

Lifestyle Interventions for Cardiovascular Risk Reduction in Women with Breast Cancer

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Abstract: Purpose: The purpose of this paper is to identify risk factors for cardiovascular disease in women with breast cancer and review healthy lifestyle behaviors as essential risk reduction strategies.

Findings: Women with breast cancer account for 22% of the 12 million cancer survivors. Women diagnosed with breast cancer often present with modifiable and non-modifiable cardiovascular risk factors and/or pre-existing co-morbid illness. Any one or a combination of these factors may increase the risk of cardiovascular disease. There is strong evidence that healthy eating and routine physical activity can reduce cardiovascular disease. Exercise improves cardiovascular fitness, body composition and quality of life in breast cancer survivors and observational studies suggest a survival benefit.

Clinical Implications: Lifestyle interventions including a healthy diet, regular physical activity, weight management and smoking cessation should be integrated into a survivorship care plan to reduce cardiovascular disease risk and promote better health for women with breast cancer.

Keywords: Breast cancer survivor, cardiovascular risk, lifestyle behaviors, health promotion.

INTRODUCTION

Among women of all ages in the United States, cardiovascular disease is the leading cause of death [1]. When compared to cancer in women, heart disease ranks as the second leading cause of death for women 45-79 years of age [2]. Yet, for selected cancers, such as breast cancer with improved survival outcomes, competing causes of death have contributed to an increase in all-cause mortality [3-5]. There are nearly 12 million cancer survivors in the United States (US) with breast cancer accounting for 41% of female survivors and 22% of all survivors. With 261,100 new cases of breast cancer (invasive and in-situ) estimated to be diagnosed in 2010 [2], the number of breast cancer survivors can be projected to increase over the next decade. Advances in cancer treatment resulting in long term survivorship and cardiotoxicity associated with adjuvant breast cancer therapy, the risk of cardiovascular disease has been cited as higher than risk of breast cancer recurrence [6] and death from heart disease is more common now than deaths attributed to breast cancer among survivors [3, 7]. Many of the risk factors associated with cardiovascular disease are modifiable. Healthy lifestyle behaviors are the foundation for risk reduction for primary and secondary prevention [8]. The purpose of this paper is to emphasize the role of lifestyle interventions for breast cancer survivors at risk for cardiovascular disease due to non-breast and breast cancer treatment related risk factors. The paper will review modifiable risk factors for cardiovascular disease in women, identify the need for cardiovascular risk assessment in women with breast cancer, describe breast

cancer treatment related sequelae that contribute to reduced cardiovascular fitness and review the effectiveness of lifestyle interventions as a cardiovascular risk reduction and breast cancer survivor health promotion strategy.

RISK FACTORS OF CARDIOVASCULAR DISEASE IN MID-LIFE AND OLDER WOMEN

Overweight, obesity, abdominal adiposity, cigarette smoking, sedentary behavior, hypertension, impaired glucose tolerance, and abnormal cholesterol are known modifiable risk factors for cardiovascular disease (CVD) in women [9, 10]. The epidemic trend of overweight and obesity among women in the US is contributing to an increased risk of CVD, diabetes, hypertension, decreased physical function and metabolic syndrome [1, 11, 12], all of which are inter-related and significantly contribute to morbidity and mortality. Depression may have an indirect effect on CVD [1], and is associated with obesity, sedentary behavior, and poorer quality of life [13, 14]. Lifestyle interventions, specifically, healthy eating and regular physical activity, can prevent or modify these CVD risk factors [1, 8, 15, 16].

NEED FOR CARDIOVASCULAR RISK ASSESSMENT IN BREAST CANCER SURVIVORS

Women diagnosed with breast cancer may be at risk for cardiac disease unrelated to cancer treatment. Forty percent of women by 50 years of age in the US population have at least one cardiac risk factor and 17% have 2 or more risk factors, increasing their lifetime risk of developing cardiovascular disease. As the majority of women are diagnosed with breast cancer after the age of 45 years, a cardiovascular risk assessment is indicated even if women are asymptomatic [17-19]. Women with newly diagnosed breast cancer often present with modifiable CVD risk factors (e.g. overweight,

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obesity, sedentary behavior), non-modifiable risk factors (e.g. race, family history heart disease) and/or pre-existing chronic illness (e.g. valvular disease, hypertension, arrhythmias, diabetes) [20-25]. Any one or a combination of these factors increases a woman’s vulnerability to developing CVD and may enhance risk of cardiovascular complications from cancer therapy Fig. (1). Pre-existing diabetes in breast cancer survivors has been associated with increased treatment toxicity and reduced survival [26-28]. Hypertension has been reported as the most common co-morbid condition in cancer patients [29, 30], has been identified as a risk factor for developing anthracycline cardiotoxicity [21, 24], a risk factor for trastuzumab toxicity [22], is associated with a poorer prognosis especially in African American breast cancer survivors [31] and has emerged as a significant side effect of targeted breast cancer agents [6, 32, 33]. A “multiple hit” hypothesis has been proposed by Jones and colleagues [18] which suggests that the presence of cardiovascular risk factors increases the risk of developing cancer treatment associated cardiotoxicity and cancer treatment can independently cause cardiovascular injury. Cancer treatment may exacerbate underlying heart disease [6, 24, 25] and result in additive cardiac compromise [18, 20]. Comparing breast cancer survivors to age matched controls, breast cancer survivors were reported to have lower cardiac reserve, cardiovascular fitness, and HDL levels, and higher resting heart rate [34, 35]. Reduced cardiovascular reserve may increase a woman’s long term risk of CVD [34].

While some data exist on co-morbid conditions in newly diagnosed women with breast cancer [29, 36], the prevalence of cardiovascular risk factors in this population has not yet been systematically collected [18]. A baseline cardiac assessment prior to breast cancer therapy is essential [20]. Cardiovascular risk assessment prior to adjuvant breast therapy identifies level of risk and provides data to target interventions, specifically Class I lifestyle interventions and pharmacologic interventions where indicated [1, 17]. Screening for psychosocial distress in women at risk for or with cardiovascular disease is also recommended [37]. Anxiety and depression are associated with poorer outcomes [14, 38-41] and younger women appear more vulnerable [14]. Risk of depression among cancer survivors is estimated to be 10-25%, and younger breast cancer survivors have poorer adjustment

and quality of life compared to older women [42]. The contribution of personal susceptibility factors and pre-existing cardiac risk factors for women who are to receive cardiotoxic cancer therapy has yet to be fully elucidated but an increased vulnerability for adverse cardiac outcomes has been suggested [18, 20, 24]. It is a critical time for cardiology and oncology to collaborate to identify and develop interventions for women newly diagnosed with breast cancer in the presence of cardiac risk factors if our goal is to enhance the quality of life for cancer survivors and decrease morbidity and mortality [43-46] Fig. (1).

THE EXPERIENCE OF ADJUVANT BREAST CANCER THERAPY

Adjuvant breast treatment includes chemotherapy, endocrine therapy and targeted agents. There is a wide variety of symptoms, many of which persist once the treatment ends [47]. Fatigue, sleep disturbance, musculoskeletal complaints, weight gain, treatment induced menopausal symptoms, cognitive changes, bone loss, painful peripheral neuropathy, anxiety, depression and fear of recurrence are common [48-59]. Women during cancer therapy decrease their levels of physical activity [60] and the de-conditioning effects of inactivity during and after therapy may further contribute to fatigue, sleep disturbances, weight gain, body composition changes, changes in insulin sensitivity, muscle atrophy, and decreased cardiovascular fitness.

Weight gain during and after breast cancer treatment is common [61, 62] and has been associated with an increased risk of recurrence and lower survival [63]. Several studies have reported body composition changes in breast cancer survivors, specifically increases in body fat and decreases in lean muscle mass over time [60, 63-66] and adjuvant Tamoxifen has been associated with increases in percent body fat [64, 67]. Early reports on weight gain in breast cancer survivors documented average gains of 14-17 pounds [57, 68]. Although continued research suggests that gains of 5-14 pounds are more common, the weight gain persists and has reported to increase over time after therapy [61, 62, 69, 70]. In a sample of 190 women with breast cancer who received adjuvant therapy, 71% gained an average of 3.7 kg in the year following therapy and among the women who lost

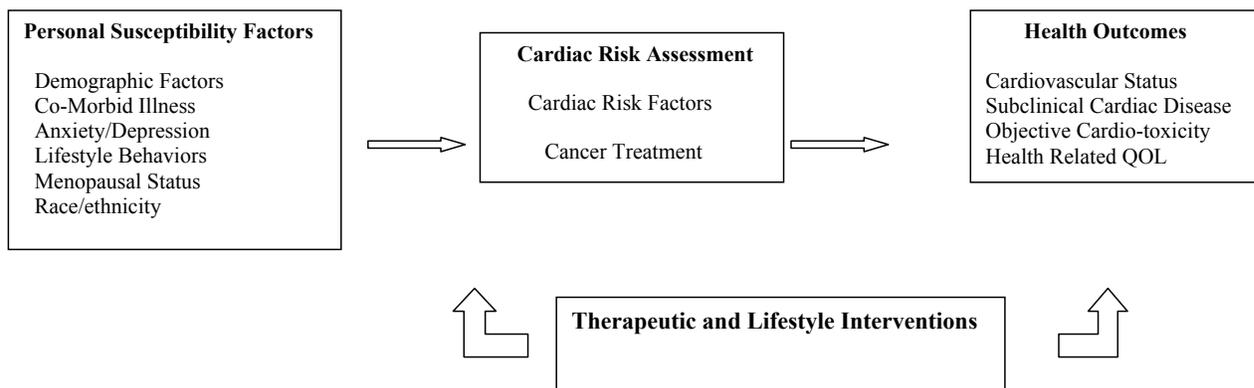


Fig. (1). Model of Cardiac Vulnerability in Women with Breast Cancer: Opportunity for Intervention.

weight in year one, 43% of them gained in years 2 and 3, exceeding their pre-treatment weight [70]. Continued weight gain in the years after adjuvant treatment may reflect societal trends in mid life and older women and may be associated with endocrine therapy, although the data are inconsistent to support the common complaints from women about weight gain and Tamoxifen.

Elevation in the systemic inflammatory marker, hsCRP, and central obesity have been associated with the development of metabolic syndrome in breast cancer survivors [71] both of which are considered significant cardiovascular risk factors [72, 73]. Monitoring weight and body composition, especially central adiposity, among breast cancer survivors is essential to target interventions [74].

The contribution of menopause to cardiovascular risk is a complex blend of chronological aging and ovarian aging [75]. While the evidence for decreased estrogen levels as a cardiac risk factor, either gradually with natural menopause, abruptly with chemotherapy induced menopause or with Aromatase Inhibitor therapy is controversial, it is strongly suggested to screen and monitor peri and postmenopausal women [75-77]. In one study with pre-menopausal women diagnosed with breast cancer who experienced amenorrhea with adjuvant therapy, there was a significant change in lipids, cholesterol, LDL, HDL and Lpa [78]. Cancer survivors are concerned about reducing their cancer recurrence risk but are also concerned about preventing morbidity and mortality from other chronic illness, such as heart disease [59]. The combination of drug induced menopause, effects of endocrine therapies and weight gain among breast cancer survivors underscores the unique potential cardiovascular disease risks for this population.

Cardiotoxicity associated with agents used in adjuvant breast cancer therapy has been well described [6, 18, 22, 24, 33, 79, 80]. In addition to the known Type I cardio-toxicity associated with anthracyclines [79], the use of targeted agents that alter genetic pathways and cellular functions has dramatically expanded the scope of cardiovascular effects of breast cancer therapy [6, 33, 80-83]. Measurement of left ventricular function (LVEF) is the standard of assessment for cancer treatment related cardiotoxicity but has failed to identify subclinical disease. The consequences of asymptomatic LVEF decline on long term cardiac function are essentially unknown [6, 35] and there is a critical need to identify patients with sub-clinical disease at higher risk of adverse cardiac outcomes [84]. Susceptibility to cardiac complications in cancer survivors is multifactorial [33] and requires the scientific and clinical knowledge of specialists in cardiology and oncology [6, 45, 85]. There is a gap in our understanding of the interplay of cardiovascular disease risk, cardiotoxicity and cardiac outcomes in cancer survivors. Identification of patients at risk for cardiac complications would direct risk reduction and therapeutic cardioprotective interventions to reduce morbidity and mortality [6, 24, 44, 86]. While we await data from needed prospective studies to better identify patients at risk for cardiac complications, lifestyle interventions have known health benefits for breast cancer survivors and mid-life women at risk for cardiovascular disease.

LIFESTYLE INTERVENTIONS FOR CARDIOVASCULAR DISEASE RISK REDUCTION

Ideal cardiovascular health includes total cholesterol <200 mg/dL, blood pressure < 120/80, fasting blood glucose < 100 mg/dL, body mass index <25 kg/m², no cigarette smoking, healthy diet, and regular physical activity of ≥150 minutes a week of moderate intensity or ≥ 75 minutes/week of vigorous intensity or a combination of intensities [1, 6]. Dietary guidelines for healthy eating for risk reduction for CVD, diabetes and cancer include a diet rich in whole grains and legumes with 5 servings of fruits and vegetables per day and limited intake of red meat, processed meats, alcohol and sugar sweetened beverages [87, 88]. There is strong epidemiologic data supporting the association of physical activity and healthy eating and lower risk of cardiovascular disease and diabetes in women [8]. Aerobic exercise at the recommended guideline of 30 minutes 5 days per week has also been shown to improve blood pressure [89], improve insulin sensitivity [90, 91] and result in better cardio-respiratory fitness [9, 91, 92]. This level of exercise intensity can maintain weight but for women who desire to lose weight, exercise at a moderate-vigorous intensity 60 minutes per day is required, and preferentially combined with calorie restriction [9, 16]. To achieve ideal cardiovascular health or reduce risk factors, Artinian and colleagues [15] comprehensively reviewed the research on physical activity and healthy eating in relationship to CVD risk reduction and provide evidence based recommendations for practice. To promote adoption and adherence to the recommended guidelines for physical activity and healthy eating, goal setting, motivational strategies, reinforcement, feedback, and problem solving skills are identified as key strategies to support healthy lifestyle behaviors [15]. The authors also stress the importance of considering culture, ethnicity and socioeconomic factors in healthy lifestyle interventions [15] as changing one's behavior is complex and approaches need to be tailored to specific populations to increase adherence and success [93].

PHYSICAL ACTIVITY AND BREAST CANCER SURVIVORS

Data from six observational studies concluded that moderate exercise (3-5 hours/week) improved all cause mortality in breast cancer survivors [94-99]. Multiple meta-analyses and systematic reviews of exercise interventions in breast cancer survivors over the past decade have reported improved cardiovascular fitness, body composition, quality of life, psychological adjustment, aerobic capacity, muscle strength and a decrease in fatigue, depression, anxiety, and sleeping disturbance [100-109]. Jones and colleagues [110] reviewed studies from 2002-2009 that systematically assessed cardiorespiratory fitness (CRF) with peak oxygen consumption and reported a statistically significant improvement in CRF for supervised exercise training compared to control groups. Overweight and obesity remain significant risk factors for breast cancer survivors and are associated with increased risk of breast cancer recurrence [111] and higher mortality risk [4, 26, 112]. In a review of 24 randomized controlled exercise trials from 1998-2008, 44% reported improvement in body composition (e.g. less fat mass,

Table 1. Recommendations for Lifestyle Behaviors for Cardiovascular Risk Reduction in Women with Breast Cancer

Lifestyle Behavior	Recommendation
Cigarette smoking	Women should avoid tobacco smoke in the environment and should quit smoking if a smoker. Refer for counseling, behavioral programs and/or pharmacotherapy.
Diet	Fruits and vegetables ≥ 4.5 cups/day Fish Twice a week Fiber 30 g/day Whole grains 3/day Nuts, legumes, seeds ≥ 4 /week Saturated fat $< 7\%$ total energy intake Cholesterol < 150 mg/day Alcohol ≤ 1 /day Sodium < 1500 mg/day <i>Trans</i> -fatty acids 0 Sugar-sweetened beverages ≤ 36 oz/week
Physical Activity	Minimum goal for women: 150 minutes of moderate-intensity aerobic exercise or 75 minutes vigorous exercise per week and muscle-strength exercises on 2-3 days per week. For optimal cardiovascular benefit, recommend 30 minutes of moderate aerobic physical activity most days of the week in episodes of at least 10 minutes each. Women who need to lose weight, 60-90 minutes of at least moderate-intensity activity preferably on every day of the week is recommended. Consider referral to established programs to assist women in goal setting, problem solving skills, self monitoring, adherence and relapse prevention. Encourage women to enroll in physical activity intervention trials.
Weight Management	Goal is BMI < 25 kg/m ² and waist circumference < 35 inches. Energy balance is the key to weight loss or maintaining current weight and requires a balance of physical activity and calorie intake. Refer women for consultation on healthy eating and energy balance. Encourage cancer survivors to enroll in weight management clinical trials.
Psychological Well-being	Breast cancer survivors should be screened for psychological distress as anxiety and depression may increase cardiovascular risk, adversely affect their recovery and decrease overall quality of life. Provide women information about normal psychological reactions to diagnosis and treatment and discuss referral for counseling and exercise.

Data adapted from [1, 8, 13, 15, 38, 42, 121]

increased lean muscle mass) [108]. Waist circumference is a well established measure of abdominal fat in cardiology, and can significantly predict women at higher cardiovascular risk even for those women within normal weight ranges [10]. While many breast cancer exercise trials have evaluated body composition, few have specifically reported changes in waist circumference. Cheema *et al.* [113] reported on a pilot aerobic resistance exercise study in women with breast cancer and waist circumference decreased after 8 weeks of exercise with no change in weight. While more sophisticated measures of body composition, such as whole body DEXA scans, may be preferred by researchers, waist circumference is a simple and reliable measure that can be incorporated into research and clinical practice.

More than half of women diagnosed with breast cancer who have participated in exercise trials have been overweight and some obese, reflecting a similar pattern of weight to women without breast cancer in the US. Only a few trials have investigated diet and exercise as an intervention for weight loss in breast cancer survivors [114-117]. Data from one trial [114] has supported the translation to an institutional clinical program [118] but randomized controlled trials

are needed that combine physical activity and diet, if we are to influence the chronic illness risks of overweight and obesity on morbidity and mortality for women with breast cancer [74, 119].

SUMMARY

Lifestyle interventions are strongly recommended for breast cancer survivors [6, 21, 22, 32, 45, 120] for health promotion and risk reduction related to chronic illness. Recognizing the relationship of risk factors across chronic illness, the American Cancer Society (ACS), the American Heart Association (AHA) and the American Diabetes Association (ADA) set forth a common agenda for healthy lifestyle behaviors to reduce health risks at primary, secondary and tertiary levels [87]. Lifestyle interventions to reduce cardiovascular risk in women includes smoking cessation, a healthy diet, regular physical activity and weight management [1] and are directly applicable to breast cancer survivors Table (1). Physical activity recommendations by the American College of Sports Medicine for cancer survivors [121] are consistent with the American Heart Association guidelines for secondary prevention [1, 8, 16] and the United

States Department of Health and Human Services [122]. For research and for clinical rehabilitation, fitness providers must be knowledgeable about the effects of cancer treatment on the ability to engage in exercise [121]. Persistent symptoms of therapy such as peripheral neuropathy [55], arthralgias [123], decreased cardiovascular reserve [18] and fatigue [124] are common and need to be incorporated into an individual prescription for an exercise program. Overweight and obesity present unique challenges to lifestyle behavior change and are often associated with chronic conditions such as knee osteoarthritis, diabetes and hypertension. Communication between oncology and cardiology in recommendations of lifestyle interventions for breast cancer survivors experiencing late effects such as decreased left ventricular function is critical to establish the best approach to individualized patient management. Finally, qualified providers for physical rehabilitation, such as physical therapists, fitness trainers in the community and clinical oncology researchers should be familiar with guidelines for exercise testing prior to implementing a physical lifestyle interventions in cancer survivors [121, 125]. Lifestyle behavior change is challenging, and maintenance of behavioral change has been shown to be quite difficult for the majority of persons. We, as oncology and cardiology providers, should establish a strong collaborative team between the patient, us and the physical fitness experts in enrolling patients in lifestyle intervention clinical trials and in promoting healthy living survivor programs in clinical practice.

REFERENCES

- Mosca, L., Benjamin, EJ, Berra, K., Bezanson, JL, Dolor, RJ, Lloyd-Jones, DM. *et al.* Effectiveness-based guidelines for the prevention of cardiovascular disease in women 2011 update: a guideline from the American Heart Association. *Circulation* 2011; 123 doi: 10.1161/CTR.0b013c31820faal8
- Jemal A, Siegel R, Xu, J, Ward E. Cancer statistics 2010. *CA Cancer J Clin* 2010; 60: 277-300.
- Chapman, J.W., Meng, D., Shepherd, L., Parulekar, W., Inge, J.N., Muss, H. *et al.* (2008). Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer. *J Natl Cancer Inst*, 100, 252-260.
- Nichols HB, Trentham-Dietz A, Egan KM, Titus-Ernstoff L, Holmes MD, Bersch AJ *et al.* Body mass index before and after breast cancer diagnosis: associations with all cause, breast cancer and cardiovascular disease mortality. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 1403-1409.
- Patnaik, JL, Byers T, DiGiuseppe C, Denberg TD & Dabelea D. The influence of co-morbidities on overall survival among older women diagnosed with breast cancer. *J Natl Cancer Inst* 2011; 103: 1101-1111.
- Maurea, N, Coppola C, Ragone G *et al.* Women surviving breast cancer but fall victim to heart failure: the shadows and lights of targeted therapy. *J Cardiovasc Med* 2010; 11: 861-868.
- Patnaik JL, Byers T, DiGiuseppe C, Dabelea D & Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. *Breast Cancer Res Treat* 2011, 13: R64 <https://breast-cancer-research.com/content/13/3/R64>
- Lloyd-Jones, DM, Hong, Y, Labarthe D, Mozaffarian D, Appel LJ, VanHorn L. *et al.* Defining and setting national goals for cardiovascular health promotion and disease reduction: The American Heart Association's strategic impact goals through 2020 and beyond. *Circulation* 2010; 121: 586-613.
- Lee VL & Foody JM. Women and heart disease. *Cardiol Clin* 2001; 29: 35-45.
- Zhang, C, Rexrode KM, vanDam RM, Li TY & Hu FB. Abdominal obesity and risk of all cause, cardiovascular and cancer mortality. *Circulation* 2008; 117: 1658-1667.
- Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA *et al.* Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung and Blood Institute scientific statement: executive summary. *Circulation* 2005; 112 e285-e290.
- deGonzalez A, Hartge P, Cerhan JR, Flint AJ, Hannan L, MacInnis RJ *et al.* Body-mass index and mortality among 1.46 million white adults. *New Engl J Med* 2010; 363: 2211-2219.
- Vaccarino V, McClure C, Johnson D, Sheps DS, Bittner V, Rutledge T *et al.* Depression, the metabolic syndrome and cardiovascular risk. *Psychosomatic Med* 2008; 70: 40-48
- Beckie TM, Fletcher GF, Beckstead JW, Schocken DD & Evans ME. Adverse baseline physiological and psychosocial profiles of women enrolled in a cardiac rehabilitation clinical trial. *J Cardiopulmonary Rehab Prev* 2008; 28: 52-60.
- Artinian, NT, Fletcher, GF, Mozaffarian, D, Kris-Etherton, P, VanHorn, L, Lichtenstein, AH, *et al.* Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation* 2010; 122: 406-441.
- Haskell, WL, Lee I, Pate RR, Powell KE, Blair SN, Franklin BA *et al.* Physical activity and public health. Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation* 2007 116. Doii: 10.1161/CIRCULATIONAHA.107.185649
- Berger, J.S., Jordan, C.O., Lloyd-Jones, D., & Blumenthal, R.S. Screening for cardiovascular risk in asymptomatic patients. *J Am Coll Cardiol* 2010; 531: 169-177.
- Jones LW, Haykowsky MJ, Swartz JJ, Douglas PS, Mackey JR. Early breast cancer therapy and cardiovascular injury. *J Am Coll Cardiol* 2007; 50: 1435-1441.
- Magne, N., Chargari, C., MacDermid, D., Conforti, R., Vedrine, L., Spano, J. & Khayat, D. Tomorrow's targeted therapies in breast cancer patients. What is the risk for increased radiation-induced cardiac toxicity? *Critical Rev Oncol/Hematol* 2010; 76: 186-195.
- Chagari C, Kirov KM, Bollet MA, Magne N, Vedrine L, Cremades S *et al.* Cardiac toxicity in breast cancer patients: from a fractional point of view to a global assessment. *Cancer Treat Rev* 2011; 37: 321-330.
- Khakoo, A.Y. & Yeh, E.T. Therapy insight: management of cardiovascular disease in patients with cancer and cardiac complications of cancer therapy. *Nature Clinical Practice Oncology* 2008; 5: 655-667.
- Martin, M., Esteva, F.J. & Alba, E. Minimizing cardiotoxicity while optimizing treatment efficacy with trastuzumab: review and expert recommendations. *The Oncologist* 2009; 14: 1-11.
- Perez, E.A., Suman, V.J. & Davidson, N.E. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008; 26: 1231-1238.
- Ewer MS & Ewer SM. Cardio-toxicity of anticancer treatments: what the cardiologist needs to know. *Nature Rev* 2010; 7: 564-575.
- Verma, S. & Ewer, MS (2010). Is cardio-toxicity being adequately assessed in current trials of cytotoxic and targeted agents in breast cancer? *Ann Oncol*, doi: 10.1093/annoncol/indq607
- Peairs KS, Barone BB, Snyder CF, Yeh, H, Stein KB, Derr RL. *Et al.* Diabetes mellitus and breast cancer outcomes: systematic review and meta-analyses. *J Clin Oncol* 2010; 29: 40-46.
- Erickson K, Patterson RE, Flatt SW, Natarajan L, Parker BA, Heath DD *et al.* Clinically defined Type 2 diabetes mellitus and prognosis in early-stage breast cancer. *J Clin Oncol* 2010; 29: 54-60.
- Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR & Hux JE. The impact of diabetes on survival following breast cancer. *Breast Cancer Res Treat* 2008; 109: 389-395.
- Harlan LC, Klabunde CN, Ambs AH, Gibson T, Bernstein L *et al.* Co-morbidities, therapy and newly diagnosed conditions for women with early stage breast cancer. *J Cancer Surv* 2009; 3: 89-98.
- Senkus E & Jassem J. Cardiovascular effects of systemic cancer treatment. *Cancer Treat Rev* 2011; 37: 300-311.
- Braithwaite D, Tammemagi CM, Moore DH, Ozanne EM, Hiatt RA, Belkora J *et al.* Hypertension is an independent predictor of survival disparity between African American and white breast cancer patients. *Int J Cancer* 2009; 124: 1213-1219.

- [32] Harbeck N, Ewer MS, DeLaurentiis M, Suter TM & Ewer SM. Cardiovascular complications of conventional and targeted adjuvant breast cancer therapy. *Ann Oncol* 2011; 22: 1250-1258.
- [33] Yardley, DA Integrating bevacizumab into the treatment of patients with early stage breast cancer: focus on cardiac safety. *Clinical Breast Cancer* 2010; 10(2): 119-129.
- [34] Jones, LW, Haylowsky, M., Pituskin, EN, Jendzjowsky, NG, Tomczak, CR, Haennel, RG & Mackey, JR. Cardiovascular reserve risk profile of postmenopausal women after chemo-endocrine therapy for hormone receptor-positive operable breast cancer. *Oncologist*, 2007; 12: 1156-1164.
- [35] Jones, LW, Haykowsky, M., Peddle, CJ, Joy, AA., Pituskin, EN, Tkachuk, LM. *Et al.* Cardiovascular risk profile of patients with HER2/neu-positive breast cancer treated with anthracycline-taxane-containing adjuvant chemotherapy and/or trastuzumab. *Cancer Epidemiol Biomarker Prev* 2007; 16(15): 1026-1031.
- [36] Patterson RE, Flatt SW, Saquib N, Rock, CL, Cann BJ *et al.* Medical co-morbidities predict mortality in women with a history of early stage breast cancer. *Breast Cancer Res Treat* 2010; 122: 859-865.
- [37] Norris, C.M., Ljubska, A., & Hegadoren, K.M. Gender as a determinant of responses to a self-screening questionnaire on anxiety and depression by patients with coronary artery disease. *Gen Med* 2009; 6: 479-487.
- [38] Szekely, A., Balong, P., Benko, E, Breuer, T., Szekely, J., Kertal, M.D. *et al.* Anxiety predicts mortality and morbidity after coronary artery and valve surgery-a 4 year follow-up study. *Psychosomatic Med* 2007; 69: 625-631.
- [39] May, H.T., Horne, B.D., Carlquist, J.F., Sheng, X., Joy, E. & Catinella, A.P. Depression after coronary artery disease is associated with heart failure. *J Am Coll Cardiol* 2009; 53, 1440-1447.
- [40] Todaro, J.F., Shen, B.J., Niaura, R. & Tikemeier, P.L. Prevalence of depressive disorders in men and women enrolled in cardiac rehabilitation. *J Cardiopulm Rehabil* 2005; 25, 71-75.
- [41] Sperus, J.A., McDonnell, M., Woodman, C.L. & Fihn, S.D. Association between depression and worse disease specific functional status in outpatients with coronary artery disease. *Am Heart J*, 2000; 140: 105-110.
- [42] Institute of Medicine. *Meeting psychosocial needs of women with breast cancer*. Washington, DC: The National Academies Press 2004.
- [43] Albini, A., Pennesi, G., Donatelli, F., Cammarota, R., De Flora, S. & Noonan, D.M. Cardio-toxicity of anticancer drugs: The need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst* 2010; 102: 14-25.
- [44] Giordano, S.H. & Hortobagoyi, G. Local recurrence or cardiovascular disease: pay now or later. *J Natl Cancer Inst* 2007; 99: 340-341.
- [45] Lenihan, D.J. & Esteva, F.J. Multidisciplinary strategy for managing cardiovascular risk when treating patients with early stage breast cancer. *The Oncologist* 2008; 13: 1224-1234.
- [46] Ewer MS & Ewer SM. Long-term cardiac safety of dose-dense anthracycline therapy cannot be predicted from early ejection fraction data. *J Clin Oncol* 2009; doi: 10.1200/JCO.2009.25.5091
- [47] Institute of Medicine. *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, DC: The National Academies Press 2006.
- [48] Cappiello, M, Cunningham, R, Knobf, MT, Erdos, D. Breast cancer survivors. Information and support after treatment. *Clin Nurs Res* 2007; 16: 278-293.
- [49] Bower JE, Ganz PA, Desmond KA, *et al.* Fatigue in breast cancer survivors: occurrence, correlates and impact on quality of life. *J Clin Oncol* 2000; 18: 743-753.
- [50] Gaillard S, Stearns V. Aromatase inhibitor-associated bone and musculoskeletal effects: new evidence defining etiology and strategies for management. *Breast Cancer Res* 2011; 13: 205-214.
- [51] Berger, AM. Update on the State of the Science: Sleep-wake disturbances in adult patients with cancer. *Oncol Nurs Forum* 2009; 36: e165-e177.
- [52] Knobf MT. Symptom distress before, during and after adjuvant breast cancer therapy. *Developments Support Care* 2000; 4: 13-17.
- [53] vanWeert E, Hoekstra-Weebers J, Otter R, Postema K, Sanderman R & van der Schans C. Cancer-related fatigue: predictors and effects of rehabilitation. *Oncologist* 2006; 11: 184-196.
- [54] Avis NA, Crawford S & Manuel J. Quality of life among younger women with breast cancer. *J Clin Oncol* 2005; 23: 3322-3330.
- [55] Bakitas M. Background noise. The experience of chemotherapy-induced peripheral neuropathy. *Nur Res* 2007; 56: 323-331.
- [56] Reid-Arndt SA, Hsieh C & Perry MC. Neuropsychological functioning and quality of life during the first year after completing chemotherapy for breast cancer. *Psycho-oncol* 2010; 19: 535-544.
- [57] Knobf, M., Mullen, J., Xistris, D., & Moritz, D. Weight gain in women with breast cancer on adjuvant chemotherapy. *Oncol Nurs Forum* 1983; 10: 28-33.
- [58] Knobf MT. Psychosocial responses in breast cancer survivors. *Semin Oncol Nurs* 2007; 23: 71-83.
- [59] Knobf MT. Carrying on. The experience of premature menopause in women with early stage breast cancer. *Nurs Res* 2002; 51: 9-17.
- [60] Irwin, M., Crumley, D., McTiernan, A. *et al.* Physical activity levels before and after a diagnosis of breast cancer. *Cancer* 2003; 97, 1746-1757
- [61] Irwin, M., McTiernan, A., Baumgarten, R.N. *et al.* Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic and lifestyle factors. *J Clin Oncol*, 2005; 23: 774-782.
- [62] McInnes, J. & Knobf, M.T. Weight gain and quality of life in women treated with adjuvant therapy for breast cancer. *Oncol Nurs Forum* 2001; 28: 675-684.
- [63] Kroenke, C.H., Chen, W.Y., Rosner, B. & Holmes, M.D. (2005). Weight, weight gain and survival after breast cancer diagnosis. *J Clin Oncol*, 2005; 23: 1370-1378.
- [64] Kutynec, C.L., McCargar, L., Barr, S.I. & Hislop, T.G. Energy balance in women with breast cancer during adjuvant treatment. *J Amer Diet Assoc* 1999; 99: 1222-1227.
- [65] Ingram, C. & Brown, J. (2004). Patterns of weight and body composition change in premenopausal women with early stage breast cancer. *Canc Nurs*, 27, 483-490.
- [66] Cheney, C.L., Mahloch, J. & Freeny, P. Computerized tomography assessment of women with weight changes associated with adjuvant treatment for breast cancer. *Am Jour Clin Nutrition* 1997; 66: 141-146.
- [67] Knobf, MT, Insogna K, DiPietro L, Fennie K & Thompson AS. An aerobic weight-loaded pilot exercise intervention for breast cancer survivors: bone remodeling and body composition outcomes. *Biol Res Nurs* 2008; 10: 34-43.
- [68] Knobf, M.T. Psychological and physical distress associated with adjuvant chemotherapy in women with breast cancer. *J Clin Oncol* 1986; 14: 678-684.
- [69] Rock, C.L., Flatt, S.W., Newman, V. *et al.* Factors associated with weight gain in women after diagnosis of breast cancer. *J Am Diet Assoc* 1999; 99: 1212-1218, 1221.
- [70] Makari-Judson G, Judson CH & Mertens WC. Longitudinal patterns of weight gain after breast cancer diagnosis: observations beyond the first year. *The Breast Journal* 2007; 13: 258-265.
- [71] Thomson, C., Thompson, P.A., Wright-Bea, J., Nardi, E., Frey, G.R. & Stopeck, A. (2009). Metabolic syndrome and elevated c-reactive protein in breast cancer survivors on adjuvant hormone therapy. *J Women's Health*, 2009; 18: 2041-2047.
- [72] Chen, T.H., Gona, P., Sutherland, P.A., Benjamin, E.S., Wilson, P.W., Larson, M.G., Vasan, R.S., Robins, S.J. Long-term c-reactive protein variability and prediction of metabolic risk. *Am Jour Med* 2009; 122: 53-61.
- [73] Hamer, M., Chida, Y. & Stamatakis, E. Association of very highly elevated c-reactive protein concentration with cardiovascular events and all-cause mortality. *Clinical Chemistry* 2010; 56: 132-135.
- [74] Wolin KY, Carson K & Colditz GA. Obesity and cancer. *Oncologist* 2010; 15: 556-565.
- [75] Bittner, V. Menopause, age and cardiovascular risk. *J Am Coll Cardiol* 2009; 54: 2374-2375.
- [76] Matthews, K.A., Crawford, S.L., Chae, C.U., Everson-Rose, S.A., Sowers, M.F., Sternfeld, B. & Sutton-Tyrell, K. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopause transition? *J Am Coll Cardiol* 2009; 54: 2366-2373.
- [77] Ewer, M.S. & Gluck, S. A woman's heart. The impact of adjuvant endocrine therapy on cardiovascular health. *Cancer* 2009; 115: 1813-1826.
- [78] Saarto, T., Blomqvist, C., Ehnholm, C., Taskinen, M. & Elomaa, I. Effects of chemotherapy-induced castration on serum lipids and apoproteins in premenopausal women with node-positive breast cancer. *J Clin Endocrinol Metab* 1996; 81: 4453-4457.

- [79] Russell R. Anthracyclines and cardiotoxicity. *Current Cardiology Reviews* 2011; 7(4): 214-220.
- [80] Hedhli N & Russell K. Cardiotoxicity of molecularly targeted agents. *Current Cardiology Reviews* 2011; 7(4): 221-233.
- [81] Chien, K.R. (2006). Herceptin and the heart: A molecular modifier of cardiac failure. *N Engl J Med*, 358(8), 789-90.
- [82] Peng, X., Pentassuglia, L. & Sawyer, D.B. Emerging anticancer therapeutic targets and the cardiovascular system: is there cause for concern? *Circ Res*, 2010; 106: 35-46.
- [83] Zambelli, A., DellaPorta, MG, Eleuteri, E, DeGiuki, L., Catalano, O., Tondini, C & Riccardi, A. Predicting and preventing cardiotoxicity in the era of breast cancer targeted therapies. Novel molecular tools for clinical trials. *The Breast*, 2010; doi: 10.1016/j.breast.2010.11.002
- [84] Jurcut, R., Wildiers, H., Ganame, J., D'hooge, J., Paridaems, R. & Voight, J. Detection and monitoring of cardiotoxicity-what does modern cardiology offer? *Support Care Cancer* 2008; 16: 437-445.
- [85] Yoon, GJ, Telli, ML, Kao, DP, Matsudo, KY, Carlson, RW & Wittcles, RM. Left ventricular dysfunction in patients receiving cardiotoxic cancer therapies. *J Am Coll Cardiol*, 2010; 56: 1644-1650.
- [86] Granger, C.B. Prediction and prevention of chemotherapy-induced cardiomyopathy. Can it be done? *Circulation*, 2006; 114: 2432-2433.
- [87] Eyre, H, Kahn R & Robertson R. Preventing cancer, cardiovascular disease and diabetes. A common agenda for the American Cancer Society, the American Diabetes Association and the American Heart Association. *Circulation* 2004; 109: 3244-3255.
- [88] Kushi LH, Byers T, Doyle C, Bandera EV, McCoullough M, Gansler T, et al. American Cancer Society guidelines on nutrition and physical activity for cancer prevention: reducing the risk of cancer with healthy food choices and physical activity. *CA Cancer J Clin* 2006; 56: 254-281.
- [89] Kokkmos PF, Narayan P & Papademetriou V. Exercise as hypertension therapy. *Cardiol Clin* 2001; 19: 507-516.
- [90] Chipkin SR, Klugh SA & Chasan-Taber L. Exercise and diabetes. *Cardiol Clin* 2001; 19: 489-505.
- [91] Dunn AL. Effectiveness of lifestyle physical activity interventions to reduce cardiovascular disease. *Amer J Lifestyle Med* 2009; 3(suppl1): 11s-18s.
- [92] Camethon MR. Physical activity and cardiovascular disease. How much is enough? *Amer J Lifestyle Med* 2009; 3(suppl1): 44s-49s.
- [93] Bosworth HB, Powers BJ & Oddone EZ. Patient self-management support: novel strategies in hypertension and heart disease. *Cardiol Clin* 2010; 28: 655-663.
- [94] Holmes MD, Chen WY, Feskanich D, Kroenke CH & Colditz GA. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005; 293: 2479-2486.
- [95] Holick CN, Newcomb PA, Trentham-Dietz A, Titus-Ernstoff L, Bersch A, Stampfer MJ et al. Physical activity and survival after diagnosis invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 379-386.
- [96] Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD et al. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the Health, Eating, Activity and Lifestyle study. *J Clin Oncol* 2008; 26: 3958-3964.
- [97] Sternfeld B, Weltzien E, Quesenberry CP, Castillo AL, Kwan M, Slattey ML & Caan BJ. Physical activity and risk of recurrence and mortality in breast cancer survivors: findings from the LACE study. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 87-95.
- [98] Bertram LA, Stefanik ML, Saquib N, Natarajan L, Patterson RE, Bardwell W et al. Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: findings from the WHEL study. *Cancer Causes Control* 2011; 22: 427-435.
- [99] Irwin ML, McTiernan A, Manson JE, Thomson CA, Sternfeld B, Stefanik ML et al. Physical activity and survival in postmenopausal women with breast cancer: results from the Women's Health Initiative. *Cancer Prev Res* 2011; 4: 522-529.
- [100] Speck RM, Courneya KS, Masse L, Duval S & Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv* 2010; 4: 87-100.
- [101] Kim C, Kang D & Park J. A meta-analysis of aerobic exercise interventions for women with breast cancer. *West J Nurs Res* 2009; 31: 437-461.
- [102] deBacker IC, Schep G, Backs FJ, Vreugdenhil G, & Kulpers H. Resistance training in cancer survivors: a systematic review. *Int J Sports Med* 2009; 30: 703-712.
- [103] Mares M & Brockow T. Exercise for women receiving adjuvant therapy for breast cancer (review). *Cochrane Collection* 2009; John Wiley & Sons.
- [104] Ferrer RA, Huedo-Medina TB, Johnson BT, Ryan S & Pescatello LS. Exercise interventions for cancer survivors: a meta-analysis of quality of life outcomes. *Ann Behav Med* 2011; 41: 32-47.
- [105] Schmitz, K.H., Holtzman, J., Courneya, K. et al. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 2005; 14: 1588-1595.
- [106] Ingram C & Visovsky C. Exercise intervention to modify physiologic risk factors in cancer survivors. *Semin Oncol Nurs* 2007; 23: 275-284.
- [107] Knobf, MT, Musanti R & Dorward J. Exercise and quality of life outcomes in patients with cancer. *Semin Oncol Nurs* 2007; 23: 285-296.
- [108] White SM, McAuley E, Estabrooks PA & Courneya KS. Translating physical activity interventions for breast cancer survivors into practice: an evaluation of randomized controlled trials. *Ann Behav Med* 2009; 37: 10-19.
- [109] Al-Majid S & Gray DP. A biobehavioral model for the study of exercise interventions in cancer-related fatigue. *Biol Res Nurs* 2008; 10: 381-391.
- [110] Jones LW, Liang, Y., Pituskin EN, Battaglini CL, Scott JM, Hornsby WE & Haykowsky M. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. *Oncologist* 2011; 16: 112-120.
- [111] Ewertz M, Jensen M, Gunnarsdottir KA, Hojris I, Jakobsen EH, Nielsen D et al. Effect of obesity on prognosis after early-stage breast cancer. *J Clin Oncol* 2010; 29: 25-31.
- [112] Chen X, Lu W, Zheng W, Gu K, Chen Z, Zheng Y & Shu X. Obesity and weight change in relation to breast cancer survival. *Breast Cancer Res Treat* 2010; 122: 823-833.
- [113] Cheema BS & Gaul CA. Full-body exercise training improves fitness and quality of life in survivors of breast cancer. *J Strength Conditioning Res* 2006; 20: 14-21.
- [114] Goodwin P, Expley MJ, Butler K, Winocur J, Pritchard K, Brazel S et al. Multidisciplinary weight management in locoregional breast cancer: results of a phase II study. *Breast Cancer Res Treat* 1998; 48: 53-64.
- [115] McTiernan A, Ulrich C, Kumai C, Bean D, Schwartz R, Mahloch J et al. Anthropometrical and hormone effects of an eight week exercise-diet intervention in breast cancer patients: results of a pilot study. *Cancer Epidemiol Biomarkers Prev* 1998; 7: 477-481.
- [116] Mefford K, Nichols JF, Pakiz B & Rock CL. A cognitive behavioral therapy intervention to promote weight loss improves body composition and blood lipid profiles among overweight breast cancer survivors. *Breast Cancer Res Treat* 2006; doi: 10.1007/s10549-006-9410-x.
- [117] Demark-Wahnefried W, Case LD, Blackwell K, Marcom PK, Kraus W, Aziz N. et al. Results of a diet/exercise feasibility trial to prevent adverse body composition changes in breast cancer patients on adjuvant chemotherapy. *Clinical Breast Cancer* 2008; 8: 70-79.
- [118] Muraca L, Leung D, Clark, A, Beduz MA & Goodwin P. Breast cancer survivors: taking charge of lifestyle choices after treatment. *European J Oncol Nurs* 2011; 15: 250-253.
- [119] Ballard-Bash R, Hunsberger S, Alciati MH, Blair SN, Goodwin P, McTiernan A, Wing R & Schatzkin A. Physical activity, weight control and breast cancer risk and survival: clinical trial rationale and design considerations. *J Natl Cancer Inst* 2009; 101: 630-643.
- [120] Khakoo AY, Liu PP, Force T, Lopez-Berestein G, Jones LW, Schneider J & Hill J. Cardiotoxicity due to cancer therapy. *Texas Heart Institute Journal* 2011; 38: 253-256.
- [121] Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM et al. American College of Sports Medicine Roundtable on exercise guidelines for cancer survivors. *Med Science Sports Exercise* 2010; doi: 10.1249.MSS.0b013e3181e0c112
- [122] Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report*. Washington DC: US Department Health Human Services, 2008.
- [123] Dent SF, Gaspo R, Kissner M, Pritchard KI. Aromatase inhibitor therapy: toxicities and management strategies in the treatment of

- postmenopausal women with hormone-sensitive early breast cancer. *Breast Cancer Res Treat* 2011; 126: 295-310.
- [124] Stricker C, Drake D, Hoyer K & Mock V. Evidence based practice for fatigue management in adults with cancer: exercise as an intervention. *Oncol Nurs Forum* 2004; 31: 963-974.
- [125] Jones LW Eves ND, Haykowsky M, Joy AA & Douglas PS. Cardio-respiratory exercise testing in clinical oncology research: systematic review and practice recommendations. *Lancet Oncology* 2008; 9: 757-765.

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