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ESTIMATING THE PROBABILITY OF LYMPHEDEMA FOLLOWING BREAST CANCER SURGERY

by

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BS, Tamkang University, Taiwan, 2005

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

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University of Pittsburgh, 2008

Breast cancer-related lymphedema is a chronic complication of breast cancer treatment. It can result not only in physical discomfort and disfigurement but also in substantial impairment of daily activities. The public health importance of this study is to determine what, if any, factors contribute to an increased risk of lymphedema as well as to establish which subgroups of patients are at increased risk. Once the factors that influence the development of lymphedema are clarified, such findings can be used to develop preventive measures.

In 2006, a 1:2 matched case-control study was carried out to determine significant predictors associated with breast cancer-related lymphedema. The results of the study showed that infection of the dominant arm, level of hand use and BMI would be significant predictors to cause lymphedema. Although the development of lymphedema still needs to be taken into account in clinical practice, this case-control study confirmed that some of risk factors can be used in prediction of lymphedema for breast cancer survivors.

Because there is no precise incidence of lymphedema at present, the present study used the incidence rate from an independent study to predict probabilities of lymphedema for a group of breast cancer survivors by utilizing some confirmed risk factors.

This study used Bayes' Theorem to develop an estimator for the probability of lymphedema given various combinations of BMI, infection, and level of hand use. The delta method was used to estimate the variance of predicted lymphedema probabilities. The results consist of a list of lymphedema probabilities for different combinations of risk factors, as well as 95% confidence limits for these probabilities. Patients who have $BMI \geq 25 kg/m^2$, infection, and medium/high of occupational/hobby hand use would have the highest risk of lymphedema (76.71%) after breast cancer surgery.

The goal of this analysis is to address issues in lymphedema formation, to determine whether a set of confirmed risk factors can predict lymphedema, and to estimate the probability of lymphedema in the final model. A well-established lymphedema predicting system for the general breast cancer survivors should be seriously taken consideration in the future.

TABLE OF CONTENTS

1.0 INTRODUCTION 1

1.1 BACKGROUND OF LYMPHEDEMA 1

1.2 PREDICTING FACTORS 2

1.2.1 Treatment-related factors 2

1.2.2 Disease-related factors 3

1.2.3 Patient-related factors 4

1.3 RESEARCH STATEMENT 5

2.0 REVIEW OF THE RELEVANT LITERATURE 6

2.1 FACTORS INFLUENCING THE DEVELOPMENT OF LYMPHEDEMA 6

2.2 SENTINEL LYMPH NODE BIOPSY VS. AXILLARY LYMPH NODE DISSECTION 8

2.3 REVIEW OF THE RESULTS FROM THE SORAN ET AL. (2006) CASE-CONTROL STUDY 9

2.4 LIMITATION 10

3.0 METHODS 11

3.1 PATIENT ACQUISITION 11

3.2 STATISTICAL ANALYSIS 11

3.2.1 Lymphedema probability estimation 12

3.2.1.1 Estimated probabilities from a case-control study 12

3.2.1.2 Incidence of lymphedema..... 13

3.2.1.3 Using Bayes' Theorem to estimate the lymphedema probability... 13

3.2.2 Variance estimation 14

4.0 RESULTS 18

4.1 THE RISK OF LYMPHEDEMA UNDER MAJOR RISK FACTORS 18

5.0 DISCUSSION 26

APPENDIX A DATA SET DESCRIPTION 29

APPENDIX B APPLIED SAS PROCEDURES AND OUTPUT 30

BIBLIOGRAPHY 39

LIST OF TABLES

Table 1 Risk Factors Related to Lymphedema: Comparison of 5 Studies 8

Table 2 Final Model Including Stratified Variables 10

Table 3 Numbers of Cases and Controls for Each Combination 12

Table 4 Lymphedema from ALND (Lin et al. 1993) 13

Table 5 Prediction Probabilities of Lymphedema for Patients with Combinations of the Significant Factors 20

Table 6 Variances and Their Coefficients in the Delta Method 21

Table 7 Incidence of Lymphedema in Published Series 22

Table 8 Comparison of Lymphedema Probabilities 23

Table A. 1 Patient's Occupation Codes 29

LIST OF FIGURES

Figure 1 Estimated Lymphedema Probability by Incidence of Lymphedema 24

Figure 2 The Difference of the Estimated Lymphedema Probabilities 25

1.0 INTRODUCTION

In the United States, breast cancer is the most common type of cancer and the second leading cause of cancer-related death in women (AmericanCancerSociety 2008). However, breast cancer mortality rates have declined recently as a consequence of advances in early detection as well as more wide-spread application of effective adjuvant therapies. In other words, breast cancer seems no longer to be a life-threatening disease and patients with breast cancer may have longer expected survival than previously. Although a variety of therapeutic interventions improve the life expectancy of breast cancer patients, complications and disabilities following breast cancer treatment still significantly decrease the quality of life for breast cancer survivors (BreastCancerOrg.).

1.1 BACKGROUND OF LYMPHEDEMA

Lymphedema is one of the most common complications after breast cancer surgery and approximately 15% to 20% breast cancer patients suffer this complication following breast cancer treatment (Petrek et al. 2000). It is caused by a build-up of lymph fluid in the tissues following breast cancer surgery or radiotherapy. Our bodies have a network of lymph nodes and lymph vessels that carry lymph fluid, similar to the way blood vessels circulate blood to all parts of the body. During surgery for breast cancer, lymph nodes and vessels are removed from the

underarm, changing the way the lymph fluid flows within that side of the upper body. This makes it more difficult for fluid in the arm to circulate to other parts of the body. If the remaining lymph vessels cannot remove enough of the fluid in the breast and underarm area, the excess fluid builds up and causes swelling, or lymphedema. The same situation would happen when using radiation treatment (Morrell et al. 2005). Since a cure has not been established at the present time, prevention of lymphedema is of key importance.

1.2 PREDICTING FACTORS

In general, risk factors of lymphedema are classified into three categories, treatment-related factors, disease-related factors, and patient-related factors.

1.2.1 Treatment-related factors

Type of surgery, radiotherapy, chemotherapy and other combined treatments are treatment-related factors for lymphedema (Geller et al. 2003; Soran et al. 2006). Nowadays, surgeons use more often conservative surgical procedures (lumpectomy, or modified radical mastectomy) rather than the traditional mastectomy. Patients who undergo lumpectomy also receive radiation therapy afterwards in order to eliminate any cancer cells that may be present in the remaining breast tissue.

Axillary lymph node dissection (ALND) is performed to determine whether cancer has spread beyond the breast. Cancer cells found in the lymph nodes suggest that the disease may have spread to other parts of the body, and surgeons usually remove most of lymph nodes in the

underarm area to control tumor spreading. There are two options for doing axillary lymph node dissection. The first option is to do a complete exploration in the underarm area for lymph nodes and to remove as many as possible. The second option is to do a sentinel lymph node biopsy (SNLB) which is a new procedure allowing the surgeon to remove many fewer lymph nodes. The sentinel lymph node is the first lymph node to which cancer is likely to spread from the primary tumor. Cancer cell may appear in the sentinel node before spreading to other lymph nodes. If SNLB is done and the sentinel lymph node does not contain cancer cells, the rest of regional lymph nodes may not need to be removed.

Radiation therapy is usually combined with surgery to treat breast cancer. In most studies, radiation therapy has been found to be a major and independent risk factor for the development of upper limb lymphedema (Kiel et al. 1996; Ozaslan et al. 2004; Starritt et al. 2004). Even without surgery, axillary radiation was associated with an increased incidence of lymphedema (Johansen et al. 2000; Kwan et al. 2002).

Some authors reported that there is no relationship between type of surgery and lymphedema (Geller et al. 2003; Powell et al. 2003; Soran et al. 2006). Patients receiving breast-conserving surgery had no difference in arm swelling relative to patients receiving mastectomy. The combination of ALND and radiation therapy has proved to be a strong predictor of lymphedema (Ozaslan et al. 2004).

1.2.2 Disease-related factors

Disease-related risk factors for lymphedema include tumor stage, nodal status, the number of lymph nodes excised, and the location of the tumor (Geller et al. 2003; Powell et al. 2003; Soran et al. 2006). Breast cancer patients would be classified by their tumor stage ranging from stage 0

to stage 4. If a breast tumor measures larger than 5 centimeters and there is significant involvement of lymph nodes and tumor spreading, such patients are classified as being in later/advanced stage (stage 3 or stage 4). The results for testing the relationship between these disease-related factors and lymphedema remain inconsistent in reported literatures. The reason for that is still unclear.

1.2.3 Patient-related factors

Patient-related factors that have been associated with lymphedema include age at diagnosis, BMI, hypertension, infection, and limb use (Geller et al. 2003; Powell et al. 2003; Soran et al. 2006). Among patient-related factors, BMI is the most significant factor to predict lymphedema. Increased BMI (≥ 25 kg/m^2) has been reported to be an important factor that increases the risk for lymphedema development (Werner et al. 1991; Ozaslan et al. 2004).

1.3 RESEARCH STATEMENT

The risk factors of lymphedema in breast cancer patients have been studied in several trials but the etiology of lymphedema is still not completely understood. A predicting tool for lymphedema should be created to help physicians and breast cancer patients understand how to prevent and control lymphedema. Soran et al. (2006) tested a set of risk factors of lymphedema and found that postoperative infection of the ipsilateral arm, level of hand use, and body mass index (BMI) were three statistically significant factors to predict the risk and severity of lymphedema. The present study used the significant predictors of lymphedema from Soran et al. (2006) and estimates the incidence probability of lymphedema in breast cancer surgery patients. The aim of our study is to investigate whether these three risk factors could accurately predict lymphedema. The results can be useful to guide physicians and breast cancer patients to prevent or lower the risk of lymphedema in favor of determining the most powerful predictors of lymphedema for the general population.

2.0 REVIEW OF THE RELEVANT LITERATURE

The improvement in the life expectancy of women with breast cancer raises important questions about how to control the complications following breast cancer treatment. Lymphedema is the most common and troublesome complication leading to decreased quality of life for breast cancer survivors (Soran et al. 2006). The etiology of lymphedema has been evaluated in many published papers but not all of the factors that contribute to the condition and the nature of their interaction have been identified. Recent public concern has focused on the efficacy of preventive strategies and therapeutic interventions in the management of lymphedema formation.

2.1 FACTORS INFLUENCING THE DEVELOPMENT OF LYMPHEDEMA

Several studies demonstrated that weight status (higher BMI) was associated with breast cancer-related lymphedema in breast cancer survivors (Werner et al. 1991; Ozaslan et al. 2004). For example, the risk and severity of lymphedema were statistically associated with postoperative infection of the ipsilateral arm and BMI. Women with an infection and higher BMI are more likely to develop lymphedema and have a higher severity level of lymphedema (Soran et al. 2006). The risk for arm lymphedema increased with increasing, BMI and women with BMI greater or equal than 30 had a 2.5-fold greater risk of arm lymphedema than lean women (Meeske et al. 2008). Overweight/obesity can be easily identified in breast cancer patients. Not

only for breast cancer is it the risk factor but also for other health problems such as cardiovascular disease, diabetes, and other cancer-related diseases. Its poor healing and high infection rate may increase the risk and the severity of lymphedema. Weight management may be a potential intervention for those at greatest risk of lymphedema to maintain optimal health-related quality of life among survivors (Paskett et al. 2007).

According to information from the webpage of breast cancer organization, breast cancer survivors should avoid using excessively the operation-side arm in the prevention of lymphedema. Among reviewed studies, three indicated that the level of hand use is associated with the risk of lymphedema (Geller et al. 2003; Soran et al. 2006; Paskett et al. 2007). The types of jobs and activities and marriage status are potential factors that may interact with the level of hand use. The more frequently breast cancer patients use their arm from the treated side, the higher the risk that they get lymphedema. Soran et al. (2006) found that high level of hand use in one's occupation such as construction worker, computer programmer, etc., is more likely to lead to lymphedema. Geller et al. (2003) found that women who work outside the home may use their arms more often and have higher risk of lymphedema than housewives. Paskett et al. (2007) also found that marriage status of breast cancer patients could result in higher risk of lymphedema formation because married women engage in more routine household chores and care of children compared with unmarried women. Table 1 shows predictive factors of lymphedema from reviewed publications.

Table 1 Risk Factors Related to Lymphedema: Comparison of 5 Studies

Risk Factors	Study				
	Soran et al.	Geller et al.	Goffman et al.	Meeske et al.	Paskett et al.
Treatment-related factors					
ALND		★			
Irradiation					
Chemotherapy		★			★
Disease-related factor					
Number of lymph node excised			★	★	★
Tumor site/size					
Patient-related factors					
Age		★(4)		★(5)	
BMI	★		★	★	★
Infection	★				
Hypertension				★	
Frequency of hand use	★(1)	★(2)			★(3)

Note: ★ Statistically significant
(1) The level of hand use was defined as low, medium and high according to the patient's job.
(2) Patients work outside the home or not. (Yes/No)
(3) Marriage status (married/single)
(4) There was a significantly increased risk of lymphedema if women were under 50 years of age.
(5) Younger age at diagnosis was associated with lymphedema.

2.2 SENTINEL LYMPH NODE BIOPSY VS. AXILLARY LYMPH NODE DISSECTION

That patients undergoing SNLB would decrease their risk of lymphedema relative to ALND has been confirmed by many studies (Geller et al. 2003; Schijven et al. 2003; Goffman et al. 2004; Francis et al. 2006; Meeske et al. 2008). In the study of comparison of morbidity between ALND and SLNB (Schijven et al. 2003), SLNB is associated with less morbidity compared to ALND in patients with primary breast cancer. Patients having had SLNB had a 5-fold lower risk of lymphedema compared to patients having had ALND. Another study done by Francis et al. reported that the overall incidence of lymphedema was 16.8% after SLNB and 47.1% after ALND. There was a statistically significant difference in severity of lymphedema between SLNB and ALND (Francis et al. 2006). The time of onset of lymphedema after breast cancer

treatment varies. It sometimes appears early and sometimes develops years later. A limited number of studies comparing the incidence of lymphedema between SLNB and ALND all have relatively short periods of follow-up time. Breast cancer patients still can possibly carry a risk for lymphedema for years even though they received SLNB instead of ALND. Therefore, long-term follow-up studies will yield more accurate assessment of the impact of SLNB in order to preventing breast cancer-related lymphedema (Soran et al. 2006). Since the major advantage of SLNB is that it may reduce lymphedema by decreasing the number of unnecessary ALND, the number of lymph nodes excised could be seen as a factor which is positively associated with lymphedema formation. Women who had 10 or more lymph nodes excised have a higher risk of lymphedema (Meeske et al. 2008).

2.3 REVIEW OF THE RESULTS FROM THE SORAN ET AL. (2006) CASE-CONTROL STUDY

In 2006, Soran et al. published a paper in assessing potential risk factors associated with the development of breast cancer-related lymphedema. Patient/clinical factors (the level of hand use and infection), patient's medical conditions (allergy, diabetes, hypertension, hypothyroidism, chronic obstructive pulmonary disease (COPD), and BMI), and disease-related factors (TNM stage, number of dissected nodes, number of positive nodes, and tumor size) were evaluated to find out significant predictors of lymphedema. The final results were that the statistically significant predictor variables were BMI, infection of the ipsilateral arm, and level of hand use. Table 2 shows parameter estimates of predictor variables (Soran et al. 2006).

Table 2 Final Model Including Stratified Variables

Variable		Logistic Regression		
		Coefficients	**OR (95% CI)**	**p-value**
Infection		3.48	32.56 (6.45, 163.41)	< 0.0001
Occupation/hobby (level of hand use)	Medium	0.77	2.16 (1.27, 3.68)	0.0045
	High	1.54	4.67 (1.61, 13.50)	
BMI(centered)*		0.10	N/A	0.0153

* BMI, Body Mass Index (kg/m^2)

2.4 LIMITATION

In general, lymphedema does not occur in all breast cancer patients treated in a similar manner but risk does increase as a result of some of risk factors, such as obesity and radiation therapy. There is no perfect way to predict the risk of lymphedema because of anatomical variations in patient's circulatory systems. It is not to be expected that any specific intervention could be adaptable to all breast cancer patients. However, a general predictive model for lymphedema still can be built to estimate the risk of lymphedema. For instance, a predicting tool for the need of complete ALND for breast cancer patients with sentinel lymph node (SLN) metastases has been developed at Memorial Sloan-Kettering Cancer Center (MSKCC) (Zee et al. 2003) by using a validated multivariate nomogram. The same prospective predicting system for lymphedema can be developed along the same lines as the MSKCC nomogram.

3.0 METHODS

3.1 PATIENT ACQUISITION

Data were obtained from the previous study which was focusing on investigation of the significant predictors and how they affect the severity of lymphedema (Soran et al. 2006). A total of 2983 female patients having breast/axillary surgery were recruited at Magee-Women's Hospital of University of Pittsburgh Medical Center between 1990 and 2000, but only 52 patients with lymphedema had adequate data for the outcome (the severity of lymphedema). The Soran et al. study design was a 1:2 matched case-control study and data were analyzed on 104 female control patients without lymphedema and 52 women with lymphedema. Our current study included the same 52 cases but included all 126 available controls matched on age, radiation therapy, and type of operation from the previous study.

3.2 STATISTICAL ANALYSIS

N:M matching was performed so that there is a varying number of cases and controls in the matched sets. A total of 178 patients (52 cases and 126 controls) were matched on age (<45, 46-54, 55-64, >65), radiation therapy (yes/no), and type of operation (Segmental Mastectomy, Modified Radical Mastectomy, and Modified Radical Mastectomy with TRAM) and categorized

into 24 N:M matched sets. If any case patients or control patients relating to a matched set were missing, the matched set was excluded from the analysis. A patient's BMI was recorded as a categorical variable by using a cut-off value 25 kg/m^2. The SAS System® (SAS Institute Inc, Cary, NC) version 9.1 was used for analysis.

3.2.1 Lymphedema probability estimation

3.2.1.1 Estimated probabilities from a case-control study

Suppose there are J combinations of major risk factors to cause lymphedema, where C_j is one of those combinations, j = 1, 2…J. Table 3 shows how the numbers of cases and controls could be displayed for each risk factor combination.

Table 3 Numbers of Cases and Controls for Each Combination

j	C_j	# cases	# controls
1	C_1	n_1	m_1
2	C_2	n_2	m_2
.	.	.	.
.	.	.	.
.	.	.	.
J	C_J	n_J	m_J
Total		N=52	M=126

Three major risk factors, BMI (<25kg/m^2, ≥ 25kg/m^2), infection (yes/no), and occupational hand use (low, medium, and high), formed 12 combinations. Therefore, the probability of a combination of risk factors given lymphedema cases (y = 1) or non-lymphedema controls (y = 0) could be shown by:

$$P\left(C_j \mid y=1\right)=\frac{n_j(number\ of\ cases\ in\ jth\ combination)}{N(total\ number\ of\ cases)} \qquad \text{where j = 1,2,…12}$$

$$P\left(C_j \mid y=0\right)=\frac{m_j(number\ of\ controls\ in\ jth\ combination)}{M(total\ number\ of\ controls)}$$

3.2.1.2 Incidence of lymphedema

The incidence of lymphedema, P(LE), could be obtained from a single study. Although the reported incidence of lymphedema after breast cancer therapy varies across treatments, Lin et al. (1993) was chosen to be the reference because it utilized breast cancer therapy, follow-up time, and a definition of lymphedema measurement that were consistent with our study. They reported that the incidence of lymphedema was present in 16% of the members of 122 patients for evaluation of morbidity due to ALND in two-year follow-up. Table 4 shows the overall incidence of lymphedema in subgroups.

Table 4 Lymphedema from ALND (Lin et al. 1993)

Lymphedema	%	No.
≥ 2 cm	16.00	19/122
≥ 3 cm	6.00	07/122
≥ 4 cm	2.00	02/122

3.2.1.3 Using Bayes' Theorem to estimate the lymphedema probability

Since the outcome probability conditioning on exposures could not be estimated through case-control studies, Bayes' Theorem used to solve this problem. This approach utilizes the

conditional and marginal probabilities of lymphedema ($y=1$), non-lymphedema ($y=0$) and a combination of lymphedema risk factors (C_j).

The lymphedema probability conditioning on a combination of risk factors could be estimated by using the equation listed below:

$$P\left(y=1 \mid C_j\right)=\frac{P\left(y=1, C_j\right)}{P(C_j)}$$

$$=\frac{P\left(C_j \mid y=1\right)P\left(y=1\right)}{P\left(C_j\right)}$$

$$=\frac{P\left(C_j \mid y=1\right)P\left(y=1\right)}{P\left(C_j \mid y=1\right)P\left(y=1\right)+P\left(C_j \mid y=0\right)P\left(y=0\right)}$$

3.2.2 Variance estimation

After calculating the estimated lymphedema probability, its variance could be estimated by the delta method. It is a method for deriving an approximate probability distribution for a function of an asymptotically normal statistical estimator from knowledge of the limiting variance of that estimator. Basically, the approximate estimated variance is similarly obtained by expanding in a Taylor series and retaining only second-order terms(Mood et al. 1974).

The numbers of cases and controls in each risk factor combination follow a multinomial distribution. For cases, $C_j \sim Multinomial\left(N, p_{1j}\right)$ and, for controls, $C_j \sim Multinomial\left(M, p_{2j}\right)$. The incidence of lymphedema was estimated from a single study and it would follow a binomial

distribution, $Y \sim Binomial(n, p)$, Y being the number of breast cancer patients with lymphedema and n being the number of patients in the source study. The probability of C_j, and Y would be asymptotic normality of the multinomial distribution:

$$P(C_j|y=1) \sim N(p_{1j}, \frac{p_{1j}(1-p_{1j})}{N})$$

$$P(C_j|y=0) \sim N(p_{2j}, \frac{p_{2j}(1-p_{2j})}{M})$$

$$P(Y) \sim N(p, \frac{p(1-p)}{N+M})$$

The estimated probability of lymphedema given risk factors would be rewritten as the following formula according to the Bayes' Theorem:

$$\hat{p} = \frac{\hat{p}_a \hat{p}_c}{\hat{p}_a \hat{p}_c + \hat{p}_b(1-\hat{p}_c)}$$

The general form of the delta method for the variance of $\hat{p}$ is : (Mood et al. 1974)

$$Var(\hat{p}) = Var(\hat{p}_a)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_a}\right\}^2 + Var(\hat{p}_b)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_b}\right\}^2 + Var(\hat{p}_c)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_c}\right\}^2$$
$$+ 2Cov(\hat{p}_a, \hat{p}_b)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_a} \cdot \frac{\partial \hat{p}}{\partial \hat{p}_b}\right\} + 2Cov(\hat{p}_a, \hat{p}_c)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_a} \cdot \frac{\partial \hat{p}}{\partial \hat{p}_c}\right\} + 2Cov(\hat{p}_b, \hat{p}_c)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_b} \cdot \frac{\partial \hat{p}}{\partial \hat{p}_c}\right\}$$

The partial derivatives of $\hat{p}$ with respect to $\hat{p}_a$, $\hat{p}_b$, and $\hat{p}_c$ are:

$$\frac{\partial \hat{p}}{\partial \hat{p}_a} = \frac{\hat{p}_b \hat{p}_c(1-\hat{p}_c)}{\left[\hat{p}_a \hat{p}_c + \hat{p}_b(1-\hat{p}_c\right]^2}$$

$$\frac{\partial \hat{p}}{\partial \hat{p}_b} = \frac{\hat{p}_a \hat{p}_c(\hat{p}_c - 1)}{\left[\hat{p}_a \hat{p}_c + \hat{p}_b(1-\hat{p}_c\right]^2}$$

$$\frac{\partial \hat{p}}{\partial \hat{p}_c} = \frac{\hat{p}_a \hat{p}_b}{\left[\hat{p}_a \hat{p}_c + \hat{p}_b(1-\hat{p}_c\right]^2}$$

Since $\hat{p}_a$, $\hat{p}_b$ and $\hat{p}_c$ are independent, the delta method gives:

$$Var\left(\hat{p}\right) = Var\left(\hat{p}_a\right)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_a}\right\}^2 + Var\left(\hat{p}_b\right)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_b}\right\}^2 + Var\left(\hat{p}_c\right)\left\{\frac{\partial \hat{p}}{\partial \hat{p}_c}\right\}^2$$

The delta method is an important general technique for calculating asymptotic distributions and thereby deducing asymptotic means, variances, and covariances (Bishop et al. 1975). Since this study uses multivariate version of the delta method, the following theorem shows the asymptotically normal distribution for a T-dimensional random vector.

Let $\hat{\theta}_n$ is a T-dimensional random vector, $\hat{\theta}_n = \left(\hat{\theta}_{n1}, ...\hat{\theta}_{nT}\right)$ and θ is a T-dimensional vector parameter, $\theta = \left(\theta_1, ...\theta_T\right)$. $\hat{\theta}_n$ has an asymptotic normal distribution in the sense that

$$\ell\left[\sqrt{n}\left(\hat{\theta}_n - \theta\right)\right] \to N(0, \sum(\theta))$$

$\sum(\theta)$ is the T x T asymptotic covariance matrix of $\hat{\theta}_n$ and is a singular covariance matrix if $\hat{\theta}_n$ has a distribution that is concentrated on a subspace of three-dimensional space. $\hat{\theta}_n$ has an approximate $N(\theta, n^{-1}\sum(\theta))$ distribution.

Suppose f is a function defined on an open subset of T-dimensional space and taking values in R-dimensional space, i.e.,

$$f\left(\theta\right) = \left(f_1(\theta), ..., f_R(\theta)\right).$$

Assuming that f has a differential at θ, $f\left(x\right)$ can be expressed in matrix notation as:

$$f\left(x\right) = f\left(\theta\right) + (x-\theta)\left(\frac{\partial f}{\partial \theta}\right)' + o\left(\left\|x-\theta\right\|\right)$$

Then the asymptotic distribution of $f\left(\hat{\theta}_n\right)$ is given by:

$$\ell\left[\sqrt{n}\left(f(\hat{\theta}_n)-f(\theta)\right)\right]\to N(0,\left(\frac{\partial f}{\partial\theta}\right)\sum(p)\left(\frac{\partial f}{\partial\theta}\right)')$$

Because phat would be approximately following a normal distribution, the 95% confidence interval of the predicted probability was estimated using the normal approximation:

$$\hat{p}\pm Z_{1-\frac{\alpha}{2}}\sqrt{Var\left(\hat{p}\right)}$$

Finally, the delta method provides a means of assessing the relative contributions of p_a, p_b and p_c to the variance of p. One can examine the variances and their coefficients to assess the greatest contribution to the overall variance estimate. A particularly large variance or coefficient would indicate when a substantial contribution to $Var\left(\hat{p}\right)$ comes from. The implication would be that reducing $Var\left(\hat{p}\right)$ could focus first on reducing the large variance or the variance associated with the large coefficient. Different estimates of the lymphedema incidence rate were chosen from published papers, and the sensitivity of lymphedema probabilities based on them would be discussed as well.

4.0 RESULTS

4.1 THE RISK OF LYMPHEDEMA UNDER MAJOR RISK FACTORS

Table 5 shows lymphedema predictions among 8 risk factor combinations. They were estimated by using the incidence rate of lymphedema of 16%. One case patient was excluded because of missing information of BMI and infection. Patients who were in combinations 4, 7, and 8 would have higher risk of lymphedema. The highest estimated lymphedema probability was 0.7671 (95% CI 0.3904 to 1.0000) for breast cancer patients with BMI $\geq$ 25kg/m^2, infection, and medium/high level of hand use. Breast cancer patients having their BMI < 25kg/m^2, infection, and frequently using their hands would have 58.54% (95% CI 0.0331 to 1.0000) risk of lymphedema after surgery. That predicted probability was higher than the 48.49% (95% CI 0.0568 to 0.9129) of those who had infection, higher BMI but low level of hand use. It is obvious that the level of occupational hand use would be a more sensitive predictor than BMI to cause lymphedema formation.

Table 6 shows variances and their coefficients to assess propagation of error in the delta method. All variances of case probability (p_a), control probability (p_b), and incidence of lymphedema (p_c) are small enough in each combination but the coefficients of p_a and p_b in combination 4, 7 and 8 are much larger than the others. That means when estimating the overall

variance of lymphedema probability in combinations 4, 7 and 8, variances of p_a and p_b should be lower down to compensate for their large coefficients.

Table 5 Prediction Probabilities of Lymphedema for Patients with Combinations of the Significant Factors

set	Risk factors combination	# cases	Case Prob.	# controls	Control Prob.	Estimated LE prob.	Variance of LE prob.	95% C.I. of LE
1	BMI < 25 No infection Low level of hand use	5	0.0980	32	0.2540	0.0685	0.0010	(0.0065, 0.1305)
2	BMI < 25 No infection Medium / high level of hand use	10	0.1961	18	0.1429	0.2073	0.0046	(0.0745, 0.3401)
3	BMI < 25 Infection Low level of hand use	N/A	N/A	1	0.0079	N/A	N/A	N/A
4	BMI < 25 Infection Medium / high level of hand use	3	0.0588	1	0.0079	0.5854	0.0794	(0.0331, 1.0000)
5	BMI $\geq$ 25 No infection Low level of hand use	8	0.1569	52	0.4127	0.0675	0.0006	(0.0184, 0.1167)
6	BMI $\geq$ 25 No infection Medium / high level of hand use	14	0.2745	19	0.1508	0.2575	0.0051	(0.1180, 0.3970)
7	BMI $\geq$ 25 Infection Low level of hand use	4	0.0784	2	0.0159	0.4849	0.0477	(0.0568, 0.9129)
8	BMI $\geq$ 25 Infection Medium / high level of hand use	7	0.1373	1	0.0079	0.7671	0.0369	(0.3904, 1.0000)
	Total	51	1.0000	126	1.0000			

Table 6 Variances and Their Coefficients in the Delta Method

set	Risk factors combination	Estimated LE prob.	Variance of LE prob.	p_a	p_b	Var(p_a) (Coeff_p_a)	Var(p_b) (Coeff_p_b)	Var(p_c) (Coeff_p_c)	95% C.I. of LE
1	BMI < 25 No infection Low level of hand use	0.0685	0.0010	0.0980	0.2540	0.0017 (0.4325)	0.0015 (0.0630)	0.0008 (0.2254)	(0.0065, 0.1305)
2	BMI < 25 No infection Medium / high level of hand use	0.2073	0.0046	0.1961	0.1429	0.0031 (0.7021)	0.0010 (1.3230)	0.0008 (1.4944)	(0.0745, 0.3401)
3	BMI < 25 Infection Low level of hand use	N/A	N/A	N/A	0.0079	N/A (N/A)	0.0001 (N/A)	0.0008 (N/A)	N/A
4	BMI < 25 Infection Medium / high level of hand use	0.5854	0.0794	0.0588	0.0079	0.0011 (**17.0248**)	0.0001 (**935.246**)	0.0008 (3.2613)	(0.0331, 1.0000)
5	BMI ≥ 25 No infection Low level of hand use	0.0675	0.0006	0.1569	0.4127	0.0026 (0.1611)	0.0019 (0.0230)	0.0008 (0.2194)	(0.0184, 0.1167)
6	BMI ≥ 25 No infection Medium / high level of hand use	0.2575	0.0051	0.2745	0.1508	0.0039 (0.4850)	0.0010 (1.6070)	0.0008 (2.0234)	(0.1180, 0.3970)
7	BMI ≥ 25 Infection Low level of hand use	0.4849	0.0477	0.0784	0.0159	0.0014 (**10.1415**)	0.0001 (**247.6070**)	0.0008 (3.4537)	(0.0568, 0.9129)
8	BMI ≥ 25 Infection Medium / high level of hand use	0.7671	0.0369	0.1373	0.0079	0.0023 (1.6941)	0.0001 (**506.6680**)	0.0008 (1.7668)	(0.3904, 1.0000)

Table 7 shows the comparison of lymphedema incidence among several published papers. The incidences range from 16% to 46.3% depending on the definition of lymphedema used, the method of measurement, the length of follow-up, and the choice of therapy in each independent study.

Table 7 Incidence of Lymphedema in Published Series

Year	Study	Type of Surgery	LE definition	Follow-up	No. patients	LE incidence
1986	Kissin et al.(1)	N/A	≧2cm	9 months	200	25.5%
1991	Werner et al. (2)	ALND, RT	≧2.5 cm	37 months	282	19.5%
1993	Lin et al. (3)	RM, MRM Lumpectomy with ALND Irradiation	≧2cm	2 years	283	16%
1993	Keramopoulos et al. (4)	SM/MRM ALND	≧2cm	6 months	104	17%
2003	Deutsch et al. (5)	RM Mastectomy+Radiotherapy Mastectomy alone	≧2cm	3 years	1665	46.3%
2005	Clark et al. (6)	Mastectomy Wide local excision Lumpectomy	PVD ≧20% aPVD_change ≧5%	3 years	188	20.7%

Note: LE: Lymphedema; RT: Radiation Therapy; RM: Radical Mastectomy; SM: Segmental Mastectomy; MRM: Modified Radical Mastectomy
(1) (Kissin et al. 1986) (2) (Werner et al. 1991) (3) (Lin et al. 1993) (4) (Keramopoulos et al. 1993)
(5) (Deutsch et al. 2003) (6) (Clark et al. 2005)

Table 8 summarizes the comparison of estimated probabilities by different incidence of lymphedema from 16% to 46.3%. For the combination of BMI≥25, infection, and medium/high level of hand use, the probabilities estimated among five different incidence of lymphedema were much higher than other risk factor combinations. The estimated probability would follow a trend by increasing of lymphedema incidence.

Table 8 Comparison of Lymphedema Probabilities

Set	Risk factors combination	Estimated LE probabilities By different incidence of Lymphedema					
		16%	**17%**	**19.5%**	**20.7%**	**25.5%**	**46.3%**
1	BMI < 25 No infection low level of hand use	0.0685	0.0733	0.0855	0.0915	0.1167	0.2497
2	BMI < 25 No infection medium / high level of hand use	0.2073	0.2194	0.2495	0.2638	0.3196	0.5420
3	BMI < 25 Infection low level of hand use	N/A	N/A	N/A	N/A	N/A	N/A
4	BMI < 25 Infection medium / high level of hand use	0.5854	0.6029	0.6423	0.6593	0.7173	0.8647
5	BMI ≥25 No infection low level of hand use	0.0675	0.0722	0.0843	0.0903	0.1151	0.2468
6	BMI ≥25 No infection medium / high level of hand use	0.2575	0.2716	0.3060	0.3221	0.3884	0.6108
7	BMI ≥25 Infection low level of hand use	0.4849	0.5030	0.5448	0.5633	0.6284	0.8099
8	BMI ≥25 Infection medium / high level of hand use	**0.7671**	**0.7798**	**0.8073**	**0.8187**	**0.8555**	**0.9372**

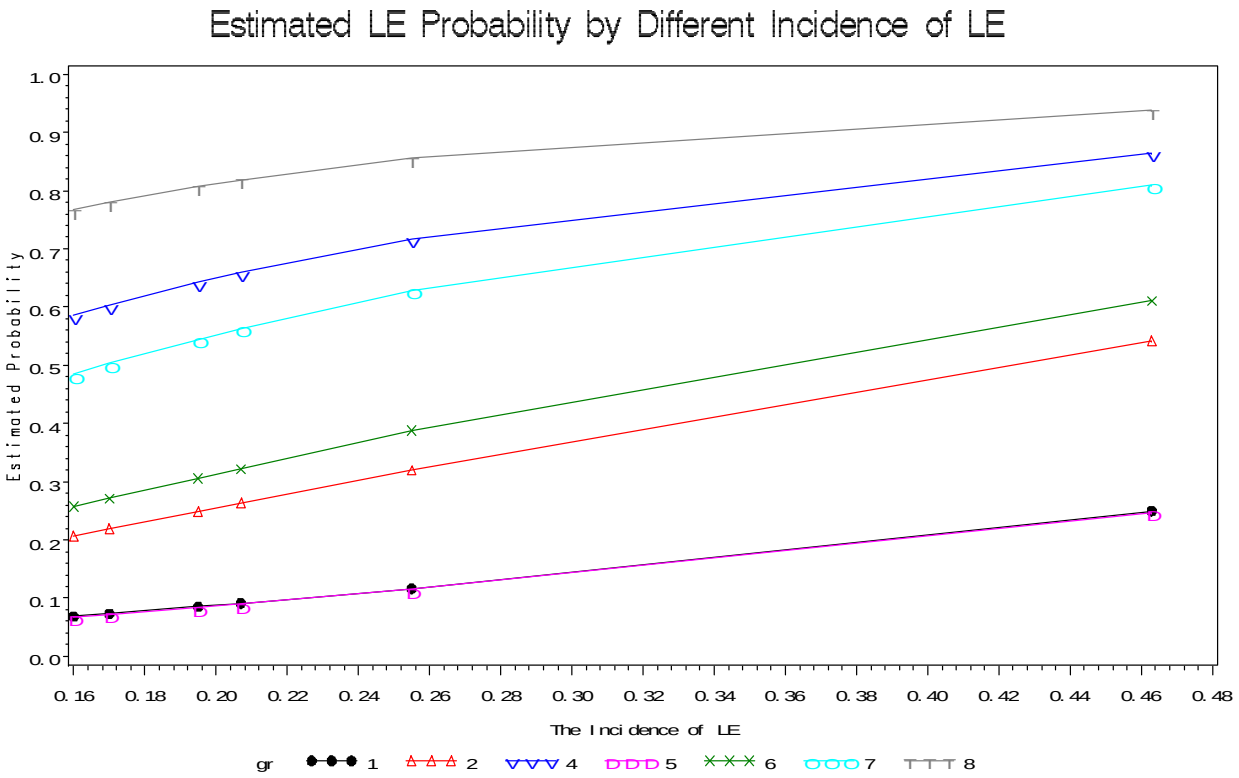

Figure 1 Estimated Lymphedema Probability by Incidence of Lymphedema

Figure 1 presents the estimated lymphedema probabilities by comparing different lymphedema incidence rates in each risk factor combination. The lines for combinations 1 and 5 are almost merged. The difference between these two risk factor combinations is the category of patient's BMI. The estimated lymphedema probabilities in combination 5 (BMI $\geq$ 25kg/m^2) were less than those estimated in combination 1 (BMI<25 kg/m^2). When BMI was grouped by cutoff 25kg/m^2, it would not influence the estimated lymphedema probability. Patients in combinations 4, 7 and 8 had higher estimated lymphedema probabilities than those in other combinations. Although the estimated probabilities in all combinations increased from 16% to 46.3% of the lymphedema incidence, it is important to detect how sensitive the estimated probabilities were to different lymphedema incidence rates.

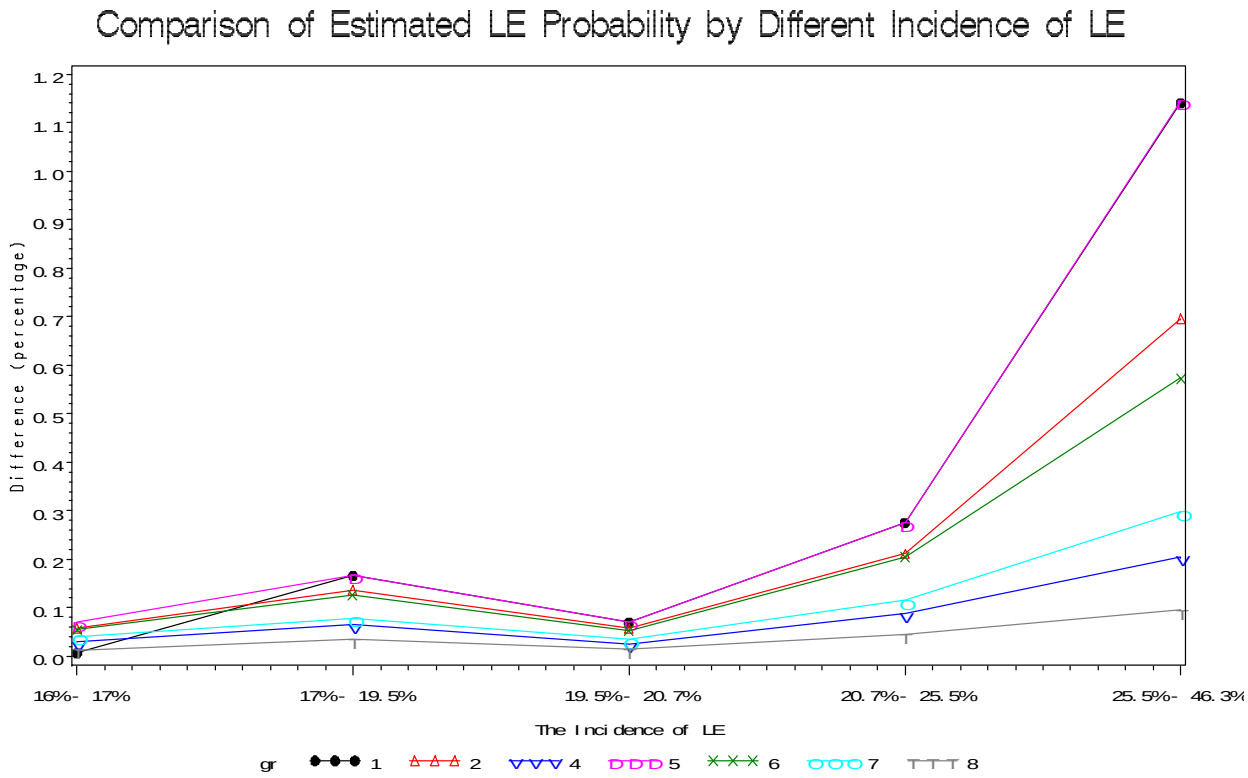

Figure 2 The Difference of the Estimated Lymphedema Probabilities

The percentage change of lymphedema probability was calculated based on the previous incidence. Figure 2 presents the percentage change of the estimated lymphedema probabilities by comparing different lymphedema incidence rates in each risk factor combination. When an incidence jumped into 46.3%, a greater percentage increase was revealed, especially in combinations 1 and 5. Higher estimated lymphedema probabilities correlated to less percentage change in different incidence rates. Patients in combination 8 had much higher lymphedema probability than patients who were in other combinations; and combination 8 also showed less variability because it had a flat and smooth line of depicting each percentage difference of lymphedema probabilities between two of incidence values. Overall, the estimated probabilities in combination 8 were relatively insensitive to changes in incidence values between 17% and 25.5%.

5.0 DISCUSSION

The purpose of this study was to estimate lymphedema probability after breast cancer surgery by three confirmed risk factors (BMI, Infection, and Occupational/hobby hand use) and to assess its variability in predicting lymphedema. Our finding indicated that patients who had their BMI greater than 25kg/m^2, infection, and medium/high level occupational/hobby hand use would significantly have high risk of lymphedema after breast cancer surgery. The predicted probability varied from 77% to 94%, depending on which incidence rate was used.

Our study used 16% of lymphedema incidence rate to estimate probabilities because this incidence rate was utilized by breast cancer surgery, follow-up time, and a definition of lymphedema measurement which were consistent with our study. The 95% confidence interval for the predicted lymphedema probability was estimated in each risk factor combination. The results show that estimated lymphedema probabilities in combinations 4 and 7 were higher and had much wider 95% CI (0.2018 to 1.0000; 0.1853 to 1.0000) than probabilities in other combinations. The highest estimated probability was shown in combination 8 and it had a fairly wide 95% CI (0.5516 to 1.0000). In contrast, the lowest lymphedema probability shown in combination 5 had the narrowest 95% CI (0.0327 to 0.1707). Therefore, it indicated that better prediction of lymphedema revealed in combinations with low estimated probabilities but combinations with high estimated probabilities did not predict lymphedema as well.

Swelling may occur at any point following axillary node dissection or radiation therapy, beginning immediately after or even delayed by several years (Paskett et al. 2007). In the literature, a broad range of incidence rates of post-operative lymphedema varies widely from 8% to 49% in ALND patients. In this study, 16% to 46.3% incidence rate was used with assessment of lymphedema probabilities. Approximately 15% to 20% of breast cancer patients develop lymphedema following breast cancer treatment (Petrek et al. 2000). Our study revealed lymphedema probabilities estimated between 19.5% and 20.7% of lymphedema incidences being similar among breast cancer patients in each risk factor combination.

We found that the predicted lymphedema probabilities for patients in combination 8 were insensitive to different lymphedema incidence rates. These predicted probabilities did not have a huge difference along incidence rates increased. However, the predicted lymphedema probabilities in combinations 1 and 5 were sensitive to incidence rates. Especially when lymphedema incidence changed to 46.3%, the estimated probabilities in these two combinations would increase tremendously. We could conclude that no matter how large we used the lymphedema incidence rate to estimate probabilities, breast cancer patients with their BMI greater than 25kg/m^2, infection, and high/medium level of hand use would have pretty stable risk of lymphedema than those who have other risk factor combinations.

Even though we found that high estimated lymphedema probabilities occurred in combinations 4, 7 and 8, the method of propagation of error indicated that these combinations were associated with high coefficients estimated by the delta method. If we plan to use these combinations of risk factor to estimate lymphedema probabilities, we should find a way to lower their coefficients or reduce the associated variances in order to improve the overall variance estimates of lymphedema probability.

This model represents a significant improvement over estimates based on three risk factors but it is limited by the small number of patients on which it was based. Furthermore, the model remains to be tested on a larger group of patients. Another limitation is the fact that the controls were sampled to match cases. They could therefore not be considered a random sample of the control population. It is possible for a reason that p_b is biased. Nevertheless, for breast cancer survivors, this nomogram was studied to provide a risk estimate that can help them for an early prevention of lymphedema. The public health importance of this study is to determine what, if any, factors contribute to an increased risk of lymphedema as well as to establish which subgroups of patients are at increased risk. Once the factors that influence the development of lymphedema are clarified, such findings can be used to develop preventive measures.

APPENDIX A

DATA SET DESCRIPTION

Table A. 1 Patient's Occupation Codes

Patient's Occupation		
1	**2**	**3**
Continous, <1/2h + <8h/day	**Continous, 1/2-1h + <8h/day**	**Continous, >1h + at least 8h/day**
None	Bank teller	Flight attendant
Retired	Secretary	Phys lab tester
Homemaker	Medical secretary	Nurse
Travel consultant	Receptionist	Registered nurse
Teller	School teacher	Nursing instructor
Sales	Speech language specialist	Computer operator
Sales representative	Teacher Aide	Physician
Buyer consolidation	School nurse	AGH
Sales adm coordinator	Dental assistant	Surg tech.
Pbx supervisor	Travel agent	Laborer
Merchandise manager	Accounting	Pianist
Office manager	Sales assistant	Piano teacher
Clerk	Marketing	Waitress
Counselor	School bus driver	
Administrator	Cook	
Auditor	professor	
Self employed	Dietary Aide	
Recruiter		
Attorney		

APPENDIX B

APPLIED SAS PROCEDURES AND OUTPUT

```
/***Read the LE dataset, code BMI and occup. hand use as dummy variables, and
define 12 groups of risk factor combination***/
option nodate pageno = 1;
data matchset;
      infile 'G:\analysis\0506.txt';
      input Set 1-2 LEcase 4 Agegr$ 6-10 Operation$ 12-19 RT$ 22 BMI 24-25
Infection 27 Occup 29;
      if Occup = 2 then Doccup_1 = 1;else Doccup_1 = 0;
      if Occup = 3 then Doccup_2 = 1;else Doccup_2 = 0;
      if BMI ge 25 then DBMI_1 = 1; else DBMI_1 = 0;
      if BMI = '.' then DBMI_1 = '.';
      if BMI < 25 and Infection = 0 and Occup = 1 then CovarSet = 1;
      if BMI < 25 and Infection = 0 and Occup = 2 then CovarSet = 2;
      if BMI < 25 and Infection = 0 and Occup = 3 then CovarSet = 3;
      if BMI < 25 and Infection = 1 and Occup = 1 then CovarSet = 4;
      if BMI < 25 and Infection = 1 and Occup = 2 then CovarSet = 5;
      if BMI < 25 and Infection = 1 and Occup = 3 then CovarSet = 6;
      if BMI ge 25 and Infection = 0 and Occup = 1 then CovarSet = 7;
      if BMI ge 25 and Infection = 0 and Occup = 2 then CovarSet = 8;
      if BMI ge 25 and Infection = 0 and Occup = 3 then CovarSet = 9;
      if BMI ge 25 and Infection = 1 and Occup = 1 then CovarSet = 10;
      if BMI ge 25 and Infection = 1 and Occup = 2 then CovarSet = 11;
      if BMI ge 25 and Infection = 1 and Occup = 3 then CovarSet = 12;
      obs +1;
run;

title1 'Matched Dataset';
proc print data = matchset;
run;

data cases;
      set matchset;
      if LEcase = 1;
run;
proc sort data=cases;
      by CovarSet;
run;

data controls;
      set matchset;
      if LEcase = 0;
```

```
run;
proc sort data=controls;
      by CovarSet;
run;

title1 'Frequency table for Cases';
proc freq data = cases;
      table DBMI_1 Infection Occup;
run;
title1 'Frequency table for Controls';
proc freq data = controls;
      table  DBMI_1 Infection Occup;
run;

proc univariate data=cases noprint;
      by CovarSet;
      var Occup;
      output out = casecounts n   = total_case;
run;
proc univariate data = controls noprint;
      by CovarSet;
      var Occup;
      output out = contcounts n = total_control;
run;

data summary;
      merge casecounts contcounts;
      caseprobs = total_case/52;
      contprobs = total_control/126;
      by CovarSet;
run;
proc print data = summary;
      title1 'Case and Control Conditional Probabilities by Covariate
Combination';
run;
title;

data temp;
      set matchset;
      if LEcase = '.' then delete;
run;
pattern1 v=s c=black;
pattern2 v=x2;
axis1 label = ('BMI') value = ( ' < 25'  ' > = 25');
axis2 label = ('Lymphedema') value = ('No' 'Yes');
proc gchart data = temp;
      hbar DBMI_1/ discrete type = freq  patternid = group  group = LEcase
      maxis = axis1 gaxis = axis2;
      title 'Bar chart for categorical BMI grouped by cases and controls';
run;
quit;
title;

/***combine medium and high level of hand use together to be one
combination***/
data combined;
      set summary;
```

```
      if CovarSet in (2,3) then ind = 2;
      else if CovarSet in (5,6) then ind = 4;
      else if CovarSet in (8,9) then ind = 6;
      else if CovarSet in (11,12) then ind = 8;
      if CovarSet = '.' then delete;
      if CovarSet = 1 then ind = 1;
      if CovarSet = 4 then ind = 3;
      if CovarSet = 7 then ind = 5;
      if CovarSet = 10 then ind = 7;
      if obs = 2|4|6|8 then count = 1;
      else if count = 0;
run;
proc sort data = combined;
      by ind;
run;
proc sql;
      create table test1 as
      select CovarSet, ind, total_case, total_control, sum(total_case) as
case, sum(total_control) as control
      from combined(where=(ind eq 2|ind eq 4|ind eq 6|ind eq 8))
      group by ind
      union select CovarSet, ind, total_case, total_control, total_case as
case,
      total_control as control from combined(where=(ind eq 1|ind eq 3|ind eq
5|ind eq 7));
quit;
proc print data = test1;
      var ind case control;
run;

data case_control;
      set test1;
            caseprobs = case/51;
            contprobs = control/126;
%macro LEstudy(p_LE=);
            phat = (caseprobs*&p_LE.)/(caseprobs*&p_LE. + contprobs*(1-
&p_LE.));
            dp1 = (contprobs*&p_LE.*(1 - &p_LE.)) / (caseprobs*&p_LE. +
contprobs* (1-&p_LE.))**2;
            dp2 = (caseprobs*&p_LE.*(&p_LE. - 1)) / (caseprobs*&p_LE. +
contprobs* (1-&p_LE.))**2;
            dp3 = (caseprobs*contprobs) / (caseprobs*&p_LE. + contprobs* (1-
&p_LE.))**2;
            Var_p1 = caseprobs*(1-caseprobs)/ 51;
            Var_p2 = contprobs*(1-contprobs)/ 126;
            Var_p3 = &p_LE.*(1-&p_LE.)/177;
            Var_phat = Var_p1*(dp1)**2 + Var_p2*(dp2)**2 + Var_p3*(dp3)**2;
            phat_lower = phat - 1.96*Var_phat**0.5;
            phat_upper = phat + 1.96*Var_phat**0.5;
            if phat_lower < 0 then phat_lower = 0;
            if phat_upper > 1 then phat_upper = 1;
run;
proc print data = case_control;
      var ind caseprobs contprobs phat Var_phat phat_lower phat_upper;
run;
quit;
%mend LEstudy;
```

```
title1 'Estimated lymphedema probability by using 16% incidence of
lymphedema';
      %LEstudy (p_LE = 0.16);
title1 'Estimated lymphedema probability by using 17% incidence of
lymphedema';
      %LEstudy( p_LE = 0.17);
title1 'Estimated lymphedema probability by using 19.5% incidence of
lymphedema';
      %LEstudy (p_LE = 0.195);
title1 'Estimated lymphedema probability by using 20.7% incidence of
lymphedema';
      %LEstudy (p_LE = 0.207);
title1 'Estimated lymphedema probability by using 25.5% incidence of
lymphedema';
      %LEstudy (p_LE = 0.255);
title1 'Estimated lymphedema probability by using 49% incidence of
lymphedema';
      %LEstudy (p_LE = 0.463);
```

Conditional Logistic Regression

The LOGISTIC Procedure

Conditional Analysis

Model Information

Data Set	WORK.MATCHSET
Response Variable	LEcase
Number of Response Levels	2
Number of Strata	21
Number of Uninformative Strata	5
Frequency Uninformative	14
Model	binary logit
Optimization Technique	Newton-Raphson ridge

Number of Observations Read	181
Number of Observations Used	173

Response Profile

Ordered Value	LEcase	Total Frequency
1	0	125
2	1	48

Probability modeled is LEcase=1.

NOTE: 8 observations were deleted due to missing values for the response, explanatory, or strata variables.

Strata Information

Stratum	Set	Stratum Frequency	LEcase 0	LEcase 1
1	1	3	2	1
2	2	4	3	1
3	3	4	2	2
4	4	2	2	0
5	5	19	11	8
6	6	22	15	7
7	7	31	23	8
8	8	11	7	4
9	9	9	9	0
10	10	5	4	1
11	11	8	6	2
12	12	4	3	1
13	13	9	7	2
14	14	11	10	1
15	15	13	8	5

Conditional Logistic Regression

The LOGISTIC Procedure

Conditional Analysis

Odds Ratio Estimates

Effect	Point Estimate	95% Wald Confidence Limits	
DBMI_1	1.861	0.640	5.411
Infection	11.953	2.376	60.124
Doccup_1	1.788	0.535	5.976
Doccup_2	27.372	7.876	95.129

Case and Control Conditional Probabilities by Covariate Combination

Obs	Covar Set	total_ case	total_ control	caseprobs	contprobs
1	.	1	.	0.01923	.
2	1	5	32	0.09615	0.25397
3	2	.	12	.	0.09524
4	3	10	6	0.19231	0.04762
5	4	.	1	.	0.00794
6	5	1	1	0.01923	0.00794
7	6	2	.	0.03846	.
8	7	8	52	0.15385	0.41270
9	8	5	17	0.09615	0.13492
10	9	9	2	0.17308	0.01587
11	10	4	2	0.07692	0.01587
12	11	1	1	0.01923	0.00794
13	12	6	.	0.11538	.

Estimated lymphedema probability by using 16% incidence of lymphedema

Obs	ind	caseprobs	contprobs	phat	Var_phat	Var_p1	Var_p2
1	1	0.09804	0.25397	0.06849	0.001000	.001733873	.001503717
2	2	0.19608	0.14286	0.20725	0.004590	.003090817	.000971817
3	2	0.19608	0.14286	0.20725	0.004590	.003090817	.000971817
4	3	.	0.00794	.	.	.	.000062488
5	4	0.05882	0.00794	0.58537	0.079400	.001085555	.000062488
6	4	0.05882	0.00794	0.58537	0.079400	.001085555	.000062488
7	5	0.15686	0.41270	0.06751	0.000629	.002593271	.001923638
8	6	0.27451	0.15079	0.25747	0.005064	.003904984	.001016309
9	6	0.27451	0.15079	0.25747	0.005064	.003904984	.001016309
10	7	0.07843	0.01587	0.48485	0.047693	.001417253	.000123977
11	8	0.13725	0.00794	0.76712	0.036936	.002321882	.000062488
12	8	0.13725	0.00794	0.76712	0.036936	.002321882	.000062488

Obs	Var_p3	sqr_dp1	sqr_dp2	sqr_dp3	phat_ lower	phat_ upper
1	.000759322	0.4235	0.063	0.22536	0.00650	0.13048
2	.000759322	0.7021	1.323	1.49443	0.07446	0.34005
3	.000759322	0.7021	1.323	1.49443	0.07446	0.34005
4	.000759322	.	.	.	0.00000	.
5	.000759322	17.0248	935.246	3.26127	0.03308	1.00000
6	.000759322	17.0248	935.246	3.26127	0.03308	1.00000
7	.000759322	0.1611	0.023	0.21940	0.01835	0.11667
8	.000759322	0.4850	1.607	2.02342	0.11799	0.39695
9	.000759322	0.4850	1.607	2.02342	0.11799	0.39695
10	.000759322	10.1415	247.607	3.45369	0.05681	0.91289
11	.000759322	1.6941	506.668	1.76679	0.39044	1.00000
12	.000759322	1.6941	506.668	1.76679	0.39044	1.00000

Estimated lymphedema probability by using 17% incidence of lymphedema

Obs	ind	caseprobs	contprobs	phat	Var_phat	phat_ lower	phat_ upper
1	1	0.09804	0.25397	0.07327	0.001124	0.00756	0.13898
2	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
3	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
4	3	.	0.00794	.	.	0.00000	.
5	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
6	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
7	5	0.15686	0.41270	0.07223	0.000704	0.02023	0.12422
8	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
9	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
10	7	0.07843	0.01587	0.50299	0.047653	0.07514	0.93085
11	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000
12	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000

Estimated lymphedema probability by using 19.5% incidence of lymphedema

Obs	ind	caseprobs	contprobs	phat	Var_phat	phat_ lower	phat_ upper
1	1	0.09804	0.25397	0.07327	0.001124	0.00756	0.13898
2	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
3	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
4	3	.	0.00794	.	.	0.00000	.
5	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
6	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
7	5	0.15686	0.41270	0.07223	0.000704	0.02023	0.12422
8	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
9	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
10	7	0.07843	0.01587	0.50299	0.047653	0.07514	0.93085
11	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000
12	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000

Estimated lymphedema probability by using 20.7% incidence of lymphedema

Obs	ind	caseprobs	contprobs	phat	Var_phat	phat_ lower	phat_ upper
1	1	0.09804	0.25397	0.07327	0.001124	0.00756	0.13898
2	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
3	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
4	3	.	0.00794	.	.	0.00000	.
5	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
6	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
7	5	0.15686	0.41270	0.07223	0.000704	0.02023	0.12422
8	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
9	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
10	7	0.07843	0.01587	0.50299	0.047653	0.07514	0.93085
11	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000
12	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000

Estimated lymphedema probability by using 25.5% incidence of lymphedema

Obs	ind	caseprobs	contprobs	phat	Var_phat	phat_ lower	phat_ upper
1	1	0.09804	0.25397	0.07327	0.001124	0.00756	0.13898
2	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
3	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
4	3	.	0.00794	.	.	0.00000	.
5	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
6	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
7	5	0.15686	0.41270	0.07223	0.000704	0.02023	0.12422
8	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
9	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
10	7	0.07843	0.01587	0.50299	0.047653	0.07514	0.93085
11	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000
12	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000

Estimated lymphedema probability by using 46.3% incidence of lymphedema

Obs	ind	caseprobs	contprobs	phat	Var_phat	phat_ lower	phat_ upper
1	1	0.09804	0.25397	0.07327	0.001124	0.00756	0.13898
2	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
3	2	0.19608	0.14286	0.21944	0.004930	0.08181	0.35706
4	3	.	0.00794	.	.	0.00000	.
5	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
6	4	0.05882	0.00794	0.60287	0.077144	0.05848	1.00000
7	5	0.15686	0.41270	0.07223	0.000704	0.02023	0.12422
8	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
9	6	0.27451	0.15079	0.27159	0.005344	0.12831	0.41488
10	7	0.07843	0.01587	0.50299	0.047653	0.07514	0.93085
11	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000
12	8	0.13725	0.00794	0.77984	0.034057	0.41813	1.00000

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