Running head: INVASIVE LOBULAR CARCINOMA

Invasive Lobular Carcinoma of the Breast and BRCA Genetic Testing

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Subjective Data

Reason For Selecting Case

This particular case was chosen for evaluation because it involves a patient the author has seen intermittently in practice since March 2006. She has had an unfortunate course of disease processes beginning with an ovarian cancer diagnosis in 2006 of which she currently has no evidence of disease. At present she has been diagnosed with an advanced stage breast cancer, which will be discussed within this case study report.

Patient Profile

Identifying Factors

A.E. is a 45-year-old Hispanic female who presented to Parkland Health and Hospital System Surgical Oncology Multidisciplinary Breast Clinic on September 16, 2009. She is an established patient of this institution.

Background Information

Chief Complaint

The patient presents to clinic following an ultrasound guided core biopsy of the left breast and left axilla performed on August 27, 2009 in the Diagnostic Mammography Department. The pathologic results of this procedure revealed invasive pleomorphic lobular carcinoma in the left breast and metastatic pleomorphic lobular carcinoma in the left axilla. She was referred to the Multidisciplinary Breast Clinic for surgical oncology evaluation.

History of Present Illness

The patient is a 45-year-old Hispanic female who presents with complaints of a self-detected palpable left breast mass that she reports has been present for one month. She was seen

by the radiologists for a bilateral diagnostic mammographic evaluation on August 24, 2009 due to the above-mentioned complaint. Mammographic and sonographic evaluations revealed a new mass (when compared to prior studies dated September 23, 2008) in the left breast along the 11:00 axis suspicious for malignancy as well as left axillary adenopathy suspicious for possible metastasis. Subsequent ultrasound guided core biopsy performed on August 27, 2009 revealed an invasive lobular breast cancer with a left axillary lymph node positive for metastatic disease. Upon further questioning, she denies palpating any other breast masses, no nipple discharge, or overlying skin changes. She reports no shortness of breath or bone pain. She denies changes in appetite, activity intolerance, or unintentional weight loss.

Past Medical History

Illnesses

1. Stage IIIC transitional cell ovarian cancer diagnosed in March 2006 for which she received intravenous Carboplatin and Taxol for three cycles (April 2006 through June 2006) and intravenous/intraperitoneal Cisplatin and Taxol for three cycles (June 2006 through August 2006).
2. Hypothyroidism

Allergies: NKDA

Surgeries

1. Exploratory laparotomy/radical hysterectomy/left ascending colon resection with reanastamosis/omentectomy/appendectomy/lymph node dissection March 2006 secondary to ovarian cancer
2. Right sentinel lymph node biopsy and left axillary lymph node dissection September 15, 2009 secondary to breast cancer with right sentinel lymph node negative and 36/36 left axillary lymph nodes positive for metastatic disease, the largest focus 2.7 cm with extracapsular extension.

Medications

1. Synthroid 75 mcg daily
2. Multivitamin OTC

Health Maintenance

1. Last Td 2006
2. Last Pap smear June 10, 2009 WNL

3. Mammogram September 23, 2008 WNL; August 24, 2009 Abnormal (BIRADS 4c)
4. Recent blood work: Complete Blood Count, Complete Metabolic Panel October 2009 within normal limits; May 2009 CA-125 WNL (9.9) and September 2009 TSH WNL (1.41)
5. Last Flu shot October 2009
6. Last eye exam September 2008
7. Last dental exam November 2008
8. Last DEXA scan February 2008 Osteopenia

Obstetrical History

1. G4 P2 (T2 P0 Ab2 L2)

Social History

The patient has been married for 22 years and has an extremely supportive relationship with her husband, sister, and daughters. She has two daughters, both of which are living. One daughter is 13 years of age and healthy. Her second daughter is 21 years of age and has also been recently diagnosed with a right breast cancer. The patient is not currently employed, but her husband does work for a construction company that does not provide health insurance. Financial concerns are present because of this, and she is currently enrolled in the county hospital's indigent care financial program. The patient does not smoke, drink, or use illicit drugs. She denies any body piercings or tattoos but does report a history of two blood transfusions while receiving chemotherapy for her ovarian cancer in 2006. She and her husband rent their home in a suburb of a large urban city with no concern for safety. Her religious preference is Catholic. She has one heterosexual partner – her husband. She has no history of sexually transmitted diseases.

Family History

Her mother is 70 years-old, alive and well, and her father is 80 years-old, alive and well. She has 5 maternal aunts and one paternal aunt, none with any form of cancer. She has one sister 52 years-old alive and well. Her maternal grandmother died at the age of 88. She had hypertension and hyperlipidemia. Her maternal grandfather died at the age of 62 of unknown

causes. Her paternal grandmother died at the age of 90 of pneumonia. Her paternal grandfather died at the age of 80 of a myocardial infarction. He also had a history of hypertension. Her oldest daughter was recently diagnosed at the age of 21 with breast cancer and is about to undergo chemotherapy, mastectomy, and radiation therapy. There are no other family members with any known cancer diagnoses.

Breast Cancer Risk History

Menarche:	Age 14
Oral contraceptives:	No history of OCP use
Gravida/Parity:	G4 P2 Ab2
First live birth:	Age 22
Breastfeeding:	Breastfed for a total of one year
Hormone replacement therapy:	No history of HRT use
Menopause:	Surgically induced menopause age 41
Family history:	None reported

(American Cancer Society, 2009)

Review of Systems

General:	No fever, chills, anorexia, or unexplained weight loss
Skin/Hair/Nails:	No excess sweating, dryness, hair loss, or nail changes
HEENT:	No vision changes, floaters, or drainage from eyes. Reports some occasional sneezing and scratchy throat from allergies. No head congestion or sinus problems. No hearing loss or changes. No difficulty swallowing. No mouth ulcerations
Neck/Lymph:	No swelling in neck. No tender lymph nodes. No difficulties with range of motion.
Chest/Lungs:	No shortness of breath, hemoptysis, or activity intolerance. No orthopnea or paroxysmal nocturnal dyspnea. She sleeps on one pillow. No coughing or wheezing.
Cardiovascular:	No chest pain or palpitations. No edema. Last EKG September 20, 2008 showing sinus bradycardia at 56 BPM.
Gastrointestinal:	No heartburn or indigestion. She reports a small amount of nausea immediately after breast cancer surgery but none since. She denies vomiting, diarrhea, constipation, or abdominal pain. No black or tarry stools. No bright red blood in stools.
Genitourinary:	No menses since hysterectomy in 2006. No incontinence or dysuria.
Endocrine:	No temperature intolerance. No polydypsia, polyuria, or polyphagia. Taking Synthroid daily for hypothyroidism diagnosed in 2004 without problems.

Musculoskeletal:	She has had some pain in the medial aspect of her left upper extremity since her left axillary lymph node dissection. She denies pain in sternum or back. She denies joint pain or swelling. No muscle weakness or pain.
Neurological:	She denies headache, dizziness, diplopia, focal weakness, or peripheral paresthesias including any residual complications from her prior chemotherapy. No seizure activity or tremors.
Psychological:	Some feelings of sadness and anxiety since recent diagnosis but denies depression.

Brief Discussion of Pathology

Invasive lobular carcinoma (ILC) is a neoplasm arising from the epithelial cells within the lobules of the breast versus the more common neoplasm, invasive ductal carcinoma (IDC), which occurs in the ducts of the breast (Kopans, 2007). Trends in the incidence rates of ILC have been found to be increasing steadily (Li, Anderson, Daling, & Moe, 2003). ILC accounts for fewer than 10% of breast malignancies and some studies have demonstrated that unlike IDC, ILC usually occurs in both breasts (Kopans). Histologically ILC is subtle in its development and often invades normal tissues without causing the strong desmoplastic response characteristic of IDC (Kopans). This insidious progression accounts for the lack of mammographic changes appreciated with this form of cancer, which subsequently leads to ILC being larger at the time of diagnosis (Kopans). ILC tends to be hormone receptor positive and has an overall better prognostic profile than IDC (Li et al.).

The breast cancer 1 (BRCA1) and breast cancer 2 (BRCA2) genes are heritable, tumor-suppressor genes that have been linked to early onset breast and ovarian cancers (Rosen, Fan, Pestell, & Goldberg, 2003). True hereditary cancers account for only 5 to 10% of all breast cancers (Kopans, 2007). While the BRCA1 gene is responsible for approximately 40 to 45% of hereditary breast cancers, it only accounts for 2 to 3% of all breast cancers (Rosen et al.). BRCA1 mutation carriers have a substantially increased risk of developing breast cancer before

the age of 30 to 40 years of age (Rosen et al.). By the age of seventy, 85 to 90% of those females with this genetic mutation will develop breast cancer and 60% will develop ovarian cancer (Rosen et al). In women with a BRCA2 gene mutation, the risk of developing breast cancer by the age of 70 is 45% and for ovarian cancer it is 11% (Kopans).

Objective Data

Physical Examination

Vital signs:	Ht: 150 cm Weight: 57.7 kg Temp: 37 BP: 112/48 Pulse: 69 Respirations: 18
General:	A.E. is a 45-year-old Hispanic female. She is an alert, pleasant, healthy appearing woman in no acute distress, though she does appear mildly anxious. She is well groomed and appears of stated age. Her performance status is 0.
Skin/Hair/Nails:	She has a right anterior chest Port-A-Cath site without any erythema or tenderness to palpation. Her skin is warm, pink, and dry. No skin rashes or lesions. No excessive dryness of skin or hair. Skin turgor is normal with brisk recoil.
Head:	Normocephalic. No lesions noted. Temporal arteries without bruit.
Eyes:	No exopthalmos. Pupils equal, round, reactive to light, and accommodation. Extraocular movements intact without nystagmus. Visual fields intact. Sclera white, conjunctiva clear without drainage. Fundoscopic exam: distinct borders of optic disc, no bulging or cupping. No hemorrhages or exudates noted. Nonicteric.
Ears:	Bilateral tympanic membranes are pearly gray with visible landmarks. Ear canals without drainage or excessive cerumen.
Nose:	Nasal mucosa pink without edema or drainage. Nasal septum midline and intact. No sinus tenderness with palpation.
Throat:	Oropharynx without erythema, exudates, ulcerations, petechiae, or thrush noted. Tonsils 2+ bilaterally. Uvula midline with symmetrical elevation. Soft and hard palate intact. Tongue midline, without deviation. No dental caries. Gums are pink.
Neck:	Full ROM. No thyromegaly. No nodules palpable. No bruit. No difficulty swallowing. Trachea midline. Carotid pulse 2+.
Lymph node survey:	She has well healed right and left axillary surgical incisions. No obvious masses were appreciated with palpation of bilateral axillae. Bilateral Jackson-Pratt drains are in place, both draining less than 30 cc’s per day of serosanguinous fluid. No preauricular, submandibular, cervical, supraclavicular, infraclavicular, or axillary lymphadenopathy is appreciated.

Chest/Lungs:	Symmetrical excursion of chest wall. Respirations unlabored. Lungs clear to auscultation bilaterally/no wheezing or rhonchi noted. No use of accessory muscles. AP/Lateral chest diameter 1:2.
Heart:	Regular rate and rhythm with normal S1 and S2. There are no murmurs, rubs, or gallops appreciated. Apical pulse 69. No edema noted.
Breasts:	Right breast with no palpable masses, nipple discharge, nipple retraction, or skin changes noted. Left breast exam reveals a 1.5 cm firm, mobile, mass in the 11:00 axis just at the edge of the areolar complex. Slight nipple retraction is noted. No skin changes are appreciated.
Abdomen:	Soft, nontender, nondistended with no hepatosplenomegaly or appreciable masses or lesions. She has surgical scars consistent with her prior surgical history of hysterectomy. Bowel sounds present in all four quadrants. No rebound or guarding. No aortic, renal, or iliac bruits. No CVA tenderness.
Genitourinary:	Deferred
Musculoskeletal:	No tenderness to palpation of the spine including vigorous percussion over the lumbar spine. No pain to palpation over the sternum or manubrium. Joints symmetrical, without swelling, redness, or edema. Full ROM of all joints. Strength equal bilaterally at 5/5.
Extremities:	Extremities are pink and warm with no lesions, cyanosis, or clubbing appreciated. Peripheral pulses are 2+ bilaterally. No edema or varicosities are noted.
Neurological:	Cranial nerves II-XII grossly intact. Finger to nose and rapid alternating movement intact. No tremors appreciated. Speech is clear and appropriate. No facial droop. Romberg negative. Normal gait. DTR's 2+ bilaterally. Sensation intact symmetrically.
Psychological:	Awake, alert, and oriented to person, place, and time. Short and long term memory intact. Patient is cooperative with appropriate response to surroundings. Answers questions appropriately.
Tests:	Mammogram August 24, 2009 – BIRADS 4c – New mass in the 11:00 axis, 1 CMFN measuring 1.0 cm X 0.8 cm X 1.6 cm. Left axillary lymphadenopathy the largest measuring 2.1 cm. Ultrasound guided core biopsy of the above mentioned masses on August 27, 2009 with pathology revealing invasive pleomorphic lobular carcinoma metastatic to the left axillary lymph nodes. Histologic grade III/III. Tumor profile: Estrogen receptor negative; Progesterone receptor negative; Her-2/neu positive by FISH Head CT September 16, 2009 – WNL Abdomen/Pelvic CT September 16, 2009 – WNL Chest CT September 16, 2009 - Two enhancing left breast nodules; pulmonary opacities cannot rule out metastases.

Bone scan September 17, 2009 – Tracer accumulation in manubrium and sternum. Heterogeneous activity is appreciated in the posterior L2 and anterior L3, L4, and L5 vertebrae which appear to localize to subtle blastic lesions concerning for metastatic disease.
BRCA gene testing October 9, 2009 – negative; however, a significant risk of an inherited component of breast and ovarian cancer is present. Calculated risk that the patient has a genetic mutation related to cancer predisposition is 58%.
L2 vertebrae lytic lesion CT guided core biopsy October 22, 2009 – Positive for malignant cells consistent with breast cancer diagnosis.

Discussion of Findings

The patient initially presented to the Surgical Oncology Clinic following an ultrasound guided core biopsy revealing metastatic grade III, invasive lobular carcinoma of the left breast. The biopsy was performed following a patient detected palpable left breast mass with subsequent mammographic evaluation revealing a new, ill-defined mass with abnormal appearing left axillary lymph nodes. At her initial visit to the clinic, a complete history and physical was performed and discussion regarding desires pertaining to breast conservation took place. A surgical procedure was planned at that time based on A.E.'s verbalization that breast conservation was not a request of hers, but she does want reconstruction if a total mastectomy is indicated. Surgical planning is also based on pathological and clinical examinations (Lyman et al., 2005).

BRCA gene mutation testing was also performed in this patient due to her history of ovarian and breast cancer as well as her young daughter's recent diagnosis of breast cancer at the age of 21 (Bosserman, 2008). The genetic counselor saw the patient on October 9, 2009 and performed a risk assessment calculating the probability of detecting a BRCA gene mutation at 54-87%. This calculation was based on Duke University's BRCAPRO model (Berry et al., 2002; Euhus et al., 2002).

Assessment

Acute Diagnosis

1. Stage IV Invasive Lobular Carcinoma of the left breast 174.9
2. Family history of breast cancer V16.3

Differential Diagnosis

1. Hereditary Breast Cancer Syndrome
2. Li-Fraumeni Syndrome

Chronic Diagnosis

1. Hypothyroidism 244.0
2. History of Stage III Ovarian Cancer 183.0

Assessment of Presenting Complaint

A.E. initially presented to the Department of Radiology Diagnostic Mammography Clinic for evaluation of a self-detected palpable left breast mass that had been present for approximately one month. A subsequent ultrasound guided core biopsy revealed invasive lobular carcinoma for which she was referred to the Multidisciplinary Surgical Oncology Clinic. The pathophysiology of ILC is discussed above. A crucial portion of this case lies in the hereditary component appreciated within the family of A.E. Genetic counseling, BRCA gene mutation testing, and genetic follow up are warranted for this family (Christopoulou & Spiliotis, 2006). Discussion of BRCA genes is presented above.

Psychosocial and End of Life Issues

Given the young age of this patient and her recent breast cancer diagnosis as well as her daughter's new cancer diagnosis, psychosocial issues should be discussed. Genetic counseling will offer answers to many questions common with this type of diagnosis. Involvement of social and psychological support services will be utilized. Given that the patient is not symptomatic, is

having no acute issues, and desires to pursue alternative forms of treatment, end of life issues will not be discussed at the present time.

Plan With Rationale

Surgical

1. Bilateral Sentinel Lymph Node Biopsy
2. Left Axillary Lymph Node Dissection (converted due to positive SLN biopsy)

Diagnostics

1. CT Abdomen/Pelvis
2. CT Chest
3. CT Head
4. Bone Scan
5. Hormone receptor status evaluation

Labs

1. BRCA testing
2. CBC
3. CMP
4. TSH

Pharmacologic

The pharmacologic interventions will be discussed in the *Continuity of Care* portion of this paper given that the medical oncology piece of this treatment plan is based on the outcomes of the above-mentioned interventions.

Psychosocial Care Issues

These issues were discussed in the above section, *Psychosocial and End of Life Issues*. The follow up plan regarding these issues will be addressed below.

Evidence-Based Basis for Plan of Care

Initial surgical plan of care based on the patient's desires regarding breast conservation consisted of a bilateral sentinel lymph node (SLN) biopsy (due to invasive neoplasm and positive axillary lymph node on ultrasound guided core biopsy) for staging purposes with subsequent

total mastectomy at a later date with coordination with plastic surgery (Lyman et al., 2005). Guidelines set forth by the American Society of Clinical Oncology for sentinel lymph node biopsy recommend this procedure for T1 tumors (≤ 2 cm) or T2 tumors (> 2 but < 5 cm). A.E.'s tumor is a T1. This course of treatment is planned when a patient desires immediate breast reconstruction. If the SLN biopsy (CPT code 38792) is negative, no radiation therapy will be necessary, and immediate reconstruction can be safely performed following a total mastectomy. If the SLN biopsy is positive, then the patient will require radiation therapy, and breast reconstruction will need to be delayed until the completion of radiation in order to prevent adverse affects of autologous tissue reconstruction. (Kronowitz & Robb, 2009).

A metastatic evaluation with CT scans and a bone scan is also indicated. Staging studies were assessed revealing a concerning blastic lesion in the lumbar spine. She was referred to medical oncology following her surgery in order to discuss neoadjuvant versus palliative chemotherapy. A plan for chemotherapy is dependent on the presence or absence of distant metastatic disease; therefore, a CT guided bone biopsy was ordered to further assess the concerning area in the lumbar spine. Small pulmonary nodules, too small to characterize, were seen on the chest CT. These were not amenable to biopsy and subsequently will be reimaged in three months. Given the patient's past medical history and recent cancer diagnosis, baseline lab studies (CMP, CBC, TSH) were performed as well.

Regarding the genetic portion of this case, consideration must be lent to the medical history as seen within this family. Given the cancer geneticist evaluation of a significantly elevated risk for a hereditary breast cancer syndrome and genetic mutation related to cancer predisposition, it is highly recommended that the patient be evaluated for the BRCA gene

mutation as well as all female first degree relatives of the patient be counseled and tested. The patient agreed to genetic testing, and blood was obtained for this assessment.

Continuity of Care

Interdisciplinary Care

1. Medical Oncology
2. Cancer Genetics

Outcome of the Intervention

In A.E's case, her right SLN biopsy was negative, and the left SLN biopsy was positive; therefore, a subsequent left axillary lymph node dissection (CPT code 38525) was performed to further evaluate extent of disease. Completion axillary lymph node dissection is routinely performed in breast cancer patients with positive sentinel lymph nodes (Karam, 2009). Pathologic evaluation revealed 36/36 lymph nodes positive for metastatic carcinoma. Estrogen and progesterone receptor status evaluated from the excised lymph nodes was negative and HER2/neu status was positive.

The results of the bone biopsy revealed malignant cells consistent with a primary breast cancer. These findings were discussed with the patient along with the recommendation for palliative chemotherapy, which includes Taxotere and Herceptin along with every 3 to 4 week Zometa (Cristofanilli et al, 2005; Lipton, 2005; Burris, 2001). Zometa is not a chemotherapeutic agent. It is classified as a bisphosphonate, a potent inhibitor of osteoclast activity, that can decrease the risk of skeletal complications that patients with bone metastases often suffer (i.e., bone pain, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy) and even delay their onset (Lipton, 2005; Michaelson & Smith, 2005). A study performed by Cristofanilli et al. (2005) evaluated the responses to primary chemotherapy as well as long-term outcomes in 122 patients with ILC and 912 patients with IDC. ILC patients tended to have a

longer recurrence-free survival (P=.004) and overall survival (P=.001) with the use of primary chemotherapy (Cristofanilli et al.). In a study by Burris (2001), the utilization of Taxotere and Herceptin in the treatment of patients with Her2/neu positive breast cancer demonstrated synergistic cytotoxic activity as evidence by the improved response rates, time to progression, and survival when these agents are prescribed together.

While A. E. has Stage IV (T1 N3a M1) invasive lobular carcinoma with bony metastases, she is asymptomatic except for her palpable breast mass. Staging is based on the American Joint Committee on Cancer staging guidelines (Singletary & Connolly, 2006). Tumor staging is established on the size of the tumor as discussed above. Regional lymph node status is based on site of affected lymph nodes (i.e., axillary, supraclavicular, infraclavicular, and/or inframammary). Stage N3a indicates metastasis in the ipsilateral infraclavicular lymph nodes. Staging of metastasis is contingent upon if metastatic lesions are or are not present after a thorough metastatic surgical, radiological, and pathological assessment has been performed. Stage M1 indicates the presence of distant metastasis (i.e., bone metastasis). Ultimately, A.E.'s pathophysiologic profile is uncharacteristic of a typical ILC tumor based on the above mentioned literature discussed given that her mass is palpable, not mammographically occult, and hormone receptor negative (Kopans, 2007; Li, 2003).

Referrals

1. Social Work (to assist with family member follow up/financial issues)
2. Psychology (assist patient in coping with her diagnosis as well as her daughter's)

Family and Patient Education

The results of the BRCA gene testing were negative. Genetic testing for BRCA1 and BRCA2 is highly sensitive, missing an estimated 15% of mutations (Berry et al., 2002).

It is important to explain to the patient that although her BRCA test was negative, not all of the genes related to breast cancer have been discovered; therefore, there is still a considerable risk of an inherited component to the breast and ovarian cancer (Walsh & King, 2007). The genetic counselors strongly recommended that all of A.E's first-degree relatives be followed as per the National Comprehensive Cancer Network management guidelines for BRCA positive patients (Bosserman, 2008; Christopoulou & Spiliotis, 2006). This would include annual breast MRI and mammogram/ultrasound alternating every six months and ovarian cancer screening starting at age 30-35 with prophylactic bilateral salpingo-oophorectomy at age 35-40. A.E.'s 13-year old daughter should consider some form of breast cancer screening in her later teen years due to her sister's age at diagnosis. The family should discuss this with the child's pediatrician. Testing for Li-Fraumeni Syndrome should also be considered for the daughters due to the early onset of breast cancer in the oldest daughter (Johns Hopkins University, 2009).

Follow Up

The patient has declined conventional medical treatment due to her past negative experiences with chemotherapy during the treatment of her ovarian cancer. At this time she wishes to pursue herbal remedies. The patient is currently asymptomatic and no change in breast mass size is detected. After a lengthy discussion and counseling regarding her best chances for short and long term survival, she agreed to return to the medical oncology clinic in 3 to 6 months for follow up once attempting alternative forms of treatment. She did agree to follow up with the youngest daughter's pediatrician regarding breast cancer screening and genetic testing as well as to discuss further genetic evaluation with her oldest daughter and sister.

References

American Cancer Society. (2009). What are the risk factors for breast cancer? Retrieved October 29, 2009, from http://www.cancer.org/docroot/CRI/content/CRI_2_4_2X_ What_are_the_risk_factors_for_breast_cancer_5.asp

Berry, D. A., Iversen, E. S., Gudbjartsson, D. F., Hiller, E. H., Garber, J. E., Peshkin, B. N., et al. (2002). BRCAPRO validation, sensitivity of genetic testing BRCA1/BRCA2, and prevalence of other breast cancer susceptibility genes. *Journal of Clinical Oncology, 20,* 2701-2712.

Bosserman, L. D. (2008). Genetic testing and management of patients with BRCA1/2-positive breast and ovarian cancers. *Community Oncology, 5*(2), 2-8.

Burris, H. A. (2001). Docetaxel (Taxotere) plus trastuzamab (Herceptin) in breast cancer. *Seminars in Oncology, 28*(Suppl 3), 38-44.

Cristofanilli, M., Gonzalez-Angulo, A., Sneige, N., Kau, S., Broglio, K., Theriault, R. L., et al. (2005). Invasive lobular carcinoma classic type: Response to primary chemotherapy and survival outcomes. *Journal of Clinical Oncology, 23*(1), 41-48.

Christopoulou, A., & Spiliotis, J. (2006). The role of BRCA1 and BRCA2 in hereditary breast cancer. *Gene Therapy and Molecular Biology, 10,* 95-100.

Euhus, D. M., Smith, K. C., Robinson, L., Stucky, A., Olufunmilayo, I. O., Cummings, S., et al. (2002). Pretest prediction of BRCA1 or BRCA2 mutation by risk counselors and the computer model BRCAPRO. *Journal of the National Cancer Institute, 94,* 844-851.

Johns Hopkins University. (2009). *Li-Fraumeni Syndrome.* Retrieved October 31, 2009, from http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=151623

Karam, A. K., Hsu, M., Patil, S., Stempel, M., Traina, T. A., Ho, A. Y., et al. (2009). Predictors of completion axillary lymph node dissection in patients with positive sentinel lymph node. *Annals of Surgical Oncology, 16*(7), 1952-1958.

Kopans, D. B. (2007). *Breast imaging* (3rd ed.). Philadelphia: Lippincott.

Kronowitz, S. J., & Robb, G. L. (2009). Radiation therapy and breast reconstruction: A critical review of the literature. *Plastic and Reconstructive Surgery, 124,* 395-408.

Li, C. I., Anderson, B. O., Daling, J. R., & Moe, R. E. (2003). Trends in incidence of invasive lobular and ductal carcinoma. *JAMA, 289,* 1421-1424.

Lipton, A. (2005). Management of bone metastases in breast cancer. *Current Treatment Options in Oncology, 6*(2), 161-171.

Lyman, G. H., Giuliano, A. E., Somerfield, M. R., Benson, A. B., Bodurka, D. C., Burstein, H. J., et al. (2005). American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *Journal of Clinical Oncology, 23,* 7703-7720.

Michaelson, M. D., & Smith, M. R. (2005). Bisphosphonates for treatment and prevention of bone metastases. *Journal of Clinical Oncology, 23,* 8219-8224.

Rosen, E. M., Fan, S., Pestell, R. G., & Goldberg, I. D. (2003). BRCA 1 gene in breast cancer. *Journal of Cellular Physiology, 196,* 19-41.

Singletary, S. E., & Connolly, J. L. (2006). Breast cancer staging: Working with the sixth edition of the AJCC cancer staging manual. *CA: A Cancer Journal for Clinicians, 56*(1), 37-47.

Walsh, T., & King, M. C. (2007). Ten genes for inherited breast cancer. *Cancer Cell, 11*(2), 103-105.

Appendix

Pedigree

Family Pedigree