographic characteristics are presented in Table 1. In summary, the sample included

30 women of mean age 49.97 years (range 33 to 72 years, SD 9.926), with 93.3% self-reporting

white ethnicity, 66.7% married, and 80% with children. All participants completed a minimum

of four years of high school education, with 30% completing four years of college, and 33%

completing graduate school. 63.3% worked full-time and 6.7% worked part time. 90% earned an

income of >60,000 USD/year. Four women had a history of diabetes, 10 had a history of

hypertension, and 5 had a history of another co-morbidity. No women had a known history of

CVD.

Table 1: Demographic Characteristics

	Number of Subjects	Percentage of Subjects
Ethnicity		
White	28	93.3
Black	1	3.3
Hispanic	1	3.3
Marital Status		
Never Married	3	10
Married	20	66.7
Divorced/Separated	5	16.7
Widowed	2	6.7
Number of Children		
0	6	20
1	6	20
2	8	26.7
3	10	33.3
Home Life		
Spouse	19	63.3
Significant Other	2	6.7
Other Family	6	20
Alone	3	10
Education		
4 Years of High School	6	20
2 Years of College	3	10
3 Years of College	2	6.7
4 Years of College	9	30
Graduate School	10	33.3
Employment		
Fulltime	19	63.3
Part-Time	2	6.7
Retired	3	10
Temporarily Not	6	20
Income		
< $20,000	1	3.3
$40,000 to $60,000	2	6.7
> $60,000	27	90
Diabetes		
No	26	86.7
Yes	4	13.3
CVD		
No	30	100
Yes	0	0
Hypertension		
No	20	66.7
Yes	10	33.3
Other Co-Morbidity		
No	25	83.3
Yes	5	16.7

Baseline Data

Baseline data is presented in Table 2. Data was available for 29 subjects; laboratory information was not obtained for one subject.

Table 2: Baseline Results

	N	Minimum	Maximum	Mean	SD
Height (in)	30	60	69	64.233	2.3034
Weight (lb)	30	120	267	158.37	35.367
Waist (in)	30	25	47.5	34.4417	5.91123
Heart rate	30	68	110	78.4	8.524
Total cholesterol	29	131	240	182.9	28.777
Triglycerides	29	40	172	94.41	35.83
LDL	29	47	173	102.31	27.131
CRP	26	0.1	38.5	4.254231	8.0367776
Lp(a)	25	2	194	35.52	57.298
Fasting insulin	28	1	91	9.04	17.171
Fasting glucose	29	63	135	93.38	14.669
Average SBP	29	97.33	168.67	124.5521	16.61541
Average DBP	29	56	96.67	76.2755	9.53907
BMI	30	18.01	52.14	27.174	6.95372
CVD Points	29	-4	19	6.59	6.068
CVD Risk	29	0.008	0.248	0.05576	0.056821
Heart Age (years)	29	29	82	49.62	18.333

Analysis

Average CVD risk was calculated according to the FGCVRAS, with an average risk of 5.58% (SD 5.68). Average heart/vascular age was 49.62 years (SD 18.33). Nine women had calculated heart/vascular ages that exceeded their physical ages (Table 3). At a cardiovascular risk of approximately 5.3%, vascular age began to exceed actual age. Using the NCEP definition,[56] six women met the criteria for metabolic syndrome; using the IDF definition,[56] five women met these criteria (Table 4). Fourteen women had at least two cardiovascular risk factors (increased waist circumference, increased fasting blood glucose, increased triglycerides, decreased HDL, or elevated systolic/diastolic blood pressure) (Table 4). A breakdown of cardiovascular risks is provided in Table 5.

Table 3: Predicted vascular age versus actual age

CVD Score	CVD % Risk	Vascular Age	Actual Age	Change
-4	0.8	29	33	-4
-2	0.9	29	34	-5
-1	1	29	39	-10
0	1.2	29	35	-6
0	1.2	29	45	-16
0	1.2	29	35	-6
1	1.5	31	49	-18
1	1.5	31	45	-14
2	1.7	34	40	-6
2	1.7	34	42	-8
3	2	36	44	-8
5	2.8	45	59	-14
6	3.3	45	50	-5
6	3.3	45	47	-2
7	3.9	48	54	-6
8	4.5	51	53	-2
8	4.5	51	54	-3
9	5.3	55	48	7
9	5.3	55	53	2
9	5.3	55	49	6
10	6.3	59	59	0
10	6.3	59	59	0
11	7.3	64	61	3
12	8.6	68	68	0
13	10	73	58	15
15	13.7	80	58	22
16	15.9	82	45	37
16	15.9	82	72	10
19	24.8	82	60	22

N=29

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Table 4: Presence of Metabolic Syndrome and Number of Risk Factors

	Number of Subjects	Total Number of Subjects Reporting on This Category
NCEP MetS	6	29
IDF MetS	5	29
Risk factors (out of 5)		29
0	9	
1	6	
2	8	
3	4	
4	2	

Risk factors = waist circumference ≥80cm (31.5in), blood glucose ≥100, triglycerides ≥150, HDL <50, BP ≥130/85

Table 5: Risk Factor Breakdown

	Number of Subjects	Subjects Reporting on This Category
Blood Glucose		29
≥ 100	8	
≥ 110	3	
Blood Pressure		30
≥ 130/85	10	
≥ 140/90	6	
BMI		30
≥ 30	7	
Waist Circumference		30
≥ 31.5 in. (88 cm)	17	
≥ 34.6 in. (80 cm)	13	
Triglycerides		29
≥ 150	2	
HDL		29
< 50	6	
Elevated Lp(a)	5	25

Dr. Anthony J. Guarino of the Massachusetts General Hospital Institute of Health Professions (MGH IHP) was consulted for additional data analysis. A simultaneous multiple regression analysis was performed to evaluate how the 11 predictor variables measured (cholesterol, LDL, triglycerides, HDL, glucose, insulin, waist circumference, CRP, BMI, mean BPS, and mean BPD) could account for and predict cardiovascular risk. The linear combination

of these 11 predictors was found to be statistically significantly related to cardiovascular risks ($F(11, 13) = 10.01$, $p < .001$). The sample multiple correlation coefficient was 0.95, demonstrating that the regression accounted for approximately 89% of the variance of cardiovascular risks. Only 4 of the 11 predictors (HDL, glucose, waist circumference, and mean BPS) were statistically significant. A multiple regression performed with only these predictors resulted in similar results, including a multiple correlation coefficient of 0.91.

The regression equation developed to predict cardiovascular risk is:

$$Y = -29 - .02X_1 - .02x_2 + .005x_3 + .002x_4$$

Where X_1 = HDL, X_2 = glucose, X_3 = waist circumference, and X_4 = mean BPS.

Table 6 presents the means, standard deviations, and intercorrelations for cardiovascular risks.

Table 6: Multiple Regression Cardiovascular Risks

Variable	M	SD	1	2	3	4
Cardio-vascular risks	.060	.057	.25	-.13	.48*	.83*
Predictor variables						
1. HDL	-1.21	.94		.13	.69*	.31
2. glucose	93.38	14.67			.42*	.05
3. waist	34.44	14.67				.46*
4.mean BPS	124.55	16.62				

NB: * = $p < .05$.

Chapter IV

Discussion

This study reveals that, at breast cancer diagnosis, women have significant CVD risk. However, the overwhelming majority of women in this study did not have cardiovascular risk assessments done by their primary care providers as is recommended by the American Heart Association and NCEP-ATP III guidelines;[70, 71] although all women report routine care by a primary care provider and insurance coverage, only 3 out of 30 women recalled ever having a cardiovascular risk assessment. Unfortunately, as described above, studies have demonstrated that cardiovascular assessments are not always done as recommended.[49, 50]

In this sample, the known CVD risk factors that most contributed to CVD risk as calculated by the FGCVRAS were HDL, glucose, waist circumference, and systolic blood pressure. While these variables, in addition to others, are all utilized in calculating the FGCVRAS, it is notable that these variables predicted the overwhelming majority of the CVD risk in this population of women newly diagnosed with breast cancer. This should be followed as the study sample grows – and throughout treatment with adjuvant chemotherapy – to determine if these variables continue to be the most important predictors of CVD risk for this population.

At baseline, women in this population also had a significant amount of CVD risk. Six out of 29 women met criteria for diagnosis of metabolic syndrome at baseline. As previously described, research indicates that breast cancer treatment with chemotherapy results in weight gain and increased waist circumference.[25] Consequently, over the next six months to one year, we can anticipate an emergence of increased CVD risk with a concurrent increase in the number of women meeting the criteria for metabolic syndrome diagnoses.

A striking correlation between elevated Lp(a) with triple-negative breast cancer, although anecdotal, was noted. In a sample of 29 women, 5 had elevated Lp(a). Research has shown that roughly 20% of Caucasians have Lp(a) of greater than 50mg/dL.[62] However, all of the elevated Lp(a) levels in this study were seen in women with triple-negative breast cancer. This phenomenon warrants further exploration and research.

Conclusion

Women diagnosed with breast cancer have baseline risk factors for CVD that need to be assessed and addressed prior to beginning potentially cardiotoxic treatments. At baseline, women diagnosed with breast cancer demonstrate a significant risk burden for CVD, and, at the same time, are not receiving the preventative care recommended by national guidelines. This risk requires further research, especially as it pertains to describing how the risk is altered by cardiotoxic cancer therapies.

Limitations

This study has several limitations. First, the sample size is small at 30 subjects. Data collection is ongoing as part of a larger parent study. This study describes only baseline characteristics of a population, and consequently cannot comment on interventions or causative factors directly. The baseline study characteristics included primarily well-educated Caucasian women with significant income. Data was collected after women were formally diagnosed with breast cancer; consequently, while this study can describe women with breast cancer at baseline, it cannot speak to the causative effects of breast cancer on CVD, or vice versa.

Summary of Research and Future Directions

Research has focused on identifying risk factors associated with CVD and subsequent predictive analyses, with a focus on prevention and early detection; while this research has

expanded to include information specific to CVD in women, there is no data specific to CVD in women with breast cancer. The same can be said of breast cancer research. There is significant research describing women's risks for developing breast cancer, with a focus on prevention and early detection. With the introduction of anthracyclines and trastuzumab as staples in breast cancer treatment, research has thus far focused on the relationships between these therapies and primarily left ventricular dysfunction.

Little research exists to describe the cardiovascular risk factors of women newly diagnosed with breast cancer. Research in this area would allow early detection of risk and, consequently, prevention of CVD in women with breast cancer. This research would also potentially lay the groundwork for future research focusing on predicting treatment-related cardiovascular events as these women receive potentially cardiotoxic breast cancer therapies.

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CVD Points							
Points	Age	HDL	Total Cholesterol	SBP Not Treated	SBP Treated	Smoker	Diabetes
<-3				<120			
-2		60+					
-1		50-59			<120		
0	30-34	45-49	<160	120-129		No	No
1		35-44	160-199	130-139			
2	35-39	<35		140-149	120-129		
3			200-239		130-139	Yes	
4	40-44		240-279	150-159			Yes
5	45-49		280+	160+	140-149		
6					150-159		
7	50-54				160+		
8	55-59						
9	60-64						
10	65-69						
11	70-74						
12	75+						

CVD Risk					
Points	Risk	Points	Risk	Points	Risk
-2 or less	Below 1%	6	3.3%	14	11.7%
-1	1.0%	7	3.9%	15	13.7%
0	1.2%	8	4.5%	16	15.9%
1	1.5%	9	5.3%	17	18.5%
2	1.7%	10	6.3%	18	21.5%
3	2.0%	11	7.3%	19	24.8%
4	2.4%	12	8.6%	20	28.5%
5	2.8%	13	10.0%	21+	Above 30%

Heart Age	Points	Heart Age
Younger than 30	8	51
31	9	55
34	10	59
36	11	64
39	12	68
45	13	73
45	14	79
48	15+	Older than 80