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14. ABSTRACT. Weight gain after breast cancer diagnosis is common, and has been associated with poorer prognosis. The goals of the study are to examine weight gain relation to treatment-related changes in sex hormone levels, and in relation to genetic polymorphisms in sex hormone pathways, accounting for potential interactions with energy balance, psychosocial factors, tumor characteristics, cancer treatment, and medication use. A prospective longitudinal study of weight gain is being conducted in 215 stage I to IIIA breast cancer patients. In 264 breast cancer patients, we did not observe any significant weight gain when all participants were considered together, and no weight gain was observed among women treated with AC-based chemotherapy compared to those who did not receive chemotherapy treatment. We examined a number of demographic and lifestyle variables and found that younger women and women in the lowest weight quartile at the time of cancer diagnosis were most likely to gain weight and show increases in percent body fat. Women with higher daily energy intake were also more likely to gain weight. Weight gain and increases in percent body fat were related to increases in circulating C-reactive protein levels, as a marker of inflammation. Women with higher C-reactive protein levels at the time of cancer diagnosis were also more likely to gain percent body fat over the subsequent 12 month period. Declines in cortisol binding globulin levels were related to positive changes in weight and BMI. Of the sex steroids assayed, only FSH and LH were observed to be related to changes in weight and/or body composition. The study will help identify women who are most susceptible to weight gain after being diagnosed with breast cancer.

15. SUBJECT TERMS
Sex hormone, genetic polymorphisms, weight gain, cohort study, diet, physical activity, psychosocial factors.

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1. Introduction

Weight gain after breast cancer diagnosis is very common, occurring in 50-95% of early stage patients undergoing adjuvant chemotherapy, and has been associated with poorer prognosis. Potentially important contributors to this weight gain may be treatment-related reductions in ovarian function and/or increases in cortisol level due to physical and psychological stress. Since sex hormones and glucocorticoids regulate body weight and adipose tissue distribution, we hypothesize that sex hormones and cortisol play a role in treatment-induced weight gain, and that complex interactions exist with genetic susceptibility, lifestyle, and psychosocial factors.
The goals of the study are to examine post-diagnostic weight change and: 1) changes in sex hormone and cortisol levels; 2) genetic polymorphisms in sex hormone pathways; 3) energy intake, physical activity, and psychosocial factors; and 4) characteristics of the cancer and treatments received. A prospective longitudinal study of weight gain is being conducted in 215 patients, aged 18 and older, with non-metastatic breast cancer (Stage I to IIIA). After informed consent, we are collecting serial biospecimens and survey data, to measure hormone levels and genetic polymorphisms, and to assess menopausal status, anthropometry, diet, physical activity, and psychological variables (fatigue, depression, social support) at baseline, 6, and 12 months. These factors will be evaluated in relation to weight changes during and following therapy. This study aims to comprehensively examine predictors and modulators of post-diagnostic weight gain in women with breast cancer using a multidisciplinary approach encompassing hormonal changes, genetic polymorphisms, and psychosocial factors. The outcome of this research may shed light on why so many women experience weight gain after breast cancer and will help guide the development of interventions targeting modifiable risk factors.

2. Body

Task 1: Study Protocol Revisions, Months 1 to 24

Study protocols and the consent form were revised to include DOD elements and were submitted to the USAMRMC Office of Research Protections, Human Research Protections Office (ORP HRPO) for review. Local IRB approval and approval from USAMRMC ORP HRPO was obtained January 8th, 2007. Beginning 10/31/2007 the eligibility criteria for the study protocol was broadened and amended from women aged 35 to 75 to women 18 years and older.

In April 2010, at the termination of funding for the project we amended the protocol to remove the 6 month visit because many breast cancer patients do not return for a clinical visit at this time and therefore the data collected was not well timed. In addition, urine samples are no longer being collected.

Task 2. Develop databases with Clinical Research Service and Information Technology department at RPCI, months 1-24.

In collaboration with the Clinical Research Services and Information Technology department at Roswell Park, a tracking database has been developed which tracks for each potential participant their study eligibility and participation status. For each participant, the system also tracks specimen collection, as well as allows for entry of all data collected by survey. The database developed uses the eResearch Technology (eRT), eData Management, eStudy

Conduct, eSafety Net software products as well as various other RPCI custom applications connected to eRT via Microsoft ODBC technology. The database is currently interfaced to RPCI's hospital information system (demographics), and the RPCI Cerner lab system (lab results), which allows all of this information to transfer electronically. The database management system is Oracle 9i. Backups of the study data to tape are performed nightly and stored in a separate physical location from the servers themselves.

In the second year we developed a supplementary questionnaire to collect information on temperature perception in breast cancer patients that was initiated July 2007. The questionnaire also collects additional information on vitamin supplement use and use of herbals and other compounds after breast cancer diagnosis. As a result, our study databases were recently updated to allow double entry of this data and we are currently in the process of entering the backlog of data collected with the supplementary questionnaire.

We are now current with our data entry and are now in the process of comparing the double data entries and resolving discrepancies.

We are working closely with the IT department to streamline our processes for detecting data discrepancies between the double entered data.

Task 3. Train study personnel to consent patients, months 1 to 6

At the start of the study a project co-ordinator was hired and trained to consent patients into the study from the breast clinic at Roswell Park Cancer Institute. In addition, a half-time study coordinator was hired in September 2006 to aid in the conduct of this study.

In January 2009 a new project co-ordinator was hired after our previous coordinator left for a new job position. She was trained to manage the study. In addition we have hired one part-time research assistant to help with patient followup. We are, however, converting this into a full-time research position to allow staff to meet all followup patients in the new Cancer Prevention Research Center at Roswell Park Cancer Institute. This is a dedicated space available to population, behavioral, clinical and basic scientists and designed for conducting prevention research projects. Meeting all study participants at follow-up visits will allow study personnel to check participant questionnaires for completeness and obtain body composition measures on the Tanita scale, which is currently being performed by nurses within the Breast Clinic. We anticipate that meeting participants will reduce attrition rate and reduce the frequency of missing data.

In the past year, we have had several interns from Buffalo State College who have helped on the project with data entry and with data management.

Task 4. Study Recruitment, Months 6-18; Participant Followup, Months 7 to 30.

Recruitment of participants who participate in the Institute's DataBank and BioRepository using consent forms with DOD language was initiated in Jan, 2007. By year 2 (5/14/08), 226 participants had been enrolled. From this group there were a total of 31 withdrawals and 5 individuals were lost to followup leaving 190 active participants.

By the end of year 3 (3/17/09), 333 participants have been enrolled. Of these, 220 out of a possible 266 women have had their 6 months followup visit (82.7%) with 46 (17%) withdrawals. A total of 211 women have been eligible for a 12 month followup, although of this 43 (20%) women have withdrawn, leaving 168 active participants. Reasons for withdrawals in the past year are provided below in table 1. Our plan will be to continue following participants in

the upcoming year, which would be expected to yield approximately 75 more participants with one year follow-up data. We will begin meeting all study participants at follow-up visits which we anticipate will reduce the attrition rate and reduce the frequency of missing data. Many of the women who withdraw from to the study do so because they are no longer being treated or followed at RPCI and do not live near the Buffalo metropolitan area.

By 07/26/2010, at the end of the grant period, we had 469 women consented into the study, with 47 (10%) withdrawn or lost to followup before their baseline data collection for a total of 422 women. Of these 412 women had provided a blood sample (97.6%) and 365 women have returned their baseline survey (86%). Of these 336 women were eligible for their 1 year followup visit. Thirty four (10%) of these women withdrew after their baseline visit and before their 1 year visit leaving a total of n=302. Of these women, 286 (95%) gave a blood sample, 272 (90%) were weighed on the Tanita Body Composition scale, and 248 (82%) filled up a followup questionnaire.

Measurement of weight, height, and body composition

Protocols to measure body composition and weight in the Roswell Park Breast clinic was established using the Tanita Body Composition analyzer, which uses the tetrapolar bioelectrical impedance technique. As well, protocols were established with clinical staff in the Breast Clinic to measure waist and hip circumferences on all newly diagnosed breast cancer patients at baseline and at followup visits. At the end of year 2, 94% of all participants at baseline have provided body composition data using the Tanita scale. For the remaining participants, use of the Tanita scale was either contraindicated, the patient was unable to stand on the scale, or the patient refused the measurement. At 6 months and 12 months of followup, the proportion of those measured by the Tanita scale were lower at 79% and 83% respectively, with 90% of all participants eligible for followup providing at least 1 followup Tanita measurement. Going forward, our study staff will begin escorting participants personally to the breast clinic to ensure that those eligible for a followup measurement will have these data collected.

At the end of year 3, 93% of participants who had not withdrawn (286/307) had provided baseline body composition measurements using the Tanita Body Composition scale. At 6 and 12 months of followup, proportions of those measured by the Tanita Scale were 80% (177/220) and 85% (145/168), respectively. Last year, we were unable to escort all participants personally to the breast clinic to ensure that all participants received a followup measurement because it was too time consuming for the staff with all their other tasks. We are, however, in the process of hiring a research assistant to allow us to meet all followup patients in the new Cancer Prevention Research Center, a dedicated space established in the past year that is available for conducting prevention research projects. Meeting all study participants at follow-up visits will allow study personnel to check participant questionnaires for completeness and obtain body composition measures on the Tanita scale before proceeding on to the main hospital to the Phlebotomy Clinic for a blood drawn and to the Breast Clinic for their scheduled clinic appointment. We anticipate that meeting participants directly will reduce the frequency of missing body composition data.

In the past year, the proportion of women with followup Tanita measurements have increased, with 95% (402/422) and 90% (272/302) of participants who had not withdrawn providing a body composition measurement at baseline and at 12 months followup, respectively.

Collection of blood and urine samples

Protocols for the collection and processing of fasting blood samples prior to surgery/treatment were developed and include banking of serum, plasma, buffy coat, and red blood cells. As well, presurgical overnight urine specimens were collected, which is accompanied by a specimen questionnaire that was developed, which asks about lifestyle, diet, and medication use in the last 2 days. Currently, fresh whole blood is sent to Labcorp for determination of HbA1C results. Serum and plasma are being stored to allow for future determination of sex hormone and cortisol levels. Originally we had planned to begin shipping serum samples periodically to Labcorp to determine hormone levels beginning in month 6, but to reduce laboratory error we will instead wait until followup is complete and have baseline, 6 months, and 1 year samples assayed simultaneously. At the end of year 2, 98% of all participants had provided a baseline blood sample. At 6 months and 12 months, 85% and 86% of those eligible for followup had provided a blood sample, with 93% of these participants providing at least 1 followup blood sample. For urine samples, 92% of patients provided pretreatment samples (after subtracting those withdrawn from the study) and of these 88% of those eligible for at least one followup urine collection have provided at least one followup urine sample.

At the end of year3, 94% of participants who have not withdrawn provided a baseline blood sample. At 6 and 12 months, the rates were 87% (191/220) and 95% (159/168), respectively. For urine samples, 90% (275/307) of those who had not withdrawn provided pretreatment samples. At 6 and 12 months, 82% (181/220) and 86% (145/168) provided followup urine samples.

At the end of the grant, 98% of participants who have not withdrawn provided a baseline blood sample. At 12 month, the rate was 95%.

Task 5. Data Management, Months 6 to 31.

We are in the process of double entering all our data into study databases. This is done by at least 2 different individuals, and periodically the two sets of data entered are compared and differences are flagged for further followup.

In the second year, two research associates were hired to help with data entry. Up to November 2007, data entry for the study had been performed largely by student volunteers and the progress was slow and the study was behind on this task. In response, two half-time research associates were hired between November and December 2007 to aid in data entry and in patient followup. Two persons were required since duplicate data entry had to be performed by different people. In addition to data entry, the two half-time research associates aid in the followup of incomplete questionnaires with participants during evening hours when participants are most likely to be at home, as well as in the scheduling of patients for followup appointments. The additional personnel were needed to handle the increased number of participants requiring active followup.

In year 3, we are current with our double data entry. We are now in the process of cleaning the data by resolving discrepancies found between the two sets of data entered.

In the past year, we have spent a lot of time working with IT to resolve data discrepancies. In addition, we recently discovered through our own data cleaning efforts that certain data discrepancies were not being detected by the program used by IT to generate a report of data discrepancies in our study database. As a consequence, we are now in the process of going back and rechecking for additional discrepancies that may have been missed in the

original pass. This includes comparing all data for Entries One and Two ourselves to check for data discrepancies. Reporting of these discrepancies to IT have allowed for updates to the data quality control program. This process is still ongoing.

Task 6. Measurement of hormone levels, Months 12 to 31.

Currently, fresh whole blood is sent to Labcorp for determination of HbA1C results. Originally we had planned to begin shipping serum samples periodically to Labcorp to determine hormone levels beginning in month 6, but to reduce laboratory error we instead waited until followup is complete and have baseline, 6 months, and 1 year samples assayed simultaneously. Originally we had proposed to use Labcorp to perform all of our hormone measurements, but based on the results of some samples sent from a different study, we were not happy with the reproducibility of measurements. As a result, we are now collaborating with Dr. Alice Ceacareanu in the School of Pharmacy at the University at Buffalo, who will perform the sex hormone assays in her laboratory, and samples for the cortisol-related measurements will now be sent to the Biobehavioral Medicine Core Facility at the University of Pittsburgh Cancer Institute, which is overseen by Dr. Dana Bovbjerg, one of my mentors. We are currently in the process of purchasing Elisa assay kits for in-house sex steroid measurements, which will begin shortly and is anticipated to be complete within 4 months. This will be carried out 573 serum samples, representing all the blood specimens we have collected to date at baseline, 6 months, and 12 months. Arrangements are being currently made to have study samples shipped to the Pittsburgh University Cancer Center for cortisol-related measurements.

In the past year, all the sex hormone measures have been completed in Dr. Alice Ceacareanu's laboratory, although the assays took longer than expected because of repeats that were performed when measurement variation was too high. The final data became available April 12, 2010. Cortisol-related measurements were performed in the Biobehavioral Medicine Core Facility at the University of Pittsburgh Cancer Institute. Because of changes in staff at Pittsburgh, these measurements were delayed and were completed at the end of February 2010. In addition, we measured c-reactive protein levels for 164 women at baseline and at 1 year followup to examine the potential role of inflammation with respect to weight gain after diagnosis.

Task 7. Postdoctoral Training, Months 1-36

Developmental meetings are held weekly and on an as needed basis to discuss progress and career development with Dr. Christine Ambrosone, the primary mentor. Frequent meetings are also held with other mentors on an as needed basis to address issues associated with the conduct of the study. I have attended several scientific conferences as part of my training including the 2007, 2008, and 2009 Annual Meetings of the American Association for Cancer Research and was the co-chair for 2007 and 2008 for the Annual Grant Writing Workshop for Associate Members, Professional Advancement Session. In 2009, I was co-chair for a Professional Advancement Session "Mentoring and Career Development Plans: Establishing Successful Relationships for Productive Careers". In 2008, I was invited by AACR to be a junior facilitator at the Leila Diamond Networking Breakfast hosted by Women in Cancer Research at the 2008 AACR Annual Meeting. I attended the AACR Molecular Epidemiology Working Group (MEG) sponsored special conference on 'Approaches to Complex Pathways in Molecular Epidemiology' from May 30 to June 2nd, 2007 and attended the 2007 AACR Frontiers

in Cancer Prevention Research meeting held from December 5-8, 2007. I continue to attend (and coordinate) the biweekly Work-in-Progess meetings in epidemiology and chemoprevention that occur within the Department of Cancer Prevention and Control at Roswell Park Cancer Institute, as well as weekly Faculty Forum, Cancer Prevention Grand Rounds, and Medical Grand Rounds seminars. My training has also been greatly enhanced by participating as a peer-reviewer for the DoD BCRP Idea and Synergism grant mechanisms in 2008 and 2009 as well as a reviewer for the Breast Cancer Campaign in the United Kingdom in 2008. I have been invited back in 2009 to participate as a peer-reviewer for the BCRP Idea and Synergism Awards as well as the Pre- and Postdoctoral fellowships in January and May.

In the past year I attended the 2010 AACR Annual Meeting held April 17-21 in Denver Colorado and presented a poster (abstract #906) entitled 'Body Temperature and Thermal Discomfort among Breast Cancer Survivors'. At the AACR annual meeting, I also served as an Associate Scientific Mentor for the AACR Survivor Program. In the past year, I attended the AACR special conference in conjunction with the AACR Molecular Epidemiology Group, which was held in Miami FL June 6-9, and focused on 'The Future of Molecular Epidemiology: New Tools, Biomarkers, and Opportunities". I continue to co-ordinate the bi-weekly Work-in-Progress meetings in epidemiology and chemoprevention within the Department of Cancer Prevention and Control. In addition, I attend a Breast Cancer Working Group, which meets monthly in the Department of Cancer Prevention and Control. My training continues to be enhanced by participation in grant review panels. In January 2010 I reviewed for the Susan G. Komen for the Cure Grants Program on the Prevention and Risk Reduction Panel (Postdoctoral Grants) and in March 2010, I reviewed for the California Breast Cancer Research Program. I was invited to review training grants for DoD as well, but had to decline because my PhD student submitted a predoctoral award application.

Task 8. Mount Sinai Center Visit, Month 12

I have not yet visited Dr. Bovbjerg yet at the Mount Sinai Center in NY and plan this in the upcoming year once the psychosocial data is cleaned and ready for data analysis.

I did not visit Dr. Bovbjerg at Mount Sinai in the past year. We have primarily stayed in contact by email and by telephone. The frequency of our discussions will increase when the psychosocial data is being analyzed, particularly when the psychosocial aspects are being examined along with cortisol levels.

Task 9. Interim Analyses, Months 12-30

We have done analyses to look at data quality and followup rates. We are currently in the process of cleaning our data and will begin analyses focused on our main hypotheses.

Data cleaning and analyses are ongoing.

Task 10. DNA extraction and Genotyping, Months 14 to 22.

As part of the blood collection protocol, buffy coats are being banked and stored to allow for DNA extraction and genotyping. We have recently completed the DNA extraction for 236 study participants and will begin genotyping proposed polymorphisms in the sex hormone and adrenal hormone pathways.

We decided not to genotype the DNA until we had results from the serum assays so that we could refine the list of genes we would like to genotype based on promising findings. The DNA is still banked and will be available for future genotyping studies.

Task 11. Merge genotyping data with data questionnaires and medical records. Month 23.

We have obtained all the clinical data for all study participants recruited to date and will merge this data with our survey data once the latter is cleaned (currently in process).

All the clinical data from the Department of Surgery, and data from the Institute's Biorepository have been merged with data collected in the Women's Health after Breast Cancer Study and is currently being analyzed.

Task 12. Final data analysis, interpretation and reporting, Months 31 to 36.

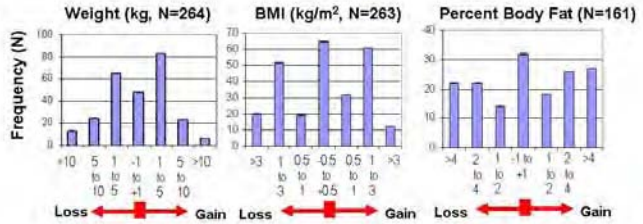
Data analysis, interpretation and reporting are ongoing.

3. KEY RESEARCH ACCOMPLISHMENTS

3.A. Preliminary Results on Determinants of Weight Gain Among Breast Cancer Patients.

We performed preliminary data analysis on determinants of weight gain examining demographic, lifestyle, and clinical factors. In addition, we have assayed several serum markers of cortisol levels as well as sex steroid levels. In our data analysis, we have examined post-diagnostic changes in these serum biomarkers and their relationship with post-diagnostic weight gain and/or change in body composition. Findings from these analyses are described below. Ongoing analyses will include examination of psychosocial variables, including perceived stress on levels of cortisol and their relationship with risk of post-diagnostic weight gain among breast cancer survivors.

Demographic and Lifestyle Variables. In 264 study participants who had data from the time of diagnosis and 12 months following their cancer diagnosis, overall significant changes in weight, body mass index, or percent body fat were not observed, as shown in Figure 1. Among all women, the median weight gain was 0.45 Kg with an interquartile range of -3.10 to 2.80. Similarly, BMI increased slightly (+0.23 kg/m^2) and total percent body fat increased slightly at 0.5%, although none



Median [Interquartile Range]			
All Women	0.45 [-3.10, 2.80]	0.23 [-1.15, 1.20]	0.50 [-2.2, 2.6]
No Chemo	0.40 [-3.00, 2.50]	0.20 [-1.10, 1.00]	0.70 [-1.9, 2.6]
Chemo	0.50 [-3.50, 3.70]	0.28 [-1.30, 1.40]	0.40 [-2.8, 2.5]

Figure 1. Change in Weight, BMI, and Percent Body Fat from time of Diagnosis to 12 months following Diagnosis.

of these changes were statistically significant.

We examined a number of demographic and lifestyle factors as potential explanatory variables for changes in weight and body composition. As shown in Figure 2, changes in body composition were found in part to be due to body composition at the time of cancer diagnosis, with women who were lighter at the time of cancer diagnosis being more likely to gain weight, BMI, and percent body fat compared to those who were heavier at the time of breast cancer diagnosis. Interestingly, obese women were found to lose weight as well as show slight declines in BMI over the 12month period.

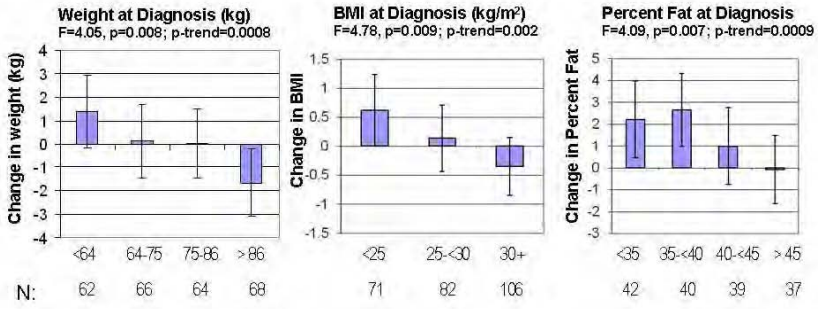


Figure 2. Change in Weight, BMI, and Percent Fat Mass over 12 months according to Body Composition at the time of Breast Cancer Diagnosis. All analyses are adjusted for race, age at diagnosis, season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec) and weight, BMI, or percent fat at diagnosis.

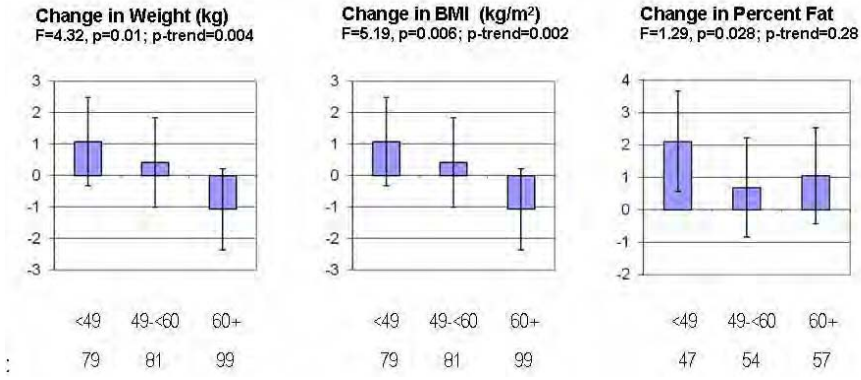


Figure 3. Change in Weight, BMI, and Percent Fat Mass over 12 months according to age at diagnosis (years). Results adjusted for race, age at diagnosis, season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec) and BMI at diagnosis.

As shown in Figure 3, women younger than age 49 were more likely to gain the weight and BMI, while older women over 60 years of age experienced weight loss and declines in BMI. Change in menopausal status, however, did not account for the weight gain observed among younger women since women who were pre-menopausal at the time of cancer diagnosis and were postmenopausal 12 months following diagnosis had a weight change of +0.15 Kg (95% CI -1.96, 2.26) compared to a gain of 0.10 Kg (95% CI: -1.10, 1.30) in women who were postmenopausal at the time of diagnosis and remained postmenopausal 12 months after diagnosis after adjustments for race, age at diagnosis, season of diagnosis and BMI at diagnosis (F=0.06, p =0.94).

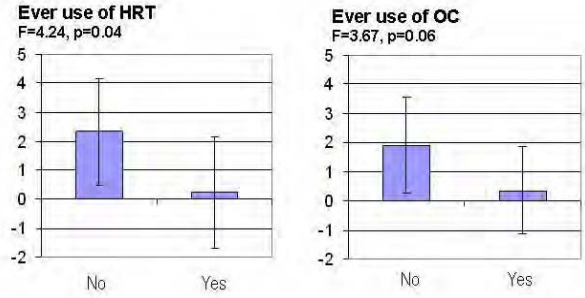


Figure 4. Change in percent fat mass over 12 months according to use of HRT and OC. Results adjusted for race, age at diagnosis, season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec) and BMI at diagnosis.

Among lifestyle variables examined, ever use of hormone replacement therapy (HRT) and oral contraceptives (OC) were not associated with either changes in weight or BMI ($p>0.41$), although ever users of HRT and OC showed no increases in percent body fat compared to non-users who showed gains in percent body fat of approximately 2% (see Figure 4). Smoking status (current, former, never) was not found to be associated with weight gain or changes in body composition (data not shown).

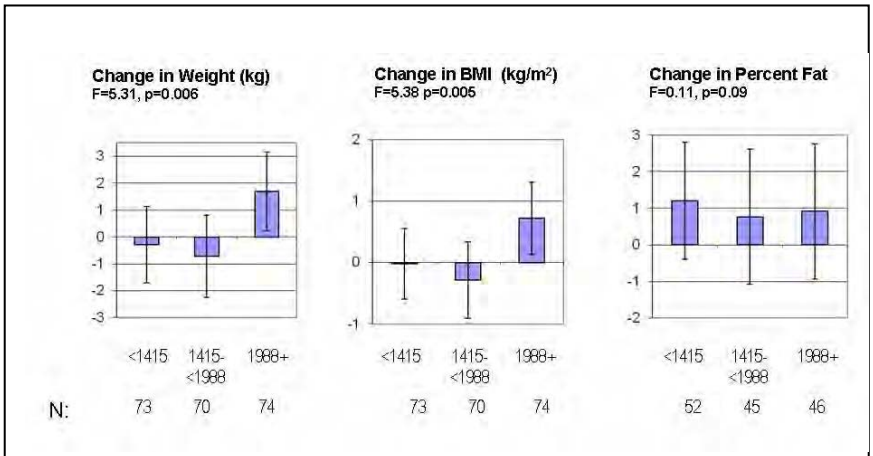


Figure 5. Change in Weight, BMI, and Percent Fat Mass over 12 months according to daily energy intake (Kcal/d). Results adjusted for race, age at diagnosis, season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec) and BMI at diagnosis.

Women with high daily energy intake were found to be more likely to gain weight, and BMI, although levels of percent body fat were not affected (see Figure 5).

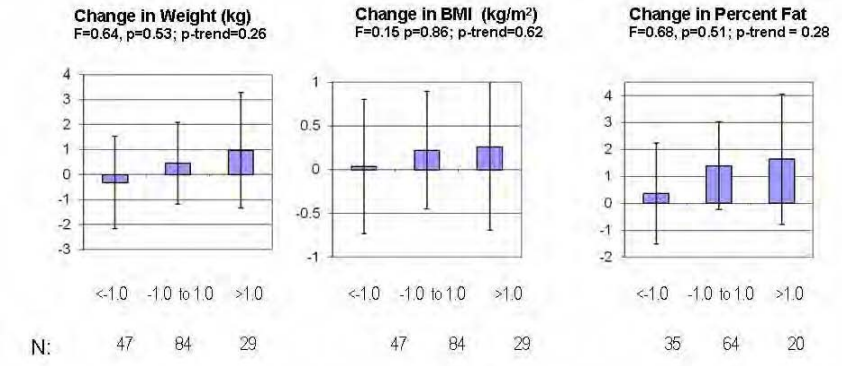


Figure 6. Change in Weight, BMI, and Percent Fat Mass over 12 months according to change in serum C-reactive protein levels (mg/l). Results adjusted for race, age at diagnosis, season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec) and BMI at diagnosis.

In preliminary analysis to determine if levels of inflammation are related to changes in weight and fat mass, we examined changes in levels of C-reactive protein over a 12 month period. Although not statistically significant, women with the greatest increases in serum CRP levels were more likely to show positive increases in weight and percent body fat compared to those who had declines or unaltered CRP levels (see Figure 6).

We also assessed relationships between feeling cold and chilled with indicators of body size. Participants were asked "To what degree have you experienced feeling inappropriately cold or chilled when others feel fine or hot?" Participants indicated their answer on a 10-point Likert scale, with 1 indicating "Not at all" and 10 indicating "A great deal". Categorizing respondents as either experiencing no symptoms (score = 1), a low degree of symptoms (score = 2 and 3), or a high degree of symptoms (4+), we were able

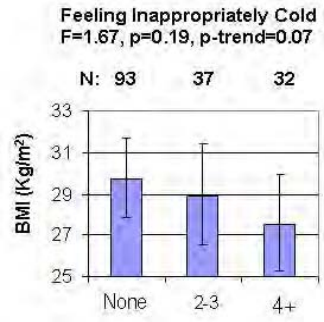


Figure 7. BMI at 12 months following BrCa diagnosis and feelings of being inappropriately cold. Analyses adjusted for race, age at diagnosis, and season of diagnosis.

to show a dose-response relationship between feelings of being inappropriately cold and BMI at 12 months following initial BrCa diagnosis (see Figure 7). Furthermore, this question was sensitive enough to be associated with *changes* in weight, BMI, and percent fat occurring over a one year period. As shown in Figure 8, women who experienced symptoms of feeling chilled had a net gain in weight, BMI, and percent body fat, while those experiencing a higher degree of symptoms (4+) had measured declines in weight, BMI, and percent body fat. These findings suggest that feeling cold and chilled may reflect changes in energy balance that occur in breast cancer patients. Future plans in data analysis includes examination of physical activity in conjunction with energy intake to more fully examine relationships between changes in energy balance that occurs after breast cancer diagnosis during treatment and changes in weight and body composition during this time period.

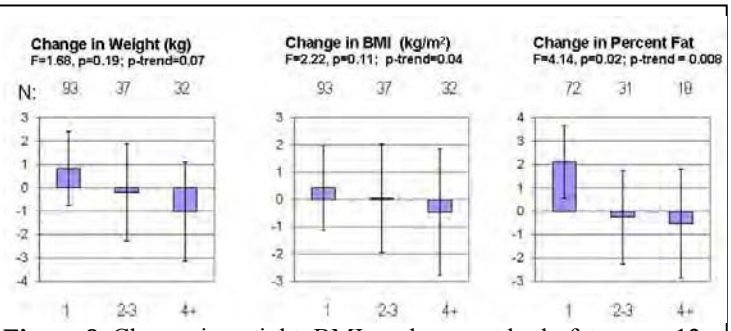


Figure 8. Change in weight, BMI, and percent body fat over a 12 month period according to degree of feeling inappropriately cold 12 months following BrCa diagnosis. Analyses adjusted for race, age at diagnosis, and season of diagnosis.

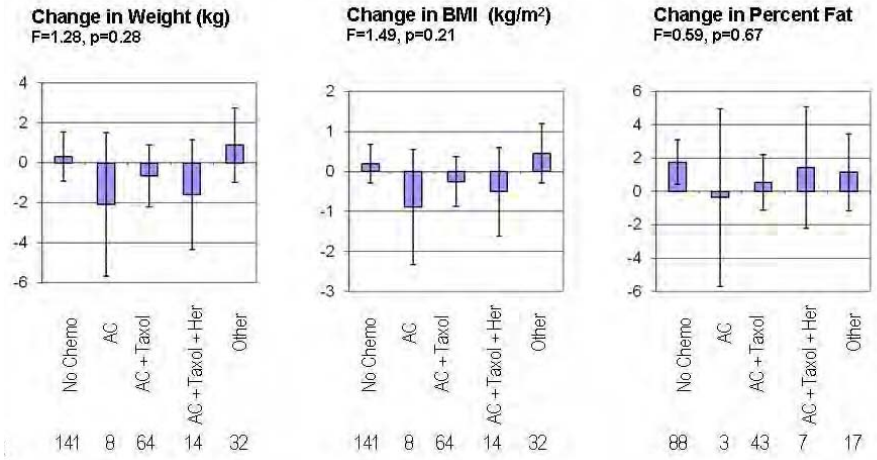


Figure 9. Change in weight, BMI, and Percent Fat Mass over 12 months according to Chemotherapy treatment. Analyses adjusted for race, age at diagnosis, and season of diagnosis.

Clinical Factors

A number of clinical variables were examined with respect to weight gain and changes in body composition. As shown in Figure 9, treatment with Adriamycin and Cytoxan (AC) –based chemotherapy was not associated with weight gain or changes in adiposity compared to women who did not receive chemotherapy. In addition, post-diagnostic weight gain and changes in body composition were not associated with ER status, cancer stage, use of

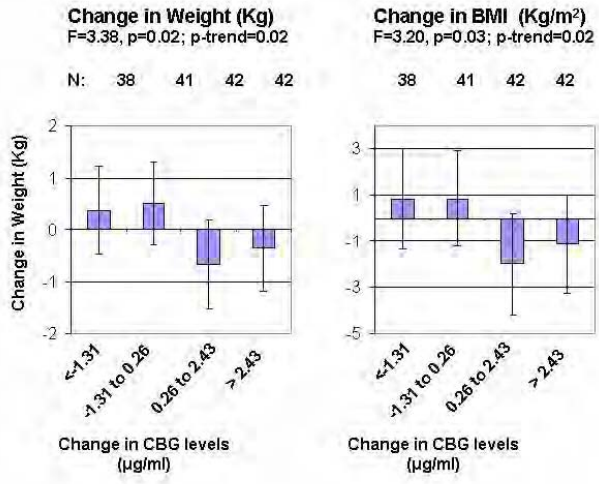


Figure 10. Declines in CBG levels are associated with increases in weight and BMI, while positive increase in CBG levels are associated with declines in weight and BMI. Results are adjusted for race, age at diagnosis, BMI at diagnosis, menopausal status at diagnosis, and cancer stage.

hormonal therapy (SERMS or aromatase inhibitors) (data not shown).

Changes in Serum Cortisol and Sex Hormones

There is increasing evidence that elevated cortisol level, regulated by the hypothalamic-pituitary-adrenal (HPA) system, is associated with increased food intake and general obesity as well as development of abdominal obesity. We assayed serum levels of cortisol, as well as 11-deoxycortisol, and 17-OH-Progesterone as precursors of cortisol, and levels of cortisol binding globulin (CBG). Unbound cortisol levels were calculated based on circulating cortisol and CBG levels. Circulating levels of ACTH, produced by the pituitary gland that stimulates the adrenal glands to release cortisol was also measured.

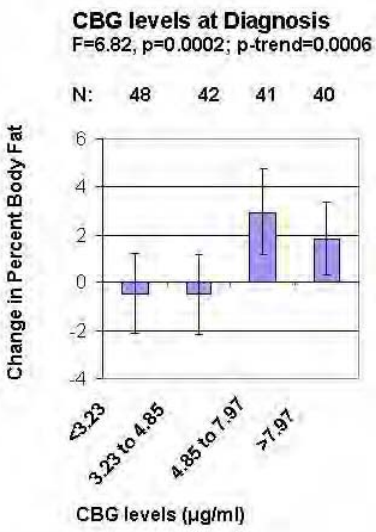


Figure 11. Higher CBG levels at the time of cancer diagnosis are associated with a positive change in percent body fat over a 12 month period. Results adjusted for race, age at diagnosis, BMI at diagnosis, menopausal status at diagnosis, and cancer stage.

Changes in weight and body composition over a 12 month period following breast cancer diagnosis were not related to circulating CBG levels at the time of cancer diagnosis or at 12 months following diagnosis, although change in CBG levels over the 12 month period was associated with changes in BMI. As shown in Figure 10, positive increases in CBG levels over this period, resulting in less circulating cortisol, was associated with declines in weight and BMI, while declines in CBG levels (associated with increased levels of free cortisol) were associated with increased weight and BMI (F=3.38, p=0.02; p-trend=0.02) after adjustment for BMI at the time of cancer diagnosis, race, season of diagnosis, menopausal status at the time of diagnosis, and cancer stage. Changes in CBG levels, however, were not associated with any changes in percent body fat (data not shown), although higher CBG levels at the time of cancer diagnosis was associated with gains in percent body fat (see Figure 11), which is opposite to what was expected. Cortisol, cortisol_11deoxycortisol, calculated levels of unbound cortisol, 17-OH-Progesterone, and ACTH levels at the time of cancer diagnosis, 12 months following diagnosis, and changes in levels during this period were not associated with changes in weight, BMI, or percent body fat (data not shown).

Decreased sex steroid levels are associated with decreased lean body mass and increased fat, including increases in visceral fat mass. The biological activity of sex hormones (estrogen and testosterone) and its relationship with weight may be modified by circulating levels of SHBG and albumin. About 30-40% of plasma estradiol is bound to SHBG, 2-3% is free estradiol, and the rest is bound to other plasma proteins, mainly albumin. To determine if changes in weight and body composition are associated with changes in sex steroid levels, we measured circulating levels of FSH. Increasing FSH levels at the time of breast cancer diagnosis, possibly indicating lower estrogen levels, was found to be inversely associated with changes in percent body fat with women in the lowest quartile of FSH showing gains in percent body fat (lsmean 2.48, 95%CI 0.61, 4.35) compared to those in the highest FSH quartile, who experienced a slight decline in

percent body fat (lsmean -0.62, 95% CI -2.54, 1.29) (F=2.36, p=0.07, p-trend =0.01), although no relationship was observed with FSH levels 12 months following breast cancer diagnosis or with change in FSH levels. In our population, FSH levels at baseline were inversely correlated with estradiol levels (r=-0.38, p<0.0001). LH levels at baseline were also inversely related to change in body fat over the 12 month period (F=3.78, p=0.01, p-trend = 0.002), with women in the lowest quartile of LH showing an increase in percent body fat (lsmean=2.09, 95% 0.31, 3.79) compared to those in the highest LH quartile, who lost percent body fat (lsmean -1.34, 95% CI -3.16, 0.46). As expected FSH and LH levels were highly correlated (r=0.78, p<0.0001), although the inverse association with estradiol levels were not as strong for LH (r=-0.19, p=0.006) compared to FSH. None of the other sex hormones assayed, including DHEAS, estradiol, estrone, progesterone, as well as total testosterone, free testosterone, or androstenedione levels were related to changes in weight, BMI, or body composition.

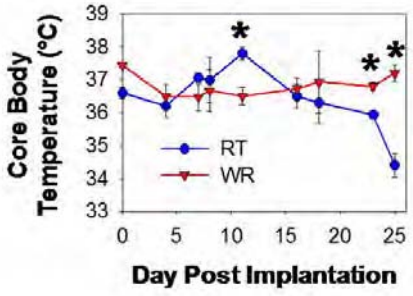


Figure 12. Mice (with tumors-CT26) housed in "normal" room temperature (RT) develop a decrease in core body temperature (blue, circles). However, if they are maintained in a preferred, warmer room (WR-28-30 °C) body temp. is stabilized (red, triangles). * p < 0.011

3.B. Development of Research Studies to Examine Body Temperature Perception and Immune Function following Breast Cancer Diagnosis.

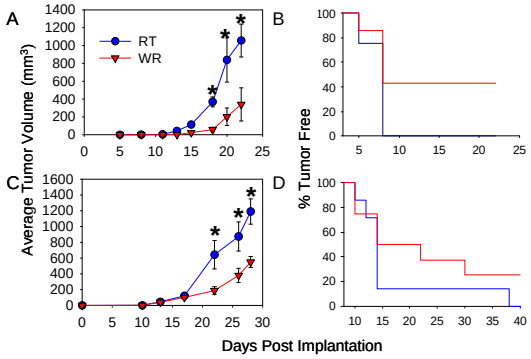


Fig. 13. C57Bl/6 mice bearing B16.F10 tumors (A&B) and BALB/c mice bearing CT26 tumors (C&D) demonstrated inhibited tumor growth (and improved survival (B,D) when housed in a warmer ambient temperature (red, triangles) in comparison to standard conditions , (blue, circles). * p <0.03

The establishment of this cohort of breast cancer survivors has led to a multi-disciplinary collaboration with Dr. Elizabeth Repasky within the Department of Immunology at the Roswell Park Cancer Institute to explore the relationship between body temperature and immune function and the significance of thermal discomfort among breast cancer survivors. This research collaboration stems from Dr. Repasky's initial observation in tumor bearing rodent models that modest increases in ambient temperature can significantly delay and/or reduce tumor growth, with effects apparently mediated by the immune system. As shown in Figure 12, body temperature in mice appears to fall as tumor growth increases. Since the energy required to maintain body temperature is directly dependent upon

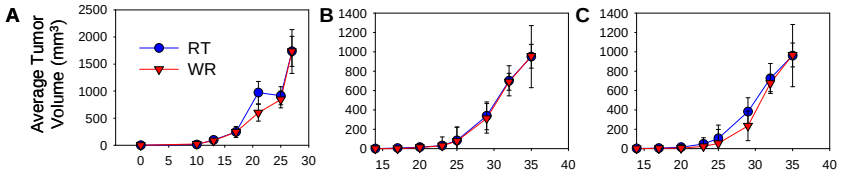


Fig.14. BALB/c depleted of CD8 T lymphocytes (A) and SCID mice (B & C) bearing CT26 tumor housed in "warm" room (WR) temperatures do not show any differences in tumor growth rate from that of mice housed in standard conditions (RT) In (C), the SCID mice were also depleted of NK cells, which had no effect.

ambient temperature, this drop in body temperature was prevented by raising ambient temperature to 28-30^{o}C, which is thermoneutral for mice. An u*nexpected and intriguing observation, however, was that support of body temperature alone (i.e., providing enough ambient heat to bring core temperature back to 37^{o}C <u>without</u> creating hyperthermia) achieved by maintaining mice in the warmer environment, could significantly delay and/or reduce tumor growth rate and improve overall survival (Figure 13).* This striking effect was observed in two different strains of mice (BALB/c and C57Bl/6) and using two aggressive cell lines to generate tumors (CT26 and B16.F10). Importantly, tumor growth delay *did not occur* in mice depleted of CD8 T lymphocytes, or in severe combined immunodeficiency (SCID) mice (which lack significant cellular immunity) supporting a primary effect of temperature on the adaptive immune response (see Figure 14).

<u>Body Temperature Changes in BrCa Patients</u>**.** As a first step in translating these findings, we investigated whether differences or changes in body temperature after cancer diagnosis are evident in BrCa patients. We examined body temperature in an initial 277 women participating in the Women's Health **a**fter **B**reast **C**ancer (ABC) Study. Tympanic temperatures at diagnosis and 12 months following diagnosis were abstracted from medical records. Prior to any treatment, body temperature was positively related to cancer stage and greater number of positive nodes (see Figure 15). Declines in body temperature after treatment were observed, and were related to higher cancer stage and treatment with chemotherapy (see Figure 16). Changes in body temperature over a one year period were associated with serum C-reactive protein (CRP) levels (a marker of systemic inflammation secreted by the liver in response to proinflammatory cytokine-peptide signals) at 12 months following cancer diagnosis. Women with the highest CRP levels compared to those with lower CRP levels were least likely to show a decline in body temperature, indicating

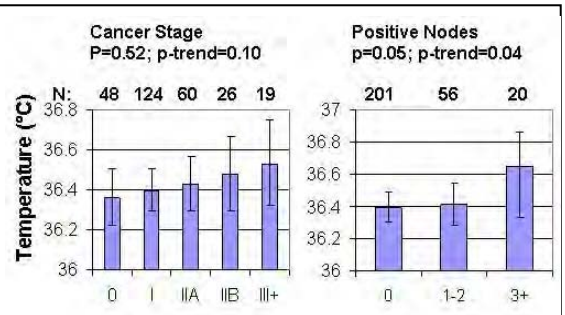


Figure 15. Stage and nodal involvement are related to body temperature at cancer diagnosis prior to treatment for 277 incident breast cancer cases. All analyses are adjusted for race, age at diagnosis, and season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec).

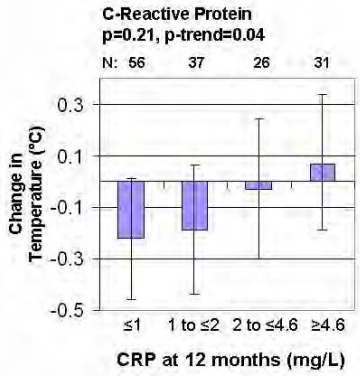


Figure 17. CRP levels at 12 months following BrCa diagnosis are inversely associated with change in body temperature from the time of diagnosis to 1 year following diagnosis. Analysis adjusted for race, age at diagnosis, season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec), and BMI at 12 months following diagnosis.

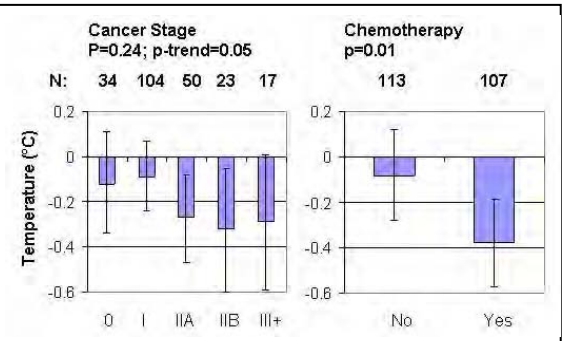


Figure 16. Declines in body temperature from the time of initial BrCa diagnosis to 12 months following diagnosis for 228 incident breast cancer cases. All analyses are adjusted for race, age at diagnosis, and season of diagnosis (Jan-Mar, Apr-Jun, Jul-Sep, Oct-Dec). Chemotherapy is additionally adjusted for tumor grade and cancer stage.

that higher levels of cytokine-mediated inflammation are associated with being able to maintain a higher body temperature after breast cancer treatment (see Figure17). These results together suggest that changes in body temperature regulation may occur in BrCa patients and supports existing data suggesting that circadian control of core body temperature may be distorted in these patients[1]. Moreover, this dysregulation may be linked with inflammatory and immune pathways as suggested by the preliminary data in mice.

Thermal Discomfort in BrCa Patients**.** As a first step in determining if breast cancer patients experience symptoms of being persistently cold, we designed a questionnaire in the second year of the study to collect information on patients' experience with thermal discomfort, focusing on feelings of being "inappropriately and excessively cold" as well as "hot flashes and sweats", with the latter included as a "control" symptom due primarily to hormone suppression therapies given for BrCa treatment. The questionnaire was directly patterned on the Multidimensional Assessment of Fatigue (MAF) scale[2, 3], a validated questionnaire assessing fatigue, which contains 16 items and measures four dimensions of fatigue experienced over the past 7 days: i.e. severity, distress, degree of interference in activities of daily living, and timing. It is one of only a few fatigue instruments that have demonstrated an ability to detect change over time[2]. The MAF is a revision of the Piper Fatigue Scale, a 41-item measure of fatigue developed for research purposes and tested with oncology patients[4, 5]. In addition to questions patterned on the MAF questionnaire, the prevalence, frequency, and severity of symptoms over the past 6 months are also assessed, and patients are asked to compare their experiences to those prior to cancer diagnosis. From July 2007 to December 2009, the questionnaire was piloted in the ABC Study and was completed by 164 participants one year after their initial breast cancer diagnosis. Among participants who completed the questionnaire, 37% of patients reported feeling inappropriately cold at least occasionally in the past 7 days compared to 43% who reported hot flashes. These symptoms, however, appeared to have distinct etiologies since hot flashes, but not feeling inappropriately cold, were more strongly associated with receipt of hormonal therapy and change in menopausal status from pre- to postmenopausal (see Figure 18). These results together suggest that changes in body temperature regulation occur in BrCa patients and that symptoms of feeling cold or chilled are distinct from those arising from hormone suppression therapies given for the treatment of BrCa.

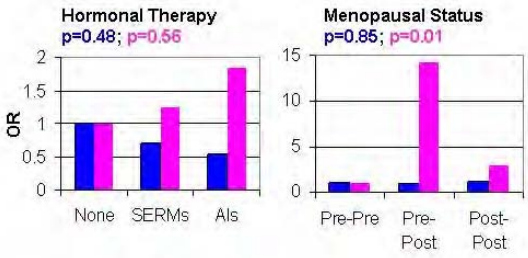


Figure 18. Factors related to reports of feeling chilled (symptom vs none; blue; N=164) or occurrence of hot flashes (symptom vs none; pink; N=162) 12 months after cancer diagnosis. All analyses are adjusted for age at diagnosis, race, and season of diagnosis. Hormonal therapy is additionally adjusted for cancer stage and tumor grade. SERM: selective estrogen receptor modulator; AI: aromatase inhibitor.

4. REPORTABLE OUTCOMES

4.1. Manuscripts

The hypothesis that thermal discomfort among BrCa cases may be an important indicator of disease prognosis is reviewed in a manuscript, which has been accepted for publication in the International Journal of Hyperthermia. The manuscript entitled 'Feeling too hot or cold after breast cancer: Is it just a nuisance or a potentially important prognostic factor?' was first-authored by Kathleen Kokolus, my PhD student that I co-mentor as a primary supervisor with Dr. Elizabeth Repasky.

4.2 Abstract Presentation

Hong CC, K Kokolus, C Ambrosone, S Edge, S Kulkarni, E Repasky. Body Temperature and Thermal Discomfort among Breast Cancer Survivors. AACR Annual Meeting, April 17-21, Denver Colorado. (Abstr 906).

4.3. Establishment of Serum and Urine Repository

This research grant has allowed for the creation of a serum and urine repository for the conduct of survivorship studies of breast cancer patients. This biorepository is unique in that it collects biospecimens annually and therefore lends itself well to studies aimed at detecting changes that occur during and after breast cancer treatment.

4.4. Establishment of Study Database

In collaboration with the Clinical Research Services and Information Technology department at Roswell Park, a comprehensive database has been developed which allows for double entry of all data collected by survey. The database developed uses the eResearch Technology (eRT), eData Management, eStudy Conduct, eSafety Net software products as well as various other Roswell Park Cancer Institute custom applications connected to eRT via Microsoft ODBC technology. The database is currently interfaced to RPCI's hospital information system (demographics), and the RPCI Cerner lab system (lab results), which allows all of this information to transfer electronically. The database management system is Oracle 9i. Backups of the study data to tape are performed nightly and stored in a separate physical location from the servers themselves.

4.5. Employment or Research Opportunities

4.5.1. Employment

Based in part on the success of the survivorship cohort developed with this grant and its broad potential as a basis for developing a number of research projects focused on survivorship research in breast cancer patients, I was promoted to an Assistant Member position at Roswell Park Cancer Institute (RPCI) effective Jan 03/08, which is equivalent to a tenure track Assistant Professor at universities. In addition, based on the research funding provided by the DoD and Komen for this project, I was invited to be a member of the Cancer Center Support Grant at RPCI. I also have an appointment as a Research Assistant Professor at the Department of Social and Preventive Medicine at SUNY University at Buffalo, and my application to be an Assistant Professor in the Department of Cancer Pathology and Prevention at Roswell Park was approved.

4.5.2. Funding Applied for based on Work Supported by Training Grant

Data generated by work supported by the multidisciplinary postdoctoral fellowship led to an invitation to submit a DoD impact award last year, although the application was ultimately not funded. An R21 grant was also submitted (not funded), to test whether hot baths can be used as a strategy among breast cancer patients to improve immune function as an adjunct to their regular treatment. Most recently, the preliminary data generated in the Women's Health after Breast Cancer Study was used to support an R01 application submitted in June, 2010.

DoD Breast Cancer Impact Award (Hong) 04/01/10-03/31/14
Dept. of the Army – USAMRAA
Does Supporting Body Tem perature Enhance Imm unity Against Breast Cancer and Im prove Quality of Life Among Survivors?
Study goals: The overall goal of this study is to achieve the first comprehensive appreciation of potential relationships between body tem perature, thermal discomfort experienced by wom en with breast cancer, cytokine expression, cytokine-driven symptoms of cancer associated sickness, and the anti-tumor immune response.

NIH, R21 (Hong) 12/01/10 – 11/30/12

Nightly baths: A strategy for altering immune function in breast cancer survivors
Study Goal: We propose to conduct a highly novel randomized intervention study to assess taking nightly hot baths as a strategy for improving immune function. We hypothesize that women receiving daily hot bath treatments will show improvements in immune function, better sleep quality, reduced fatigue and better quality-of-life, and fewer symptoms of thermal discomfort.

NIH R01 (Hong) 04/01/2011-02/20/2016
Body Temperature: An immune and prognostic marker in breast cancer?
The goal of this research will be to determ ine if body temperature and/or feelin gs of being inappropriately cold ref lect immune profiles a ssociated with breast cancer prognosis using a prospective hospital-based cohort study of 1,700 incident breast cancer cases.

5. Conclusion

We will continue to perform data analysis and manuscript preparation. From a public health viewpoint, findings from this study may indicate ways to improve women's health after breast cancer and to optimize their long-term survival. Future planned directions for this cohort of breast cancer patients include the translation of findings from animal research showing a link between body temperature regulation and cancer prognosis. We propose in our R01 application to examine potential relationships between body temperature, thermal discomfort experienced by women with breast cancer, immune phenotype, and cytokine-driven symptoms of cancer associated sickness. Identification of key immune patterns related to breast cancer prognosis,

body temperature, symptoms of thermal discomfort, and/or clusters of cytokine-related symptoms experienced by BrCa patient is critical for the design of future interventions aimed at altering or supporting body temperature because studies can target these cytokines/cytokine patterns as intermediate biomarkers of long-term prognosis. Another direction of future research will be to increase understanding of how obesity might adversely affect breast cancer prognosis through effects on immune function, and how these differences are reflected in differences in body temperature and/or symptoms of being cold. Moreover, if future proposed research shows that body temperature and/or feelings of being persistently cold are robust prognostic factors, the existence of extensive data on modifiable risk factors from our study questionnaires will allow evaluation of these factors with respect to body temperature and symptom levels. Greater understanding of these relationships will provide insight into potentially modifiable factors and interventions that may impact body temperature and/or symptoms of thermal discomfort.

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Appendices

1. **Review manuscript accepted for publication**
2. **CV for Chi-Chen Hong**

Appendix 1. Review Manuscript Accepted for Publication

Int. J. Hyperthermia, Month?? 2010; ??(?): 1–19

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RESEARCH ARTICLE

Feeling too hot or cold after breast cancer: Is it just a nuisance or a potentially important prognostic factor?

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(Received 17 February 2010; Revised 5 July 2010; Accepted 6 July 2010)

Abstract

There is widespread recognition among both patients and caregivers that breast cancer patients often experience debilitating deficiencies in their ability to achieve thermal comfort, feeling excessively hot or cold under circumstances when others are comfortable. However, this symptom receives little clinical or scientific attention beyond identification and testing of drugs that minimise menopausal-like hot flushes. Could some of these symptoms represent an important prognostic signal? Could thermal discomfort be among other cytokine-driven sickness behaviour symptoms seen in many breast cancer patients?. While the literature reveals a strong link between treatment for breast cancer and some menopausal vasomotor symptoms (e.g. hot flushes), there is little data on quantitative assessment of severity of different types of symptoms and their possible prognostic potential. However, recent, intriguing studies indicating a correlation between the presence of hot flushes and lower development of breast cancer recurrence strongly suggests that more study on this topic is needed. In comparison to reports on the phenomenon of breast cancer-associated hot flushes, there is essentially no scientific study on the large number of women who report feeling excessively cold after breast cancer treatment. Since similar acquired thermal discomfort symptoms can occur in patients with cancers other than breast cancer, there may be as yet unidentified cancer – or treatment-driven factor related to temperature dysregulation. In general, there is surprisingly little information on the physiological relationship between body temperature regulation, vasomotor symptoms, and cancer growth and progression. The goal of this article is twofold: (1) to review the scientific literature regarding acquired deficits in thermoregulation among breast cancer survivors and (2) to propose some speculative ideas regarding the possible basis for thermal discomfort among some of these women. Specifically, we suggest a potential association with excessive pro-inflammatory cytokine activity, similar to other cytokine-driven symptoms experienced after breast cancer, including fatigue and depression. We highlight the similarity of some breast cancer-associated thermal discomfort symptoms to those which occur during fever, suggesting the possibility that there may be common underlying changes in pro-inflammatory cytokine activity in both conditions. We anticipate that this contribution will stimulate additional scientific interest among researchers in identifying potential mechanisms and prognostic significance of this under-studied aspect of breast cancer biology and survivorship.

Keywords: *fever, menopausal vasomotor symptoms, pro-inflammatory cytokines, sickness behaviour symptoms*

Introduction

This article was prepared to familiarise cancer researchers and thermal medicine specialists with the fact that a large percentage of patients report the onset of a significant degree of acquired thermal discomfort symptoms after cancer, some of which are very similar to those vasomotor symptoms experienced during menopause. While patients with various types of cancer report this symptom, breast cancer far outweighs the other cancers in terms of association with thermal discomfort symptoms. Breast cancer patients frequently feel excessively hot and/or cold under ambient temperature conditions in which others are able to adjust easily to achieve thermal comfort. Some report feeling quite cold for long periods of time. As judged from the large anecdotal information available regarding this problem on various breast cancer websites

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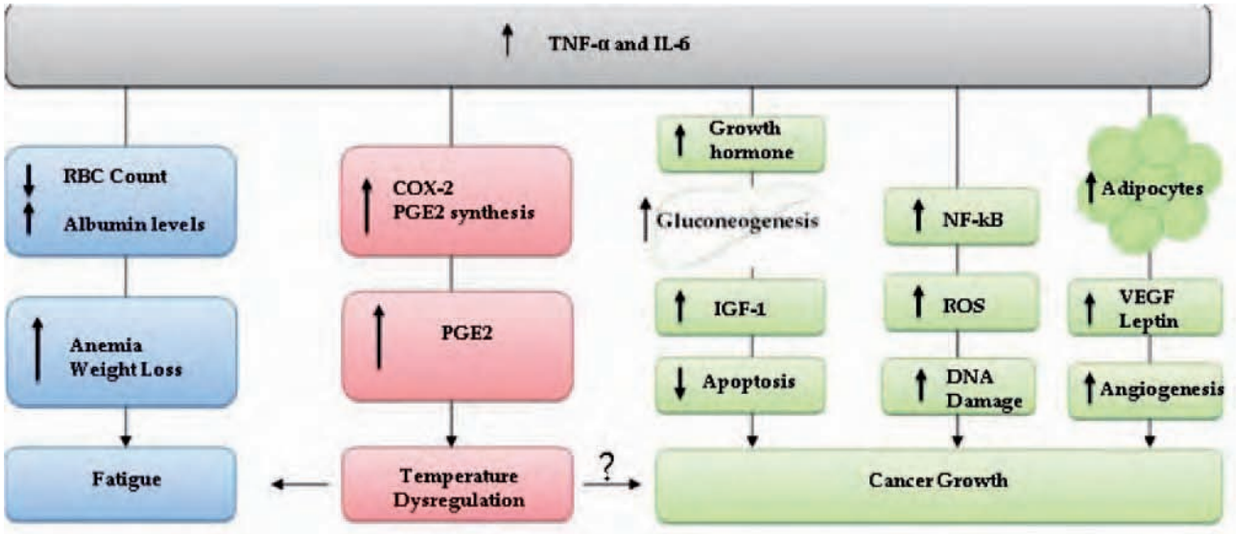

Figure 2. ▮▮▮▮.

body temperatures below 36°C compared to a mean temperature of 36.7°C measured in a group of college-aged students [44]. The mechanisms leading to declining body temperatures in aging populations are unclear, but include clinical and environmental influences such as nutrition and medication [45]. Interestingly, body temperature in elderly individuals with various morbidities are significantly lower compared to body temperature in young adults, while temperatures among healthy elderly individuals remain similar to their younger counterparts [46]. This observation could present interesting ramifications in cancer research as cancer patients (putatively unhealthy) may be more prone to additional thermal regulatory issues not seen in other age-matched populations.

In addition, the elderly respond to cold stress differently from younger individuals. Several studies report that the elderly are less efficient at maintaining core body temperature under cold stress [45, 47, 48], which appears to be mediated by an impaired ability to undergo vasoconstriction [49, 50]. Heat stress, however, does not seem to pose as much of a problem among older adults, and has not been shown to correlate to warmer body temperatures [51, 52]. In addition, older individuals have a lower RMR than younger individuals, which may indicate metabolic deterioration and alter overall energy balance [53]. Several factors including sodium-potassium pump activity, fat mass, maximal aerobic power, and menopausal status are important factors influencing the decline of RMR in the elderly [54].

Effects of thyroid hormones on thermoregulation

The thyroid gland may be another target of investigation for a better understanding of temperature dysfunction in breast cancer patients. Thyroid hormones are responsible for the increased heat production normally required for humans to maintain body temperature above that of the environment [55]. Also, a direct association between breast cancer and enlarged thyroid glands has been shown. Both an increased mean thyroid volume and larger percentages of individuals with enlarged thyroid glands were shown to be significantly greater in women with breast cancer than age-matched controls [56]. Clearly, further investigation of the effects of breast cancer treatments on the thyroid gland and production of thyroid hormones, and on whether these effects are present in the same patients with defective thermoregulation, are needed. If an association is revealed, it may stimulate new research on identification of new thyroid-related targets through which thermal discomfort may be alleviated.

Feeling too hot: Menopausal vasomotor symptoms of overheating/sweating among cancer patients

Hot flushes and the role of sex hormones

A very common thermoregulatory alteration is the experience of hot flushes, which are characterised by sudden episodes of flushing and/or sweating and a sensation of heat, often preceded or followed by chills [57–59]. These sensations are a normal occurrence in about 75% of healthy women, particularly during menopause [60]. In healthy women, hot flushes follow a circadian rhythm similar to that of their core body temperature, with hot flush frequency and intensity increasing when core body temperature is at its apex [61, 62]. However, as will be detailed later, the correlation between core body temperature

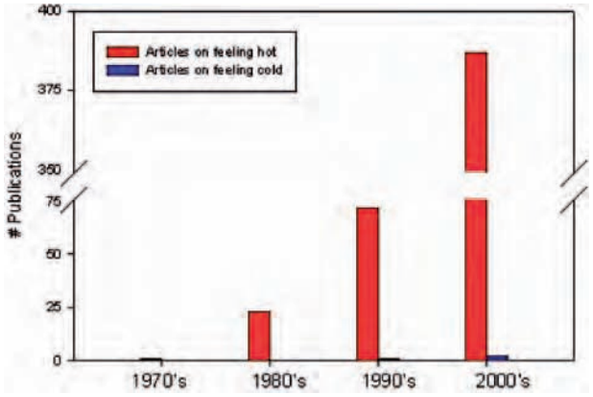

Figure 3. ▮▮▮▮.

and the circadian patterns of hot flushes is disrupted in cancer patients [63]. Studies have found that women susceptible to hot flushes show a reduction in their 'thermoregulatory null zone', which is the temperature range between sweating and onset of shivering [64–66]. Among symptomatic women with reduced thermoregulatory null zones, changes in core body temperatures are more detectable, which induces changes in hormones and/or neurotransmitters that lead to a hot flush [63, 66].

Menopause, either natural or therapeutically induced, is considered to be a key instigator for temperature dysregulation. As shown in Figure 3, female reproductive hormones, oestrogen and/or progesterone, affect the mechanisms regulating blood flow to the skin [67–70], and hot flushes have been found to be influenced by the diameter of blood vessels that deliver blood to the skin and the volume of blood in these vessels [26]. Oestrogen promotes vasodilation and therefore reductions in oestrogen occurring during menopause restrict the body's ability to efficiently dissipate heat [26]. Oestrogen therapy has been shown to alleviate some of these symptoms by decreasing body temperature and lowering the temperature at which vasodilation is initiated [68, 69]. Conversely, progesterone has been suggested as an inhibitor of vasodilation [71]. Studies have found that oestrogen replacement therapies reduce the incidence of hot flushes when combined with a progestin, which mimics progesterone, although the effect is not additive [72]. Although decreased oestrogen levels are implicated as a major factor in thermoregulatory control, few studies have been conducted to determine the precise physiological mechanism(s) by which oestrogen controls thermoregulation. Moreover, oestrogen deprivation alone is not a sufficient cause of hot flushes as oestrogen levels do not differ between symptomatic and asymptomatic postmenopausal women [60, 73–75], and frequency and severity of hot flushes have not been correlated to plasma [60, 76], urinary [60, 77], or vaginal [60, 77] oestrogen measurements. Thus, other mechanisms are likely to be involved in the etiology of hot flushes [78].

Menopausal symptoms among breast cancer patients

Although most women experience hot flushes as they age and become menopausal, women with a history of breast cancer appear to have more severe symptoms [63, 79, 80]. Sudden onset of treatment-induced menopausal symptoms among breast cancer patients are common, with these individuals being over five times more likely to report hot flushes than those with no history of breast cancer [81]. Hot flushes have been postulated to be an independent predictor of tamoxifen efficacy among breast cancer patients, and data from the Women's Healthy Eating and Living (WHEL) randomised trial of 1,551 women found that women who reported hot flushes among those taking tamoxifen were less likely to develop recurrent breast cancer than those who did not report hot flushes [2]. Similarly in the Arimidex, tamoxifen alone or in combination (ATAC) trial, the appearance of new vasomotor symptoms or joint symptoms in response to oestrogen depletion was associated with lower subsequent recurrence compared to women who not report these symptoms [3]. Despite being a possible predictor of better disease prognosis menopausal symptoms lead to declines in quality of life among breast cancer patients by interfering with daily activities, sleep patterns, and self esteem [58, 82]. Because of the prominence of these symptoms following hormone suppression treatments, it is important to understand the causal mechanism for these symptoms in order to develop alleviation treatments without affecting the prognosis or efficacy of breast cancer treatments prescribed. Subsequent improvements in quality of life would be expected to promote treatment adherence, particularly with respect to long-term use of anti-estrogens, and would be expected to optimise disease prognosis.

Hormone suppression medications commonly used in breast cancer treatment regimens include use of selective oestrogen replacement modulators (SERMs) and aromatase inhibitors (AIs) [83–86]. Chemotherapeutic drugs also contribute to the high degree of thermal dysfunction in breast cancer patients because of their negative impact on ovarian function often causing premature and unnatural menopause due to rapid declines in oestrogen levels [63, 80, 87] (see Figure 3).

In addition to hormone-mediated effects, hot flushes among breast cancer patients appear to be potentially influenced by a number of other factors.

For instance, recent studies show that serum interleukin-8 (IL-8) concentrations in women who report hot flushes are significantly higher compared to women who do not experience hot flushes [88]. Given that IL-8, a pro-inflammatory cytokine involved in immune function, has been associated with breast cancer invasiveness and angiogenesis [89], understanding the biological relationship between thermoregulation and immune function, if any, may be important for disease prognosis (see below).

The pathophysiology of breast cancer itself may also make breast cancer patients more susceptible to hot flushes. Breast cancer can disrupt circadian rhythms, thereby altering the release of reproductive hormones [90], and altering circadian control of body temperature [62, 63]. The thermoregulatory null zone sets the bounds within which core body temperature is regulated in humans [64–66]. When the thermoregulatory null zone is reduced in women experiencing a hot flush, increases in core body temperatures are more detectable by the individual and therefore inducing additional discomfort [63, 66]. It is important to note that hot flushes do not result from an increased heating of blood, but instead from signals sent to the hypothalamus resulting in the release of large amounts of blood into regions that are normally set to remain cooler, such as the skin [26]. Whether these physiological factors are involved in reducing risk of breast cancer recurrence in patients who experience hot flushes (as in the case reported by the WEHL and ATAC trials described above) is not known.

Treatments used to alleviate hot flushes among breast cancer patients

Although a great deal of current scientific literature has been already been dedicated to studying patients who feel too hot after cancer treatment (see Table I), many questions remain. Understanding the mechanisms targeted by drugs used to alleviate hot flush symptoms may help researchers gain insight into why hot flushes and other thermal regulatory issues arise in patients following cancer. Most hot flush treatments work by mimicking or supplementing oestrogen allowing for increased vasodilation and heat to be efficiently dissipated from the body. The use of oestrogen supplements to reduce hot flush symptoms has been shown to be effective, but comes with increased risk of heart disease and breast cancer. Therefore, these supplements are generally used only as a last resort in healthy women [91] and not recommended for breast cancer patients, particularly those with oestrogen receptor positive disease [92]. Non-hormonal treatment for hot flushes is currently an active research area in both healthy women and women with breast cancer. This topic has been recently reviewed by a number of authors and is summarised in Figure 3 [70, 78, 93, 94].

Selective serotonin reuptake inhibitors (SSRIs) such as sertraline are generally prescribed as antidepressants, but have been shown to reduce hot flush symptoms in users. SSRIs have been shown to reduce hot flushes in the general population [95, 96] as well as in breast [97–99] and prostate [100] cancer patients. Encouragingly, sertraline is safe in combination with tamoxifen and the combination of these drugs results in fewer and less severe hot flushes [97]. However, the effects of these drugs are not consistent between individuals. Unfortunately, no obvious factor such as age or health has been identified to determine the strength of an individual's response to SSRI treatment on hot flush occurrence [95]. Black cohosh, a plant extract that acts on serotonin by an uncertain mechanism [101], however, has not been found to decrease the frequency or intensity of hot flush [102].

Venlafaxine is another antidepressant used to alleviate hot flushes in breast cancer patients [103, 104]. Venlafaxine differs from sertraline because it is a serotonin-norepinephrine reuptake inhibitor (SNRI), which in addition to acting on serotonin also acts on norepinephrine, although its efficacy in relieving hot flushes is lower than that associated with medroxyprogesterone acetate (MPA), a progestin [105]. Additional alternative therapies are being investigated to alleviate hot flush symptoms. Clonidine, a drug used to treat high blood pressure, has been found safe to use in conjunction with tamoxifen and is capable of reducing hot flushes resulting from breast cancer treatment [106]. The effects of isoflavones, such as soya and clover, are inconsistent in the current literature. Soya works as a phytoestrogen in humans as it binds to oestrogen receptors and has been shown in some studies to reduce hot flush symptoms [107–109] while others report no significant differences between soya and placebo [110, 111] and red clover and placebo [112]. Magnetic therapy has been found to be unsuccessful in hot flush treatment [58].

Occurrence of hot flushes in cancer populations other than breast cancer

While the phenomenon of hot flushes is most widely reported among breast cancer patients, hot flushes are also reported for other cancer sites, especially those in which hormone suppression treatments are common (Table I). Men with prostate cancer who undergo chemical or surgical castration to lower sex hormone levels have a high frequency of hot flushes following treatment [113, 114]. Alleviation of hot flushes in these patients has been achieved with low

doses of megestrol acetate [86, 114]. Another common treatment for prostate cancer is the use of gonadotropin-releasing hormone agonist goserelin, which reduces the secretion of testosterone by reducing gonadotropin secretion and inducing hypogonadism. Goserelin is used as an adjuvant in combination with irradiation. The combination of these treatments will improve control and survival in prostate cancer patients but up to 62% of patients receiving this treatment report hot flushes [113]. Anti-depressants have been shown to help relieve hot flushes in male patients recovering from prostate cancer similarly as in women with breast cancer. It is possible that anti-depressants relieve hot flushes in prostate cancer patients due to a stabilising effect on the autonomic nervous system [100]. Preliminary studies by Kouriefs et al. report the use of antidepressants for relieving hot flushes in prostate cancer patients [59]. In addition, hot flushes have been reported among ovarian cancer patients treated with leuprolide acetate, a gonadotropin releasing hormone agonist [115–117], which lowers oestrogen levels.

Feeling too cold: Symptoms of persistent chill among breast cancer patients

Evidence for symptoms of cold stress among breast cancer patients

Much less recognised in the scientific community is the possibility that a subset of cancer patients report experiencing symptoms of being persistently and inappropriately cold after cancer diagnosis and treatment. To date, this symptom has primarily been reported anecdotally, particularly among women participating in breast cancer support groups. Interestingly, one report on the economics of hidden costs associated with breast cancer mentions the increased need for extra 'heating, bedding, clothing, electric blanket, heater, thermal underwear, baths, towels and high calorie foods' identified by women as needed to deal with excessive coldness [118]. This symptom is frequently clustered together clinically and scientifically with reports of hot flushes and attributed to menopause or hormone suppression therapy. However, we propose that assuming cold stress to be related to menopausal symptoms may overlook the importance of various thermoregulatory changes that may occur among breast and other cancer patients.

Much of the clinical and scientific evidence indicating that some cancer patients might experience cold stress after cancer diagnosis either comes from case reports or indirectly from studies that were focused on some other primary hypotheses. As a result, this symptom has not been explored rigorously. On careful examination however, findings from some studies do indicate that symptoms related to cold stress might be part of a distinct pathological mechanism that is separate from menopausal and hormone-related causes. For example, a study that used factor analysis to validate a survey measuring pain among 100 early stage organ non-specific cancer outpatients receiving chemotherapy (38 men, 62 women) identified feeling numb and being cold as important clusters loading onto a distinct factor [119]. Another study reviewing cancer-related fatigue indicated that changes in body processes, including feeling cold, occurred only in fatigued or exhausted patients [120]. Chemotherapy has also been linked to feeling cold; a study of 40 women receiving chemotherapy reported that 14% of women receiving six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) experienced 'feeling cold in the chest and arm' following their therapy [121]. In addition to breast cancer, feeling cold has been associated with testicular cancer, lasting several years following treatment [122]. A study of 277 testicular cancer survivors and 392 non-cancer controls showed that the cases felt significantly colder when compared to controls [122].

Some recent studies may shine further light on molecular pathways that may be involved in the manifestation of symptoms of cold stress. Endothelin-1 (ET-1) can alter temperature detection thresholds among cancer patients. ET-1 acts as a growth factor in various malignancies [123], is overexpressed in breast carcinomas, and has been linked to poorer disease prognosis [124]. In a randomised study, Hans et al. [125] examined the effect of ET-1 injection, a known vasoconstrictor, on spontaneous pain and temperature perception in healthy male volunteers. They found that high doses of ET-1 altered both cold and heat detection thresholds. The cold thresholds were significantly increased by a 10^{-10} M dose of ET-1 after 60 min ($p < 0.05$) whereas all doses above 10^{-6} M elicited a significant dose-dependent increase in heat detection threshold ($p < 0.05$) [125]. They concluded that the observed changes in heat detection developed sooner, lasted longer and were more pronounced than the changes observed in cold detection [125]. These finding raise the possibility that ET-1 may alter temperature preferences. Since ET-1 expression has also been linked to breast cancer tissue, it warrants further investigation into the epidemiological and clinical factors that contribute to altered ET-1 concentrations and their influence on temperature regulation and disease prognosis in this group.

In future studies aimed at characterising this thermal symptom and elucidating its clinical significance, several questions should be posed. What proportion of breast cancer patients have symptoms

of being persistently chilled? What is the frequency and severity of these symptoms? What degree of distress and interference in activities of daily living and timing do these symptoms have? When do breast cancer patients experience these symptoms with respect to disease diagnosis and treatment? How long do these symptoms persist after treatment? What are the perceived reasons for their experience and what are the treatments patients have tried to cope with these symptoms? Also important is determining whether there is an accompanying change in body temperature and whether changes in body temperature or symptoms of feeling persistently cold are related to disease course and/or treatment efficacy. If it is found, through observational epidemiological studies, that an actual increase in body temperature occurs, is it possible that breast cancer patients develop deficiencies in their ability to perceive thermal comfort. Conversely, if a decline in body temperature is observed, is it possible that this is a physiological response to toxic breast cancer treatments, similar to that seen in animal models in response to harmful exposures. Several of these possibilities are discussed below.

Evidence for hypothermia among animal models

While scientific study examining cold stress in clinical populations and its significance is in its infancy (see Figure 1), there is a growing body of evidence in animal models indicating that hypothermia, induced by immune mediators, occurs in response to harmful environmental exposures. Murine models have shown evidence that body temperatures may drop in response to various exposures, such as bacterial lipopolysaccharide (LPS) [18, 126]. Additionally, studies in various animal models report decreased core body temperature in response to adverse events such as food restriction [127], hypoglycaemia [128, 129], hypoxia [130, 131], dehydration [132], and infection [133–136]. These studies suggest that declines in body temperature could be a possible mechanism for defending the body against harmful exposures. This idea is further supported by studies showing that exposure to nickel or cadmium metal decreases metabolic rates in mice making them hypothermic [137]. The decrease in temperature helps the body fight toxins in two ways: first by attenuating the toxicity of the chemical by reducing its conversion into an active intermediate, and second, by decreasing the rate of respiration and further uptake of toxin [18]. It is possible that chemotherapy may be perceived as a toxin and therefore result in declining body temperature among breast cancer patients as they undergo and complete breast cancer treatment. Thus, there is evidence from animal models indicating that cold stress in humans could be mechanistically distinct from the symptoms arising from hormone suppression therapy. A second possibility regarding underlying mechanism causing feelings of excessive chill may relate to thermal perception alterations similar to that which occurs during fever, in which an individual can feel quite cold, despite normal or even elevated body temperatures, due to underlying inflammatory changes in the immune system. This possibility is discussed below.

Potential link between thermoregulation, pro-inflammatory cytokines, and immune function

Pro-inflammatory cytokines and sickness behaviour symptoms in breast cancer patients

Chemotherapy treatment in breast cancer patients promotes increases in plasma levels of pro-inflammatory cytokines [156, 157]. Additionally patients unresponsive to chemotherapy have significantly higher IL-6 levels than responsive patients [158]. Elevated cytokine levels, including IL-1, IL-6, IL-8, and IL-18 have been correlated with disease stage and progression of cancer [159, 160]. These cytokines have been etiologically implicated in a number of sickness behaviours experienced by breast cancer patients, including fatigue [161–163], sleep disturbance [162], depressed mood [164], and loss of appetite [165]. While symptom severity often declines with time, some symptoms remain for years after the initial cancer diagnosis [161], possibly indicating a long-term effect of pro-inflammatory cytokines on disease-related symptoms as well as outcomes. These symptoms have been well studied, and found to be related to increased cytokine levels of interleukin-1-beta (IL-1β), tumour necrosis factor-alpha (TNF-α), and/or IL-6 [156, 166]. As shown in Figure 4, increased levels of TNF-α and IL-6 are correlated with decreased red blood cell production, higher levels of albumin, weight loss, anaemia, and fatigue [166]. In addition, TNF-α and IL-6 have various metabolic actions including increased adipocyte production and gluconeogenesis [167].

The pathway through which these cytokine mediators act may also promote cancer growth [167] (see Figure 4) and this is an important research area which has received much recent attention. For instance, TNF-α and IL-6 promote up-regulation of growth hormone receptors in the liver which stimulate gluconeogenesis and insulin-like growth factor 1 (IGF-1) production [168]. Overproduction of IGF-1 promotes cancer growth by induction of anti-apoptotic events [169]. TNF-α activates nuclear factor kappa-light-chain-enhancer of activated B cells

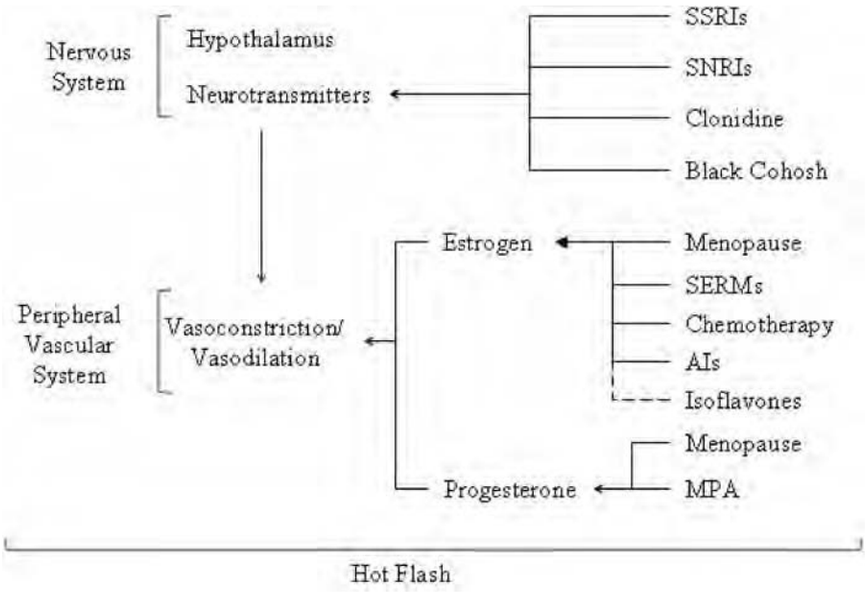

Figure 4. ▮▮▮▮.

(NF-B) that increases levels of reactive oxygen species (ROS) [170]. ROS might induce DNA damages such as deletions, frame shifts, and rearrangements leading to tumour progression [171]. Visceral fat accumulation is associated with increased production of vascular endothelial growth factor (VEGF), that aids in cell proliferation and migration [172]. Finally, increased adipocyte production initiates various processes that ultimately promote tumour growth. Leptin, a hormone that plays roles in various biological pathways, is produced predominantly by adipose tissue. In humans, plasma levels of leptin correlate with total body fat, with high concentrations present in obese women [173]. Leptin promotes cancer growth through angiogenesis via increased levels of metalloproteinase in various cancer sites including prostate, colon, endometrial, and breast cancer [174].

Importantly, we are intrigued by the fact that the same pro-inflammatory cytokines implicated in supporting cancer growth are known to play a critical role in the generation of fever, a condition in which patients also report feelings of thermal discomfort (e.g. feeling intermittently excessively chilled or overheated). Thus, as outlined further below, we speculate that elevated levels of pro-inflammatory cytokines in breast cancer patients may also be linked to at least some symptoms of thermal dysregulation.

Fever – a natural mechanism that can create feelings of excessive chills and overheating

Fever is defined as 'a state of elevated core temperature, which is often, but not necessarily, part of the defensive response of multicellular organisms (host) to the invasion of live microorganisms or inanimate matter recognised as pathogenic or alien by the host' [175]. Pyrogenic cytokines are produced by phagocytic cells as part of the innate immune system and these signalling molecules cause an increase in the thermoregulatory set-point in the hypothalamus thereby creating a febrile response [176]. Several pro-inflammatory cytokines are critical in generating the hyperthermic condition of fever (see Figure 4), and also in the regulation of the immune responses. Normally secreted in small amounts, pyrogenic cytokines including IL-1, IL-6, and TNF-α, are able to mediate fever caused by infection, with cancer patients often secreting abnormally large amounts [166]. These circulating cytokines are thought to affect centres of thermoregulation in the hypothalamus by inducing expression of cyclooxygenase 2 (COX-2), which leads to increased production of prostaglandins [177]. Specifically, increased concentration of prostaglandin E2 (PGE2) is thought to affect thermoregulatory neurons and lead to a rise in core body temperature [15]. PGE2 plays a predominant role in the inflammatory response and modulates a variety of immune responses, including cytokine production.

Studies dealing with fever are often difficult to compare, because of differing opinions as to what constitutes normal body temperature [15]. Furthermore, various demographic characteristics, such as age, sex, and weight, as well as experimental variables including time of day, may affect temperature readings. Importantly, when an individual has a fever, and even before febrile temperatures are

recorded, he/she will often report feeling cold [178, 179] rather than feeling hot, and will exhibit heat-seeking behaviour. After the new set point in body temperature is reached, the same individual may experience the sensation of overheating and may even notice extensive sweating. We speculate that some of the same heat-seeking behaviour that accompanies a fever-generated feeling of cold could be involved in patients who report excessive and persistent chills after breast cancer. Generation of a fever-like state could also help to explain intermittent feelings of being too cold and too hot in some breast cancer patients. If this relationship between cytokine production and thermal discomfort is found in breast cancer patients, it could indicate previously unrecognised relationships between the mechanisms underlying thermoregulation and thermal comfort, and cytokine driven signals from the immune system. Furthermore, it would strongly support the need for further study devoted to particular thermal discomfort symptoms since these symptoms may provide important prognostic information.

The relationship between thermoregulation and immune response

Current evidence suggests that inflammation and immune function play a significant role in thermoregulation. Further, there is growing evidence that use of mild hyperthermia as part of cancer therapy may positively influence the anti-tumour immune system [11]. Systemic inflammation is associated with both fever and hypothermia [180]. Fever occurs as a response to mild systemic inflammation, which is mediated by COX-2, whereas, severe inflammation results in hypothermia and appears to be mediated by COX-1, but not COX-2 [181]. In rat models of systemic inflammation induced by bacterial LPS, core body temperature changes appear to depend upon the ambient temperature and the LPS dose [182]. At neutral or slightly warm temperatures, fever is the common response and is monophasic when the dose of LPS is low, but is polyphasic when the dose is high [180]. In contrast, at cooler ambient temperatures, hypothermia followed by fever is the predominant response, with the magnitude of the hypothermia increasing with the LPS dose [183, 184]. A number of studies have shown that animals respond to LPS with warmth-seeking behaviour and fever, although at high LPS doses, emulating systemic inflammation, animals will first demonstrate cold-seeking behaviour and hypothermia followed by warmth-seeking behaviour and fever [185].

Romanovsky et al. and others have suggested that while fever may be beneficial because of its immunostimulant and antimicrobial effects, these benefits may be offset by the high energetic cost associated with maintaining a high body temperature [133]. As a result, it is possible that when an inflammatory stimulus is severe enough to threaten energy reserves, processes that conserve energy may come into effect. In this context, leptin, a hormone which plays a central role in both energy homeostasis and the inflammatory response, may serve as the signal that ties together energy balance and inflammation [186]. Immune activation of leptin production is thought to involve neuroendocrine pathways, although these mechanisms are still poorly understood [186].

Because pro-inflammatory cytokines have been identified as performing key roles in thermal dysregulation (fever), cancer-related sickness behaviour, and various metabolic functions it is reasonable to hypothesise that there may be a relationship between the production of pro-inflammatory cytokines and symptoms of thermal discomfort among breast cancer patients. In addition, these symptoms may be clustered with other cytokine-related symptoms reported among breast cancer patients. Epidemiological and clinical studies to address this important possibility are currently needed.

Thermal discomfort, thermal therapy and possible connections to the immune system

Straub et al. suggest that elevated pro-inflammatory cytokine levels act as a signal for the need of energy-rich fuels by the immune system [187]. Available energy levels in the body are significantly influenced by the requirements for heat production and/or heat dissipation. Fever, which is most often indicative of heightened immune activity due to infectious agents, is accompanied by an increase in body temperature due in large part to signals in the brain encouraging heat-seeking behaviour, as demonstrated in many animal models [188]. When breast cancer patients feel inappropriately cold, is this a signal employing physiological and behavioural mechanisms to conserve and generate heat energy for other activities, such as the immune system? Since metabolic energy could be drained by a cold individual attempting to attain thermal comfort, less energy will be available for other homeostatic functions, which might include the immune response unless that individual obtains body temperature support by finding warmer ambient conditions (e.g. adding more clothes or turning up the thermostat). Thus, we wonder whether feeling persistently cold has a negative impact on the immune system and could even signal poorer disease prognosis among cancer patients and that appropriate energy conserving interventional strategies (e.g. hyperthermia or warming thermal therapy) should be employed. Indeed, because cold stress among breast cancer patients may be indicative of changes

in underlying immune function (e.g. production of pro-inflammatory cytokines) or increased metabolic needs, there could be therapeutic benefit in the use of thermal therapies to help support overall energy balance. For example, if a patient exhibits persistent chills, and this is found to be associated with other symptoms of metabolic sickness, perhaps benefit would be obtained by interventions involving frequent mild thermal therapies designed to alleviate thermal discomfort and reduce excessive pro-inflammatory cytokine production. Moreover, supporting the energy requirements of maintaining body temperature may be expected to allow redirection of energy use in the body to support other energy requiring functions, such as enhanced immune function.

Indications that temperature manipulation may be a potentially effective treatment strategy to enhance anti-tumour immune function are supported indirectly by findings from several preclinical and clinical studies showing that mild systemic whole body hyperthermia can potentiate the anti-tumour effects of various cytotoxic agents and can stimulate the immune system [11, 12, 189, 190].

Mild systemic fever-range whole body hyperthermia both *in vitro* and *in vivo* can regulate the production of pro-inflammatory cytokines such as IL-6 and TNF-α from activated macrophages [191]. Several immune activities have been shown to be enhanced by mild heating [192-195]. IL-6 has been shown to play a critical role in mediating at least some of the immunological effects of fever range hyperthermia on T-lymphocytes [196, 197]. Immunological changes have also been observed in both cancer patients and healthy volunteers whose core temperatures were increased modestly in a warm water bath [198]. In summary, while considerable data supports the notion that providing mild hyperthermia could enhance the immune system, much more data is needed in regard to the anti-tumour immune response. However, an attractive rationale for a new clinical indication for mild hyperthermia may be the goal of alleviation of the persistent excessive chills experienced by many women with breast cancer.

Opportunities for future research directions

The information provided here supports the need for the cancer research community to take a more rigorous approach to the study of thermal discomfort symptoms among breast cancer survivors. In order to obtain a precise and accurate assessment of the effects of thermal dysfunction a wide range of interdisciplinary studies will be necessary. A combination of epidemiological, clinical, biological, and immunological studies will need to be employed to determine the risk factors and underlying etiologic mechanisms for thermal dysregulation among breast cancer patients, and the significance of these symptoms with disease prognosis. Although there are an overwhelming number of studies published on hot flushes, greater emphasis is needed to improve understanding of causal mechanisms for these vasomotor menopausal symptoms in breast cancer patients. Since these symptoms can be quite debilitating, affecting patient compliance with the use of anti-oestrogen therapies for example, it is important to learn how to alleviate them without affecting treatment efficacy or risk of disease recurrence. Recent findings from the WHEL and ATAC studies [2, 3] support the provocative idea that better treatment outcomes are related to development of menopausal vasomotor symptoms. If confirmed, clinical studies can be designed to test the use of these symptoms as a means of providing therapy tailored to breast cancer patients.

In comparison to studies on hot flushes, the possibility that some cancer patients may feel persistently cold has never been scientifically recognised, and studies to characterise this symptom and understand the underlying etiological mechanism have never been conducted. A first step in conducting this research might be to design an observational epidemiological study that will provide a thoughtful prospective examination of potential relationships between body temperature, thermal discomfort experienced by women with breast cancer, immune phenotype, disease prognosis, and cytokine-driven symptoms of cancer-associated sickness. Identification of key immune patterns related to breast cancer prognosis, body temperature, symptoms of thermal discomfort, and cytokine-related symptoms experienced by breast cancer patients will be critical for the design of future intervention studies aimed at altering or supporting body temperature as a potential strategy for supporting immune function among cancer patients. Such studies may be able to target these cytokines as intermediate biomarkers of long-term prognosis. If body temperature and/or feelings of being persistently cold are found in initial observation studies to be robust prognostic factors for breast cancer, it will be important to identify modifiable risk factors for body temperature and/or symptoms of being persistently cold. Greater understanding of these relationships will provide insight into potentially modifiable factors and interventions that may be designed to impact body temperature and/or symptoms of thermal discomfort, which may in turn improve anti-tumour immune activity and disease prognosis.

Conclusions

This article has highlighted the phenomenon of thermal discomfort, which is highly prevalent in breast cancer patients. Overall, the information presented here supports the idea that patients' reports of being too hot or too cold should not be simply discounted as an annoying side effect of treatment or of menopausal symptoms. The emerging evidence indicating that some vasomotor symptoms may be associated with treatment outcomes and disease recurrence is intriguing. Further study is needed to determine whether this easily recognisable symptom can provide a simple means for assessing treatment efficacy among individual breast cancer patients in order to support individualised therapies optimising disease outcomes. A second intention of this review is to draw attention to the possibility that some breast cancer survivors may feel persistently and inappropriately cold and have diminished ability to easily maintain thermal comfort. We hypothesise that these symptoms may reflect changes in the levels or activity of pro-inflammatory cytokines involved in activating immune function and may serve as a signal for altered immune activity among cancer patients, including those diagnosed with breast cancer. As a first step in interrogating this hypothesis, a prospective epidemiological study is needed to determine whether body temperature is dysregulated among breast cancer survivors and whether this is related to specific immune patterns or cytokine expression patterns associated with poorer disease prognosis.

The established links between febrile symptoms, the immune response and pro-inflammatory cytokines, combined with a growing literature indicating a positive relationship between mild hyperthermia and the immune system present several compelling hypotheses regarding thermal discomfort symptoms in breast cancer patients. Addressing these hypotheses will optimally require interdisciplinary study by scientists interested in breast cancer epidemiology and thermal physiology/immunology, as well as in metabolism and inflammation.

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192. Ostberg JR, Patel R, Repasky EA. Regulation of immune activity by mild (fever-range) whole body hyperthermia: Effects on epidermal Langerhans cells. Cell Stress Chaperones 2000;5(5):458–461.
193. Ostberg JR, Dayanc BE, Yuan M, Oflazoglu E, Repasky EA. Enhancement of natural killer (NK) cell cytotoxicity by fever-range thermal stress is dependent on NKG2D function and is associated with plasma membrane NKG2D clustering and increased expression of MICA on target cells. J Leukoc Biol 2007;82(5):1322–1331.
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195. Park HG, Han SI, Oh SY, Kang HS. Cellular responses to mild heat stress. Cell Mol Life Sciences 2005;62(1):10–23.
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Appendix 2. CV of Chi-Chen Hong

Curriculum Vitae
(current as of 08/04/10)

Chi-Chen Hong, Ph.D.

Work Address: Roswell Park Cancer Institute
Department of Cancer Control and Prevention
Elm & Carlton Streets
Buffalo NY, 14263
Phone: (716) 845-7785
Fax: (716) 845-8125
Email: chi-chen.hong@roswellpark.org

Education

1990	BSc	University of Toronto (Nutritional Sciences)
1993	MSc	University of Toronto (Nutritional Sciences)
2004	PhD	University of Toronto (Epidemiology)

Postdoctoral Training

09/04-04/06 Postdoctoral Research Affiliate, Roswell Park Cancer Institute, Buffalo, NY.

Academic Appointments

05/06-01/08	Affiliate Member, Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY.
05/06-01/08	Instructor of Oncology, Roswell Park Cancer Institute, Buffalo, NY
12/07-	Research Assistant Professor, Department of Social and Preventive Medicine, SUNY at Buffalo, Buffalo, NY.
01/08-	Assistant Professor and Member, Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY.
05/08-	Assistant Professor, Department of Cancer Pathology and Prevention, Roswell Park Cancer Institute, Buffalo, NY.

Awards and Honours

1991	University of Toronto Open Master's Fellowship, University of Toronto.
1992	Tied for first place in the Canadian Society for Nutritional Sciences Wyeth Graduate Student Competition, CSEB annual meeting, Victoria BC.
1992	One of twelve winners of the American Institute of Nutrition/Proctor & Gamble Graduate Student Research Award Abstract Competition, FASEB annual

	meeting, Anaheim CA.
1992	Life Sciences Summer Graduate Research Award, University of Toronto.
1992	University of Toronto Open Doctoral Fellowship, University of Toronto.
1993	University of Toronto Open Doctoral Fellowship, University of Toronto.
1995	University of Toronto Open Doctoral Fellowship - declined
1995-7	National Health Research and Development Program Ph.D Fellowship, Canada.
2002-3	Postgraduate Fellowship, Department of Medicine, University of Toronto
2006-7	Postdoctoral Award, Breast Cancer Research and Education Program, New York State Department of Health.
2006-9	United States Department of Defence Breast Cancer Research Program Multidisciplinary Postdoctoral Award.

Other Professional Activities

American Association for Cancer Research

2006	Associate Scientific Mentor, Scientist, Survivor Program, American Association for Cancer Research Annual Meeting, Mar 31-Apr 4, 2006.
2007-10	Member, Associate Member Council, American Association for Cancer Research.
05/07-04/08	Editor, Associate Member News & Networking, Associate Member Council, American Association for Cancer Research.
2007	Member, Organizing Committee, 10th Annual Grant Writing Workshop for Associate Members, Professional Advancement Session, 2007 Annual Meeting.
2007	Co-developed Associate Member Council Proposal for New Early-Career Funding Mechanisms Using AACR Centennial Funds. Presented August 10-11, Philadelphia. Fellowship mechanism announced Jan 2008.
2008	Member, Organizing Committee, 11th Annual Grant Writing Workshop for Associate Members, Professional Advancement Session, 2008 Annual Meeting, San Diego, CA (April 12-16, 2008).
2008	Facilitator, Leila Diamond Networking Breakfast hosted by Women in Cancer Research, AACR Annual Meeting 2008, San Diego, CA (April 12-16, 2008).
2009	Co-chair, Organizing Committee, Mentoring and Career Development Plan Workship: Establishing Successful Relationship for Productive Careers. Professional Advancement Session, AACR Annual Meeting 2009, Denver, CO (April 18-22).
2010	Associate Scientific Mentor, Scientist, Survivor Program, AACR Annual Meeting 2010, Washington DC (Apr 18-Apr 22).

RPCI Institutional Activities

2005-present	Coordinator, Work-in-Progress Meetings in the Dept of Cancer Prevention and Control.
2007-present	Member, Cancer Center Support Grant
12/06-12/07	Member, Survivorship Program Steering Committee
02/08-05/08	Member, Tactical Working Group focused on Institute Strategic Initiatives: member of Behavioral subgroup focused on Survivorship, Disparities, and

	Psychosocial Initiatives.
02/08-05/08	Member, Soluble Factors Subgroup reporting to Microenvironment Tactical Working Group focused on development of Institute Strategic Initiatives.
09/08-	Member, '10 Questions' Group focused on development of QOL Questionnaire for Institute Initiative in Survivorship Research.

University of Toronto Institutional Activities

1995	Cofounder, student group examining procedures for PhD comprehensive examinations in the Epidemiology Program at the University of Toronto. Produced a position paper for comprehensive examination procedures, which was submitted to the Departmental Chair. All recommendations in the position paper were adopted by the department.
1996 and1997	Student-elected representative, PhD Comprehensive Examination Committee.
1996	PhD representative, Research Association of Toronto Epidemiology Students (RATES), Department of Preventive Medicine and Biostatistics.
1996-98	Co-founding member and coordinator, weekly Epidemiologic Workshop Series, Department of Public Health Sciences.
1996-97	Member, Admissions Work Group reporting to the Advisory Committee on Graduate Training in Epidemiology, Graduate Department of Community Health.
1996-97	Member, Communications Work Group reporting to the Advisory Committee on Graduate Training in Epidemiology, Graduate Department of Community Health.
1997	Member, "Naming" Work Group for merged departments, Department of Preventive Medicine and Biostatistics.
1997	Member, Advisory Committee for (new) Chair, Department of Public Health Sciences.

Professional Associations

Associate Member, American Association for Cancer Research (AACR) – Since 2004.
Member, Molecular Epidemiology Group (MEG), AACR - Since 2004.
Member, Women in Cancer Research (WICR), AACR – Since 2007.
Member, Society for Epidemiologic Research (SER) – Since 2004.

Peer Review Activities

Journal Peer Review for**:**

BMC Cancer (2005-)
Breast Cancer Research (2005-)
Breast Cancer Research and Treatment (2009-)
Cancer Epidemiology Biomarkers and Prevention (2007-)
Cancer Research (2005-)
Cell Biochemistry and Function (2009-)
Clinical Cancer Research (2008-)
International Journal of Cancer (2005-)
Obesity (2006-)

Oncology Research (2005-)
Preventing Chronic Disease (2004-)

Grant Review Committee Member (Ad hoc)

2007	United States Army Medical Research and Materiel Command (USAMRMC) Breast Cancer Research Program: Idea and Synergism Grants, August 12-14, Alexandria VA.
2008	Breast Cancer Campaign, United Kingdom and the Republic of Ireland.
2008	United States Army Medical Research and Materiel Command (USAMRMC) Breast Cancer Research Program: Idea Grants, July 16-18, Reston VA.
2009	United States Army Medical Research and Materiel Command (USAMRMC) Breast Cancer Research Program: Idea and Postdoctoral Grants, Jan 21-23, Reston VA.
2009	United States Army Medical Research and Materiel Command (USAMRMC). 2009 Congressionally Directed Medical Research Programs (CDMRP), Breast Cancer Training Clinical & Experimental Therapeutics Panel: Postdoctoral Fellowship Award and Predoctoral Fellowship Award. May 3-5, 2009.
2010	Susan G. Komen for the Cure Grants Program, Prevention and Risk Reduction Panel, Postdoctoral grants, January 29, 2010.
2010	California Breast Cancer Research Program, teleconference, March 31, 2010.

Educational Contributions

2006-9	Guest lecturer, “Hormones and Breast Cancer”, RPN 532 Oncology for Scientists, Roswell Park Division of the University at Buffalo, SUNY.
2008	Co-Instructor, RPN525RP Cancer Epidemiology, University at Buffalo, SUNY Spring 2008.
2009	Guest lecturer, “Cancer Epidemiology”, Conversations in Oncology for RPCI Residents, Roswell Park Division of the University at Buffalo, SUNY, September 8, 2009.

Student Mentoring

PhD Students

01/07-06/09	Yulin Li, “Effects of Quantified ER & other Signaling Factors on Breast Cancer Cancer Prognosis”, Roswell Park Cancer Institute, PhD dissertation committee member.
06/2009-to present	Katie Kokulus, “Body Temperature, clinical and demographic risk factors, and immune function”, PhD Student, Dept of Immunology, Committee co-chair.

Master of Science Students

2007-08/2008 Charlotte Hinkle, "Interaction Between Glycemic Index and Load with *CYP17* Genotype and Breast Cancer Risk", Roswell Park Cancer Institute, MS committee member.

Interns and rotation students

2006 Co-mentor for summer student, Elizabeth Jones (University of New York at Albany)

07/08-08/08 Mary Pilarz, "The Impact of Multivitamin Consumption of the Perception of General Health Among Breast Cancer Patients", Summer Research Student, Research Advisor.

01/09-03/09 Katie Kokulus, Body Temperature, Temperature Perception, and Clinical Risk Factors, Dept of Immunology, Roswell Park Cancer Institute, PhD Student Rotation Research Advisor.

Research Support

Current Grants
Active Research Support

BCRF Ambrosone (PI) 10/01/09-09/30/10
Breast Cancer Research Foundation
Basal-like breast cancer in black and white women: an "Out of Africa" hypothesis
Study goals: The goal of this study is to examine potential differences in a panel of inflammatory and immune markers between black and white women, and to assess polymorphisms in key genes in those pathways in relation to breast cancer risk among both groups, and for specific breast cancer subtypes.
Role: Co-I

Awarded, Awaiting Funding

R01 CA105274-07 Kushi (PI) 07/01/10 – 06/30/15
Kaiser Perm/NCI
Prospective Study of Breast Cancer Survivorship
Study Goals: In this competing renewal to study a cohort of women newly diagnosed with breast cancer through Kaiser Permanente, we will evaluate the effects of diet, physical activity, and CAM, as well as host and tumor genetic variability in relation to hazard of recurrence.
Role: Co-I

NYS CO26588 Ceacareanu (PI); Hong (Co-PI) 6/01/10 – 5/31/12
Peter T. Rowley Breast Cancer

NYSDOH

Modulation of Inflammatory Response by Diabetes Management in Breast Cancer Patients
Study Goals: The aims of the study will be to determine if Type II diabetic breast cancer patients have poorer disease prognosis compared to non-diabetic patients, and to determine if this is mediated by differences in insulin resistance and/or inflammatory cytokines. The study will also evaluate whether prognosis is modified by the type of anti-diabetic medication used to disease management, i.e. insulin secretagogues vs. non-secretagogues.
Role: Co-PI

U01 ESES019435-01 (Kushi) 8/1/10 - 7/31/15
UCSF/NIH/NIEHS
The CYGNET Study: Enironmental and Genetic Determinants of Maturations
Study Goal: The Cohort study of Young Girls' Nutrition, Environment, and Transitions (CYGNET) study is a prospective cohort study of pre-pubertal girls examining environmental, lifestyle, and genetic factors in the development of early puberty and other hallmarks of maturation.

Pending Grants

P01 CA151135-01 (Ambrosone) 07/01/10 – 06/30/15
NIH
Epidemiology of Breast Cancer subtypes in African American Women: a Consortium
Study Goal: The overall goal of this Program Project is to pool data, samples and expertise from 4 of the largest studies of breast cancer in African-American women and to identify genetic and non-genetic risk factors for early onset, basal-like breast cancers.
Role: Co-I

R01 (Hong) 04/01/2011-02/20/2016
NIH
Body Temperature: An immune and prognostic marker in breast cancer?
Study Goal:The goal of this research will be to determine if body temperature and/or feelings of being inappropriately cold reflect immune profiles associated with breast cancer prognosis using a prospective hospital-based cohort study of 1,700 incident breast cancer cases.
Role: PI

R01 (McCann) 04/01/2011 – 03/31/2016
NIH
Diet Composition, effects on miRNAs and metabolomics, and breast cancer outcomes.
Study Goal: The objective in the present study is to confirm the relationships between diet composition and expression of specific miRs predicted to target genes in cancer and energy balance pathways and to determine relationships with metabolomic profiles, breast cancer characteristics, prognosis, and survival.
Role: Co-I

Completed Grants

DoD W81XWH0610401 Hong (PI) 04/01/06-03/31/10
US Army Med Res and Dev Command
Determinants of Weight Gain in Women with Early Stage Breast Cancer
Study goals: The goal of this study is to comprehensively examine predictors and modulators of post-diagnostic weight gain in women with breast cancer using a multidisciplinary approach encompassing hormonal changes, genetic polymorphisms, and psychosocial factors.
Role: PI

BCTR104906 Hong (PI) 05/01/06-04/30/10
Susan G. Komen Breast Cancer Foundation
Determinants of Weight Gain in Women with Early Stage Breast Cancer
Study goals: The goal of this study is to comprehensively examine predictors and modulators of post-diagnostic weight gain in women with breast cancer using a multidisciplinary approach encompassing hormonal changes, genetic polymorphisms, and psychosocial factors.
Role: PI

McCann (PI); Hong (Co-I) 11/01/05-12/31/07
RPCI Alliance Foundation
Low Glycemic Diet Intervention in Women at High Risk for Breast Cancer
Study goals: The goal of this study is to assess the feasibility of promoting long-term adoption of a low glycemic index diet among women at high risk for breast cancer, and to estimate its effect on breast cancer related biomarkers, including those associated with carbohydrate, growth, and steroid hormone metabolism.
Role: Co-I

Ambrosone (PI); Hong (Co-PI) 11/01/05-12/31/07
RPCI Alliance Foundation
Determinants of Weight Gain in Women with Early Stage Breast Cancer
Study goals: The goal of this study is to comprehensively examine predictors and modulators of post-diagnostic weight gain in women with breast cancer using a multidisciplinary approach encompassing hormonal changes, genetic polymorphisms, and psychosocial factors.
Role: Co-PI

C020918 Hong (PI) 01/01/06 – 12/31/08
Health Research Science Board/NYSDOH
Determinants of Weight Gain in Women with Early Stage Breast Cancer
Study goals: The goal of this study is to comprehensively examine predictors and modulators of post-diagnostic weight gain in women with breast cancer using a multidisciplinary approach encompassing hormonal changes, genetic polymorphisms, and psychosocial factors.
Role: PI

Tritchler (PI), 1998-2000 12 calendar
CBCRI $62,986
Breast Density: Effect of coffee, caffeine and methylxanthine intake and CYP1A2 Activity.
Study Goal: To examine the relationship between coffee and caffeine intake on CYP1A2 activity, an indicator of estrogen metabolism, and their relationship to breast density levels

as a marker of breast cancer risk. This grant was developed and written by Hong to fund her PhD thesis research.
Role: Additional Author and Project Director (this grant was written to fund my PhD research)

Scientific Publications

Original peer-reviewed articles

1. **Hong CC**, HJ Thompson, C Jiang, GL Hammond, D Tritchler, M Yaffe, NF Boyd. *Val158Met* Polymorphism in *Catechol-O-methyltransferase* (*COMT*) Gene Associated with Risk Factors for Breast Cancer. Cancer Epidemiol Biomarkers Prev 9:838-47, 2003.

2. **Hong CC**, B-K Tang, V Rao, S Agarwal, L Martin, D Tritchler, M Yaffe, NF Boyd. Cytochrome P450 1A2 (CYP1A2) activity, mammographic density, and oxidative stress: a cross-sectional study. Breast Cancer Res 6:R338-351, 2004.

3. **Hong C-C**, B-K Tang, GL Hammond, D Tritchler, M Yaffe, NF Boyd. Cytochrome P450 1A2 (CYP1A2) activity and risk factors for breast cancer: a cross-sectional study. Breast Cancer Res 6: R352-365, 2004.

4. **Hong CC**, HJ Thompson, C Jiang, GL Hammond, D Tritchler, M Yaffe, NF Boyd. Association between the *T27C* polymorphism in the *cytochrome P450c17α* (*CYP17*) gene and risk factors for breast cancer. Breast Cancer Res Treat 88:217-230, 2004.

5. Yang J, C Ambrosone, **C Hong**, J Ahn, C Rodriguez, M Thun, E Calle. Relationships between polymorphisms in NOS3 and MPO genes, cigarette smoking, and risk of postmenopausal breast cancer. Carcinogenesis 28:1247-53, 2007.
6. **Hong CC**, CB Ambrosone, J Ahn, J-Y Choi, ML McCullough, VL Stevens, C Rodriguez, MJ Thun, EE Calle. Genetic variability in iron-related oxidative stress pathways (*Nrf2, NQO1, NOS3,* and *HO1*), iron intake, and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 16: 1784-94, 2007.

7. McCann SE, WE McCann WE, **CC Hong**, JR Marshall, SB Edge, M Trevisan, P Muti, JL Freudenheim. Dietary patterns related to glycemic index and load and risk of pre- and postmenopausal breast cancer in the Western New York Exposures and Breast Cancer (WEB) Study. Am J Clin Nutr 86: 465-71, 2007.

8. Ambrosone CB, PG Shields, JL Freudenheim, **CC Hong**. Re: Commonly studied single-nucleotide polymorphisms and breast cancer: results from the Breast Cancer Association Consortium. J Natl Cancer Inst 99:487, 2007.

9. Choi JY, ML Neuhouser, M Barnett, **CC Hong**, AR Kristal, M Thornquist, IB King, G Goodman, CB Ambrosone. Iron intake, oxidative stress-related genes (MnSOD and MPO), and prostate cancer risk in CARET cohort. Carcinogenesis 29:964-70, 2008.

10. Li Y, CB Ambrosone, MJ McCullough, J Ahn, VL Stevens, MJ Thun[3], **C Hong**[+]. Oxidative Stress Related Genotypes, Fruit and Vegetable Consumption, and Postmenopausal Breast Cancer Risk. Carcinogenesis 30: 777-84, 2009.

11. Choi JY, WE Barlow, KS Albain, **CC Hong**, JG Blanco, RB Livingston, W Davis JM Rae, I-T Yeh, LF Hutchins, PM Ravdin, S Martino, AP Lyss, CK Osborne, MD Abeloff, DF Hayes, CB Ambrosone. Nitric oxide synthase variants and disease-free survival among treated and untreated breast cancer patients in a Southwest Oncology Group Clinical Trial. Clin Cancer Res 15: 5258-66, 2009.

12. Choi JY, J Smitha, P Link, S McCann, **CC Hong**, W Davis, M Nesline, C Ambrosone, A Karpf. Association between global DNA hypomethylation in leukocytes and risk of breast cancer. Carcinogenesis, 30: 1889-97, 2009.

13. Kokolus K[++], **CC Hong**, **EA** Repasky, Thermal discomfort after breast cancer: Hormone imbalance or a signal from the immune response? Int J Hyperthermia 2010; (Accepted, revision pending)

14. Ambrosone CB, **CC Hong,** S Yao, J Shankar, JR Palmer, F Ademuyiwa, DO Erwin, K Lee. Breast Cancer in African-American Women: An Evolutionary/Adaptive Perspective. Under review at JCO.

[+] **senior corresponding author**

[++] **PhD student under supervision**

Published Abstracts

1. Li ETS, **Hong C**, van Zeggeren A, Luo S, Segura A. 1991. Central 5-Hydroxytryptamine turnover and food intake after buspirone administration in lean and obese Zucker rats. NAASO/SSIB Joint Meeting, Sacramento, California. October 20-23, 1991 (Abstract F16).

2. **Hong C**, Li ETS. 1992. Normal dexfenfluramine induced satiety vs delayed food induced satiety in obese Zucker rats. CFBS 35: (Abstr 138).

3. **Hong C**, Li ETS. 1992. Carbohydrate but not protein elicits abnormal satiety responses in obese Zucker rats and is normalized by dexfenfluramine pretreatment. Faseb J (Abstr 1587).

4. Hong C, N Boyd, H Thompson, C Jiang S Michal, D Tritchler. Breast Density: Effect of Polymorphisms in the Steroid Metabolism Genes *Catechol-O-Methyltransferase* (*COMT*) and *Cytochrome P450c17* (*CYP17*). American Association for Cancer Research Meeting, San Francisco, California. April 1 - 5, 2000. (Abstr 2038).

5. **Hong C**, HJ Thompson, C Jiang, GL Hammond, D Tritchler, M Yaffe, NF Boyd. Val158Met Polymorphism in *Catechol-O-methyltransferase* (*COMT*) Gene Associated with Risk Factors for Breast Cancer. AACR Conference: Frontiers in Cancer Prevention Research, Boston Massachusetts. October 14-18, 2002. (Abstr D220).

6. **Hong C-C**, HJ Thompon, C Jiang, G Hammond, D Tritchler, M Yaffe, NF Boyd.

Polymorphism in P450 c17α (CYP17) gene interacts with insulin and diet to modify mammographic density levels. Proc Amer Assoc Cancer Res (2nd ed) 44: 5448 , 2003.

7. McGuire C, **C-C Hong**, L Sun, R Hegele, S Minkin, NF Boyd. The genetics of mammographic density: evidence of gene-gene interaction. Abstract #2922, AACR, March 27-31,2004, Orlando, Florida.

8. **Hong C**, E Calle, C Rodriguez, M Thun, J Ahn, C Ambrosone. *Glu298Asp* polymorphism in *Nos3* gene and breast cancer risk. Abstract 3262, AACR Annual Meeting, April 16-20, 2005, Anaheim, California.

9. Jiyoung Ahn, Christine Ambrosone, **Chi-Chen Hong**, Marjorie L. McCullough, Carmen Rodriguez, Michael J. Thun, Eugenia E. Calle. *NQO1* and *NRF2* Genotypes, Iron Intake, and Breast Cancer Risk. Abstract 5378, AACR Annual Meeting, April 1-5, 2006, Washington, D.C.

10. **Hong CC**, K Kokolus, C Ambrosone, S Edge, S Kulkarni, E Repasky. Body Temperature and Thermal Discomfort among Breast Cancer Survivors. AACR Annual Meeting, April 17-21, Denver Colorado. (Abstr 906).

Invited Lectures/Presentation

1994	Task Force on the Primary Prevention of Cancer, Toronto, ON, "Cancer Prevention: Population vs. High Risk Approaches".
1994	Task Force on the Primary Prevention of Cancer, Toronto, ON, "Alcohol as a risk factor for cancer".
1994	Department of Medical Biophysics, University of Toronto, Toronto, ON, "Artificial Pregnancy and Breast Cancer Risk".
2004	Prevention Grand Rounds, Roswell Park Cancer Institute, Buffalo, NY, Variation in steroid hormone metabolism genes and enzymes and their relationship with mammographic density and other risk factors for breast cancer.
2007	Prevention Grand Rounds, Roswell Park Cancer Institute, Buffalo, NY, "Genetic Variability in Iron-Related Oxidative Stress Pathways (*Nrf2*, *NQO1*, *NOS3*, and *HO1*), Iron Intake, and Risk of Postmenopausal Breast Cancer in the American Cancer Society CPS Nutrition II Cohort".
2007	Hope, Faith & Love, 6th Annual Komen Breast Cancer Survivor Luncheon, Buffalo, NY, "Women's Health after Breast Cancer: A study to understand why breast cancer survivors gain weight.
2008	Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA. "Weight Gain after Breast Cancer: Causes and Concerns", Jan 16, 2008.
2009	Sheehan Health Network, Buffalo, NY. "Hot baths as a potential treatment for breast cancer survivors". June 20, 2009.

2009 Department of Social and Preventive Medicine, Seminar Series, SUNY University at Buffalo, Buffalo, NY. "Body temperature and immune function in breast cancer patients". December 4, 2009.

Participant

2006 US Department of Defense, Breast Cancer Research Program (BCRP) Leading Innovative Networking and Knowledge Sharing (LINKS) Meeting. July 20-21, 2006. Baltimore MD

2009 US Department of Defense, Breast Cancer Research Program (BCRP) Leading Innovative Networking and Knowledge Sharing (LINKS) Meeting. Feb 9-10, 2009, Vienna, VA

2010 US Department of Defense, Breast Cancer Research Program (BCRP) Leading Innovative Networking and Knowledge Sharing (LINKS) Meeting. Feb 16-17, 2010, Chantilly,VA