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PRECISION ASSESSMENT OF HETEROGENEITY OF LYMPHEDEMA PHENOTYPE, GENOTYPES AND RISK PREDICTION

Mei R. Fu, PhD, RN, FAAN¹, Yvette P. Conley, PhD², Deborah Axelrod, MD, FACS^{2,3}, Amber A. Guth, MD, FACS^{2,3}, Gary Yu, DrPH¹, Jason Fletcher, PhD¹, and David Zagzag, MD, PhD⁵

¹NYU Rory Meyers College of Nursing, New York University, New York, NY

²School of Nursing, University of Pittsburgh, Pittsburgh, PA

³Department of Surgery, New York University School of Medicine, New York, NY

⁴NYU Laura and Isaac Perlmutter Cancer Center, New York, NY

⁵Pathology and Neurosurgery, Division of Neuropathology, Microvascular and Molecular Neuro-Oncology Laboratory, NYU Langone Medical Center, New York, NY

Abstract

Lymphedema following breast cancer surgery is considered to be mainly due to the mechanical injury from surgery. Recent research identified that inflammation-infection and obesity may be the important predictors for lymphedema. The purpose of this exploratory research was to prospectively examine phenotype of arm lymphedema defined by limb volume and lymphedema symptoms in relation to inflammatory genes in women treated for breast cancer. A prospective, descriptive and repeated-measure design using candidate gene association method was used to enroll 140 women at pre-surgery and followed at 4–8 weeks and 12 months post-surgery. Arm lymphedema was determined by a perometer measurement of 5% limb volume increase from baseline of pre-surgery. Lymphedema symptom phenotype was evaluated using a reliable and valid instrument. Saliva samples were collected for DNA extraction. Genes known for inflammation were evaluated, including lymphatic specific growth factors (VEGF-C & VEGF-D), cytokines (IL1- α , IL-4, IL6, IL8, IL10, & IL13), and tumor necrosis factor- α (TNF- α). No significant associations were found between arm lymphedema phenotype and any inflammatory genetic variations. IL1- α rs17561 was marginally associated with symptom count phenotype of 8 symptoms. IL-4 rs2070874 was significantly associated with phenotype of impaired limb mobility and fluid accumulation. Phenotype of fluid accumulation was significantly associated with IL6 rs1800795, IL4 rs2243250 and IL4 rs2070874. Phenotype of discomfort was significantly

***Corresponding Author:** Mei R. Fu, PhD, RN, FAAN, Associate Professor/Tenured, College of Nursing, New York University, 433 First Avenue, 4th Floor, Room 424, New York, NY 10010, Telephone: 212-998-5314, Cell: 973-986-1758, Fax: 212-995-3143, mf67@nyu.edu.

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Conflicts of Interest

The authors declare no conflict of interest.

associated with VEGF-C rs3775203 and IL13 rs1800925. Precision assessment of heterogeneity of lymphedema phenotype and understanding the biological mechanism of each phenotype through the exploration of inherited genetic susceptibility is essential for finding a cure. Further exploration of investigative intervention in the context of genotype and gene expressions would advance our understanding of heterogeneity of lymphedema phenotype.

Keywords

breast cancer; lymphedema; symptoms; symptom clusters; limb volume; arm lymphedema; heterogeneity of phenotype; genotype; risk prediction; lymphedema symptoms

INTRODUCTION

Lymphedema, an abnormal accumulation of lymph fluid in the ipsilateral body area or upper limb, remains an ongoing major health problem affecting more than 40% of 3.1 million breast cancer survivors in the United States (1–3). The experience of lymphedema has been linked to clinically relevant and detrimental outcomes, such as disability and psychological distress, both of which are known risk factors for breast cancer survivors' poor quality of life (QOL) and survivorship (4–7). While mechanical injury from cancer treatment (e.g. surgery, lymph node procedure, radiation) is considered the main contributor to the risk of lymphedema, research has also found that inflammation-infection and higher body mass index (BMI>30) are the main predictors of lymphedema (8–10). It remains puzzling that up to 23% of survivors who only had lumpectomy with sentinel lymph node biopsy (SLNB) of 1 or 2 lymph nodes removed have developed lymphedema, while some survivors who had mastectomy with more than 10 lymph nodes removed have not (11–14). It is possible that genetic variations may be one of the important factors that influence breast cancer survivors' responses to the inflammatory processes and vulnerability to lymphedema, including responses to trauma (surgery and radiation) and triggering factors (infection, burns, minor injuries, higher BMI or obesity). Single nucleic polymorphisms (SNPs) known to influence gene expression and therefore protein levels of inflammatory cytokines and lymphatic specific growth factors have been identified from the non-lymphedema and lymphedema literature (15–24).

Precision assessment of lymphedema phenotype among breast cancer survivors remains a huge challenge in research and clinical practice. Traditionally, lymphedema has been diagnosed by healthcare providers' observations of swelling. Research focus has been on measuring limb girth, limb volume or limb size to evaluate phenotype of arm swelling (hereafter arm lymphedema) with arbitrarily defined criteria of >2-cm increase in limb girth, >200-mL limb volume, or >5% limb volume and bioimpedance ratio (2,6,25–26). Yet, lymphedema phenotypes may include symptoms related to lymph fluid accumulation (hereafter, lymphedema symptoms), including arm swelling, breast swelling, chest wall swelling, heaviness, firmness, tightness, stiffness, pain, aching, soreness, tenderness, numbness, burning, stabbing, tingling, arm fatigue, arm weakness, and limited movement in shoulder, arm, elbow, wrist and fingers (25–26). More importantly, lymphedema symptom phenotype may indicate an early stage of lymphedema in which changes cannot be detected

by current objective measures of limb volume (25–29). There is a critical need to understand heterogeneity of lymphedema phenotype in relation to inflammatory genetic variations to advance precision assessment of lymphedema phenotype and related biological mechanism. The purpose of this exploratory research was to prospectively examine phenotype of arm lymphedema and lymphedema symptoms in relation to inflammatory genes in breast cancer survivors.

MATERIAL AND METHODS

Ethical Consideration

This study was approved by the Institutional Review Board of the study institute in the metropolitan area of New York.

Research Design

We employed a prospective, descriptive and repeated-measure design using candidate gene association method that enabled phase-specific monitoring of lymphedema phenotypes prior to surgery (baseline), at 4–8 weeks and 12 months post-surgery.

Procedures

Researchers were trained for obtaining informed consent and collecting data. Protection of human subjects was ensured by following the guidelines set forth by the Institutional Review Board and successful recruitment procedures used in our prior studies (25,28,30). Written consent to the study was obtained. Procedures for using the perometer and bioimpedance device (25,28,30) as well as collecting saliva samples were followed as recommended by the manufacturers.

Study Participants

Between December 2011 and April 2014, we enrolled 140 women at pre-surgery baseline and followed the participants at 4–8 weeks and 12 months post-surgery. Study participants were over 21 years or older, had a first time diagnosis of breast cancer (Stage I–III), and were scheduled for surgical treatment of lumpectomy or mastectomy, including SLNB, lymph node dissection or axillary lymph node dissection and neoadjuvant or adjuvant therapy (8–10); Women were excluded if they had (1) prior history of lymphedema and breast cancer; (2) renal or heart failure, cardiac pacemaker or defibrillator, artificial limbs or pregnancy.

Phenotype Measures

Demographic & Clinical Information—Demographic and clinical information were collected: breast cancer treatment, stage of disease, cancer location, type of adjuvant therapy and treatment complications (4,25,27).

Height & BMI—Height was measured to the nearest 0.1 cm with a portable stadiometer without shoes. An electrical bioimpedance device (InBody 520, Biospace Co., Ltd) was used to measure weight and BMI (28). The device assesses weight and automatically calculates BMI using the formula: weight (kg) / height (m²).

Infra-red Perometer Measurement—Perometry 350S was performed on each arm. A 3-dimensional limb image was generated and limb volume was calculated for each participant. This optoelectronic method has a standard deviation of 8.9 ml (arm), less than 0.5% of limb volume with repeated measuring (29–30).

Lymphedema Symptom Assessment—*The Lymphedema and Breast Cancer Symptom Experience Index* is a valid and reliable self-report instrument to assess symptoms related to lymph fluid accumulation (25,27,31).

DNA Data Collection

Selection of Genes and polymorphisms (SNPs)—Genes were selected for this exploratory investigation based on functional implications from previous publications. Table 1. These inflammatory genes include lymphatic specific growth factors (VEGF-C & VEGF-D), cytokines (IL1-*a*, IL-4, IL6, IL8, IL10, & IL13) and tumor necrosis factor-*a* (TNF-*a*). Functional SNPs known for inflammation and lymphatic specific growth factors were selected for the genes where these types of functional SNPs have been documented. VEGF-C and VEGF-D do not have any known functional SNPs. Therefore these genes were evaluated using tagging SNPs (tSNP) that cover the variability in the entire gene as well as the 5' flanking promoter regions. The criteria used for selection of tSNPs were based on a MAF cutoff of 20%, R^2 cutoff of 80% using Pairwise Tagger for a Caucasian population (<http://hapmap.ncbi.nlm.nih.gov/>) (32).

Sample collection and DNA extraction—Saliva sample collections were conducted using the *Oragene* DNA self-collection kit from DNA Genotek Corporation. DNA were extracted using the protocol and reagents for extraction supplied with the *Oragene* kit.

Genotype data collection. Genotype data collection—The MassArray i-PLEX Gold SNP Assay (Sequenom, San Diego, CA, USA) was utilized for genotype data collection. Amplification and MassExtend primers were designed with MassARRAY Assay Design 3.1.

Genotyping Quality—Reliability evaluation included checks of expected homozygosity to observed homozygosity at each marker; allele frequencies; genotype call rates; and checks for Hardy-Weinberg Equilibrium consistency (33–34). To ensure robust genetic association analyses, quality control filtering of SNPs was performed. SNPs with call rates of < 95% or Hardy-Weinberg p values of < 0.001 were excluded.

Statistical Analysis

Defining Phenotypes—Because even a 5% limb volume increase enables detectable differences in QOL, arm lymphedema phenotype was defined as a perometer measurement of 5% limb volume increase from pre-surgery baseline in the ipsilateral arm in comparison with the changes in the contralateral arm (5). Since >8 symptoms enables detectable differences in 5% and 200 mL limb volume increase as well as QOL (5,25,31), phenotype of symptom count was categorized into three groups: 0 symptom, 1–7 symptoms, and 8 symptoms at 4–8 weeks and 12 months post-surgery. As symptoms may denote clusters as groups of more than two symptoms that occur together indicating different biological

mechanism (31,35), we performed exploratory factor analysis using principal component analysis (PCA) with a varimax rotation to examine if symptoms presented as clusters. Suitability of the data for PCA was supported by the KMO test (4–8 weeks = 0.762, 12 months = 0.790), indicating an adequate sample size for factor analysis and Bartlett's test of sphericity (*Approx. Chi-Square*= 4–8 weeks = 1805.124, *df*=253, *p*<0.001; 12 months = 2285.879, *df*= 325, *p* < 0.001). It was theorized there were three factors identifying symptom clusters (impaired limb mobility, fluid accumulation, and discomfort), which was supported by the rotated factor solutions (scree plot, variance explained, factors with at least 5 variables loading > 0.4, minimal cross loadings. Three-factor solutions explained 49.7% and 52.5% of the variance in reported symptoms at 4–8 weeks and 12 months post-surgery. Table 5.

Phenotype and Genotype Analysis—SPSS version 22 (IBM, Armonk, NY, USA) was used for statistical analysis. Descriptive statistics were calculated for demographic and clinical characteristics. All point estimates were generated with 95% confidence intervals. Means and standard deviations were used to summarize continuous variables; frequencies and percentages were used to summarize categorical variables. Distributions of the phenotype variables, including (a) limb volume by perometer 5%; (b) count of lymphedema symptoms (0 symptom; 1–7symptoms; 8 symptoms); and (c) symptom clusters (reporting 2 or more symptoms related to impaired limb mobility, fluid accumulation and discomfort), were summarized at each time point (pre-surgery, 4–8 weeks and 12 months post-surgery) and associations with demographic and clinical covariates were estimated. Chi-square analyses were performed to estimate for the associations between categorical demographic and clinical predictors, genotypes (i.e. SNPs for proinflammatory genes) and phenotype variables. Fisher's exact tests were conducted when data did not meet the assumptions of Pearson's chi-square (cells with expected counts < 5). Independent groups t-tests and ANOVAs were used to compare groups on continuous variables, Mann-Whitney and Kruskal-Wallis test of ranks was used for data that were not normally distributed. No adjustments were conducted due to the exploratory nature of the study that would require confirmation in future subsequent research (36–37). Co-dominant mode of genetic allelic (0, 1, 2) inheritance (i.e., rare-allele homozygosity, heterozygosity and reference category of common-allele homozygosity) was assumed in statistical analyses, using a trend test with 1 degree of freedom (36–37).

RESULTS

Phenotypic Characteristics

A total of 136 participants completed the study with only 3.8% attrition rate (n=4 patients). Data from these four patients were not included in the data analysis. The participants were women of a mean age of 52 years with more than 66% having at least a bachelor degree. More than one-half of the participants were married (58.8%) and the majority of participants was employed (83.1%). Among the participants, 60.3% were white, followed by black/ African American (19.9%), Asian (9.6%) and Hispanic (8.8%). The majority of the participants had adjuvant chemotherapy (70.7%), radiation therapy (70%), lumpectomy

(48.5%) and mastectomy (51.4%). Table 2. Hardy-Weinberg Equilibrium p -value > 0.01 were for all SNPs.

Arm Lymphedema Phenotype by Limb Volume and Genetic Variations

At 4–8 weeks post-surgery, 16.2% participants had arm lymphedema defined by $\geq 5\%$ limb volume increase from baseline in the ipsilateral arm. At 12 months post-surgery, 22.8% participants exceeded $\geq 5\%$ limb volume increase. Table 2. Limb volume change from pre-surgery baseline at 4–8 weeks post-surgery was significantly correlated ($r = 0.503$; $p < 0.01$) with limb volume change from baseline at 12 months post-surgery. At 4–8 weeks post-surgery, participants with $\geq 5\%$ limb volume increase were on average 5 years older. At 12 months post-surgery, marital status significantly related to limb volume: more participants who were married had $\geq 5\%$ limb volume increase. Of those that have limb volume of $< 5\%$ at 4–8 weeks post-surgery, 14.9% had $\geq 5\%$ limb volume at 12 months post-surgery. Those who had $\geq 5\%$ limb volume increase at 4–8 weeks post-surgery, 36.4% improved to have $< 5\%$ limb volume at 12 months post-surgery. No significant associations were found between arm lymphedema phenotype defined by $\geq 5\%$ limb volume increase and any inflammatory-related genetic variations.

Symptom Count Phenotype and Genetic Variations

Prior to surgery, only one participant reported more than 8 symptoms and 18 had 1–7 symptoms; all of these participants had received neoadjuvant chemotherapy or radiation prior to surgery. At 4–8 weeks post-surgery, all participants reported at least one symptom: 46% participants had ≥ 8 symptoms and 53.7% 1–7 symptoms. At 12 months post-surgery, 10.3% participants were symptom free, while 26.5% participants reported ≥ 8 symptoms and 63.2% 1–7 symptoms. There was a significant correlation between the number of symptoms reported at 4–8 weeks and 12 months post-surgery ($r = 0.382$; $p < 0.01$). Type of surgery and number of nodes removed were related to symptoms reported at 4–8 weeks post-surgery: a larger proportion of those who underwent mastectomy with immediate reconstruction ($p = 0.024$) and had more lymph nodes removed ($p = 0.014$) reported 8 or more symptoms. At 12 months post-surgery, more participants who had a Bachelor's degree or less reported ≥ 8 symptoms. Table 3.

IL1- α (rs17561) was marginally associated with symptom count phenotype of ≥ 8 symptoms at 4–8 weeks ($p = 0.045$) and 12 months post-surgery ($p = 0.050$). Participants with genotype of rs17561 (IL1- α) homozygous T/T had 3.16 odds at 4–8 weeks post-surgery and 2.51 odds at 12 months post-surgery for phenotype of ≥ 8 symptoms as compared with homozygous G/G as the reference group. Table 4.

Symptom Clusters and Genetic Variations

Prior to surgery, identification of symptom phenotypes was not feasible as 86% of participants were symptom free. Table 5 presents the factor loadings from PCA analysis of symptom reports. At 4–8 weeks post-surgery, 58.1% participants were classified as the phenotype of impaired limb mobility, 86.0% discomfort, and 55.9% fluid accumulation. At 12 months post-surgery, 55.2% participants were classified as the phenotype of impaired limb mobility, 38.2% discomfort, and 44.1% fluid accumulation. Weight and BMI were

significantly related to fluid accumulation at 4–8 weeks ($p = 0.025$) and 12 months post-surgery ($p=0.010$) and discomfort 4–8 weeks ($p = 0.041$) and 12 months post-surgery ($p = 0.040$). Table 6.

IL-4 (rs2070874) was associated with phenotype of impaired limb mobility ($p=0.022$) and fluid accumulation ($p=0.007$). Phenotype of fluid accumulation was associated with IL6 (rs1800795) ($p=0.025$) and IL4 (rs2243250 & 2070874). Phenotype of discomfort was associated with rs3775203 (VEGF-C) ($p=0.012$) and rs1800925 (IL13) ($p=0.007$). Participants with genotype of rs2070874 (IL-4) homozygous T/T had 2.76 odds for phenotype of impaired limb mobility as compared with homozygous C/C as the reference group. Participants with genotype of rs1800795 (IL-6) heterozygous C/G had 3.30 odds for phenotype of fluid accumulation as compared with homozygous G/G; participants with genotype rs2070874 (IL-4) homozygous T/T had 2.76 odds for phenotype of fluid accumulation in comparison with homozygous C/C as the reference group; those with genotype rs2243250 (IL-4) homozygous T/T had 2.07 odds for phenotype of fluid accumulation in comparison with homozygous C/C. Participants with genotype rs3775203 (VEGF-C) heterozygous A/C had 4.70 odds for phenotype of discomfort as compared with homozygous C/C; those with genotype rs1800925 (IL-13) homozygous T/T had 6.29 odds and heterozygous T/C had 2.04 odds for discomfort phenotype as compared with homozygous C/C. Table 4. Additive model revealed that participants with two of the three SNPs (rs1800795, rs2070874, and rs2243250) had 5.29 odds for the phenotype of fluid accumulation. Participants with both SNPs (rs3775203 and rs1800925) had 12.86 of odds for phenotype of discomfort. Table 7.

DISCUSSION

Prior studies on lymphedema following breast cancer surgery used different criteria for the phenotype of arm lymphedema either by $>5\text{cm}$ of limb girth comparison or bioimpedance ratio and explored genes known for primary lymphedema and cytokine genes (22–24). Our study used well-defined criteria for heterogeneous phenotypes lymphedema: arm lymphedema by 5% limb volume increase, phenotype of symptom count, and symptom clusters. Specific phenotypic factors were identified for each phenotype: age and marital status for arm lymphedema; mastectomy with immediate reconstruction and numbers of lymph node removed for phenotype of 8 symptoms; weight, BMI, neoadjuvant chemotherapy, radiation, mastectomy, and lower level of education for phenotype of symptom clusters: impaired limb mobility, fluid accumulation and discomfort. This supports heterogeneity of lymphedema phenotype beyond arm lymphedema.

Our study is the first to explore the associations between genetic susceptibility targeting identified phenotypic risk factors of inflammation and heterogeneous phenotypes of lymphedema. No significant associations were found between conventional defined arm lymphedema defined by 5% limb volume increase from baseline and inflammatory genes. Yet, genes related to inflammation, IL1- α rs17561, IL4 rs2070874 and rs2243250, IL6 rs1800795, IL-13 rs1800925, and gene strong for regulating lymphangiogenesis, VEGF-C rs3775203, are found associated with symptom count phenotype of 8 symptoms and symptom cluster phenotype of impaired limb mobility, fluid accumulation, and discomfort.

Only one study evaluated genes related to inflammation with lymphedema defined by bioimpedance ratio and found that IL4 rs2227284 homozygous (C/C + C/A vs A/A) had a 69% decrease in the odds of developing lymphedema (23–24). Our study found genotype IL4 rs2070874 homozygous T/T increased in 2.76 odds for phenotype of fluid accumulation and IL4 rs2243250 (IL-4) homozygous T/T 2.07 odds for phenotype of fluid accumulation in comparison with homozygous C/C. IL4 has the ability to activate macrophages into M2 macrophages which function in tissue repair, fibrosis and the regulation of inflammation (23). Further research is needed to evaluate the role of IL4 in the development of lymphedema, especially phenotype of fluid accumulation and impaired limb mobility.

Our study found that genotypes are significantly associated with symptom cluster phenotype: IL4 rs2070874 for impaired limb mobility; IL6 rs1800795, IL4 rs2070874, IL4 rs2243250 for fluid accumulation; VEGF-C rs3775203 and IL-13 rs1800925 for discomfort. More importantly, individuals who had at least two of the three risk genotypes (IL6 rs1800795, IL4 rs2070874, and IL4 rs2243250) increased in 5.29 odds for the fluid accumulation. Individuals who had both VEGF-C rs3775203 and IL6 rs1800925 genotypes increased in 12.86 of odds for discomfort. This provides support for heterogeneity of lymphedema phenotypes, especially phenotype of symptom clusters based on biological mechanisms. It is important to include symptom phenotypes in future research and clinical practice. Patients who report symptoms with the identified genotypes should be considered to have higher risk for early and precision intervention.

We are aware of the limitations of the sample size and 12-month follow-up. Yet, the study provided an opportunity to assess the feasibility of this approach and necessary information for subsequent confirmation research. The strengths of our study included well-defined phenotypes, adequate sample size for an exploratory study, well-designed prospective and consecutive repeated measurement of heterogeneous phenotypes at meaningful time points, and selection of genes related to well-established phenotypic risk factors of inflammation.

CONCLUSIONS

Precision assessment of heterogeneity of lymphedema phenotype and understanding the biological mechanism of each phenotype through the exploration of inherited genetic susceptibility is a logical step for finding a cure for this chronic condition (38). For example, phenotype of fluid accumulation is identified to be associated with inflammatory mechanism as evidenced by not only significant associations with IL6 rs1800795, IL4 rs2243250 and IL4 rs2070874 but also higher BMI (>30), which is associated with polymorphisms of IL6 and elevated IL6 level (16, 17,19). Further evidence includes that interventions to promote lymph fluid flow and optimize BMI have demonstrated positive effects for phenotype of fluid accumulation (30). Further exploration of the intervention to promote lymph flow and optimize BMI and other existing treatments in the context of genotype and gene expressions could further advance our understanding of biological mechanism of each phenotype. Future prospective research should focus on a priori recognition of inherited genetic susceptibility to facilitate risk prediction, more precisely assess lymphedema phenotypes and provide increased precision in targeted intervention. Such research could assist in further discerning biological mechanisms of heterogeneity of lymphedema phenotype.

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Highlights for Review

- Lymphedema, an abnormal accumulation of lymph fluid in the ipsilateral body area or upper limb, remains an ongoing major health problem affecting more than 40% of 3.1 million breast cancer survivors in the United States (1-3).
- Lymphedema following breast cancer surgery is considered to be mainly due to the mechanical injury from surgery. Recent research identified that inflammation-infection and obesity may be the important predictors for lymphedema.
- Genetic variations may be one of the important factors that influence breast cancer survivors' responses to the inflammatory processes and vulnerability to lymphedema, including responses to trauma (surgery and radiation) and triggering factors (infection, burns, minor injuries, higher BMI or obesity).
- No significant associations were found between arm lymphedema phenotype and any inflammatory genetic variations.
- IL1-*a* rs17561 was marginally associated with symptom count phenotype of 8 symptoms. IL-4 rs2070874 was significantly associated with phenotype of impaired limb mobility and fluid accumulation.
- Phenotype of fluid accumulation was significantly associated with IL6 rs1800795, IL4 rs2243250 and IL4 rs2070874. Phenotype of discomfort was significantly associated with VEGF-C rs3775203 and IL13 rs1800925.
- Precision assessment of heterogeneity of lymphedema phenotype and understanding the biological mechanism of each phenotype through the exploration of inherited genetic susceptibility is essential for finding a cure.

Table 1

Selected SNPs: Genes, Chromosome, Function

tagSNPs	Gene	Chromosome	Function	Functional SNPs
rs1800587 rs17561	IL1- <i>a</i>	*Chro.2q14-21	Proinflammatory, primary initiator of inflammation response	–380 A/G –889 C/T
rs2070874 rs2243250	IL4	Chro.5 132.01-132.02 Mb	Inflammation and wound repair	the T allele of the –590C/T polymorphism of the IL4 gene Interleukin-4 (IL-4) –589
rs1800795 rs1800796	IL6	Chro. 7p21-24	Proinflammatory, primary initiator of inflammation response, growth factors, obesity	–174 C/G –572 G/C
rs4073	IL8	Chro. 4	Proinflammatory chemokines, activation of neutrophils	–251 A/T
rs1800871 rs1800872 rs1800896	IL10	Chro.1	Anti-inflammatory, regulates T-cell and macrophage function	–819 C/T –592 –1082 G/A
rs1800925 rs20541	IL13	Chro. 5q31	Anti-inflammatory, inhibits the production of proinflammatory cytokines and chemokines, including IL1, IL6, & IL8	Chromosome: 5; NC_000005.9 (131993865..131996801
rs1800610 rs1800629 rs361525	TNF- <i>a</i>	Chro. 6 p21.3	Proinflammatory, key immunemediator	–IVS1+90 G/A –308 G/A –251 T/A
rs1485766 rs3775203 rs3775195 rs11947611 rs4604006	VEGF C	Chro. 4	Lymphatic specific growth factor, strong regulator of lymphangiogenesis, hyperplastic lymphatic vessels, lymphedema. **VEGF C binds to and activates VEGFR3 and VEGFR2 receptors on lymphatic epithelium.	None known
rs6527518 rs6632528 rs6632474 rs4830939 rs1285844	VEGF D	Chro. X	Lymphatic specific growth factor receptor, lymphedema	None known

*Chro: chromosome

Demographic and Clinical Characteristics by Phenotype of Arm Lymphedema By 5% Limb Volume Increase

Table 2

	Limb Volume Change At 4-8 Weeks Post-Surgery						Limb Volume Change At 12-months Post-Surgery					
	<5%			5%			<5%			5%		
	n=114			n=22			n=105			n=31		
	Mean	SD	Mean	SD	p		Mean	SD	Mean	SD	p	
Age	51.3	10.8	56.5	12	0.046 ^a						0.695 ^a	
Weight (pounds)	157.1	35.8	171.4	33.1	0.085 ^a						0.168 ^a	
BMI	27.3	6.3	29.9	5.7	0.070 ^a						0.114 ^a	
	n	%	n	%	p		n	%	n	%	p	
Education												
Associates degree or less	35	30.7	10	45.5			45	33.1	32	30.5	13	41.9
Bachelor's degree	55	48.2	7	31.8			62	45.6	49	46.7	13	41.9
Graduate degree	24	21.1	5	22.7	0.306 ^c		29	21.3	24	22.9	5	16.1
Marital status												0.455 ^b
Married/partnered	69	60.5	11	50			80	58.8	64	61	16	51.6
Divorced/Widowed	14	12.3	6	27.3	0.203 ^c		20	14.7	11	10.5	9	29
Single, never partnered	31	27.2	5	22.7			36	26.5	30	28.6	6	19.4
Ethnicity												
Black/African American	23	20.2	4	18.2			27	19.9	21	20	6	19.4
White Non-Hispanic	69	60.5	13	59.1	0.525 ^c		82	60.3	64	61	18	58.1
Asian	12	10.5	1	4.5			13	9.6	10	9.5	3	9.7
Hispanic/Latino	8	7	4	18.2			12	8.8	8	7.6	4	12.9
Other	2	1.8	0	-			2	1.5	2	1.9	0	-
Employment												
Unemployed	17	14.9	6	27.3	0.210 ^c		23	16.9	16	15.2	7	22.6
Employed	97	85.1	16	72.7			113	83.1	89	84.8	24	77.4
Surgery												
Mastectomy	12	10.5	3	13.6	0.602 ^c		15	11	11	10.5	4	12.9

	Limb Volume Change At 4-8 Weeks Post-Surgery						Limb Volume Change At 12-months Post-Surgery					
	<5%			5%			<5%			5%		
	Mean	SD	n=114	Mean	SD	n=22	Mean	SD	n=105	Mean	SD	n=31
	54	47.4		12	54.5		66	48.5	53	50.5	13	41.9
Lumpectomy	48	42.1		7	31.8		55	40.4	41	39	14	45.2
Mastectomy with immediate reconstruction	Mean 3.2	SD 3.1		Mean 3.8	SD 2.3		Mean 3.3	SD 2.9	Mean 3.3	SD 3	Mean 3.2	SD 2.7
Nodes removed						0.164 ^d						0.090 ^d
Nodes removed Median	Median 2			Median 3.5			Median 2		Median 2			
Chemotherapy	n = 63			n=12			n=75		=54		n=21	
Neoadjuvant	17	27	5	41.7		0.318 ^c	22	29.3	14	25.9	8	38.1
Adjuvant	46	73	7	58.3			53	70.7	40	74.1	13	61.9
Radiation												
No	34	32.4	4	18.2		0.186 ^b	38	29.9	32	33	6	20
Yes	71	67.6	18	81.8			89	70.1	65	67	24	80

^aIndependent groups t-test
^bPearson Chi-square
^cFisher's exact test
SD: Standard Deviation

Table 3

Demographic And Clinical Characteristic By Symptom Count Phenotype

	Symptoms reported At 4-8 Weeks Post-surgery						Symptoms reported At 12 months Post-surgery					
	1-7 Symptom n =73			8 Symptoms n=63			0 Symptom n=14			1-7 Symptoms n=86		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	52.8	10.3	51.4	11.9	0.461 ^a		53.3	13.9	52.5	10.7	50.8	11.1
Weight (pounds)	158.7	35.9	160.3	35.4	0.787 ^a		144.5	21.4	158.8	35.6	166.8	38.7
BMI	27.9	6.5	27.6	6.2	0.765 ^a		25.4	4.1	27.6	6.5	29.0	6.5
	n	%	n	%	p		n	%	n	%	n	%
Education												
Associates degree or Less	25	34.2	20	31.7	0.582 ^b		1	7.1	26	30.2	18	50
Bachelor's degree	35	47.9	27	42.9			10	71.4	40	46.5	12	33.3
Graduate degree	13	17.8	16	25.4			3	21.4	20	23.3	6	16.7
Marital status					0.808 ^b							
Married/partnered	45	61.6	35	55.6			6	42.9	50	58.1	24	66.7
Divorced/Widowed	10	13.7	10	15.9			5	35.7	11	12.8	4	11.1
Single, never partnered	18	24.7	18	28.6			3	21.4	25	29.1	8	22.2
Ethnicity					0.400 ^c							
Black/African American	11	15.1	16	25.4			2	14.3	17	19.8	8	22.2
White Non-Hispanic	49	67.1	33	52.4			8	57.1	56	65.1	18	50
Asian	7	9.6	6	9.5			1	7.1	8	9.3	4	11.1
Hispanic/Latino	5	6.8	7	11.1			3	21.4	3	3.5	6	16.7
More than One Race	1	1.4	1	1.6			0	-	2	2.3	0	-
Employment					0.360 ^b							
Unemployed	10	13.7	13	20.6			2	14.3	15	17.4	6	16.7
Employed	63	86.3	50	79.4			12	85.7	71	82.6	30	83.3

	Symptoms reported At 4-8 Weeks Post-surgery						Symptoms reported At 12 months Post-surgery								
	1-7 Symptom		8 Symptoms				Total Sample		0 Symptom		1-7 Symptoms		8 Symptoms		
	n =73		n=6 3				N=136		n=14		n=86		n=36		
	Mean	SD		Mean		p	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p
Surgery															
Mastectomy	4	5.5	11	17.5		0.024 ^b	15	11	0	-	7	8.1	8	22.2	0.158 ^c
Lumpectomy	42	57.5	24	38.1	66		48.5	8	57.1	44	51.2	14	38.9		
Mastectomy with immediate reconstruction	27	37	28	44.4			55	40.4	6	42.9	35	40.7	14	38.9	
Nodes removed Mean (SD)	Mean 2.7	SD 2.1	Mean 4.1	SD 3.9		0.014 ^d	Mean 3.3	SD 2.9	Mean 2.6	SD 1.7	Mean 3.4	SD 3.3	Mean 3.4	SD 2.1	0.620 ^d
Nodes removed Median	Median 2		Median 3				Median 2		Median 2		Median 2		Median 3		
Chemotherapy	n = 35		n = 40				n= 75		n = 7		n = 39		n = 29		
Neoadjuvant	5	14.3	17	42.5		0.011 ^b	22	29.3	0	-	11	28.2	11	37.9	0.116 ^c
Adjuvant	30	85.7	23	57.5	53		70.7	7	100	28	71.8	18	62.1		
Radiation															
No	21	31.3	17	28.3		0.712 ^b	38	29.9	7	50	24	30.8	7	20	0.119 ^c
Yes	46	68.7	43	71.7	89		70.1	7	50	54	69.2	28	80		

^a ANOVA

^b Pearson Chi-square

^c Fisher's exact test

^d Kruskal-Wallis test

SD: Standard Deviation

Table 4

Odds Ratio of Genotypes and Phenotypes

SNPs	Genotype	0 Symptoms	1-7 Symptoms	>7 Symptoms	p value	OR (95% CI)	OR 95% CI
4-8 Weeks Post-Surgery		n; %	n; %	n; %			1-7 vs 7+ Symptoms
IL1- <i>a</i> rs17561	GG	1/2; 50.0%	40/64; 62.5%	38/55; 69.1%	0.045	----- <i>a</i>	1.00
	GT	0/2; 0.0%	22/64; 34.4%	11/55; 20.0%		----- <i>a</i>	0.53 (0.20, 1.32)
	TT	1/2; 50.0%	2/64; 3.1%	6/55; 19.9%		----- <i>a</i>	3.16 (0.52, 33.44)
12 Months Post-Surgery						0 vs 1-7 Symptoms	1-7 vs 7+ Symptoms
IL1- <i>a</i> rs17561	GG	7/14; 50.0%	47/74; 63.5%	25/33; 75.8%	0.050	1.00	1.00
	GT	5/14; 25.7%	24/74; 32.4%	4/33; 12.1%		0.71 (0.17, 3.19)	0.31 (0.07, 1.07)
	TT	2/14; 14.3%	3/74; 4.1%	4/33; 12.1%		0.22 (0.02, 3.23)	2.51 (0.39, 18.25)

SNPs	Genotype	No Limb Mobility (< 2 Symptoms)	Limb Mobility (2+ Symptoms)	p-value	OR (95% CI)
4-8 Weeks Post-Surgery		n; %	n; %		
IL4 rs2070874	CC	21/52; 40.4%	33/68; 48.5%	0.022	1.00
	TC	28/52; 53.8%	22/68; 32.4%		0.50 (0.21, 1.17)
	TT	3/52; 5.8%	13/68; 19.1%		2.76 (0.64, 16.65)
SNPs	Genotype	No Fluid Accumulation (< 2 Symptoms)	Fluid Accumulation (2+ Symptoms)	p-value	OR (95% CI)
4-8 Weeks Post-Surgery		n; %	n; %		
IL6 rs1800795	GG	42/54; 77.8%	22/65; 33.8%	0.025	1.00
	CG	7/54; 13.0%	40/65; 61.5%		3.30 (1.18, 10.08)
	CC	5/54; 9.3%	3/65; 4.6%		0.63 (0.09, 3.50)

SNPs	Genotype	No Limb Mobility (< 2 Symptoms)	Limb Mobility ($2+$ Symptoms)	p-value	OR (95% CI)
IL4 rs2070874	CC	21/54; 38.9%	54/66; 50.0%	0.007	1.00
	TC	30/54; 55.6%	20/66; 30.3%		0.42 (0.18, 1.00)
	TT	3/54; 5.6%	13/66; 19.7%		2.76 (0.64, 16.65)
IL4 rs2243250	CC	19/55; 34.5%	26/65; 40.0%	0.033	1.00
	TC	30/55; 54.5%	22/65; 33.8%		0.54 (0.22, 1.30)
	TT	6/55; 10.9%	17/65; 26.2%		2.07 (0.62, 7.59)
SNPs	Genotype	No Discomfort (< 2 Symptoms)	Discomfort ($2+$ Symptoms)	p-value	OR (95% CI)
4-8 Weeks Post-Surgery		n; %	n; %		
VEGF-C rs3775203	CC	13/17; 76.5%	35/93; 37.6%	0.012	1.00
	AC	3/17; 17.6%	38/93; 40.9%		4.70 (1.14, 27.44)
	AA	1/17; 5.9%	20/93; 21.5%		7.43 (0.95, 331.15)
12 Months Post-surgery					
IL13 rs1800925	CC	40/73; 54.8%	14/45; 31.1%	0.007	1.00
	TC	28/73; 38.4%	20/45; 44.4%		2.04 (0.82, 5.15)
	TT	5/73; 6.8%	11/45; 24.4%		6.29 (1.62, 26.61)

^aDue to the small sample size for 0 symptom.

Table 5

Factor loadings with varimax rotation for symptom cluster phenotypes.

	4-8 Weeks post-surgery			12-Months post-surgery		
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
	Impaired Limb Mobility	Fluid Accumulation	Discomfort	Impaired Limb Mobility	Discomfort	Fluid Accumulation
Limited Shoulder Movement	0.850	0.131	0.227	0.650	-0.091	0.031
Limited Elbow Movement	0.742	0.023	-0.010	0.621	-0.222	0.297
Limited Wrist Movement	0.300	0.331	-0.070	0.410	-0.044	0.519
Fingers Limited	0.190	-0.214	0.546	0.370	-0.149	0.741
Limited Arm Movement	0.852	0.158	0.236	0.783	0.189	0.104
Hand swelling	-	-	-	0.546	0.050	0.599
Arm Swelling	0.320	0.627	-0.108	0.553	0.226	0.577
Breast Swelling	-0.079	0.753	0.180	-0.075	0.220	0.669
Chest Wall Swelling	0.178	0.688	0.170	0.091	0.328	0.487
Firmness	0.331	0.554	0.033	0.784	.009	0.187
Tightness	0.784	0.133	0.182	0.785	.270	-0.034
Heaviness	0.401	0.521	0.090	0.794	.310	0.148
Fibrosis (Toughness or thickness of skin)	0.074	0.418	0.015	0.588	.101	0.476
Stiffness	0.728	0.120	0.333	0.618	.198	0.095
Tenderness	0.457	0.324	0.489	0.418	0.562	0.207
Hotness/Increased temperature	-0.231	0.558	0.280	0.419	0.301	0.265
Redness	0.030	0.710	0.163	-0.037	0.164	0.363
Blistering	-	-	-	-0.069	0.736	0.024
Pain	0.341	-0.065	0.529	0.306	0.602	0.289

	4-8 Weeks post-surgery			12-Months post-surgery		
	Factor 1	Factor 2	Factor 3	Factor 1	Factor 2	Factor 3
	Impaired Limb Mobility	Fluid Accumulation	Discomfort	Impaired Limb Mobility	Discomfort	Fluid Accumulation
Numbness	0.296	0.301	.321	0.299	0.145	0.520
Burning	-0.215	0.328	0.556	-0.065	0.436	0.522
Stabbing	-0.163	0.359	0.694	-0.111	0.733	0.211
Tingling (pins and needles)	0.086	0.080	0.466	0.085	0.587	0.146
Arm or hand fatigue	0.237	0.102	0.694	0.412	0.606	0.033
Arm or hand weakness	0.278	0.118	0.719	0.508	0.558	-0.053
Seroma	-	-	-	0.199	0.688	0.150
Initial Eigenvalues	6.587	2.777	2.073	8.657	2.972	2.012
% of variance	28.641	12.076	9.012	33.296	11.429	7.739
% of cumulative variance	28.641	40.717	49.729	33.296	44.725	52.464

* Bold values denote factor loading > 0.40, -'s indicate symptoms not reported by any patients

Table 6

Demographic and Clinical Characteristics by Symptom Clusters Phenotype

Demographic and Clinical Characteristics by Phenotype of Impaired Limb Mobility											
	Impaired Limb Mobility Symptoms at 4-8 Weeks Post-Surgery				Total		Impaired Limb mobility Symptoms at 12 Months Post-Surgery				
	<2 Symptoms n = 57		2+ Symptoms n = 79		p	<2 Symptoms n = 61		2+ Symptoms n = 75		p	
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		
Age	52.7	10.31	51.8	11.7	0.640 ^a	53.6	10.5	50.9	11.5	0.695 ^a	
Weight (pounds)	162.1	34.8	157.5	36.3	0.459 ^a	158.9	38.9	159.8	33.0	0.881 ^a	
BMI	28.7	6.2	27.0	6.3	0.132 ^a	27.4	6.4	28.0	6.3	0.563 ^a	
	n	%	n	%	p	n	%	n	%	p	
Education											
Associates degree or less	22	38.6	23	29.1	0.182 ^b	14	23.0	31	41.3	0.030 ^b	
Bachelor's degree	27	47.4	35	44.3		29	47.5	33	44.0		
Graduate degree	8	14.0	21	26.6		18	29.5	11	14.7		
Marital status											
Married/partnered	32	56.1	48	60.8	0.864 ^b	36	59.0	44	58.7	0.834 ^b	
Divorced/Widowed	9	15.8	11	13.9		10	16.4	10	13.3		
Single, never partnered	16	28.1	20	25.3		15	24.6	21	28.0		
Ethnicity											
Black/African American	11	19.3	16	20.3	0.960 ^b	12	19.7	15	20.0	0.682 ^c	
White Non-Hispanic	36	63.2	46	58.2		36	59.0	46	61.3		
Asian	5	8.8	8	10.1		5	8.2	8	10.7		
Hispanic/Latino	4	7.0	8	10.1		6	9.8	9	8.0		
More than One Race	1	1.8	1	1.3		2	3.3	0	-		
Employment											
Unemployed	8	14.0	15	19.0	0.447 ^b	7	11.5	16	21.3	0.168 ^b	
Employed	49	86.0	64	81.0		54	88.5	59	78.7		
Surgery					<0.001 ^b					0.057 ^b	

Demographic and Clinical Characteristics by Phenotype of Impaired Limb Mobility														
	Impaired Limb Mobility Symptoms at 4-8 Weeks Post-Surgery				Total				Impaired Limb mobility Symptoms at 12 Months Post-Surgery					
	<2 Symptoms		2+ Symptoms						<2 Symptoms	2+ Symptoms				
	n = 57		n = 79						n = 61		n = 75			
	Mean	SD	Mean	SD	p				Mean	SD	Mean	SD	p	
Mastectomy	3	5.3	12	15.2					3	4.9	12	16.0		
Lumpectomy	40	70.2	26	32.9					35	57.4	31	41.3		
Mastectomy with immediate reconstruction	14	24.6	41	51.9					23	37.7	32	42.7		
Nodes removed	Mean	SD	Mean	SD					Mean	SD	Mean	SD	0.269 ^d	
	2.8	2.2	3.7	3.6	0.111 ^d				2.9	2.2	3.7	3.6		
Nodes removed (Median)	Median 2		Median 3						Median 2		Median 3			
Chemotherapy	n = 28		n = 47						n = 25		n = 50		0.004 ^b	
Neoadjuvant	3	10.7	19	40.4					2	8.0	20	40.0		
Adjuvant	25	89.3	28	59.6					23	92.0	30	60.0		
Radiation														
	13	25.0	25	33.3	0.313 ^b				23	41.8	15	20.8	0.010 ^b	
Yes	39	75.0	50	66.7					32	58.2	57	79.2		
Demographic and Clinical Characteristics by Phenotype of Fluid Accumulation														
	Fluid Accumulation Symptoms at 4-8 Weeks Post-Surgery				Total				Fluid Accumulation Symptoms at 12 Months Post-Surgery					
	<2 Symptoms		2+ Symptoms						<2 Symptoms		2+ Symptoms			
	n=60		n=76						n =76		n = 60			
	Mean	SD	Mean	SD	p				Mean	SD	Mean	SD	p	
Age	50.4	11.2	53.5	10.9	0.105 ^a				52.1	11.1	52.2	10.7	0.955 ^a	
Weight (pounds)	153.0	37.3	164.5	33.7	0.063 ^a				153.4	32.7	167.1	37.9	0.025 ^a	
BMI	26.4	6.2	28.8	6.2	0.032 ^a				26.5	5.9	29.2	6.4	0.010 ^a	
	n	%	n	%	p				n	%	n	%	p	
Education					0.730 ^b								0.168 ^b	
Associates degree or less	20	33.3	25	32.9					45	33.1	24	40.0		

Demographic and Clinical Characteristics by Phenotype of Impaired Limb Mobility												
	Impaired Limb Mobility Symptoms at 4-8 Weeks Post-Surgery				Total		Impaired Limb mobility Symptoms at 12 Months Post-Surgery					
	<2 Symptoms		2+ Symptoms		p	N= 136	<2 Symptoms		2+ Symptoms		2+ Symptoms	
	Mean	SD	Mean	SD			Mean	SD	Mean	SD	Mean	SD
Bachelor's degree	29	48.3	33	43.4			62	45.6	35	46.1	27	45.0
Graduate degree	11	18.3	18	23.7			29	21.3	20	26.3	9	15.0
Marital status												
Married/partnered	40	66.7	40	52.6	0.124 ^b		80	58.8	46	60.5	34	56.7
Divorced/Widowed	5	8.3	15	19.7			20	14.7	10	13.2	10	16.7
Single, never partnered	15	25.0	21	27.6			36	26.5	20	26.3	16	26.7
Ethnicity												
Black/African American	11	18.3	16	21.1	0.966 ^c		27	19.9	13	17.1	14	23.3
White Non-Hispanic	38	63.3	44	57.9			82	60.3	48	63.2	34	56.7
Asian	5	8.3	8	10.5			13	9.6	8	10.5	5	8.3
Hispanic/Latino	5	8.3	7	9.2			12	8.8	6	7.9	9	10.0
More than One Race	1	1.7	1	1.3			2	1.5	1	1.3	1	1.7
Employment												
Unemployed	8	13.3	15	19.7	0.323 ^b		23	16.9	13	17.1	10	16.7
Employed	52	86.7	61	80.3			113	83.1	63	82.9	50	83.3
Surgery												
Mastectomy	6	10.0	9	11.8	0.818 ^b		15	11.0	6	7.9	9	15.0
Lumpectomy	28	46.7	38	50.0			66	48.5	34	44.7	32	53.3
Mastectomy with immediate reconstruction	26	43.3	29	38.2			55	40.4	36	47.4	19	31.7
Nodes removed	Mean 3	SD 2.1	Mean 3.5	SD 3.5	0.845 ^d		Mean 3.3	SD 2.9	Mean 3.3	SD 3.2	Mean 3.3	SD 2.6
Nodes removed (Median)	Median 2		Median 2				Median 2		Median 2		Median 2	
Chemotherapy	n = 35		n = 40		0.006 ^b		n = 75		n = 37		n = 38	
												0.051 ^b

Demographic and Clinical Characteristics by Phenotype of Impaired Limb Mobility										
	Impaired Limb Mobility Symptoms at 4-8 Weeks Post-Surgery				Total		Impaired Limb mobility Symptoms at 12 Months Post-Surgery			
	<2 Symptoms		2+ Symptoms		p	N= 136	<2 Symptoms		2+ Symptoms	
	Mean	SD	Mean	SD			Mean	SD	Mean	SD
	n = 57		n = 79				n = 61		n = 75	

Demographic and Clinical Characteristics by Phenotype of Discomfort														
	Discomfort Symptoms at 4-8 Weeks Post-Surgery					Total		Discomfort Symptoms at 12 months Post-Surgery						
	<2 Symptoms		2+ Symptoms		p	N= 136	SD	<2 Symptoms		2+ Symptoms		Mean	SD	p
	n	%	Mean	SD				n	%	n	%			
Age	n = 19		n = 117		0.865 ^a		52.1	n = 84		n = 52		52.6	10.6	0.696 ^a
	Mean	SD	Mean	SD				Mean	SD	Mean	SD			
Weight (pounds)	4	21.1	41	35.0	0.480 ^c		45	n = 136		n = 84		51.9	11.5	36.2
	10	52.6	52	44.4				Mean	SD	Mean	SD			
BMI	5	26.3	24	20.5	0.655 ^a		27.7	n = 117		n = 52		26.9	5.9	6.7
	27.1	4.7	27.8	6.6				Mean	SD	Mean	SD			
Education	n	%	n	%	p		n	n = 136		n = 84		n	%	p
								Mean	SD	Mean	SD			
Associates degree or less	4	21.1	41	35.0	0.480 ^c		45	n = 136		n = 84		21	25.0	46.2
	10	52.6	52	44.4				Mean	SD	Mean	SD			
Marital status	5	26.3	24	20.5	0.480 ^c		29	n = 136		n = 84		20	23.8	17.3
								Mean	SD	Mean	SD			
Married/partnered	9	47.4	71	60.7	0.474 ^c		80	n = 136		n = 84		49	58.3	59.6
	3	15.8	17	14.5				Mean	SD	Mean	SD			
Divorced/Widowed	7	36.8	29	24.8	0.474 ^c		36	n = 136		n = 84		22	26.2	26.9
								Mean	SD	Mean	SD			
Single, never partnered					0.982 ^c		27	n = 136		n = 84		14	16.7	25.0
								Mean	SD	Mean	SD			
Ethnicity	4	21.1	23	19.7	0.982 ^c		27	n = 136		n = 84		13	16.7	25.0
								Mean	SD	Mean	SD			
Black/African American					0.982 ^c		27	n = 136		n = 84		13	16.7	25.0
								Mean	SD	Mean	SD			

Demographic and Clinical Characteristics by Phenotype of Discomfort												
	Discomfort Symptoms at 4-8 Weeks Post-Surgery					Total			Discomfort Symptoms at 12 months Post-Surgery			
	<2 Symptoms		2+ Symptoms			N= 136			<2 Symptoms		2+ Symptoms	
	n = 19	Mean	SD	Mean	SD	Mean	SD	p	n = 84	Mean	SD	p
White Non-Hispanic	11	57.9	60.7	71	60.7	82	60.3		54	64.3	53.8	
	2	10.5	9.4	11	9.4	13	9.6		8	9.5	9.6	
	2	10.5	8.5	10	8.5	12	8.8		6	7.1	11.5	
	0	-	1.7	2	1.7	2	1.5		2	2.4	-	
Employment												
Unemployed	4	21.1	16.2	19	16.2	23	16.9	0.741 ^c	14	16.7	17.3	0.923 ^b
Employed	15	78.9	83.8	98	83.8	113	83.1		70	83.3	82.7	
Surgery												
Mastectomy	0	-	12.8	15	12.8	15	11.0	0.292 ^c	7	8.3	15.4	0.035 ^b
Lumpectomy	10	52.6	47.9	56	47.9	66	48.5		36	42.9	57.7	
Mastectomy with immediate reconstruction	9	47.4	39.3	46	39.3	55	40.4		41	48.8	26.9	
Nodes removed	Mean 3.5	SD 5.2	Mean 3.2	SD 2.3	Mean 3.3	SD 2.9	Median 2	0.238 ^d	3.1	2.3	4.2	0.027 ^d
Nodes removed (Median)	Median 2	Median 2	Median 2	Median 2	Median 2	Median 2	Median 2		Median 2	Median 2	Median 2	
Chemotherapy	n =6		n = 69		n =75		n =40	0.664 ^c	n =35			0.165 ^b
Neoadjuvant	1	16.7	30.4	21	30.4	22	29.3		9	22.5	37.1	
Adjuvant	5	83.3	69.6	48	69.6	70.7	31	53	77.5	22	62.9	0.001 ^b
Radiation								0.370 ^b				
No	7	38.9	28.4	31	28.4	38	29.9		32	41.0	12.2	0.001 ^b
Yes	11	61.1	71.6	78	71.6	89	70.1		46	59.0	87.8	

^aIndependent groups t-test

^bPearson Chi-square

^cFisher's exact test

^dKruskal-Wallis test

SD Standard Deviation

Table 7

Genotype Additive Models

Genotypes	Phenotype of Fluid Accumulation		
IL6 rs1800795 IL4 rs2070874 IL4 rs2243250	No Fluid Accumulation (< 2 Symptoms)	Fluid Accumulation (2 + Symptoms)	P = 0.005 OR (95% CI)
0	41/54; 75.9%	31/64; 48.4%	1.00
1	10/54; 18.5%	18/64; 28.1%	2.38 (0.89 – 6.59)
2	3/54; 5.6%	12/64; 18.8%	5.29 (1.25 – 31.13)
3	0/54; 0.0%	3/64; 4.7%	-----
Genotypes	Phenotype of Discomfort		
VEGF-C rs3775203 IL13 rs1800925	No Discomfort (< 2 Symptoms)	Discomfort (2 + Symptoms)	P = 0.022 OR (95% CI)
0	6/17; 35.3%	14/93; 15.0%	1.00
1	10/17; 58.8%	49/93; 52.7%	2.10 (0.53 – 7.73)
2	1/17; 5.9%	30/93; 32.3%	12.86 (1.30 – 610.42)