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The purpose of the study is to observe the relative contribution of thyroid function, sex-hormonal levels, physical activity, psychological state and nutritional intake on changes in body weight in a group of breast cancer patients, receiving adjuvant chemotherapy.
Based on the preliminary observations, weight gain in breast cancer patients may be a phenomenon resulting from hormonal and lifestyle changes and offers an opportunity for prevention and improved prognosis.

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Introduction:

Weight Gain in Breast Cancer Patients on Chemotherapy

It is estimated that over 182,800 new cases of female breast cancer will be diagnosed in the United States in 2000 and 41,200 will die of this disease.[1] Most of these patients will be diagnosed with stage I or II disease, and a significant proportion of these women will be treated with chemotherapy in addition to surgery and/or radiation therapy. Although the benefits of adjuvant chemotherapy and radiation therapy are well established, and although several side effects such as cancer cachexia challenge the health professionals, one of the most distressing side effect as reported by patients is weight gain.[2-8] Weight gain in this population may prove to be a more serious side effect than others, since it can not only decrease quality of life but may potentially increase rate of recurrence and threaten long-term survival.[7, 9-11] The impact of weight gain may be even more profound, because it may predispose women to heart disease, diabetes, gall bladder disease, endometrial cancer and orthopedic disturbances. These chronic illnesses may pose a greater concern, since women with early stage breast cancer will be cured of the disease but may suffer long term negative consequences as a result of treatment.

Prevalence and Magnitude of Weight Gain in Breast Cancer Patients During Chemotherapy: Weight gain, anywhere from 5-50lbs in breast cancer patients receiving adjuvant therapy has now been documented consistently for the past two decades.[12-13] Significant weight gain occurred in 50-96% of all breast cancer patients receiving adjuvant chemotherapy[3] irrespective of stage of disease, more so among premenopausal women compared to post menopausal women.[9] In addition, significant gain in weight has been observed in patients receiving prednisone as a chemotherapeutic regimen[14-15] or when multiple agents are used[10, 12] compared to single agent therapies. Bonadonna et al found that longer duration of chemotherapy increased the total amount of weight gained[16] and oral agents produce greater weight gains than infusion-based therapies.[17]

Consequences of Weight Gain: More recent findings suggest that obesity at time of diagnosis is an adverse prognostic indicator even after the administration of chemotherapy.[18] We and other have observed that obesity in postmenopausal node positive patients was a negative prognostic indicator[15, 19] and the risk for disease recurrence among obese patients was 1.33-1.5 times that of the non-obese population.[9, 18] Camoriano, in addition reported 1.6 times greater risk of death in premenopausal women who gained weight.[9]

Possible Mechanisms: While the cause of weight gain in breast cancer patients remains unknown it, is most likely a result of several contributing factors. Some proposed explanations include psychological factors such as change in coping mechanisms leading to a change in eating behavior, change in activity level due to fatigue or disruption of normal lifestyle, hormonal changes, and the metabolic effects of chemotherapy or radiotherapy.

Purpose:

The purpose of this study is to prospectively and systematically observe the relative contribution of each viable mechanism such as nutritional intake, activity levels, body composition, hormonal function, thyroid function, coping mechanisms and fatigue scores on weight gain in breast cancer patients on chemotherapy.

Objectives

Specific Aim 1: To characterize the severity and course of weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 2: To examine the impact of chemotherapy-induced change in activity levels on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 3: To examine the effect of chemotherapy-induced hyperphagia on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 4: To examine the effect of chemotherapy-induced sex-hormone level changes on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 5: To examine the effect of chemotherapy-induced change in thyroid function on weight gain among women undergoing adjuvant chemotherapy.
Specific Aim 6: To systematically investigate the relative contribution of thyroid function, sex-hormonal levels, physical activity, body composition, psychological state and nutritional intake on changes in body weight in a group of pre-menopausal and post-menopausal stage I-III breast cancer patients, receiving adjuvant chemotherapy.

Key Research Accomplishments:

As planned and described in the Statement of Work, Task 1 of recruitment and data collection and Task 2 - abstraction of Medical record data during months 1-36, of which months 0-36 is currently reported, has been successful, thus far. The first two months of the study was spent organizing (a) Instruments and procedures to be used in the study, (b) Consent form and procedures, (c) establishing procedures for recruitment from various medical oncology clinics at the cancer Center, (d) timely, safe blood draws thus preventing duplication of draws, (d) preventing any additional patient visit to the center, (e) collaboration with lab to plan for safe, accurate and timely handling of blood and transport.

Task 1: Subject Recruitment: The patient sample selected for the study is to include a total of 200 consecutive pre-menopausal and post-menopausal patients recruited over a 36 month period, with primary, operable, Stage I to IIIB, axillary lymph node positive and negative breast cancer patients who have consented to be treated using one of two adjuvant or systemic chemotherapy protocols at the H. Lee Moffitt Cancer Center & Research Institute during the study period. Women, of all races and ethnicity, between ages 25 and 75, and breast cancer patients who will receive at least 75% Cytoxan, Methotextrate, 5FU (CMF), Cytoxan, Cytoxan, Adriamycin and 5FU(CAF) or Cytoxan and Adriamycin (CA) chemotherapy regimens with or without radiation therapy at first screening contact will be admitted to the study. Currently 195 subjects have been recruited, of whom 183 have completed the 6 month treatment/observation phase of the study, and an additional 17 subjects are currently active in this protocol. As predicted we had eighteen (22) dropouts in the study, fourteen (14) were unable to complete their activity records, three(3) of whom did not wish to participate, five (5) too ill to complete monitors. We have thus successfully recruited almost 195/200 of the sample planned for the study, in a period of 36 months. We have requested a no-cost extension, which was approved, in order that the final and 6 month follow-up data collection on the remaining subjects could be completed.

Data Collection: Upon recruitment, and upon receiving consent from subjects, the following data were collected, as planned:

1.Confirmation of the accuracy of eligibility information, including the using an initial screening form.
2.Demographic information, personal and medical history, hormonal and reproductive history, exercise, smoking and alcohol use history will be obtained by an RD using the Epidemiological Questionnaire.
3.Anthropometric measurements such as subject's height, weight, skinfolds and circumference measurements.
4.Twenty (20) ml of blood will be drawn into heparinized tubes in a non-fasting state at the same time of day, between 7:00 AM and 12:00 noon, for each individual to obtain 10 ml of serum for analysis of total and free estradiol, sex-hormone binding globulin, thyroid binding globulin assessment for T3 uptake.
5.Subjects will be asked to complete a self-administered version of the Stanford-five city Project Questionnaire to monitor Activity Levels.
6. Standard 2-day diet record(TDFR).
7. Menstrual histories will be obtained from all peri- and pre-menopausal subjects. This information will be recorded on the FDFR.
8.The Profile of Mood States Fatigue Subscale (POMS-F), a scale to measure fatigue (Appendix 6) will be used to quantify fatigue in these subjects.[37]
9.The Ways of Coping Checklist (WOCC) consists of 66 items that describe a broad range of cognitive and behavioral strategies people use to manage internal and/or external demands in specific stressful encounters defined here as breast cancer treatment, will be used.[38]

We have observed that several patients have had difficulty completing the 4-day food records during the 3 to 4 chemotherapy treatments. During those situations, the research team has been able to obtain a 24-hour recall or a 2-day record of intake from the patient or a family member. Apart from this instrument, we have had excellent compliance to completion of serial information from our breast cancer patients.

Task 2: Abstraction of Medical Record Data:
Upon completion of the study, data regarding patient's disease related prognostic indicators is currently being extracted from their medical chart. Quality control procedures for data collection and abstraction have been ongoing. We are currently continuing to obtain information on tumor size, ER/PR positivity, DNA ploidy status and proliferative indices such as Ki-67, which are routinely available for this group of patients. Abstraction of medical records data has been completed for 170/195 patients, who have completed the observational period of the study.

Nutritional Intervention in Patients post completion of the study period:
As reported in our initial report, upon completion of the study, we have felt the need for and have had several requests from medical oncologists and patients for continued follow-up of patients who have gained weight during chemotherapy. We have established a structured "Moffitt Weight Management Program", which is currently offered as a pilot program, specifically for this post-treatment Breast Cancer Patient group to enable them to successfully manage weight, post-treatment. The program includes 8-1 hour sessions and incorporates body composition and nutritional analysis, Behavior Management, Assessing fitness and incorporating physical activity and improving food choices towards long-term weight management. This program has also

included clientile from the Lifetime Cancer Screening Program, include those women who have been genetically screened as high risk for breast cancer.

Task 3: Data Entry & Analysis:
Data entry has been initiated since November 1999 and all pertinent data with regard to patients who have completed the study to date have been entered into this data bank. Quality control procedures for data entry continues to be applied, as planned. Preliminary results were analyzed in September 2001. It is anticipated that all data collection will be complete in February of 2002 with the remaining patients completing treatment.

Results:
To date, 195 subjects have been recruited, of whom 183 have completed the 6 month treatment/observation phase of the study, and an additional 17 subjects are currently active in this protocol. Preliminary data analysis of one hundred and eighty three (183) subjects who were recruited during the 36 months of the study was completed. We have requested a no-cost extension to complete observation and analysis of the 17 remaining subjects.

Preliminary data on 183 (out of 200 anticipated) patients are reported at this time. The demographic data of the patient population is described in Table 1. The average age of this group of consecutively recruited breast cancer patients was 49.65 (SD 9.93). The population was predominantly(88%) with 12% other minority groups in the Tampa Bay area. The most significant observation was the high percentage (72%) of current smokers and smokers with a history of smoking an average of 5.27(SD 10.77) packyears. We have observed this in our previous studies where over 50% of breast cancer patients were smokers.The baseline weight and body mass index in this group of women were below normal ranges observed in the American population.

Patient characteristics with regard to stage of disease and chemotherapy is provided in Table 2. Most patients were Stage I or II cancers (95%) with patients with stage II breast cancer (65%)being the most predominant group receiving Cytoxan/Adriamycin (62%). Reproductive profiles of this patient population is presented in Table 3. Forty percent (40.2%) were post menopausal with 32.3% on hormone replacement therapy. Sixty (60.3%) used birth control pills. Weight gain and change in activity level, resulting from fatigue are displayed in Table 4. Weight gain of over 5lbs was observed in over 20% of the patient population during chemotherapy. Over 30% of the patient population demonstrated a significant decrease in the average hours worked (> 5 hours/week) and 47% of subjects reported fatigue. Change in steroid hormonal and thyroid hormone markers is presented in Table 5. Free and total estradiol levels decreased significantly (<0.0001) in this group from start to end of chemotherapy. Of the 59.8% who were premenopausal prior to therapy, 76% were amenorrheic post therapy. Sex-hormone binding globulin significantly (<0.0001) increased in this population from baseline to post therapy. Serum total triiodothyronine-3 (T3) levels decreased significantly in this population from baseline to post chemotherapy(p=0.07). This marked decrease was observed in 58% post chemotherapy indicative of lowering thyroid function. The baseline mean serum total T3 levels in the breast cancer patient population in this study was 1.04 nmol/L, which is lower than the ranges reported in normal adults as well as diabetic patients by Hansen et al(1999),[19] decreasing

further to 0.98 nmol/L after chemotherapy. Normal serum T3 resin uptake levels in the adult are 1.2 – 2.9 nmol/L. Serum T3 levels are normally low in hypothyroidism, similar to what we observed in this patient group. In addition, for every 4-5 patients recruited in this clinical trial, one (1) was not entered in the study because the subject had a diagnosis of hypothyroidism at entry and were on thyroid hormone therapy. Patients on thyroid hormone therapy were excluded from our study. Thus 20-25% of the breast cancer population were hypothyroid and on treatment at diagnosis, even prior to chemotherapy compared to 8-10% who may be subclinically hypothyroid [20] in the general population.

Reportable Outcomes:

Preliminary results of this study has been presented as an abstracts, poster session or plenary sessions in the following National and International Meetings:

1. Kumar NB, Riccardi D, Allen K, Cantor A, Jacobsen P. Horton J, Minton S, Balducci & Lyman GH. Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal, Body Composition and Behavioral Mechanisms. Proc of the US Army Breast Cancer research Program Meeting, Era of Hope, 2000. Kumar NB, Riccardi D, Allen K, Cantor A, Jacobsen P. Horton J, Minton S, Balducci L & Lyman GH. Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal, Body Composition and Behavioral Mechanisms. Abstract accepted for Podium Presentation, Proceedings of the 5th International Symposium on Predictive Oncololgy & Therapy. November 2-5, 2000.
2. Kumar NB, Riccardi D, Allen K, Cantor A, Jacobsen P. Horton J, Minton S, Balducci L & Lyman GH. Weight Gain in Breast Cancer Patients on Chemotherapy: Exploring Hormonal, Body Composition and Behavioral Mechanisms: Preliminary results. Proc. of the Annual Meeting of the American Institute of Cancer Research, 2001

Conclusion:

In this study examining the etiology of weight gain in patients undergoing chemotherapy, we observed weight gain, fatigue and decreased ovarian and thyroid function in 183 patients. Our study was exploratory in nature and we examined several factors as potentially contributing to weight gain in this patient population. Although the benefits of adjuvant chemotherapy and radiation therapy are well established, and although several side effects challenge the health professionals, the most distressing side effects as reported by breast cancer patients during treatment are weight gain, fatigue, depression and loss of ovarian function- symptoms that affect the quality of that extended survival time, including its effects on productivity, family functioning, and both medical and psychiatric comorbidity. Based on the results of our study, we hypothesize that women at high risk for breast cancer may suffer from subclinical hypothyroidism even prior to diagnosis, worsening to more overt clinically symptomatic hypothyroidism, manifested by symptoms of fatigue, depression, weight gain and ovarian failure, post chemotherapy

The association between thyroid disorders and breast cancer has long been a subject of debate. Although several studies have shown the association between thyroid disease and predisposition to breast cancer, others have not shown this association.[21-23] Most of these studies identified thyroid disease from clinical histories and medical records and therefore did not consider specific, reliable indices of thyroid function. Epidemiological studies have shown geographical variations in the prevalence of breast cancer and attribute this variation at least in part to thyroid function.[24] Japanese women suffering from Hashimoto's disease have reportedly a 5-fold increase in breast cancer risk compared to those without evidence of autoimmune thyroid disease.[25] However, when the association of Hashimoto's disease and breast cancer was studied in the US,[26] this risk was not evident. Recent studies have reported an increased prevalence of antithyroid antibodies in patients with breast cancer.[27-28] Research has in addition demonstrated that clinically evident non-toxic goiter is significantly more common in breast cancer patients than in age-matched controls.[29] It has also been suggested that hormonal agents, cytotoxic drugs and radiation therapy may influence thyroid function in breast cancer patients. Several pathogenic factors may be attributed to this association. Firstly, since both breast cancer and hypothyroidism may have a genetic predisposition, the genetic association cannot be discounted. The presence of an iodine pump in both the thyroid and the breast[30] makes the association of the effect of thyroid on breast, biologically plausible.[31] Clinical trials have shown a resolution of fibrocystic breast disease and breast pain in women treated with elemental iodine.[32]

Although the classic clinical spectrum of hypothyroidism with symptoms of lethargy and myxedema is well known to the practitioner, it is rarely seen in today's clinical practice.[20] In contrast, practitioners frequently see patients with very mild thyroid dysfunction. Unlike patients with overt hypothyroidism, these patients have normal levels of thyroxine and triiodothyronine and only mild elevation in thyrotropin levels. This condition is commonly termed "subclinical hypothyroidism" or "mild hypothyroidism".[20,33] We hypothesize that women at high risk for breast cancer may suffer from subclinical hypothyroidism even prior to diagnosis, worsening to more overt clinically symptomatic hypothyroidism, manifested by symptoms of fatigue, depression, weight gain and ovarian failure, post chemotherapy. Chemotherapeutic agents have been shown to cause fibrotic changes and follicular destruction and pre and peri-menopausal women have been observed to have reduced serum estradiol levels during chemotherapy.[34,35] Even though not clearly established, it is questionable if the abrupt menopause induced by chemotherapy can aggravate a latent predisposition towards developing thyroid dysfunction. Especially with increasing doses in adjuvant and neo-adjuvant chemotherapy and combination therapies including radiation therapy, induction of subclinical hypothyroidism is a possibility. In addition to increase in body fat, menopause is also known to trigger a change in body fat distribution with a shift from gluteal/femoral fat to the abdominal area which is associated with lowered metabolic activity[34-37], which can be demonstrably prevented with estrogen replacement therapy. Variations in basal metabolic rate (BMR) of up to 6%-10% have also been reported to occur during the course of the menstrual cycle[38-39] possibly secondary to changes in the endocrine state.[34-35] This effect may be even more exaggerated in women with pre-existing subclinical hypothyroidism.

Even if subclinical hypothyroidism is identified in similar patient populations, the potential risks and benefits of thyroid hormone therapy has been debated for two decades. The possible advantage of treating subclinical hypothyroidism is to first prevent this progressing to overt hypothyroidism and to secondly to prevent symptoms of mild hypothyroidism. There have been three published randomized, prospective, placebo-controlled trials of therapy for subclinical hypothyroidism, of which two observed significant response to treatment[40-41] and one found no effect of therapy.[42] However, the positive findings in the earlier studies that indicate remarkable symptom improvement with thyroxine therapy is encouraging. The extent to which patients with subclinical hypothyroidism will respond to thyroid hormone therapy or the extent to which these symptoms are reversible, especially in the breast cancer patient population, have never been examined and remain unanswered.

Based on this observational study funded by the DOD, we have submitted a research proposed to the NCI under the Exploratory/Development (R21) grant mechanism. Our goal is to first characterize variances in thyroid function, including subclinical abnormalities, in breast cancer patients compared to controls, and to evaluate the efficacy of treating this subgroup of breast cancer patients with thyroid hormone therapy to prevent progression to overt hypothyroidism, in addition to studying the extent to which symptoms of weight gain, depression, amenhorrhea and fatigue can be reversed and cancer mortality improved.
Our Specific Aims Proposed:

Specific Aim 1: To measure thyroid function in newly diagnosed breast cancer patients compared to disease-free, age and menopausal-matched controls.

Specific Aim 2: To observe the change in markers of thyroid function in breast cancer patients screened for thyroid abnormalities, receiving adjuvant chemotherapy, from baseline to end of chemotherapy compared to unscreened patients and disease-free controls.

Specific Aim 3: To observe the efficacy of treating the subgroup of breast cancer patients on chemotherapy, who are identified with subclinical to overt hypothyroidism, with thyroid hormone therapy (0.088micrograms/day as starting dose), as indicated by changes in serum measurements of thyroid function, ovarian function, fatigue scores, depression, and anthropometrics as compared to unscreened breast cancer patients receiving chemotherapy and a disease-free control population.

Other Aims:

Specific Aim 4: To determine the correlation between thyroid function and markers of body composition and body mass index in newly diagnosed breast cancer patients compared to disease-free controls and changes in these markers from baseline to post chemotherapy.

Specific Aim 5: To observe the correlation between thyroid function tests and serum steroid hormone concentration that are indicative of ovarian function, such as serum total

and free estradiol, follicular stimulating hormone and luteinizing hormone levels at diagnosis and post chemotherapy.

Specific Aim 6: To observe the correlation between thyroid function and markers of prognosis such as tumor size, Ki-67, ER/PR, stage of disease, tumor grade and Her2 status in breast cancer patients at diagnosis.

Specific Aim 7: To observe incidence of sick euthyroid syndrome in breast cancer patients during chemotherapy by observing change in thyroid function including reverse T3 at baseline to post treatment.

After our specific aims are achieved, we will be in a position to conduct a larger randomized clinical trial of the intervention, for which we will seek funding through the traditional mechanism. We thank the Department of Defense for funding our project to examine the etiology of weight gain in this patient population, which has resulted in findings that have implications in the quality of life and mortality of this patient population and certainly in clinical practice.

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Table 1: Demographics (n=182)			
Variables		**Mean**	**SD**
	Age (years)	49.65	9.93
	Height (cms)	164.53	6.59
	Weight (lbs)	136.46	31.8
	BMI (kg/m^2)	26.33	5.58
Race			%
	African American		5
	Asian		2
	Hispanic		4
	Caucasian		88
	Other		1
Smoker		Yes	No
		72%	28%
Pack years		5.27	(SD)10.77

Table 2: Patient Characteristics (n= 183)	
Diagnosis	%
Stage I	30
Stage II	65
Stage IIB	1
Stage III	4
Chemotherapy	(%)
CA	62
CA + Taxol	28
Other	10

Table 3: Reproductive Profile	n-183	
Variables	**Mean**	**SD**
Age at Menarche	12.49	1.52
Full Term Pregnancies	1.54	1.65
Number of Months Breast Fed	7.34	10.86
	Yes	No
Menopause	40.20%	59.89%
Hormone Replacement Therapy	32.30%	67.70%
Birth Control Pill Use	60.30%	39.70%

Table 4: Change in weight and physical activity from baseline to post chemotherapy	(n=183)
Variables	**%**
Weight	
+< 5 lbs	77%
+5-10 lbs	17%
+>10 lbs	6%
Hours worked outside the home	%
-<5	69%
-5-10	9%
->10 hours	22%

Table 5: Change in Hormonal Variables (n= 183)

Variables	Pre Chemotherapy		Post Chemotherapy		P (pre vs post Chemo therapy)
	Mean	SD	Mean	SD	
Steroid Hormones					
Free Estradiol	0.913	1.03	0.395	1.12	<0.0001
Total Estradiol	55.86	65.42	24.4	75.11	<0.0001
SHBG	46.37	25.09	59.37	30.55	<0.0001
Thyroid Hormones					
Total T3	1.04	0.25	0.98	0.14	<0.07