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# **Exploration of Weight Gain in Female Breast Cancer Survivors**

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# EXPLORATION OF WEIGHT GAIN IN FEMALE BREAST CANCER SURVIVORS

A thesis submitted In Partial Fulfillment of the Requirements for the Degree of Master of Science in Nursing at Minnesota State university, Mankato

> By Mary Kay Baker Johnson

> > November 2012

Signature Page

#### Abstract:

Breast cancer is no longer a guaranteed death sentence. Many women today can look forward to a long and healthy life after treatment for breast cancer. However, weight gain is an ongoing, distressing and common problem for women treated for breast cancer. The primary purpose of this study was to gain knowledge about the phenomena of weight gain in females treated for breast cancer. A descriptive cross-sectional study was conducted in a natural setting. **Sample:** Electronic medical records for 100 female breast cancer survivors who visited a private suburban medical oncology clinic for treatment and/or on-going follow-up for a breast cancer diagnosis.

Variables: Age, menopausal status, interventions, and symptoms/side effect profiles. Data Analysis: Descriptive statistics for all study variables were computed to examine the nature of the data collected. Relationships among study variables were described using appropriate inferential statistics. Findings: Only surgical intervention demonstrated a statistically significant though weak relationship with weight gain. A weak relationship that approached statistical significance was found between hormonal blocking agents and weight gain. No statistically significant relationships were found between depression, fatigue or pain and weight gain. Sexual dysfunction and weight gain demonstrated a weak relationship that approached statistical significance. A weak positive correlation between anxiety and weight gain was statistically significant. Analysis revealed few relationships between identified symptoms and weight gain. Unexpected findings included significant relationships among multiple different symptoms. Weight gain over time was inconsistent.

**Implications:** Further study is needed to gain a better understanding of the factors related to weight gain for breast cancer survivors. Health care providers need to initiate discussions aimed at identifying the unique concerns and issues faced by these women. Nurse educators need to prepare students to be skilled and comfortable in initiating discussion about sexuality, intimacy and other sensitive issues with women coping with breast cancer.

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#### **CHAPTER I**

#### INTRODUCTION

The good news on the breast cancer front is that, thanks to all the research and resulting new treatments available, women are living longer, cancer free after receiving a breast cancer diagnosis. The efforts aimed at promoting, screening and early detection for breast cancer have made the cancers that are found more amendable to treatment and cure. However, because there has been so much emphasis on trying to save breast cancer patients lives, not as much attention has been focused on the long-term side effects and consequences for women receiving often very toxic treatments (Vivar, 2005).

Providing nursing care in the infusion center at an outpatient medical oncology clinic that cares primarily for women with breast cancer has given me an opportunity to hear the ongoing issues and concerns women face in the months and years after treatment is complete. My personal experience and observations have led to me believe that weight gain after diagnosis and treatment for breast cancer is very distressing to women.

Now that women often are living 10-20 plus years after treatment, some of these concerns are surfacing. For many years, one of the areas I have heard women complain about most frequently is weight gain after receiving breast cancer treatment. They believe that the weight they gained was not proportionate to either their diet or how their activity/exercise pattern. Many women I have cared for stated they felt they should not complain. Rather because weight gain is so minor and they are the lucky ones to survive, they should just be thankful to be alive. However, their bodies, minds and spirits bear scars from the treatments that saved their lives (Falk, 2010; Fobair, 2009; Huber, 2006;

Rowland, 2009). Until recently there was no evidence-based research that addressed this phenomenon.

A diagnosis of breast cancer in itself creates a type of emotional distress that is not common to some other types of cancer (Knobf, 2007 & 2011). Society has placed a tremendous emphasis on women's physical appearance in general, and their breasts in particular, as symbols of their sexuality, beauty and desirability for a partner. The thought of losing a breast can threaten the self-esteem and sense of femininity of even the strongest women. Fear of rejection and disfigurement can even prevent some women from seeking proper medical care.

I have heard many times daily that women are very concerned about their weight gain even when they feel they are not eating more nor less active in their day-to-day lives. Women who never had a weight problem suddenly do. Patients often jokingly comment that they think the only good thing about having chemotherapy is that they will lose weight from the side effects of the drugs. Most often they are disappointed to find that is not the case and more often than not, they actually have gained weight. In caring for breast cancer survivors even 10-15 years after completing treatment, many of them have continued to gain weight.

My observation is that over time, there have been great improvements in both surgical approach and technique used for breast cancer treatment and results achieved with reconstructive surgery. Women appear to be less fearful of the deformity resulting from breast surgery than they were in the past. Today, even hair loss is considered tolerable to many women because they know it is temporary, and hope for a long healthy life after treatment makes it worthwhile. My observation is that weight gain frequently

does not stop after the treatment is complete and may continue up to five plus years after diagnosis

Thanks to new and better treatments and earlier diagnosis for many women today cure is possible. For other women their breast cancer may not be completely eradicated but newer therapies and treatments can keep it from progressing or at least slow the progression. When survival was measured in weeks or months, the side effects or consequences of treatment were not considered a real concern because, after all, women were just grateful to be alive. What is now known is that the long-term side effects or complications of successful treatment can alter overall quality of life (Cella, 2006; Fallowfield, 1999; Knobf, 2001, 2006; Lindsey, 2004; Thomas, 2003). Weight gain is one major side effect that influences quality of life (QOL). Once the acute phase of treatment is complete, it is critical that health care providers focus on strategies to manage all on-going side effects of treatment affecting QOL. Today it is not uncommon to hear breast cancer discussed as a chronic disease that requires management in a manner similar to that of other chronic diseases.

Therefore, it is important for nurses in this field who are the direct providers of patient care, to have knowledge and understanding of this weight gain phenomenon. Nurses often spend hours at a time for weeks or months in close contact building trusting relationships with breast cancer patients. Thus, nurses are in an excellent position to assist in the process of transitioning from a mentality of just surviving to that of thriving as survivors. Finding ways to help women improve their QOL in the months and years to come falls clearly into the domain of nursing.

Oncology nurses, long known for their desire and ability to expand their care of patients beyond providing the physician-ordered medical treatments, routinely and wisely include the psychosocial aspects of living with a potentially terminal illness. The nursing model of care looks at the physical, mental and spiritual responses of patients and their families to receiving such a frightening diagnosis. Nurses know and understand that how patients interpret and perceive what they are told when given such a devastating diagnosis is filtered through the lens of their own unique life experiences. What their experiences have taught them will directly influence their ability to cope and respond with the positive attitude that will have a direct impact on their overall quality of life. This nursing practice of holistic care for the cancer patient clearly places the nurse practitioner in the best position to address quality of life issues and weight gain clearly is an issue that needs to be addressed for the breast cancer patient/survivor.

#### **Problem Statement**

Few studies have been conducted that examine the various evidence-based treatments for breast cancer to determine how they influence weight gain in women. Research has shown that weight gain during and/or after treatment for breast cancer is common (Chen, 2009; DeMark-Wahnefried, 2001; Goodwin, 1999; Vance, 2010). Weight gain is one of the most distressing concerns reported by patients treated for breast cancer (Falk, 2010; Hormes, 2008; Knobf, 2011; Rowland, 2009). For many patients, concern for weight gain may limit treatment options considered, possibly affecting longterm recovery, recurrence rate and ultimate survival. Therefore, the purpose of this study was to gain knowledge about the phenomenon of weight gain in women treated for breast cancer describing the prevalence and degree of weight gain and identifying factors related to it.

#### **Research questions**

1. How are chemotherapy, radiation therapy, hormonal therapy and surgical intervention related to weight gain in women with breast cancer?

2. How are pre-diagnosis weight, age at diagnosis and menopausal status at diagnosis related to amount of weight gain?

3. How does post-treatment weight gain change over time?

4. What is the relationship of fatigue, anxiety, depression, sexual dysfunction and pain with increased weight gain?

#### **Conceptual definitions**

Age at diagnosis: Chronological age at time of cancer diagnosis.

<u>Adjuvant therapy</u>: Therapy given after the primary treatment. In breast cancer treatment, this refers to post-surgical treatment such as chemotherapy, hormonal therapy and radiation therapy.

Chemotherapy: The use of chemical agents/drugs to systemically treat cancer.

<u>Hormonal therapy</u>: The use of "anti-hormone" medications that block the effects of certain hormones upon cancer cells that depend on hormones to grow. For breast cancer treatment, estrogen and progesterone are the hormones that need to be blocked.

<u>Menopausal status</u>: Whether a woman is still menstruating or has ended her menstrual cycles.

<u>Radiation Therapy</u>: The use of high-energy x-rays aimed directly at known tumors to kill the fast multiplying cancer cells.

<u>Surgery</u>: Surgical removal of cancerous tumors including differing amounts of surrounding breast tissue, muscle and lymph nodes.

#### Summary

The significant issues related to weight gain in breast cancer patients are increase in the recurrence rate of breast cancer, negative body image, decreased self esteem, lowered quality of life, increased fatigue, decreased ability to exercise or participate in physical activities, development of comorbidities, including depression, and a myriad of other potentially life threatening diagnoses. Research demonstrates a significant positive correlation between weight gain, even in small amounts, and an increase in the rate of breast cancer recurrence. A negative body image, often associated with weight gain, interferes with intimate relationships. Increased fatigue associated with weight gain limits the ability to perform expected work and role functions. The decreased ability to exercise or perform other physical activities limited by weight gain perpetuates further weight gain and does not allow for the natural release of endorphins associated with exercise, leaving patients more vulnerable to depression. Weight gain predisposes patients to high blood pressure, heart disease, vascular disease, stroke, diabetes, joint deterioration. Because of all these significant issues breast cancer patients experiencing weight gain often experience a lowered quality of life.

Weight gain in women treated for breast cancer is a significant concern. There is a knowledge deficit of both the causes of post-treatment weight gain and which interventions will best help manage the problem. Before we can address the problems related to weight gain, or effectively treat it, we need to know more about the factors related to it.

## **CHAPTER II**

#### BACKGROUND

During the last 10-15 years researchers began looking at the phenomenon of weight gain after breast cancer treatment and found that weight gain during and/or after treatment is common (Chen, 2009; DeMark-Wahnefried, 2001; Goodman, 1999; Vance, 2010). Weight gain is one of the most consistently distressing concerns reported by patients treated for breast cancer (Falk, 2010; Hormes, 2008; Knobf, 2011; Rowland, 2009). For many patients, concern for weight gain may limit treatment options considered, possibly affecting long-term recovery, recurrence rate and ultimate survival. Younger women who are typically more concerned with appearance and body image and may already be at risk for highly aggressive cancers are also at higher risk for weight gain during and after treatment (Rock, 2000; Enger, 2004). Weight gain also increases the risk of recurrence (Vance, 2010; Rock 1998; Falk, 2010). This evidence has ushered in a new era of adding weight management to the list of issues that need to be addressed as part of a total breast cancer treatment regimen.

Much of the discussions surrounding the decisions for treatment, focus on identifying the risk/benefit ratio of potential harm from toxic treatments vs. expected overall quality of life. Every woman has a different set of expectations and requirements to be present in her life for her to feel the benefits outweigh the risks. For many, body size and shape contribute heavily to the perception of what constitutes a good quality of life. Research is clear that increased weight increases the risk of breast cancer recurrence, so it is imperative that we learn what causes weight gain so we are able to design and implement individual protocols and programs that meet the unique needs of every woman with breast cancer.

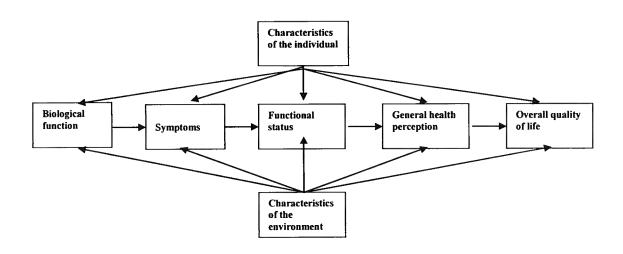
#### **Conceptual Model**

A modified version of Ferrans' (2005) revised Health Related Quality of Life (HRQOL) conceptual model was used to develop the study. This model demonstrates just how complicated it is to determine the causes and consequences of weight gain as it relates to breast cancer treatment. The definition of QOL is different for everyone. It is a "subjective assessment of ones well-being that includes all of the elements described in the model and serves to determine an individual's personal satisfaction with life and overall quality of life" (Ferrans 2005). HRQOL is intentional at relating a person's QOL to their health. While it can be difficult to separate all the elements that make up QOL for HRQOL, it is important to do so if we want to offer more personalized ongoing care that meets the unique health related needs of each woman living with a breast cancer diagnosis.

The original HRQOL model developed by Wilson and Cleary (1995) attempted to identify five determinants that exist on a "continuum of increasing biological, social, and psychological complexity" (1995, p. 60). These determinants are biological factors, symptoms, functioning, general health perceptions and overall quality of life. Individual characteristics and environment influence all of the determinants.

Ferran's purpose in developing the revised HRQOL model based on the work of Wilson and Cleary (1995) was to fill a need "for causal models that clearly indicate the elements of HRQOL and their determinants" (Ferrans, 2005, p. 336). Ferran's revision

focuses on the characteristics of individuals and their environments to assess how these factors influence health outcomes. Suggestions for applying the model from a nursing perspective are also presented in Ferran's revision.



#### Model of Health-Related Quality of Life

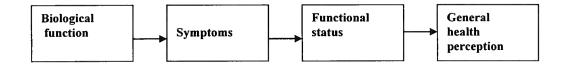
after Ferrans et al (2005)

In this model the top box represents the individuals' unique demographic, biological, developmental and psychological makeup. These characteristics of the individual influence each of the five boxes in the middle. These five boxes each represent a different type of patient outcomes. The box on the bottom represents the environmental characteristics that interact and influence each of the identified patient outcomes.

By identifying these individual characteristics and attributes early and looking at how they interact with biological function, nurses will be able to minimize the risk of recurrence and improve long term HRQOL. Demographics such as age, sex, marital status and ethnicity have been identified as factors that can influence the development of breast cancer. Biological traits such as family history, genetics, BMI and skin color also e influence the risk for a variety of diseases as well as breast cancer and need to be included in the diagnostic process and treatment plan. Developmental status at the time of treatment is important for explaining information in a manner that is easily understood. If we try to encourage lifestyle changes that may be difficult to adopt, and the reason behind the needed change is not clearly understood, women are less likely to follow through. Understanding is also very important when we are giving women test results or new diagnoses to limit unnecessary fear and anxiety. A person's baseline knowledge, beliefs, life experiences and attitudes will directly affect their psychological response and adjustment to a cancer diagnosis. Knowing whether a person is intrinsically or extrinsically motivated will help us tailor recommendations and treatment plans that have a high potential for success. The level of resilience a person has demonstrated in the past, when confronted with difficult circumstances, provides insight into how she may respond to a cancer diagnosis (Ferrans, 2005).

Characteristics of the environment in which someone grows up or currently lives can be defined as social or physical. The current environment has a significant impact on perception, response and coping with a breast cancer diagnosis. The physical environment can be toxic and detrimental to health. Living with second hand smoke or in a neighborhood that has contaminated water or air obviously affects biological health. The work environment also can have a powerful influence on health outcomes. Social environmental characteristics include relationships with family and friends. Previous experiences with health care in general or specifically with providers are important influences on how a woman approaches coping with and managing her new diagnosis. Both the physical and social environment can have either a positive or a negative influence on health.

Because the focus of this study was to identify the prevalence of weight gain and its relationship to various treatments for breast cancer through the evaluation of past and current medical records, access to detailed information related to environmental and individual characteristics was not available. While acknowledging the importance of these influences, this study focused on the first four boxes in the middle of the schematic below. These boxes represent patient outcomes.



Ferrans (2005) describes biological function as a broad view of molecular, cellular, and whole organ processes. "Alterations in biological function directly or indirectly affect all components of health, including symptoms, functional status, perceptions of health and overall quality of life" (p. 338). The assessment and identification of past and current biological function serve as the base for determining a short and long-term treatment plan for a woman with a new diagnosis of breast cancer.

Wilson and Cleary (1995, p. 61) describe shifting our thinking away from the biological and physiological variables to symptom variables as a way to begin exploring

the whole person and her perception of HRQOL. Symptoms are defined as "a patient's perception of an abnormal physical, emotional, or cognitive state" (Ferans, 2005).

Functional status has many components. How a person is able to function in her usual roles, psychologically, socially, and physically are addressed here. How a woman perceives her ability or disability will influence her functional performance. In Ferrans' (2005) revised model, functional status is viewed by focusing on the optimization of the function that remains. Ferrans refers to Leidy's (1994) framework, which describes functional status as including four dimensions: "functional capacity, functional performance, functional capacity utilization and functional reserve (Leidy, 1994).

#### **Review of Literature**

#### Factors related to weight gain in women diagnosed with breast cancer

Age at diagnosis is a significant factor considered when making decisions regarding the best treatment plan for an individual patient (Aebi, 2007; Mattle, 2005). Younger women often are in the middle of raising families and building careers. Taking the time to care for their own health has a great impact on the overall functioning of the family. Younger women have more years to live with the uncertainty for their futures. Some young women have not yet had children and they know that their future ability to do so will be compromised or eliminated (Duffy, 2009; Gorman, 2011; Thewes, 2005). Young pre-menopausal women who's cancer is hormone (estrogen or progesterone) sensitive have a greater risk of being plunged into sudden and complete menopause without any time to transition or prepare for such extreme loss of hormone function throughout their body (Cella, 2006; Knobf, 2006; Fallowfield 1999). Finally, younger women tend to have more aggressive and difficult to treat cancers (Clive, 2002).

Women's bodies and emotions go through many changes as it progresses through the reproductive years. Typically, the transition for a woman from her fertile years through peri-menopause to her menopause is gradual, covering several years. This allows her time to cope and prepare mentally and physically for the inevitable physical and emotional changes she will experience. She has the opportunity to share this time of life with her peers making it a little less stressful and difficult. A young woman, who suddenly finds herself menopausal, with all that encompasses, is denied the comfort and camaraderie of sharing the experience with other women who are her peers (Knobf, 2001). One of the commonly recognized menopausal changes for many women is a redistribution of fat and frequently weight gain (Abdulnour, 2012; Wildman, 2012). It's no secret that women experience different menopausal symptoms in different degrees of intensity resulting in varying levels of disruption to their overall sense of quality of life (Elavsky, 2012; Green, 2011; Hunter, 2011).

Chen and associates (2011), in their population based cohort study of 4,561 women with breast cancer, assessed weight at diagnosis and again 18 month later, while looking at socio-demographics as well as clinical and lifestyle factors. They found in that significantly greater weight gain was associated with younger age, premenopausal status, mixed hormonal receptor status and more advanced disease.

Goodwin et al (1999) studied 535 women, with newly diagnosed, loco-regional breast cancer at time of diagnosis and again one year later. They assessed diet, activity, and tumor and treatment variables. Their findings show while weight gain is common after breast cancer in general, use of adjuvant chemotherapy and onset of menopause to be the strongest predictors of this weight gain. Vance et al (2010) found the same results: premenopausal women who received chemotherapy showed the greatest propensity to weight gain even years after diagnosis. The authors also noted that even when women did not gain weight, their body composition changed to one favoring an increase in fat gain with loss of lean muscle mass.

#### Relationship between different treatments for breast cancer and weight gain

**Chemotherapy:** The class of drugs most commonly used for breast cancer treatment is the alkylation agents; Adrimycin, Carboplatin, Cisplatin and Cytoxan being the most frequently used. These drugs are known to cause direct damage to the ovaries and their functioning "resulting in irregular menses, amenorrhea (permanent or reversible), menopausal symptoms, and late effects of menopause, such as bone loss" (Knobf, 2006).

Denmark-Wahnefried et al (2001) and Goodwin et al (1999) were among the first to evaluate weight gain after a breast cancer diagnosis. Their findings of body composition changes following chemotherapy showed an increase in fat gain with lean tissue loss, and weight gain that was not explained by dietary intake, and therefore more dangerous for overall health. Since a decrease in physical activity is common during breast cancer treatment, findings of this study point to the importance of encouraging exercise with an emphasis on resistance training of the lower body to help prevent weight gain and build muscle.

Vance et al (2011) performed a comprehensive review of literature from 1975-2009 and looked at the type and cause of weight gain seen with chemotherapy administration. Their conclusion was "these data do not support overeating as a cause of weight gain among breast cancer patients who receive chemotherapy". The data suggest, however, that chemotherapy induced weight gain is distinctive and indicative of sarcopenic obesity along with evidence of reduced physical activity, supporting the need for interventions focused on exercise, especially resistance training in the lower body to prevent weight gain.

**Hormone therapy:** Across the board, all types of hormone blocking treatments are thought to cause weight gain. One category of drugs commonly used is the selective estrogen receptor modulators (SERMS). These drugs selectively bind to the estrogen receptors in breast and other estrogen sensitive tissues, thus preventing estrogen from binding to the estrogen sensitive tumor cells. There are two ways for the body to produce estrogen. The first is by the ovaries of pre-menopausal women. The other is through a process called aromatization. After menopause, the adrenal glands release androstenedione. This adrenal steroid eventually meets the aromatase enzyme, which converts it to estrogen. This other category of anti-hormone drugs most commonly prescribed is the aromatase inhibitors (AI), named for their ability to block the aromatization process and prevent the production of extra-ovarian estrogen.

The most commonly prescribed and well-known SERM is Tamoxifen, which is most often prescribed for premenopausal women. The most commonly prescribed AIs are Arimidex, Aromasin and Femara. Each of these drugs have a similar side effect profile that includes, weight gain, fatigue, arthralgias, myalgias, hot flashes, vaginal discharge or dryness, decreased libido, depression, headaches, flu-like symptoms, insomnia and diarrhea. Tamoxifen also can be a factor in the development of uterine cancer and a higher risk of blood clots, so women who still have a uterus need to be watched closely for signs and symptoms of endometrial thickening or cancer. Progestin therapies such as magestrol, have shown the highest rate and amount of weight gain among all the hormone treatments. Fortunately, this type of treatment is seldom used since the development of the SERMS and AIs.

Most of the recent research related to the use of adjuvant hormonal treatment for early and advanced stage breast cancer attempts to sort out the differences in tolerability, side effect profiles and effectiveness. There is no question that the treatments are a very effective and important part of ongoing treatment and prevention of recurrence, but if the side effects are such that they diminish HRQOL, many women stop taking them all together. Thomas (2003) and Cella (2006) evaluated HRQOL issues and the impact of hormonal treatments on prevention of recurrence. Their findings were similar in that some of the most frequently mentioned bothersome side effects reported were, as mentioned above, weight gain, decreased libido, muscle aches, joint pain, vaginal dryness leading to dysparenunia, hot flashes, night sweats, difficulty sleeping, mood swings, irritability, anxiety, headaches and lightheadedness.

**Radiation therapy:** This local therapy is not directly associated with weight gain in breast cancer patients. The side effect profile relates specifically to the area radiated. Skin damage and sensitivity are common and some women even have long-term problems with tightening, decreased sensitivity to stimulation, and thickening of the skin requiring ongoing physical therapy to soften the tissues and improve mobility of the chest wall, shoulder and arm. The radiated breast may shrink or become misshapen, often-affecting body image and clothing fit. Falk (2010) studied body image in long term-term breast

cancer survivors and concluded that breast cancer diagnosis and treatment with surgery and radiation therapy was associated with impaired QOL, increased mental distress, reduced health, decreased self-esteem and body-image. Weight gain was certainly one of the most reported complaints.

The one side effect that is generally common to all women who receive radiation therapy is fatigue. Fatigue often prevents women from performing their routine physical activities resulting in an indirect impact on weight gain, self-esteem and depression. Women who are usually active and fit find it very distressing to have such limited energy. Many women feel they are letting down others when they can't fulfill their normal roles and functions. This can lead to the development of psychological distress. Some women cope with this general fatigue and distress by eating which obviously will cause weight gain. In turn this coping stategy often leads to decreased self esteem and poor body image and the cycle can continue if the fatigue is not managed effectively resulting in further weight gain. Overall HRQOL will likely be significantly diminished if these needs are not addressed.

**Surgical intervention:** Surgeries such as lumpectomy, mastectomy, lymph node removal or dissection and breast reconstruction cause pain, lymphedema and mobility issues that limit activity immediately post-op and sometimes even lifelong. Along with the physical scars, many women carry the emotional scars of their surgery including decreased self-esteem, a poor body image and a desire to hide their body's changes from others. These physical and emotional losses can lead to the development of depression, anxiety, disrupted intimate and sexual relationships (Hormes, 2008).

In their study of post-op breast cancer patients, Yurek et al (2000) found that women who had undergone breast reconstruction had the most disturbed sexual behavior patterns. Since the time of this study, there have been major improvements in surgical breast reconstruction. Even though women might have different post-surgical experiences today, Yurek et al's findings are relevant because they indicate the importance of assessing expectations and understanding reasons for choosing reconstruction. Helping women understand what realistically can be accomplished surgically, in their unique situation, will help improve post-operative sexual and bodychange stress levels.

#### **Summary**

It is clear that many factors and the relationships among them are involved in the phenomenon of weight gain following treatment for breast cancer. Age at diagnosis and time since treatment are important factors to include when looking at this phenomenon. Recent research suggests younger women tend to have a more difficult time managing their post-diagnosis weight. A woman's menopausal status alone or in conjunction with the type of treatment received may influence weight changes post treatment. Additionally, any side effects or symptoms experienced because of treatment, or a woman's mental and emotional state before, during, and after diagnosis and treatment may affect post diagnosis weight gain. The significance a woman attaches to her weight and appearance in general will most likely affect her overall body image and sense of self-esteem. Having the ability to perform her normal roles and responsibilities will be important to how she rates her overall HROOL.

# CHAPTER III

#### **METHODS**

**Design**: Descriptive cross-sectional study conducted in a natural setting. Data consisted of categorical, ordinal and interval-level information abstracted from medical records. **Sample:** A sample of 100 charts was drawn from the electronic medical necords of female breast cancer survivors who visited a private suburban medical oncology clinic for treatment and/or on-going follow-up for a breast cancer diagnosis during the months of November 2011 and May through June of 2012. Records were excluded if the women transferred care to the clinic during or shortly after treatment if complete documentation of the medical history was not present. Women who had un-controlled metastatic disease and were also followed by palliative care or hospice were excluded from the study. Some long term survivors, who had followed one of the physicians from another practice, and did not have complete documentation for weight at diagnosis, were included if there were at least 6 years of documentation available, since a trend in continued weight gain would be apparent and applicable to the study. In this situation, first documented weight was used as pre-diagnostic weight. All stages of cancer were sampled unless they fell into one of the exclusion categories listed above.

Study Variables: Age, menopausal status, surgical intervention, treatment received and symptoms/side effect profiles.

**Ethical Considerations:** Sample was derived from medical records only. Permission to access electronic medical records was granted by the medical director of the clinic. (Appendix A)

**Instruments:** Investigator-developed data abstraction tool: (Appendix B) **Data Collection:** Biological function was assessed by collecting data on pre-diagnosis and current age, menopausal status and weight. Data on whether menopause was natural or chemotherapy or surgically induced was collected when available. Pathology reports were reviewed for type and size of tumor, lymph node status, hormone receptor status as well as local or distant metastases. Type of treatment received, including surgery, radiation therapy and hormonal therapy was abstracted.

Symptom complaints were assessed by abstracting physician notes.

Overall functional capacity was measured by data related to return to work, previous activities, social functioning and performance of assigned family roles and duties. Sexual function was measured by documentation of decreased libido, pain with intimacy, and information related to body image and self-esteem based on the woman's perception of her functional ability and self report.

Overall HRQOL was measured by a documented statement from the patient that directly links weight gain to a lowered perception of HRQOL.

**Data Analysis:** SPSS 9.0 was used to conduct data analyses. Descriptive statistics for all study variables were computed to determine the nature of the data collected. Relationships among study variables were described using appropriate inferential statistics. Specifically, categorical variables were examined using Chi-square test statistic. Ordinal and interval data were analyzed using correlation coefficients. Ordinal variables with low frequencies in one or more ranks were redefined (data collapsed into fewer ranks) in order to compute the appropriate test statistic.

**Limitations:** Medical records do not always specifically address how a woman sees her overall quality of life but physician dictation often does give indication as to how she is coping and integrating her disease into her everyday life. To avoid bias that could result from investigator relationships with some of the patients whose records were included, only information documented in the medical record was used. Data related to individual and environmental characteristics are sometimes inconsistent or missing.

Additionally, only two points in time were used for weight measurement, date of diagnosis and date of most recent appointment. This potentially limited the ability to determine when weight changed.

# CHAPTER IV

#### FINDINGS

**Descriptive Analysis:** The electronic medical records of one hundred women with a breast cancer diagnosis were examined. All records were obtained from one oncology clinic associated with a hospital, in a large Midwestern city. The age at diagnosis ranged from 28 to 76 years old. Current age ranged from 33 to 87 years old. At diagnosis 47 participants were pre-menopausal and 53 were post-menopausal at diagnosis. Current menopausal status showed that twelve women remained pre-menopausal and eighty-eight are now menopausal. Of the thirty-five women whose menopausal status changed from pre to post-menopausal four women had a natural menopause, twenty-one had a chemotherapy-induced menopause and six had a surgical menopause secondary to the breast cancer diagnosis.

Of the sampled one hundred women fifty-five received chemotherapy that included an alkylation agent and fifty-three received radiation therapy. Eighty-six women had some type of breast surgery for their breast cancer including lumpectomy, unilateral mastectomy, bilateral mastectomy or prophylactic bilateral mastectomy. Twenty-eight women had lymph node involvement at diagnosis, ten experienced a recurrence of their original cancer, and three others were diagnosed with a new breast cancer.

Sixty-two women received some type of hormone therapy aimed at blocking or suppressing the effects of estrogen or progesterone on the tumor cells. Twenty-one women received a SERM alone, seventeen received an AI alone, and twenty-five received both a SERM and AI, two of which received a progestin in addition to the SERM and AI.

Seventy-one women complained of fatigue and thirty-five reported decreased libido, uncomfortable physical symptoms, such as vaginal dryness, or both. These symptoms affected their sexuality and physical intimacy to the extent that they were bothersome to them and their partners. Hot flashes were a problem for thirty-one of the women while thirty complained of sleep difficulties that often were associated with night sweats. Forty-one women struggled with anxiety and nineteen expressed feeling depressed. Sixteen felt anxiety and depression were both a problem for them. Twenty-six women reported significant ongoing pain associated with their cancer treatment that was disruptive to their lives. Overall sixty-five women described problems with more that one of these symptoms and four reported experiencing them all.

Forty-one participants weighed less than 150 lbs at diagnosis and thirty of them gained weight. Twenty-six weighed 150-174 lb and fifteen gained weight. Seventeen women weighed 175 lbs to 199 lbs at diagnosis with ten of them gaining weight. Eleven women weighed 200-249 lbs at diagnosis and four of them gained additional weight after their diagnosis. Four women weighed greater than 250 lbs at diagnosis with one gaining additional weight.

#### **Inferential Analysis:**

Research Question # 1. How are chemotherapy, radiation therapy, hormonal therapy and surgical intervention related to weight gain in women with breast cancer?

#### Table 1. ANOVA Analysis

Variables	F	Sig
Weight gain & chemotherapy	.320	.573
Weight gain & radiation therapy	.011	.916
Weight gain & hormonal therapy	2.131	.101
Weight gain & surgical intervention	3.314	.023

This question was answered using an analysis of variance procedure (Table 1). Neither breast cancer treatment with chemotherapy nor with radiation therapy showed a statistically significant relationship with weight gain. For women who received some type of hormone treatment aimed at blocking rapid tumor cell growth in the presence of the body's own hormones- (i.e. estrogen or progesterone), a weak relationship that approached statistical significance was found. Surgery for breast cancer did demonstrate a statistically significant though weak relationship with weight gain.

Research Question # 2. How are pre-diagnosis weight, age at diagnosis and menopausal status at diagnosis related to amount of weight gain?

**Table 2. Bivariate Correlations** 

Variables	r	p
Weight gain & Pre-diagnostic age	260**	.009
Weight gain & Pre-diagnostic weight	236*	.019

The first part of this question related to age and pre-diagnostic weight was answered by calculating Pearson's r (Table 2). The relationship between pre-diagnostic weight and weight gain showed a negative, weak association that is statistically significant. A

woman's age at diagnosis also demonstrated a negative though weak association that is highly statistically significant. The second part of the question related to menopausal status at diagnosis was answered using an analysis of variance procedure. Those women who were pre-menopausal at diagnosis had a higher average weight gain than those who were post-menopausal at diagnosis. The difference in mean weight gain revealed a statistically significant (F = 6.226, p = .014).

#### Research Question # 3. How does post-treatment weight gain change over time?

This question was answered using an analysis of variance procedure. The scores on the years from diagnosis variable were not normally distributed (negatively skewed), so the cases were divided into quartiles. Quartile one was less than or equal to 2 years since diagnosis (27 cases); quartile two was > 2 years to < 5 years (22 cases); quartile three was equal to or greater than 5 years to <8 years (26 cases) and quartile 4 was equal to or greater than 8 years (25 cases). There was no statistically significant difference in the mean weight gain among the quartiles. Thus, there was no linear relationship between amount of time from diagnosis and weight gain. Examination of the mean weight gain for each quartile revealed that the women in quartile one was negative. This suggests that, on average, during the first 2 years following diagnosis women lose or maintain their pre-diagnosis weight. Mean weight gain increased for quartile 2, then decreased for quartile 3, then increased again in the 4<sup>th</sup> quartile. These data suggest the possibility of a curvilinear relationship between weight gain and years since diagnosis. Research Question # 4. What is the relationship of fatigue, anxiety, depression, sexual dysfunction and pain with increased weight gain?

Variables	F	p
Weight gain & fatigue	.003	.956
Weight gain & pain	.390	.534
Weight gain & sexual dysfunction	2.144	.123
Weight gain & depression	.064	.800

Table 4. ANOVA analysis

For this question, analysis of variance (Table 4) revealed no statistically significant relationship between depression, fatigue or pain and weight gain. For sexual dysfunction and weight gain, the *F* value suggests a weak relationship that approaches statistical significance. Calculation of Spearman's rho showed a weak positive correlation (r = .233) between anxiety and weight gain that was statistically significant (p = .02). While the analysis revealed few relationships between these symptoms and weight gain, there were some significant relationships among the different symptoms.

#### **Unexpected findings:**

During the initial examination of the data, several relationships appeared to be present. Therefore, additional analyses were conducted to look more closely at these relationships. Using a chi-square analysis (Table 5) the relationships that had the strongest correlation and were statistically significant were: current menopausal status and sexual function; chemotherapy and fatigue; and radiation therapy and sexual

# <u>Table 5. Relationships Among Treatment and Symptom Variables using</u> <u>Chi-squared Value</u>

	Xsq	p
VARIABLES		-
Chemotherapy & fatigue	19.427	.000
Chemotherapy & sexual function	3.190	.203
Chemotherapy & symptoms	5.178	.075
Radiation therapy & fatigue	10.59	.001
Radiation therapy & sexual function	7.748	.021
Radiation therapy & symptoms	1.248	.536
Hormonal therapy & fatigue	1.292	.731
Hormonal therapy & sexual function	3.399	.757
Hormonal therapy & symptoms	8.141	.228
Surgical intervention & fatigue	4.202	.240
Surgical intervention & sexual function	4.694	.584
Surgical intervention & symptoms	2.851	.827
Lymph node status & fatigue	4.089	.043
Lymph node status & sexual function	7.838	.020
Lymph node status & symptoms	7.536	.023
Metastases & fatigue	8.366	.004
Metastases & sexual function	1.654	.437
Metastases & symptoms	1.740	.419
Pre-diagnostic menopausal status & fatigue	.077	.781
Pre-diagnostic menopausal status & sexual function	5.455	.065
Pre-diagnostic menopausal status & symptoms	2.439	.295
Current menopausal status & fatigue	1.885	.597
Current menopausal status & sexual function	13.784	.032
Current menopausal status & symptoms	9.688	.138

functioning; lymph node status and fatigue along with sexual function and symptoms; metastases and fatigue. Other relationships that were approaching statistical significance though weakly related included premenopausal status and sexual functioning and chemotherapy and symptoms.

# CHAPTER V

## DISCUSSION

The purpose of this study was to gain further understanding of the factors related to the phenomenon of weight gain in female breast cancer survivors. Most recent research does agree that there are many factors responsible for this occurrence. Numerous studies have reported a link between chemotherapy and change in body composition that favored sarcopenic weight gain. Others have suggested that the cause of post-treatment weight gain is related to hormonal changes that result directly or indirectly from treatment. Still other studies describe metabolic changes that favor weight gain. Consistently, studies have reported that diet alone is not responsible for post treatment weight gain in breast cancer patients. It appears there may be changes in how the body uses the food ingested. Some of the latest findings indicate a need for change in the type of exercise performed and an increase in the amount of strength training and weight bearing exercise to combat the effects of breast cancer treatment and potential weight gain.

Of the treatments examined in this study (chemotherapy, radiation therapy, hormonal therapy and surgery), as a potential cause for weight gain, only surgery demonstrated a statistically significant, though weak, correlation. In addition, the weak relationship between hormonal treatments and weight gain approached statistical significance.

These findings are consistent with the inconsistent findings of other researchers. It was expected from the review of literature that chemotherapy and hormonal therapy

would emerge as significant factors in the weight gain of breast cancer survivors (Goodwin et al, 1999; Vance et al, 2010). It was surprising that the data from this sample revealed only an association between surgical treatment and weight gain.

When looking at the demographics age, weight and menopausal status at diagnosis for clues as to the cause of weight gain, pre-diagnostic weight revealed a negative statistically significant, though weak, correlation with post-treatment weight gain. Age at diagnosis and weight gain showed a negative though weak relationship that was highly statistically significant. For women who were pre-menopausal at diagnosis there was a higher average weight gain than for women who were already menopausal at diagnosis. These findings are consistent with the findings of Chen (2011) and Goodwin (1999) that greater weight gain was associated with younger age and pre-menopausal status. Vance (2010) agreed that these demographics were influential adding that this weight gain can continue for years after completing treatment, which was inconsistent with the findings in this sample.

Analysis of symptoms reported by breast cancer survivors has revealed that some of the most bothersome and frequently reported include depression, anxiety, pain, sexual dysfunction and fatigue. The current study found that anxiety and weight gain show a positive statistically significant relationship. In addition, women who complained of some type of physical or emotional sexual dysfunction experienced more weight gain than those who did not. Because the correlation only approached statistical significance, the finding is tentative. These relationships have not been studied and reported in the literature, so the findings represent new findings.

The HRQOL model can help understand how some of the symptoms identified previously might affect functional status. Using this model, I was able to evaluate how changes in biological function may trigger symptoms such as fatigue, nausea, memory loss and pain. Receiving a breast cancer diagnosis and treatment is known to affect many women's self-esteem, sense of femininity, body image and overall sexual functioning. These changes can affect mood states causing anxiety and depression leading to more difficulty coping with the symptoms experienced and the diagnosis itself. Actual or feared weight gain can itself be devastating for many women and often affects their perception of their overall QOL. All of these symptoms need to be addressed in the ongoing care for a woman with breast cancer to assist her to find an improved level of HRQOL. For example reports of, or treatment for, anxiety or depression might influence perception or function. Actual weight gain might also influence functional status. Altered body image and physical difficulty performing usual activities can also interfere with intimate relationships. Complaints of fatigue suggest decreased functional performance and reserve.

Receiving chemotherapy or radiation therapy showed a significant relationship to feeling fatigued, and the relationship between chemotherapy, symptoms such as hot flashes, sleep disturbance, anxiety, depression, and pain approached significance. Most of these symptoms along with fatigue have been identified in other research as factors related to weight gain in the general public and specifically in cancer survivors (Darga, 2007; Denmark, 2001; Falk, 2010; Vance, 2010). No other significant relationships were found among these other variables.

In line with findings of other researchers, this study indicates that there is no simple answer as to what causes or how to prevent post treatment weight gain in breast cancer survivors. Most frequently many factors are implicated. Finding ways to identify the factors that are unique to each woman diagnosed with breast cancer will be critical to providing individual treatment plans that meet the needs of each woman in her own life circumstances.

From the perspective of the modified HRQOL model assessing each woman's current and past environment while getting to know her individual characteristics, strengths and weaknesses, is critical to providing quality care. Each person's perceptions and interpretations are filtered through the lens of her own life experiences. If these perceptions and unique environments are not understood, nurses might miss the opportunity to help her improve her overall HRQOL.

While the findings and conclusions of this study do not provide a definitive reason for the cause of weight gain associated with breast cancer treatment they do demonstrate how complicated it is. The important role nurses can play in identifying factors that are unique to each individual woman and how they may relate to weight gain cannot be overemphasized.

#### **Implications for Research**

It is important for nurses who are the direct providers of care to understand this weight gain phenomenon. Suggested further study includes evaluating breast cancer patients' weight at prescribed intervals to obtain data that are more specific over time. Regular, periodic weight measurements would facilitate detecting a trend of weight loss at certain intervals followed by weight gain as suggested in this study. Further study

focused on improving understanding of the lived experience of women coping with a breast cancer diagnosis would assist in development and implication of an individual plan of care that meets the physical and psychosocial needs of each woman treated for breast cancer.

#### **Implications for Practice**

Medical oncology, known for its focus on diagnostics and treatments is not always ready to evaluate emotional and mental health. Advanced practice nurses are well prepared to help women identify and manage the emotional distress they may encounter, resulting from the physical changes associated with their treatment for breast cancer, as they progress through treatment to survivorship. Because nurses often spend hours at a time for weeks or months in close contact building trusting relationships with breast cancer patients, they are in an excellent position to gain an understanding of each woman's unique situation and how it might affect her response to treatment.

Most women are willing to try to cope with the side effects when offered ideas to help manage the symptoms. Sometimes just switching to a different one in the same category can make a big difference in the side effect profile a woman experiences when she feels the side effects are intolerable and too disruptive to her HRQOL. Knowing the proven high rate of effectiveness as well as the frequency of side effects of these drugs, makes it extremely important to take the time for frequent visits, or other forms of contact with women, when they start taking these medications. This will allow problems and concerns to be assessed quickly and hopefully managed well enough so she will continue to take the prescribed medications. From personal experience, the most frequently heard reason for stopping the anti-hormone medications is intolerable side effects that have too much negative impact on HRQOL. As the number of young women diagnosed and successfully treated for breast cancer increases, the impact on sexual relationships and intimacy will need to be in the forefront of the minds of cancer care providers.

#### **Implications for Education**

Nurse educators need to prepare students to be skilled and comfortable in initiating discussions about sexuality, intimacy and other sensitive issues. It is imperative to improving the HRQOL of women treated for breast cancer for oncology nurses who spend many hours in direct contact with them, to understand the importance of building trusting relationships and be open to discussing these sensitive topics so women will feel comfortable bringing up their personal concerns.

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# Appendix A

## UNIVERSITY OF MINNESOTA MEDICAL CENTER B FAIRVIEW

Southdale Cancer Clinic University of Minnesota Medical Center, Fairnew - Edma 6363 France Ave. S., Suite 610 Edma, MN 55435 Tel 952-836-3645 Fax 952-836-3646

July 10, 2012

Re: Mary Kay Johnson, RN

To Whom It May Concern:

Please let this letter serve as written authorization for Mary Kay Johnson to access medical records through Fairview Southdale Cancer Clinic for the use of research purposes in completion of her master's thesis for the family nurse practitioner program.

Thank you in advance for your attention to this matter. Please feel free to contact me for any clarifications or further information.

Respectfully yours.

Bouluen

Barbara Bowers, MD Medical Oncologist

# Appendix B

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30         64         66         165         102         2         act         2 y         1         3           31         65         72         165         25         act         y         3 y         3,54           33         60         61         160         160         1         act         y         n         n         1,2           34         67         70         160         144         2         tat         y         n         n         1,2           35         46         123         13         1         3         1,2         3         y         y         1,2,3           36         46         133         13         1         3         1,2         3         y         y         1,2,3           43         44         43         133         13         1         3         att         2,1         n         n         1,2,3           44         60         71         14         13         2         att         2,1         1         n         1,2,3           45         60         13         13         13         3         14         1,2							act		1 y					356
32       37       59       109       107       27       27       17       2.34         34       46       50       105       14       2       1 <td>30</td> <td>54</td> <td>56</td> <td>165</td> <td>162</td> <td>2</td> <td>act</td> <td></td> <td></td> <td>1</td> <td></td> <td></td> <td></td> <td></td>	30	54	56	165	162	2	act			1				
33         40         51         150         148         1         acc         1,2         y <t< td=""><td></td><td></td><td></td><td></td><td></td><td>2</td><td>act</td><td></td><td>у 2 ч</td><td>3 y 1 v</td><td></td><td>3 у</td><td></td><td></td></t<>						2	act		у 2 ч	3 y 1 v		3 у		
35         46         52         178         173         1         ac         y         n         n         12           36         47         96         169         1         3         12         39         40         60         193         193         40         60         193	33	40	51	150	148			1,2,3		4				2,3,4
38         7         89         150         162         2         act         j         y         y         y         y         1.3.6           38         46         54         123         135         1         act         1         3y         y         y         1.2.3         1.2.3           38         46         54         123         135         1         3ct         1         3y         y         y         1.2.3														17
$  \begin{array}{ccccccccccccccccccccccccccccccccccc$												у		
39         40         42         132         137         1         1 act         1         3y         y         y         6           40         60         76         44         73         97         2         tc         2y         2n         n         1,2,35         1           41         43         44         47         76         94         77         198         1         3         1,2         1         n         1         1,2         1         1         1         1         1,2         1 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>3 n</td> <td></td> <td></td> <td></td> <td></td>										3 n				
40       68       74       145       123       2       ach       1       1       5         41       00       64       65       27       1       n									1	3 y 3 y		у		
42       76       84       173       187       2 $2$ $2$ $n$ </td <td></td>														
A4       A4 <td< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td>1C</td><td></td><td></td><td></td><td>п</td><td></td><td></td><td>1,2,3,5</td></td<>							1C				п			1,2,3,5
46       59       71 r       7 r       2       cmf       y       1 n       n         47       62       68       162       163       2       acteh       1       3 y       1       3.3 5         46       53       57       227       1       3 act       1       3 y       1       1       1         50       53       102       116       1	43							n						
					158			1,2	v					1,2
48       51       57       272       1       3 act       1       3 u       1       <	46	62	75	134		2			У	1 n				
49       53       59       100       157       2       2 act       1       3       1       3       1       1       3       1       <												2		
51       50       53       129       135       1       3 act       1y       3 n       1       1,3         52       39       46       115       132       1       1       2       3 n       1       1       1,3         53       66       69       132       139       2       act       2,3       3       1,3       1,3         56       52       55       119       115       2       3 crd       1,2       y       1 n       1,3       1,3         56       52       55       119       114       2       1,2       3       1,2       3       1,2       3       1,2       3       1,2,3       1,3       1,2,3       1,2,3       1,3       1,2,3       1,3       1,2,3       1,3       1,2,3       1,3       1,2,3       1,3       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,2,3       1,4       1,4       1,	49	53	58	160	157	2				1 n				1
S2       39       46       115       122       1       1       2       2       1       3<												2 y		
S4       47       50       177       186       2       th       39       1,2       3         S5       S5       S5       119       15       2       3       1       1       3       1       3       1       3       1       3       1       3       1       3       1       3       1       3       1       3       1       3       1       3       1       3       3       1       1       1       1       1       3       1       3       1       3       1       3       1       3       1       1       1       2       2       3       1       1       1       3       1       1       1       3       1       1       1       3       1       1       1       3       1       1       1       3       1									.,					1,2,3
56       52       55       119       115       2       2       3       1       1,3         56       42       59       138       134       2       1,2       y       1n       3       3       1,2       1,2       1n       3       3       1,2       2,12       3       1,3       3       1,2       y       1n       3       3       1,3       3       1,2       y       1n       1,3       3       1,3       3       1,3       3       1,3       3       1,3       3       1,3       3       1,3       3       1,3       3       1,3       3       1,3       3       1,3       3       1,3       1,3       3       1,3												n		
56       42       59       138       145       1       3 ord       12       y       1 n       3       3       3       3       3       3       149       1       5       1,2       y       2       2,12       3,1         58       53       60       139       149       1       5       1,2       y       3       3       1,2,3       1,2,3       3       1,2,3       3       3       3       1,2,3       3       3       3       1,2,3       3       3       2       3,3       3       1,2,3       3       3       4       3       3       4       3       3       4       3       4       4       4       3       1,1       1,2,3       3       1       1,2,3       3       1       1,2,3       3       1       1,2,3       3       1       1,3       1       1,3       1       1,3       1       1,3       1       1,3       1       1,3       1       1,3       1,1       1,3       1,1       1,3       1,1       1,3       1,1       1,3       1,1       1,3       1,1       1,3       1,1       1,3       1,1       1,3       1,3							ten		2				1,2	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $							3 cmf	1,2						
							5	1,2						
61       61       62       212       207       3       2 y       1 y       n       3         63       41       41       204       185       2       act h       y       n       4         63       41       41       204       185       2       act h       y       n       4         66       32       34       147       156       act h       y       3       2y       123         66       32       34       147       156       act h       y       3 n       y       1,23         68       65       87       147       118       2 tch       y       3 n       2y       1,23         70       48       48       103       138       1       1 tc       2       y       n       y       1,23,45         71       44       45       193       198       1       3 tch       1       2       2,4       3,5       3,5       3,5       3,5       3,5       3,5       3,5       3,5       3,5       3,5       3,5       3,5       1,5       1,2       y       1,3       3       3       3,6       3,5       3,5 </td <td>59</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>-</td> <td>3</td> <td></td> <td></td> <td></td> <td>1,</td>	59								-	3				1,
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$							5 act		2 v	3 y 1 v				
64       65       70       196       195       2	62	71	71	111	128	2			2 y	1 ก		n		
65       47       50       171       166       1       2       1       1       1       3       n       y       4       3       3       4       4       4       4       4       4       4       4       4       4       4       4       1       1       2       1       y       3       3       2       y       1       1.2.3         66       65       67       48       49       135       141       1       2       y       3       2       y       1.2.3         68       70       71       44       45       183       196       1       3       1       1       y       1       2       y       2,1.2.3,4       3.5       7.3       3       7       1.2.3,45       3.5       7.3       3       7       1.2.3,45       3.5       7.5       3.6       1.2.1,45       3       3       7       3.3       7       3.2       7.2       3.3       7.2       3.3       7.2       3.3       7.2       3.2       7.2       3.5       7.3       6.1       6.1       1.7       7.2       7.2       3.3       7.2       2.5       1.2.3,45							act h							1
67       48       49       135       141       1       2 tch       y       3 n       1       1       12       y       3 n       1	65	47	50	171	166					n				
68       65       67       147       118       2       tc       1,2       y       3       2 y         70       48       48       140       138       1       1 tc       y       n       2         71       44       45       193       1       3 tc       y       n       y       n       y         71       44       45       193       13       tc       1       2       y       n       y         73       63       77       188       159       2       1.2       y       3       2       y       1,2.3,45         74       42       50       150       166       1       2       y       3       y       3         75       64       80       179       167       2       3       y       3       y       3         76       51       58       150       160       12       2       3       y       13       3         76       61       67       124       126       3       ac       y       1       y       1       y       1,2,2,5       1,2,2,2,5       1,2,3,4 <tr< td=""><td></td><td></td><td></td><td></td><td></td><td>1</td><td></td><td></td><td></td><td></td><td></td><td>у «</td><td></td><td></td></tr<>						1						у «		
70484814013811 tcyny71444519319811 tc12y212.3.47256701361242act1.2y2.3y1.2.3.4573637718815921.2y33574425015516612y33575646017916723y3576616724420622 n3y2,51,2.578616724422622 n3332,537869751241263ac2 n3332,538064177186202y1 n22,51,2,581586811713421 y1122,58348541091031511 y122,3,4,584656817617322 y1 n22,3,4,5856417916613 cmf1 21 n2,3,4,586406115922 n1 n2,3,4,58861651631331 42 n </td <td>68</td> <td>65</td> <td>87</td> <td>147</td> <td>118</td> <td></td> <td></td> <td>1,2</td> <td></td> <td>3</td> <td></td> <td></td> <td></td> <td>1,2,0</td>	68	65	87	147	118			1,2		3				1,2,0
71       44       45       193       198       1       3 cht       1,2       y       2,3       y       2,1,2,3,4         73       63       77       188       159       2       act       1,2       y       2,3       y       1,2,3,45         74       42       50       155       185       1       2       1y       3       -       5         76       51       58       150       160       1       2       -       3       y       3       -       3         76       51       58       141       172       cmf       -       3       y       2,5       1,2,3,4         78       61       67       234       206       2       ac       2 n       -       3         79       61       67       234       206       2       -       y       1 n       2       2,5       1,2,3,5         78       61       67       234       206       2       -       y       1 n       2       2,5       1,2,2,3       3       3       3       1,8       1 act       1 y       1       1,2       2,5       1,2       <							1 10							
73637718815921,2y2,3y1,2,3,4574425515516612y1y357664801791672y1y3y35766161141172cmf3y2,51,2,3,5786167234205222n3y2,51,2,3,57861672342052cmf2n3333333332,5.2,3,57969751241262ac2n2n3.3.3.313914811 act hy1yy1,22,3.3806417318620221y1n1,2.3.3.3.313914811 act hy1yy1,22,3.3834854109103151.3.4.4.3.4.4.4.2.2.4.4.4.2.2,3,4,5.4.4.4.2.2.2.2.2.2.2.2,3,4,5.2,3,4,5.2,3,4,5.2,3,4,5.2,3,4,5.2.2.2.2.2.2.2.2.2.2,3,4,5.2,3,4,5.2,3,4,5.2,3,4,5 </td <td>71</td> <td>44</td> <td>45</td> <td>193</td> <td>198</td> <td>1</td> <td>3 tch</td> <td></td> <td></td> <td></td> <td></td> <td>У</td> <td></td> <td>2 1,2,3,4</td>	71	44	45	193	198	1	3 tch					У		2 1,2,3,4
74 $42$ $50$ $155$ $166$ $1$ $2$ $y$ $3$ $y$ $3$ $76$ $51$ $58$ $150$ $160$ $1$ $2$ $y$ $3$ $y$ $3$ $77$ $45$ $61$ $141$ $172$ $cmf$ $3$ $y$ $2,5$ $1,2,35$ $78$ $61$ $67$ $234$ $206$ $2$ $2n$ $3$ $70$ $69$ $75$ $124$ $126$ $3$ $ac$ $2n$ $3$ $80$ $64$ $73$ $186$ $202$ $2n$ $3$ $2$ $2,5$ $81$ $58$ $68$ $117$ $134$ $2$ $1y$ $12$ $2,3$ $82$ $28$ $33$ $39$ $148$ $1$ $1$ $12$ $2,1$ $1,2$ $2,3$ $1,2$ $2,3,4,5$ $3,3,4,5$ $1,2$ $2,1$ $2,3,4,5$ $3,3,4,5$ $2,3,4,5$ $3,3,4,5$ $2,3,4,5$ $3,3,4,5$ $2,3,4,5$ $3,3,4,5$ $3,3,$							act							3,5
76       51       58       150       160       1       2       3       y       3         77       45       61       141       172       cmf       3       y       2,5       1,3,5         78       61       67       234       206       2       2       2       3       13       14       14       14       12       2,3       1,2       2,3       1,2       3       4       4       4       4       12       12       1,3       1,2       2,3,5       1,2       1	74		50	155	166		2			3				
77 $45$ $61$ $141$ $172$ $cmf$ $3$ $y$ $2,5$ $1,2,3,5$ $78$ $61$ $67$ $234$ $206$ $2$ $2n$ $3n$ $3n$ $y$ $2,5$ $79$ $69$ $75$ $124$ $126$ $3$ $ac$ $2n$ $2n$ $3n$ $80$ $64$ $73$ $186$ $202$ $2$ $y$ $1n$ $2$ $2,5$ $81$ $58$ $66$ $177$ $134$ $2$ $1y$ $y$ $1,2$ $2,5$ $82$ $28$ $33$ $139$ $148$ $1$ $1$ acth $y$ $1y$ $y$ $1,2$ $2,3$ $83$ $48$ $54$ $109$ $103$ $1$ $5$ $1$ </td <td></td> <td></td> <td></td> <td></td> <td></td> <td>2</td> <td>2</td> <td></td> <td>У</td> <td></td> <td></td> <td></td> <td></td> <td>5</td>						2	2		У					5
78       61       67       234       206       2       2       2       2       3         79       69       75       124       126       3       ac       2       2       3       3         80       64       73       186       202       2       y       1       1       2       2.5         81       58       68       117       134       1       1 act h       y       1       2       2.3         82       28       33       139       148       1       1 act h       y       1       y       1,2       2,3         84       65       68       176       173       2       2y       1 n       1,2       2,3         85       41       70       167       166       1       3 act 1.2       7       y       y       2,2,4,5         86       40       61       155       15       3 act 1.2       y       1 n       y       1,2       1,2,3,5         88       61       65       133       143       2       tch       2 y       1 n       1,2       1,2,2,4,5         89       42       51<						1						y y	2,5	1,2,3,5
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81.       58       66       117       134       2       1 sct h       y       1							ac		v			2		
83       48       54       109       103       1       5       1	81.	58	68	117	134	2			1 y					
84       65       68       176       173       2       2 y       1 n         85       41       70       167       166       1       3 cmf       1 y       1 n       4         86       40       61       155       1       3 cmf       1 y       1 n       y       2,3,4,5         87       44       49       112       121       1       3 ach       1.2       7       y       y       2,3,4,5         88       61       65       133       43       2       tch       2 y       1 n       2,3,5         89       42       51       156       187       1       3 ach       2 y       1 n       1,2       1,2,3,4         90       62       64       165       159       2 cmf       2 n       1 n       1,2       1,2,3,4         91       73       85       224       231       2 cmf       2 n       2 n       1,2       1,2,3,4         92       31       62       180       200       2       5 cmf ptc       y       3 y       3 y       1,2,3,4         93       46       49       101       105       1 2										1 y		У	1,2	2,3
86       40       61       155       1       3 ach       1.2       y       1 n       y       2.3,45         87       44       49       112       121       1       3 ach       1.2       y       1 n       y       y       2.3,45         88       61       65       133       143       2       tch       2y       1       2.3,5         89       42       51       156       187       1       3 act       1.2       y       1 y       2.3,5         90       62       64       165       159       2       2.4       2y       1 n       2.3,5         90       62       64       165       159       2       2.4       2y       1 n       1,2       1,2,3,4         91       73       85       224       231       2       cmf n       2,9       1,2       1,2       3 at         92       31       62       101       105       1       2       1,2       3 at       1,2       7       3 y       1,2         94       63       68       148       145       2       2 y       1       1,2       2 y       1 <td>84</td> <td>65</td> <td>68</td> <td>176</td> <td>173</td> <td>2</td> <td></td> <td></td> <td></td> <td>1 n</td> <td></td> <td></td> <td>.,_</td> <td></td>	84	65	68	176	173	2				1 n			.,_	
87       44       49       112       121       1       3 act       1.2       7       y       y       2       2.2.3.4.5         88       61       65       133       143       2       tch       2 y       1       2.3.5         89       42       51       156       187       1       3 act       1.2 y       1 y       1,2       1.2.3.5         90       62       64       165       159       2       2 y       1 y       1,2       1.2.3.3         90       62       64       165       159       2       2 y       1 n       1,2       1.2.3.3         91       73       85       242       210       2       5 cmfg, tc       2 n       2 n       1.2 <td></td> <td></td> <td></td> <td>167</td> <td></td> <td></td> <td></td> <td>17</td> <td></td> <td>1 n</td> <td></td> <td>v</td> <td></td> <td>2345</td>				167				17		1 n		v		2345
89       42       51       156       187       1       3 act       12       y       1 y       1,2       1,2.3         90       62       64       165       159       2       2y       1 n       1       1,2       1,2.3         91       73       85       224       231       2       cmf       1,2       2 n       1       1,2.3         92       31       62       180       200       2       5 cmf\u00efte, c       y       3 y       3 y       1,2.3         93       46       49       101       105       1       2       1,2       3 y       3 y       1,2.3         94       63       68       148       145       2       2 y       1,2       3 n       y       2.1,2.4         95       62       69       224       200       2       1,2       3 n       y       2.1,2.4         96       58       62       157       171       2       1,2       3 n       y       1,5         97       48       52       151       162       2       ac       2 y       3       1,5         98       61       <					121				'			y y		2 1,2,3,4,5
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91       73       85       224       211       2       cmf       1,2       2 n         92       31       62       180       200       2       5 cm/p, tc       y       3 y       3 y       1,23,4         93       46       49       101       105       1       2       1,2       3       1,2         94       63       68       148       145       2       2 y       1       2       1,2         95       62       69       224       200       2       1,2       3 n       y       2,1,2         96       58       62       157       171       2       1,2       3 n       y       1,5         97       48       52       151       162       2       1 y       1       1,5         98       61       65       186       200       2       ac       2 y       3       1,5         99       45       56       154       168       1       3 cmf       1,2       2 n       2 n       2 1,3         90       45       56       154       168       1       3 cmf       1 y       3,5       3,5	90	62	64	165	159	2		1					1,∡	1,2,3
93       46       49       101       105       1       2       1,2       3       1,2         94       63       68       148       145       2       2y       1       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,2       1,3       1,5 <td< td=""><td>91</td><td></td><td></td><td>224</td><td>231</td><td></td><td></td><td>1,2</td><td></td><td></td><td></td><td>3</td><td></td><td></td></td<>	91			224	231			1,2				3		
94       63       68       145       2       2y         95       62       69       224       200       2       1,2       3n       y       2,1,2         96       58       62       157       171       2       1,2       y       1       1,5         97       48       52       151       162       2       1y       1       1,5         98       61       65       186       200       2       ac       2y       3         99       45       56       154       168       1       3 cmf       1,2       2 n       2 n       2,1         99       45       56       154       168       1       3 cmf       1,2       2 n       2 n       2,1         90       53       59       198       214       5 act       2       1 y       3,5								1,2	у			эy	1,2	÷1,23,4
96         58         62         157         171         2         1,2         y         1           97         48         52         151         162         1y         1         1,5           98         61         65         186         200         2         ac         2 y         3           98         45         56         154         168         1         3 cmf         1,2         2 n         2 n         2,3           100         53         59         198         214         5 eact         2         1 y         3,5	94	63	68	148	145	2			2 у					
97         48         52         151         162         2         1 y         1         1,5           98         61         65         186         200         2         ac         2 y         3									y			У		2 1,2
99 45 56 154 168 1 3 cm/ 1,2 2 n 2 1,3 100 53 59 198 214 5 act 2 1 y 3,5	97	48	52	151	162	2			1 y	1				1,5
100 53 59 198 214 5 act 2 1 y 3.5								1.2	2 <b>y</b>					2 1.3
זט דוטז 65 132 134 2 2 2 n y 2,3,4,5	100	53	59	198	214	5			2	1 y				3.5
	ועד	01	65	132	134	2			۷	2 n		У		2,3,4,5