UNIVERSITY OF CALIFORNIA, SAN DIEGO

SAN DIEGO STATE UNIVERSITY

DIABETES AND BREAST CANCER:

THE WOMEN'S HEALTHY EATING & LIVING STUDY

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy

in

Public Health (Epidemiology)

by

Kirsten Diann Erickson

Committee in charge:

University of California, San Diego

Professor John P. Pierce, Chair
Professor Loki Natarajan
Professor Ruth E. Patterson
Professor Tony Reid

San Diego State University

Professor Suzanne P. Lindsay
Professor Caroline Macera

2011

The Dissertation of Kirsten Diann Erickson is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

San Diego State University

2011

DEDICATION

I would like to dedicate this dissertation to my greatest **LIFE** teachers:

To my parents, Bruce and Mary,

To "my rock", Mikey,

and to Tony,

who all lead by example.

"Example is not the main thing in influencing others. It is the only thing."

Albert Schweitzer (1875-1965);
Philosopher, Physician, Nobel Peace Prize Winner

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACS, American Cancer Society

ACSM, American College for Sports Medicine

ADS, American Diabetes Association

BMI, body mass index

ER, estrogen receptor

HbA1C, hemoglobin A1C

HEAL, Health, Eating, Activity and Lifestyle

MET, metabolic equivalent

NHS, Nurses' Health Study

PA, physical activity

PAR, physical activity recall

PR, progesterone receptor

SSDI, Social Security Death Index

WHI, Women's Health Initiative

WHEL, Women's Healthy Eating & Living

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to profoundly thank Dr. John Pierce for his guidance, wisdom and unwavering support as the chair of my dissertation committee. Despite his relentless work schedule, he always took the time to meet with me and guide me in the right direction and provide invaluable feedback on countless tables and manuscript drafts. To say that I had the opportunity to train under the best would be an understatement.

I would also like to thank Dr. Ruth Patterson who arrived to UCSD right at the time I was initiating my dissertation research—very fortuitous timing because her strategic guidance, manuscript writing advice and editing prowess proved vital. Likewise, the statistical expertise and genius of Dr. Loki Natarajan served as the most instructive biostatistics training I've ever received and elevated the analytical caliber of the dissertation papers. I'd like to thank Dr. Sue Lindsay and Dr. Carol Macera for their constant support, and I'd like to thank Dr. Tony Reid—for it was his advice, encouragement and years of mentorship that helped me find and cross the doctoral finish line.

I would like to thank everyone involved with the making the WHEL Study possible, including all of the women who served as participants in the WHEL Study. I'd like to especially thank Shirley Flatt for her invaluable help in the dissertating process—from teaching me the nuances in the WHEL dataset to the tricks of writing SAS code, I'm sure I'm not the only student to realize that Shirley is the WHEL wizard behind the curtain. I'd also like to offer a special thanks to the UCSD Cancer Prevention and Control team, namely Susan Wancewicz, Hollie Ward, Chris Hayes and Aimee Humphrey, for their expert assistance.

Chapter 2, in full, is a reprint of the material as it appears in the Journal of Clinical Oncology 2010. Kirsten Erickson, Ruth E. Patterson, Shirley W. Flatt, Loki Natarajan, Barbara A. Parker, Dennis D. Heath, Gail A. Laughlin, Nazmus Saquib, Cheryl L. Rock, John P. Pierce. The dissertation author was the primary investigator and author of this material.

Chapter 3 is currently being prepared for the submission for the publication of the material. Kirsten Erickson, Ruth E. Patterson, Loki Natarajan, John P. Pierce. The dissertation author was the primary investigator and author of this material.

Chapter 4 is currently being prepared for the submission for the publication of the material. Kirsten Erickson, Ruth E. Patterson, Loki Natarajan, John P. Pierce. The dissertation author was the primary investigator and author of this material.

VITA

2001	Bachelor of Arts, University of California, San Diego
2004	Master of Public Health, San Diego State University
2004-2006	Clinical Research Coordinator, Moores UCSD Cancer Center
2006-Present	Assistant Director, Clinical Trials Office, Moores UCSD Cancer Center
2011	Doctor of Philosophy, Public Health (Epidemiology), University of California, San Diego/San Diego State University

PUBLICATIONS

Loureiro, K.D., Kao, K., Jones, K.L., Alvarado, S. ,Chavez,C., Dick, L.,Felix ,R., Johnson, D. Chambers, C.D. Birth Outcomes in Children of Women Exposed to Topical Tretinoin During Early Pregnancy. 2005. American Journal of Medical Genetics Part A, 2: 117-121

Trivedi, M., Budihardjo, I., Loureiro, K.D., Reid, T.R., Ma, J.D. Epothilones: a novel class of microtubule-stabilizing drugs for the treatment of cancer. Future Oncology, August 2008, Vol. 4, No. 4, Pages 483-500 (doi: 10.2217/14796694.4.4.483)

Erickson K, Kritz-Silverstein D, Wingard DL, et al: Birth weight and cognitive performance in older women: the Rancho Bernardo study. Arch Womens Ment Health 13:141-6

Patterson RE, Flatt SW, Saquib N, et al: Medical comorbidities predict mortality in women with a history of early stage breast cancer. 2010. Breast Cancer Res Treat

Erickson K, Patterson RE, Flatt SW, et al: Clinically defined type 2 diabetes mellitus and prognosis in early-stage breast cancer. J Clin Oncol 29:54-60

ABSTRACT OF THE DISSERTATION

DIABETES AND BREAST CANCER:

THE WOMEN'S HEALTHY EATING & LIVING STUDY

by

Kirsten Diann Erickson

Doctor in Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2011
San Diego State University, 2011

Professor John P. Pierce, Chair

Diabetes and breast cancer are common diseases with a massive public health impact. With continual advancements in breast cancer detection and treatment diffusing into clinical practice, the population of breast cancer survivors is growing with a current estimate of 2.5 million women. Meanwhile the prevalence of type 2 diabetes continues to increase at alarming rates, largely attributed to the growing obesity epidemic. The overarching goal of this dissertation was to address current gaps in the scientific literature using data from the Women's Healthy Eating and Living (WHEL) Study- a randomized controlled trial designed to test whether a dietary pattern high in vegetables, fruit, and

fiber and low in fat would reduce the risk of recurrence and all-cause mortality among women previously treated for early-stage breast cancer. The specific dissertation objectives were to: 1) assess the effects of prevalent diabetes on breast cancer disease-free survival and overall survival, 2) assess the effects of pre-cancer body mass index (BMI) and post-diagnosis weight change on the risk of incident diabetes and 3) assess the effects of physical inactivity, weight gain, and obesity on long-term worsening of glycemic control.

Dissertation results showed that diabetes was independently associated with a statistically significantly higher risk of all-cause mortality in breast cancer survivors. A significant contribution was made by providing evidence suggesting that the severity or duration of diabetes may affect the risk of breast cancer recurrence and mortality. This dissertation also provides new evidence that women who experience major weight loss with subsequent regain after breast cancer are at twofold greater risk of becoming diabetic than women who maintain their pre-cancer weight. With the vast majority of breast cancer patients surviving more than 5 years beyond diagnosis, oncologists are challenged to expand their focus from acute care to managing the long-term health consequences of breast cancer. This dissertation provides compelling evidence that lifestyle changes may improve the length and quality of life of breast cancer survivors, and thus represents a significant contribution towards an issue of global public health concern.

CHAPTER 1

Background and Significance

BACKGROUND AND SIGNIFICANCE

Diabetes and breast cancer are common diseases with a massive public health impact and are diagnosed within the same individual more frequently than would be expected by chance, even after adjusting for age. For more than half a century, clinicians have reported the occurrence of patients with concurrent diabetes and cancer. In 1959, Joslin et al.[1] stated, "Studies of the association of diabetes and cancer have been conducted over a period of years, but evidence of a positive association remains inconclusive." Since then, many more studies have been conducted and evidence is mounting that diabetes and breast cancer are positively associated- however, added information has also incited more questions concerning the complexities of that association.

Breast cancer is now the most common malignant neoplasm in females, affecting 1 of every 8 American women.[2] Type 2 diabetes, a metabolic disorder characterized by hyperglycemia and insulin resistance, affects about 7% of U.S. women overall and 12-15% of U.S. women older than 60 years.[3] However, it's been estimated that up to16-20% of women who have been diagnosed with breast cancer also have diabetes.[4-6]

With continual advancements in breast cancer detection and treatment diffusing into clinical practice, the population of breast cancer survivors is growing with a current estimate of 2.5 million women.[7] Meanwhile, the prevalence of type 2 diabetes continues to increase at alarming rates, largely attributed to the growing obesity epidemic. Although there is mounting evidence that shows diabetes is associated with reduced survival, its associations with breast cancer recurrence and breast cancer-specific

mortality are less clear.[8] Leading theories for the biological plausibility of a prognostic association implicate metabolic derangements such as hyperglycemia, hyperinsulinemia and insulin resistance.[9-11] However, it remains uncertain whether the association between diabetes and breast cancer is direct (e.g., due to hyperglycemia), whether diabetes is a marker for underlying biologic factors that alter cancer risk (e.g. insulin resistance or hyperinsulinemia), or whether the association is indirect due to common risk factors such as obesity. Also, whether breast cancer prognosis is influenced by the duration of diabetes is a critical and complex issue.

Unfortunately, many women report gaining weight as a result of their breast cancer diagnosis and treatment and only a small percentage return to their pre-cancer weight.[12-14] Moreover, the amount of weight gained after diagnosis of breast cancer is larger than would be expected in the general population and occurs at an accelerated rate compared to age-matched healthy women.[14] Studies also consistently show marked drops in physical activity levels after a breast cancer diagnosis.[15] Although there are well-established associations between type 2 diabetes and being overweight or obese in the general population, far less is known about the impact that post-cancer physical inactivity, weight and weight gain may have on the diabetes risk in breast cancer survivors. This represents a critical issue because in addition to disproportionately affecting breast cancer patients, these factors may significantly increase their risk for developing diabetes, which in turn, may increase their risk for poor cancer outcomes as well as cardiovascular disease.

In June 2010, the American Diabetes Association (ADA) and the American Cancer Society (ACS) issued a consensus report calling attention to the association between diabetes and cancer, noting "the entanglement of lifestyle risk factors, common biological links and potential mediating solutions between the two diseases". The ADA/ACS report, or a summary thereof, was published in four of the world's leading scientific journals with the stated aim of addressing "the current gaps in evidence and potential research and epidemiologic strategies for developing more definitive evidence in the future." [16-19] The overarching goal of this dissertation is to address some of these gaps using data from the Women's Healthy Eating and Living (WHEL) Study- a randomized controlled trial designed to test whether a dietary pattern high in vegetables, fruit, and fiber and low in fat would reduce the risk of recurrence and all-cause mortality among women previously treated for early stage breast cancer.

Although the dietary intervention did not alter the risk of developing breast cancer events or improve overall survival over the mean 7.3 years of follow-up, the WHEL Study has provided an invaluable opportunity to explore the diabetes and breast cancer association.

Dissertation Theme

This dissertation targets two important facets in the relationship between diabetes and breast cancer: (1) the association between prevalent diabetes and breast cancer prognosis and (2) the association between incident diabetes and modifiable risk factors commonly observed among breast cancer patients, namely obesity, weight gain and physical inactivity. The WHEL Study is uniquely positioned to address the dissertation

aims for several reasons. First, 3,088 women who were within four years of their breast cancer diagnosis were enrolled and loss to follow-up was minimal (vital status was confirmed on 96% of the cohort). The majority of studies on diabetes and breast cancer prognosis do not have data on breast cancer recurrence. This represents a current gap in the evidence which the WHEL Study and this dissertation can address.

Secondly, detailed information on major potential confounders in the diabetes and breast cancer association was collected, including: cancer characteristics which were extracted from medical records and oncologist-verified; lifestyle risk factors such as physical activity which were assessed at 5 time points using standardized questionnaires; and anthropometric measures such as height and weight which were clinically measured at the same 5 time points throughout the study.

Thirdly, the WHEL Study had a biorepository which housed archived blood samples collected at the clinic visits, thus enabling this dissertation to incorporate the diabetes biomarker, hemoglobin A1C (HbA1C). The HbA1C assay provides a precise measure of chronic glycemic levels and is the test of choice for the diagnosis and management of diabetes. Most studies investigating the diabetes and breast cancer association have relied upon self-reported diabetes or registry data to identify diabetes cases. Given that symptomless screening for diabetes is rare and 30% of those with the disease may be undiagnosed, the HbA1C assay represents a pivotal feature of this dissertation. For instance, the first study addresses whether the relationship between diabetes and breast cancer prognosis is strengthened, reduced, or maintained when women with undiagnosed diabetes are included. The second study uses HbA1C levels to

measure incident diabetes in relation to post-cancer weight gain, and the third study measures the worsening of glycemic control using HbA1C levels in relation to physical inactivity and weight gain. In addition to identifying undiagnosed diabetes, the HbA1C assay enables for a diabetes risk continuum to be explored.

Dissertation Aims

- Study #1: Utilize the HbA1C assay in addition to self-report to identify prevalent diabetes. Assess the effects of prevalent diabetes on breast cancer disease-free survival and overall survival.

- Study #2: Utilize the HbA1C assay in addition to self-report to exclude prevalent diabetes and to measure incident diabetes. Assess the effects of pre-cancer body mass index (BMI) and post-diagnosis weight change on the risk of incident diabetes in breast cancer survivors.

- Study #3: Utilize the HbA1C assay to measure 6-year change in glycemic control. Assess the effects of physical inactivity, weight gain, and obesity on worsening of long-term glycemic control in breast cancer survivors.

REFERENCES

1. Joslin EP, Lombard HL, Burrows RE, et al: Diabetes and cancer. N Engl J Med 260:486-8, 1959

2. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71-96, 2008

3. Cowie CC, Rust KF, Byrd-Holt DD, et al: Prevalence of diabetes and high risk for diabetes using hemoglobin A1c criteria in the U.S. population in 1988-2006. Diabetes Care

4. Srokowski TP, Fang S, Hortobagyi GN, et al: Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 27:2170-6, 2009

5. Tammemagi CM, Nerenz D, Neslund-Dudas C, et al: Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 294:1765-72, 2005

6. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285:885-92, 2001

7. American Cancer Society: Breast Cancer Facts and Figures 2007-2008. Atlanta, GA, American Cancer Society, 2008.

8. Peairs KS, Barone BB, Snyder CF, et al: Diabetes Mellitus and Breast Cancer Outcomes: A Systematic Review and Meta-Analysis. J Clin Oncol, 2011

9. Goodwin PJ: Insulin in the adjuvant breast cancer setting: a novel therapeutic target for lifestyle and pharmacologic interventions? J Clin Oncol 26:833-4, 2008

10. Goodwin PJ, Ennis M, Bahl M, et al: High insulin levels in newly diagnosed breast cancer patients reflect underlying insulin resistance and are associated with components of the insulin resistance syndrome. Breast Cancer Res Treat 114:517-25, 2009

11. Goodwin PJ, Ennis M, Pritchard KI, et al: Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 20:42-51, 2002

12. Kroenke CH, Chen WY, Rosner B, et al: Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 23:1370-8, 2005

13. Saquib N, Flatt SW, Natarajan L, et al: Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the women's healthy eating and living (WHEL) study. Breast Cancer Res Treat 105:177-86, 2007

14. Vance V, Mourtzakis M, McCargar L, et al: Weight gain in breast cancer survivors: prevalence, pattern and health consequences. Obes Rev, 2010

15. Irwin ML, Crumley D, McTiernan A, et al: Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer 97:1746-57, 2003

16. Giovannucci E, Harlan DM, Archer MC, et al: Diabetes and cancer: a consensus report. CA Cancer J Clin 60:207-21, 2010

17. Giovannucci E, Harlan DM, Archer MC, et al: Diabetes and cancer: a consensus report. Diabetes Care 33:1674-85, 2010

18. Mitka M: Report clarifies scientists' understanding of association between diabetes and cancer. JAMA 304:731-2, 2010

19. Renehan A, Smith U, Kirkman MS: Linking diabetes and cancer: a consensus on complexity. Lancet 375:2201-2, 2010

CHAPTER 2

Clinically Defined Type 2 Diabetes Mellitus and Prognosis in Early Stage Breast Cancer

ABSTRACT

Purpose: Self-reported diabetes has been associated with poor breast cancer outcomes. Research is needed to investigate biologically determined glycemic control with breast cancer prognosis.

Methods: Archived baseline blood samples from the WHEL Study were used to measure hemoglobin HbA1C (HBA1C) among 3003 early stage breast cancer survivors (age of diagnosis 28-70 years) followed for a median of 7.3 years for additional breast cancer events and 10.3 years for all-cause mortality. HbA1C levels provide an accurate, precise measure of chronic glycemic levels. Cox regression analysis was performed to assess whether baseline HbA1C levels predicted disease-free and overall survival.

Results: Only 5.8% of women had chronic hyperglycemia (defined as HbA1C levels > 6.5%). Those with HbA1C > 6.5% were older and more likely to be less educated, non-white ethnicity, obese and have more advanced breast cancer at diagnosis. HbA1C was significantly associated with overall survival (ptrend < 0.0001). After adjusting for confounders, risk of all-cause mortality was twice as high in women with HbA1C >7.0% compared to women with A1C <6.5% (hazard ratio [HR], 2.35; 95% CI, 1.56 to 3.54). For disease-free survival, there was a nonsignificant 30% increase in risk for HbA1C levels >7.0% (HR,1.26; 95% CI, 0.78 to 2.02). During study follow-up, previously diagnosed rather than undiagnosed diabetes appeared to account for the increased risk.

Conclusions: Chronic hyperglycemia is statistically significantly associated with reduced overall survival in early stage breast cancer survivors. Further study of diabetes and its relationship to breast cancer outcomes is warranted.

INTRODUCTION

Type 2 diabetes mellitus (diabetes) is increasing rapidly in the population at large and studies suggest that 16-20% of women who have had breast cancer have diagnosed diabetes as a comorbidity.[1-3] Symptomless screening for diabetes is rare and 30% of those with the disease may be undiagnosed.[4] Some research estimates that diabetes can remain undiagnosed for 5-10 years and therefore disease symptoms or complications may accompany the diagnosis. 5

A number of studies have indicated that diabetes is associated with higher mortality in breast cancer patients,[1-3, 6-11] but it is unclear whether this is driven by a worse breast cancer prognosis or from competing risks such as cardiovascular disease. Recently, Patterson and colleagues[12] reported that self-reported diabetes was associated with more than a twofold increase in both breast cancer events and all-cause mortality. Whether the relationship between diabetes and breast cancer prognosis would be strengthened, reduced, or maintained when women with undiagnosed diabetes are included is unclear. It is also uncertain whether the additional mortality risk is specific to breast cancer or reflects the general higher mortality risk of diabetes. [13]

The A1C assay is the test of choice for monitoring diabetes management because it provides a precise measure of chronic glycemic levels. Research indicates HbA1C may also be used to diagnose diabetes, as a cut-point value of 7.0% is associated with increased risk of microvascular complications.[15] More recently, an International Expert Committee recommended the use of a cut-point of 6.5% to definitively diagnose diabetes.[14] However, the Endocrinology Society has published their reservations about this recommendation.[16]

In this secondary analysis, we explore the association of HbA1C levels and cut-points with breast cancer progression. We measured HbA1C levels in archived blood samples of participants in The WHEL Study, a multisite randomized trial that tested the effect of an intensive dietary intervention on new breast cancer events and survival. For study outcomes, we consider both breast cancer disease-free survival and overall survival.

PATIENTS AND METHODS

Participants

Between 1995 and 2000, the WHEL Study enrolled 3,088 women within 4 years of diagnosis of early-stage breast cancer (American Joint Committee on Cancer, 4th edition: stage I [>1 cm], II, or IIIA). Exclusions included: (1) diagnosed with a comorbidity requiring a specific diet or using a medication that contraindicated a high-fiber diet and (2) insulin dependence. After an average of 7.3 years of follow-up, breast cancer and vital status were confirmed on 96% of the original cohort. Details of the

study have been reported previously.[17-18] Internal review boards at each site approved the study and all participants were provided written informed consent before enrolling.

Baseline Measures

Medical records pertaining to the initial cancer diagnosis were collected and information was extracted and oncologist-verified on cancer characteristics and treatment including: tumor stage and grade, tumor hormone receptor status, type of surgery, radiation, chemotherapy, and anti-estrogen use. Weight and height were measured using standard procedures and body mass index [BMI, weight (kg)/height (m2)] was calculated. Fasting blood was collected into and separated using standard procedures and stored at -80˚C. The study assessed demographics, self-reported menopausal status, and behavioral and lifestyle measures with standardized questionnaires at baseline. For this paper, ethnicity was dichotomized into white/non-Hispanic and other (Hispanic/Latina, African-American, Asian, Pacific Islander, mixed/other).

Physical health, associated with prognosis in the WHEL Study[19], was assessed using the well-validated SF-36. [20] Following previous research, the physical health summary score was dichotomized as either "low" (bottom two quintiles) or "moderate/high".[19] The frequency, duration, and intensity of physical activity were assessed using the nine items from the Women's Health Initiative (WHI) Personal Habits Questionnaire, which were validated in a subsample of WHEL participants[21] and converted into metabolic equivalent tasks (METs) as previously described.[22] A self-administered health status questionnaire queried a series of physician-identified comorbid

conditions (including prediabetes and diabetes-requiring or not requiring insulin) and medications including insulin and oral hypoglycemics ("blood sugar lowering pills").

HbA1C

HbA1C was measured in September 2009 using ion exchange high-performance liquid chromatography [D-10 System, Bio-Rad® ; Laboratories, Hercules, California] on archived samples of washed red blood cells collected at the baseline clinic visit. Performance of the D-10 HbA1C methodology was assessed by inclusion of known quality control samples as high (10.0%) and low (5.8%) HbA1C levels. The coefficient of variation was 1.5% and 1.6%, respectively, for within-day runs and 1.9% and 1.9% for between-day runs. Laboratory personnel performing these assays were blinded to study outcomes.

Assessment of Study Outcomes

The primary outcome was overall survival defined as the time from study entry (on average 2 years since diagnosis) to death from any cause. Throughout the study, information about hospitalizations or new breast cancer events was obtained by semiannual telephone interviews. Any reported event/death led to a medical record/death certificate review by two independent study physicians. Breast cancer event-free survival (disease-free survival) was defined as the time from date of enrollment to the development of a new breast cancer event (i.e. locoregional or distant breast cancer or new primary). Follow-up time was censored at the last documented staff contact date or

at study completion (June 2006). Mortality data were updated through September 2009 using the Social Security Death Index (SSDI). To measure accuracy of SSDI matching, sensitivity analyses were performed on censoring cut-points and supported the chosen approach. Median follow-up time was 7.3 years for breast cancer event-free survival and 10.3 years for overall survival.

Statistical Analysis

Initial analyses included a simple plot of the proportion of study events by HbA1C. Kaplan-Meier curves of overall survival and disease-free survival were calculated for the three HbA1C categories (< 6.5%, 6.5-6.9%, >7.0%) with differences assessed statistically by the log rank test. Univariate Cox proportional hazards models examined effects on disease-free and overall survival for each of the following: HbA1C, demographic variables (age, ethnicity, education level, marital status), tumor characteristics (stage, grade, receptor status), breast cancer treatment history (years since diagnosis, ever use anti-estrogen, radiation, chemotherapy, lumpectomy or mastectomy), and other health measures (menopausal status (pre-, peri-, post-menopausal), BMI, physical health and physical activity level). We also examined the interaction terms between HbA1C and each of the covariates, none of which were statistically significant ($p>0.05$). A backward elimination model omitted covariates that either had a p value >0.05 or changed the HbA1C hazard ratio by less than 10 percent. The variables of ethnicity, age, education, physical activity and physical health were retained based on a priori assumption. The assumption of proportional hazards was checked for each model using plots of time-dependent coefficients estimated from Schoenfeld residuals. To

explore how self-reported diabetes factored into the association between HbA1C and breast cancer events, the frequency of breast cancer events in each HbA1C category was counted and stratified by self-report diabetes status and use of "blood sugar lowering medication". All tests were two-tailed and analyses were conducted in SAS version 9.2.[23]

RESULTS

Variables Associated with HbA1C Level

HbA1C levels were measured on 97% (3003/3008) of the study cohort and ranged from 4.2% to 13.9% (median=5.6%). Most women (93.8%) had an HbA1C level <6.5%, 3.1% had a level 6.5-6.9% and 3% had a level >7% (Table 2.1). Participants with HbA1C levels > 6.5% were on average 3.5 years older (standard error 0.65, $p < 0.0001$), less likely to be college educated ($p < 0.05$) and more likely to be sedentary ($p < 0.01$) than participants with HbA1C < 6.5%. White/non-Hispanic participants were less likely than other participants to have A1C levels > 6.5% ($p < 0.0001$). Other variables strongly associated with greater A1C category were higher BMI, poor physical health and higher stage breast cancer (all $p < 0.0001$).

Additional Breast Cancer Events and All-cause Mortality

As of June 2006, 503 participants had a breast cancer event over the median 7.3 years of follow-up (Table 2.2). The majority of events were distant recurrences (n=344, 68%), followed by locoregional recurrences (n=81, 16%) and new breast primaries

(n=78, 16%). As of September 2009, 414 deaths were recorded over a median follow-up of 10.3 years. The majority of deaths were due to breast cancer (n=331, 80%), followed by other cancer (n=41, 10%), other causes (n=22, 5%) and heart disease (n=11, 3%).

Unadjusted Analyses

Figure 1 shows the proportion of all-cause mortality for seven categories of HbA1C and displays a marked increase in events for those with HbA1C >7.0% with 35% mortality for women with HbA1C over 8.0% dying within the follow-up period. The unadjusted hazard ratio for continuous HbA1C (per 1-unit increase) and overall survival was 1.29 (95% CI, 1.16 to 1.43). The Kaplan-Meier curve for overall survival displays a statistically significant association among the three HbA1C categories (Figure 2.1). Compared to women with HbA1C <6.5%, those with HbA1C 6.5 to 6.9% were 60% (HR=1.6, 95% CI, 1.00 to 2.57) and those with HbA1C > 7.0% were three times (HR=3.01, 95% CI, 2.05 to 4.43) more likely to die during follow-up.

The unadjusted hazard ratio for continuous HbA1C (per 1-unit increase) and disease-free survival was 1.00 (95% CI, 0.86 to 1.14). The Kaplan-Meier curve for breast cancer disease-free survival (Figure 2.1) indicates that participants with an HbA1C >7.0% had a non-significantly higher event rate (40%) compared to those with HbA1C <6.5% (HR=1.40, 95% CI, 0.88 to 2.21). The increase in risk across HbA1C categories reached borderline statistical significance (p=0.11).

Adjusted Analyses

After constructing a multivariate Cox model using backward elimination, the key covariates of stage and grade were retained in overall survival model. The additional covariates of age, ethnicity, education, physical activity, physical health, and BMI were included based on a priori assumptions. After adjustment for stage, grade, age, ethnicity, education, physical activity, and physical health, the hazard ratio for continuous HbA1C (per 1-unit increase) and overall survival was 1.20 (95% CI, 1.07 to 1.34). In the fully adjusted model the risk of death for those with HbA1C 6.5 to 6.9% was no longer statistically significant, however, HbA1C >7% was associated with a 2.4-fold increase in risk (HR=2.35, 95% CI, 1.56 to 3.54) (Table 2.3). In models adjusting for the same covariates, neither continuous nor categorical HbA1C was significantly associated with risk of breast cancer recurrence (Table 2.3).

HbA1C vs Self-Reported Diabetes in Relation to Breast Cancer Events

To investigate how undiagnosed diabetes factored into the association between HbA1C and breast cancer events, the distribution of breast cancer events by HbA1C category was stratified by self-report diabetes status. Of the 3% of participants with A1C >7.0%, less than half (37/91) reported that they had diabetes on the baseline self-report questionnaire, and only 10% (9/94)of the 3% with HbA1C 6.5 to 6.9% reported diabetes (Table 2.4). The majority of women (76.8%) who reported diabetes also indicated the use of blood sugar lowering medication, and notably, these women had a twofold higher rate of additional breast cancer events than women who did not report diabetes (32.6% vs 15.6%, $p<0.01$). Of the 13 women who reported diabetes and no use of blood sugar lowering medication, 2 experienced breast cancer events and both had an HbA1C >7.0%,

this computes to an incidence of 15.4%, nearly identical to the incidence of 15.6% found in women who did not report diabetes.

DISCUSSION

Compared to women with HbA1C <6.5%, those with HbA1C >7.0% had a statistically significant 2.4 times greater risk of all-cause mortality during the median 10.3 years of follow up. This association of higher HbA1C with worse overall survival was independent of age, race, BMI, cancer stage and grade, physical health and physical activity, and is similar in magnitude to previous WHEL Study findings using self-reported diabetes as the measure of exposure.[12] However, those with HbA1C >7.0% had a 26% higher rate of additional breast cancer events compared to those with HbA1C < 6.5% rather than the significant doubling of risk identified with self-reported diabetes. 12 While a 26% increase in risk is clinically meaningful, this study did not have the power to detect an adjusted hazard ratio of 1.26 as statistically significant.

Despite the growing body of evidence that diabetes predicts a poor prognosis following a diagnosis of breast cancer, two important questions remain to be answered: is there a threshold of glycemic status at which the risk for poor prognosis significantly increases; and is the increased mortality risk among breast cancer survivors with diabetes driven by an increase in cancer recurrence or due to competing diabetes-related comorbidities such as cardiovascular disease? Findings in the present study suggest that HbA1C may be associated with breast cancer prognosis in a nonlinear fashion, that is, a threshold effect may exist in the diabetic range of HbA1C levels >7.0%, and in individuals considered at very high risk for diabetes (those who are obese and have a high

HbA1C in addition to at least one other risk factor for diabetes). Eighty percent of the deaths in this study cohort were due to breast cancer, and because of the much smaller number of non-breast cancer deaths, power was lacking to formally evaluate if non-cancer related deaths accounted for the statistically significant difference in overall survival time among the three HbA1C levels.

In this large study of breast cancer survivors, measured HbA1C more than doubled the number of women with diabetes compared to self-report identification, however inclusion of these undiagnosed diabetes cases attenuated the previously identified diabetes association with additional breast cancer events.[12] Diagnosis of type 2 diabetes is most likely to occur in women experiencing symptoms. Therefore it is likely that women with self-reported diabetes had longer disease duration and a history of worse glycemic control than those identified by HbA1C assays. Thus, our results could reflect the effect of severity and duration of diabetes on the risk of additional breast cancer events. Supporting this hypothesis, women who reported taking blood sugar lowering medications for their diabetes (presumably reflective of more advanced disease) carried the highest risk of additional breast cancer events and mortality.

Diabetes may directly influence breast cancer progression and outcomes via several mechanisms including pathways mediated by high levels of insulin and insulin-like growth factors (IGF), sex hormones and inflammatory markers. Both inflammation and obesity have biological effects that could promote cancer, and the hyperinsulinemia that is associated with these conditions may itself augment cell proliferation and survival.[24-26] Clinical studies support this thesis. For example, Goodwin et al reported that

non-diabetic women whose fasting insulin levels were in the highest compared to lowest quartile were at a three-fold increased risk of death following breast cancer independent of BMI. [27] Other studies using markers of insulin resistance, such as elevated waist-to-hip ratio[28] and presence of metabolic syndrome,[29] also found associations with a worse prognosis after breast cancer.

A diagnosis of diabetes may have indirect adverse effects on breast cancer outcomes by influencing medical decision-making regarding breast cancer screening and management.[30] Studies have documented reduced breast cancer screening rates among diabetic women[31] leading to later stage at diagnosis. Additionally, postmenopausal breast cancer patients with diabetes frequently have one or more preexisting comorbid conditions at diagnosis (eg, heart disease, chronic obstructive pulmonary disease, hypertension, and arthritis) [32], often leading clinicians to follow less aggressive cancer treatments[33-37] associated with lower survival rates.[2] Although we identified women with diabetes as more likely to have a later stage cancer at diagnosis and thus controlled for it in multivariate models, we found no statistically significant differences in chemotherapy treatment or anti-estrogen use.

Two other studies in addition to the earlier WHEL report[12] found that the presence of comorbidities negatively affected breast cancer survival,[1,38] with diagnosed diabetes exerting a negative effect on survival independent of disease stage at cancer diagnosis.[1,38] Examining diabetes specifically, Lipscombe et al. conducted a population-based study evaluating the effect of diagnosed diabetes on breast cancer survival after adjusting for comorbidity[9]. That study found that diabetes was associated with a nearly

40% increase in 5-year all-cause mortality, similar to that seen in diabetic women without breast cancer, suggesting that breast cancer survival is reduced in women with diabetes due to diabetes-related causes rather than direct effects of diabetes on cancer outcomes. In contrast, a study by Fleming et al. did not find diabetes to be a significant risk factor for increased mortality in breast cancer patients. However, that study only examined 1-year mortality[39].

Diabetes is part of a cluster of problems and the present study was unable to differentiate whether the effects observed were specific to HbA1C levels. Insulin dependence and diet restrictions were exclusion criteria for The WHEL Study so our findings cannot be generalized to these sub-populations. Another sub-group with limited representation was women taking oral hypoglycemic medications; at baseline, the study had 43 such participants. Given the long natural history of recurrence in estrogen receptor positive breast cancer, it would be important to examine the role of HbA1C predicting late breast cancer events. At the completion of the main study in 2006, many participants did not re-consent for active follow-up. Thus, we limited reporting of additional breast cancer events to the average 7.3 years of the main study. However, we continued with passive follow-up for survival using the Social Security Death Index, thus strengthening the study with an additional 3 years of follow-up for this outcome.

Additional strengths of this study include the reliable, accurate measurement of long term glycemia with HbA1C assays, high rate of participant response, minimal missing blood samples, detailed, verified patient data on tumor and treatment

characteristics extracted directly from medical records, and cancer events confirmed by two independent oncologists.

In summary, we found that chronic hyperglycemia, as indicated by elevated HbA1C levels, is independently associated with a statistically significant higher risk of all-cause mortality in breast cancer survivors. We also show evidence that a large percentage of breast cancer survivors who have diabetes do not know or do not report having diabetes. Of the women with HbA1C levels >7.0%, 60% did not report having diabetes and even more striking, 90% of the women with A1C levels between 6.5% and 7.0% did not report having diabetes or prediabetes.

Diabetes, hyperglycemia, hyperinsulinemia and associated metabolic disorders can be controlled and may present an opportunity for improving prognosis in early stage breast cancer survivors. These data suggest that clinicians should consider measuring HbA1C in breast cancer patients with symptoms of hyperglycemia or those at high risk for diabetes. These findings are hypothesis generating and this association requires replication before HbA1C is routinely introduced into clinical practice. Nonetheless, randomized trials of interventions that target glycemic control in relation to both disease-free and overall survival endpoints may be warranted in this population.

Chapter 2, in full, is a reprint of the material as it appears in the Journal of Clinical Oncology 2010. Kirsten Erickson, Ruth E. Patterson, Shirley W. Flatt, Loki Natarajan, Barbara A. Parker, Dennis D. Heath, Gail A. Laughlin, Nazmus Saquib, Cheryl L. Rock, John P. Pierce. The dissertation author was the primary investigator and author of this material.

REFERENCES

1. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285:885-92, 2001

2. Srokowski TP, Fang S, Hortobagyi GN, et al: Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 27:2170-6, 2009

3. Tammemagi CM, Nerenz D, Neslund-Dudas C, et al: Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 294:1765-72, 2005

4. Cowie CC, Rust KF, Ford ES, et al: Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. Diabetes Care 32:287-94, 2009

5. Harris MI, Klein R, Welborn TA, et al: Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care 15:815-9, 1992

6. Barone BB, Yeh HC, Snyder CF, et al: Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. Jama 300:2754-64, 2008

7. Lipscombe LL, Goodwin PJ, Zinman B, et al: Increased prevalence of prior breast cancer in women with newly diagnosed diabetes. Breast Cancer Res Treat 98:303-9, 2006

8. Jee SH, Ohrr H, Sull JW, et al: Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293:194-202, 2005

9. Lipscombe LL, Goodwin PJ, Zinman B, et al: The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat 109:389-95, 2008

10. Zhou XH, Qiao Q, Zethelius B, et al: Diabetes, prediabetes and cancer mortality. Diabetologia

11. Giordano SH, Jiralerspong S, Lopez A, et al: Diabetes, obesity and survival in a large cohort of early-stage breast cancer patients [abstract]. J Clin Oncol. 2010; 28 (15 suppl). Abstract 1503.

12. Patterson RE, Flatt SW, Saquib N, et al: Medical comorbidities predict mortality in women with a history of early stage breast cancer. Breast Cancer Res Treat

13. Giovannucci E, Harlan DM, Archer MC, et al: Diabetes and Cancer: A Consensus Report. CA Cancer J Clin. Advance online publication. doi: 10.3322/caac.20078, 2010

14. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32:1327-34, 2009

15. Buell C, Kermah D, Davidson MB: Utility of A1C for diabetes screening in the 1999 2004 NHANES population. Diabetes Care 30:2233-5, 2007

16. The Endocrine Society Statement on the Use of A1C for Diabetes Diagnosis and Risk Estimation. Retrieved from http://www.endo- society.org/advocacy/upload/TES-Statement-on-A1C-Use.pdf, 2010

17. Pierce JP, Natarajan L, Caan BJ, et al: Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 298:289-98, 2007

18. Pierce JP, Faerber S, Wright FA, et al: A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials 23:728-56, 2002

19. Saquib N, Pierce JP, Saquib J: Poor physical health predicts time to additional breast cancer events and mortality in breast cancer survivors. Psychooncology, in press

20. Ware JE, Jr., Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473-83, 1992

21. Johnson-Kozlow M, Rock CL, Gilpin EA, et al: Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav 31:193-202, 2007

22. Hong S, Bardwell WA, Natarajan L, et al: Correlates of physical activity level in breast cancer survivors participating in the Women's Healthy Eating and Living (WHEL) Study. Breast Cancer Res Treat 101:225-32, 2007

23. SAS Institute Inc.: Version 9.2. Cary, NC, USA. 2008

24. Belfiore A, Frittitta L, Costantino A, et al: Insulin receptors in breast cancer. Ann N Y Acad Sci 784:173-88, 1996

25. Mathieu MC, Clark GM, Allred DC, et al: Insulin receptor expression and clinical outcome in node-negative breast cancer. Proc Assoc Am Physicians 109:565-71, 1997

26. Papa V, Belfiore A: Insulin receptors in breast cancer: biological and clinical role. J Endocrinol Invest 19:324-33, 1996

27. Goodwin PJ, Ennis M, Pritchard KI, et al: Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. J Clin Oncol 20:42-51, 2002

28. Borugian MJ, Sheps SB, Kim-Sing C, et al: Waist-to-hip ratio and breast cancer mortality. Am J Epidemiol 158:963-8, 2003

29. Pasanisi P, Berrino F, De Petris M, et al: Metabolic syndrome as a prognostic factor for breast cancer recurrences. Int J Cancer 119:236-8, 2006

30. Tabaei BP, Herman WH, Jabarin AF, et al: Does diabetes care compete with the provision of women's preventive care services? Diabetes Care 28:2644-9, 2005

31. Beckman TJ, Cuddihy RM, Scheitel SM, et al: Screening mammogram utilization in women with diabetes. Diabetes Care 24:2049-53, 2001

32. Yancik R, Ries LG, Yates JW: Breast cancer in aging women. A population-based study of contrasts in stage, surgery, and survival. Cancer 63:976-81, 1989

33. Satariano WA: Comorbidity and functional status in older women with breast cancer: implications for screening, treatment, and prognosis. J Gerontol 47 Spec No:24-31, 1992

34. Newschaffer CJ, Penberthy L, Desch CE, et al: The effect of age and comorbidity in the treatment of elderly women with nonmetastatic breast cancer. Arch Intern Med 156:85-90, 1996

35. Bergman L, Dekker G, van Kerkhoff EH, et al: Influence of age and comorbidity on treatment choice and survival in elderly patients with breast cancer. Breast Cancer Res Treat 18:189-98, 1991

36. Satariano WA, Ragland DR: The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 120:104-10, 1994

37. West DW, Satariano WA, Ragland DR, et al: Comorbidity and breast cancer survival: a comparison between black and white women. Ann Epidemiol 6:413-9, 1996

38. Louwman WJ, Janssen-Heijnen ML, Houterman S, et al: Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 41:779-85, 2005

39. Fleming ST, Pursley HG, Newman B, et al: Comorbidity as a predictor of stage of illness for patients with breast cancer. Med Care 43:132-40, 2005

Table 2.1 Participant characteristics by baseline A1C in a cohort of US breast cancer survivors (n = 3003)

	A1C			p-value
	< 6.5%	**6.5- 6.9%**	**≥ 7.0%**	
	n=2818	n=94	n=91	
Demographics				
Age (years)	50.6 (8.79)	54.1 (8.64)*	53.7 (8.23)*	< .0001
Ethnicity/race				<.0001
White, Non-Hispanic	2436 (86.4%)	72 (76.6%)	61 (67.0%)	
Nonwhite	382 (13.6%)	22 (23.4%)	30 (33.0%)	
College educated	1545 (54.8%)	44 (46.8%)	40 (44.4%)	0.017
Married	1989 (71.1%)	57 (62.0%)	59 (65.6%)	0.095
Breast cancer characteristics				
Cancer stage at diagnosis				< 0.001
Stage I	1109 (39.4%)	33 (35.1%)	25 (27.8%)	
Stage II	1579 (56.0%)	51 (54.3%)	55 (61.1%)	
Stage IIIA	130 (4.6%)	10 (10.6%)	10 (11.1%)	
Grade				0.978
1	1127 (40.0%)	39 (41.5%)	39 (43.3%)	
2	1018 (36.1%)	31 (33.0%)	29 (32.2%)	
3	231 (8.2%)	9 (9.6%)	7 (7.8%)	
Tumor receptor status				0.336
ER+/PR+	1733 62.9%)	62 (66.7%)	56 (62.9%)	
ER+/PR-	338 (12.3%)	8 (8.6%)	10 (11.2%)	
ER-/PR+	119 (4.3%)	1 (1.1%)	7 (7.9%)	
ER-/PR-	565 (20.5%)	22 (23.7%)	16 (18.0%)	
Treatment				
Radiation	1729 (61.4%)	51 (54.3%)	68 (75.6%)	0.008
Chemotherapy	1963 (69.7%)	65 (69.2%)	63 (70.0%)	0.991
Lumpectomy	1354 (48.0%)	36 (38.3%)	51 (56.7%)	0.044
Mastectomy	1463 (51.9%)	58 (61.7%)	39 (43.3%)	0.044
Ever use anti-estrogen	1909 (63.7%)	71 (75.5%)	67 (74.4%)	0.128
Years since diagnosis	2.0 (1.04)	2.0 (1.04)	2.0 (0.97)	0.901
Other health measures				

Table 2.1 continued

	A1C			p-value
	< 6.5% n=2818	**6.5- 6.9%** n=94	**≥ 7.0%** n=91	
Body mass index (kg/m^2)	26.9 (5.70)	32.1 (7.51)*	34.2 (8.58) *†	<.0001
Obese (≥ 30 kg/m^2)	681 (24.2%)	52 (55.3%)	63 (70.0%)	<.0001
Poor physical health	1169 (41.5%)	51 (54.3%)	56 (62.2%)	<.0001
Sedentary (< 150 MET-min/wk)	545 (19.3%)	30 (31.9%)	26 (28.6%)	0.001
Menopausal status				0.026
Pre	328 (11.7%)	3 (3.2%)	5 (5.6%)	
Post	2230 (79.3%)	85 (90.4%)	77 (85.6%)	
Peri	256 (9.1%)	6 (6.4%)	8 (8.9%)	

*p < .05 for comparison with A1C < 6.5% category
† p < .05 for comparison with A1C 6.5-6.9% category

Table 2.2 Association of baseline A1C and outcomes in a cohort of US breast cancer survivors followed for a median of 7.3 years for breast cancer events and median of 10.3 years for all-cause mortality (n = 3003)

	A1C		
	< 6.5%	**6.5- 6.9%**	**≥ 7.0%**
	n = 2818	n = 94	n = 91
Breast cancer events (n=503)	**466 (16.5%)**	**18 (19.1%)**	**19 (20.9%)**
New Primary	73 (2.6%)	3 (3.2%)	2 (2.2%)
Loco-regional	75 (2.7%)	3 (3.2%)	3 (3.3%)
Distant	318 (11.3%)	12 (12.8%)	14 (15.6%)
All-cause mortality (n=414)	**368 (13.1%)**	**18 (19.1%)**	**28 (30.8%)****
Breast cancer	307 (10.9%)	11 (11.7%)	13 (14.4%)
Other cancer	34 (1.2%)	3 (3.2%)	4 (4.4%)
Heart disease	5 (0.2%)	2 (2.1%)†	4 (4.4%)*
Other	15 (0.5%)	2 (2.1%)	5 (5.5%)*
Unknown	7 (0.2%)	0 (0.0%)	2 (2.2%)

** Chi-square $p < 0.0001$ comparison with A1C < 6.5% category
* Fisher's exact $p < 0.001$ comparison with A1C < 6.5% category
† Fisher's exact $p < 0.05$ comparison with A1C < 6.5% category

Table 2.3 Multivariate hazard ratios of overall survival and disease-free survival according to baseline A1C in a cohort of US breast cancer survivors with a median 10.3 years of survival follow up and a median of 7.3 years follow-up for additional breast cancer events (n=3003)

A1C	**Death Events/ Cell Total**	**Multivariate Model Overall Survival**		**Breast Cancer Events/ Cell Total**	**Multivariate Model Disease-Free Survival**	
		HR (95% CI)	*p*		HR (95% CI)	*p*
< 6.5%	368/2818	1.00†	_____	466/2818	1.00†	_____
6.5- 6.9%	18/94	1.33 (0.82, 2.16)	0.25	18/94	1.11 (0.69, 1.80)	0.67
≥ 7.0%	28/91	2.35 (1.56, 3.54)	0.0001	19/91	1.26 (0.78, 2.02)	0.34

* Adjusted for stage, grade, age, ethnicity, education, physical activity, physical health
† Reference category

Table 2.4 Breast cancer events (n/Cell Total) and A1C stratified by self-reported type 2 diabetes mellitus (diabetes) in a cohort of US breast cancer survivors (n=3088)

	A1C				
Self-report	**< 6.5%** (n=2818)	**6.5-6.9%** (n=94)	**≥ 7.0%** (n=91)	**Missing A1C** (n=85)	**Total Events**
No diabetes	353/2287 (15.4%)	14/71 (19.7%)	7/47 (14.9%)	17/76 (18.4%)	391/2481 (15.6%)
Diabetes, no medication	0/5 (0%)	0/2 (0%)	2/6 (33.3%)	0/0 (0%)	2/13 (15.3%)
Diabetes, medication	2/4 (50%)	2/7 (28.6%)	10/31 (32.2%)	0/1 (0%)	14/43 (32.6%)†
Missing*	109/522 (21%)	2/14 (14%)	0/7 (0%)	1/8 (12.5%)	112/551 (20.3%)†

*Includes 5 women who completed the baseline health status questionnaire but did not complete question on diabetes

† Chi-square $p < 0.01$ for comparison with self-report stratum of "No diabetes"

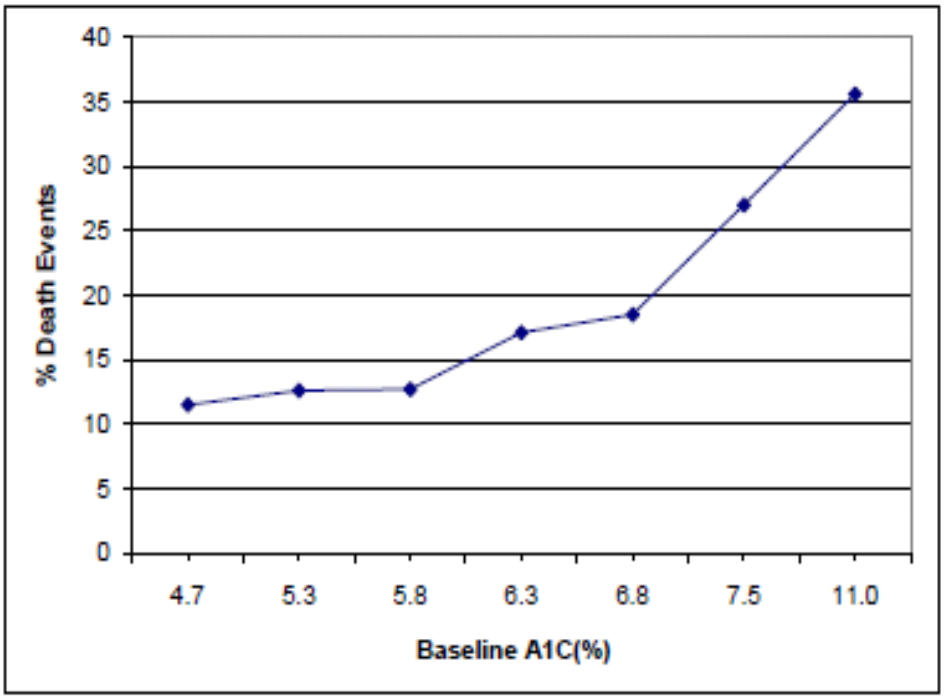


Figure 2.1 All-cause mortality events and baseline A1C in a cohort of U.S. breast cancer survivors with median 10.3 years of survival follow-up (n = 3003)

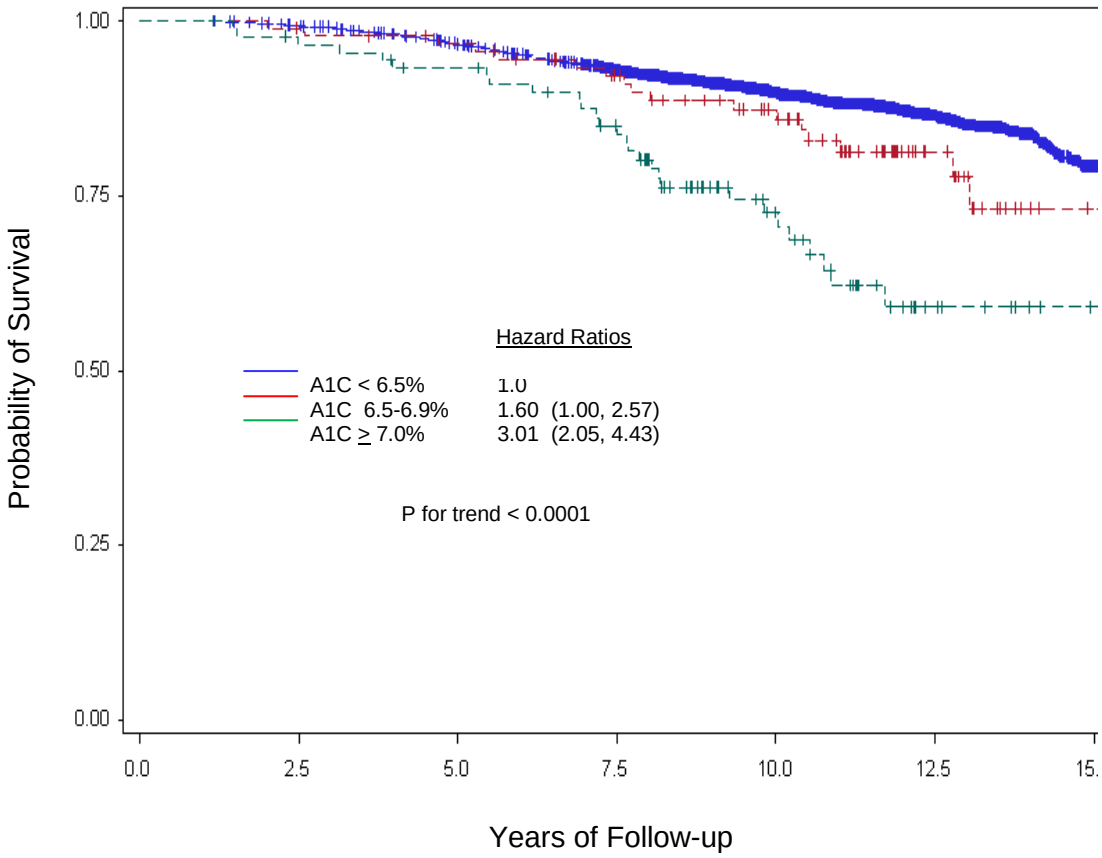


Figure 2.2 Kaplan-Meier estimates of overall survival with median of 10.3 years survival follow-up according to baseline A1C in a cohort of US breast cancer survivors (n = 3003)

Hazard ratio, 95% confidence intervals and p for trend are taken from Cox model.

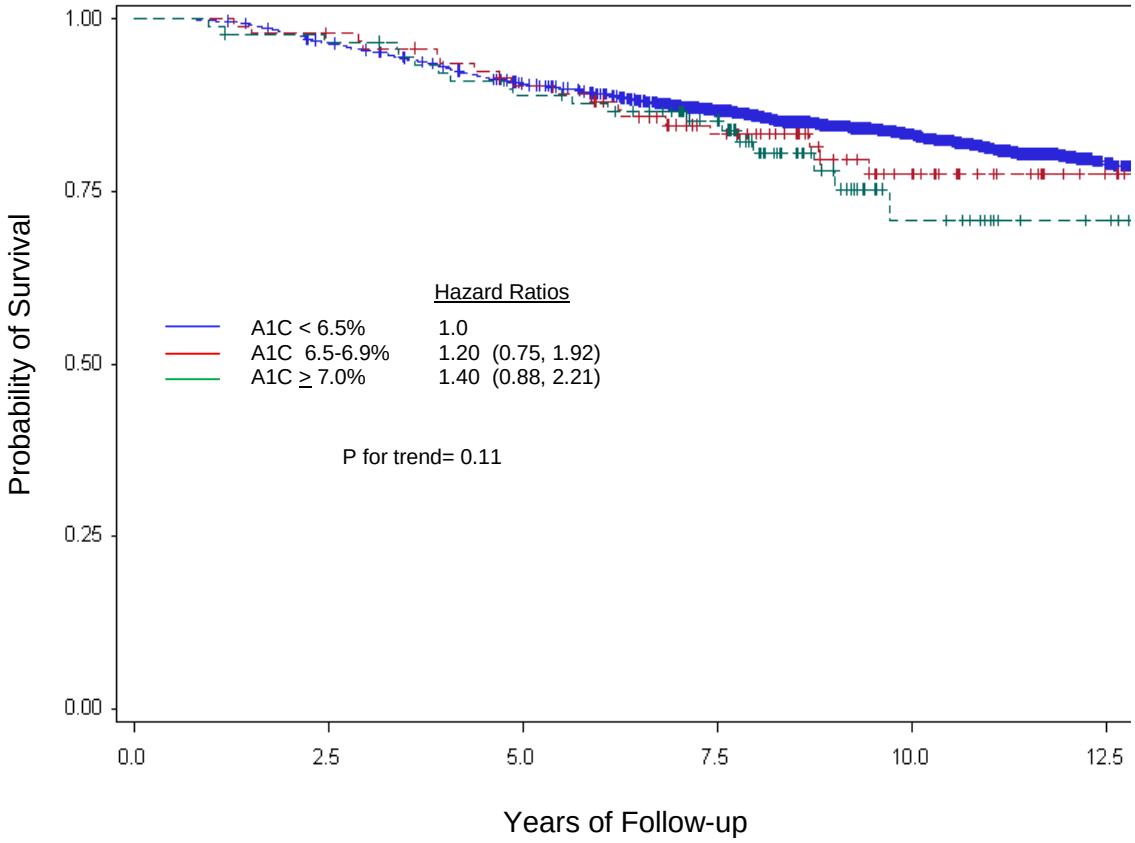


Figure 2.3 Kaplan-Meier estimates of breast cancer event-free survival with median of 7.3 years follow-up according to baseline A1C in a cohort of US breast cancer survivors (n = 3003)

Hazard ratio, 95% confidence intervals and p for trend are taken from Cox model.

CHAPTER 3

Obesity, Weight Change, and Diabetes Risk in Breast Cancer Survivors

ABSTRACT

Purpose Diabetes may be an independent risk factor for breast cancer recurrence and is a known risk factor for untimely mortality. Weight gain during and post-cancer treatment is common among patients. Our study investigates the effect of post-diagnosis weight change on diabetes risk.

Methods 1617 breast cancer survivors at low risk for diabetes (HbA1C<6.0%), identified from The Women's Healthy Eating & Living Study, reported pre-cancer weight and were weighed at 5 time points. Post-diagnosis weight change was categorized: stable (+ 5%), moderate gain (>5% to <10%), major gain (> 10%), and lost > 5% of weight with subsequent regain. Logistic regression evaluated association of pre-cancer BMI and post-diagnosis weight change with incident diabetes, defined by self-report or HbA1C > 6.5%.

Results 54 (3.3%) women became diabetic over 6 years. Chemotherapy predicted weight gain. Women in the major loss-regain weight category had higher mean pre-cancer BMI than women with stable weight ($p<0.05$) and experienced mean weight decrease from pre-cancer to study entry of 16.6 (11.4) lbs, an amount fully regained by year 6. Adjusting for chemotherapy, pre-cancer BMI and other covariates, major weight gain and major loss-regain weight were positively associated with incident diabetes with risk estimates 2.1 (95% CI, 1.1 to 4.5) and 2.3 (95% CI, 1.1 to 4.9) compared to stable weight.

Conclusions Major weight gain following breast cancer diagnosis doubles the risk of becoming diabetic. Women who majorly lose and regain weight have a similar increased diabetes risk and tend to be significantly overweight or obese pre-cancer.

INTRODUCTION

The rising obesity epidemic in Americans is putting women, including breast cancer survivors, at significant increased risk of diabetes. Recently, the American Diabetes Association (ADA) and the American Cancer Society (ACS) issued a consensus report calling attention to the association between diabetes and cancer, noting the entanglement of lifestyle risk factors, common biological links and potential mediating solutions between the two diseases.[1] Among breast cancer patients, diabetes is associated with decreased overall survival[2-12] and emerging evidence shows a possible association with increased risk of recurrence or new primary.[3,6,12-13]

Unfortunately, many women report gaining weight as a result of their breast cancer diagnosis and treatment[14-24] and only a small percentage return to their pre-cancer weight.[25] Studies show that the amount of weight gained after diagnosis of breast cancer is larger than would be expected in the general population and occurs at an accelerated rate compared to age-matched healthy women.[20,24,26,27] Weight gain in breast cancer patients may increase their risk for developing diabetes, which may also increase their risk for poor cancer outcomes as well as cardiovascular disease.

The objective of this secondary analysis was to investigate the independent effects of pre-cancer body mass index (BMI) and post-diagnosis weight change on the risk of

incident diabetes in a large, prospective cohort of breast cancer survivors participating in the Women's Healthy Eating & Living (WHEL) Study.

PATIENTS AND METHODS

Participants

Between 1995 and 2000, the WHEL Study enrolled 3,088 women within 4 years of diagnosis of early-stage breast cancer (American Joint Committee on Cancer, 4th edition: stage I [>1 cm], II, or IIIA). Details of the study have been reported previously.[28-29] Eighty five percent (n= 2,621) of participants were alive and did not experience a breast cancer event by the year 6 study visit and were thus potentially eligible for this analysis. Of these women, 686 (26%) were excluded because they did not provide blood samples at the year 6 clinic visit. For this secondary analysis, additional exclusions were applied: (1) missing self-report data on pre-cancer weight (n=20), (2) no HbA1C measure at the baseline visit due to lack of blood sample (n=24), (3) baseline HbA1C > 6.0% (n=254), and (3) self-reported type 2 diabetes (non-insulin dependent) at baseline (n=20). The resulting sample size was 1617. Internal review boards at each site approved the study and all participants provided written informed consent before enrolling.

Measurement of covariates

Cancer characteristics and treatment such as tumor stage (I, II or III), tumor hormone receptor status, chemotherapy (yes, no), and tamoxifen use (yes, no), were obtained from medical records and verified by an oncologist. Standard questionnaires administered at baseline ascertained demographic characteristics, lifestyle, medical and

weight history variables. For this analysis, ethnicity was dichotomized into white/non-Hispanic and other (Hispanic/Latina, African-American, Asian, Pacific Islander, mixed/other). Other demographic variables used included: education (college-graduate, non-graduate), age at cancer diagnosis dichotomized (<60 and > 60 years old), smoking (ever, never). Menstrual status at cancer diagnosis (pre-menopausal vs. post-menopausal) was defined by comparing age at cancer diagnosis to self-reported age at menopause. The frequency, duration, and intensity of physical activity at the baseline visit were assessed using nine items from the Women's Health Initiative Personal Habits Questionnaire, which were validated in a subsample of WHEL participants[30] and converted into metabolic equivalent tasks (METs) as previously described. [31]

BMI was calculated as weight (kg)/height (m^2) and obesity status defined as normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (> 30 kg/m^2). Height was clinically measured at study entry and used to calculate pre-cancer BMI. Post-diagnosis weight change was calculated by subtracting the pre-cancer diagnosis weight from the first post-cancer weight measured at the WHEL baseline visit and dividing the difference by pre-cancer weight and multiplying by 100. Percentage of post-diagnosis weight change was separated into four categories: stable weight (+ 5%), moderate weight gain (>5% to <10%) major weight gain (> 10%) and lost > 5% of weight with subsequent regain (hereafter referred to as 'major loss-regain' category). These categories of percent weight change were chosen because they are commonly used as weight management goals for reducing the risk of obesity, heart disease, diabetes and cancer. [32-34]

Measurement of incident diabetes

The primary outcome was incident diabetes defined by self-report at any of the clinic follow-up visits (years 1, 2 or 3, 4, 6) or by year 6 HbA1C level > 6.5%.35 A self-administered health status questionnaire at each study visit was used to obtain information regarding physician-identified comorbid conditions including diabetes. Baseline and follow-up (year 6) HbA1C was measured in September 2009 using ion exchange high-performance liquid chromatography [D-10 System, Bio-Rad® ; Laboratories, Hercules, California] on archived samples of washed red blood cells. Performance of the D-10 HbA1C methodology was assessed by inclusion of known quality control samples with high (10.0%) and low (5.8%) HbA1C levels; the coefficients of variation were 1.5% and 1.6%, respectively, for within-day runs and 1.9% and 1.9%, respectively, for between-day runs.

Statistical Analysis

To show how weight changed over the follow-up period, a plot with mean values and standard errors was constructed for each category of post-diagnosis weight change. Descriptive statistics were computed for covariates across the categories of post-diagnosis weight change using F-tests for continuous covariates and chi-square tests for the categorical covariates. Descriptive statistics for baseline demographic and health information were computed and compared by incident diabetes status. Differences between women without and with incident diabetes were computed and tested for significance by means of F-tests derived from generalized linear models. Bivariate comparisons of categorical variables were performed using chi-square tests derived from logistic regression models.

To address potential confounding in the relationship between post-diagnosis weight change and incident diabetes, a covariate was included in the final multivariate model of diabetes risk if it: (1) was associated with post-diagnosis weight change ($p < 0.05$) and (2) modified the magnitude of association between post-diagnosis weight change and incident diabetes by >10%. Covariates that met these criteria were: age at cancer diagnosis, physical activity level at study entry, menopausal status, and chemotherapy history. Several variables were included in the multivariate model based on apriori selection. Specifically, race/ethnicity was included based on research showing diabetes risk varies by race/ethnicity.[36] Cancer stage was included because the association between cancer and diabetes is of central interest to this study and few studies have included cancer stage as a predictor variable for diabetes risk. The time from cancer diagnosis to study entry was included because this was the time frame in which the weight change variable measured and therefore would be an important factor to account for given that weight change was the exposure of interest.

Primary outcome comparisons of incident diabetes by post-diagnosis weight change, pre-cancer BMI and other covariates were analyzed and presented as odds ratios and 95% confidence intervals derived from a multivariate logistic regression model. Significance was analyzed using Wald chi-square tests. A linear test for trend was estimated by modeling the categorical variables of pre-cancer BMI and post-diagnosis weight change on an ordinal scale and assessed for statistical significance ($p<0.05$). To assess whether post-diagnosis weight change had a differential effect on diabetes risk by pre-cancer BMI category, an interaction term of pre-cancer BMI and post-diagnosis

weight change was tested using exact logistic regression but was not statistically significant and thus not included in the multivariate model.

All statistical tests were two-tailed and analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Mean weight measures at one year pre-cancer and at WHEL study entry through the 6 years of follow up are presented for each category of post-diagnosis weight change (Figure 1). Stable weight represented the largest percentage (44%) of post-diagnosis weight change, followed by the categories of major weight gain (24%), moderate weight gain (19%) and major loss-regain weight (14%). Prior to cancer diagnosis, women in the stable category were borderline overweight (BMI = 25.3 + 5.1 kg/m2) while women in the weight gain categories had a mean pre-cancer BMI in the normal range (24.9 $\pm$ 4.3 kg/m^2 and 24.5 $\pm$ 4.0 kg/m^2 for moderate and major weight gain groups, respectively). Women in the major loss-regain weight category were significantly overweight pre-cancer (BMI= 27.0 $\pm$ 5.4 kg/m2). In the categories of moderate and major weight gain, the mean (SD) increases in pounds from one year pre-diagnosis to WHEL Study entry were 10.7 (3.1) and 25.2 (11.4), respectively. In the major loss-regain weight category, the mean decrease in pounds from one year pre-diagnosis to study entry was 16.6 (11.4), an amount that was subsequently regained in full by the year 6 follow-up visit.

Table 1 presents bivariate associations between selected covariates and each category of post-diagnosis weight change (stable weight = reference level). Compared to

women in the stable weight category, women in the moderate weight gain category had a higher mean BMI at study entry, were less likely to have a college education, more likely to have received treatment with chemotherapy and reported statistically significantly lower levels of physical activity at study entry ($p < 0.05$). Women in the major weight gain category exhibited the greatest number of statistically significant differences in covariates relative to women in the stable weight category, including: younger mean age at cancer diagnosis, more time from cancer diagnosis to study entry, higher mean BMI at study entry, less likely to have a college education, less likely to be post-menopausal at cancer diagnosis, more likely to have received chemotherapy and less likely to have received tamoxifen ($p<0.05$). Women in the major loss-regain weight category had a statistically significantly higher mean pre-cancer BMI and a shorter time from cancer diagnosis to study entry compared to women in the stable weight category ($p < 0.05$).

In this cohort of 1617 breast cancer survivors, 54 (3.3%) women became diabetic over 6 years of follow-up with 19 (35.2%) self-reporting diabetes and the remaining identified by (year 6) HbA1C level > 6.5% (Table 2). Diabetes incidence was not associated with race/ethnicity, marital status, age at cancer diagnosis, menopausal status at cancer diagnosis, cancer stage at diagnosis or chemotherapy history ($p>0.05$). Although mean study entry HbA1C levels were in the normal range for both groups of women, those with incident diabetes had a statistically significantly higher mean HbA1C level at study entry compared to women who did not develop diabetes with values of 5.76% and 5.47%, respectively ($p<0.0001$).

Odds ratios and corresponding confidence limits derived from the multivariate model of diabetes risk are presented in Table 3. Adjusting for pre-cancer BMI and other covariates, the post-diagnosis weight change categories of major weight gain and of major loss-regain weight were positively associated with incident diabetes with risk estimates of 2.1 (95% CI, 1.1 to 4.5) and 2.3 (95% CI, 1.1 to 4.9), respectively, compared to the stable weight category. The test statistic for a linear trend of diabetes risk across the categories of post-diagnosis weight change was statistically significant ($p = 0.03$). Relative to normal pre-cancer weight, pre-cancer adiposity was the strongest predictor of incident diabetes with an adjusted odds ratio of 2.2 (1.1 to 4.6) for overweight and 5.6 (2.8 to 11.4) for obesity (test for linear trend, $p < 0.0001$).

DISCUSSION

In this study, women who experienced major weight gain after breast cancer diagnosis or major weight loss with subsequent regain were at twofold greater risk of becoming diabetic than women who maintained their pre-cancer weight. We found that chemotherapy and pre-menopausal status predicted major weight gain which is consistent with other studies on post-diagnosis weight change in breast cancer patients. [37-44] Research also shows that the pattern of weight gain typical of breast cancer patients receiving chemotherapy occurs with no associated gains or perhaps even losses in lean tissue. This pattern of weight gain can lead to a body composition phenotype known as sarcopenic obesity which has been associated with insulin resistance and glycemic abnormalities in the general population[45] as well as shorter overall survival time in cancer patients. [46-47] Three separate studies have now reported that weight loss after a breast

cancer diagnosis is associated with increased mortality. [14, 48-49] However, in each study, those who were obese at diagnosis (BMI ≥30 kg/m^2) were the most likely to be in the large weight loss group. None of these reports included information on whether the observed weight loss was maintained. In this report, we were able to utilize multiple post-diagnosis weight measures to address this issue. Specifically, our study data indicate that women who lost significant weight in the early years following their diagnosis were overweight or obese before diagnosis and regained the weight in the additional years of follow-up. Both high initial weight and weight gain are negative prognostic factors for diabetes development and other competing comorbidities that threaten overall survival time. Our findings corroborate studies that have shown the process of recovering large amounts of body weight is itself an independent risk factor for the development of diabetes, especially when the patient is overweight or obese before the weight loss and regain occurs.[50]

To our knowledge this was the first study to measure diabetes risk in a large cohort of breast cancer survivors, using HbA1C in addition to self-report to identify incident diabetes. Diabetes incidence was quite low (3.3%) which may be attributed to several factors: (1) self-selection bias given that our sample was comprised of a subcohort of women participating in a healthy dietary intervention study, (2) high proportion of white women represented in the study, (3) exclusion of women at high risk of diabetes (baseline HbA1C > 6.0%), and (4) exclusion of women who died or experienced a breast cancer event before year 6 of WHEL Study follow-up.

Strengths of our study include clinically measured weight over six years of follow-up, verified patient data on tumor and treatment characteristics, and a high rate of participant response. However, our study was subject to certain limitations. For instance, chemotherapy regimens and estrogen modulating agents have improved since the 1990s when the majority of women in our study were diagnosed and completed initial treatments. These factors could have an impact on post-diagnosis weight change. Also, although study entry and follow-up visit weights were measured in the clinic, data on pre-cancer weight was self-reported. However, it is unlikely that self-reported pre-cancer weight influenced the effect of post-diagnosis weight change on diabetes risk as research supports self-reported weight to be a reliable measure of actual weight. [51] In this study subsample, correlation was high between self-reported study entry weight and clinically measured study entry weight (Pearson coefficient = 0.98).

In summary, diabetes is known to be associated with an increased risk of breast cancer incidence, recurrence and mortality. Our study provides new insight into the relationship between pre-cancer weight, post-diagnosis weight change, and diabetes risk. Although further research is needed to validate the adverse effects of major weight loss-regain on diabetes risk in breast cancer survivors, these data suggest that oncologists monitor patients for weight gain during and after cancer treatment to guard against diabetes development which may, in turn, improve long term prognosis.

Chapter 3 is currently being prepared for the submission for the publication of the material. Kirsten Erickson, Ruth E. Patterson, Loki Natarajan, John P. Pierce. The dissertation author was the primary investigator and author of this material.

REFERENCES

1. Giovannucci E, Harlan DM, Archer MC, et al: Diabetes and cancer: a consensus report. CA Cancer J Clin 60:207-21

2. Barone BB, Yeh HC, Snyder CF, et al: Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 300:2754-64, 2008

3. Du W, Simon MS: Racial disparities in treatment and survival of women with stage I-III breast cancer at a large academic medical center in metropolitan Detroit. Breast Cancer Res Treat 91:243-8, 2005

4. Erickson K, Patterson RE, Flatt SW, et al: Clinically Defined Type 2 Diabetes Mellitus and Prognosis in Early-Stage Breast Cancer. J Clin Oncol

5. Lipscombe LL, Goodwin PJ, Zinman B, et al: The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat 109:389-95, 2008

6. Patterson RE, Flatt SW, Saquib N, et al: Medical comorbidities predict mortality in women with a history of early stage breast cancer. Breast Cancer Res Treat 122:859-65

7. Peairs KS, Barone BB, Snyder CF, et al: Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol 29:40-6

8. Srokowski TP, Fang S, Hortobagyi GN, et al: Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 27:2170-6, 2009

9. Tammemagi CM, Nerenz D, Neslund-Dudas C, et al: Comorbidity and survival disparities among black and white patients with breast cancer. JAMA 294:1765-72, 2005

10. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, et al: Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer 120:1986-92, 2007

11. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285:885-92, 2001

12. Schrauder MG, Fasching PA, Haberle L, et al: Diabetes and prognosis in a breast cancer cohort. J Cancer Res Clin Oncol

13. Li CI, Daling JR, Tang MT, et al: Relationship between diabetes and risk of second primary contralateral breast cancer. Breast Cancer Res Treat 125:545-51

14. Caan BJ, Kwan ML, Hartzell G, et al: Pre-diagnosis body mass index, post-diagnosis weight change, and prognosis among women with early stage breast cancer. Cancer Causes Control 19:1319-28, 2008

15. Chlebowski RT, Aiello E, McTiernan A: Weight loss in breast cancer patient management. J Clin Oncol 20:1128-43, 2002

16. Demark-Wahnefried W, Rimer BK, Winer EP: Weight gain in women diagnosed with breast cancer. J Am Diet Assoc 97:519-26, 529; quiz 527-8, 1997

17. Goodwin PJ, Ennis M, Pritchard KI, et al: Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. J Clin Oncol 17:120-9, 1999

18. Gu K, Chen X, Zheng Y, et al: Weight change patterns among breast cancer survivors: results from the Shanghai breast cancer survival study. Cancer Causes Control 21:621-9

19. Heideman WH, Russell NS, Gundy C, et al: The frequency, magnitude and timing of post-diagnosis body weight gain in Dutch breast cancer survivors. Eur J Cancer 45:119-26, 2009

20. Irwin ML, McTiernan A, Baumgartner RN, et al: Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol 23:774-82, 2005

21. Kroenke CH, Chen WY, Rosner B, et al: Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol 23:1370-8, 2005

22. McInnes JA, Knobf MT: Weight gain and quality of life in women treated with adjuvant chemotherapy for early-stage breast cancer. Oncol Nurs Forum 28:675-84, 2001

23. Tredan O, Bajard A, Meunier A, et al: Body weight change in women receiving adjuvant chemotherapy for breast cancer: a French prospective study. Clin Nutr 29:187-91

24. Vance V, Mourtzakis M, McCargar L, et al: Weight gain in breast cancer survivors: prevalence, pattern and health consequences. Obes Rev

25. Saquib N, Flatt SW, Natarajan L, et al: Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the women's healthy eating and living (WHEL) study. Breast Cancer Res Treat 105:177-86, 2007

26. Campbell KL, Lane K, Martin AD, et al: Resting energy expenditure and body mass changes in women during adjuvant chemotherapy for breast cancer. Cancer Nurs 30:95-100, 2007

27. Rock CL, Flatt SW, Newman V, et al: Factors associated with weight gain in women after diagnosis of breast cancer. Women's Healthy Eating and Living Study Group. J Am Diet Assoc 99:1212-21, 1999

28. Pierce JP, Faerber S, Wright FA, et al: A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials 23:728-56, 2002

29. Pierce JP, Natarajan L, Caan BJ, et al: Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 298:289-98, 2007

30. Johnson-Kozlow M, Rock CL, Gilpin EA, et al: Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav 31:193-202, 2007

31. Hong S, Bardwell WA, Natarajan L, et al: Correlates of physical activity level in breast cancer survivors participating in the Women's Healthy Eating and Living (WHEL) Study. Breast Cancer Res Treat 101:225-32, 2007

32. Bantle JP, Wylie-Rosett J, Albright AL, et al: Nutrition recommendations and interventions for diabetes--2006: a position statement of the American Diabetes Association. Diabetes Care 29:2140-57, 2006

33. Doyle C, Kushi LH, Byers T, et al: Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 56:323-53, 2006

34. Kushi LH, Byers T, Doyle C, 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 56:254-81; quiz 313-4, 2006

35. Gillett MJ: International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes: Diabetes Care 2009; 32(7): 1327-1334. Clin Biochem Rev 30:197-200, 2009

36. Shai I, Jiang R, Manson JE, et al: Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 29:1585-90, 2006

37. Demark-Wahnefried W, Peterson BL, Winer EP, et al: Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 19:2381-9, 2001

38. Aslani A, Smith RC, Allen BJ, et al: Changes in body composition during adjuvant chemotherapy for breast cancer. Appl Radiat Isot 49:637-8, 1998

39. Aslani A, Smith RC, Allen BJ, et al: Changes in body composition during breast cancer chemotherapy with the CMF-regimen. Breast Cancer Res Treat 57:285-90, 1999

40. Cheney CL, Mahloch J, Freeny P: Computerized tomography assessment of women with weight changes associated with adjuvant treatment for breast cancer. Am J Clin Nutr 66:141-6, 1997

41. Freedman RJ, Aziz N, Albanes D, et al: Weight and body composition changes during and after adjuvant chemotherapy in women with breast cancer. J Clin Endocrinol Metab 89:2248-53, 2004

42. Harvie MN, Campbell IT, Baildam A, et al: Energy balance in early breast cancer patients receiving adjuvant chemotherapy. Breast Cancer Res Treat 83:201-10, 2004

43. Irwin ML, McTiernan A, Baumgartner RN, et al: Changes in body fat and weight after a breast cancer diagnosis: influence of demographic, prognostic, and lifestyle factors. J Clin Oncol 23:774-82, 2005

44. Visovsky C: Muscle strength, body composition, and physical activity in women receiving chemotherapy for breast cancer. Integr Cancer Ther 5:183-91, 2006

45. Srikanthan P, Hevener AL, Karlamangla AS: Sarcopenia Exacerbates Obesity-Associated Insulin Resistance and Dysglycemia: Findings from the National Health and Nutrition Examination Survey III. PLoS ONE 5:e10805

46. Prado CM, Lieffers JR, McCargar LJ, et al: Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 9:629-35, 2008

47. Roubenoff R: Excess baggage: sarcopenia, obesity, and cancer outcomes. Lancet Oncol 9:605-7, 2008

48. Chen X, Lu W, Zheng W, et al: Obesity and weight change in relation to breast cancer survival. Breast Cancer Res Treat 122:823-33

49. Nichols HB, Trentham-Dietz A, Egan KM, 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 18:1403-9, 2009

50. Dulloo AG, Jacquet J, Montani JP: Pathways from weight fluctuations to metabolic diseases: focus on maladaptive thermogenesis during catch-up fat. Int J Obes Relat Metab Disord 26 Suppl 2:S46-57, 2002

51. Olivarius NF, Andreasen AH, Loken J: Accuracy of 1-, 5- and 10-year body weight recall given in a standard questionnaire. Int J Obes Relat Metab Disord 21:67-71, 1997

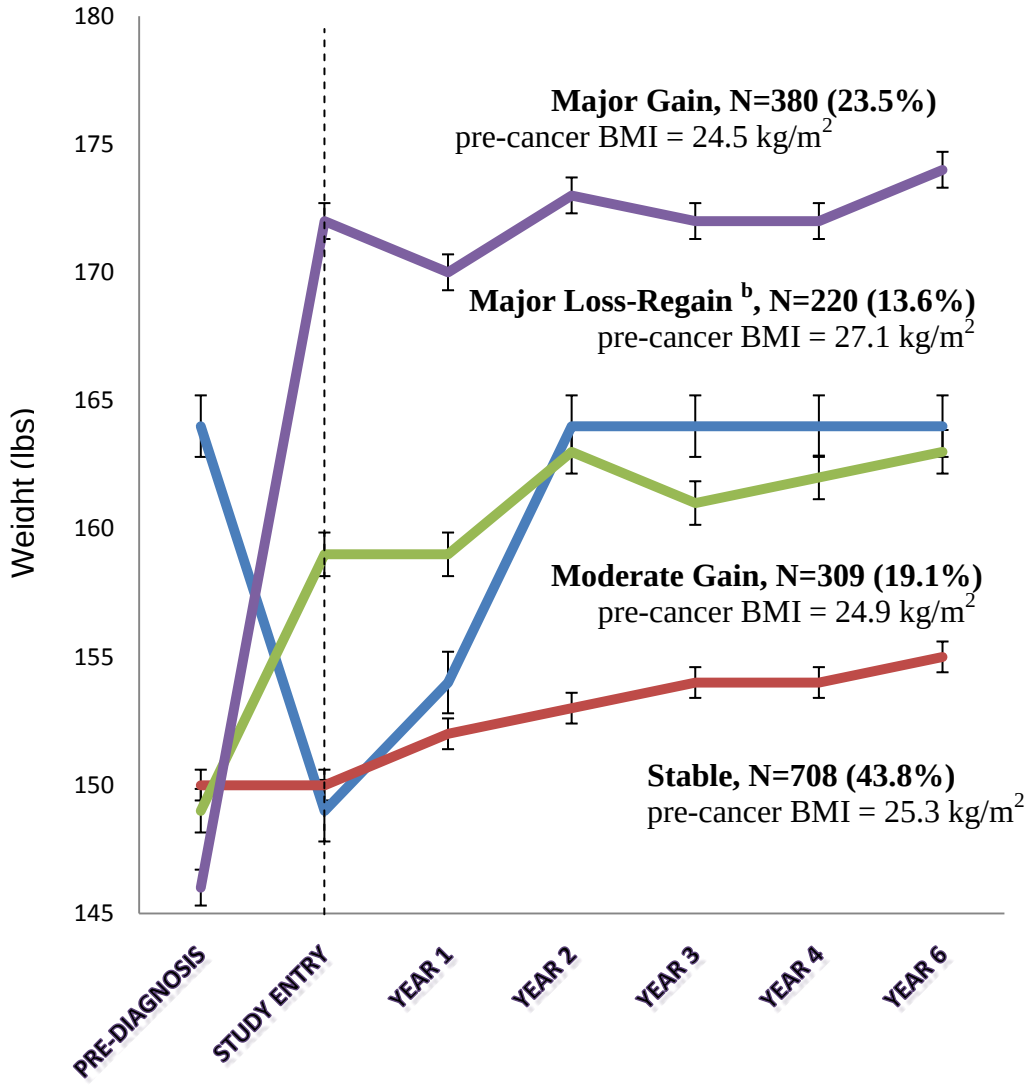


Figure 3.2 Mean weight measures (and standard errors) at one year pre-cancer and at WHEL study entry through 6 years of follow up, stratified by category of post-diagnosis weight change [a] (N = 1,617)

[a] Post-diagnosis weight change was calculated by subtracting the **pre-cancer diagnosis weight** from the **study entry weight** and dividing the difference by pre-cancer diagnosis weight and multiplying by 100. Four categories of the post-diagnosis weight change variable defined by percentage cut points: stable weight (+ 5%), moderate weight gain (>5% to <10%) major weight gain (> 10%) and lost > 5% weight.

[b] The regain of weight occurred over the 6 year follow-up period but only 2 time points (pre-cancer diagnosis, study entry) used to define the post-diagnosis weight change variable.

Table 3.1 Characteristics of women with a history of early-stage breast cancer in the WHEL Study by categories of post-diagnosis body weight change (n=1617)

	Post-Diagnosis Weight Change [a]			
	Stable N=708	**Moderate Gain N=309**	**Major Gain N=380**	**Major loss-regain [b] N = 220**
Continuous Parameters	**Mean (SD)**			
Age at diagnosis (yrs)	51.0 (9.2)	51.6 (8.6)	49.7 (7.5)*	52.0 (8.6)
Diagnosis to study entry (yrs)	1.9 (1.1)	2.1 (1.0)	2.3 (1.0)*	1.7 (1.0)*
Pre-cancer BMI (kg/m^2)	25.3 (5.1)	24.9 (4.7)	24.5 (4.0)*	27.1 (5.3)*
BMI at study entry (kg/m^2)	24.6 (4.9)	25.5 (4.3)*	29.3 (5.1)*	25.2 (5.1)
Physical activity at study entry (MET-min/week)	987 (885)	817 (837)*	830 (809)*	948 (917)
A1C level, study entry (%)	5.5 (0.3)	5.5 (0.3)	5.5 (0.3)	5.5 (0.3)
Categorical Parameters	**N (%)**			
White, non-Hispanic				
White	621 (87.7)	274 (88.7)	331 (87.1)	220 (91.7)
African American	14 (2.0)	8 (2.6)	13 (3.4)	6(2.5)
Hispanic	28 (4.0)	13 (4.2)	18 (4.7)	9 (3.8)
Asian American	32 (4.5)	9 (2.9)	7 (1.8)	5 (2.1)
Mixed/Other	13 (1.8)	5 (1.6)	11 (2.9)	0 (0.0)
College graduate	436 (61.6)	165 (53.4)*	199 (52.4)*	145 (60.4)
Married	506 (71.7)	228 (74.3)	267 (71.0)	180 (75.0)
Postmenopausal at diagnosis	635 (89.7)	275 (89.0)	312 (82.1)*	213 (88.8)
Cancer stage at diagnosis				
I	317 (44.8)	143 (46.3)	153 (40.3)	98 (40.8)
II	306 (43.2)	131 (42.4)	184 (48.4)	113 (47.1)
III	85 (12.0)	35 (11.3)	43 (11.3)	29 (12.1)
Received chemotherapy	439 (62.0)	220 (71.2)*	274 (72.3)*	155 (64.9)
Received tamoxifen	471 (66.6)	193 (62.5)	224 (59.0)*	160 (66.7)

* $p < 0.05$, stable weight as the comparison level

[a] Post-diagnosis weight change was calculated by subtracting the **pre-cancer diagnosis weight** from the **study entry weight** and dividing the difference by pre-cancer diagnosis weight and multiplying by 100. Four categories of the post-diagnosis weight change

Table 3.1 continued

variable defined by percentage cut points: stable weight (+ 5%), moderate weight gain (>5% to <10%) major weight gain (> 10%) and lost > 5% weight.

[b] The regain of weight occurred over the 6 year follow-up period but only 2 time points (pre-cancer diagnosis, study entry) used to define the post-diagnosis weight change variable.

Table 3.2 Characteristics of women with incident diabetes vs. without diabetes in a large cohort of early stage breast cancer survivors, the WHEL Study (N = 1617)

	No Diabetes N = 1583	**Incident Diabetes N = 54**	
	Mean (SD)		***P****
Age at diagnosis (yrs)	51.0 (8.5)	51.8 (8.0)	0.50
Time diagnosis to study entry (yrs)	2.0 (1.0)	2.0 (1.0)	0.86
Pre-cancer weight (lbs)	149.8 (30.3)	176.1 (44.7)	<0.0001
Weight at study entry (lbs)	156.0 (32.4)	182.2 (43.0)	<0.0001
Pre-cancer BMI (kg/m^2)	25.1 (4.7)	29.8 (6.7)	<0.0001
BMI at study entry (kg/m^2)	26.2 (5.1)	30.8 (6.2)	<0.0001
Physical activity at study entry (MET-min/week) [a]	924(871)	608 (664)	0.01
HbA1C level at study entry (%)	5.47 (0.31)	5.76 (0.20)	<0.0001
	N (%)		***P*** [†]
Race/Ethnicity			0.22
White	1400 (88.4)	46 (85.2)	
African American	39 (2.5)	2 (3.7)	
Hispanic	68 (4.3)	0	
Asian American	48 (3.0)	5 (9.3)	
Mixed/Other	28 (1.8)	1 (1.9)	
College education	922 (58.2)	23 (42.6) [†]	0.02
Married [b]	1143 (72.6)	38 (70.4)	0.72
Postmenopausal at diagnosis	1386 (87.6)	49 (90.7)	0.49
Cancer stage at diagnosis			0.89
I	689 (43.5)	22 (40.7)	
II	708 (44.7)	26 (48.2)	
III	186 (11.8)	6 (11.1)	
Received chemotherapy	1056 (66.8)	32 (59.3)	0.25
Pre-cancer BMI (kg/m^2)			<0.0001
<25	936 (59.1)	15 (27.8)	
25-29.9	435 (27.5)	18 (33.3)	
$\geq$ 30	212 (13.4)	21 (38.9)	

Table 3.2 continued

	No Diabetes N = 1583	**Incident Diabetes N = 54**	
	N (%)		***P*†**
Post-diagnosis weight change [c]			
Stable	691 (43.7)	17 (31.5)	0.08
Moderate gain	300 (19.0)	9 (16.7)	
Major gain	365 (23.1)	15 (27.8)	
Major loss-regain [d]	207 (13.1)	13(24.1)	

* P-value derived from analysis of variance F-test
† P-value derived from logistic regression chi-square test

[a] Physical activity variable had skewed distribution. Median and (interquartile range) values for women without and with diabetes were 705 (1110) and 435 (765), respectively

[b] Numbers do not total 1617 due to missing data

[c] Post-diagnosis weight change was calculated by subtracting the **pre-cancer diagnosis weight** from the **study entry weight** and dividing the difference by pre-cancer diagnosis weight and multiplying by 100. Four categories of the post-diagnosis weight change variable defined by percentage cut points: stable weight (+ 5%), moderate weight gain (>5% to <10%) major weight gain (> 10%) and lost > 5% weight.

[d] The regain of weight occurred over the 6 year follow-up period but only 2 time points (pre-cancer diagnosis, study entry) used to define the post-diagnosis weight change variable.

Table 3.3 Multivariate logistic regression model [a] of incident diabetes among 1,617 women with a history of early stage breast cancer, the WHEL Study

	OR	95% CI	*p*	*p* (trend)
Primary Exposure Variables				
Pre-cancer BMI (kg/m^2)				<.0001
<25	*Ref*	--	--	
25-29.9	2.24	1.10 to 4.56	0.026	
≥ 30	5.61	2.77 to 11.37	<.0001	
Post-diagnosis weight change [b]				
Stable	*Ref*	--		0.03
Moderate gain	1.25	0.54 to 2.90	0.600	
Major gain	2.12	1.06 to 4.46	0.049	
Major loss-regain [c]	2.29	1.07 to 4.90	0.034	
Covariates				
Race/ethnicity				
White	*Ref*	--	--	
Nonwhite	1.37	0.62 to 3.03	0.436	
Age at cancer diagnosis (continuous)	1.00	0.96 to 1.04	0.955	
Cancer stage				
I	*Ref*	--	--	
II	1.35	0.70 to 2.61	0.365	
II	1.23	0.44 to 3.44	0.691	
Menopausal status at cancer diagnosis				
Pre	*Ref*	--	--	
Post	1.38	0.52 to 3.65	0.522	
Chemotherapy				
No	*Ref*	--	--	
Yes	0.63	0.31 to 1.28	0.201	
Years cancer diagnosis to study entry (continuous)	1.04	0.78 to 1.37	0.803	
Physical activity level, study entry (continuous, per 100 MET-min/wk)	0.96	0.92 to 1.00	0.070	

Ref = reference level

[a] Analyses adjusted for all variables listed in the table.

[b] Post-diagnosis weight change was calculated by subtracting the **pre-cancer diagnosis weight** from the **study entry weight** and dividing the difference by pre-cancer diagnosis weight and multiplying by 100. Four categories of the post-diagnosis weight change variable defined by percentage cut points: stable weight (+ 5%), moderate weight gain (>5% to <10%) major weight gain (> 10%) and lost > 5% weight.

[c] The regain of weight occurred over the 6 year follow-up period but only 2 time points (pre- cancer diagnosis, study entry) used to define the post-diagnosis weight change variable.

CHAPTER 4

Long-term Worsening of Glycemic Control in Breast Cancer Survivors:

How Physical Inactivity, Weight Gain and Obesity Impact Risk

ABSTRACT

Purpose A progressive relationship between hemoglobin A1C levels (HbA1C) and all-cause mortality has been observed in women who have been diagnosed with breast cancer. Physical inactivity is common among breast cancer patients and is known to be associated with obesity and weight gain. Our study investigates the associations of physical inactivity, weight gain and obesity with worsening glycemic control over six-years of follow up in a large cohort of breast cancer survivors.

Methods 1864 breast cancer survivors identified from The Women's Healthy Eating & Living Study were clinically weighed and self-reported physical activity (PA) levels at 5 time points. PA was averaged and dichotomized as >10 vs < 10 MET-hr/week. Weight change, calculated as percent of total body weight change from baseline to year 6 ((year 6 weight – baseline weight)/baseline weight*100), was dichotomized as > 5% vs <5% gain. Logistic regression (LR) was employed to evaluate independent and adjusted effects of physical inactivity, weight gain and obesity with worsened glycemic control, defined by > 0.5% increase in HbA1C level from baseline to year 6.

Results Of1864 women, 317 (17%) experienced worsening of glycemic control. Women who were obese at baseline were 2.02 times more likely to have worsened glycemic control by year 6 compared to women who were not obese at baseline ($p < 0.0001$). Likewise, women who gained >5% body weight over 6 years were 1.97 times more likely to have worsened glycemic control compared to women who gained < 5% ($p < 0.0001$).

The association between PA level and worsened glycemic control was highly attenuated after adjustment for obesity and weight gain (OR = 1.11; 95% CI: 0.86-1.44).

Conclusions Physical inactivity is associated with uncontrolled weight which worsens glycemic control and increases risk of chronic disease among breast cancer survivors. Interventions combining physical activity with weight loss goals are warranted, particularly among the obese.

INTRODUCTION

Diabetes, a metabolic disorder characterized by hyperglycemia, is well established as a risk factor for reduced survival and may be an independent risk for breast cancer incidence and recurrence. Moreover, a progressive relationship between hemoglobin A1C levels (HbA1C) and all-cause mortality has been observed in women with a breast cancer history. Although not specific to breast cancer survivors, there is considerable research on how the lifestyle factors of physical inactivity, obesity and weight gain worsen glycemic control and increase diabetes risk. [1-3] Unfortunately, the ability to maintain a consistent exercise regimen after breast cancer is often disrupted due to fatigue and other symptoms experienced during and after treatment. [4-7] Studies consistently show marked drops in physical activity levels after a breast cancer diagnosis. [8-11] For instance, in a prospective cohort of breast cancer patients participating in The Health, Eating, Activity and Lifestyle (HEAL) Study, physical activity was reduced in some women by more than 50% from pre-diagnosis to post-diagnosis levels depending on type of treatment. [11] Moreover, the largest decreases were observed among the heavier

patients implying a greater potential for weight gain among women who were already overweight.

The Women's Healthy Eating and Living Study (WHEL) provides a unique opportunity to investigate the associations of physical inactivity, weight gain and obesity with long-term change in glycemic control in a large cohort of breast cancer survivors. Specifically, this analysis evaluates the independent effects of physical inactivity (<10 MET-hr/wk), weight gain (> 5%) and obesity (BMI > 30 kg/m2) on worsening of glycemic control, as measured by a 0.5 unit increase in HbA1C level from baseline to year 6 of study follow-up.

PATIENTS AND METHODS

Between 1995 and 2000, the WHEL Study enrolled 3,088 women within 4 years of diagnosis of early-stage breast cancer (American Joint Committee on Cancer, 4th edition: stage I [>1 cm], II, or IIIA). Details of the study have been reported previously. 12,13 Eighty five percent (n= 2,621) of participants were alive and did not experience a breast cancer event by the year 6 study visit and were thus potentially eligible for this analysis. Of these women, 757 (29%) were excluded because they did not provide blood samples at the baseline (n= 83) or year 6 clinic visit (n=674). The resulting sample size was 1864. Internal review boards at each site approved the study and all participants provided written informed consent before enrolling.

Data Collection

Cancer characteristics and treatment information were obtained from medical records and verified by an oncologist. Height and weight were clinically measured at the baseline visit and used to calculate body mass index (BMI, kg/m^2). Standard questionnaires administered at baseline ascertained demographic characteristics (age, race/ethnicity, education level) and certain lifestyle factors (smoking status, alcohol intake). The frequency, duration, and intensity of physical activity (PA) at the baseline and follow-up visits (years 1, 2 or 3, 4, and 6) were assessed using nine items from the Women's Health Initiative (WHI) Personal Habits Questionnaire and converted into metabolic equivalent task (METs) minutes per week in accordance with Ainsworth's compendium of physical activities as previously described.[14] In short, the questionnaire assessed frequency, duration, and speed of walking outside the home and frequency and duration of participation in each of three intensity levels of exercise: mild, moderate, or strenuous. Mild activity was assessed as 3 METs, moderate activity as 5 METs, and vigorous activity as 8 METs. Walking, slow, average, fast, and very fast were assessed as 2, 3, 4, and 6 METs, respectively. The PA measure was validated against an accelerometer and the Physical Activity Recall (PAR) among a subset of WHEL Study participants (n= 74) and found to have validity and sensitivity comparable to that of PAR. [15] Compared to the accelerometer, the WHI physical activity measure did not provide a significantly different PA estimate (+6 min or 4%, $p = .95$).

At baseline and follow-up visits, participants were asked to complete a self-administered questionnaire regarding whether they were currently being treated for a wide variety of diseases and conditions, including diabetes and cardiovascular risk factors

(hypertension and high blood cholesterol). These diseases/conditions were selected based on prevalence in this population and their potential to predict outcomes in breast cancer survivors. The questionnaire on comorbidities was added to the WHEL baseline assessment protocol after recruitment had begun so data was available for 1530 (82.1%) of the 1864 women included in this sample.

Baseline and year 6 HbA1C levels were measured in September 2009 using ion exchange high-performance liquid chromatography [D-10 System, Bio-Rad® ; Laboratories, Hercules, California] on archived samples of washed red blood cells. Performance of the D-10 HbA1C methodology was assessed by inclusion of known quality control samples with high (10.0%) and low (5.8%) HbA1C levels; the coefficients of variation were 1.5% and 1.6%, respectively, for within-day runs and 1.9% and 1.9%, respectively, for between-day runs.

Statistical Analysis

BMI categories were defined as normal weight (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (> 30 kg/m^2). Weight gain was calculated as percent of total body weight change from baseline to year 6 ((year 6 weight – baseline weight)/baseline weight*100) and dichotomized > 5% versus <5%. The weight gain cut point of 5% was chosen because it is commonly used as a weight management goal for reducing the risk of obesity, heart disease, diabetes and cancer.[16-18] A composite variable with four levels was constructed using the obesity and weight gain variables: not obese and weight gain < 5.0%, not obese and weight gain > 5.0%, obese and weight gain < 5.0%, obese and weight gain > 5.0%.

PA levels (MET-hr/wk) across the five time points were averaged and then dichotomized according to PA guidelines of10.0 MET-hr/wk, which equates to 150 minutes/week of moderate-pace walking or the equivalent amount of other exercise durations/intensities. This cut point is consistent with the joint position statement recently issued by the American Diabetes Association (ADA) and the American College for Sports Medicine (ACSM).[19]

Potential covariates assessed included: age at study entry (<44, 44-54, 55-65, >65 years), race/ethnicity (white/non-Hispanic, other), education (college graduate, non-graduate), tumor stage (I, II or III), chemotherapy history (yes, no), tamoxifen use (yes, no), post-menopausal at study entry (yes, no), smoking status (current, past, and never smokers), alcohol intake [none, 1-19 g/day (equivalent to <2 drinks/day), and > 20 kg/m2].

The change in HbA1C levels from baseline to year 6 (year 6 HbA1C – baseline HbA1C) was calculated and dichotomized: > 0.5% representing worsening of glycemic control and < 0.5% serving as the reference level. The cut point of 0.5% was selected because diabetes, cardiovascular and mortality risk have been shown to increase with 0.5 unit increases of HbA1C level. 20-22

To examine the relationship of demographic factors, cancer characteristics, lifestyle factors and other health measures with long-term glycemic control, variable means and frequencies were computed and compared using F-tests and chi-square tests, respectively. Three logistic regression models were constructed to evaluate the independent effects of PA (model 1), weight gain (model 2) and obesity (model 3). A

fourth logistic regression model was constructed which included all lifestyle risk factors simultaneously. Covariates were assessed for inclusion into these multivariate models if they were associated with the risk factor of interest and modified the corresponding magnitude of association by > 10%. Baseline HbA1C was not included as a covariate due to multicollinearity as determined by box plots of baseline HbA1C by baseline obesity status which showed insufficient overlap of baseline HbA1C distributions between the obese versus non-obese. Age, race/ethnicity, and education were included in all of the multivariate models based on apriori selection.

To assess whether adherence to PA guideline or weight gain had a differential effect on glycemic control by obesity, interaction terms were tested using exact logistic regression but were not statistically significant and thus not included in the multivariate model.

To investigate the relationship between weight and PA level over time, a plot was constructed with mean PA levels at each of the 5 time points stratified by the obesity-weight gain composite variable. Differences in mean values were tested for statistical significance using F-tests. All statistical tests were two-tailed and analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Worsening glycemic control

Seventeen percent (n=317) of women in this sample experienced a worsening of glycemic control as defined by a 0.5 unit increase or greater in HbA1C level from

baseline to year 6. The mean baseline HbA1C level of these women was 5.5 (0.5) and the mean HbA1C level at year 6 was 6.3 (0.9). The remaining 83% (n=1547) of women whose HbA1C level increased < 0.5 units had a mean baseline HbA1C level of 5.7 (0.6) and an unchanged mean value of 5.7 (0.5) at year 6. Table 1 presents comparisons of sample characteristics by category of HbA1C change (> 0.5% versus < 0.5%). Although the prevalence of self-reported diabetes at study entry did not differ (both < 2%), there was a statistically significantly higher percentage of self-reported diabetes at year 6 in women whose HbA1C level increased > 0.5 units versus < 0.5 units (9% versus 3%, p<0.0001). Similarly, the prevalence of high cholesterol at study entry was not statistically significantly different between women whose HbA1C level increased > 0.5 versus <0.5 units (5.9% versus 7.5%, p=0.31); while there was a statistically significantly greater percentage of high cholesterol at year 6 in women whose HbA1C level increased > 0.5 versus < 0.5 units (20.8% versus 29.6%, p<.001). There was a statistically significantly higher prevalence of hypertension at baseline and year 6 in women who experienced HbA1C increase > 0.5% versus < 0.5% (19.4% versus 12.1% at baseline; 21.7% versus 33.9% at year 6; both p-values < .001).

Worsened glycemic control was not associated with any of the demographic variables or cancer characteristics (p>0.05). All lifestyle factors (physical activity, weight gain and obesity) were statistically significantly associated with worsened glycemic control (p < 0.01). Specifically, women whose HbA1C levels increased > 0.5% versus < 0.5% were more likely to be obese at study entry, not meet PA guidelines and experience weight gain of 5% or more over the 6 years of study follow-up. The mean percentage

gain nearly doubled for women whose HbA1C levels increased > 0.5% versus 0.5% (5.4 versus 2.3, p<.0001).

Odds ratios and corresponding confidence limits derived from four logistic regression models of glycemic control and lifestyle risk factors are presented in Table 2. All models adjusted for age, race/ethnicity, and education. Model 1 shows that women who did not adhere to PA guidelines were at a 40% increased risk of worsened glycemic control (p=.03). Model 2 shows that women who gained 5% or more of their baseline weight were at 1.88 times greater risk of worsened glycemic control (p<.0001). Model 3 shows that women who were obese at study entry were at 1.98 times greater risk of worsened glycemic control (p<.0001). Model 4, inclusive of all lifestyle risk factors, shows the association between PA level and worsened glycemic control was highly attenuated after adjustment of obesity and weight gain (OR = 1.11; 95% CI: 0.86-1.44) while obesity and weight gain remained strongly associated with worsened glycemic control (p<0.0001). Specifically, women who were obese at study entry were 2.02 times more likely to have worsened glycemic control by year 6 compared to women who were not obese at study entry (p < 0.0001). Likewise, women who gained 5% or more of their baseline body weight over 6 years of follow-up were 1.97 times more likely to have worsened glycemic control compared to women who gained < 5% (p < 0.0001).

Figure 1 plots the mean values of PA levels (MET-hr/week) reported at each study visit stratified by the composite variable of obesity and weight gain. Non-obese women that gained < 5% of their baseline weight represented the largest number of women (n=902, 48.4% of the total sample) followed by non-obese women that gained

>5% (28.4%, n=530), obese women that gained < 5% (16.1%, n=300) and obese women that gained >5% (7.1%, n=132). Large differences in PA levels were observed between non-obese and obese women from baseline through year 6 ($p<.0001$). Among non-obese women, baseline PA level did not statistically significantly differ at study entry according to weight gain status ($p>.05$); however, PA levels from years1-6 were statistically significantly lower in women who gained >5% of their baseline weight compared to women who gained <5% ($p<.05$). Among the obese, PA levels did not statistically differ according to weight gain status from baseline through year 4 ($p>.05$). However, as figure 1 depicts with the non-overlapping standard error bars, there was marginal statistical significance at year 6. Specifically, obese women that gained >5% weight reported 3.5 fewer MET-hours/week compared to obese women that gained <5%, with a 95% confidence limit of -7.6 to 0.5 MET-hours/week. Also depicted in figure 1, obese women that gained >5% of their baseline weight tended to steadily decrease their PA level after year 1, dropping below the recommended PA guidelines after year 3.

DISCUSSION

After adjustment for demographic and lifestyle factors, obesity and weight gain > 5% remained strongly and independently associated with worsened long-term glycemic control, both conveying approximately twice the magnitude of risk relative to their respective comparison groups of non-obese women and women gaining < 5% weight over the 6 years of follow-up. However, after adjustment for obesity and weight gain, the association of physical inactivity and worsened glycemic control was attenuated and lost statistical significance. Similar findings of attenuation have been reported in the Nurses'

Health Study (NHS), [23] and may be attributed to several factors. For instance, it is possible to the extent that physical activity causes individuals to have lower BMI, adjustment for BMI in regression models may constitute statistical overcorrection and result in underestimation of the true beneficial effect of physical activity. Furthermore, overweight and obese people are less likely to engage in physical activity, because excess body weight may increase the difficulty of physical activity. This self-selection of heavy subjects for lower physical activity levels could account in part for the attenuation of the physical activity–diabetes relationship in regression models that include adjustment for BMI. Given that supporting evidence continues to accumulate that physical activity reduces chronic disease risk both directly through its impact on hormones and indirectly through its impact on weight control,[24] caution should be undertaken when simultaneously adjusting for physical activity and weight-related factors in multivariate models of health risk.

To our knowledge this was the first study to measure long-term change in glycemic control in relation to physical inactivity, weight gain and obesity—all of which are major lifestyle risk factors known to be prominent among breast cancer survivors.

Factors that may affect the generalizability of our study findings are the high proportion of white women represented and the exclusion of women who died or experienced a breast cancer event before year 6 of WHEL Study follow-up. It is also possible that self-selection bias was present given that the sample was comprised of a subcohort of women participating in a healthy dietary intervention study. Strengths of our study include clinically measured weight and biologically measured glycemic control

over six years of survivorship follow-up. Another strength was the assessment of PA level at five time points, allowing us to assess the potential effect of PA levels averaged over six years of follow-up. However, a limitation of the PA data was that it was based on self-report, which is known to include random error. However, the study used a standardized PA recall procedure and an objective PA measure (7-day accelerometer) within a subset of WHEL Study participants. [15] The PA questionnaire had strong agreement (73%) with the accelerometer measure and had 100% sensitivity for meeting the PA guideline.

In conclusion, our results show that obesity and weight gain are strongly associated with significant worsening of long-term glycemic control among breast cancer survivors. Given that a high proportion of breast cancer patients are concomitantly sedentary and obese/overweight, clinical trials are needed to investigate whether increased physical activity in combination with reduced adiposity can prevent or delay diabetes incidence as well as improve long-term prognosis.

Chapter 4 is currently being prepared for the submission for the publication of the material. Kirsten Erickson, Ruth E. Patterson, Loki Natarajan, John P. Pierce. The dissertation author was the primary investigator and author of this material.

REFERENCES

1. Knowler WC, Barrett-Connor E, Fowler SE, et al: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393-403, 2002

2. Pan XR, Li GW, Hu YH, et al: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 20:537-44, 1997

3. Tuomilehto J, Lindstrom J, Eriksson JG, et al: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 344:1343-50, 2001

4. Berglund G, Bolund C, Fornander T, et al: Late effects of adjuvant chemotherapy and postoperative radiotherapy on quality of life among breast cancer patients. Eur J Cancer 27:1075-81, 1991

5. Bower JE, Ganz PA, Desmond KA, et al: Fatigue in breast cancer survivors: occurrence, correlates, and impact on quality of life. J Clin Oncol 18:743-53, 2000

6. Herman DR, Ganz PA, Petersen L, et al: Obesity and cardiovascular risk factors in younger breast cancer survivors: The Cancer and Menopause Study (CAMS). Breast Cancer Res Treat 93:13-23, 2005

7. Michael YL, Kawachi I, Berkman LF, et al: The persistent impact of breast carcinoma on functional health status: prospective evidence from the Nurses' Health Study. Cancer 89:2176-86, 2000

8. Blanchard CM, Courneya KS, Stein K: Cancer survivors' adherence to lifestyle behavior recommendations and associations with health-related quality of life: results from the American Cancer Society's SCS-II. J Clin Oncol 26:2198-204, 2008

9. Courneya KS, Katzmarzyk PT, Bacon E: Physical activity and obesity in Canadian cancer survivors: population-based estimates from the 2005 Canadian Community Health Survey. Cancer 112:2475-82, 2008

10. Irwin ML, Crumley D, McTiernan A, et al: Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer 97:1746-57, 2003

11. Irwin ML, McTiernan A, Bernstein L, et al: Physical activity levels among breast cancer survivors. Med Sci Sports Exerc 36:1484-91, 2004

12. Pierce JP, Natarajan L, Caan BJ, et al: Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. JAMA 298:289-98, 2007

13. Pierce JP, Faerber S, Wright FA, et al: A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials 23:728-56, 2002

14. Bertram LA, Stefanick ML, Saquib N, et al: Physical activity, additional breast cancer events, and mortality among early-stage breast cancer survivors: findings from the WHEL Study. Cancer Causes Control 22:427-35

15. Johnson-Kozlow M, Rock CL, Gilpin EA, et al: Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. Am J Health Behav 31:193-202, 2007

16. Bantle JP, Wylie-Rosett J, Albright AL, et al: Nutrition recommendations and interventions for diabetes--2006: a position statement of the American Diabetes Association. Diabetes Care 29:2140-57, 2006

17. Doyle C, Kushi LH, Byers T, et al: Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 56:323-53, 2006

18. Kushi LH, Byers T, Doyle C, 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 56:254-81; quiz 313-4, 2006

19. Colberg SR, Sigal RJ, Fernhall B, et al: Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary. Diabetes Care 33:2692-6

20. Erickson K, Patterson RE, Flatt SW, et al: Clinically defined type 2 diabetes mellitus and prognosis in early-stage breast cancer. J Clin Oncol 29:54-60

21. Selvin E, Steffes MW, Zhu H, et al: Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 362:800-11

22. Cheng P, Neugaard B, Foulis P, et al: Hemoglobin a1c as a predictor of incident diabetes. Diabetes Care 34:610-5

23. Hu FB, Manson JE, Stampfer MJ, et al: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345:790-7, 2001

24. Eyre H, Kahn R, Robertson RM: Preventing cancer, cardiovascular disease, and diabetes: a common agenda for theAmerican Cancer Society, the American Diabetes Association, and the American Heart Association. CA Cancer J Clin 54:190-207, 2004

Table 4.1 Characteristics of WHEL participants (N=1864) stratified by change in A1C level [a]

	Δ HbA1C < 0.5%		**Δ HbA1C ≥ 0.5%**		***p***
	N	**Mean (SD) or %**	**N**	**Mean (SD) or %**	
Demographic characteristics					
Age, mean (SD)	1547	53.6 (8.6)	317	52.8 (8.6)	.16
Age group (%)					
<44	207	13.4%	48	15.1%	.23
45-54	666	43.1%	131	41.3%	
55-65	511	33.0%	115	36.3%	
>65	162	10.5%	23	7.3%	
Race/ethnicity					
Non-Hispanic White	1341	86.7%	269	84.9%	.09
African American	54	3.5%	11	3.5%	
Hispanic-American	73	4.7%	10	3.2%	
Asian-American	47	3.0%	19	6.0%	
Other	31	2.0%	8	2.5%	
College graduate (%)	882	57.1%	172	54.3%	.36
Cancer history characteristics					
Tumor stage (%)					
I	666	43.0%	138	43.5%	.96
II	695	45.0%	140	44.2%	
III	185	12.0%	39	12.3%	
Chemotherapy (%)	1019	66.0%	221	69.7%	.20
Tamoxifen use (%)	558	36.1%	105	33.1%	.31
Lifestyle factors					
Smoking status					
Never	889	57.5%	197	62.1%	.61
Former	524	33.9%	103	32.5%	

Table 4.1 continued

	Δ HbA1C < 0.5%		**Δ HbA1C ≥ 0.5%**		***p***
	N	**Mean (SD) or %**	**N**	**Mean (SD) or %**	
Current	133	8.6%	17	5.4%	
Alcohol (%)					
0	889	57.5%	197	32.1%	.11
1-19 g/day	354	22.7%	71	22.4%	
20+ g/day	303	19.8%	49	15.5%	
Physical activity level [b], MET-	1547	15.7 (12.7)	317	13.9 (12.4)	.02
Not meeting PA guidelines (%)	168	40.2%	149	47.0%	.03
BMI at study entry, mean kg/m^2	1547	26.6 (5.6)	317	28.0 (6.1)	<.0001
BMI at study entry (%)					
<25.0	720	46.5%	118	37.2%	<.0001
25-29.9	503	32.5%	91	28.7%	
≥ 30.0	324	21.0%	108	34.1%	
Weight gain [c], mean (SD)	1547	2.3 (9.3)	317	5.4 (10.1)	<.0001
Weight gain [c] ≥ 5% (%)	510	33.0%	152	48.0%	<.0001
Comorbidities (self-report)					
	Events		**Events**		
Diabetes (%)					
Baseline*	15	1.2%	5	1.8%	0.43
Year 6*	43	2.9%	28	9.1%	<.0001
Hypertension (%)					
Baseline*	152	12.1%	54	19.4%	<.001
Year 6*	324	21.7%	104	33.9%	<.0001
High cholesterol (%)					
Baseline*	74	5.9%	21	7.5%	.31
Year 6*	311	20.8%	91	29.6%	<.001

PA = physical activity
[a] HbA1C% change calculated as: (year 6 HbA1C – baseline HbA1C)
[b] Physical activity level calculated by averaging reported levels (MET-hr/wk) baseline to year 6
[c] Weight gain calculated as: ((year 6 weight – baseline weight)/baseline weight*100)
* denotes missing data, denominator in percentage calculation is less than n=1547 or n=317 in respective categories

Table 4.2 Logistic regression models of HbA1C increase ≥ 0.5% over 6 years of follow-up, The WHEL Study (n=1864)

	β	SE	OR (95% CI)	*p*
Model 1. Physical Activity +				
Age at study entry (yrs)				
< 44	reference		1.0	.29
45-54	-0.04	0.10	0.81 (0.55,1.19)	
55-65	0.10	0.11	0.93 (0.62,1.39)	
>65	-0.24	0.16	0.65 (0.39,1.01)	
Race/ethnicity				
White, non-Hispanic	reference		1.0	.54
Nonwhite	0.05	0.06	1.18 (0.84,1.67)	
College graduate				
Yes	reference		1.0	.55
No	0.04	0.06	1.12 (0.88,1.43)	
Physical activity [a]				
Meeting guidelines	reference		1.0	.03
Not meeting guidelines	0.13	0.06	1.31 (1.10,1.67)	
Model 2. Weight gain +				
Age at study entry (yrs)				
< 44	reference		1.0	.28
45-54	-0.06	0.10	0.85 (0.58,1.24)	
55-65	0.15	0.11	1.04 (0.69,1.56)	
>65	-0.21	0.16	0.73 (0.44,1.21)	
Race/ethnicity				
White, non-Hispanic	reference		1.0	.34
Nonwhite	0.08	0.09	1.18 (0.84,1.67)	
College graduate				
Yes	reference		1.0	.37
No	0.06	0.06	1.12 (0.88,1.43)	
Weight gain [b]				
< 5%	reference		1.0	<.0001
≥ 5%	0.32	0.06	1.88 (1.47,2.41)	
Model 3. Obesity + covariates				
Age at study entry (yrs)				

Table 4.2 continued

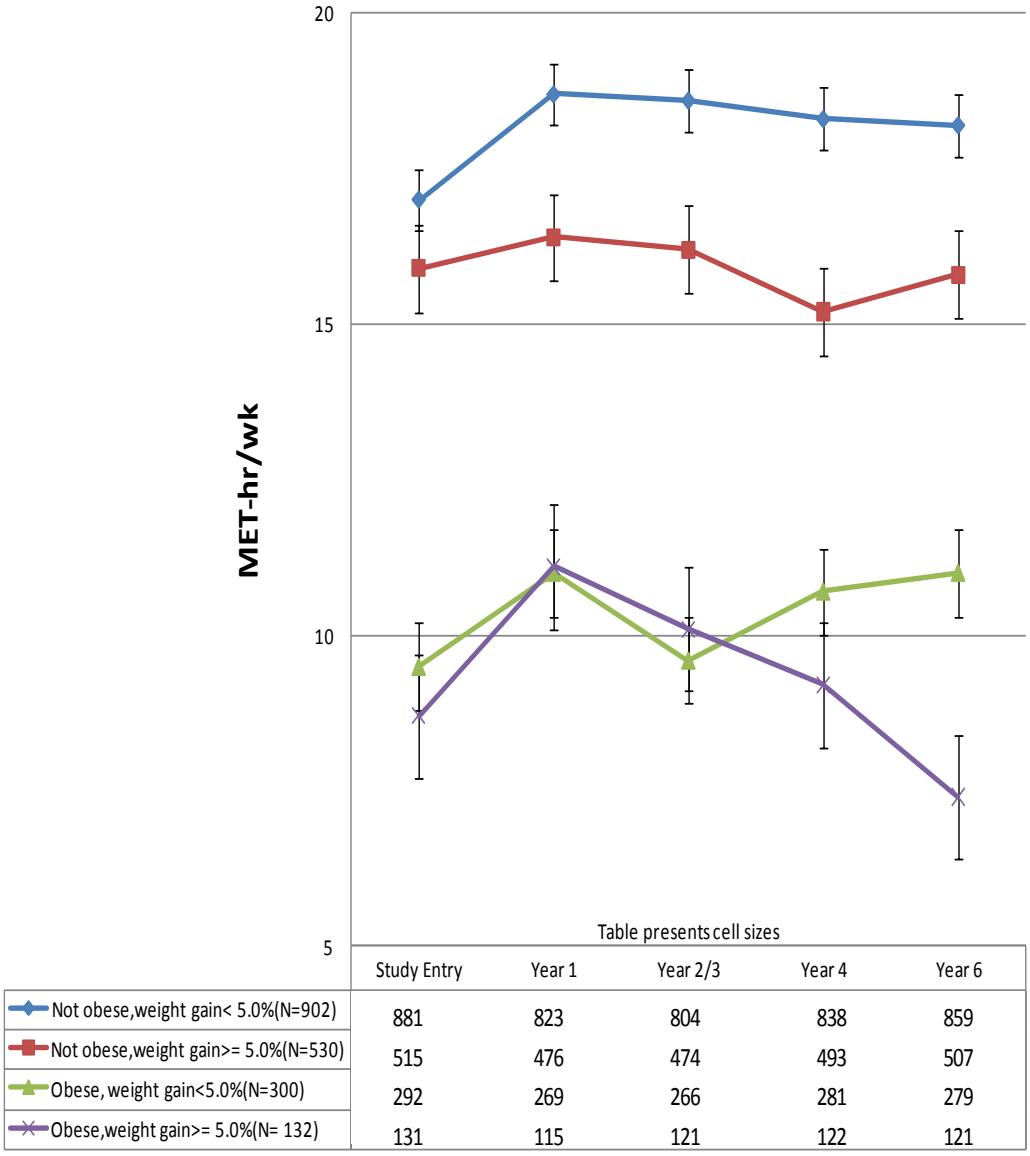
	β	SE	OR (95% CI)	*p*
< 44	reference		1.0	.15
45-54	-0.05	0.10	0.73 (0.50,1.07)	
55-65	0.08	0.11	0.83 (0.6,1.24)	
>65	-0.29	0.16	0.58 (0.35,0.96)	
Race/ethnicity				
White, non-Hispanic	reference		1.0	.60
Nonwhite	0.05	0.09	1.10 (0.78,1.55)	
College graduate				
Yes	reference		1.0	.71
No	0.02	0.06	1.05 (0.81,1.34)	
Obese at study entry				
No	reference		1.0	<.0001
Yes	0.34	0.07	1.98 (1.52,2.59)	
Model 4. PA, weight gain,				
Age at study entry (yrs)				
< 44	reference		1.0	.26
45-54	-.07	.10	0.81 (0.55,1.21)	
55-65	.14	.12	1.01 (0.67,1.51)	
>65	-.21	.16	0.70 (0.42,1.18)	
Race/ethnicity				
White, non-Hispanic	reference		1.0	.48
Nonwhite	.06	.09	1.13 (0.80,1.61)	
College graduate				
Yes	reference		1.0	.87
No	.01	.06	1.02 (0.79,1.32)	
Physical activity [a]				
Meeting guidelines	reference		1.0	.42
Not meeting guidelines	.05	.06	1.11 (0.86,1.44)	
Weight gain [b]				
< 5%	reference		1.0	<.0001
≥ 5%	.34	.06	1.97 (1.53,2.53)	
Obese at study entry				
No	reference		1.0	<.0001
Yes	.35	.07	2.02 (1.53,2.66)	

PA=Physical Activity

Table 4.2 continued

[a] Physical activity level calculated by averaging reported levels (MET-hr/wk) from baseline through year 6. Meeting guidelines defined as > 10 MET-hr/wk which equates to 150 minutes/week of moderate-pace walking or the equivalent amount of other exercise durations/intensities

[b] Weight gain calculated as: ((year 6 weight – baseline weight)/baseline weight*100)



Error bars = standard error of the mean

Figure 4.1 Mean physical activity level (MET-hr/wk) reported at each WHEL Study visit, stratified by weight-related composite risk variable (N=1864)

CHAPTER 5

Discussion

DISCUSSION

With the increasing incidence of diabetes and the growing population of breast cancer survivors, improved understanding of the diabetes and breast cancer association is paramount. Investigation into the long-term prognostic impact of diabetes on breast cancer survivorship and into the modifiable risk factors that can prevent or delay diabetes occurrence is necessary to provide evidence which may guide clinicians involved in the follow-up care of women who have a breast cancer history.

The objectives of this dissertation were to: 1) assess the effects of prevalent diabetes on breast cancer disease-free survival and overall survival, 2) assess the effects of pre-cancer body mass index (BMI) and post-diagnosis weight change on the risk of incident diabetes and 3) assess the effects of physical inactivity, weight gain, and obesity on long-term worsening of glycemic control.

Summary of findings

Study #1: Clinically Defined Type 2 Diabetes Mellitus and Prognosis in Early Stage Breast Cancer

Consistent with the literature, this study found that diabetes was independently associated with a statistically significant higher risk of all-cause mortality in breast cancer survivors. However, measured HbA1C more than doubled the number of women with diabetes compared to self-report identification and inclusion of these undiagnosed diabetes cases attenuated the previously identified diabetes association with additional breast cancer events. Given that a diagnosis of type 2 diabetes is most likely to occur in women experiencing symptoms, it is likely that women with self-reported diabetes had

longer disease duration and a history of worse glycemic control than those identified by HbA1C assays. Thus, these study results could reflect the effect of severity or duration of diabetes on the risk of additional breast cancer events. Supporting this hypothesis, we found that women who reported taking blood sugar lowering medications for their diabetes (presumably reflective of more advanced disease) carried the highest risk of additional breast cancer events and mortality. These findings address one of the current gaps in evidence as outlined in the 2010 ADA/ACS consensus report: "whether cancer risk [prognosis] is influenced by duration of diabetes is a critical and complex issue and may be further complicated by multidrug therapy often necessary for diabetes treatment".

Although our study suggests that diabetes duration is an important factor in breast cancer prognosis, the results do not provide definitive evidence. Our findings also suggest that HbA1C may be associated with breast cancer prognosis in a nonlinear fashion, that is, a threshold effect may exist in the diabetic range of HbA1C levels >7.0%, and in individuals considered at very high risk for diabetes (those who are obese and have clinically elevated HbA1C in addition to at least one other risk factor for diabetes). Thus, future research should investigate whether there is a threshold of glycemic status at which the risk for poor prognosis significantly increases and assess whether the increased mortality risk among breast cancer survivors with diabetes is driven by an increase in cancer recurrence or due to competing diabetes-related comorbidities such as cardiovascular disease.

Study #2: Obesity, Weight Change, and Diabetes Risk in Breast Cancer Survivors

To our knowledge this was the first study to measure diabetes risk in a large cohort of breast cancer survivors, using HbA1C in addition to self-report to identify incident diabetes. This study provided new evidence that women who experience major weight gain after breast cancer diagnosis or major weight loss with subsequent regain are at twofold greater risk of becoming diabetic than women who maintain their pre-cancer weight. Although previous studies have reported that weight loss after a breast cancer diagnosis is associated with increased mortality, those same studies show that women who were obese at diagnosis (BMI ≥30 kg/m2) were the most likely to be in the large weight loss group. None of these reports included information on whether the observed weight loss was maintained. In this report, we were able to utilize multiple post-diagnosis weight measures to address this issue. Specifically, our study data indicate that women who lost significant weight in the early years following their diagnosis were overweight or obese before diagnosis and regained the weight in the additional years of follow-up. Both high initial weight and weight gain are negative prognostic factors for diabetes development and other competing comorbidities that threaten overall survival time. Our findings corroborate studies that have shown the process of recovering large amounts of body weight is itself an independent risk factor for the development of diabetes, especially when the patient is overweight or obese before the weight loss and regain occurs.

As reported in the first study of this dissertation and in other literature, diabetes is known to be associated with reduced survival in breast cancer survivors. Moreover, we found that a threshold effect may exist between clinically elevated HbA1C levels and adverse breast cancer outcomes. The second study of this dissertation provides new

insight into the relationship between pre-cancer weight, post-diagnosis weight change, and diabetes risk. Although further research is needed to validate the adverse effects of major weight loss-regain on diabetes risk in breast cancer survivors, these data suggest that oncologists should monitor patients for weight gain during and after cancer treatment to guard against diabetes development which may, in turn, improve long term prognosis.

Study#3: Long-term Worsening of Glycemic Control in Breast Cancer Survivors: How Physical Inactivity, Weight Gain and Obesity Impact Risk

The study showed that physical inactivity was independently associated with worsened long-term glycemic control as defined by a 0.5 unit increase in HbA1C levels over 6 years of follow-up. However, after adjustment for obesity and weight gain, the association of physical inactivity and diabetes risk was attenuated and lost statistical significance. This represents an important finding that needs to be investigated further. It is possible that adjustment for BMI in regression models may constitute statistical overcorrection and result in underestimation of the true beneficial effect of physical activity. Given that supporting evidence continues to accumulate that physical activity reduces chronic disease risk both directly through its impact on hormones and indirectly through its impact on weight control, caution should be undertaken when simultaneously adjusting for physical activity and weight-related factors in multivariate models of health risk.

Unlike physical inactivity, obesity and weight gain > 5% remained strongly and independently associated with worsened long-term glycemic control, both conveying

approximately twice the magnitude of risk relative to their respective comparison groups of non-obese women and women gaining < 5% weight over the 6 years of follow-up.

To our knowledge this was the first study to measure diabetes risk in terms of worsening glycemic control and in relation to major lifestyle risk factors known to be prominent among breast cancer survivors. Given that a high proportion of breast cancer patients are concomitantly sedentary and obese/overweight, clinical trials are needed to investigate whether increased physical activity in combination with reduced adiposity can prevent or delay diabetes incidence as well as improve long-term prognosis.

Implication of findings

With the vast majority of breast cancer patients surviving more than 5 years beyond diagnosis, oncologists are challenged to expand their focus from acute care to managing the long-term health consequences of breast cancer. Although more research is needed, opportunities exist for oncologists to promote lifestyle changes that may improve the length and quality of life of their patients.

Diabetes, hyperglycemia and associated metabolic disorders can be controlled and may present an effective opportunity for improving prognosis in early-stage breast cancer survivors. Given the high prevalence of physical inactivity, weight gain and obesity in breast cancer survivors and their effects on diabetes risk, randomized controlled clinical trials of interventions targeting weight management through increased physical activity are needed, particularly among women who are overweight/obese and/or experience significant weight gain after breast cancer.