A Case for Onco-Cardiology:

Late Cardiac Effects after Treatment for Breast Cancer

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This is to acknowledge that Thomas C. Andrews, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Andrews will not be discussing off-label uses in his presentation.

Biographical Sketch

Dr. Andrews graduated from Vanderbilt University School of Medicine and completed residency training in Internal Medicine, and fellowship training in Cardiovascular Diseases at the Brigham and Women's Hospital, Boston, MA. He served on the faculty at UTSW from 1996-2000 and rejoined the faculty in 2011 after a period of time in private practice in Dallas. His clinical and research interests are focused in the area of onco-cardiology. This new area of cardiology is concerned with the effects of cancer and its treatments on the cardiovascular system. Dr. Andrews also leads the cardiology clinic in UT Southwestern's new Clinical Center at the Park Cities, and is available to see onco-cardiology and general cardiology outpatients on a daily basis.

In the 1980's there was little overlap between the disciplines of cardiology and oncology. At that time, late cardiotoxicity of the anthracyclines was the predominant issue uniting the two fields. In the past 2 decades, the list of cardiotoxic drugs has grown considerably. (figure 1) Growth accelerated further with the development of the tyrosine kinase inhibitors, many of which cause hypertension, congestive heart failure or both. New oncology drug development now routinely includes an assessment of cardiotoxicity, and cardiologists and oncologists increasingly work together in the management of acute toxicities and in cancer survivorship programs where late cardiac effects are major factors in longterm morbidity and mortality. Across the country, major medical centers are developing specific programs to manage these patients, as the field of "onco-cardiology" is born.

Chemotherapeutic Agents	Incidence of LVD and HF (%)
Anthracyclines	
Doxorubicin[12,15]	3–26*
Epirubicin	0.9–3.3†
Idarubicin[18]	5–18
Mitoxantrone[18]	2.2–15
Alkylating agent	
Cyclophosphamide[48]	7–28
Taxanes	
Paclitaxel[51]	5–15
Docetaxel[50]	2.3–8
Targeted agents	
Antibody-based TKIs	
Bevacizumab[51,54]	0.8–2.2
Pertuzumab[57]	3.4–6.9‡
Trastuzumab[50]	2–28
Small-molecule TKIs	
Dasatinib[50]	2–4
Lapatinib[58]	1.6
Imatinib[50]	0.5–1.7
Sunitinib[55,61]	4–28
Proteasome inhibitor	
Bortezomib[63]	7–15†

Figure 1: Agents associated with left ventricular dysfunction and heart failure.[1]

There are many topics within onco-cardiology of potential interest to the general medical staff at an academic institution. For example, many of the new tyrosine kinase inhibitors effect signaling pathways common to tumor cells and cardiac tissue, and understanding these interactions may help design cleaner drugs in the future. The monoclonal antibody traztuzumab , used primarily in the adjuvant treatment of breast cancers overexpressing Her 2/neu receptors, was found to have significant cardiotoxicity when given concomitantly with anthracyclines. Drugs targeting VEGF often cause malignant hypertension in addition to their anti tumor effects. Other agents effect cardiac repolarization and predispose to arrhythmias. 5-flurouracil and similar agents may cause coronary vasoconstriction and occasionally myocardial infarction. Hormonal therapies effect serum lipids and may predispose to coronary events. As new drugs come to market and enter "real world practice" case

reports of new toxicities are common, and in most cases late cardiovascular effects of these agents are unknown.

Rather than recite a long list of drugs and their side effects, or discuss the molecular biology of tyrosine kinase inhibitors and their toxicities, I have elected to start at the bedside and see what we can learn from the story of a long term survivor of breast cancer. Improved survival of breast cancer has paradoxically allowed the late effects of treatment to manifest. For example, in the medicare population with early stage breast cancer the risk of dying of cardiovascular disease actually exceeds the risk of dying of breast cancer (figure 2).[2] In my presentation today, I will discuss in some detail the late cardiac effects of adriamycin therapy, which I believe is an under-appreciated toxicity in its early forms. I wil also cover how radiation therapy affects long term risk of coronary artery disease, and how to integrate that risk factor in to traditional risk assessments. Finally, I will discuss how breast cancer and cardiovascular disease share several important risk factors, and how attention to these risk factors can decrease risk of both conditions.

	Women Age 67-79 Years			
Mortality	DCIS (n = 4,798)	Stage I (n = 14,765)	Stage II (n = 8,539)	Stage III/IV (n = 2,923)
5-year mortality				
%*	11	13	26	70
95% CI	10 to 12	13 to 14	25 to 27	69 to 72
No.	513	1,960	2,227	2,058
Cause of death				
Breast cancer				
%	7	18	47	76
95% CI	5 to 10	16 to 20	45 to 49	74 to 78
Other cancers				
%	25	20	11	7
95% CI	22 to 29	18 to 22	9 to 12	6 to 8
Cardiovascular disease				
%	27	26	17	8
95% CI	23 to 31	24 to 28	16 to 19	7 to 9

Figure 2: Cause of death in elderly women with breast cancer based on stage at presentation.[2]

Case report: 11 year survivor of Stage III Breast cancer

In 2002 at age 44, CC was diagnosed with a small invasive ductal carcinoma of the left breast. At surgery, she was found to have 4 involved nodes, and the final pathological stage was IIIa (T1 N2M0). The tumor was estrogen and progesterone receptor negative and it overexpressed Her 2/neu. She was initially treated at an outside institution with 4 cycles of adriamycin and cytoxan, followed by taxotere and radiation of the left breast and internal mammary nodes. Her baseline left ventricular ejection fraction was 68% falling to 51% at the end of her initial therapy. At UT Southwestern she was treated with a year of traztuzumab with careful cardiac monitoring, and she did well without further drop in ejection fraction or symptoms of heart failure. An echocardiogram in 2008 showed an ejection fraction of 55% and diastolic dysfunction.

She had trouble with obesity throughout her treatment and subsequent surveillance. Over the course of the last 2-3 years she developed glucose intolerance and increasingly elevated blood pressure.

She is minimally symptomatic and happy with her quality of life. She practices Zumba and kick boxing weekly. Occasionally she is dyspneic climbing stairs. Her medications include only synthroid and amitryptiline.

On physical exam, her blood pressure is elevated at 176/98. BMI is 37.5. Only other finding is a soft systolic murmur. Lab tests showed LDL of 138, HDL of 45, and triglycerides of 175. Hemoglobin A1c was 6.1%, with a fasting blood glucose of 113 mg/dl.

An echocardiogram showed an ejection fraction of 61%, grade 1 diastolic dysfunction, a dilated left atrium and mild mitral regurgitation. On a treadmill exercise test, she walked for 5 minutes on a Bruce protocol and achieved 6 METS of work, about 80% of predicted for a sedentary woman of her age. There was no evidence for ischemia.

In many ways, this is the story of a successful treatment of breast cancer. She has a high likelihood of long-term cure, despite her age at diagnosis and the advanced stage. Now as a long-term survivor she faces different challenges—late cardiovascular effects of her breast cancer treatment and the re-expression of her un-modified risk factors as cardiovascular disease.

Anthracycline cardiotoxicity

Left ventricular dysfunction and systolic heart failure associated with anthracyclines was identified in the 1970s. Subsequently, risk factors have been elucidated that increase the likelihood of cardiotoxicity: extremes of age (<4 or >65 years), female gender, pre-existent cardiovascular disease or risk factors (hypertension, coronary disease, valvular disease), co-administration with other cardiotoxins (e.g. traztuzumab), and various dosing considerations including total dose, bolus dosing, and higher individual doses. Once established, the left ventricular dysfunction associated with anthracyclines was felt previously to be irreversible. [3]

The pathophysiology of anthracycline toxicity is still under active investigation, including at our institution. The most widely accepted mechanism is cardiomyocyte damage from free radical generation. Other proposed mechanism include transcriptional changes in intracellular ATP, downregulation of sarcoplasmic reticulum calcium-ATPase, depressed cardiac glutathione peroxidase activity, mitochondrial abnormalities and changes in topoisomerase II beta. From a histologic standpoint, the characteristic changes include myofibrillar loss and vacuolization with extensive interstitial fibrosis (figure 3)[4]

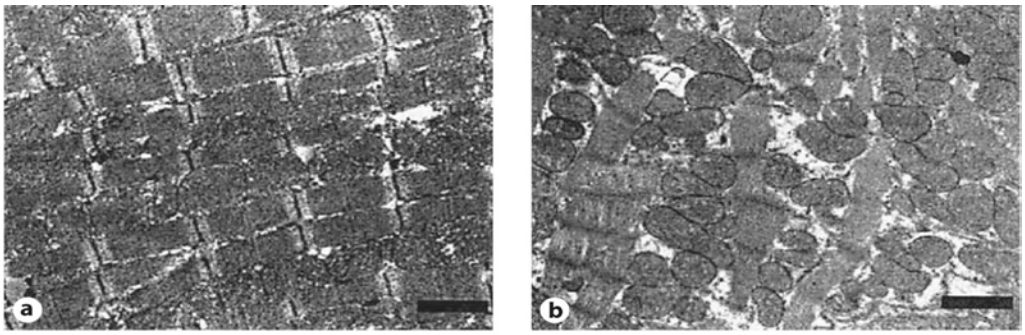


Figure 3: a) normal myocardium. b) anthracycline toxicity demonstrating myofibrillar loss and vacuolization with extensive interstitial fibrosis. [4]

Previous schemes for the diagnosis of adriamycin cardiotoxicty have focused on changes in systolic function. Typically, a fall in ejection fraction of 10% or more has been used to define the presence or absence of toxicity in a binary manner. Toxicity is classified as early (first year) or late (after first year). Overall incidence of late toxicity varies markedly depending on total amount of drug delivered. At 400 mg/m2 the incidence is reported as 3-5%, while at 700 mg/m2 the incidence is 18-48%. When given in the adjuvant setting for breast cancer, the dose is rarely greater than 240 mg/m2 with a 1-2% incidence of heart failure reported in the literature. It has long been recognized that a much greater proportion of patients in the adjuvant setting demonstrate markers of diastolic dysfunction. The extent to which these diastolic abnormalities manifest as clinical heart failure ("HFPEF") is not known.

The exact incidence of anthracycline toxicity is not precisely known. Despite the well known association with LV dysfunction, there have been few long term studies in breast cancer patients. Doyle analyzed outcomes from 31,748 breast cancer patients using SEER Medicare database utilizing ICD9 codes for cardiomyopathy, congestive heart failure, heart disease and myocardial infarction. Incidence of endpoints was compared for patients receiving various types of chemotherapy including CMP (cytoxan, methotrexate and flurouracil) , adriamycin along and in combination as CAF (cytoxan, adriamycin and flurouracil). Adriamycin was associated with a hazard ratio of 2.48 for cardiomyopathy and 1.38 for heart failure. (figure 4) Looking at the incidence of cardiotoxicity in the 5 years following diagnosis, the incidence was elevated for the adriamycin containing regimen through year 5, with a cumulative 5 year event rate of 9-10%.(figure 5) [5]

Table 4. Cox Proportional Hazards Model for Cardiac Disease Outcomes Among Patients Who Received Chemotherapy Compared With Patients Who Did Not Receive Chemotherapy*

	CHEMO		CMF		DOX		CAF	
Cardiac Disease	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
CM	1.55	1.38 to 1.74	1.33	1.11 to 1.59	2.48	2.10 to 2.93	2.33	1.83 to 2.96
CHF	1.20	1.14 to 1.27	1.13	1.03 to 1.23	1.38	1.25 to 1.52	1.29	1.12 to 1.50
HD	1.22	1.17 to 1.26	1.14	1.07 to 1.21	1.35	1.26 to 1.44	1.37	1.24 to 1.51
MI	1.03	0.87 to 1.21	1.08	0.83 to 1.40	0.90	0.64 to 1.26	1.09	0.70 to 1.71

Abbreviations: CAF, cyclophosphamide, doxorubicin, fluorouracil; DOX, doxorubicin; CHEMO, chemotherapy; CHF, congestive heart failure; CM, cardiomyopathy; CMF, cyclophosphamide, methotrexate, fluorouracil; HD, heart disease; MI, myocardial infarction.
*Controlled for age, race, stage, year of diagnosis, pre-existing HD, comorbidity, and year of diagnosis.

Figure 4: Heart disease outcomes in patients receiving chemotherapy for Breast cancer.[5]

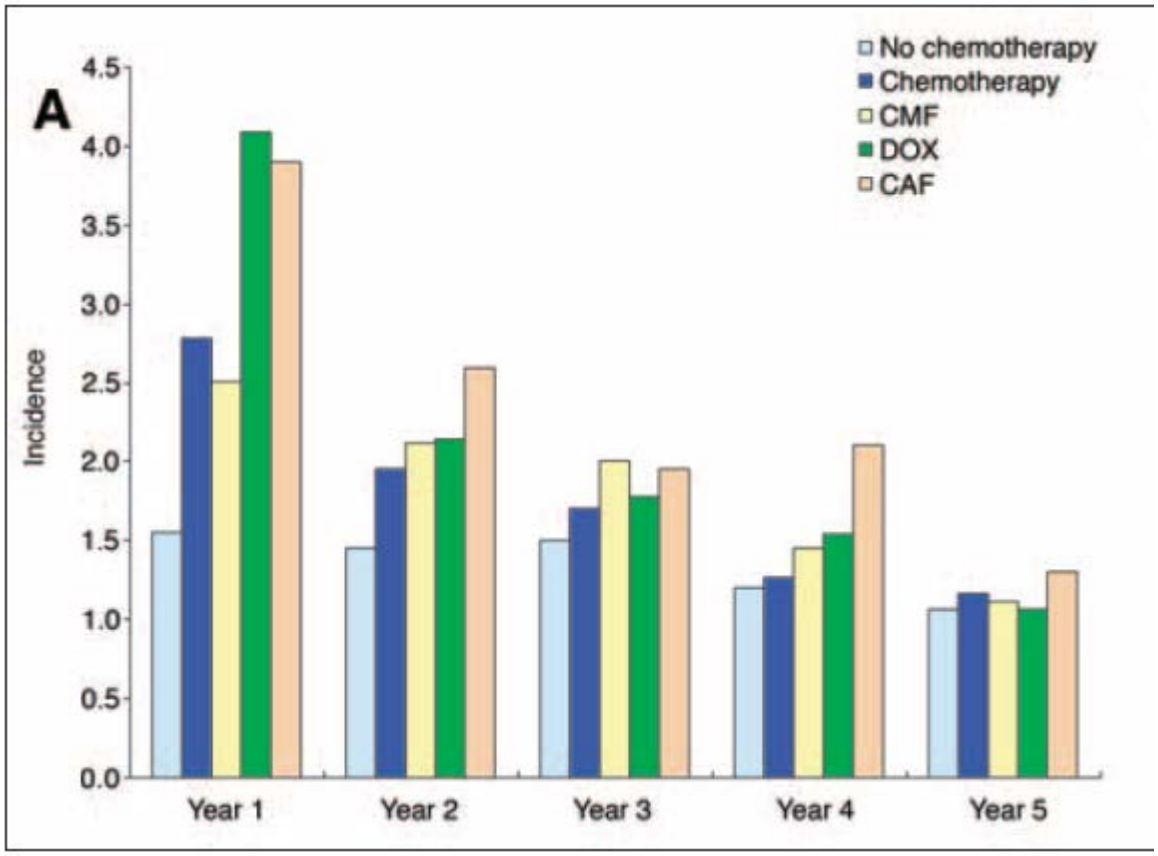


Figure 5: Incidence of cardiomyopathy in the first 5 years after chemotherapy for breast cancer[5]

Recently, there have been attempts to redefine anthracycline cardiotoxicity using contemporary advanced imaging techniques. For example, an echocardiographic measurement of systolic function called strain rate imaging has shown potential in the detection of early toxicity. Our cardiac MRI imaging group at UT Southwestern, led by Dr. Susan Mateluvicius, has recently reported cMRI findings in anthracycline toxicity showing delayed enhancement with gadolinium contrast in patients with left ventricular dysfunction. Newer protocols are under development that may identify interstitial fibrosis

and redefine the way we think about adriamycin, moving from a binary "yes/no" definition based on ejection fraction to a continuous variable based on the amount of fibrosis. We suspect that the abnormalities in diastolic function are related to interstitial fibrosis and may be an important contributor to the exercise intolerance and breathlessness in anthracycline recipients with preserved cardiac systolic function. Currently, our group is collaborating with the cardiac imaging group at Wake Forest to obtain funding for a multicenter study using cardiac MRI to more precisely look at structural and functional changes in the myocardium after chemotherapy for breast cancer. We suspect that the incidence of LV systolic and diastolic dysfunction will be far greater than reported in database studies.

There have been a number of different agents studied as potential protectants against anthracycline cardiotoxicity. Dexrazoxane is an iron chelator that decreases the formation of free radicals. When administered with anthracyclines, there is a decrease in the incidence of heart failure. (figure 6). However, there has been worry that the anti-tumor effects are also diminished and current recommendations for this drug in the adult population are limited.[6]

	DZR		PLA		
Group	No	%	No	%	*P*
Total no of patients	168		181		
Patients with cardiac event on study	25	15	57	31	< 001*
Patients with CHF on study	0	0	8	4	
Patients with CHF off study	0	0	7	4	
Total no. of patients with CHF	0	0	15	8	< 001*

Figure 6: Incidence of adriamycin associated CHF with dexrazoxane vs placebo. [6]

There has been considerable interest in prophylaxis with beta blockers and/or angiotensin converting enzyme inhibitors. For example, carvedilol has been shown to prevent the decrease in ejection fraction seen with anthracyclines. In a study from Greece, an average of over 500 mg/m2 of adriamycin was administered to breast cancer patients. A moderate dose of carvedilol prevented the mean 17% drop in ejection fraction seen with placebo. (figure 7).[7]

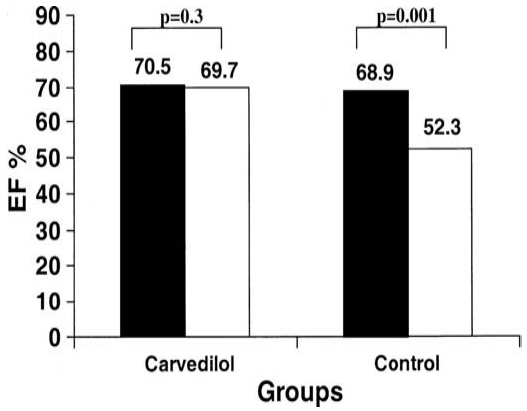


Figure 7: Carvedilol prevents LV dysfunction associated with approximately 525 mg/m2 adriamycin administration .[7]

Similarly, Cardinale and colleagues reported successful attenuation of cardiotoxicity with ACE inhibitors. They identified patients at high risk of developing left ventricular dysfunction based on abnormal troponin levels during treatment with high dose chemotherapy. They randomized 114 patients to a moderate dose of enalapril vs placebo. Enalapril resulted in maintenance of ejection fraction, while the placebo group dropped significantly over the subsequent year. (figure 8) [8]

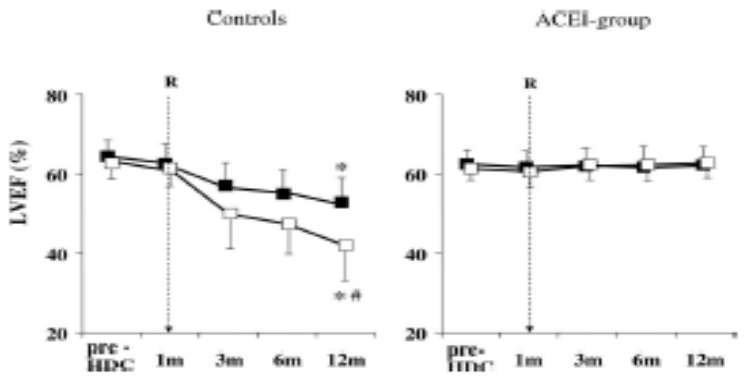


Figure 8. Effect of enalapril on ejection fraction after high dose chemotherapy. [8]

Ther is some preliminary data to suggest that statin drugs may have a role in protecting against anthracycline cardiotoxicity. The rationale for such an effect is related to the so-called "pleiotrophic effects" of statins (those not directly related to their cholesterol lowering properties), particularly their ability to decrease vascular inflammation and oxidative stress. Most of the data has come from animal studies. An observational study from Australia in 628 women with newly diagnosed breast cancer examined the effects of uninterrupted statin therapy during the first 2.5 years after treatment with antrhacyclines. This study demonstarted a hazard ratio of 0.3 (95% CI 0.1-0.9, p+0.03) for the development of heart failure in statin patients compared with those not taking statins continuously.[9] This study had many limitations, particularly since heart failure diagnosis was based on a broad variety of DRG codes rather than a strict definition of systolic heart failure. In addition, the anthracycline dose was nearly twice that used in the adjuvant setting in the US. Consequently, the overall incidence of heart failure was 13%, much higher than what would be expected in the US population. However, the results are intriguing and the hypothesis probably warrants testing in a clinical trial.

There is a growing body of evidence to suggest that exercise may prevent or attenuate adriamycin cardiotoxicity, although almost all of the studies have been in mouse or rat models. Potential mechanisms include decreased apoptosis, upregulation of AMPK pathway, favorable modification of myocardial calcium handling, and anti-oxidant effects. Little human data are available regarding the efficicacy of this treatment, although clinical trials are underway. [10]

Once cardiotoxicity is identified, standard heart failure therapies are generally recommended. Cardinale's group reported a marked time interaction between the end of chemotherapy and the diagnosis of left ventricular dysfunction and institution of heart failure therapies (figure 9). When therapy is instituted in the first 2 months, most patients respond to treatment, while therapy instituted more than 6 months after completion of therapy was uniformly futile.[11] These data suggest that additional early cardiac monitoring may be warranted after completing anthracycline therapy in order to identify asymptomatic left ventricular dysfunction and treat aggressively prior to permanent damage.

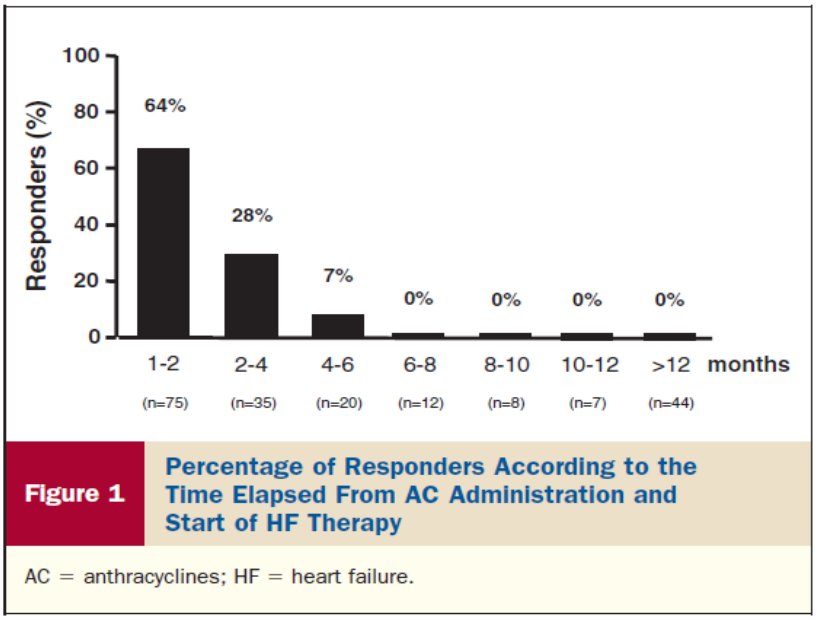


Figure 9: Response to heart failure treatment from time elapsed from adriamycin administration.[11]

In summary, while anthracycline cardio-toxicity is an old problem, there has been recent progress in the characterization, prevention and treatment of this entity. It may be best to consider anthracycline damage a disease of progressive myocardial fibrosis, manifesting initially as abnormalities of diastolic function and ending with refractory systolic heart failure. It can be successfully prevented and treated with traditional heart failure medications, and with further understanding of its pathophysiology, targeted therapies may be on the horizon. I recommend a cardiovascular evaluation within the first 6 months after patients have completed anthracycline treatment to screen for left ventricular dysfunction and to educate patients in how to possibly mitigate late effects via scrupulous attention to control of other cardiac risk factors and adherence to an exercise program.

Cardiovascular effects of radiation in breast cancer

Over the past several decades, the initial surgical management of breast cancer has shifted from mastectomy to lumpectomy and radiation treatment whenever possible. Since the heart predominantly fills the left chest, radiation of the left breast exposes the heart to much more radiation than does

radiation of the right breast. When the internal mammary nodes are included in the radiation field, the cardiac exposure is even higher. Much of what we have learned about radiation in breast cancer comes from our experience in Hodgkin Lymphoma patients receiving mantle irradiation with much greater cardiac exposure, and thus higher rates of radiation induced coronary disease, valvular disease, pericardial and myocardial disease. At the cardiac exposure in breast cancer, damage is primarily limited to the coronaries, particularly the left anterior descending coronary artery. There are a number of observational studies demonstrating an increased risk of late coronary disease in left vs. right irradiated breast cancers, with a relative risk of about 2 (Figure 10).[12] The increase risk of CAD typically appears greater than a decade after radiation. Newer radiation techniques result in less cardiac exposure, but it will take many years of observation to determine whether this translates into less CAD risk. For example, in the study displayed in Figure 11, there is a suggestion that more modern techniques may result in less cardiac mortality. These data are also potentially skewed by advances in the treatment of coronary artery disease, with subsequent lower mortality rate for incident disease.

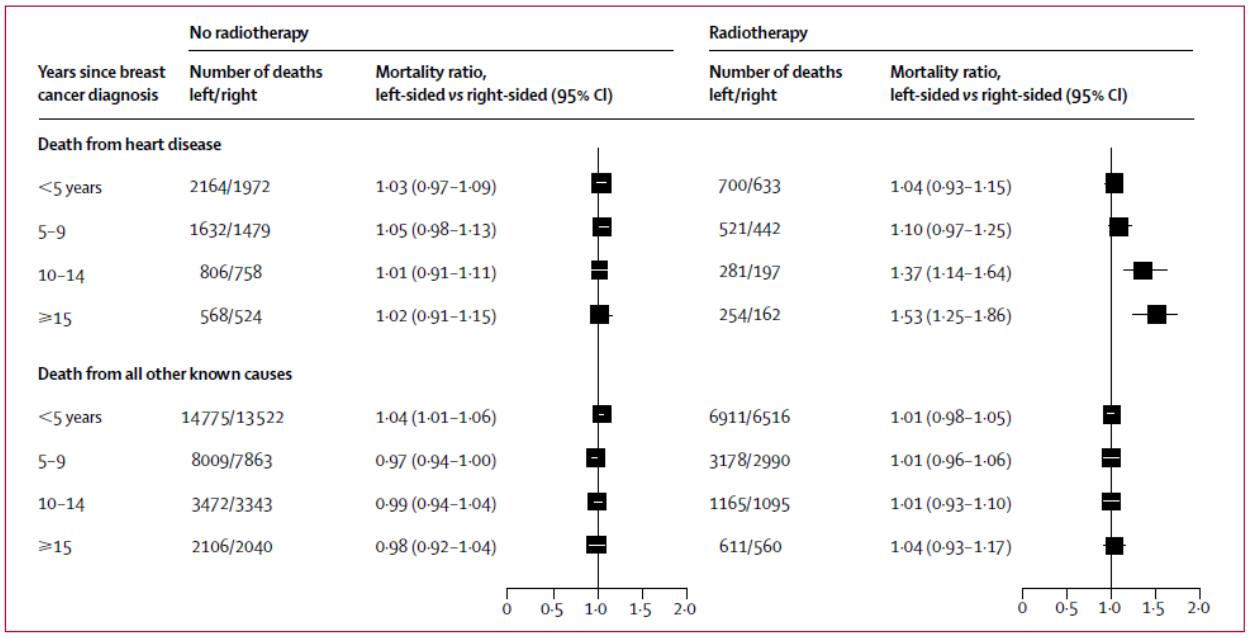


Figure 10: Risk of death comparing right vs left breast radiotherapy. [12]

Years from breast cancer diagnosis to cardiac death	No radiotherapy		Radiotherapy	
	Cardiac deaths left/right	Cardiac mortality ratio, left-sided *vs* right-sided (95% CI)	Cardiac deaths left/right	Cardiac mortality ratio, left-sided *vs* right-sided (95% CI)
Diagnosed 1973–82				
<5 years	717/679	0·98 (0·89–1·09)	230/180	1·19 (0·98–1·45)
5–9	673/614	1·04 (0·93–1·15)	189/145	1·21 (0·97–1·50)
10–14	469/441	1·00 (0·87–1·13)	157/106	1·42 (1·11–1·82)
≥15	515/480	1·01 (0·89–1·15)	234/145	1·58 (1·29–1·95)
Diagnosed 1983–92				
<5 years	880/785	1·06 (0·96–1·16)	245/227	1·00 (0·84–1·20)
5–9	815/729	1·07 (0·97–1·18)	249/218	1·08 (0·90–1·29)
≥10	390/361	1·04 (0·90–1·20)	144/108	1·27 (0·99–1·63)
Diagnosed 1993–2001				
<5 years	567/508	1·05 (0·93–1·18)	225/226	0·95 (0·79–1·14)
5–9	144/136	1·02 (0·81–1·29)	83/79	0·99 (0·73–1·35)

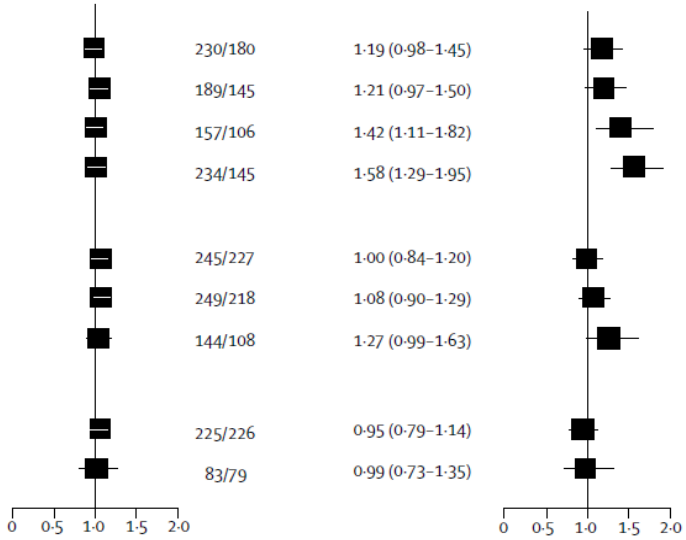


Figure 11: Risk of death comparing right vs left breast radiotherapy by decade of treatment. [12]

From a histopathologic perspective, the coronary disease from radiation exposure can take different forms. For example, Figure 12 displays the coronary artery of a teenage boy who died of a myocardial infarction about a year after receiving mantle radiation for Hodgkins lymphoma. There is massive intimal proliferation noted.[13] Figure 13 displays two segments of the same arteriole from an irradiated myometrium, one normal, and an adjacent segment involved with lipid laden macrophages and occluded by thrombus.

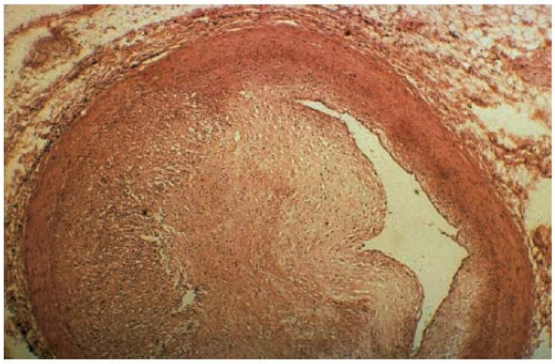


Figure 11. Coronary artery (LAD) of a 15-year-old boy who died with a large myocardial infarct 16 months after receiving 40 Gy to the mantle for Hodgkin's disease. There is severe eccentric narrowing produced by extensive myointimal proliferations. H&E. Reproduced with permission from Fajardo LF. Editorial: Radiation-induced coronary artery disease. Chest 1977;71:563–64.

Figure 12: Coronary disease after radiation for Hodgkin Lymphoma[13]

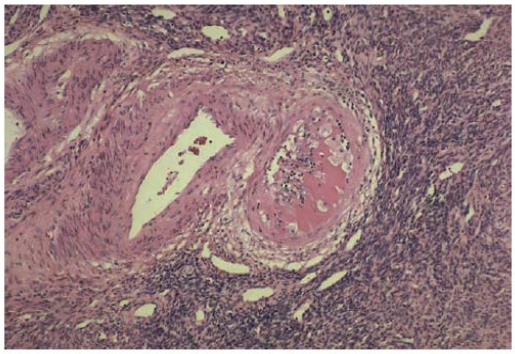


Figure 9. As illustrated here, vascular injury is often segmental: these are two adjacent profiles of the same arteriole in an irradiated myometrium. The left one is normal while the right one has many lipid-laden macrophages in the intima and is occluded by a thrombus. H&E.

Figure 13: Coronary disease in irradiated myometrium showing segmental coronary disease.[13]

Based on data derived primarily from Hodgkin lymphoma patients, there appears to be a significant interaction between radiation and the development of coronary disease. Figure 14 shows data from a large series of irradiated Hodgkin patients with the hazard ratios for traditional cardiac risk factors. Although the numbers were too small to fully analyze each variable, it appears that coronary artery disease in the presence of radiation damage is accelerated by additional traditional risk factors. [14] Extrapolating from these data, a reasonable strategy for patients with irradiated left breast cancers is to aggressively treat these risk factors when present, considering the radiation as an independent factor that doubles overall risk. Based on the Framingham risk score, our patient CC has an 18.5% 10 year risk of CAD events, not counting her borderline diabetes. So without any further imaging, we know she needs aggressive treatment.

Covariate	No./Total (%) of Patients With CAD†		Hazard Ratio (95% CI)	*P* Value
	Covariate Present	Covariate Absent		
Patient-Related Variables				
Hypertension	20/57 (35)	22/347 (6)	3.0 (1.6-5.8)	.002
Hypercholesterolemia	22/86 (26)	8/169 (4)	3.0 (1.2-7.4)	.02
Diabetes mellitus	6/20 (30)	36/384 (9)		NF
Family history of CAD	16/90 (18)	6/212 (3)		NF
Older than median age at radiation therapy	36/208 (17)	6/196 (3)	8.1 (3.2-20.3)	<.001
Smoking history	26/157 (17)	10/203 (5)		NF
Male sex	30/242 (12)	12/162 (7)	2.9 (1.4-6.0)	.01

Figure 14: Patient related covariates in the development of CAD in irradiated Hodgkin lymphoma patients. [14]

In the Hodgkin's population, there has been some preliminary data using coronary artery calcium scoring and coronary CT angiography to screen for asymptomatic early coronary disease. Such an approach makes some sense if finding non-obstructive disease would lead to more aggressive risk factor management. In the breast cancer population, particularly the premenopausal women are at low baseline risk and such screening might be reasonable. Figure 15 shows data from a series of Hodgkins survivors undergoing coronary artery calcium scoring. A very low (0) or very high (>1000) calcium score was quite helpful at correctly classifying patients.[15] Coronary CT angiography involves considerably more radiation as well as the administration of IV contrast. Thus,it probably is of limited usefulness in the lower risk breast cancer population.

Coronary artery calcium score and coronary artery disease

CAC Score (volume score)	HL Survivors With No Signs or Symptoms of CAD	HL Survivors With Documented CAD	Percentage With Documented CAD
0	8	0	0
1–199	27	2*	7
200–999	5	3	38
≥1,000	0	2	100

Figure 15: CAC score in irradiated Hodgkin's survivors. [15]

My recommendation regarding is to increase by 50% the Framingham risk score of women who have received radiation to the left breast. For our patient, her risk score would be approximately 28%. This increase in risk is similar to adding diabetes as a risk factor.

Breast cancer and cardiovascular disease: obesity and physical inactivity as common risk factors

Obesity is a well-recognized risk factor for both breast cancer and cardiovascular disease. Ample data suggest that obesity also is associated with a worse survival in breast cancer, including the study by Goodwin et al displayed in Figure 16. In this study, 10 year survival was approximately 10% lower comparing women in the 4th quartile for BMI to those in the 2nd quartile.[16] Protani and colleagues performed a meta-analysis of 36 observational studies and demonstrated a pooled hazard ratio for mortality of 1.33 for obese patients compared with non-obese breast cancer patients.[17]

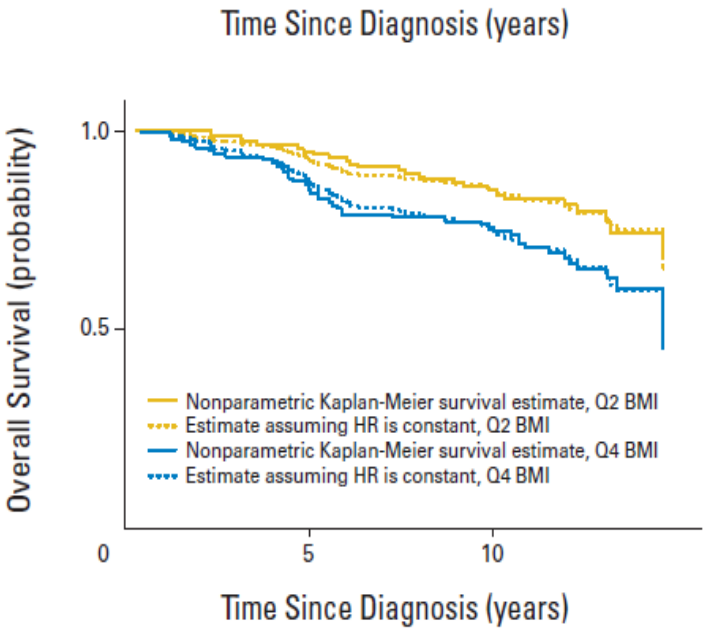


Figure 16: Survival comparing 2nd and 4th quartile of BMI in patients with breast cancer. [16]

Obesity is closely linked with metabolic abnormalities including higher levels of plasma insulin, elevated serum lipids, and others. In the same study by Goodwin, elevated insulin levels were associated with higher rates of breast cancer recurrence in the first 5 years after diagnosis (figure 17).[16]

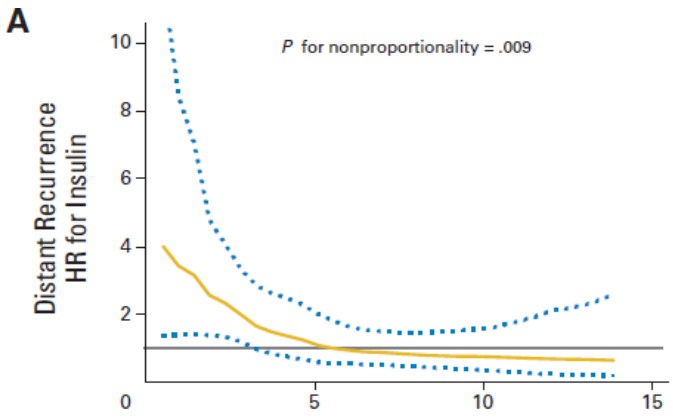


Figure 17: Recurrence of breast cancer based on plasma insulin. [16]

As a risk factor for breast cancer, both obesity and type 2 diabetes is stongest and most consistent in women with postmenopausal breast cancer. Most breast cancers in this population ore estrogen receptor positive, and obesity increases the synthesis of estrogen in adipose tissue through increased expression of aromatase. A second possible mechanism of the effects of obesity on breast cancer involves the increased expression of inflammatory factors. Hypoxia and increased amounts of saturated fatty acids through several different pathways result in increased inflammatory mediators,

which may increase the risk of breast cancer progression and mortality. For example the NFkB signaling pathway has been shown to be important in the growth of resistant breast cancer cells in cell culture. Some of these inflammatory mediators, particularly PGE2, have been shown to increase aromatase production in the breasts of obese women, which leads to local production of estrogen and feeds tumor growth. There has been interest in targeting COX2 as a treatment for breast cancer, as its expression is correlated with reduced survival, higher tumor grade and more aggressive disease. Results with aspirin and other NSAIDS have been mixed.[18] The recent interest in statin use to potentially reduce cancer related mortality may be in part related to the anti-inflammatory effects of statins, although a number of other potential mechanisms have been proposed .[19]

Obesity also results in a dysregulated metabolism with insulin resistance, increased synthesis of leptin by adipose tissue, and decreased synthesis of adiponectin. (figure 18) Insulin and IGF-1 may increase the risk of a number of cancers by the activation of pathways including Ras and MAPK, and others. Leptin and adiponectin may influence breat cancer risk and groth via effect on the AMPK pathway, which has an antiproliferative role. Metformin probably stinulates AMPK, and there has been a growing interest to determine whether it may also be useful in the treatment of breast and other cancers. Metormin has been shown to decrease aromatase expression in breast tissue culture and one small stgudy showed that given fo r2 weeks between biopsy and breast surgery, metformin resulted in a significant decrease in the proliferation marker Ki67. Thus, there is considerable interest in developing specific activators of AMPK based on these and other data.[18]

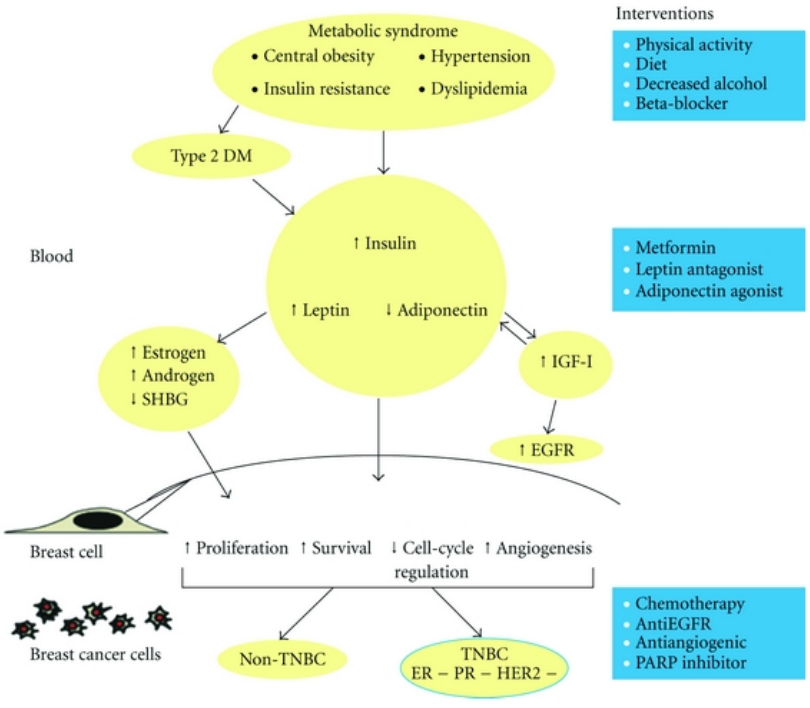


Figure 18: Dysregulated metabolism in obesity and Breast cancer.[18]

A number of studies have demonstrated a link between fitness and decreased risk of cancer. Figure 19 shows data from the Cooper Clinic here in Dallas which nicely demonstrate an inverse relationship between baseline fitness and the risk of dying of breast cancer.[20] Unfortunately, in this dataset, information was bit available for non-fatal breast cancers, and it may be that fit patients are more likely to have a cancer diagnosed at an earlier stage.

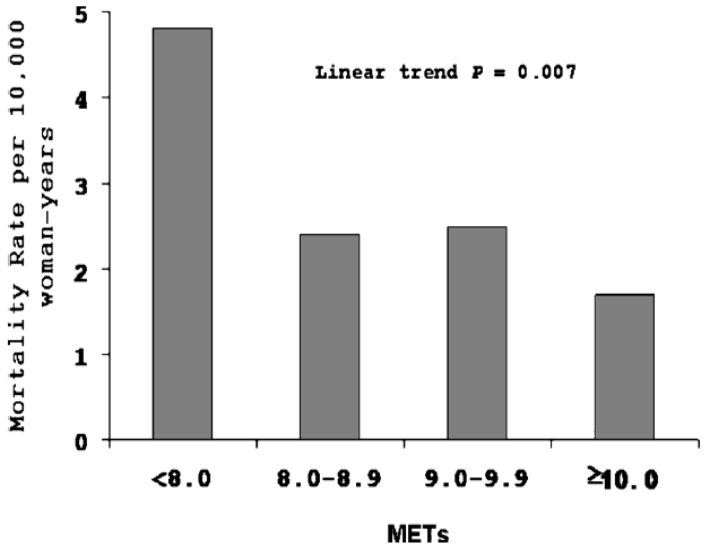


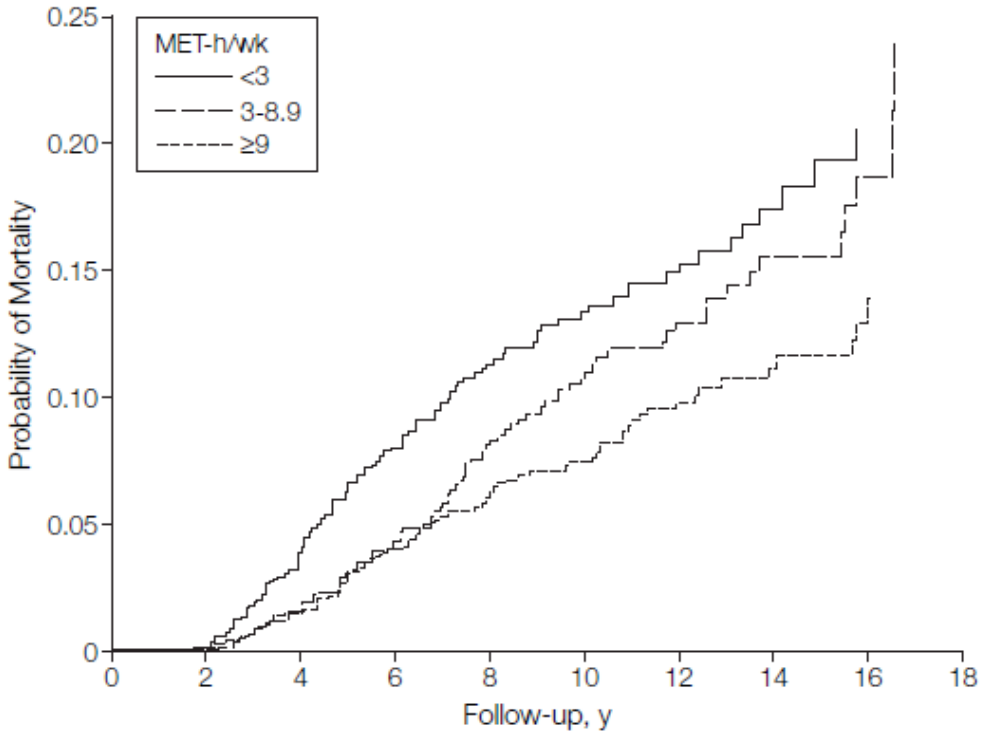
Figure 19: Mortality from breast cancer based on baseline fitness level.[20]

Once diagnosed with cancer, most patients decrease their activity. In this study shown in Figure 20, patients with stage 1 breast cancer on average decreased all physical activity by 2.6 hours a week (a decrease of 13.8%). [21]

	Hours per week (mean ± SE)		
Activity level	In situ (n = 185 patients)	Stage I (n = 479 patients)	Stage II and IIIa (n = 148 patients)
Total PA[b]			
Before diagnosis	18.5 ± 0.3	18.9 ± 0.1	19.2 ± 0.3
After diagnosis	17.8 ± 0.8	16.3 ± 0.4	17.5 ± 0.9
Absolute difference	−0.7 ± 0.8	−2.6 ± 0.4[c,d]	−1.7 ± 0.9[d]
% Difference	−3.8%	−13.8%	−8.9%

Figure 20: Change in physical activity levels after the diagnosis of breast cancer. [21]

While it is not surprising that patients with breast cancer are more sedentary while they are in the early stages of treatment, many studies have shown an inverse relationship between physical activity and breast cancer mortality. In Figure 21, data from breast cancer patients identified as part of the Nurses Health Study show a clear relationship between exercise after diagnosis and mortality.[22]



No. at Risk

Physical Activity, MET-h/wk									
<3	959	957	809	573	407	286	222	83	43
3-8.9	862	862	767	569	489	372	184	84	31
≥9	1166	1166	1066	773	692	449	290	164	86

Figure 21: Relationship between physical activity and mortality after the diagnosis of breast cancer. [22]

Many of these observational studies have shown a dose relationship between the amount of exercise and the degree of mortality reduction as well. What are some possible explanations for these findings?

One possible link between exercise and breast cancer mortality is its effect on obesity and the metabolic syndrome. In a small randomized trial of exercise in breast cancer survivors, Fairey and colleagues demonstrated a reduction in insulin like growth factor and insulin–like growth factor binding protein 3. The anit-inflammatory effects of exercise may be another possible mediator of the effects of exercise on breast cancer survival. Pierce and colleagues showed a similar association between elevated C-reactive protein and serum amyloid A protein with decreased total and disease free survival after breast cancer.[23] In a small exercise intervention study in breast cancer survivors, Fairey and colleagues demonstrated a reduction in C-reactive protein after 15 weeks of training.[24]

These and additional data have convinced many of the importance of exercise in breast cancer survivorship. At the Moncrief cancer center in Ft. Worth, a UT Southwestern facility, cancer survivors are offered structured exercise training funded by a grant from CPRIT, and the grant renewal includes a onco-cardiology clinic with an emphasis on lifestyle modifications to decrease breast cancer recurrence and prevent cardiovascular disease.

Conclusions

Let us conclude today be looking back at our patient. Does CC have late anthracycline cardiotoxicity? The answer is probably yes, although our imaging techniques are not yet able to provide a definitive answer about interstitial fibrosis. Certainly, she demonstrated an acute deterioration of systolic function during her early treatment, and her most recent echocardiogram shows diastolic dysfunction (which could also be due in part to hypertension and aging). I suspect that cardiotoxicity is partly to blame for her poor exercise capacity, and may improve if she dedicates herself to exercise training. Based on Framingham risk scores and left breast radiation, her risk of CAD is very high. Statistically, she will most likely die of coronary disease. Some of the same risk factors that put her at risk for breast cancer now put her at risk for cardiovascular disease. Her risk can be partially mitigated by aggressive control of her risk factors, with an emphasis on weight loss and exercise, the latter which will likely also reduce her risk of recurrent breast cancer. I propose that it is not the sole responsibility of the oncologists to provide excellent care for cancer survivors. The growing number of cancer survivors in the United States is reflected in each of our clinics every day, and I would remind each of us to take a moment and ask ourselves how the therapy that cured the cancer may have created another disease called cancer survivorship.

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