UTILIZATION PATTERNS OF LYMPH NODE DISSECTION IN ENDOMETRIAL CANCER PATIENTS WITHOUT DISTANT METASTASIS IN THE UNITED STATES

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DEDICATION

This dissertation is dedicated to my family, whose support and sacrifice carried me throughout this process; to my friends, whose encouragement motivated me; to my mentors, near and far, whose guidance and confidence led me here; and to CLP, my inspiration and my compass, whose dreams I pursue as part of my own.

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Introduction

Endometrial cancer is the most common gynecologic cancer in the United States, and patients with early-stage endometrioid adenocarcinoma have a favorable prognosis. Over the past decade, the gynecologic oncology community has debated whether potential harms of systematic lymph node dissection (LND) outweigh potential benefits for these patients. To minimize number of nodes removed, sentinel lymph node dissection (SLND) is under investigation as an alternative. However, ongoing uncertainty of LND/SLND best practices may result in variations in disease management and discrepant outcomes.

Methods

Three retrospective cohort studies examined LND/SLND use in patients with endometrioid adenocarcinoma. Two examined temporal and geographic variations, respectively, utilizing the Surveillance, Epidemiology, and End Results (SEER) 18 dataset for the years 2004 through 2015. The third used the SEER-Medicare dataset from 2003 through 2016 to quantify and compare the risk of developing 6-month post-surgical lymphedema, lymphocele, hemorrhage, ileus, infection, thrombosis, and all-cause death by number of lymph nodes removed (0, 1-4, 5-9, or 10+).

Results

Time trend analyses found LND increased from 2004 through 2008, followed by a significant decline through 2015. SLND was rare and did not increase significantly. Significant geographic variation existed for LND use but not SLND. Per 1,000 patients, analyses of 6-month post-surgical complications found 6.5 experienced lymphedema, 3.9 experienced lymphocele, 15.7 experienced hemorrhage, 28.7 experienced ileus, 37.1 experienced infection, 18.6

experienced thrombosis, and 19.8 died. Controlling for size of primary tumor, tumor grade, comorbidities, race/ethnicity, age at diagnosis, adjuvant chemotherapy, and radiotherapy, adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) showed greater risk for ileus (HR: 1.53; 95% CI: 1.24-1.90), infection (HR: 1.52; 95% CI: 1.25-1.83), and thrombosis (HR: 1.41; 95% CI: 1.09-1.82) when comparing removal of 10+ nodes versus 0 nodes.

Conclusion

Overall, these studies found significant temporal and geographic variation in LND, as well as increasing risk of post-surgical complications associated with increasing numbers of lymph nodes removed. Should continued research into SLND find strong evidence that it effectively detects cancer spread, patients may benefit through decreased risk of post-surgical ileus, infection, and thrombosis.

Brian E. Dixon, PhD, MPA, Chair

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LIST OF ABBREVIATIONS

AJCC: American Joint Committee on Cancer

APC: Annual percent change

BMI: Body mass index

CI: Confidence interval

FIGO: International Federation of Gynecology and Obstetrics

HR: Hazard ratio

LND: Lymph node dissection

NCCN: National Comprehensive Cancer Network

NCI: National Cancer Institute

OR: Odds ratio

RCT: Randomized controlled trial

SEER: Surveillance, Epidemiology, and End Results

SLND: Sentinel lymph node dissection

U.S.: United States

CHAPTER 1

INTRODUCTION

1.1. Epidemiology of Endometrial Cancer

Endometrial cancer is the most commonly diagnosed gynecological cancer and the ninth most commonly diagnosed cancer in women in the United States (U.S.) overall[1]. Annual incidence of this disease is 27.8 per 100,000 women[1], which has increased over the past decade[2]. This translated to nearly 66,000 incident U.S. cases in 2020[1] alone. Approximately 84% of new diagnoses are endometrioid adenocarcinoma, with the majority being diagnosed in earlier stages of disease[3]. Prognosis is generally favorable for this histology, with a 5-year relative survival of 83% overall[3].

1.2. Lymph Node Dissection for Endometrial Cancer

National and international guidelines call for the use of total or radical hysterectomy and bilateral salpingo-oophorectomy combined with lymph node assessment during the treatment and staging process for endometrial cancer[4,5]. However, the use of lymph node dissection (LND) for this cancer has been the subject of controversy for patients with endometrioid adenocarcinoma, particularly those with presumed earlier stage disease[6–18]. Although considered integral to comprehensive staging and adjuvant therapy selection[5,19], the appropriate number of lymph nodes to remove in this population is unclear[20], and debate remains regarding LND's utility among these women due to inconsistent evidence of benefit.

Two pivotal randomized controlled trials (RCTs) evaluated the use of systematic lymphadenectomy in presumed early-stage endometrial cancer patients[6,7]. The first was conducted from 1996 through 2006 among 31 medical centers in Italy and Chile. Panici et al.[6] randomly assigned 514 women aged 75 years or younger with preoperative stage I endometrioid or adenosquamous endometrial carcinoma to receive standard hysterectomy with bilateral

salpingo-oophorectomy with (n=264) or without (n=250) systematic lymphadenectomy. Systematic lymphadenectomy consisted of the removal of 20 pelvic lymph nodes which were then analyzed by a pathologist. Para-aortic lymph nodes were removed only at the providers' discretion. For the no-lymphadenectomy arm, bulky lymph nodes were removed if detected by palpation[6]. Adjuvant therapy was administered at the discretion of the treating provider within one month of surgery for both study groups. Median follow-up time was 49 months. Systematic lymphadenectomy found a higher number of lymph node metastases compared to the no-lymphadenectomy (13.3% vs 3.2%; p< .001), and significantly more post-operative complications occurred among the systematic lymphadenectomy group (31% vs. 14%, p=0.001). Additionally, 5-year disease-free survival was calculated to be 81% in the lymphadenectomy group compared to 82% in the no-lymphadenectomy group (p=0.68), and 5-year overall survival was 86% in the lymphadenectomy group compared to 90% in the no-lymphadenectomy group (p=0.50). While results of the study cast doubt on the necessity of systematic lymphadenectomy in women with presumed early-stage endometrial carcinoma, critics have argued its selection of low-risk patients limited the evaluation of the potential therapeutic effect of LND[21]. Further, systematic para-aortic lymphadenectomy was not performed, which may have resulted in lymph node metastases remaining in the systematic LND group and limiting therapeutic benefit[6,21]. Finally, adjuvant therapy was not standardized, and similar use among high-risk groups in each treatment arm may have contributed to the similar survival outcomes[21].

A second RCT, the ASTEC (A Study in the Treatment of Endometrial Cancer) trial, was conducted in 85 centers in the United Kingdom, South Africa, Poland, and New Zealand between 1998 and 2005 and included 1408 women with presumed early-stage endometrial carcinoma who were randomly allocated to the standard surgery plus systematic LND group (n=704) or standard surgery alone (n=704) group[7]. After surgery, women considered to have medium or high risk of disease recurrence were randomly assigned into another trial to assess efficacy of radiotherapy treatment. Median number of lymph nodes harvested was 12 for the LND group and 2 for the

standard therapy group, and the authors reported a greater number of early post-operative complications among the LND group[7]. Median follow-up time was 37 months. Five-year overall survival was calculated to be 80% in the LND group and 81% in the standard surgery group (p=0.83), and 5-year recurrence-free survival was 73% in the LND group and 79% in the standard surgery group (p=0.14). The authors concluded that systematic lymphadenectomy showed no benefit among women with presumed early-stage disease. However, one major limitation of this study was a lack of standardized protocol across participating centers regarding what defined systematic lymphadenectomy. Number of nodes removed varied substantially, as did surgical approach[7,22]. As such, this lack of standardization may preclude drawing any overall conclusions regarding effectiveness of the procedure[22]. In addition, another limitation was that while medium- to high-risk patients were randomized into a second trial to assess radiotherapy, other low-risk patients who were not randomized into the second trial were still able to undergo adjuvant therapy, including radiation, based on their providers' discretion. This lack of standardization for follow-up therapy also may have obscured LND-related variations[23]. Finally, as the prognosis for the included patient population was generally favorable, sample size may have been inadequate to detect a statistically significant difference between groups over the length of the study period[24].

In contrast to these RCTs, observational studies have yielded conflicting results. Several observational studies have demonstrated improved survival among patients undergoing LND[9,12,13], but limitations of these studies included lack of control for confounding factors and limited sample sizes. Differing from these results, a retrospective chart review of endometrioid carcinoma patients found no differences in survival between those exposed to LND and those unexposed, but this study, too, was limited by a small sample size, short follow-up time (median: 26 months), and lack of control for confounders[14]. A larger retrospective cohort study of 1502 patients with a longer follow-up period similarly showed no overall survival benefit among patients at low risk for recurrence[15].

Lack of clarity about LND usefulness is further exacerbated within the context of potential harms resulting from the surgery. Such complications may include lymphedema, lymphocele, ileus, thrombosis, infection, and bleeding [25–27]. In the RCTs described above, researchers found the incidence of early [6,7] and late [6] post-operative complications to be significantly higher among patients who underwent LND compared to those who did not, although sample sizes were limited in their ability to parse out rates of specific complications other than lymphedema. This higher incidence of complications overall combined with the uncertainty regarding possible benefit has generated debate regarding whether potential harms from the procedure outweigh any potential benefits for these women.

1.3. Sentinel Lymph Node Dissection for Endometrial Cancer

As research has recently cast doubt on the necessity and scope of LND in some early-stage patients, alternative approaches, such as sentinel lymph node dissection (SLND), have been explored[28–33]. SLND involves the injection of radioactive dye or indocyanine-green (ICG) to allow for the identification and removal of the lymph nodes to which cancer cells are most likely to spread from the primary tumor[34]. In theory, use of this technique allows for detection of possible metastases while minimizing the number of lymph nodes removed compared to systematic lymphadenectomy, thereby facilitating accurate staging while reducing the risk of surgical morbidities. In conjunction with dye injection, the application of an SLN mapping algorithm has been found to contribute to the detection of metastatic endometrial cancer[19,35,36]. While researchers have found the SLND can yield satisfactory sensitivity, specificity, positive predictive value, and negative predictive value[31,37,38], provider experience, patient body mass index (BMI), and dye selection and injection location all have been identified as possibly influencing the success of SLN identification[29,36,37,39,40].

While the SLND technique may be considered a “targeted” approach in endometrial cancer staging by limiting the number of lymph nodes that are removed[36], it is still unclear whether patient survival, morbidities, or quality of life are improved compared to comprehensive

lymphadenectomy[41–44]. However, despite remaining uncertainties about the SLND approach, the National Comprehensive Cancer Network (NCCN) guidelines currently consider the technique to be an option among patients for whom no metastasis is visible via imaging studies and who have no obvious extrauterine disease at exploration[4].

1.4. Real-world Impact of LND and SLND for Endometrioid Adenocarcinoma Patients

Given the continued lack of consensus in approach to LND and SLND for endometrial endometrioid adenocarcinoma within the gynecologic oncology community, broad variations in disease management approaches are likely[45–50] and may lead to discrepant outcomes. However, these real-world variations in disease management and morbidity outcomes have not been fully elucidated, highlighting a need to describe practice patterns to understand the current state of the field.

Previous research of LND trends for endometrioid adenocarcinoma conducted through 2012 showed an increase in LND use until approximately 2007, and then a slight decline or stabilization[51–53]. However, only one of these studies, whose population consisted of higher-risk stage I patients, adjusted for relevant covariates within the statistical model[53]. As tumor characteristics, such as grade and depth of myometrial invasion, have been found to have significantly changed in the endometrial cancer population over time[51], adjustment for such factors is essential within the model to control for potential confounding. This is particularly important given their potential influence on the providers' decision-making regarding LND use[19]. Additionally, stratifications by cancer stage have been presented[52], but such analyses can present biased results, as those who have undergone LND may be more likely to be classified at more advanced stages due to discovery of lymph node metastases.

While limited information is available through 2012 regarding LND trends in the endometrial cancer population, such information is not available for SLND trends. A single study has been conducted for uterine cancer overall[54], but endometrial-specific information was not

available. Additionally, statistical adjustments were not made for relevant covariates in SLND decision-making, including tumor grade or depth of invasion.

Available information on nationwide geographic differences in LND/SLND use is limited to two published studies with differing patient populations and conflicting conclusions in regards to geographic variability[53,54]. Cripe et al.[53] utilized the National Cancer Database to analyze LND use in higher-risk presumed stage I endometrioid adenocarcinoma patients with tumors that were >2 cm in size, had >50% myometrial invasion (MI), or had grade 3 or 4 disease. Significant differences were found geographically for the New England, West North Central, and West South Central U.S. Census Divisions when compared to the Pacific division, with patients in the three mentioned divisions being less likely to undergo LND than those in the Pacific. A major limitation to the study design included the omission of patients with presumed lower-risk disease characteristics (e.g., tumors <2cm, <50 MI, or grade 1 or 2), a population for whom LND is most frequently debated[6,7,20]. In a separate study, Wright et al. [54] utilized the Perspective Database and performed analyses of SLND use among women with uterine cancer. The researchers found no difference between the Northeastern, Midwest, South, or West U.S. regions. The primary limitations to this study were the inclusion of general uterine cancers rather than endometrial cancers specifically, and the omission of covariates found to be relevant in LND/SLND decision-making, such as tumor histology and grade.

In addition to evaluating temporal and geographic differences in the use of lymphadenectomy strategies, it is essential to understand the balance of benefits versus harms of LND among patients with presumed early-stage endometrioid adenocarcinoma in real-world practice. As previously described, two prominent RCTs and several observational studies have shown no survival benefit in the use of LND in lower risk endometrial cancer populations [6,7,14,15], while other observational studies have shown a survival benefit does exist[9,12,13]. As this disagreement regarding the potential benefits of LND continues, of note is that potential harms are rarely evaluated in depth beyond lymphedema, particularly among large observational

studies[6,7,55–62]. Such limited available information precludes meaningful evaluation of the benefit-harm balance in LND use, leaving providers and patients with incomplete information when making treatment-related decisions. As such, further research regarding an inclusive list potential harms resulting from LND is warranted to allow for more complete and informed decision-making.

In summary, while a rise and subsequent fall over time in the use of general LND in endometrioid adenocarcinoma patients nationwide has been observed in limited earlier studies[51,63], temporal trends of SLND in light of these LND changes have not been evaluated thoroughly. Additionally, available information on geographic variations in LND/SLND is minimal for patients with presumed early-stage disease. Finally, evaluation of morbidity outcomes based on extent of LND has not occurred with a large sample size at a nationwide level, resulting in an incomplete understanding of the balance of benefits and harms.

1.5. Purpose

The purpose of this research was to describe practice patterns related to LND/SLND use and morbidity and mortality outcomes in endometrial endometrioid adenocarcinoma patients without distant metastasis in the U.S. Three studies addressed these topics: 1) Temporal trends in the use of LND/SLND among patients with endometrial adenocarcinoma.; 2) Geographic variation in the use of LND/SLND among patients with endometrial adenocarcinoma; and 3) Post-surgical complications among patients with endometrial adenocarcinoma by extent of lymphadenectomy. These three studies and their findings are described in Chapters 2, 3, and 4 of this dissertation, respectively. Finally, Chapter 5 highlights the main results of these studies and discusses their clinical impact, together with suggestions for future research.

CHAPTER 2

TEMPORAL TRENDS IN THE USE OF LYMPH NODE DISSECTION AND SENTINEL LYMPH NODE DISSECTION AMONG PATIENTS WITH ENDOMETRIAL ADENOCARCINOMA

2.1. Introduction

Endometrial cancer is the fourth most commonly diagnosed cancer for women in the United States (U.S.), affecting nearly than 66,000 in 2020 alone[1]. Although generally considered to have a favorable prognosis, an observed recent increase in incidence and mortality for this cancer[64] serves as a reminder to continue efforts to identify best practices for disease management. In recent decades, one area of controversy has been the use of lymphadenectomy in this patient population[6–15], with clinical guidance regarding such use evolving over time. For example, in 2006, the National Comprehensive Cancer Network (NCCN) issued guidelines that advised that all patients with endometrioid endometrial cancer without lymphadenectomy contraindications undergo complete surgical staging inclusive of lymph node dissection (LND) due to its potential therapeutic benefit[65]. In 2009, guidelines continued to recommend LND for all medically operable patients[66], but it was acknowledged there was growing contention regarding this practice following two randomized controlled trials disputing its benefit in early-stage patients[6,7]. By 2015, NCCN guidelines advocated a selective and tailored approach to lymphadenectomy for endometrial cancer in order to prevent systematic overtreatment, and the possibility of using sentinel lymph node dissection (SLND) was being investigated[67]. Most recently, NCCN clinical oncology guidelines for uterine cancer continue to advocate a tailored approach and state that sentinel lymph node mapping with ultrastaging may increase detection of lymph node metastasis in patients whose disease appears to be confined to the uterus[4].

Previous research of LND trends for endometrioid adenocarcinoma conducted through 2012 showed an increase in LND use until approximately 2007/2008, and then a slight decline or

stabilization[51–53]. However, only one of these studies, whose population consisted only of higher-risk stage I patients, adjusted for relevant covariates within the statistical model[53]. As tumor characteristics, such as grade and depth of myometrial invasion, have been found to have significantly changed in the endometrial cancer population over time[51], adjustment for such factors is essential within the model to control for possible confounding. This is particularly important given their potential influence on providers' decision-making regarding LND use[19]. Additionally, researchers have presented stratifications by cancer stage[52], but such analyses can present biased results, as those who have undergone LND may be more likely to be classified at more advanced stages due to discovery of lymph node metastases.

In addition to the limited information regarding LND trends in the endometrial cancer population, very little information is available for trends in SLND use. A single claims-based study has been conducted for uterine cancer overall for the years 2011 through 2015[54]. It was found SLND use increased six-fold for uterine cancer over the time period. However, information specific to endometrioid adenocarcinoma, which has been at the forefront of the debate, was not available. Additionally, relevant clinical covariates in SLND decision-making, including tumor grade and depth of invasion, were unavailable and therefore not included in the analysis.

Given evolving clinical guidelines and limited information on concomitant real-world practice changes, the purpose of this study was to evaluate temporal trends in LND and SLND for patients diagnosed with endometrioid adenocarcinoma between 2004 and 2015 in the U.S. in the context of these changing national guidelines.

2.2. Methods

2.2.1. Data Source

The Surveillance, Epidemiology, and End Results (SEER) 18 dataset was utilized for this retrospective cohort study for the years 2004 through 2015. SEER collects data from population-based cancer registries throughout the United States. The data from the 18 included registries

cover approximately 28% of the U.S. population and were chosen specifically to be representative of the diverse demographics of the country[68].

2.2.2. Study Population

Eligible patients in the dataset were those diagnosed with endometrioid adenocarcinoma endometrial cancer without distant metastasis. Patients were included if their records included ICD-O-3 site codes C54.0-C54.3, C54.8, C54.9, and C55.9; histology/behavior code 8380/3; American Joint Committee on Cancer [AJCC] 6th Edition M0 OR MX; and a diagnosis year any time from 2004 to 2015. Selection based on the "M" of the TNM staging system rather than by stage was chosen to coincide with National Comprehensive Cancer Network (NCCN) guidelines which state that SLND may be an option for women for whom no metastasis is visible via imaging studies[69]. Patients were excluded if they were missing data on whether lymph node dissection was performed. This research was approved as an exempt study by the Indiana University Institutional Review Board given its secondary use of an existing dataset.

2.2.3. Sample Size

Sample size calculations were conducted using PASS 15 statistical software[70] and were based on a 2-sided statistical test with a power of 0.80, α=0.05. It was estimated that the SEER dataset had sufficient sample sizes to detect an odds ratio (OR) of 1.10 for LND analyses and an OR of 1.25 for SLND analyses when comparing to a reference year of 2004.

2.2.4. Statistical Analysis

Trends in use of LND and SLND were evaluated using Joinpoint Regression (version 4.6.0.0, NCI)[71] and SAS (version 9.4)[72]. The exposure of interest was year of diagnosis. A 2-sided p-value of <0.05 was considered statistically significant.

2.2.5. LND Analysis

LND was coded as a dichotomous variable. Removal of 0 lymph nodes was categorized as "LND no," and removal of 1 or more lymph nodes was categorized as "LND yes." Covariates included in the model were International Federation of Gynecology and Obstetrics (FIGO)

size/extent of primary tumor (reference: FIGO T1a), FIGO tumor grade (reference: grade 1)[73], geography (U.S. Census Division, reference: New England), age at time of initial diagnosis (reference: <40 years), and race/ethnicity (reference: white, non-Hispanic).

Frequencies and percentages were calculated for all categorical variables. First, to evaluate temporal changes in LND use, crude and stratified Joinpoint regression analyses were conducted with a resulting annual percent change (APC). The percentage of patients undergoing LND was modeled in the Joinpoint program over one-year intervals using a log-transformed dependent variable. Stratification was performed for all categorical variables.

Next, simple logistic regression analyses for the association between independent variables (year of diagnosis, geography, size/extent of primary tumor, tumor grade, age, race/ethnicity) on the utilization of LND or SLND were conducted. Finally, a multilevel logistic regression analysis using both random effects (year and geography) and fixed effects models was conducted. Year and geographic region were collapsed into larger categories as described below for SLND as a secondary analysis for comparison purposes.

2.2.6. SLND Analysis

SLND was coded as a dichotomous variable, with those undergoing sentinel node biopsy only, sentinel biopsy in addition to other regional nodes at the same time, and sentinel biopsy in addition to other regional nodes at different times being coded as "SLND yes," and all others coded as "SLND no." Classification of "SLND yes" was summarized by "sentinel node biopsy only," "sentinel biopsy in addition to other regional nodes at the same time," and "sentinel biopsy in addition to other regional nodes at different times."

The logistic regression analyses for SLND were conducted in the same manner as for LND. However, due to small sample sizes per year, year was collapsed into fewer categories to protect patient confidentiality and to provide statistical stability: 2004-2005, 2006-2007, 2008-2009, 2010-2011, 2012-2013, and 2014-2015. Similarly, U.S. Census divisions were collapsed into Census regions (Northeast, Midwest, South, and West)

In any case of extremely small sample size (<10 patients), analyses were not conducted.

2.2.7. Sensitivity Analysis

Sensitivity analyses for all logistic regression analyses were conducted excluding patients with unknown metastasis (MX) to evaluate if the inclusion of these patients influenced study findings. In addition, analyses using collapsed categories (year and geography) similar to those for SLND were conducted for LND overall in order to assess the impact of consolidating the categories within these variables.

2.3. Results

2.3.1. Study Population Characteristics

A total of 89,944 patients were eligible and included in this study (Figure 2.1). The number of cases reported in the SEER data increased over the time period (Table 2.1). The majority of patients were white, non-Hispanic (n=66,334, 74%) and were largely in their 50s (n=27,680, 31%) or 60s (n=28,519, 32%). The tumor did not extend beyond the body of the uterus (T1) in 81% (n=72,986) of patients, and 54% (n=39,614) of those with known grade (n=73,988) had grade 1 disease. The Pacific states contributed the largest number of patients with 41,967 women, or 47% of the study cohort.

Figure 2.1. Study Population Selection Diagram

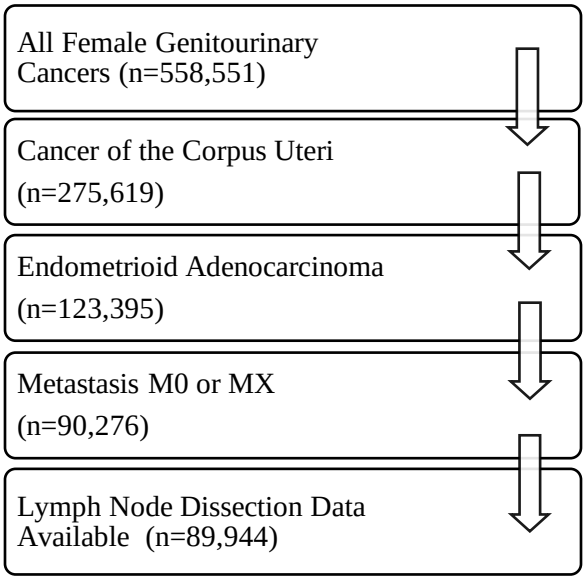


Table 2.1. Study Participant Characteristics by Exposure to LND/SLND

	All Patients	Patients Undergoing LND (% of all patients)	Patients Undergoing SLND[a] (% of all patients)
Total Patients	n=89,944	n=53,616 (59.6%)	n=1,371 (1.5%)
Metastasis Status			
No Metastasis (M0)	88,279	53,263 (60.7%)	1,361 (1.5%)
Unknown Metastasis (MX)	1,665	353 (21.2%)	10 (0.6%)
Year of Diagnosis			Suppressed[b]
2004	5,551	3,080 (55.5%)	
2005	5,870	3,353 (57.1%)	
2006	6,292	3,807 (60.5%)	
2007	6,622	4,150 (62.7%)	
2008	6,858	4,336 (63.2%)	
2009	7,409	4,561 (61.6%)	
2010	7,754	4,759 (61.4%)	
2011	8,008	4,824 (60.2%)	
2012	8,556	4,995 (58.4%)	
2013	8,538	5,008 (58.7%)	
2014	9,171	5,333 (58.2%)	
2015	9,315	5,410 (58.1%)	
Year of Diagnosis (Collapsed)			
2004-2005	11,421	6,433 (56.3%)	17 (0.2%)
2006-2007	12,914	7,957 (61.6%)	26 (0.2%)
2008-2009	14,267	8,897 (62.4%)	63 (0.4%)
2010-2011	15,762	9,583 (60.8%)	117 (0.7%)
2012-2013	17,094	10,003 (58.5%)	445 (2.6%)
2014-2015	18,486	10,743 (58.1%)	703 (3.8%)
US Census Division			Suppressed
New England Division	4,928	3,099 (62.9%)	
Mid Atlantic Division	12,748	8,277 (64.9%)	
East North Central Division	5,407	3,042 (56.3%)	

West North Central Division	4,413	2,359 (53.5%)	
South Atlantic Division	7,626	4,999 (65.6%)	
East South Central Division	5,038	2,809 (55.8%)	
West South Central Division	3,253	1,782 (54.8%)	
Mountain Division	4,564	2,655 (58.2%)	
Pacific Division	41,967	24,594 (58.6%)	
US Census Region			
Northeast	17,676	11,376 (64.4%)	607 (3.4%)
Midwest	9,820	5,401 (55.0%)	24 (0.24%)
South	15,917	9,590 (60.3%)	152 (0.95%)
West	46,531	27,249 (58.6%)	588 (1.3%)
Size/Extent of Primary Tumor			Suppressed
T1a	22,309	10,327 (46.3%)	
T1b	33,407	20,509 (61.4%)	
T1c	12,930	10,197 (78.9%)	
T1 NOS	4,340	1,314 (30.3%)	
T2a	2,888	2,039 (70.6%)	
T2b	3,678	2,951 (80.2%)	
T2 NOS	1,232	722 (58.6%)	
T3a	5,544	4,309 (77.7%)	
T3b	1,203	787 (65.4%)	
T3 NOS	60	35 (58.3%)	
T4	349	185 (53.0%)	
TX	1,998	240 (12.0%)	
missing	*6*		
Tumor Grade			
Grade 1	39,614	19,413 (49.0%)	557 (1.4%)
Grade 2	24,263	17,093 (70.5%)	365 (1.5%)
Grade 3	10,111	8,082 (79.9%)	154 (1.5%)
missing	*15,956*		

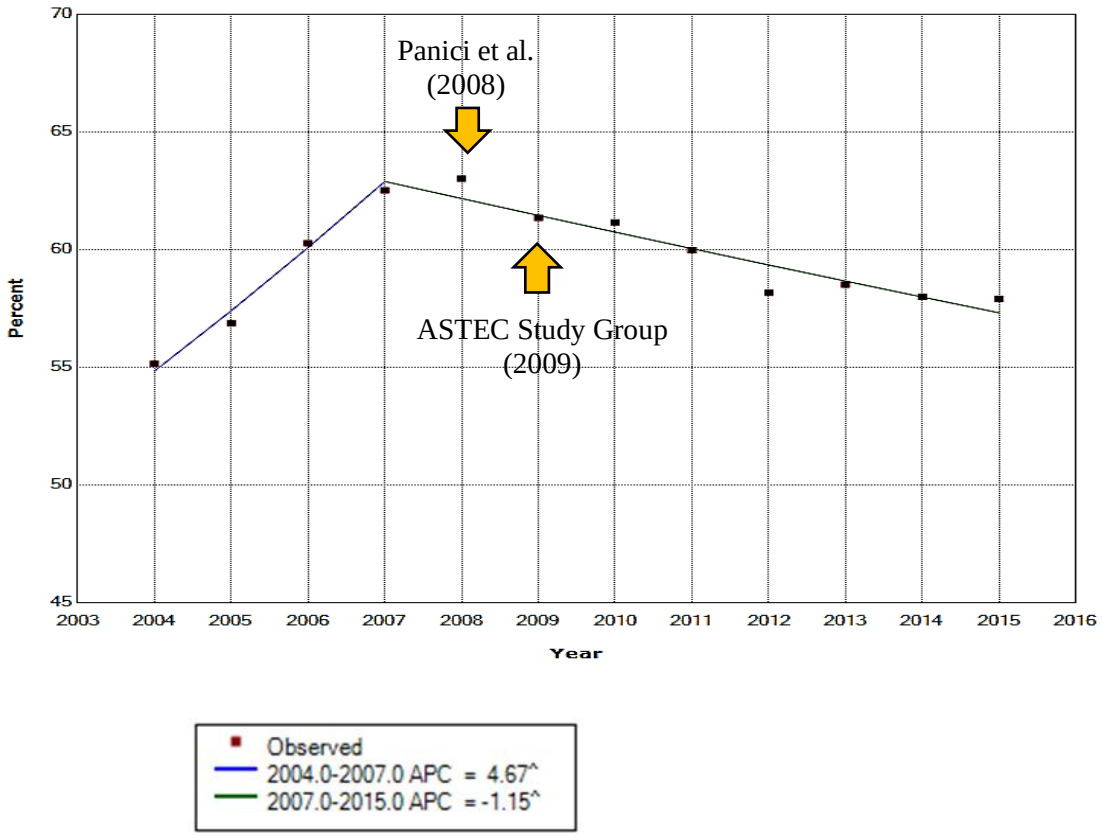
Race/Ethnicity			Suppressed
White, non-Hispanic	66,334	39.814 (60.0%)	
Black/African American	5,925	3,461 (58.4%)	
American Indian/Alaska Native	575	309 (53.7%)	
Asian/Pacific Islander	7,018	4,499 (64.1%)	
Hispanic/Latino	9,516	5,291 (55.6%)	
Unknown	576	242 (42.0%)	
Age (years)			
<40	3,527	1,574 (44.6%)	40 (1.1%)
40-49	9,443	5,104 (54.0%)	136 (1.4%)
50-59	27,680	16,441 (59.4%)	432 (1.6%)
60-69	28,519	18,032 (63.2%)	495 (1.7%)
70-79	14,094	9,160 (65.0%)	206 (1.5%)
80+	6,681	3,305 (49.5%)	62 (0.9%)

[a]SLND patients are a subset of all LND patients; [b]Results are suppressed if any stratum has an LND or SLND exposure in <10 patients

2.3.2. LND Analysis

There were statistically significant trends in the use of LND observed in the crude Joinpoint analysis (Figure 2.2). From 2004 to 2007, the use of LND experienced a significant positive annual percent change (APC) of 4.67% (p=0.002). However, from 2007 through 2015, use of LND declined significantly at an annual rate of 1.15% (p<0.001). In stratified Joinpoint analyses, changes in LND use over time varied by age group, geography, size/extent of disease, grade, and race/ethnicity. The years in which these changes occurred differed by variable and by stratum (Appendix A).

Figure 2.2. Crude Joinpoint Regression Analysis of LND Use in Endometrial Adenocarcinoma Patients, 2004-2015 (n=89,944), with Timing of Relevant Randomized Controlled Trials



^Indicates that the Annual Percent Change is significantly different from zero at the alpha = 0.05 level. Final selected model: 1 Joinpoint; Abbreviation: APC, annual percent change

In simple regression analyses, year of diagnosis was significantly associated with undergoing LND ($p<0.001$) (Table 2.2). Compared to 2004, peak LND use occurred in 2008 (OR: 1.38; 95% CI: 1.28, 1.48) in adjusted analyses. All independent variables were statistically significant factors in the use of LND in both unadjusted and multilevel logistic regression model adjusted for year, geography, size/extent of tumor, race/ethnicity, and age. In adjusted analyses, a woman was 45% more likely to undergo LND in 2008 than in 2004. A woman remained 19% more likely to undergo LND in 2015 than in 2004 (Table 2.2).

Table 2.2. Crude and Adjusted Analyses for Relationship between Variables of Interest and LND in the US (n=89,944)

	Crude			Adjusted[a]		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Year of Diagnosis			<0.001			0.014
2004	1.00	*Reference*		1.00	*Reference*	
2005	1.07	(0.99, 1.15)		1.07	(0.98, 1.16)	
2006	1.23	(1.14, 1.32)		1.24	(1.15, 1.35)	
2007	1.35	(1.25, 1.45)		1.36	(1.26, 1.48)	
2008	1.38	(1.28, 1.48)		1.45	(1.34, 1.57)	
2009	1.29	(1.20, 1.38)		1.35	(1.24, 1.46)	
2010	1.28	(1.19, 1.37)		1.34	(1.24, 1.45)	
2011	1.22	(1.13, 1.30)		1.29	(1.19, 1.39)	
2012	1.13	(1.05, 1.21)		1.16	(1.07, 1.25)	
2013	1.14	(1.06, 1.22)		1.16	(1.07, 1.25)	
2014	1.12	(1.04, 1.19)		1.15	(1.06, 1.24)	
2015	1.11	(1.04, 1.19)		1.19	(1.10, 1.29)	
US Census Division			<0.001			0.025
New England	1.00	*Reference*		1.00	*Reference*	
Mid Atlantic	1.09	(1.02, 1.17)		1.13	(1.04, 1.22)	
East North Central	0.76	(0.70, 0.82)		0.82	(0.75, 0.90)	
West North Central	0.68	(0.62, 0.73)		0.67	(0.61, 0.73)	
South Atlantic	1.12	(1.04, 1.21)		1.12	(1.02, 1.22)	
East South Central	0.74	(0.69, 0.81)		0.72	(0.66, 0.79)	
West South Central	0.72	(0.65, 0.78)		0.65	(0.58, 0.71)	
Mountain	0.82	(0.76, 0.89)		0.91	(0.82, 1.00)	
Pacific	0.84	(0.79, 0.89)		0.85	(0.80, 0.92)	
Size/Extent of Primary Tumor			<0.001			<0.001
T1a	1.00	*Reference*		1.00	*Reference*	
T1b	1.85	(1.78, 1.91)		1.64	(1.57, 1.70)	
T1c	4.33	(4.12, 4.55)		3.39	(3.20, 3.59)	
T1 NOS	0.50	(0.47, 0.54)		0.50	(0.47, 0.55)	

T2a	2.79	(2.56, 3.03)		2.28	(2.08, 2.51)	
T2b	4.71	(4.32, 5.13)		3.32	(3.01, 3.66)	
T2 NOS	1.64	(1.46, 1.85)		1.23	(1.07, 1.41)	
T3a	4.04	(3.78, 4.34)		2.78	(2.57, 3.01)	
T3b	2.20	(1.94, 2.48)		1.36	(1.17, 1.57)	
T3 NOS	1.62	(0.97, 2.72)		0.84	(0.47, 1.52)	
T4	1.31	(1.06, 1.62)		0.72	(0.57, 0.92)	
TX	0.16	(0.14, 0.18)		0.15	(0.13, 0.18)	
Tumor Grade			<0.001			<0.001
Grade 1	1.00	*Reference*		1.00	*Reference*	
Grade 2	2.48	(2.40, 2.57)		2.19	(2.11, 2.27)	
Grade 3	4.14	(3.93, 4.37)		3.63	(3.43, 3.85)	
Race/Ethnicity			<0.001			<0.001
White, non-Hispanic	1.00	*Reference*		1.00	*Reference*	
Black/African American	0.94	(0.89, 0.99)		0.87	(0.81, 0.93)	
American Indian/Alaska Native	0.77	(0.66, 0.91)		0.93	(0.76, 1.15)	
Asian/Pacific Islander	1.19	(1.13, 1.25)		1.34	(1.25, 1.42)	
Hispanic/Latino	0.83	(0.80, 0.87)		0.88	(0.84, 0.93)	
Unknown	0.48	(0.41, 0.57)		0.78	(0.63, 0.96)	
Age (years)			<0.001			<0.001
<40	1.00	*Reference*		1.00	*Reference*	
40-49	1.46	(1.35, 1.58)		1.22	(1.11, 1.34)	
50-59	1.82	(1.69, 1.95)		1.36	(1.25, 1.49)	
60-69	2.13	(1.99, 2.29)		1.42	(1.31, 1.55)	
70-79	2.30	(2.14, 2.48)		1.34	(1.22, 1.46)	
80+	1.22	(1.12, 1.32)		0.65	(0.59, 0.72)	

[a]Adjusted for year of diagnosis, geography, size/extent of primary tumor, tumor grade, race/ethnicity, and age

2.3.3. SLND Analysis

A total of 1,371 women underwent SLND over the time period. The crude proportion of all patients with endometrioid adenocarcinoma who underwent SLND was 1.5% overall, with 0.1% in 2004-2005 and 3.8% in 2014-2015 (Figure 2.3). Of those undergoing SLND, a total of 585 (43%) underwent SLND only and not conventional LND. An additional 751 (55%) of patients underwent SLND and conventional LND at the same time. The remaining 35 (2%) women underwent the SLND procedure at a different time than conventional LND .

Figure 2.3. Percent of Patients with Endometrioid Adenocarcinoma Undergoing LND and SLND, 2004-2015 (n=89,944)

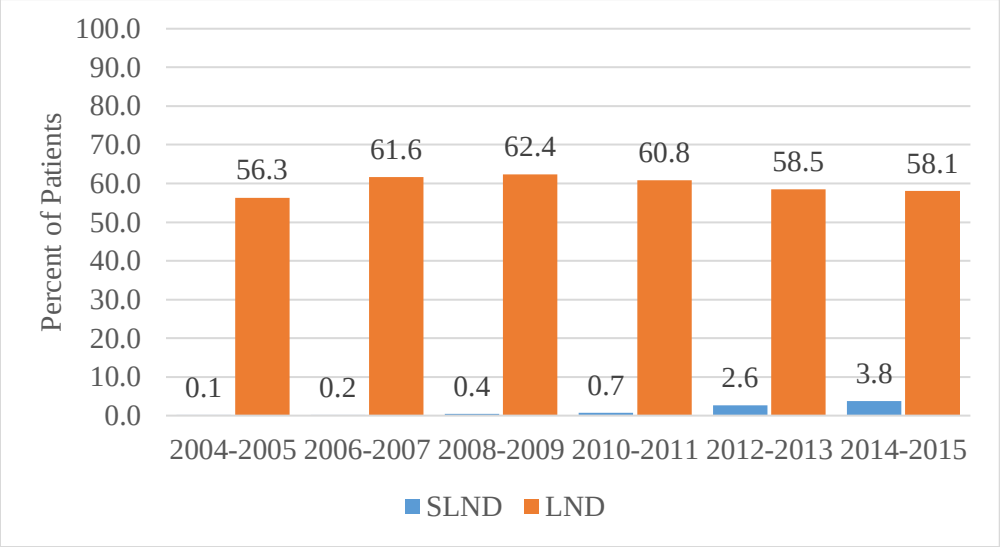
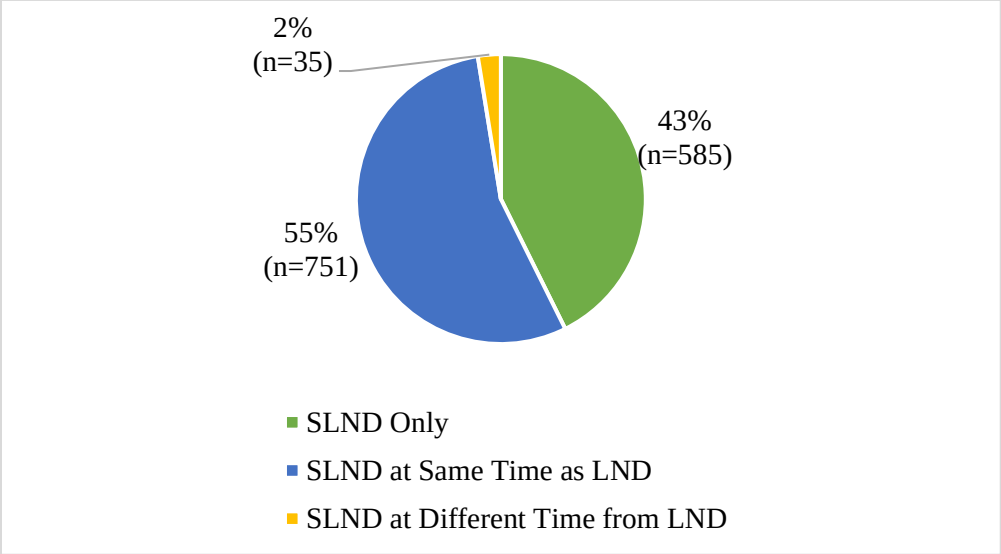


Figure 2.4. Timing of Sentinel Lymph Node Dissection in the Context of Lymph Node Dissection during Surgery (n=1,371)



Unadjusted logistic regression showed that year of diagnosis, geography, and age were significantly associated with SLND (all $p<0.05$), but tumor grade was not (Table 2.3). In adjusted analyses, only age remained significant ($p=0.003$). Race/ethnicity and tumor size were not included in the analysis due to small sample sizes ($n<10$) in several strata.

2.3.4. Sensitivity Analysis

Repeating simple and multilevel logistic regression analyses with patients with unknown metastasis (MX) did not alter the significance of any of the results for either LND or SLND (data not shown). When adjusted analyses with collapsed year and geography categories were repeated for LND, year and Census region were no longer significantly associated with undergoing LND (Table 2.3).

Table 2.3. Crude and Adjusted Analyses for SLND and LND in the US by Collapsed Categories (n=89,944)

Sentinel Lymph Node Dissection						
	Crude			Adjusted[a]		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Year of Diagnosis			<0.001			0.060
2004-2005	1.00	*Reference*		1.00	*Reference*	
2006-2007	1.35	(0.73, 2.50)		1.56	(0.83, 2.94)	
2008-2009	2.98	(1.74, 5.09)		3.31	(1.88, 5.82)	
2010-2011	5.02	(3.01, 8.35)		6.07	(3.56, 10.4)	
2012-2013	12.9	(11.0, 29.1)		20.5	(12.3, 34.2)	
2014-2015	26.5	(16.4, 42.9)		31.3	(18.8, 52.1)	
US Census Region			<0.001			0.116
Northeast	1.00	*Reference*		1.00	*Reference*	
Midwest	0.07	(0.05, 0.10)		0.06	(0.04, 0.10)	
South	0.27	(0.23, 0.32)		0.26	(0.21, 0.32)	
West	0.36	(0.32, 0.40)		0.37	(0.33, 0.43)	
Tumor Grade			0.50			0.114
Grade 1	1.00	*Reference*		1.00	*Reference*	
Grade 2	1.07	(0.94, 1.22)		1.09	(0.95, 1.25)	
Grade 3	1.09	(0.91, 1.30)		1.20	(1.00, 1.45)	
Age (years)			<0.001			0.003
<40	1.00	*Reference*		1.00	*Reference*	
40-49	1.27	(0.89, 1.82)		1.38	(0.93, 2.07)	
50-59	1.38	(1.00, 1.91)		1.25	(0.86, 1.82)	
60-69	1.54	(1.11, 2.13)		1.21	(0.84, 1.76)	
70-79	1.29	(0.92, 1.82)		1.02	(0.69, 1.52)	
80+	0.82	(0.55, 1.22)		0.74	(0.46, 1.17)	

Lymph Node Dissection						
	Crude			Adjusted[a]		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Year of Diagnosis			<0.001			0.063
2004-2005	1.00	*Reference*		1.00	*Reference*	
2006-2007	1.25	(1.18, 1.31)		1.26	(1.18, 1.32)	
2008-2009	1.29	(1.22, 1.35)		1.35	(1.28, 1.42)	
2010-2011	1.20	(1.15, 1.26)		1.26	(1.20, 1.34)	
2012-2013	1.09	(1.04, 1.15)		1.10	(1.04, 1.16)	
2014-2015	1.08	(1.03, 1.23)		1.12	(1.07, 1.19)	
US Census Region			<0.001			0.115
Northeast	1.00	*Reference*		1.00	*Reference*	
Midwest	0.68	(0.64, 0.71)		0.71	(0.67, 0.75)	
South	0.84	(0.80, 0.88)		0.78	(0.74, 0.82)	
West	0.78	(0.76, 0.81)		0.85	(0.82, 0.89)	
Tumor Grade			<0.001			<0.001
Grade 1	1.00	*Reference*		1.00	*Reference*	
Grade 2	2.48	(2.40, 2.57)		2.50	(2.41, 2.59)	
Grade 3	4.15	(3.93, 4.37)		4.31	(4.09, 4.55)	
Age (years)			<0.001			<0.001
<40	1.00	*Reference*		1.00	*Reference*	
40-49	1.46	(1.35, 1.58)		1.38	(1.27, 1.51)	
50-59	1.82	(1.69, 1.95)		1.67	(1.54, 1.81)	
60-69	2.13	(1.99, 2.29)		1.87	(1.72, 2.03)	
70-79	2.30	(2.14, 2.48)		1.82	(1.67, 1.99)	
80+	1.22	(1.12, 1.32)		0.87	(0.79, 0.95)	

[a]Adjusted for region, years, tumor grade, and age

2.4. Discussion

Overall, the use of LND for the care of women diagnosed with endometrial adenocarcinoma has been declining since 2008. The findings of the Joinpoint analyses for LND were in line with earlier studies that included time trend evaluations[51–53]. While stratification of variables paints a complex picture of varying trends dependent on tumor characteristics, demographics, and geographic factors, the Joinpoint findings were further supported by multilevel logistic regression analysis, which controlled for a variety of potential confounders and still demonstrated an overall decline in use in recent years.

The noted decline around the 2007/2008 timeframe coincides approximately with the publication of two randomized controlled trials (RCTs) that called into question the benefits of utilizing LND in all patients with endometrial cancer[6,7]. At that time, lymphadenectomy remained a part of NCCN recommendations due to limitations of the RCTs' methods[66], such as short follow-up times, failure to control for extent of LND, and failure to control for follow-up therapy[23,24]. However, despite guidelines to the contrary, the current study shows that this overall decline continued through 2015. Given the greater emphasis on tailored approaches to lymphadenectomy in this population in more recent NCCN guidelines[4,8,69], future studies are warranted to evaluate whether a decline in LND use has continued and the extent to which it has occurred. It is possible that these changes in NCCN guidelines may initiate a greater decline in LND use in this population given the broader acceptance of the tailored approach, but this can only be confirmed with further studies utilizing the most recent data.

This is the first registry-based nationwide study that assesses SLND temporal trends in the context of LND changes in patients with endometrial cancer, specifically. Although small sample sizes ultimately prevented thorough adjusted analyses for SLND changes over time, year of diagnosis was approaching statistical significance ($p=0.06$) in this study. As such, revisiting these analyses in the future would be well-served when larger sample sizes are available, particularly given the greater acceptance of the procedure in clinical guidelines from the past 5

years[8,19,69]. That the sensitivity analysis conducted for LND showed a loss of significance for the time variable once categories were collapsed is evidence that such consolidation may have influenced the observed level of significance, and the inclusion of additional years of data could potentially provide a large enough sample for adjusted analyses. Additionally, the nationwide prevalence of SLND use in this population (5%[54]) that was used in initial sample size calculations was shown to be an overestimate for the study period, and sample sizes for future studies should base calculations on the lower prevalence of 1.5% found in this study.

The majority (55%) of patients who underwent SLND did so in conjunction with general LND. This may point to the ongoing experimental nature of the technique. However, the observed increase in its use from 0.1% of all patients in 2004-2005 to 3.8% in 2014-2015, combined with an overall recent decrease in LND use, may point to a paced but growing interest in the technique as a viable alternative to general LND among providers. It is indicative of the search for the ideal balance of benefits and harms associated with lymph node removal in this growing population, which is also reflected in the evolution of clinical guidance such as that provided by NCCN.

Several limitations to this study exist. Multiple variables found to bear possible influence on exposure to LND were unavailable in the SEER dataset. These include surgical approach (e.g., laparotomy vs. laparoscopy vs. robotic), comorbidities, hospital type, and insurance coverage[53,54]. The lack of availability of these variables in the SEER dataset prevented any analyses that could determine their significance. In addition, their exclusion could potentially lead to the omission of relevant variables in adjusted statistical models.

Research regarding SLND has unique potential limitations because the technique has just recently begun to gain acceptance within the field[69]. As a result, early research on the topic will likely continue to be limited by small sample sizes. However, establishing a baseline understanding of the current state of the technique remains essential for future comparisons. Finally, data are not available within the SEER dataset regarding failed mappings of sentinel

lymph nodes. Because of this, it is possible the number of patients identified as undergoing SLND in the dataset is an underestimation of attempted SLND.

2.5. Conclusions

NCCN guidelines have presented a cautious but evolving approach to the use of LND and SLND in the endometrial cancer population. Following two pivotal studies[6,7] on LND in patients with endometrial cancer more than a decade ago, LND use is on the decline overall. However, it remains to be seen if greater clinical acceptance of increasingly tailored strategies, as advocated in the most recent NCCN guidelines, will be reflected in real-world practice nationwide through less use of LND overall and increased use of SLND. Additionally, as more recent national data are released in the future, the acceptance and utilization of SLND can be further elucidated. Finally, in understanding temporal trends in these components of disease management, we can develop a clearer context for possible changes in patient outcomes that may occur over time in a cancer population that is currently experiencing an increase in new cases and deaths[64].

CHAPTER 3

GEOGRAPHIC VARIATION IN LYMPH NODE DISSECTION AND SENTINEL LYMPH NODE DISSECTION AMONG PATIENTS WITH ENDOMETRIAL ADENOCARCINOMA

3.2. Introduction

Endometrial cancer is the most common gynecological cancer in the United States (U.S.), and its incidence is on the rise[64]. In 2020 alone, more than 66,000 new cases were estimated to be diagnosed[1]. Prognosis is generally favorable when diagnosed at an early stage, and the large majority of cases (approximately 84%) are diagnosed at stage I or II providing the opportunity for curative resection[3].

Traditionally, national and international guidelines have called for the use of total or radical hysterectomy and bilateral salpingo-oophorectomy combined with lymph node dissection (LND) during the treatment and staging process for nearly all patients with endometrial cancer[5,66,74]. However, conflicting evidence of benefit of full LND in patients with early-stage disease has cast doubt on its necessity in some cases. Neither of the two randomized controlled trials (RCTs) evaluating LND use in early-stage patients found a significant survival benefit in the LND groups compared to those without LND as controls, and post-operative complications were higher in those undergoing LND than controls[6,7]. Despite their findings, conclusions of these RCTs were limited by short follow-up times and failure to control for histological covariates and follow-up therapy. Observational studies have yielded inconsistent results, with some showing improved survival among patients undergoing LND[9,12,13] and others finding no survival benefit[14,15]. Limitations of these observational studies included lack of control for confounding factors, short follow-up times, and limited sample sizes.

In response to conflicting evidence regarding the benefit of LND in patients with early-stage endometrial cancer, researchers and providers have pursued sentinel lymph node dissection

(SLND) as an alternative approach to traditional LND. SLND involves the injection of radioactive dye or indocyanine-green (ICG) to allow for the identification and removal of the lymph nodes to which cancer cells are most likely to spread from the primary tumor[69]. This allows for the detection of possible metastases while minimizing the number of lymph nodes removed compared to general lymphadenectomy, thereby facilitating accurate staging and adjuvant therapy selection while reducing the risk of surgical morbidities. Additionally, the application of a sentinel lymph node (SLN) mapping algorithm in conjunction with dye injection has been found to contribute to the successful detection of metastatic endometrial cancer[35,69,75]. This growing evidence for the usefulness of sentinel lymph node dissection (SLND) in this patient population[33,37,75] has prompted the revision of clinical guidelines in order to advise clinicians to use a more tailored approach with the inclusion of SLND as an acceptable alternative to full LND in select lower-risk patients[8,69]. However, uncertainty about strength of evidence, access to inadequate instrumentation, and lack of training contribute to providers' decision not to utilize the technique[39,40].

While patient- and provider-level factors have been found to come into play with variation in LND/SLND use, geographic variations in surgical management of patients undergoing LND/SLND are not well characterized in the U.S. As best practices become further clarified, understanding such variation is essential in ensuring access to high quality care for women across the country in order to limit health disparities based on geographic accessibility[76,77]. This study was designed to describe geographic differences in the use of LND/SLND utilizing the nationwide registry-based Surveillance, Epidemiology, and End Results (SEER) 18 Program dataset in order to identify real-world disease management patterns. In addition, secondary analyses examined geographic variation within California alone, as this state contributed a substantial proportion of cases to the dataset.

3.3. Materials and Methods

3.3.1. Data Source

The data source for this retrospective cohort study was the National Cancer Institute's (NCI) SEER 18 Program dataset[68]. SEER collects data from population-based cancer registries throughout the United States. Since 2000, registries from 18 geographic sites have been included, covering approximately 28% of the U.S. population. Data through December 2015 were available at the time of this study. This research was approved as an exempt study by the Indiana University Institutional Review Board given its secondary use of an existing dataset.

3.3.2. Definition of Variables

The exposure of interest was geographic location and consisted of groupings of SEER registry sites. For nationwide analyses, SEER registry sites were grouped by U.S. Census Division[78] (Table 3.1) and compared. In cases of small sample sizes, divisions were collapsed further and categorized by U.S. Census Region. Additionally, as the state of California contributed four of the 18 registries in this study as part of the Pacific Division, a California-only analysis compared these four registries.

The outcome of undergoing LND was coded as a dichotomous variable, with 0 lymph nodes removed categorized as "LND no" and 1 or more lymph nodes removed categorized as "LND yes." The outcome of undergoing SLND was coded as a dichotomous variable, with those undergoing sentinel node biopsy only, sentinel biopsy in addition to other regional nodes at the same time, and sentinel biopsy in addition to other regional nodes at different times being coded as "SLND yes," and all others coded as "SLND no."

3.3.3. Study Population

Patients in the SEER dataset eligible for this study were women: 1) with surgically staged endometrioid adenocarcinoma of the uterus, identified by ICD-O-3 site codes C54.0-C54.3, C54.8, C54.9, and C55.9 and histology/behavior code 8380/3; 2) without distant metastasis

(American Joint Committee on Cancer [AJCC] M0 or MX); 3) diagnosed between January 2004 and December 2015. Women were excluded if data regarding LND use were missing.

3.3.4. Statistical Analysis

Analyses were conducted using SAS version 9.4[72]. Maps were created using ArcGIS Desktop version 10.4.1[79].

3.3.5. Lymph Node Dissection Analyses

Descriptive statistics in terms of frequencies and percentages were calculated for the included categorical variables. For nationwide analyses of LND, sites were grouped by U.S. Census Division, with New England as the reference group. For California analyses, each registry represented a geographic site, with the Greater California registry as the reference group. Additional independent variables were size/extent of primary tumor (reference: FIGO T1a), tumor grade (reference: grade 1), year of diagnosis (reference: 2004), age of diagnosis (reference: <40 years), and race/ethnicity (reference: white, non-Hispanic). Tumor grade was defined using ICD-O-2 coding in SEER[80]. Grading was recoded according to the FIGO staging system prior to analysis, with ICD-O-2 grade 1 recoded to FIGO grade 1, ICD-O-2 grade 2 recoded to FIGO grade 2, and ICD-O-2 grades 3 and 4 recoded to FIGO grade 3[73].

Simple logistic regression analyses were performed for all independent variables on LND use as the outcome of interest. Crude odds ratios (ORs), 95% confidence intervals (CIs), and p-values were calculated. Next, a multilevel logistic regression analysis was performed, and adjusted ORs, 95% CIs, and p-values for random effects (geography and year) and fixed effects (size/extent of primary tumor, tumor grade, age of diagnosis, and race/ethnicity) were calculated. Significance level for all analyses was evaluated at $\alpha=0.05$.

3.3.6. Sentinel Lymph Node Dissection Analyses

The analysis with SLND as the outcome of interest utilized methods similar to those for the LND outcome described above. However, due to the rarity of SLND, collapsing of groups became necessary to protect patient privacy. The 9 Census Divisions were grouped into the 4

Census Regions of Northeast, Midwest, South, and West (Table 3.1), and years were collapsed as 2004-2005, 2006-2007, 2008-2009, 2010-2011, 2012-2013, and 2014-2015. California registries for within-state comparisons did not require additional collapsing.

Table 3.1. SEER Cancer Registry by U.S. Census Region and U.S. Census Division

U.S. Census Region	U.S. Census Division	Included SEER Registries
Northeast	1 - New England	Connecticut
	2 - Mid-Atlantic	New Jersey
Midwest	3 - East North Central	Detroit
	4 - West North Central	Iowa
South	5 - South Atlantic	Atlanta Greater Georgia Rural Georgia
	6 - East South Central	Kentucky
	7 - West South Central	Louisiana
West	8 – Mountain	New Mexico Utah
	9 – Pacific	Alaska Native Greater California Hawaii Los Angeles San Francisco-Oakland San Jose-Monterey Seattle-Puget Sound

3.3.7. Sensitivity Analyses

All analyses included patients known not to have metastasis (M0). These analyses were then repeated including patients with unknown metastasis status (MX) to determine if significance of independent variables was altered with the inclusion of MX patients. An additional post-hoc analysis compared combined California registries to all other states from the Pacific Division with registries (Alaska, Hawaii, and Washington) in order to determine if significant heterogeneity in LND/SLND use existed among Pacific registry states given California's large proportion of cases.

3.3.8. Sample Size Estimates

Sample size estimates to accurately characterize the utilization of LND were obtained via PASS 15 statistical software [70]. Parameters for sample size calculations for the U.S. analyses included a 2-sided statistical test using a power of 0.80, $\alpha = 0.05$, a baseline probability of undergoing LND of 60%, a categorical exposure variable of interest within which 10% of the population falls in the reference group (New England), and independence of exposure variables. For California-specific secondary analyses, the parameters for LND sample size calculations were: 2-sided statistical test using a power of 0.80, $\alpha = 0.05$, a baseline probability of undergoing LND of 60%, a categorical exposure variable of interest within which 50% of the population falls in the reference group (Greater California), and independence of exposure variables. Based on sample size calculations, nationwide and California analyses were expected to be able to detect odds ratios (ORs) of 1.10 or greater when comparing to the respective reference groups.

Parameters for sample size calculations for the outcome of undergoing SLND nationwide were: a 2-sided statistical test using a power of 0.80, $\alpha = 0.05$, a baseline probability of undergoing SLND of 5%, a categorical exposure variable of interest within which 10% of the population falls within the reference group, and independence of covariates. For California, the parameters were identical except for the proportion of the population in the reference group, which was 50%. The SEER dataset was considered sufficient to detect ORs of 1.25 or higher comparing SLND use to the reference geographies nationwide and in California.

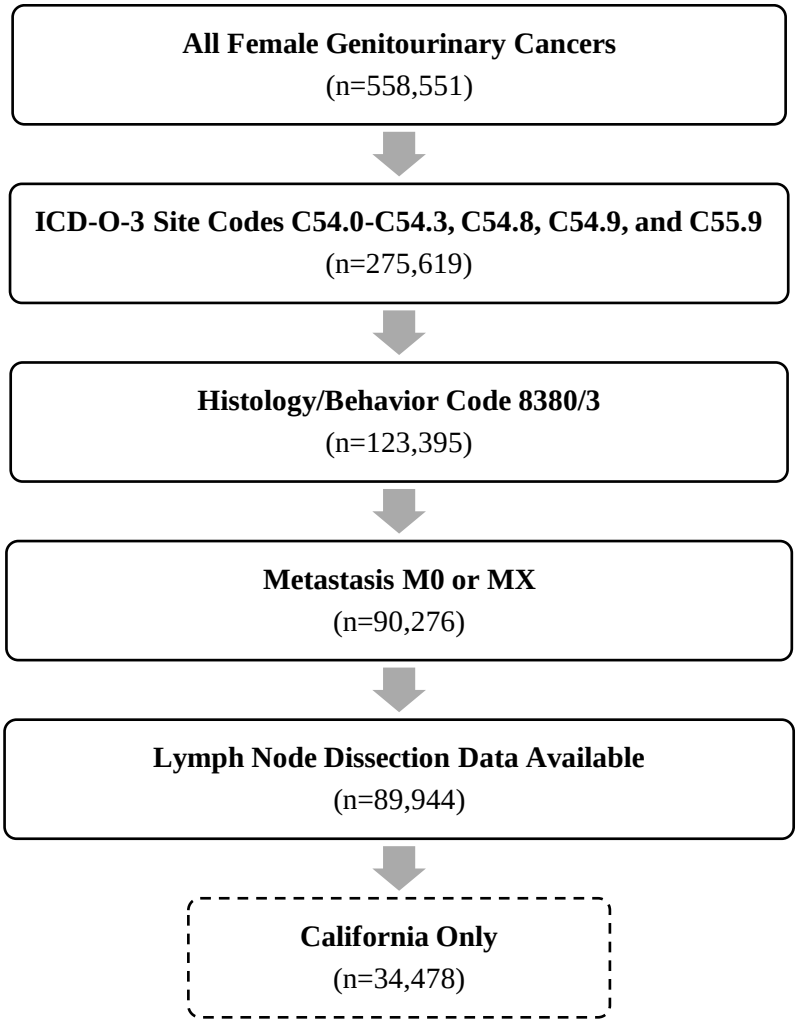
3.4. Results

3.4.1. Study Population Characteristics

A total of 89,944 patients met all eligibility criteria for inclusion in this study. Of these, 34,478 were from California-based registries and were also included in secondary analyses (Figure 3.1). Patient characteristics are presented in Table 3.2. The extent of the primary tumor was classified as T1a in 22,309 patients (25%), and a majority (n=39,614, 54%) presented with grade 1 disease (Table 3.2). Most patients (n=66,334, 74%) were non-Hispanic white. The age

groups contributing the largest number of patients were 50-59 years (n=27,680, 31%) and 60-69 years (n=28,519, 32%). A total of 1,665 women (1.9%) had unknown metastasis status (MX).

Figure 3.1. Study Population Selection Diagram



Similar patient characteristics were observed among the California subgroup with the exception of racial/ethnic distribution. Compared to the full study cohort, the California subpopulation had a higher proportion of Asian/Pacific Islander (13% vs. 8%) and Hispanic/Latino (19% vs. 11%) patients.

Table 3.2. Study Participant Characteristics by Geography of Analysis

	United States (n=89,944)	California Only (n=34,478)
Underwent LND		
Yes	53,616 (59.6%)	20,025 (58.1%)
No	36,328 (40.4%)	14,453 (41.9%)
Underwent SLND		
Yes	1,371 (1.5%)	299 (0.9%)
No	88,573 (98.5%)	34,179 (99.1%)
Metastasis Status		
No Metastasis (M0)	88,279 (98.2%)	33,942 (98.5%)
Unknown Metastasis (MX)	1,665 (1.9%)	536 (1.6%)
US Census Division		
New England	4,928 (5.5%)	--
Mid Atlantic	12,748 (14.2%)	--
East North Central	5,407 (6.0%)	--
West North Central	4,413 (4.9%)	--
South Atlantic	7,626 (8.5%)	--
East South Central	5,038 (5.6%)	--
West South Central	3,253 (3.6%)	--
Mountain	4,564 (5.1%)	--
Pacific	41,967 (46.7%)	34,478 (100.0%)
US Region		
Northeast	17,676 (19.7%)	--
Midwest	9,820 (10.9%)	--
South	15,917 (17.7%)	--
West	46,531 (51.7%)	34,478 (100.0%)
Year of Diagnosis		
2004	5,551 (6.2%)	2,008 (5.8%)
2005	5,870 (6.5%)	2,206 (6.4%)
2006	6,292 (7.0%)	2,297 (6.7%)

2007	6,622 (7.4%)	2,483 (7.2%)
2008	6,858 (7.6%)	2,600 (7.5%)
2009	7,409 (8.2%)	2,768 (8.0%)
2010	7,754 (8.6%)	2,959 (8.6%)
2011	8,008 (8.9%)	3,141 (9.1%)
2012	8,556 (9.5%)	3,379 (9.8%)
2013	8,538 (9.5%)	3,310 (9.6%)
2014	9,171 (10.2%)	3,640 (10.6%)
2015	9,315 (10.4%)	3,689 (10.7%)
Year of Diagnosis (Collapsed)		
2004-2005	11,421 (12.7%)	4212 (12.2%)
2006-2007	12,914 (14.4%)	4780 (13.9%)
2008-2009	14,267 (15.9%)	5368 (15.6%)
2010-2011	15,762 (17.5%)	6100 (17.7%)
2012-2013	17,094 (19.0%)	6689 (19.4%)
2014-2015	18,486 (20.6%)	7329 (21.3%)
Size/Extent of Primary Tumor		
T1a	22,309 (24.8%)	8,411 (24.4%)
T1b	33,407 (37.0%)	12,697 (36.8%)
T1c	12,930 (14.4%)	5,104 (14.8%)
T1 NOS	4,340 (4.8%)	1,583 (4.6%)
T2a	2,888 (3.2%)	1,247 (3.6%)
T2b	3,678 (4.1%)	1,441 (4.2%)
T2 NOS	1,232 (1.4%)	460 (1.3%)
T3a	5,544 (6.2%)	2,235 (6.5%)
T3b	1,203 (1.3%)	460 (1.4%)
T3 NOS	60 (0.1%)	25 (0.1%)
T4	349 (0.4%)	137 (0.4%)
TX	1,998 (2.2%)	651 (1.9%)
missing	*6*	

Tumor Grade		
Grade 1	39,614 (53.5%)	16,303 (56.3%)
Grade 2	24,263 (32.8%)	8,838 (30.5%)
Grade 3	10,111 (13.7%)	3,823 (13.2%)
missing	*15,956*	*5,514*
Race/Ethnicity		
White, non-Hispanic	66,334 (73.8%)	21,577 (62.6%)
Black/African American	5,925 (6.6%)	1,383 (4.0%)
American Indian/Alaska Native	575 (0.6%)	196 (0.6%)
Asian/Pacific Islander	7,018 (7.8%)	4,337 (12.6%)
Hispanic/Latino	9,516 (10.6%)	6,685 (19.4%)
Unknown	576 (0.6%)	300 (0.9%)
Age (years)		
<40	3,527 (3.9%)	1,465 (4.3%)
40-49	9,443 (10.5%)	3,772 (10.9%)
50-59	27,680 (30.8%)	10,688 (31.0%)
60-69	28,519 (31.7%)	10,585 (30.7%)
70-79	14,094 (15.7%)	5,322 (15.4%)
80+	6,681 (7.4%)	2,646 (7.7%)

3.4.2. Lymph Node Dissection Results

A total of 60% (n=53,616) of patients nationwide underwent LND from 2004-2015, ranging from 54% (n=2,359) in the West North Central Division to 66% (n=4,999) in the South Atlantic Division (Table 3.3). In both simple and multilevel logistic regression nationwide analyses, all independent factors evaluated were significantly associated with LND (Table 3.4). There was significant geographic variation in LND. Compared to those in New England, women in Middle Atlantic (OR: 1.13, 95% CI: 1.04, 1.22) and South Atlantic (OR: 1.12, 95% CI: 1.02, 1.22) states were more likely to undergo LND. Those in Mountain states experienced similar prevalence (OR: 0.91, 95% CI: 0.82, 1.00). All others were found to be significantly less likely to undergo LND compared to patients in New England (Figure 3.2).

In California analyses, unadjusted logistic regression for the state of California found all independent factors to be significantly associated with LND (Table 3.4). Size/extent of primary tumor ($p<0.001$), tumor grade ($p<0.001$), race/ethnicity ($p<0.001$), and age ($p<0.001$) remained significant in multilevel logistic regression analyses, but there were no longer significant associations with registry ($p=0.113$) or year of diagnosis ($p=0.052$).

3.4.3. Sentinel Lymph Node Dissection Results

Nationwide, 1.5% (n=1,371) of all patients with endometrial adenocarcinoma in the SEER dataset underwent SLND over the time period. SLND was performed in 3.4% (n=607), 0.24% (n=24), 0.95% (n=152), and 1.3% (n=588) of all patients in the Northeast, Midwest, South, and West regions, respectively (Table 3.3). Unadjusted logistic regression analyses found U.S. Census Region ($p<0.001$), collapsed year ($p<0.001$), and age ($p<0.001$) to be significantly associated with undergoing SLND within the endometrial cancer population. Tumor grade was not significantly associated with SLND ($p=0.50$) (Table 3.4). When analyses were adjusted for each of these factors, Census Region ($p=0.115$), collapsed year ($p=0.060$), and grade ($p=0.114$) were not significant. Only age ($p=0.003$) was significantly associated with a patient undergoing SLND (Table 3.5).

In California, 0.9% (n=299) of all patients with endometrial cancer underwent SLND (Table 3.2). Unadjusted California analyses found registry ($p<0.001$) to be significantly associated with SLND. However, this did not remain significant in adjusted analyses inclusive of registry, collapsed year, and grade (Table 3.5). Statistical power due to small sample sizes was insufficient to evaluate tumor size/extent and patient race/ethnicity in the California SLND analyses.

Table 3.3. Study Participant Characteristics by Exposure to LND/SLND

	All Patients	LND (% of all patients)	SLND[a] (% of all patients)
Total Patients	n=89,944	n=53,616 (59.6%)	n=1,371 (1.5%)
Metastasis Status			
No Metastasis (M0)	88,279	53,263 (60.7%)	1,361 (1.5%)
Unknown Metastasis (MX)	1,665	353 (21.2%)	10 (0.6%)
Geography			
New England Division	4,928	3,099 (62.9%)	Suppressed[b]
Mid Atlantic Division	12,748	8,277 (64.9%)	
East North Central Division	5,407	3,042 (56.3%)	
West North Central Division	4,413	2,359 (53.5%)	
South Atlantic Division	7,626	4,999 (65.6%)	
East South Central Division	5,038	2,809 (55.8%)	
West South Central Division	3,253	1,782 (54.8%)	
Mountain Division	4,564	2,655 (58.2%)	
Pacific Division	41,967	24,594 (58.6%)	
California	*34,478*	*20,025 (58.1%)*	*299 (0.9%)*
Greater California	*18,964*	*10,337 (54.5%)*	*83 (0.4%)*
Los Angeles	*8,512*	*5,031 (59.1%)*	*124 (1.5%)*
San Francisco	*4,942*	*3,301 (66.8%)*	*37 (0.8%)*
San Jose-Monterey	*2,060*	*1,356 (65.8%)*	*55 (2.7%)*
US Region			
Northeast	17,676	11,376 (64.4%)	607 (3.4%)
Midwest	9,820	5,401 (55.0%)	24 (0.24%)
South	15,917	9,590 (60.3%)	152 (0.95%)
West	46,531	27,249 (58.6%)	588 (1.3%)
Year of Diagnosis			Suppressed
2004	5,551	3,080 (55.5%)	

2005	5,870	3,353 (57.1%)	
2006	6,292	3,807 (60.5%)	
2007	6,622	4,150 (62.7%)	
2008	6,858	4,336 (63.2%)	
2009	7,409	4,561 (61.6%)	
2010	7,754	4,759 (61.4%)	
2011	8,008	4,824 (60.2%)	
2012	8,556	4,995 (58.4%)	
2013	8,538	5,008 (58.7%)	
2014	9,171	5,333 (58.2%)	
2015	9,315	5,410 (58.1%)	
Year of Diagnosis (Collapsed)			
2004-2005	11,421	6,433 (56.3%)	17 (0.2%)
2006-2007	12,914	7,957 (61.6%)	26 (0.2%)
2008-2009	14,267	8,897 (62.4%)	63 (0.4%)
2010-2011	15,762	9,583 (60.8%)	117 (0.7%)
2012-2013	17,094	10,003 (58.5%)	445 (2.6%)
2014-2015	18,486	10,743 (58.1%)	703 (3.8%)
Size/Extent of Primary Tumor			Suppressed
T1a	22,309	10,327 (46.3%)	
T1b	33,407	20,509 (61.4%)	
T1c	12,930	10,197 (78.9%)	
T1 NOS	4,340	1,314 (30.3%)	
T2a	2,888	2,039 (70.6%)	
T2b	3,678	2,951 (80.2%)	
T2 NOS	1,232	722 (58.6%)	
T3a	5,544	4,309 (77.7%)	
T3b	1,203	787 (65.4%)	
T3 NOS	60	35 (58.3%)	
T4	349	185 (53.0%)	
TX	1,998	240 (12.0%)	
Tumor Grade			
Grade 1	39,614	19,413 (49.0%)	557 (1.4%)

Grade 2	24,263	17,093 (70.5%)	365 (1.5%)
Grade 3	10,111	8,082 (79.9%)	154 (1.5%)
Race/Ethnicity			Suppressed
White, non-Hispanic	66,334	39.814 (60.0%)	
Black/African American	5,925	3,461 (58.4%)	
American Indian/Alaska Native	575	309 (53.7%)	
Asian/Pacific Islander	7,018	4,499 (64.1%)	
Hispanic/Latino	9,516	5,291 (55.6%)	
Unknown	576	242 (42.0%)	
Age (years)			
<40	3,527	1,574 (44.6%)	40 (1.1%)
40-49	9,443	5,104 (54.0%)	136 (1.4%)
50-59	27,680	16,441 (59.4%)	432 (1.6%)
60-69	28,519	18,032 (63.2%)	495 (1.7%)
70-79	14,094	9,160 (65.0%)	206 (1.5%)
80+	6,681	3,305 (49.5%)	62 (0.9%)

[a] Patients undergoing SLND are a subset of all patients undergoing LND; [b]Results are suppressed if any stratum has an LND or SLND exposure in <10 patients

Table 3.4. Crude and Adjusted Analyses for Relationship between Variables of Interest and LND in the US and California

U.S. (n=89,944)						
	Crude			Adjusted[a]		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
US Census Division			<0.001			0.025
New England	1.00	*Reference*		1.00	*Reference*	
Mid Atlantic	1.09	(1.02, 1.17)		1.13	(1.04, 1.22)	
East North Central	0.76	(0.70, 0.82)		0.82	(0.75, 0.90)	
West North Central	0.68	(0.62, 0.73)		0.67	(0.61, 0.73)	
South Atlantic	1.12	(1.04, 1.21)		1.12	(1.02, 1.22)	
East South Central	0.74	(0.69, 0.81)		0.72	(0.66, 0.79)	
West South Central	0.72	(0.65, 0.78)		0.65	(0.58, 0.71)	
Mountain	0.82	(0.76, 0.89)		0.91	(0.82, 1.00)	
Pacific	0.84	(0.79, 0.89)		0.85	(0.80, 0.92)	
Year of Diagnosis			<0.001			0.014
2004	1.00	*Reference*		1.00	*Reference*	
2005	1.07	(0.99, 1.15)		1.07	(0.98, 1.16)	
2006	1.23	(1.14, 1.32)		1.24	(1.15, 1.35)	
2007	1.35	(1.25, 1.45)		1.36	(1.26, 1.48)	
2008	1.38	(1.28, 1.48)		1.45	(1.34, 1.57)	
2009	1.29	(1.20, 1.38)		1.35	(1.24, 1.46)	
2010	1.28	(1.19, 1.37)		1.34	(1.24, 1.45)	
2011	1.22	(1.13, 1.30)		1.29	(1.19, 1.39)	
2012	1.13	(1.05, 1.21)		1.16	(1.07, 1.25)	
2013	1.14	(1.06, 1.22)		1.16	(1.07, 1.25)	
2014	1.12	(1.04, 1.19)		1.15	(1.06, 1.24)	
2015	1.11	(1.04, 1.19)		1.19	(1.10, 1.29)	
Size/Extent of Primary Tumor			<0.001			<0.001
T1a						
T1b	1.00	*Reference*		1.00	*Reference*	
T1c	1.85	(1.78, 1.91)		1.64	(1.57, 1.70)	
T1 NOS	4.33	(4.12, 4.55)		3.39	(3.20, 3.59)	

T2a	0.50	(0.47, 0.54)		0.50	(0.47, 0.55)	
T2b	2.79	(2.56, 3.03)		2.28	(2.08, 2.51)	
T2 NOS	4.71	(4.32, 5.13)		3.32	(3.01, 3.66)	
T3a	1.64	(1.46, 1.85)		1.23	(1.07, 1.41)	
T3b	4.04	(3.78, 4.34)		2.78	(2.57, 3.01)	
T3 NOS	2.20	(1.94, 2.48)		1.36	(1.17, 1.57)	
T4	1.62	(0.97, 2.72)		0.84	(0.47, 1.52)	
TX	1.31	(1.06, 1.62)		0.72	(0.57, 0.92)	
	0.16	(0.14, 0.18)		0.15	(0.13, 0.18)	
Tumor Grade			<0.001			<0.001
Grade 1	1.00	*Reference*		1.00	*Reference*	
Grade 2	2.48	(2.40, 2.57)		2.19	(2.11, 2.27)	
Grade 3	4.14	(3.93, 4.37)		3.63	(3.43, 3.85)	
Race/Ethnicity			<0.001			<0.001
White, non-Hispanic	1.00	*Reference*		1.00	*Reference*	
Black/African American	0.94	(0.89, 0.99)		0.87	(0.81, 0.93)	
American Indian/Alaska Native	0.77	(0.66, 0.91)		0.93	(0.76, 1.15)	
Asian/Pacific Islander	1.19	(1.13, 1.25)		1.34	(1.25, 1.42)	
Hispanic/Latino	0.83	(0.80, 0.87)		0.88	(0.84, 0.93)	
Unknown	0.48	(0.41, 0.57)		0.78	(0.63, 0.96)	
Age (years)			<0.001			<0.001
<40	1.00	*Reference*		1.00	*Reference*	
40-49	1.46	(1.35, 1.58)		1.22	(1.11, 1.34)	
50-59	1.82	(1.69, 1.95)		1.36	(1.25, 1.49)	
60-69	2.13	(1.99, 2.29)		1.42	(1.31, 1.55)	
70-79	2.30	(2.14, 2.48)		1.34	(1.22, 1.46)	
80+	1.22	(1.12, 1.32)		0.65	(0.59, 0.72)	
California (n=34,478)						
	Crude			**Adjusted[a]**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Registry			<0.001			0.113
Greater California	1.00	*Reference*		1.00	*Reference*	

Los Angeles	1.21	(1.15, 1.27)		1.44	(1.32, 1.57)	
San Francisco-Oakland SMSA	1.68	(1.57, 1.79)		1.21	(1.08, 1.36)	
San Jose-Monterey	1.61	(1.46, 1.77)		0.78	(0.73, 0.83)	
Year of Diagnosis			<0.001			0.052
2004	1.00	*Reference*		1.00	*Reference*	
2005	1.06	(0.94, 1.20)		1.02	(0.91, 1.15)	
2006	1.19	(1.06, 1.35)		1.15	(1.03, 1.29)	
2007	1.11	(0.99, 1.23)		1.09	(0.97, 1.22)	
2008	1.18	(1.05, 1.33)		1.17	(1.04, 1.31)	
2009	1.08	(0.96, 1.21)		1.10	(0.98, 1.23)	
2010	1.03	(0.92, 1.16)		1.04	(0.93, 1.16)	
2011	1.01	(0.90, 1.13)		1.04	(0.93, 1.16)	
2012	0.95	(0.85, 1.06)		1.00	(0.89, 1.11)	
2013	0.94	(0.84, 1.05)		0.99	(0.89, 1.11)	
2014	0.95	(0.85, 1.06)		0.99	(0.89, 1.11)	
2015	0.95	(0.85, 1.06)		1.01	(0.90, 1.15)	
Size/Extent of Primary Tumor			<0.001			<0.001
T1a						
T1b	1.00	*Reference*		1.00	*Reference*	
T1c	1.83	(1.73, 1.93)		1.61	(1.51, 1.71)	
T1 NOS	4.51	(4.17, 4.88)		3.55	(3.24, 3.89)	
T2a	0.54	(0.48, 0.61)		0.54	(0.48, 0.62)	
T2b	3.33	(2.92, 3.79)		2.68	(2.32, 3.11)	
T2 NOS	5.48	(4.78, 6.29)		4.00	(3.42, 4.68)	
T3a	1.80	(1.49, 2.17)		1.29	(1.03, 1.61)	
T3b	4.37	(3.92, 4.87)		3.00	(2.65, 3.40)	
T3 NOS	2.63	(2.17, 3.19)		1.54	(1.22, 1.93)	
T4	2.31	(1.02, 5.23)		1.12	(0.45, 2.77)	
TX	2.00	(1.41, 2.82)		0.99	(0.66, 1.48)	
	0.65	(0.05, 0.09)		0.07	(0.04, 0.10)	
Tumor Grade			<0.001			<0.001
Grade 1	1.00	*Reference*		1.00	*Reference*	
Grade 2	2.67	(2.52, 2.82)		2.36	(2.22, 2.50)	

Grade 3	4.80	(4.40, 5.24)		4.21	(3.82, 4.63)	
Race/Ethnicity			<0.001			<0.001
White, non-Hispanic	1.00	*Reference*		1.00	*Reference*	
Black/African American	0.77	(0.69, 0.86)		0.65	(0.57, 0.74)	
American Indian/Alaska Native	0.72	(0.54, 0.95)		0.82	(0.59, 1.15)	
Asian/Pacific Islander	1.17	(1.10, 1.25)		1.11	(1.02, 1.21)	
Hispanic/Latino	0.80	(0.76, 0.85)		0.82	(0.76, 0.88)	
Unknown	0.44	(0.35, 0.56)		0.69	(0.50, 0.93)	
Age (years)			<0.001			<0.001
<40	1.00	*Reference*		1.00	*Reference*	
40-49	1.50	(1.32, 1.69)		1.21	(1.05, 1.40)	
50-59	1.87	(1.67, 2.09)		1.32	(1.15, 1.51)	
60-69	2.21	(1.97, 2.46)		1.40	(1.22, 1.60)	
70-79	2.41	(2.15, 2.71)		1.29	(1.11, 1.49)	
80+	1.34	(1.18, 1.52)		0.59	(0.50, 0.69)	

[a]Final model adjusted for registry, year of diagnosis, size/extent of primary tumor, tumor grade, race/ethnicity, and age

Figure 3.2. Comparison of LND Use in Patients with Endometrial Cancer by U.S. Census Division (Reference: New England), 2004-2015

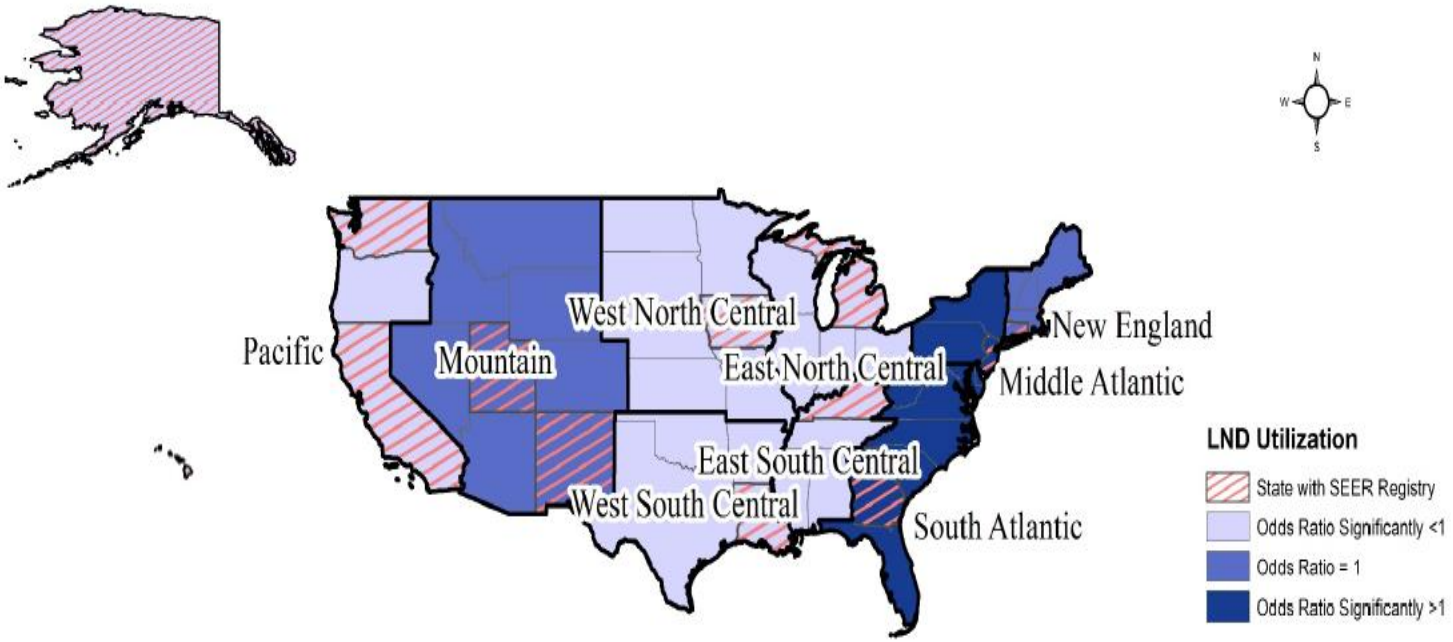


Table 3.5. Crude and Adjusted Analyses for SLND in the U.S. and California

US (n=89,944)						
	Crude			**Adjusted[a]**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
US Census Region			<0.001			0.116
Northeast	1.00	*Reference*		1.00	*Reference*	
Midwest	0.07	(0.05, 0.10)		0.06	(0.04, 0.10)	
South	0.27	(0.23, 0.32)		0.26	(0.21, 0.32)	
West	0.36	(0.32, 0.40)		0.37	(0.33, 0.43)	
Years			<0.001			0.060
2004-2005	1.00	*Reference*		1.00	*Reference*	
2006-2007	1.35	(0.73, 2.50)		1.56	(0.83, 2.94)	
2008-2009	2.98	(1.74, 5.09)		3.31	(1.88, 5.82)	
2010-2011	5.02	(3.01, 8.35)		6.07	(3.56, 10.4)	
2012-2013	12.9	(11.0, 29.1)		20.5	(12.3, 34.2)	
2014-2015	26.5	(16.4, 42.9)		31.3	(18.8, 52.1)	
Tumor Grade			0.50			0.114
Grade 1	1.00	*Reference*		1.00	*Reference*	
Grade 2	1.07	(0.94, 1.22)		1.09	(0.95, 1.25)	
Grade 3	1.09	(0.91, 1.30)		1.20	(1.00, 1.45)	
Age (years)			<0.001			0.003
<40	1.00	*Reference*		1.00	*Reference*	
40-49	1.27	(0.89, 1.82)		1.38	(0.93, 2.07)	
50-59	1.38	(1.00, 1.91)		1.25	(0.86, 1.82)	
60-69	1.54	(1.11, 2.13)		1.21	(0.84, 1.76)	
70-79	1.29	(0.92, 1.82)		1.02	(0.69, 1.52)	
80+	0.82	(0.55, 1.22)		0.74	(0.46, 1.17)	
California (n=34,478)						
	Crude			**Adjusted[b]**		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
California Registry			<0.001			0.122
Greater California	1.00	*Reference*		1.00	*Reference*	

Los Angeles	3.36	(2.54, 4.45)		0.41	(0.27, 0.63)	
San Francisco-Oakland	1.72	(1.16, 2.53)		1.03	(0.68, 1.56)	
San Jose-Monterey	6.24	(4.42, 8.80)		0.30	(0.22, 0.40)	
Years			<0.001			0.073
2004-2005	1.00	*Reference*		1.00	*Reference*	
2006-2007	0.88	(0.36, 2.12)		0.98	(0.44, 2.15)	
2008-2009	2.28	(1.68, 6.60)		2.20	(1.12, 4.33)	
2010-2011	3.33	(1.68, 6.59)		2.97	(1.56, 5.65)	
2012-2013	4.06	(2.08, 7.91)		3.79	(2.02, 7.11)	
2014-2015	8.06	(4.24, 15.34)		6.51	(3.53, 12.0)	
Tumor Grade			0.106			0.220
Grade 1	1.00	*Reference*		1.00	*Reference*	
Grade 2	0.72	(0.53, 0.98)		0.76	(0.56, 1.04)	
Grade 3	0.88	(0.59, 1.30)		0.91	(0.61, 1.35)	

[a]Adjusted for region, collapsed years, tumor grade, and age; [b]Adjusted for registry, collapsed years, and tumor grade

3.4.4. Sensitivity Analyses

A total of 1,665 (1.9%) patients had unknown metastasis status. Repeating analyses with these patients included did not alter the significance of any of the results. For this reason, MX patients were included in all analyses in order to maximize the SLND sample size.

Sensitivity analyses comparing the Pacific states of California (n=34,478), Alaska (n=58), Hawaii (n=1,884), and Washington (n=5,547) found that state was not significantly associated with LND use (p=0.178) in the adjusted analysis, which included year (p=0.052), size/extent of tumor (p<0.001), grade (p<0.001), age group (p<0.001), and race/ethnicity (p<0.001) (data not shown). Sample sizes were insufficient to compare SLND use by state.

3.5. Discussion

Geographic analysis of disparities in cancer management strategies is vital to promoting equitable access nationally[76,77]. The current study is a large, registry-based nationwide analysis of geographic variations in LND/SLND use among the endometrial adenocarcinoma population in the U.S. This research shows that the use of LND varies significantly geographically by U.S. Census Division, even when adjusting for other known tumor-specific covariates, such as size/extent and grade, as well as demographic and temporal variables. As clarifications on LND/SLND best practices arise, understanding these geographic differences can help to maximize equity in patient outcomes nationwide by identifying and targeting areas that stray from these guidelines.

Several international surveys of gynecologic oncologists have noted variations in disease management strategies[39,40,49,81]. Some of these studies suggest that these variations may be due to differences among the providers themselves, such as year of fellowship completion, uncertainty about evidence regarding best practices, and lack of training in SLND[40,49,81]. Access—or lack thereof—to adequate technology also may influence LND/SLND decision-making[39,40]. Though informative for understanding possible explanations for practice variations, these surveys provide little understanding of the patient populations that are affected by such differences. Additionally,

the surveys were frequently limited by small sample sizes, selection bias, low response rates, and lack of statistical adjustment for confounding factors.

While the variation in the present study was evident between Census divisions, it did not present significantly between California registries. This suggests that similarities in treatment patterns may exist in locations in proximity to each other. One possible explanation for this is the availability of gynecologic oncologists to the patient population. As access to gynecologic oncologists varies by geography within the U.S.[76,82], it is possible that an association exists between the presence of gynecologic oncologists in an area and prevalence of LND/SLND use, and this hypothesis deserves further investigation. However, as the aforementioned surveys of gynecologic oncologists have noted[39,40,49,81], variation exists even among these providers. Improving provider understanding of current best practices, providing training on SLND, and ensuring access adequate technology could potentially aid in improving consistency in management strategies across the country.

Much like the present study, Cripe et al.[53] found geographic variation nationally in LND use in endometrial adenocarcinoma patients, although the variations presented differently from those observed in the SEER registries. The researchers utilized the National Cancer Database to analyze LND use in "higher risk" patients for whom LND was indicated: those with presumed stage I endometrioid adenocarcinoma with tumors that were >2 cm in size, had >50% myometrial invasion (MI), or had grade 3 or 4 disease. Patients in New England, West North Central, and West South Central U.S. Census Divisions were less likely to undergo LND when compared to the Pacific division. These results conflict with those of the current study, which found LND to be more common in New England compared to the Pacific Division. However, the differing patient populations could partially explain these differences, as Cripe and colleagues included only those deemed "higher risk" for metastasis[53]. This omission of patients with presumed lower-risk disease characteristics (e.g., tumors <2cm, <50 MI, or grade 1 or 2) thereby excludes a population for whom LND is more frequently debated[12,13,20]. The present study investigated all use of LND

among the endometrial adenocarcinoma population, adjusting for the "high risk" variables when available. As such, it may be concluded that the Census divisions along the eastern U.S. exhibit higher use of LND in endometrial adenocarcinoma patients overall.

Analyses of SLND offered different conclusions from those of LND in the U.S. In the current study, SLND did not vary significantly by geographic region. However, it was necessary to compare Census regions rather than divisions due to small sample sizes, and it is possible that such broad groupings led to a loss of variation among the geographies. Furthermore, sample size estimations in the planning phase were based on a baseline probability of 5% for undergoing SLND[54], but the current study found SLND use in only 1.5% of patients in the U.S during this time period. As such, the actual sample size was likely insufficient to detect statistically significant differences in the prevalence of SLND between geographies despite the wide range of 0.24% in the Midwest to 3.8% in the Northeast. Similarly, California did not show significant differences between registries, but only 0.9% of all patients had undergone SLND overall.

One claims-based retrospective cohort study has included comparisons of patient exposure to SLND use by geography in the U.S. Wright et al.[54] utilized the Perspective Database for an analysis of SLND use among 28,262 women with uterine cancer from 2011 to 2015. Differing from the current study, the researchers included general uterine cancers rather than endometrial adenocarcinoma specifically, and covariates considered potentially clinically relevant in LND/SLND decision-making, such as tumor histology and grade, were not available in the dataset[54]. However, similar to the present study, the researchers found no difference in SLND use between the Northeastern, Midwest, South, or West U.S. regions. Also similar to the present study, the broad regional groupings rather than smaller divisional groupings in these two studies may have precluded sufficient differentiation between geographies. It is possible that once sample sizes are larger and representative of more numerous geographies, significant differences may be observed. Given evolving guidelines in standard of care and possible changes in use of SLND in these patients in the years from 2016 to date, future research is warranted.

Limitations to the current study must be noted. The choice to collapse the 18 SEER registries into U.S. Census Division categories was to allow for a meaningful interpretation of geographic variations rather than registry-based variations for 18 different sites. This grouping of the 18 SEER registries by Census Division resulted in unequal distribution of registries and sample sizes. For example, some geographies consisted of a single SEER registry, such as New England, and others included several, such as the Pacific Division with 7. However, the separate analysis of California, which contributed 4 of the 7 Pacific registries, showed no significant in-state variation. An additional post-hoc sensitivity analysis comparing Pacific states did not show significant intra-Division differences.

The SEER dataset does not contain data regarding provider specialty, surgical approach (e.g., laparotomy vs. laparoscopy vs. robotic), lymphovascular space invasion (LVSI), comorbidities, hospital type, or insurance coverage for the included years, which may be associated with LND/SLND use[53,54,83]. The lack of availability of these variables in the SEER dataset may have led to the omission of potentially relevant variables in statistical models.

Research regarding SLND has unique potential limitations because the technique is only recently receiving widespread acceptance for the endometrial cancer population[8]. While researchers have found the SLND can yield satisfactory sensitivity and negative predictive value[31,37], provider experience, patient body mass index (BMI), and dye selection and injection location all have been identified as possibly influencing the success of SLN identification[37,75]. Given such barriers to successful SLN mapping, analyses may be limited due to small numbers of patients undergoing successful SLND. However, establishing baseline frequencies remains essential in understanding any ongoing changes in SLND use. Additionally, data are not available within the SEER dataset regarding failed mappings of SLNs. As such, it is possible the number of patients identified as undergoing SLND in the dataset is an underestimation of attempted SLND.

3.6. Conclusion

Geographic variations in the use of LND and SLND thus far are informative only in the investigation of practice patterns, rather than providing substantial insight in variation of patient outcomes[84]. Despite surgical management recommendations provided by national and international organizations[5,69], the reality in the clinical setting varies substantially. Much of this variation may be due to incomplete evidence of benefits and risks associated with LND and SLND, inconsistent access to sufficient technology, and differences in provider training and experience. As best practices become clarified, however, it will become essential to identify locations that stray from these strategies and to target them for practice improvement in order to address any resultant geographic disparities in patient outcomes. In doing so, patients may experience not only improvements in survival across the country, but possible reductions in unnecessary harms as well.

CHAPTER 4

POST-SURGICAL COMPLICATIONS AMONG PATIENTS WITH ENDOMETRIAL ADENOCARCINOMA BY EXTENT OF LYMPHADENECTOMY

4.2. Introduction

Endometrial cancer is the fourth most commonly diagnosed cancer among women in the United States, with an annual incidence of 28 per 100,000 women[1]. Although generally considered to have a favorable prognosis, a recent increase in incidence and mortality for this cancer[64] serves as a reminder to remain vigilant in identifying best practices and improving disease management strategies. In recent years, one area of research receiving substantial attention is the use of lymph node dissection (LND) in women with presumed early-stage endometrioid adenocarcinoma[6–18]. Although considered integral to comprehensive staging and adjuvant therapy selection[5,19], the appropriate number of lymph nodes to remove in this population is unclear[20] due to limited evidence of benefit in preventing recurrence or increasing survival. For example, two randomized controlled trials (RCTs) found no survival benefit in patients undergoing systematic lymphadenectomy compared to standard surgery[6,7]. Observational studies have provided inconsistent evidence, as some have shown a survival benefit to systematic LND[13,12,9,16] while others have not[14,15,17,85]. As such, debate remains regarding LND's utility among women with presumed early-stage disease.

In response to this debate, researchers are exploring an alternative to systematic LND, sentinel lymph node dissection (SLND)[28–33,37,75,86–91]. Currently, research generally centers on injection sites, dye use, algorithm use, and the ability of SLND to identify nodal metastases in comparison to systematic LND[30,92]. Surgical metrics[93] and survival outcomes[87] also have been investigated in a more limited capacity and point toward SLND as a viable alternative to systematic LND. As a result of this ongoing research, clinical guidance regarding use of LND is evolving, shifting away from systematic lymphadenectomy and toward the use of sentinel lymph

node dissection (SLND) in select patients[4,66,67,69]. However, little is known regarding outcomes other than survival.

Surgical complications are also of importance to patients and providers, although they are often secondary outcomes within clinical trials with relatively small sample sizes[6,7], precluding any meaningful conclusions. The purpose of this study was to investigate several outcomes in addition to mortality that are informative in the benefit-harm decision-making process for this patient population but are frequently overlooked in clinical trials due to few events among smaller sample sizes[6,7]. Using a large, nationwide dataset, the current research aims to quantify the risk of lymphedema, lymphocele, hemorrhage, ileus, infection, thrombosis, and all-cause death associated with the extent of lymph node resection.

4.3. Materials and Methods

4.3.1. Study Design

This retrospective cohort study utilized the SEER-Medicare dataset for the years 2003-2016. The dataset consists of a linkage of two large population-based datasets in the United States. The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) collects data from population-based cancer registries throughout the country. Within the SEER-Medicare dataset, SEER data identify incident cases of cancer and provide detailed information including year of diagnosis, number of lymph nodes removed, morphology code, size/extent of primary tumor, tumor grade, radiotherapy exposure, age of diagnosis, race, and ethnicity[94].

Medicare is the primary insurer for the U.S. population aged 65 years and older[95], and an estimated 93% of all cancer cases in SEER aged 65 years and older are found in the Medicare enrollment file[95]. Within the SEER-Medicare dataset, Medicare provides claims data from hospital, outpatient, and physician providers, including information on the date of surgery and the use of chemotherapy[95,96]. The Medicare claims files to obtain are the Patient Entitlement and Diagnosis Summary File (PEDSF); the Medicare Provider Analysis and Review (MEDPAR) file,

which includes all Part A (inpatient) short stay, long stay, and skilled nursing facility (SNF) bills; the Carrier claims file, which includes Part B (outpatient) physician/supplier bills; and the Outpatient claims file (also Part B), which includes claims from institutional outpatient providers[97].

This research was approved as an exempt study by the Indiana University Institutional Review Board given its secondary use of an existing dataset.

4.3.2. Study Population

Eligible patients were women aged 66 years or over, with surgically staged endometrioid adenocarcinoma of the uterus, identified by ICD-O-3 site codes C54.0-C54.3, C54.8, C54.9, and C55.9[98] and histology/behavior code 8380/3[99], without distant metastasis (American Joint Committee on Cancer [AJCC] 6th Edition M0 OR MX), and diagnosed between January 2004 and December 2015. The age of 66 years was selected to allow for a minimum of 1 year of data prior to diagnosis in order to identify pre-existing comorbid conditions. Patients with non-Medicare health maintenance organization (HMO) enrollment were excluded due to risks of incomplete data in the Medicare dataset[100].

4.3.3. Sample Size

Parameters for sample size determination were a 2-sided statistical test with a power of 0.80, $\alpha = 0.05$, an overall event rate of 10%[6], and assumed independence of the covariates. The study required a sample size of approximately 8,600 women to detect a hazard ratio (HR) of 1.10 when comparing categories of numbers of lymph nodes removed on surgical complications of interest.

4.3.4. Statistical Analysis

The exposure of interest in this study was LND/SLND, classified by number of lymph nodes removed: 0, 1-4, 5-9, and 10+. The underlying assumption in this study was that the removal of 1-4 nodes represents a bilateral SLND, 5-9 represents a unilateral SLND and unilateral full LND, and 10+ represents a full, bilateral LND. The surgical complications

evaluated were coded as dichotomous outcomes, “yes” or “no.” They included 6-month post-surgical lymphedema (“yes” or “no”), lymphocele, hemorrhage, ileus, infection, thrombosis, and all-cause death, defined using the ICD-9-CM, ICD-10-CM, and HCPCS codes during the 6-month post-surgery period (Appendix B).

The 6-month post-surgical timeframe began at the date of hysterectomy. It was identified within the Medicare portion of the SEER-Medicare dataset[96] using the codes presented in Appendix C. For those patients known to have undergone surgical staging but for whom a date could not be identified, hysterectomy date was imputed, with the 15th day of the month of diagnosis utilized as an approximate surgery date. For those with known surgical dates, a median value of time from diagnosis to time of surgery was calculated for descriptive purposes.

Patient records were searched in the year prior to surgery for any pre-existing occurrences of the outcomes of interest, and any patient with such a prevalent condition was excluded from analyses for that particular outcome. Patient comorbidities were accounted for through the use of the NCI Comorbidity Index[101,102], calculated based on comorbidities identified through inpatient and outpatient claims. This was accomplished by searching for ICD-9-CM, ICD-10-CM, and HCPCS diagnostic codes 1 year before surgery date.

SAS version 9.4[72] was used for all analyses. Descriptive statistics in terms of frequencies and percentages were calculated for categorical variables. Chi-square analyses compared patient characteristics across LND exposure groups to determine whether significant differences existed between groups. Covariates included size/extent of primary tumor (reference: FIGO T1a), tumor grade (reference: grade 1), NCI Comorbidity Index score (0 [reference], 1, and 2+), race/ethnicity (reference: white, non-Hispanic), age at diagnosis (66-69 [reference], 70-74, 75-79, 80-84, and 85+), exposure to adjuvant chemotherapy (reference: no), and exposure to radiotherapy (reference: no). Chemotherapy codes are presented in Appendix D.

Cumulative hazard of experiencing an event for each exposure group was estimated per 6-month period using Nelson-Aalen estimating methods[103]. Additionally, stratified cumulative

hazard was estimated for each of the covariates to assess their relationship with post-surgical complications. Cox proportional-hazards analyses compared outcomes over the time period for the LND exposure groups, adjusting for relevant covariates. For each event of interest, follow-up times for a patient began at date of hysterectomy and continued until the event occurred within the 6-month post-surgical period or was censored at death or at the end of the 6-month period, whichever occurred first. Hazard ratios (HRs), 95% confidence intervals (CIs), and p-values were calculated, with significance evaluated at $\alpha=0.05$.

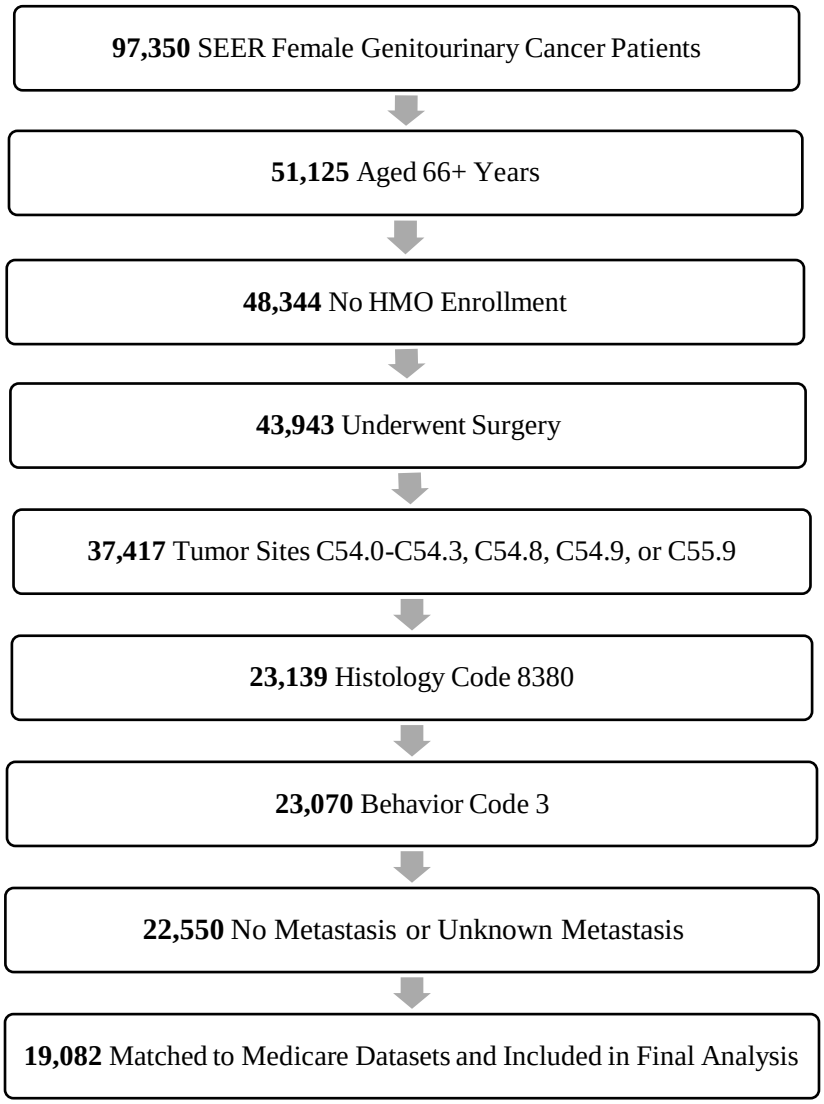
To evaluate the impact of surgery date imputation on the results, sensitivity analyses were conducted including only patients for whom a confirmed surgery date appeared in the SEER-Medicare dataset.

4.4. Results

4.4.1. Study Population

A total of 19,082 women met study inclusion criteria (Figure 4.1). Of these, 11,621 had confirmed surgery dates within the Medicare dataset. Surgery dates were estimated for the remaining women based on date of diagnosis. Among those with known hysterectomy dates, the median time from diagnosis to surgery was 38 days.

Figure 4.1. Study Population Selection Diagram



Women aged 66-69 years old constituted the largest age group at 34% of the study population, and most (83.4%) were white, non-Hispanic (Table 4.1). Grade 1 tumors were the most common (37%), as was a tumor extent equating to FIGO T1b (40%). A total of 29% of the study population received radiotherapy, and few underwent chemotherapy (8%). Approximately 32% of women had 0 lymph nodes removed and examined. In contrast, 44% had 10 or more nodes removed. Chi-square analyses comparing LND groups by demographic and tumor characteristics found significant differences for all variables (Table 4.1).

4.4.2. Assessment of Outcomes

Stratified and adjusted analyses were not possible for lymphocele due to small numbers of events in several LND strata (Table 4.2). In analyses adjusted for year of diagnosis, age at diagnosis, race/ethnicity, tumor grade, extent of primary tumor, radiation treatment, chemotherapy, and NCI Comorbidity Score, extent of LND was significantly associated with ileus ($p=0.002$), infection ($p<0.001$), and thrombosis ($p=0.01$), with 10+ nodes removed yielding greatest risk. When comparing the 10+ node group to the reference of 0 nodes removed, HRs (95% CIs) were 1.53 (1.24-1.90) for ileus, 1.52 (1.25-1.83) for infection, and 1.41 (1.09-1.82) for thrombosis. A significant association was not found between extent of LND and lymphedema ($p=0.12$), hemorrhage ($p=0.26$), or death ($p=0.21$) in adjusted analyses.

Significant associations of other relevant covariates were found among the outcomes of interest in adjusted models (Table 4.3). In the 6-month post-surgical timeframe, age was found to be significantly associated with lymphedema ($p=0.01$), ileus ($p<0.001$), and death ($p<0.001$), with increasing age associated with increasing risk. Year of diagnosis was significantly associated with lymphedema ($p=0.02$), infection ($p<0.001$), thrombosis ($p<0.001$), and death ($p=0.01$). Association between year and ileus could not be evaluated due to small numbers of ileus events in some strata for year. Race/ethnicity was associated with infection ($p<0.001$), with black/non-Hispanic and Hispanic/Latino women experiencing a greater risk than white/non-Hispanic women. Tumor grade was significantly associated with infection ($p=0.01$) and death ($p<0.001$), with risk increasing with grade. Size/extent of primary tumor was significantly associated with ileus ($p<0.001$), infection ($p=0.04$), thrombosis ($p<0.01$), and death ($p<0.001$). Radiation therapy was associated with decreased risk of ileus ($p=0.002$), infection ($p<0.001$), thrombosis ($p<0.001$), and death ($p<0.001$). NCI comorbidity score was significantly associated with lymphedema ($p=0.003$), ileus ($p<0.001$), infection ($p<0.001$), thrombosis ($p<0.001$), and death ($p<0.001$), with higher comorbidity scores generally associated with higher risk of complications. Chemotherapy exposure was found to be significantly associated with a decreased risk of death ($p<0.001$).

4.4.3. Sensitivity Analysis

All analyses were repeated excluding data from women with imputed surgery dates (Appendix E). Due to small group sizes in some strata among women with confirmed surgery dates, year of diagnosis and size/extent of primary tumor needed to be excluded from all models. For comparison purposes, the imputed dataset was also reanalyzed omitting year of diagnosis and size/extent of primary tumor. Association with extent of lymph node removal remained statistically significant for ileus ($p<0.01$), infection ($p<0.01$), and thrombosis ($p<0.01$) in the group with known dates for hysterectomy. Association of LND was not significant for lymphedema ($p=0.12$), hemorrhage ($p=0.52$), or death ($p=0.63$). In summary, association of LND with the outcomes of interest was did not differ between the imputed date and confirmed date datasets, and as such, the larger dataset was utilized to maximize sample sizes among strata

Table 4.1. Study Population Characteristics by Number of Lymph Nodes Removed

		Number of Lymph Nodes Removed				
	Total	0 Nodes	1-4 Nodes	5-9 Nodes	10+ Nodes	
	Frequency (%)[a]	Frequency (%)[a]	Frequency (%)[a]	Frequency (%)[a]	Frequency (%)[a]	p-value[b]
Total Patients	19,082 (100%)	6,154 (32.3%)	1,854 (9.7%)	2,758 (14.5%)	8,316 (43.6%)	
Age						<0.001
66-69 years	6,510 (34.1%)	2,100 (34.1%)	588 (31.7%)	912 (33.1%)	2,910 (35.0%)	
70-74 years	5,487 (28.8%)	1,621 (26.3%)	512 (27.6%)	806 (29.2%)	2,548 (30.6%)	
75-79 years	3,568 (18.7%)	1,087 (17.7%)	365 (19.7%)	514 (18.6%)	1,602 (19.3%)	
80-84 years	2,218 (11.6%)	751 (12.2%)	252 (13.6%)	353 (12.8%)	862 (10.4%)	
85+ years	1,299 (6.8%)	595 (9.7%)	137 (7.4%)	173 (6.3%)	394 (4.7%)	
Year of Diagnosis						<0.001
2004	1,208 (6.3%)	455 (7.5%)	144 (7.8%)	172 (6.2%)	437 (5.3%)	
2005	1,302 (6.8%)	462 (7.5%)	149 (8.0%)	182 (6.6%)	509 (6.1%)	
2006	1,414 (7.4%)	456 (7.4%)	148 (8.0%)	190 (6.9%)	620 (7.5%)	
2007	1,412 (7.4%)	416 (6.8%)	147 (7.9%)	222 (8.1%)	627 (7.5%)	
2008	1,427 (7.5%)	401 (6.5%)	134 (7.2%)	192 (7.0%)	700 (8.4%)	
2009	1,596 (8.4%)	495 (8.0%)	155 (8.4%)	235 (8.5%)	711 (8.6%)	
2010	1,673 (8.8%)	509 (8.3%)	154 (8.3%)	231 (8.4%)	779 (9.4%)	
2011	1,713 (9.0%)	531 (8.6%)	138 (7.4%)	238 (8.6%)	806 (9.7%)	
2012	1,775 (9.3%)	621 (10.1%)	136 (7.3%)	228 (8.3%)	790 (9.5%)	
2013	1,798 (9.4%)	576 (9.4%)	160 (8.6%)	286 (10.4%)	776 (9.3%)	
2014	1,901 (10.0%)	615 (10.0%)	204 (11.0%)	292 (10.6%)	790 (9.5%)	
2015	1,863 (9.8%)	617 (10.0%)	185 (10.0%)	290 (10.5%)	771 (9.3%)	
Race/Ethnicity						<0.001
White, Non-Hispanic	15,911 (83.4%)	5,219 (84.8%)	1,474 (79.5%)	2,264 (82.1%)	6,954 (83.6%)	
Black, Non-Hispanic	1,171 (6.1%)	357 (5.8%)	165 (8.9%)	185 (6.7%)	464 (5.6%)	
Hispanic/Latino	789 (4.1%)	383 (6.2%)	129 (6.7%)	176 (6.4%)	523 (6.3%)	
Other/Unknown	1,211 (6.4%)	195 (3.2%)	86 (4.6%)	133 (4.8%)	375 (4.5%)	

FIGO Tumor Grade						<0.001
Grade 1	7,090 (37.2%)	3,067 (49.8%)	632 (34.1%)	866 (31.4%)	2,525 (30.4%)	
Grade 2	5,904 (30.9%)	1,514 (24.6%)	632 (34.1%)	974 (35.3%)	2,784 (33.5%)	
Grade 3	2,949 (15.5%)	542 (8.8%)	331 (17.9%)	451 (16.4%)	1,625 (19.5%)	
Unknown	3,139 (16.5%)	1,031 (16.8%)	259 (14.0%)	467 (16.9%)	1,382 (16.6%)	
Size/Extent of Tumor						<0.001
T1a	3,271 (17.1%)	1,546 (25.1%)	328 (17.7%)	369 (13.4%)	1,028 (12.4%)	
T1b	7,696 (40.3%)	2,756 (44.8%)	705 (38.0%)	1,073 (38.9%)	3,162 (38.0%)	
T1c	4,606 (24.1%)	1,030 (16.7%)	424 (22.9%)	783 (28.4%)	2,369 (28.5%)	
T2a	771 (4.0%)	196 (3.2%)	81 (4.4%)	120 (4.4%)	374 (4.5%)	
T2b	1,002 (5.3%)	203 (3.3%)	104 (5.6%)	157 (5.7%)	538 (6.5%)	
T3a	1,330 (7.0%)	298 (4.8%)	153 (8.3%)	195 (7.1%)	684 (8.2%)	
T3b	305 (1.6%)	80 (1.3%)	44 (2.4%)	44 (1.6%)	137 (1.7%)	
T4	101 (0.5%)	45 (0.7%)	15 (0.8%)	17 (0.6%)	24 (0.3%)	
Received Chemotherapy						<0.001
No	17,538 (91.9%)	5,887 (95.7%)	1,691 (91.2%)	2,501 (90.7%)	7,459 (89.7%)	
Yes	1,544 (8.1%)	267 (4.3%)	163 (8.8%)	257 (9.3%)	857 (10.3%)	
Received Radiation						<0.001
No	13,257 (69.5%)	5,021 (81.6%)	1,258 (67.9%)	1,795 (65.1%)	5,183 (62.3%)	
Yes	5,561 (29.1%)	1,072 (17.4%)	568 (30.6%)	925 (33.5%)	2,996 (36.0%)	
Unknown	264 (1.4%)	61 (1.0%)	28 (1.5%)	38 (1.4%)	137 (1.7%)	
NCI Comorbidity Score						0.001
0	16,705 (87.5%)	5,306 (86.2%)	1,634 (88.1%)	2,428 (88.0%)	7,337 (88.2%)	
1	1,779 (9.3%)	609 (9.9%)	166 (9.0%)	250 (9.1%)	754 (9.1%)	
2+	598 (3.1%)	239 (3.9%)	54 (2.9%)	80 (2.9%)	225 (2.7%)	

[a]Due to rounding, some totals may not equal 100%; [b]Chi-Square Analysis

Table 4.2. Cumulative Hazard of Outcomes of Interest as Events per 1000 Women per 6-Month Period (n=19,082)

Outcome of Interest	Number at Risk	Cumulative Hazard (Events per 1000 Women)	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Lymphedema[a]	19,041	6.5		0.12		0.12
0 Nodes	6,136	5.4	*Reference*		*Reference*	
1-4 Nodes	1,850	3.8	0.71 (0.31, 1.58)		0.67 (0.30, 1.53)	
5-9 Nodes	2,753	6.6	1.21 (0.68, 2.15)		1.17 (0.65, 2.11)	
10+ Nodes	8,302	8.1	1.48 (0.97, 2.24)		1.47 (0.95, 2.28)	
Lymphocele[b]	19,079	3.9		--		--
0 Nodes	6,153	--	--		--	
1-4 Nodes	1,854	--	--		--	
5-9 Nodes	2,757	--	--		--	
10+ Nodes	8,315	--	--		--	
Hemorrhage[a]	19,039	15.7		0.37		0.26
0 Nodes	6,139	17.3	*Reference*		*Reference*	
1-4 Nodes	1,846	12.5	0.72 (0.46, 1.13)		0.69 (0.44, 1.08)	
5-9 Nodes	2,753	13.4	0.78 (0.53, 1.13)		0.74 (0.51, 1.09)	
10+ Nodes	8.301	15.9	0.92 (0.71, 1.89)		0.87 (0.67, 1.14)	
Ileus[c]	19,010	28.7		0.002		0.001
0 Nodes	6,127	22.7	*Reference*		*Reference*	
1-4 Nodes	1,844	34.2	1.51 (1.12, 2.04)		1.49 (1.10, 2.01)	
5-9 Nodes	2,751	26.5	1.17 (0.88, 1.56)		1.19 (0.89, 1.58)	
10+ Nodes	8,288	32.7	1.45 (1.18, 1.78)		1.53 (1.24, 1.90)	
Infection[a]	19,036	37.1		<0.001		<0.001
0 Nodes	6,134	27.2	*Reference*		*Reference*	

1-4 Nodes	1,852	36.2	1.33 (1.00, 1.77)		1.25 (0.94, 1.67)	
5-9 Nodes	2,749	38.9	1.43 (1.12, 1.82)		1.37 (1.07, 1.75)	
10+ Nodes	8,301	44.0	1.63 (1.35, 1.95)		1.52 (1.25, 1.83)	
Thrombosis[a]	18,998	18.6		0.024		0.010
0 Nodes	6,144	16.2	*Reference*		*Reference*	
1-4 Nodes	1,847	18.4	1.14 (0.77, 1.68)		1.09 (0.74, 1.62)	
5-9 Nodes	2,746	14.2	0.87 (0.60, 1.27)		0.89 (0.61, 1.29)	
10+ Nodes	8,291	21.8	1.35 (1.06, 1.72)		1.41 (1.09, 1.82)	
Death[a]	19,082	19.8		0.08		0.21
0 Nodes	6,154	23.4	*Reference*		*Reference*	
1-4 Nodes	1,854	20.5	0.87 (0.61, 1.25)		0.79 (0.55, 1.14)	
5-9 Nodes	2,758	16.7	0.71 (0.51, 0.99)		0.72 (0.51, 1.00)	
10+ Nodes	8,316	18.0	0.77 (0.61, 0.97)		0.87 (0.69, 1.11)	

[a]Adjusted model included Number of Nodes Removed, Year of Diagnosis, Age of Diagnosis, Race/Ethnicity, Tumor Grade, Extent of Primary Tumor, Radiation Treatment, Chemotherapy, and NCI Comorbidity Score; [b]Suppressed due to some LND strata with <11; [c]Adjusted model included Number of Nodes Removed, Age of Diagnosis, Race/Ethnicity, Tumor Grade, Extent of Primary Tumor, Radiation Treatment, Chemotherapy, and NCI Comorbidity Score

Table 4.3. Adjusted Hazard Ratios for Covariates on Outcomes of Interest

	Lymphedema[a]	Hemorrhage[a]	Ileus[b]	Infection[a]	Thrombosis[a]	Death[a]
	p-value Adjusted HR (95% CI)	p-value Adjusted HR (95% CI)	p-value Adjusted HR (95% CI)	p-value Adjusted HR (95% CI)	p-value Adjusted HR (95% CI)	p-value Adjusted HR (95% CI)
Nodes Removed	p=0.12	p=0.26	p=0.001	p<0.001	p=0.01	p=0.21
0	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
1-4	0.67 (0.30, 1.53)	0.69 (0.44, 1.08)	1.49 (1.10, 2.01)	1.25 (0.94, 1.67)	1.09 (0.74, 1.62)	0.79 (0.55, 1.14)
5-9	1.17 (0.65, 2.11)	0.74 (0.51, 1.09)	1.19 (0.89, 1.58)	1.37 (1.07, 1.75)	0.89 (0.61, 1.29)	0.72 (0.51, 1.00)
10+	1.47 (0.95, 2.28)	0.87 (0.67, 1.14)	1.53 (1.24, 1.90)	1.52 (1.25, 1.83)	1.41 (1.09, 1.82)	0.87 (0.69, 1.11)
Age	p=0.01	p=0.56	p<0.001	p=0.05	p=0.14	p<0.001
66-69 years	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
70-74 years	1.54 (0.92, 2.56)	1.12 (0.83, 1.50)	1.02 (0.80, 1.29)	0.83 (0.69, 1.01)	1.09 (0.82, 1.44)	1.11 (0.80, 1.53)
75-79 years	2.21 (1.31, 3.73)	1.15 (0.82, 1.60)	1.45 (1.14, 1.84)	0.88 (0.71, 1.08)	1.19 (0.88, 1.63)	1.61 (1.17, 2.23)
80-84 years	2.46 (1.36, 4.44)	1.37 (0.95, 1.98)	1.62 (1.24, 2.12)	0.85 (0.66, 1.09)	1.23 (0.87, 1.75)	2.14 (1.54, 2.98)
85+ years	2.64 (1.33, 5.24)	1.03 (0.62, 1.69)	1.87 (1.36, 2.55)	0.60 (0.42, 0.86)	1.64 (1.12, 2.42)	2.57 (1.81, 3.64)
Year of Diagnosis	p=0.02	p=0.53	--	p<0.001	p<0.001	p=0.01
2004	*Reference*	*Reference*		*Reference*	*Reference*	*Reference*
2005	0.93 (0.06, 14.9)	1.55 (0.76, 3.17)		0.97 (0.62, 1.50)	0.46 (0.24, 0.83)	0.84 (0.51, 1.38)
2006	7.57 (0.97, 59.3)	1.85 (0.93, 3.67)		2.08 (1.43, 3.01)	0.95 (0.60, 1.53)	1.00 (0.62, 1.59)
2007	5.95 (0.74, 47.7)	1.42 (0.69, 2.91)		1.43 (0.96, 2.12)	0.93 (0.58, 1.50)	0.63 (0.37, 1.07)
2008	6.85 (0.87, 54.2)	1.92 (0.97, 3.81)		1.44 (0.97, 2.12)	1.03 (0.65, 1.64)	0.84 (0.52, 1.37)
2009	4.78 (0.59, 38.9)	2.02 (1.04, 3.95)		0.95 (0.63, 1.44)	0.83 (0.52, 1.33)	0.69 (0.42, 1.12)
2010	5.93 (0.75, 47.0)	1.14 (0.55, 2.35)		1.46 (1.00, 2.14)	0.58 (0.35, 0.97)	0.82 (0.51, 1.31)
2011	5.19 (0.65, 41.6)	1.60 (0.81, 3.16)		0.91 (0.60, 1.37)	0.27 (0.15, 0.51)	0.50 (0.30, 0.85)
2012	7.50 (0.97, 57.9)	1.85 (0.95, 3.62)		0.86 (0.57, 1.30)	0.49 (0.29, 0.83)	0.43 (0.25, 0.74)
2013	12.8 (1.72, 95.9)	1.73 (0.88, 3.40)		0.78 (0.51, 1.19)	0.40 (0.23, 0.70)	0.63 (0.38, 1.03)
2014	12.3 (1.64, 91.7)	1.34 (0.66, 2.69)		0.70 (0.46, 1.07)	0.52 (0.31, 0.88)	0.59 (0.36, 0.99)

2015	9.90 (1.31, 75.2)	1.68 (0.85, 3.32)		0.49 (0.31, 0.78)	0.58 (0.35, 0.96)	0.47 (0.28, 0.80)
Race/Ethnicity	p=0.59	p=0.10	p=0.18	p<0.001	p=0.20	p=0.09
White, Non-Hisp.	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Black, Non-Hisp.	1.30 (0.68, 2.52)	1.30 (0.85, 1.99)	1.27 (0.92, 1.74)	1.41 (1.08, 1.84)	1.28 (0.86, 1.90)	1.53 (1.07, 2.18)
Hispanic/Latino	0.61 (0.25, 1.51)	0.57 (0.31, 1.04)	0.84 (0.57, 1.22)	1.47 (1.08, 1.84)	1.17 (0.77, 1.77)	1.28 (0.86, 1.91)
Other/Unknown	0.93 (0.38, 2.30)	0.71 (0.36, 1.37)	0.73 (0.45, 1.19)	0.63 (0.40, 1.01)	0.56 (0.28, 1.14)	1.02 (0.58, 1.78)
Tumor Grade	p=0.72	p=0.56	p=0.36	p=0.01	p=0.52	p<0.001
Grade 1	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Grade 2	0.92 (0.57, 1.49)	0.93 (0.71, 1.24)	1.04 (0.84, 1.29)	1.29 (1.07, 1.55)	1.11 (0.85, 1.45)	1.43 (1.07, 1.91)
Grade 3	1.13 (0.65, 1.96)	0.91 (0.63, 1.30)	1.21 (0.94, 1.56)	1.35 (1.07, 1.70)	1.27 (0.92, 1.74)	2.75 (2.03, 3.72)
Unknown	1.22 (0.74, 2.01)	0.76 (0.53, 1.10)	0.95 (0.73, 1.24)	1.36 (1.07, 1.73)	1.16 (0.83, 1.63)	1.63 (1.15, 2.32)
Size of Tumor	p=0.40	p=0.20	p<0.001	p=0.04	p<0.001	p<0.001
T1a	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
T1b	1.15 (0.65, 2.05)	0.77 (0.55, 1.08)	1.05 (0.80, 1.37)	1.13 (0.90, 1.43)	0.95 (0.68, 1.32)	1.13 (0.77, 1.65)
T1c	1.09 (0.57, 2.09)	1.15 (0.79, 1.68)	1.22 (0.91, 1.65)	1.43 (1.10, 1.85)	1.21 (0.83, 1.75)	1.88 (1.26, 2.81)
T2a	0.96 (0.32, 2.91)	1.14 (0.63, 2.09)	1.57 (1.01, 2.43)	1.27 (0.83, 1.94)	1.61 (0.93, 2.78)	2.49 (1.41, 4.41)
T2b	1.38 (0.57, 2.09)	1.25 (0.72, 2.17)	1.43 (0.93, 2.19)	1.28 (0.87, 1.90)	1.49 (0.88, 2.52)	3.27 (1.98, 5.42)
T3a	2.26 (1.09, 4.67)	1.06 (0.63, 1.78)	1.32 (0.89, 1.95)	1.27 (0.89, 1.81)	2.01 (1.29, 3.13)	4.77 (3.10, 7.33)
T3b	1.50 (0.42, 5.38)	1.61 (0.74, 3.51)	2.32 (1.35, 4.00)	2.16 (1.29, 3.61)	2.73 (1.38, 5.40)	9.96 (5.88, 16.9)
T4	<0.01(<0.001,>100)	0.56 (0.08, 4.12)	7.50 (4.38, 12.9)	1.93 (0.84, 4.47)	5.38 (2.48, 11.6)	18.7 (10.8, 32.3)
Chemotherapy	p=0.84	p=0.07	p=0.16	p=0.36	p=0.88	p<0.001
No	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Yes	1.06 (0.58, 1.93)	1.43 (0.70, 3.25)	1.22 (0.92, 1.62)	1.13 (0.87, 1.46)	0.97 (0.67, 1.41)	0.42 (0.28, 0.65)
Radiation	p=0.63	p=0.53	p=0.002	p<0.001	p<0.001	p<0.001
No	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Yes	0.92 (0.60, 1.41)	0.97 (0.73, 1.29)	0.69 (0.56, 0.85)	0.70 (0.58, 0.84)	0.59 (0.45, 0.77)	0.20 (0.15, 0.28)
Unknown	1.52 (0.54, 4.25)	1.51 (0.70, 3.25)	1.05 (0.58, 1.93)	1.66 (1.04, 2.65)	0.99 (0.46, 2.13)	1.08 (0.60, 1.95)

NCI Comorbidity Score	p=0.003	p=0.56	p<0.001	P<0.001	p<0.001	p<0.001
0	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
1	2.04 (1.30, 3.21)	1.08 (0.74, 1.58)	1.43 (1.11, 1.84)	1.49 (1.19, 1.87)	1.74 (1.29, 2.35)	2.42 (1.85, 3.16)
2+	2.06 (0.99, 4.27)	1.35 (0.77, 2.36)	1.86 (1.29, 2.69)	1.56 (1.09, 2.25)	2.14 (1.38, 3.34)	3.47 (2.50, 4.83)

[a]Adjusted model included Number of Nodes Removed, Year of Diagnosis, Age of Diagnosis, Race/Ethnicity, Tumor Grade, Extent of Primary Tumor, Radiation Treatment, Chemotherapy, and NCI Comorbidity Score; [b]Adjusted model included Number of Nodes Removed, Age of Diagnosis, Race/Ethnicity, Tumor Grade, Extent of Primary Tumor, Radiation Treatment, Chemotherapy, and NCI Comorbidity Score

4.5. Discussion

In the context of the ongoing uncertainty regarding extent of LND required for optimal endometrial cancer outcomes, research typically focuses on impact on cancer recurrence and survival outcomes [6,7,14,15,87,104–106], which leaves patients and providers with an incomplete picture of the benefit-harm balance of LND. To provide clarification on complications that may influence LND use in patients without distant metastasis, this study utilized a dataset inclusive of more than 19,000 women with endometrial cancer to examine the association of extent of LND with 7 post-surgical complications of interest: lymphedema, lymphocele, hemorrhage, ileus, infection, thrombosis, and all-cause death. Events of interest were quantified as the number of events per 1000 women over a 6-month post-surgical timeframe. Adjusted HRs were used to compare events by extent of LND. In adjusted analyses, within 6 months post-surgery, a greater number of lymph nodes removed was associated with greater risk of ileus, infection, and thrombosis, but not lymphedema, hemorrhage, or death.

Evaluation of potential LND harms is generally limited to studies with few events of interest due to sample size limitations, thus precluding statistical comparisons. The exception to this is lymphedema, which impacted a range of 0.2%-13% of women in RCTs[6,7]. Recent observational studies have found an incidence ranging from 3% to 16% of patients[107,108]. The cumulative hazard in this study shows approximately 7 out of 1,000 women per 6-month post-operative period experience lymphedema, with another 4 per 1,000 experiencing lymphocele. While these rates suggest a lower risk in the current study compared to others, it must be noted that the use of claims data may result in the omission of less severe cases for which medical intervention was not pursued. For example, Wedin et al.[108] found that women were less likely to identify themselves as having lymphedema compared to providers' assessments. As such, the current claims study is likely inclusive of lymphedema cases for which severity prompted affected women to seek medical attention. In addition, the 6-month follow-up period specified in this analysis does not allow for any cases diagnosed after this study's timeframe. Yoshihara et

al.[109] found that as many as 60% of cases of long-term lymphedema develop more than 1 year after endometrial cancer surgery. As such, it is possible the cases identified in this study represent fewer than 40% of cases that may eventually be diagnosed. Finally, it is possible that the use of SEER diagnosis date to impute surgery date resulted in later imputed surgical dates than if a Medicare diagnosis date had been used[110]. If this were the case, early post-operative complications such as lymphedema may have been missed upon follow-up.

Two RCTs concluded that women who have undergone standard surgery plus systematic LND experienced greater frequency of ileus and thrombosis compared to women who have undergone standard surgery alone, although sample sizes were insufficient to determine statistical significance[6,7]. In those studies, LND impact on other patient outcomes of interest included fewer than 5 of each of the events among study groups, thus limiting any conclusions on LND-related risk. With its large dataset, the present study found the extent of LND was significantly associated with ileus, infection, and thrombosis with the 10+ nodes group showing the greatest risk compared to those with 0 nodes removed. This provides support to the idea of limiting the number of lymph nodes removed in order to reduce risk of ileus, infection, and thrombosis among women undergoing surgical management for endometrial cancer. Also, as no significant association was found in this study between extent of LND and death 6 months post-surgery, reduction in the number of lymph nodes may result in an overall reduction of post-surgical complications without an increased risk of death in the short-term. Evolving professional guidelines regarding the use of SLND in this population reflect an increasing acceptance of limiting the number of nodes removed when possible[4], and this study adds further support to this position.

Several limitations to this study exist. First, the use of claims data may have led to the omission of less severe cases for the outcomes of interest, as patients may not have sought medical attention. As such, events may be underreported. In addition, the patient population in this study consisted of women aged 66+ years, and as such, the findings may not be generalizable

to younger populations. Further, the 6-month follow-up period may not have been sufficient to capture longer-term surgery-related complications, such as late-onset lymphedema, and cancer recurrence within this short timeframe also was not assessed. Additionally, there may have been confounding by indication, as several variables were not available to include in the analysis, such as body mass index and lymphovascular space invasion, and their inclusion in the statistical model may have altered significance of the results for other covariates. Similarly, data on surgical approach (open versus laparoscopic) were unavailable within the included time period, and for this reason, the current study does not have the ability to determine if there is a difference in surgical morbidity as measured between the open and laparoscopic procedures. As an increase in utilization of minimally invasive procedures occurred over the time period, from 10% of all endometrial cancer hysterectomy and staging surgeries in 2004 to nearly 70% in 2012[111], lack of control for these changes is a limitation. However, in controlling for year of diagnosis, some of the resulting variation due to shifts in approach may be lessened. Finally, date of surgery was imputed for approximately 40% of the patient population. If imputed date was far from the actual surgical date, cases for outcomes may have fallen outside the imputed 6-month timeframe for outcome assessment. For example, as the median time from date of diagnosis to confirmed hysterectomy date was 38 days, it is possible complications occurring the last month of the 6-month period were missed, thus undercounting the outcomes of interest.

4.6. Conclusion

Despite its limitations, this large study allowed for investigation of the risk of 7 post-surgical complications in patients with endometrial cancer. Through the use of a large, linked registry and claims dataset, sufficient numbers of patients were available to compare impact of extent of LND for 6 of the 7 outcomes of interest, thereby contributing to a more thorough understanding of the benefit-harm balance involved in the utilization of LND in these women. As such, patients and providers alike may have a clearer understanding of the potential risks associated with LND to incorporate into their disease management strategies.

CHAPTER 5

CONCLUSIONS

Utilizing the large registry-based SEER and SEER-Medicare datasets, this research consisted of three retrospective cohort studies aimed at evaluating the utilization of LND/SLND and their related outcomes among women with endometrial endometrioid adenocarcinoma. The first two studies addressed LND/SLND utilization patterns and found significant temporal and geographic variation in the use of LND in the U.S. from 2004 to 2015. They also pointed to an emerging but limited use of SLND. The third study evaluated the potential impact of variations in the number of lymph nodes removed during endometrial cancer surgery and found that 6-month post-surgical outcomes of ileus, infection, and thrombosis occurred at higher rates among women who underwent more extensive LND compared to those with no nodes removed.

Surgical management guidelines have presented a cautious but evolving approach to the use of LND/SLND in the endometrial cancer population over the past decade following two pivotal studies[6,7]. Similar to previous studies[51–53], the research presented here found a significant decline in LND use beginning around 2008, and the present study illustrates this decline continued through 2015 as guidelines evolved toward tailored management strategies. In addition to this continuing LND trend, this research was the first to evaluate SLND trends among women with endometrioid adenocarcinoma, noting that SLND use remained rare through 2015 with only 3.8% of patients undergoing the procedure in 2014-2015. Of note, in 2015, the National Comprehensive Cancer Network's (NCCN) guidelines for uterine neoplasms began advocating a selective and tailored approach to lymphadenectomy for endometrial cancer in order to prevent systematic overtreatment, and the possibility of using sentinel lymph node dissection (SLND) was being investigated[67]. Most recently, NCCN continued to advocate a tailored approach of sentinel lymph node mapping with ultrastaging in patients whose disease appears to be confined

to the uterus[4]. Although an observed increase in frequency was not found to be statistically significant in the current study, future evaluation is warranted as guidelines have continued to evolve since the included study years. This would allow for robust analyses with sufficient power to detect temporal changes in the years since SLND gained more widespread acceptance in clinical guidance. In understanding such patterns of disease management, it is possible develop a clearer context for trends in patient outcomes for a cancer that is affecting an increasing number of women[64].

The present research was the first to evaluate geographic variation in LND and SLND use with a study population that included women with endometrioid adenocarcinoma at lower risk for metastasis, such as those with low-grade tumors or small tumor sizes. Adjusting for relevant clinical factors, LND varied significantly by U.S. Census Division in the SEER dataset between 2004 and 2015, with LND use highest in the southeastern U.S. and lowest in the midwestern states. While this research did not include an analysis on geographic variations in patient outcomes, the geographic variation of LND use noted here is reflective of ongoing debate regarding LND in this patient population, and future research centered on geographic disparities in outcomes is warranted. Despite surgical management recommendations provided by national and international organizations[4,5], real-world clinical usage of LND varies substantially. Much of this variation may be due to incomplete evidence of benefits and harms associated with LND and SLND, inconsistent access to sufficient technology, and differences in provider training and experience. As best practices become clarified, however, it will become essential to target locations that stray from these strategies to address any resultant geographic disparities in patient outcomes, thereby emphasizing equity of treatment regardless of geographic location.

To inform patients and providers of the potential harms of LND based on the number of lymph nodes removed, the investigation into 6-month post-operative complications utilized a linked registry- and claims-based dataset inclusive of more than 19,000 women with endometrioid adenocarcinoma. The use of the extensive SEER-Medicare dataset allowed for

quantification of post-surgical complications that occur only in limited numbers in clinical trials or institution-based studies. Adjusted analyses for the outcomes of lymphedema, hemorrhage, ileus, infection, thrombosis, and all-cause death found that extent of lymph node removal was not associated with 6-month post-surgical lymphedema, hemorrhage, or death. However, compared to removal of 0 nodes, removal of 10+ lymph nodes was significantly associated with increased risks of ileus, infection, and thrombosis. Therefore, should ongoing research find SLND to be effective in identifying cancer spread in endometrioid adenocarcinoma patients, the reduction in removed lymph nodes may translate to fewer patients experiencing these associated complications. Additionally, longer-term studies of these risks would help to determine if and how these risks may change over time. Finally, future observational studies specifically addressing variations in patient outcomes based on clearly defined LND and/or SLND techniques are warranted as this area of disease management evolves.

The three aforementioned studies' strengths included large sample sizes and extensive information on clinical variables related to disease management, such as tumor grade and size. However, variables such as provider specialty, surgical approach (e.g., laparotomy vs. laparoscopy vs. robotic), lymphovascular space invasion (LVSI), and hospital type were not available in the SEER dataset, and their omission may have altered the significance of other included variables. In addition, the claims-based SEER-Medicare dataset utilized in the third study may have excluded women with less severe cases for the outcomes of interest, as patients may not have sought medical attention for milder conditions. As such, events may be underreported. In addition, inclusion of women aged 66+ years only may limit the study's generalizability to younger populations. Finally, the 6-month follow-up period may not have been sufficient to capture longer-term surgery-related complications, so the findings of the study apply only to short-term outcomes.

Despite their limitations, together, these three studies paint a picture of broad variations in endometrial cancer management strategies capable of creating inequitable patient experiences.

Changes over time are reflective of ongoing research into evidence-based practices and the resultant evolving guidelines. Variations across geographies are indicative of the continuing controversy regarding the usefulness of LND and its alternative of SLND, prompting providers to lean heavily on professional judgment and available resources in the absence of clear best practices. As the research presented here found surgical outcomes such as ileus, infection, and thrombosis to differ by number of lymph nodes removed, the observed variations in LND use may translate into disparities in patients' experience of post-operative complications. Should the use of SLND become a viable alternative that can be used consistently nationwide, patients may benefit through decreased risk of complications while still undergoing surgical staging to allow for comprehensive treatment decision-making.

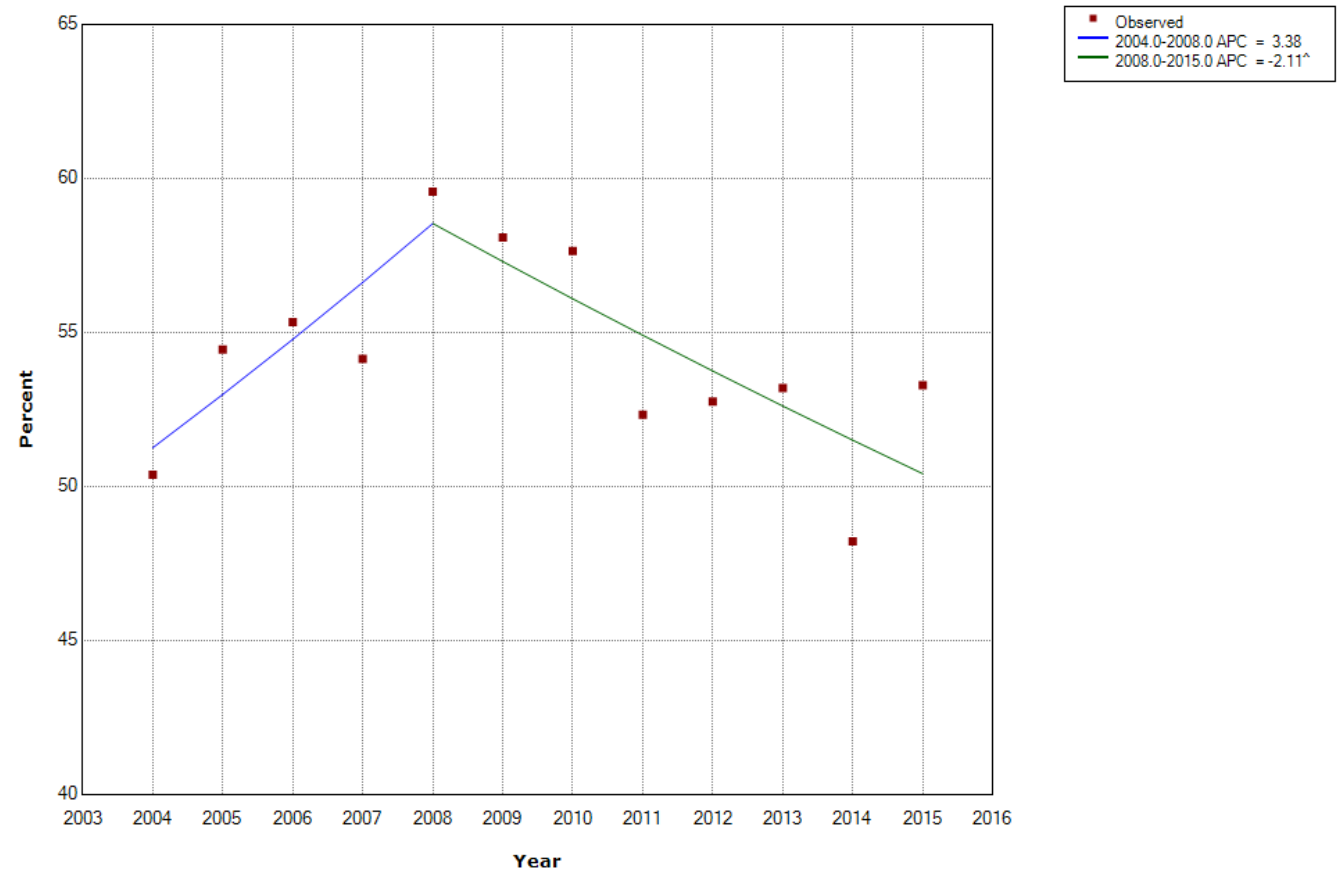
APPENDIX A: Stratified Joinpoint Analyses

1) Supplemental Figures 1a-1f: Stratification by Age Group, 2004-2015

Supplemental Figure 1a. Joinpoint analysis for LND use among patients aged <40 years (n=3,527)

^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 1b. Joinpoint analysis for LND use among patients aged 40-49 years (n=9,443)

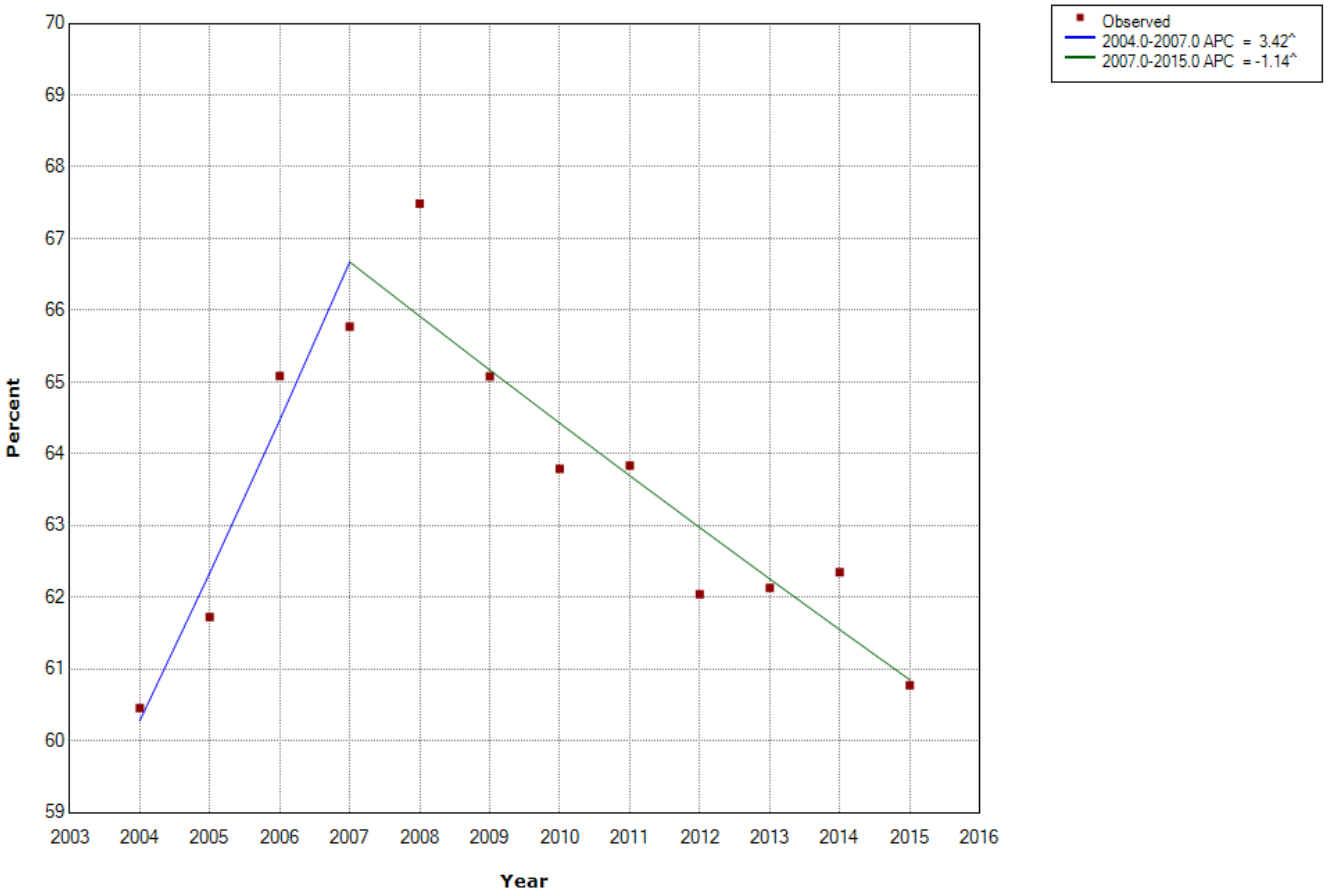


^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 1c. Joinpoint analysis for LND use among patients aged 50-59 years (n=27,680)

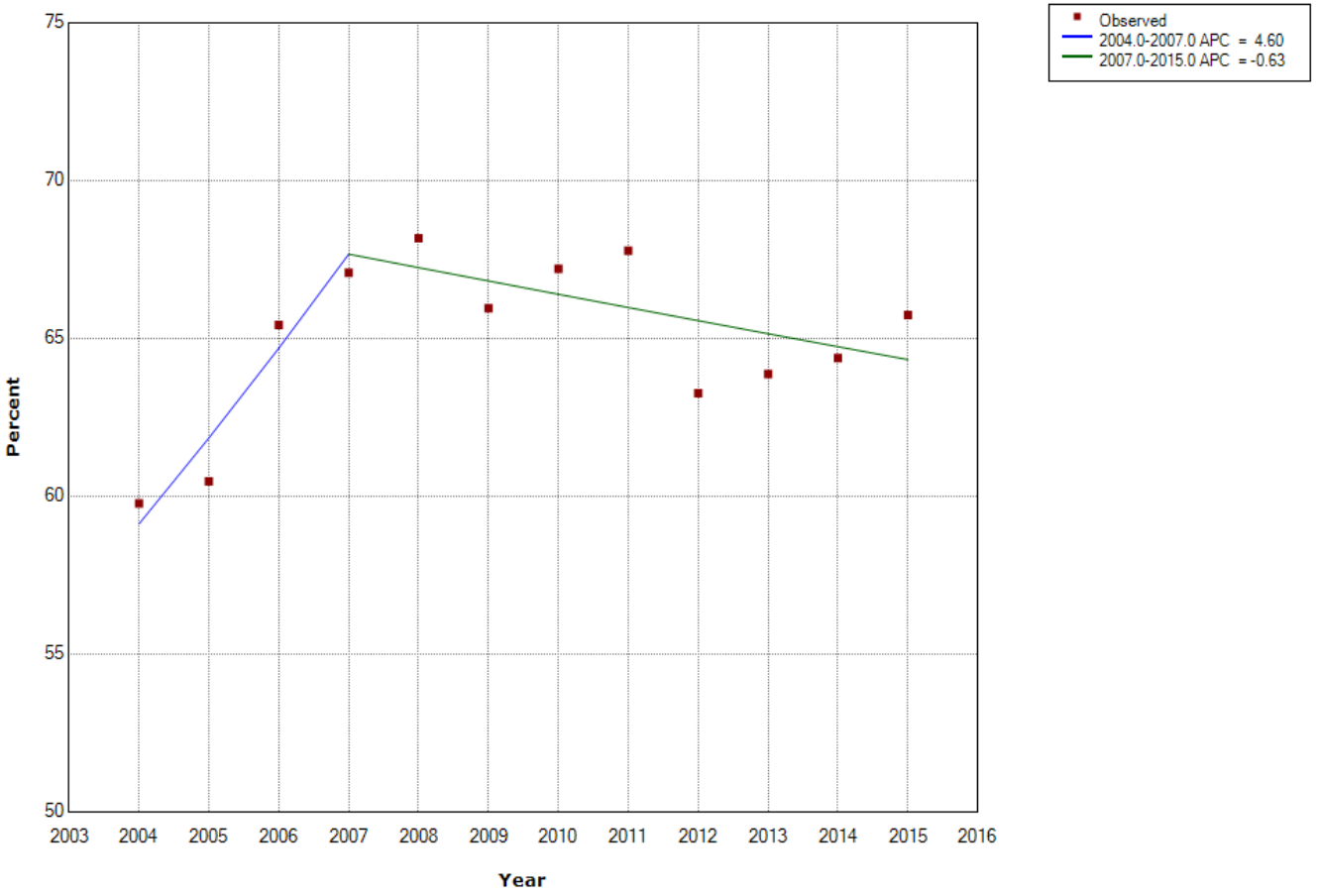
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 1d. Joinpoint analysis for LND use among patients aged 60-69 years (n=28,519)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 1e. Joinpoint analysis for LND use among patients aged 70-79 years (n=14,094)



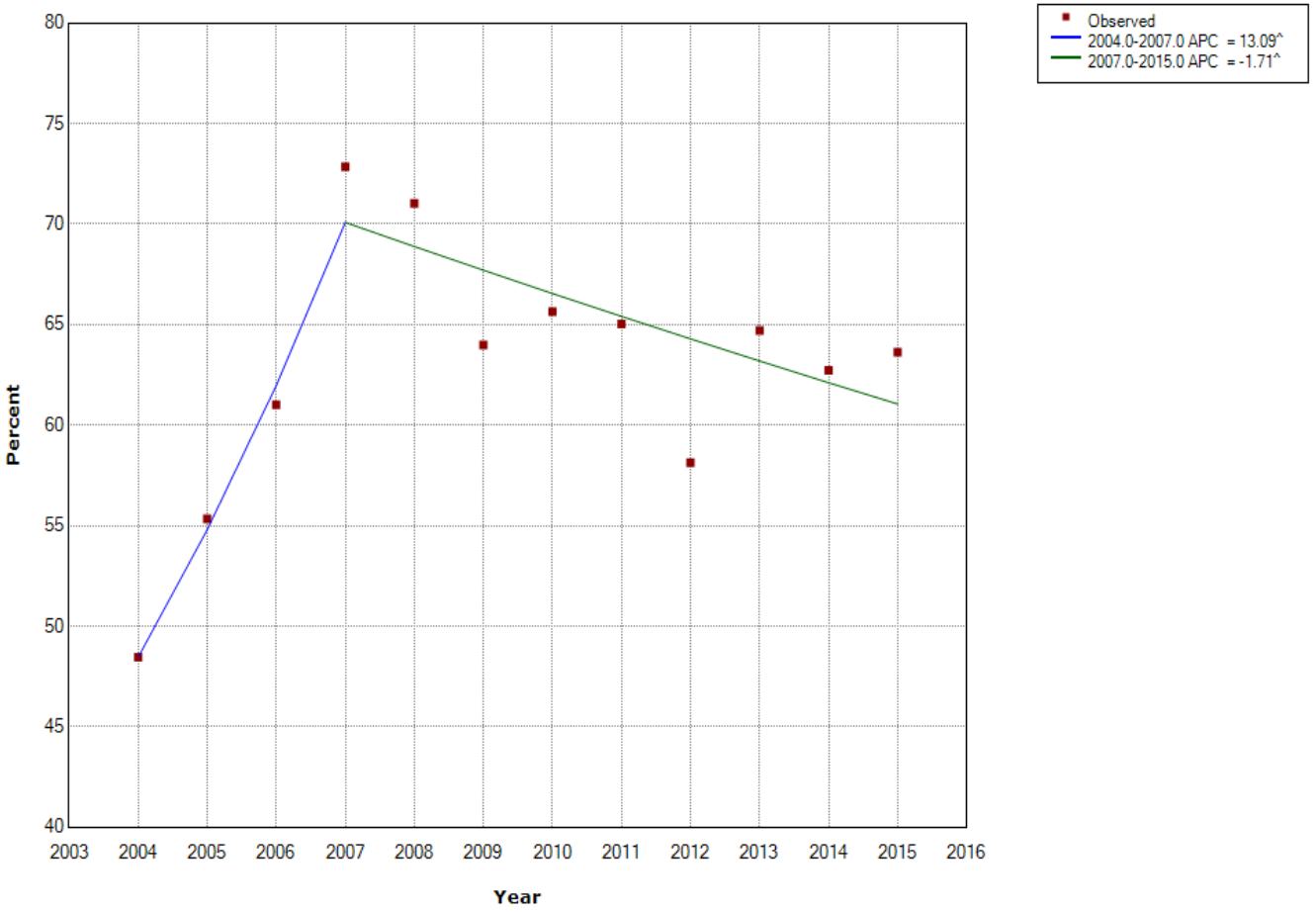
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 1f. Joinpoint analysis for LND use among patients aged 80+ years (n=6,681)

^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

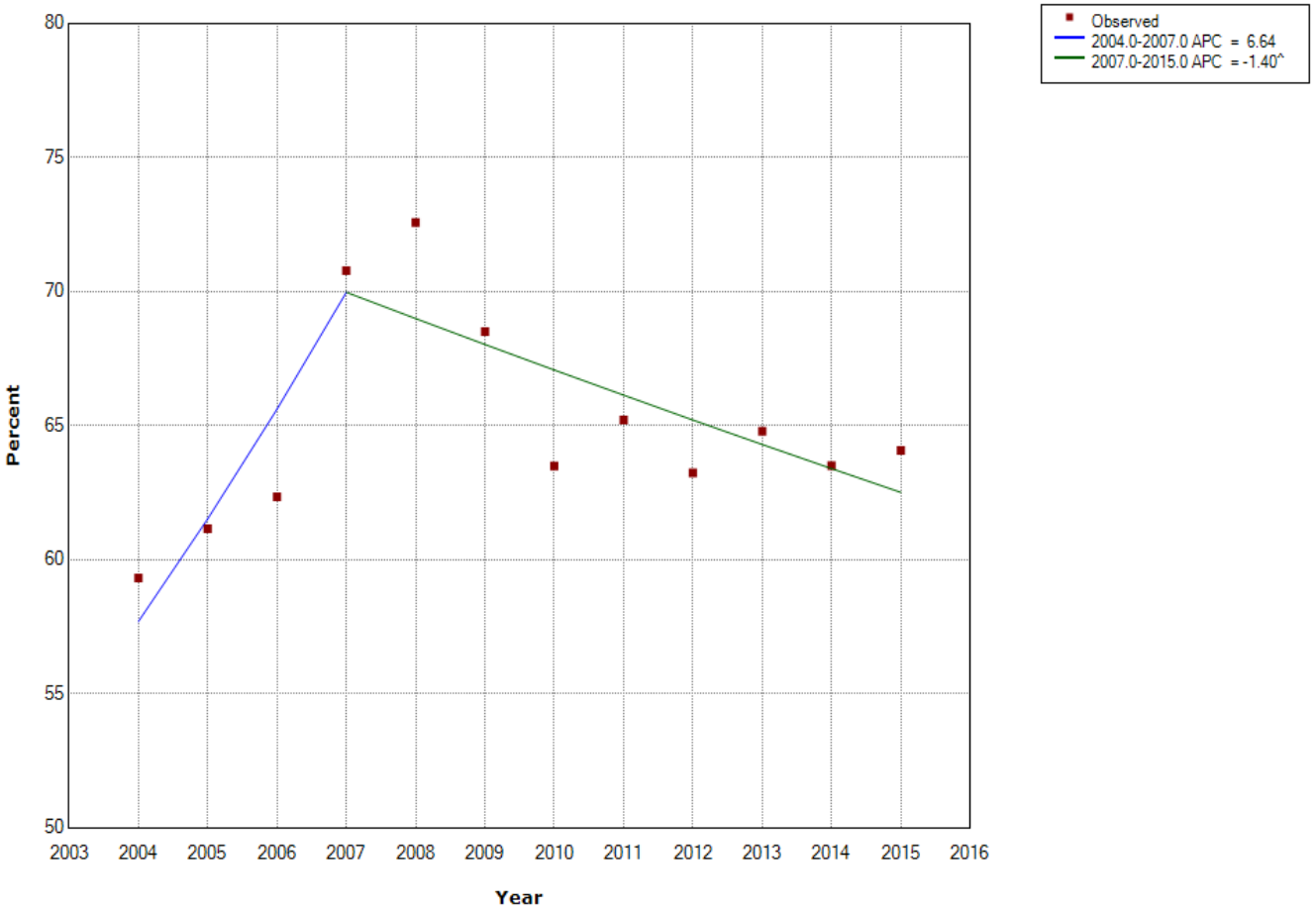
2) Supplemental Figures 2a-2i: Stratification by U.S. Division, 2004-2015

Supplemental Figure 2a: Joinpoint analysis for LND use among patients in New England division (n=4,928)



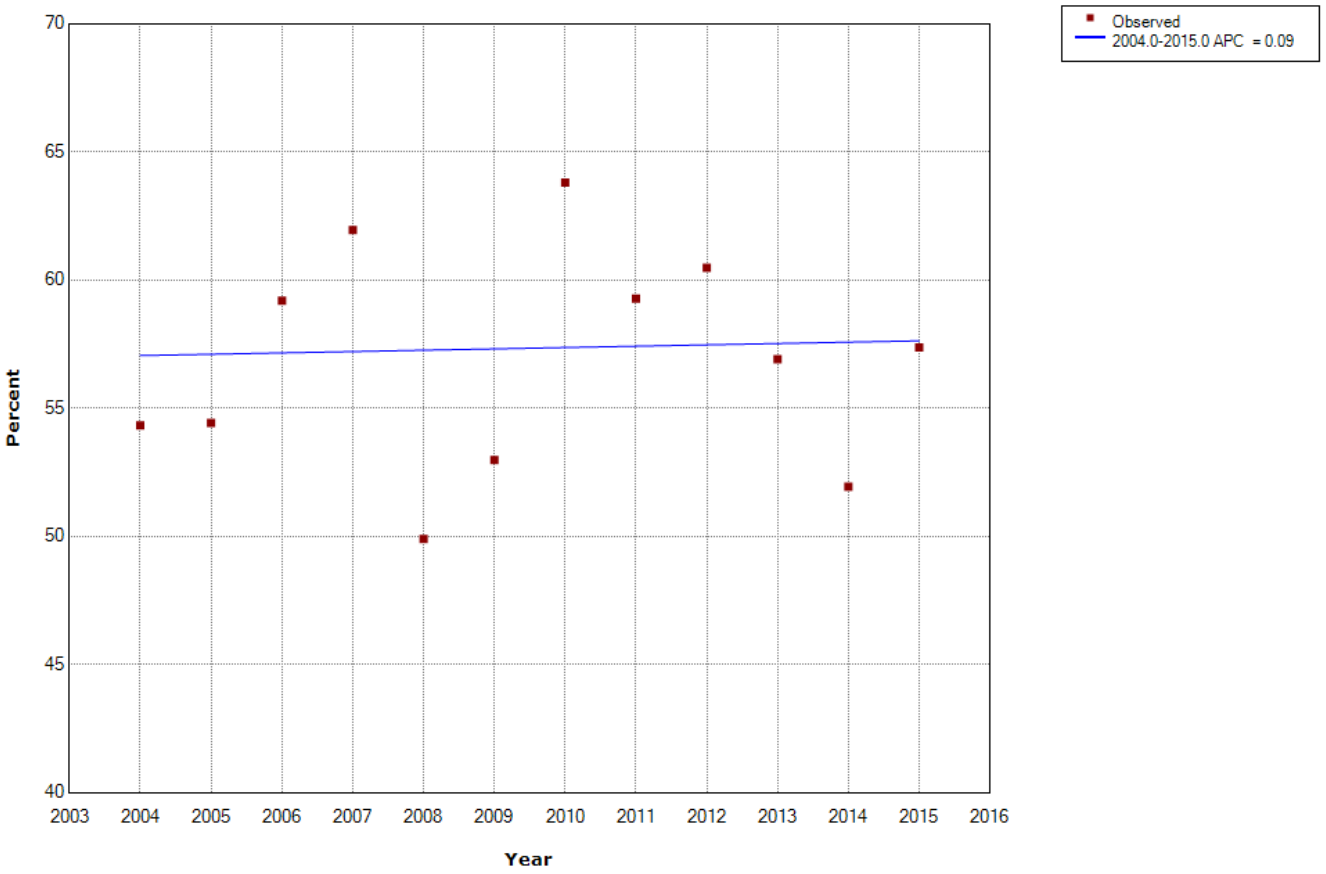
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 2b: Joinpoint analysis for LND use among patients in Mid Atlantic division (n=12,748)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 2c: Joinpoint analysis for LND use among patients in East North Central division (n=5,407)

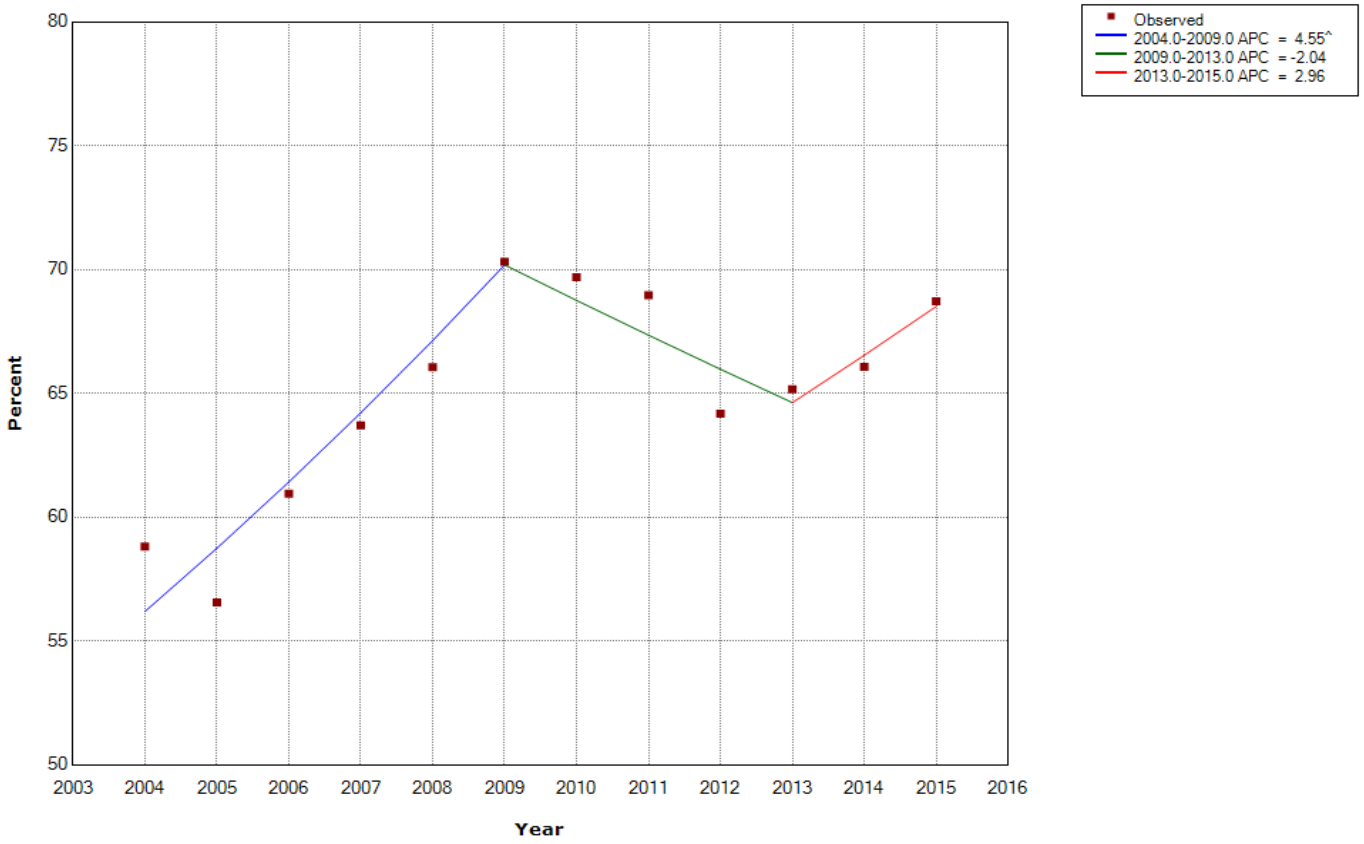


^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 2d: Joinpoint analysis for LND use among patients in West North Central division (n=4,413)

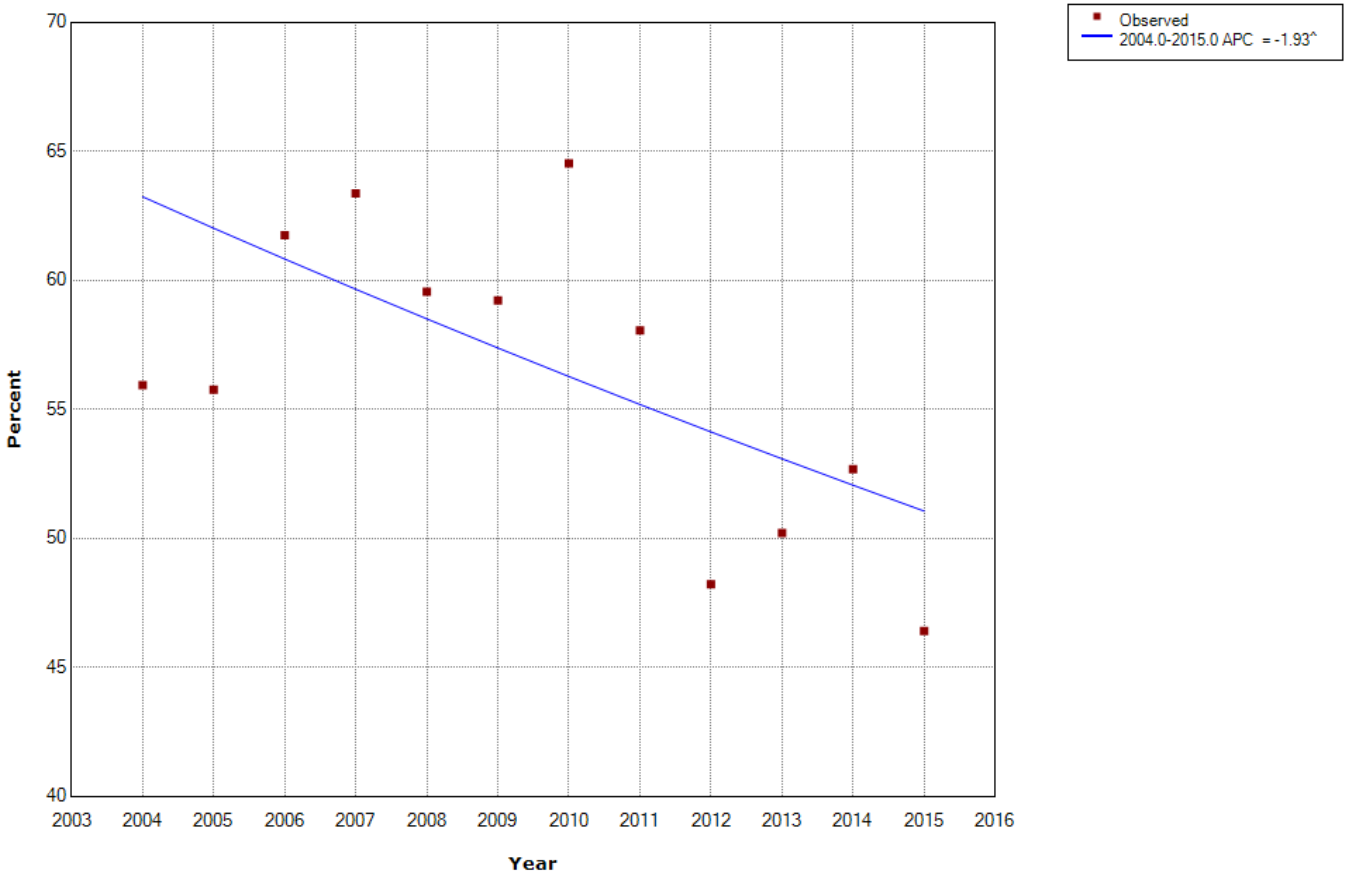
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 2e: Joinpoint analysis for LND use among patients in South Atlantic division (n=7,626)



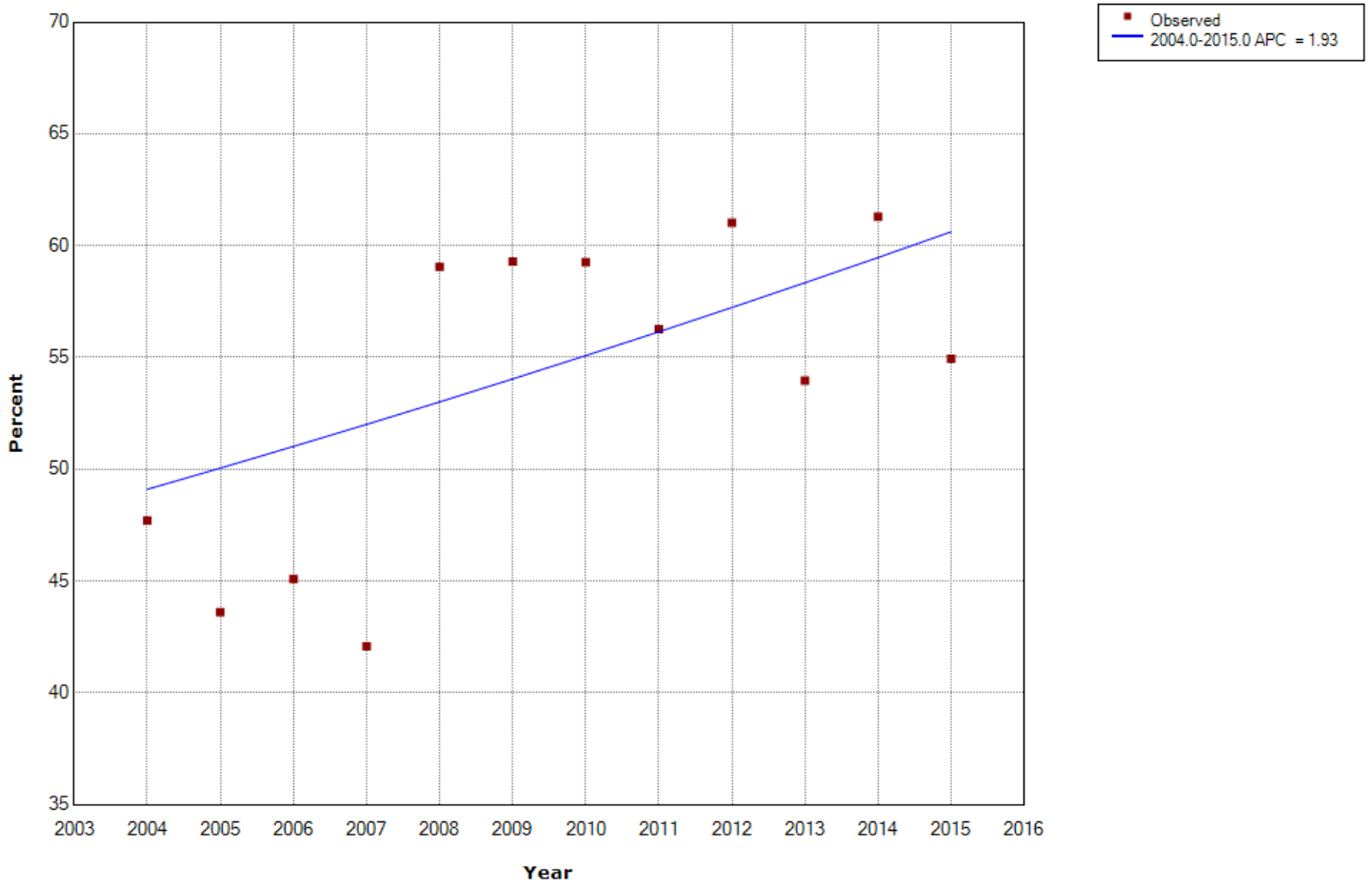
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 2 Joinpoints.

Supplemental Figure 2f: Joinpoint analysis for LND use among patients in East South Central division (n=5,038)



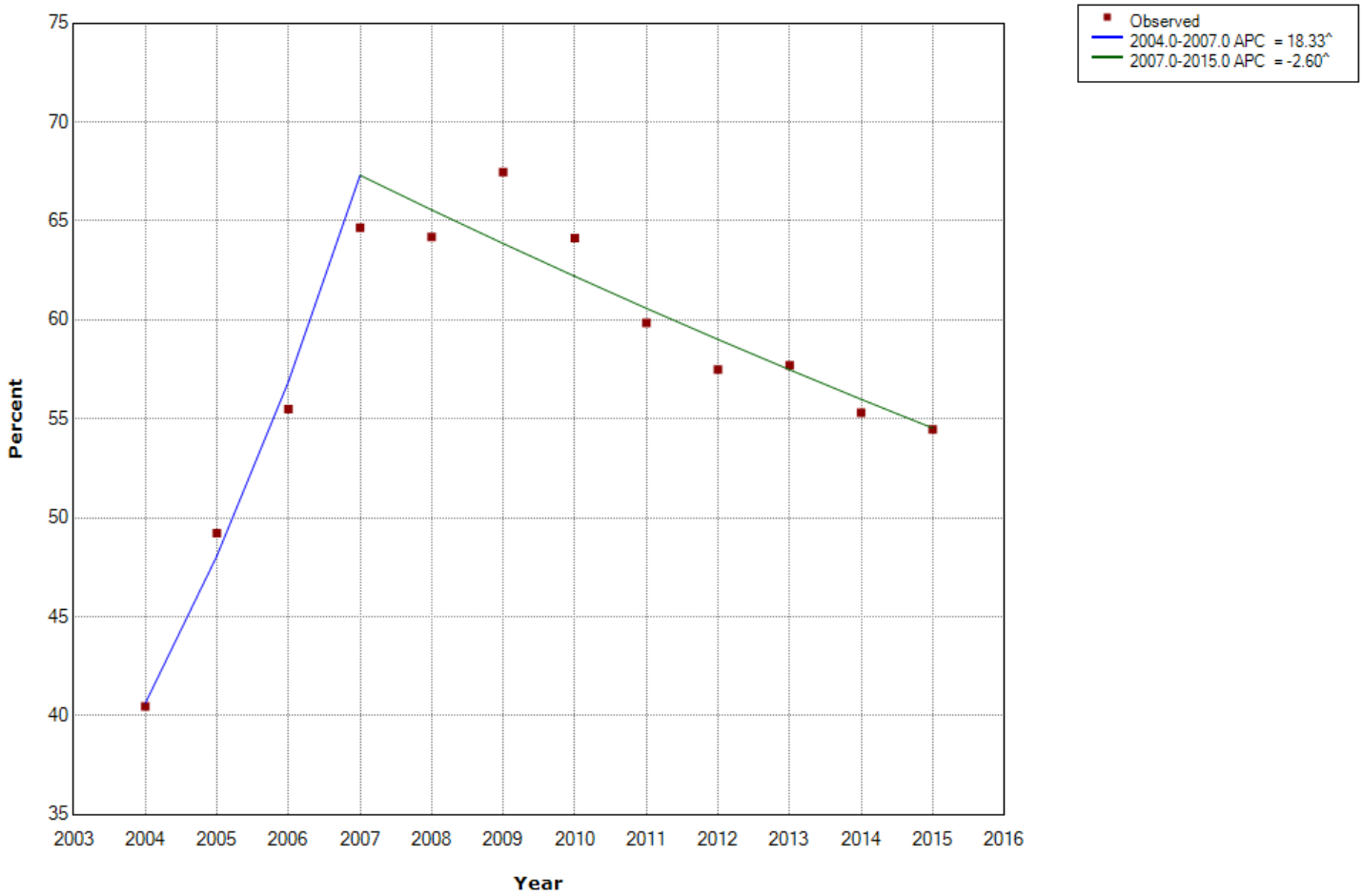
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 2g: Joinpoint analysis for LND use among patients in West South Central division (n=3,253)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 2h: Joinpoint analysis for LND use among patients in Mountain division (n=4,564)



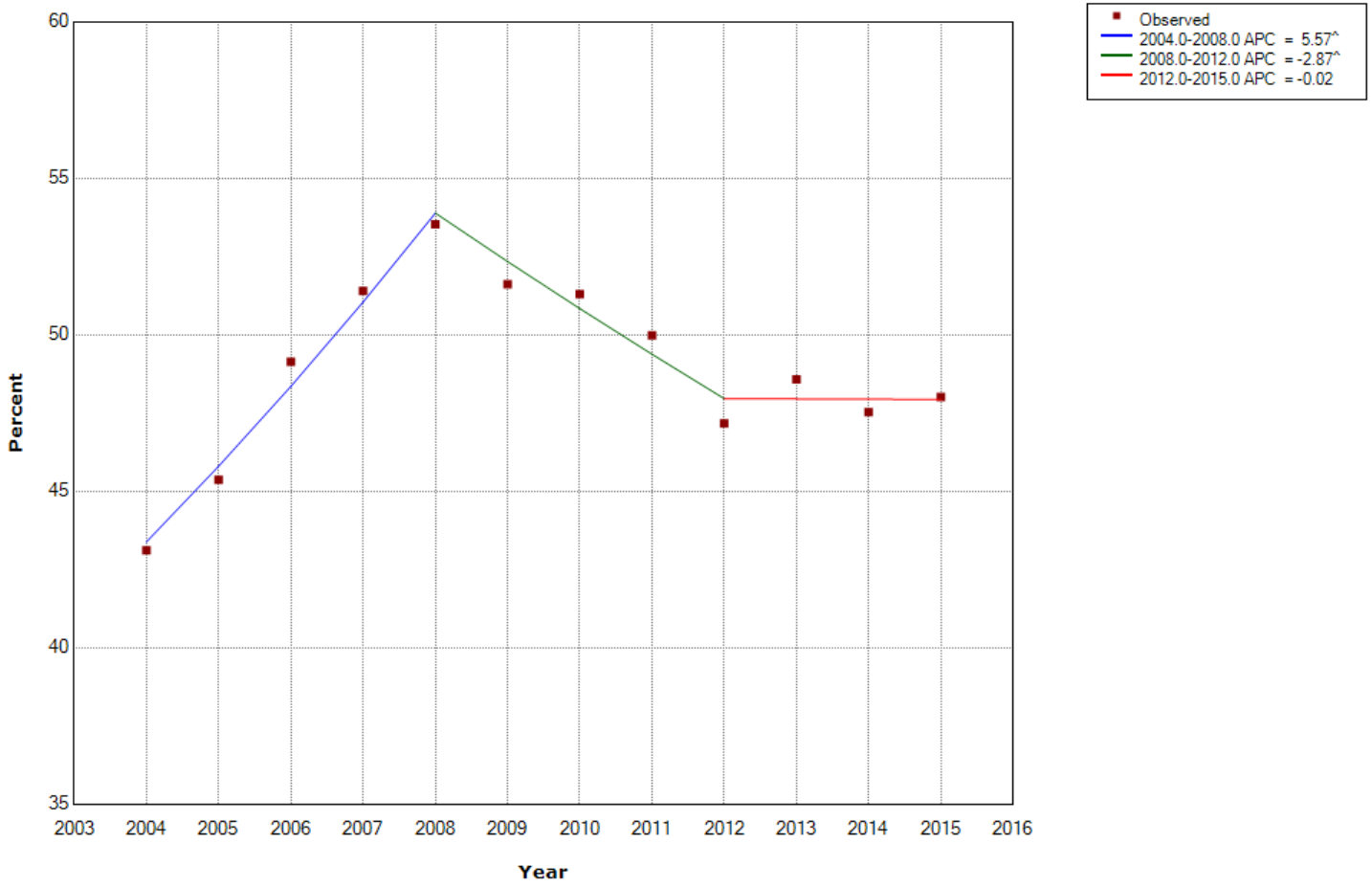
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 2i: Joinpoint analysis for LND use among patients in Pacific division (n=41,531)

^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

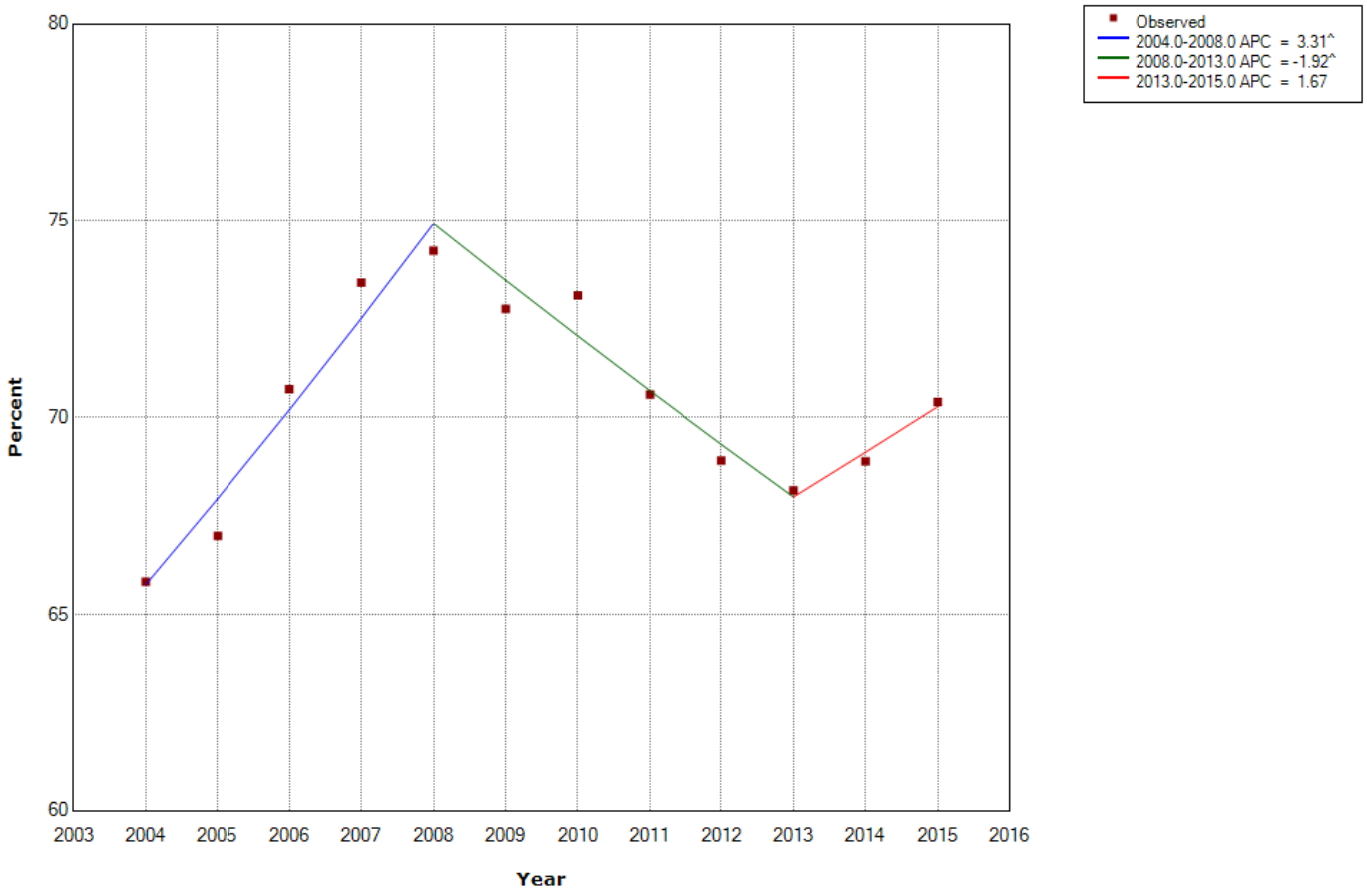
3) Supplemental Figures 3a-3c: Stratification by Grade, 2004-2015

Supplemental Figure 3a: Joinpoint analysis for LND use among patients with grade 1 disease (n=39,614)



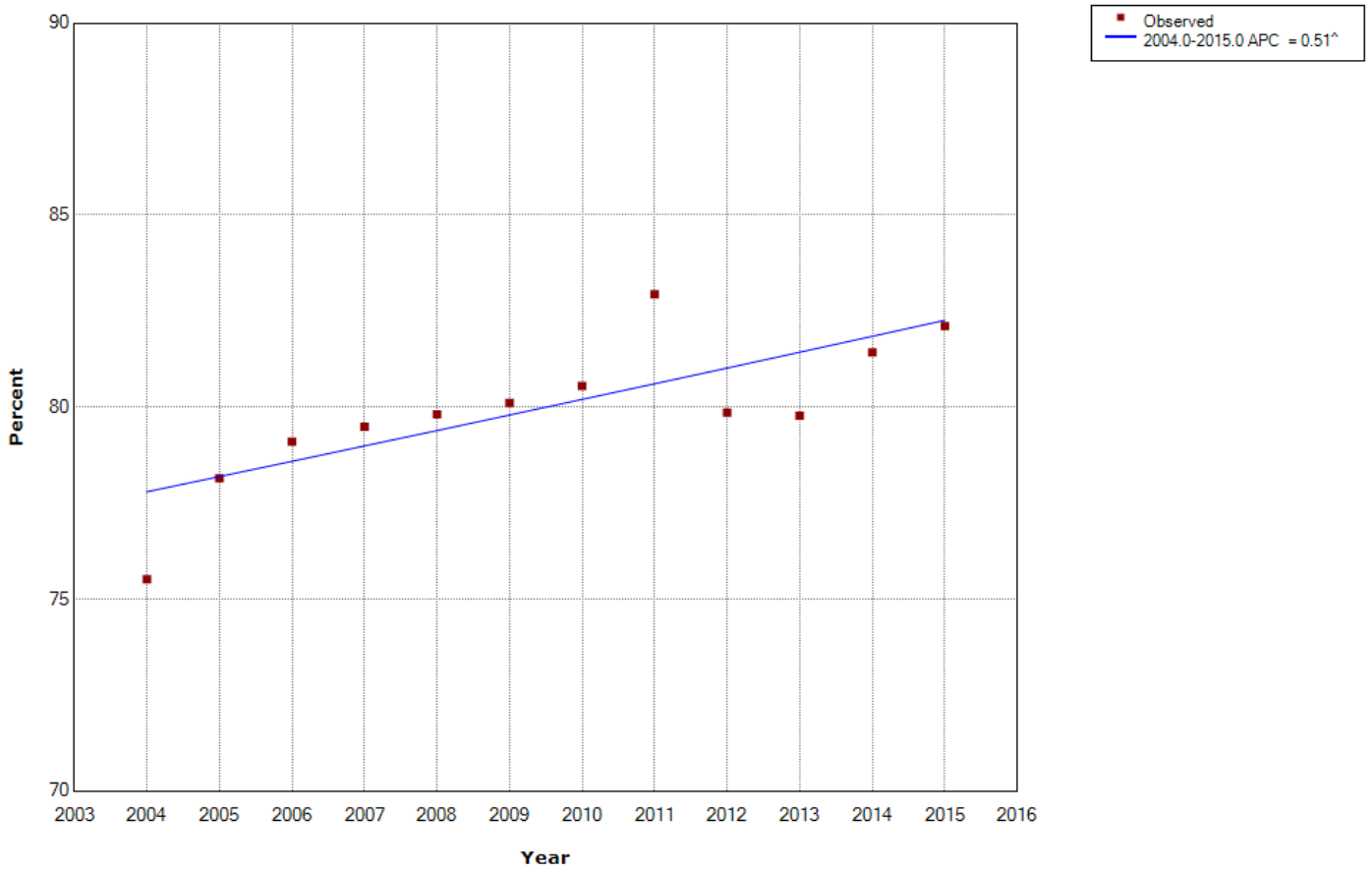
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 2 Joinpoints.

Supplemental Figure 3b: Joinpoint analysis for LND use among patients with grade 2 disease (n=24,263)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 2 Joinpoints.

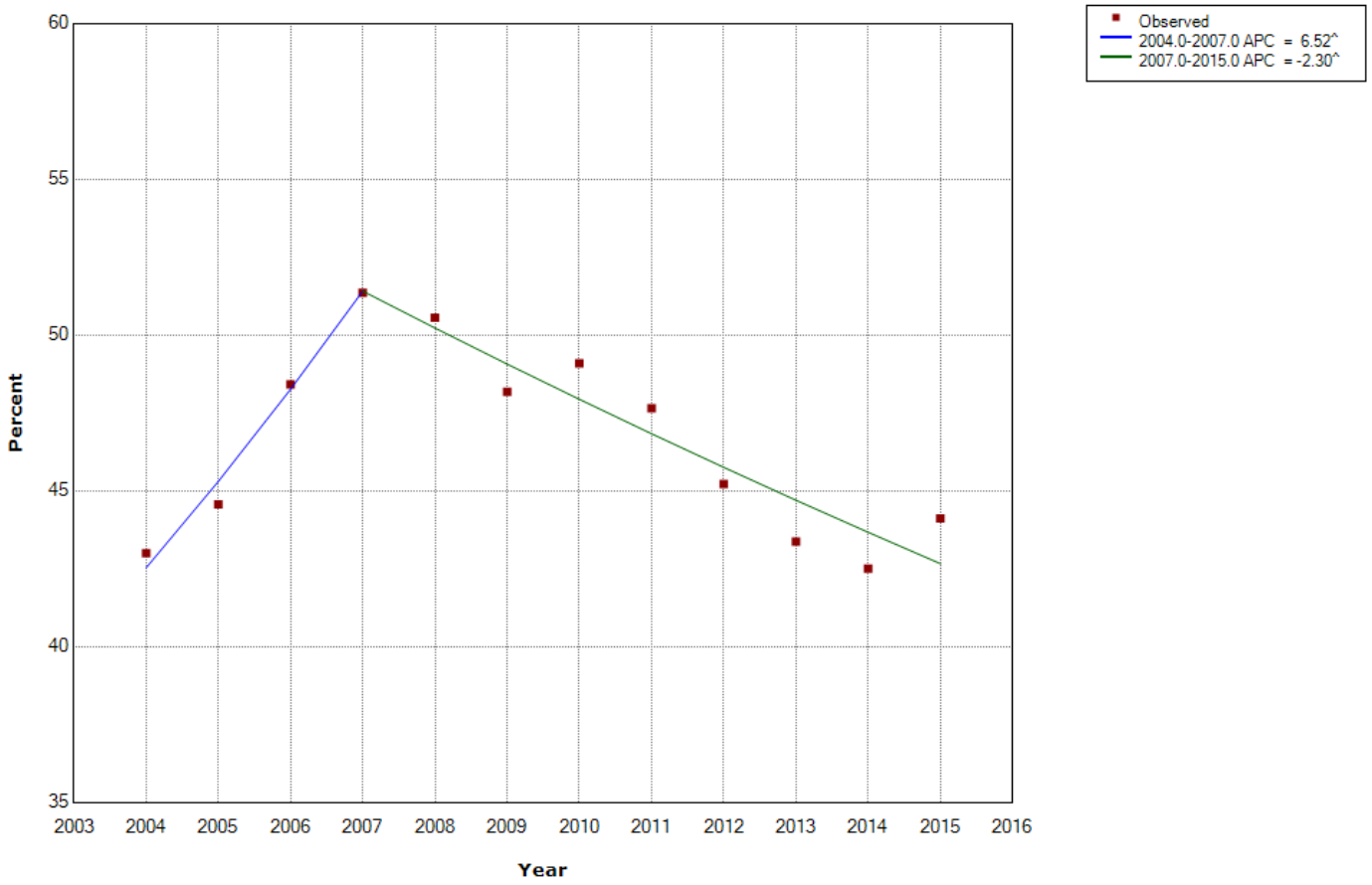
Supplemental Figure 3c: Joinpoint analysis for LND use among patients with grade 3 disease (n=10,111)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

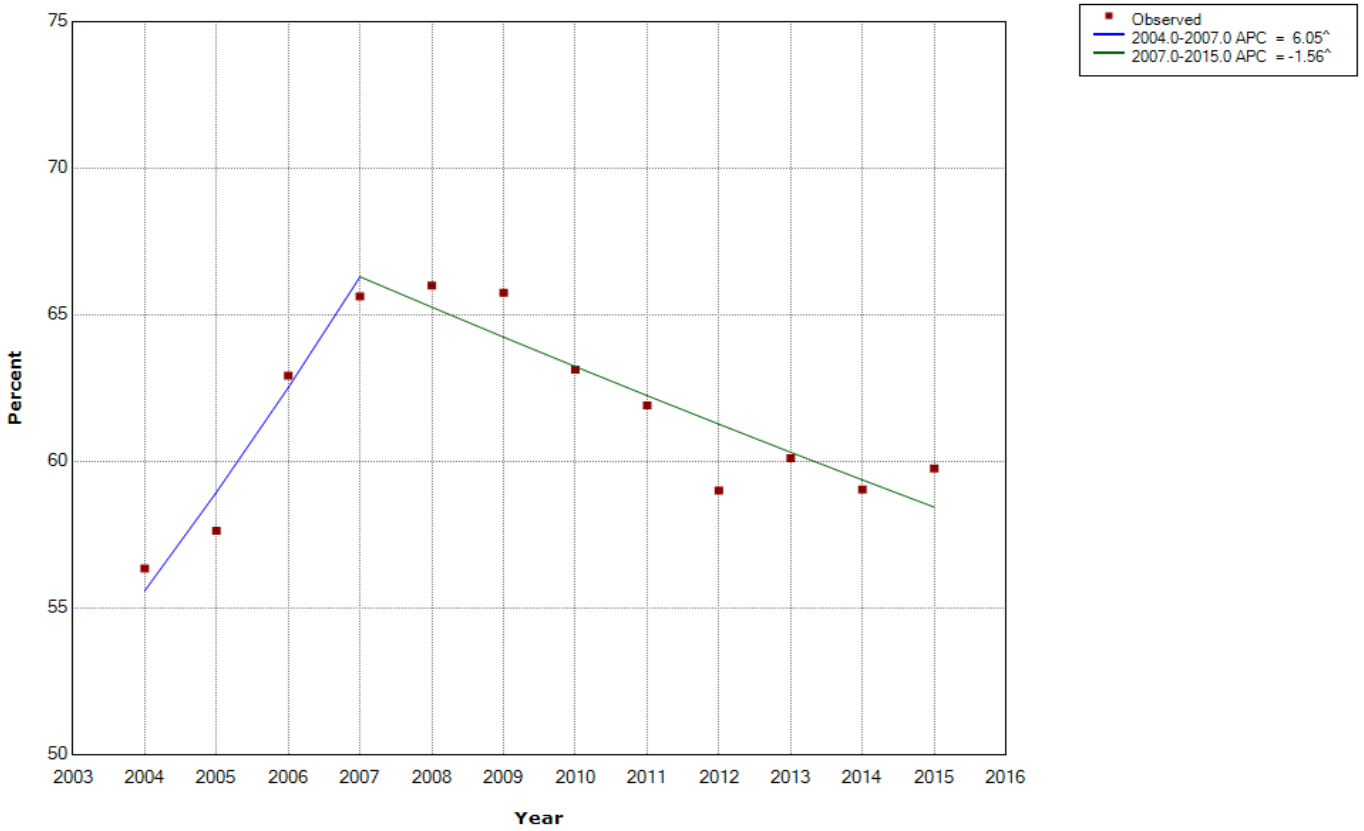
4) Supplemental Figures 4a-4j: Stratification by Size/Extent of Primary Tumor, 2004-2015

Supplemental Figure 4a: Joinpoint analysis for LND use among patients with T1a primary tumor (n=22,309)



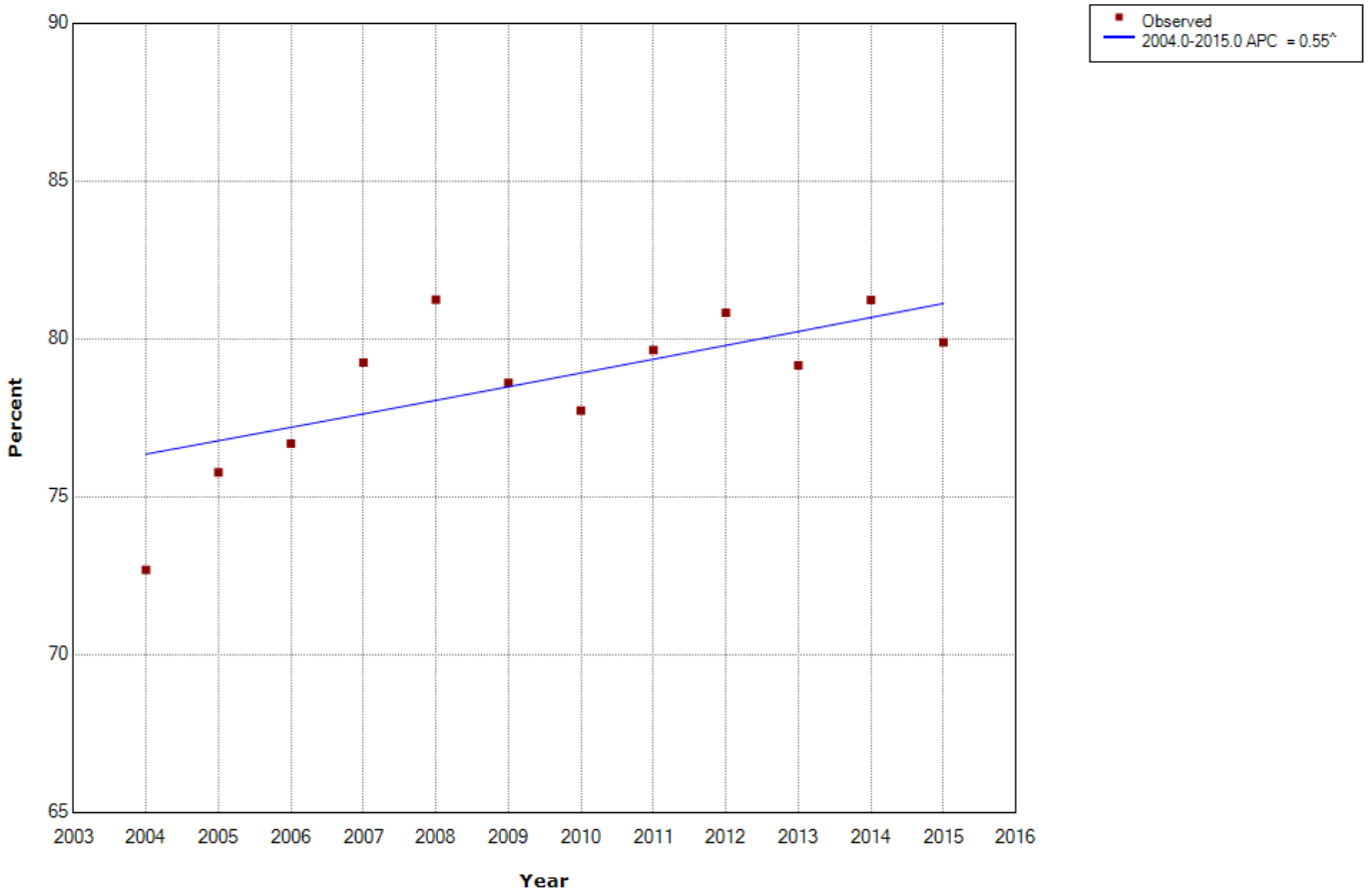
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 4b: Joinpoint analysis for LND use among patients with T1b primary tumor (n=33,407)



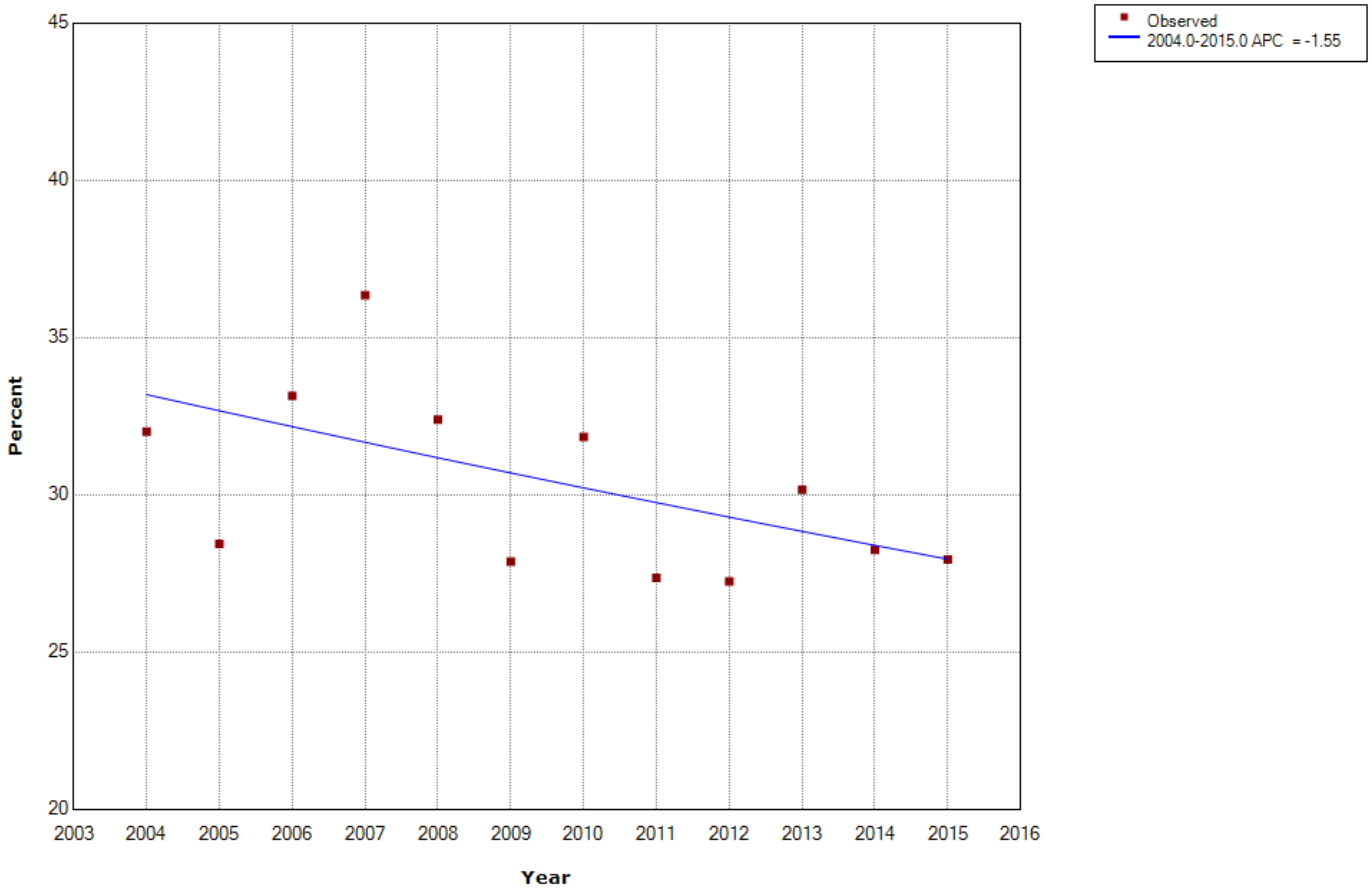
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 4c: Joinpoint analysis for LND use among patients with T1c primary tumor (n=12,930)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 4d: Joinpoint analysis for LND use among patients with T1 NOS primary tumor (n=4,340)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

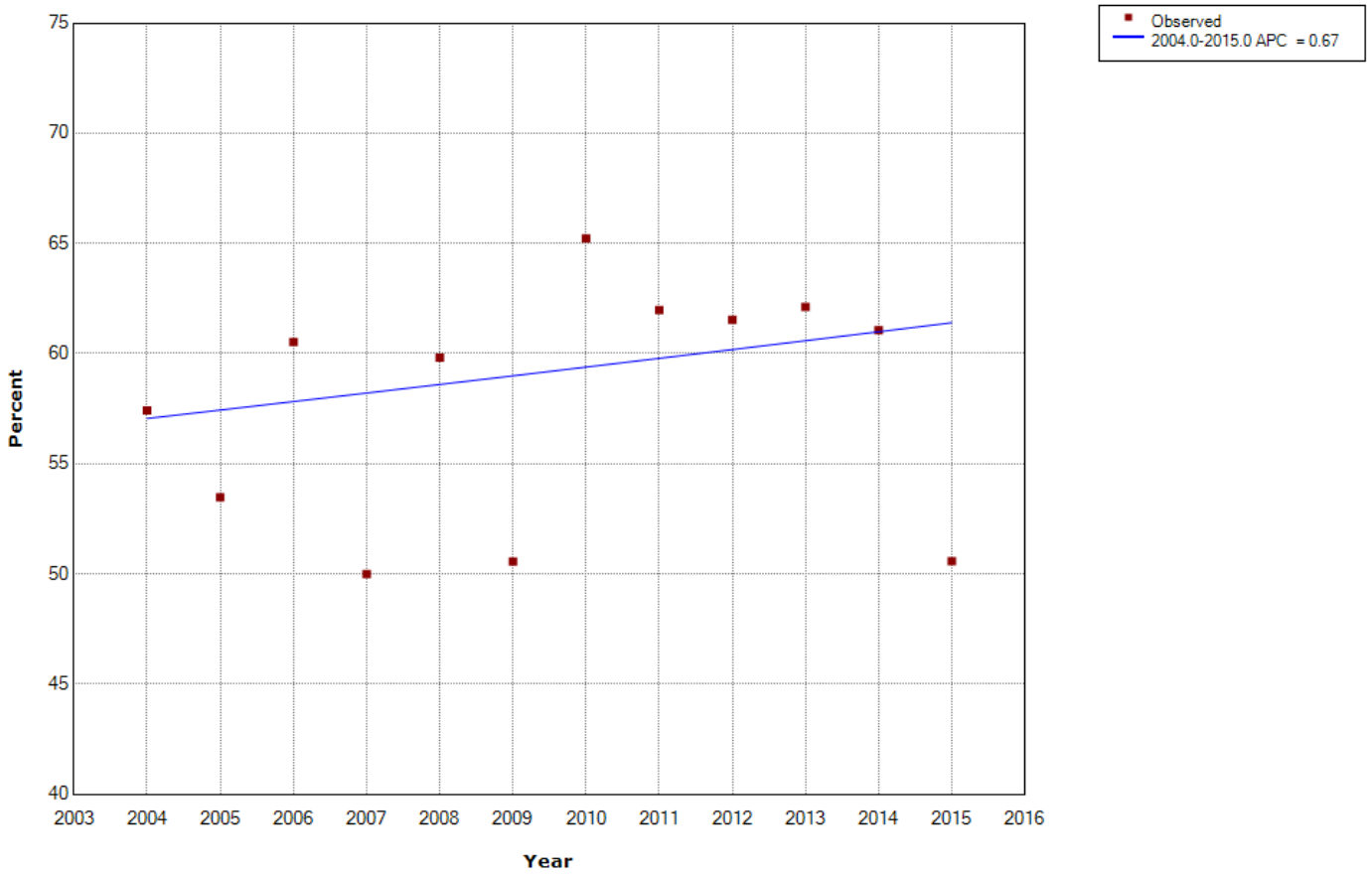
Supplemental Figure 4e: Joinpoint analysis for LND use among patients with T2a primary tumor (n=2,888)

^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 4f: Joinpoint analysis for LND use among patients with T2b primary tumor (n=3,678)

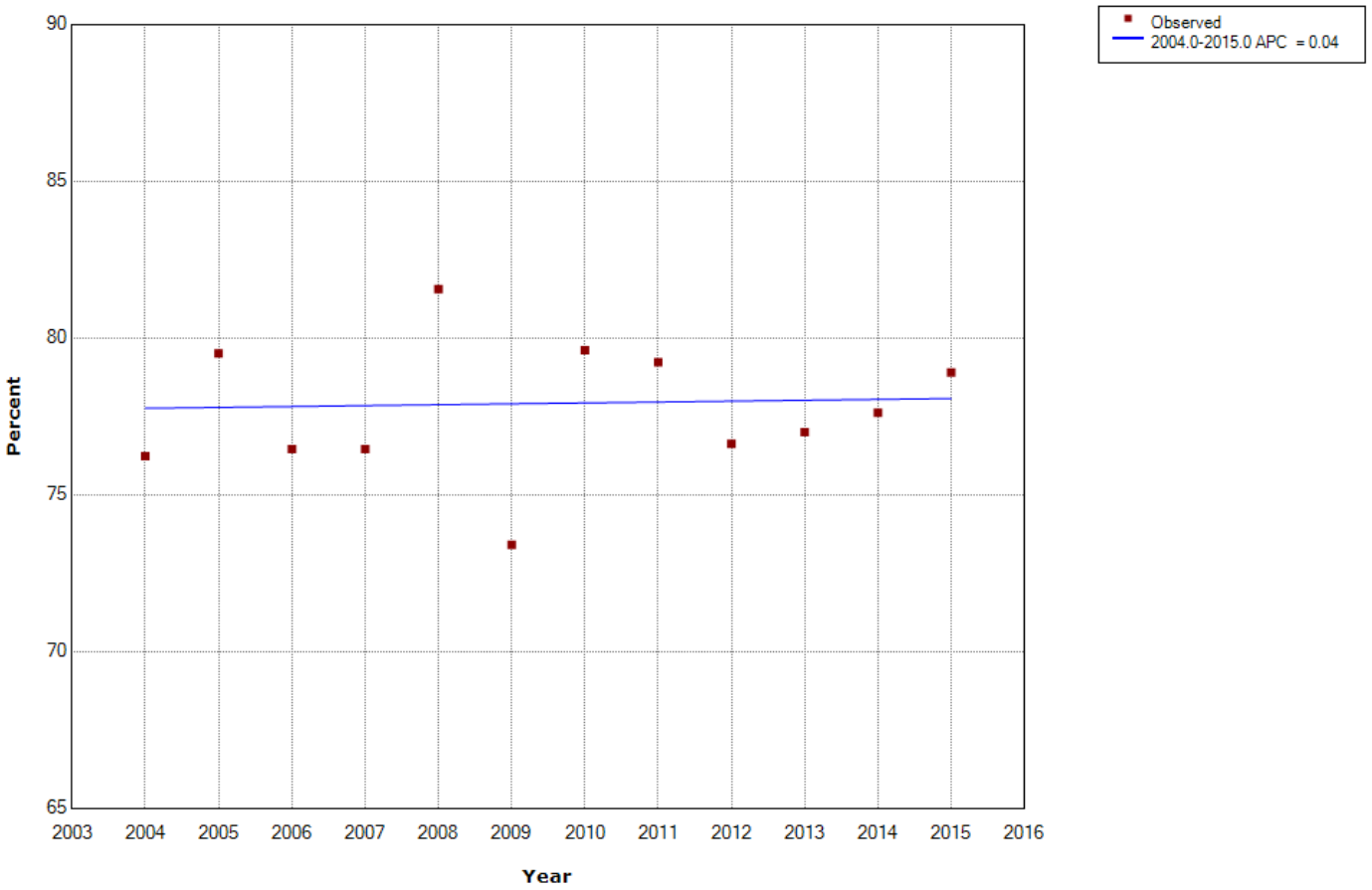
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 4g: Joinpoint analysis for LND use among patients with T2 NOS primary tumor (n=1,232)



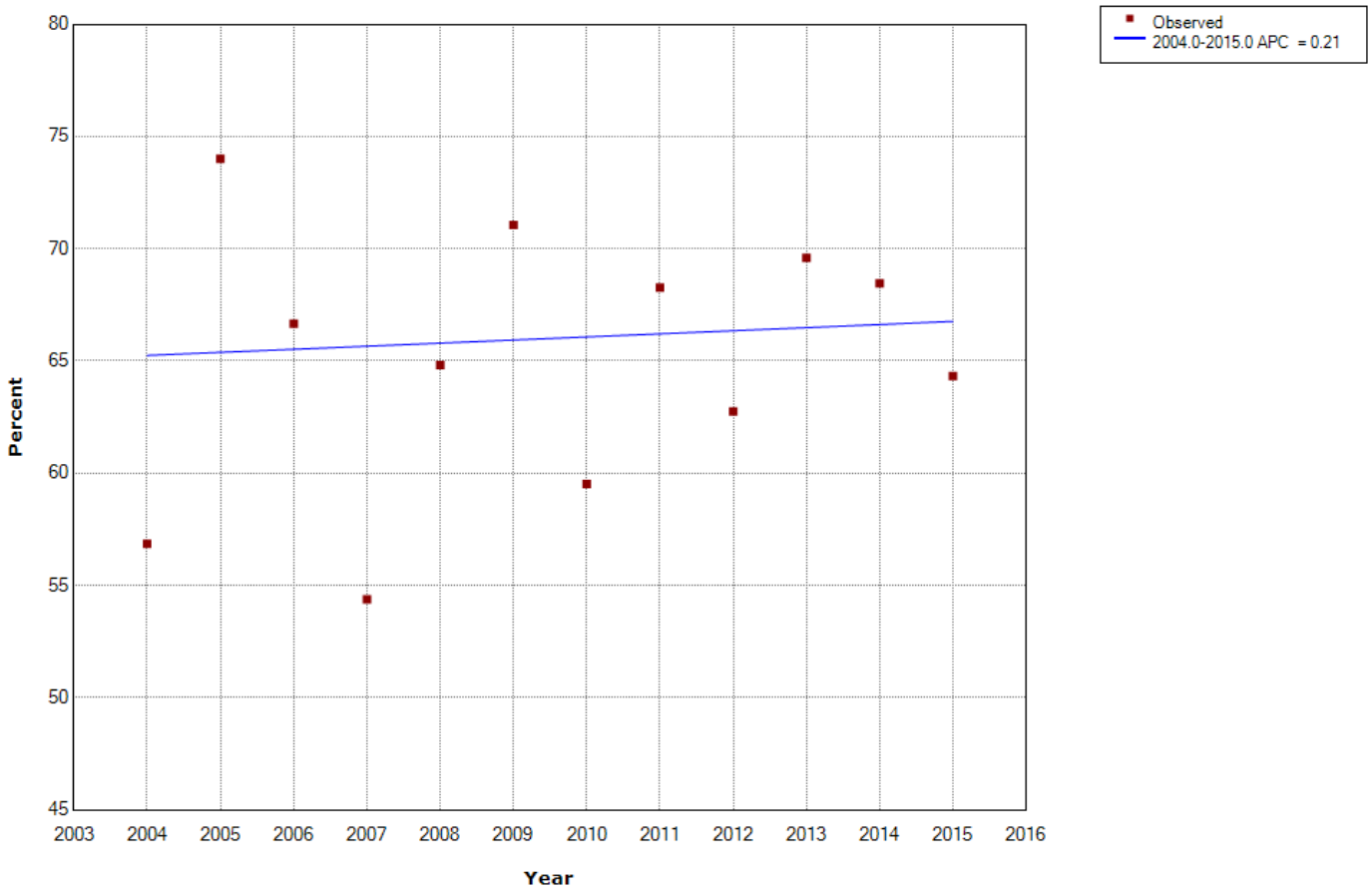
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 4h: Joinpoint analysis for LND use among patients with T3a primary tumor (n=5,544)



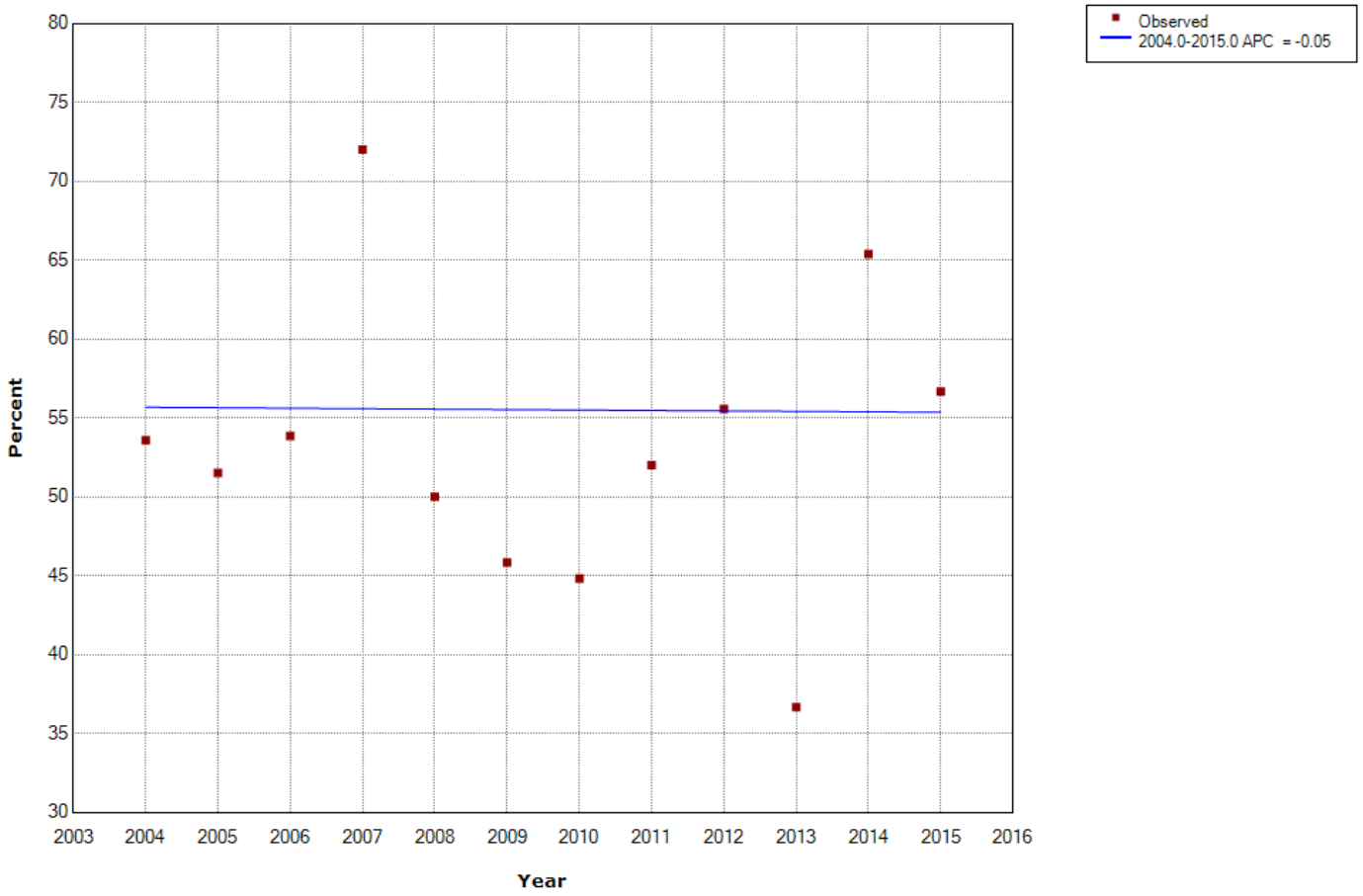
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 4i: Joinpoint analysis for LND use among patients with T3b primary tumor (n=1,203)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

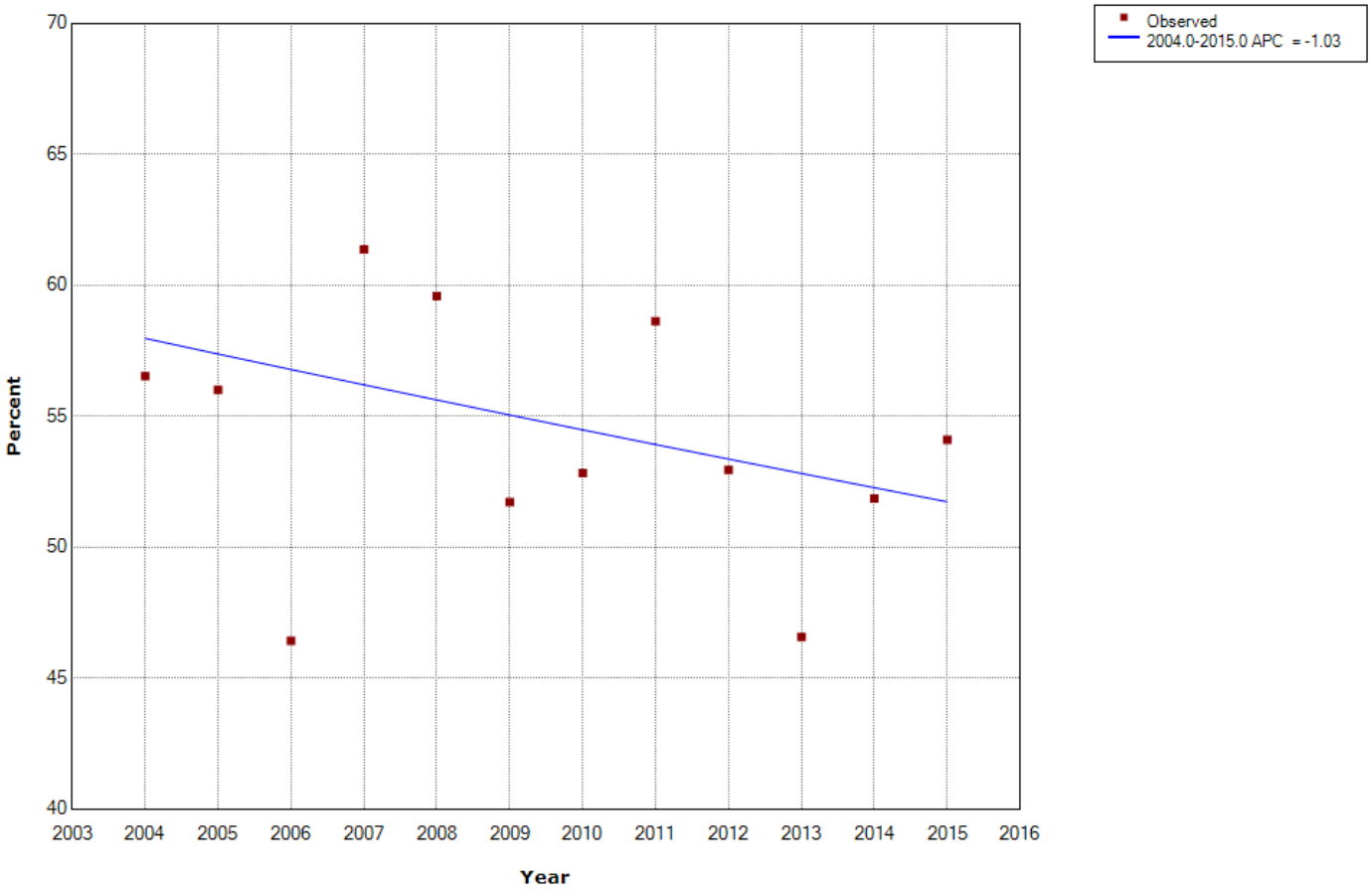
Supplemental Figure 4j: Joinpoint analysis for LND use among patients with T4 primary tumor (n=349)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

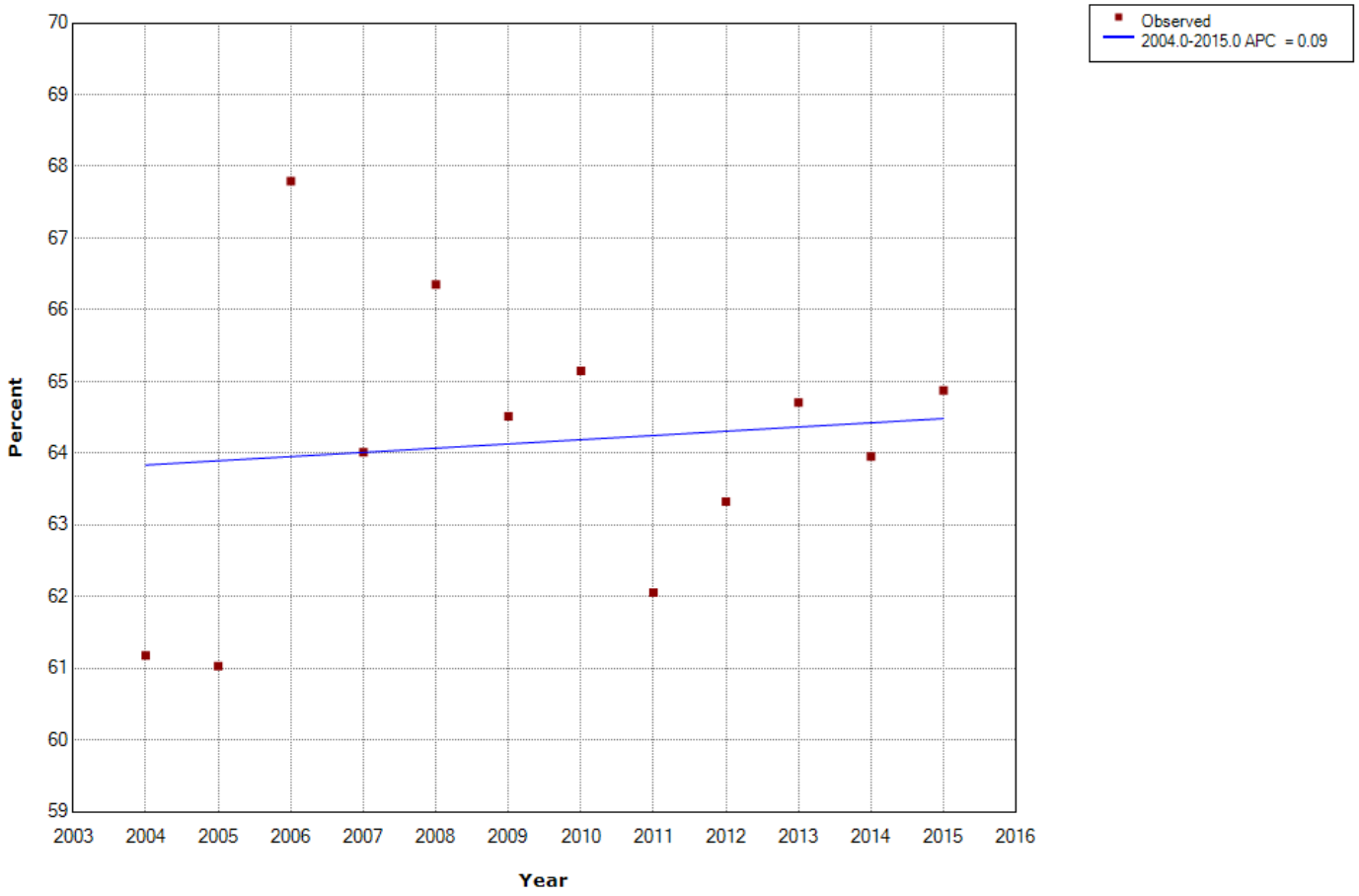
5) Supplemental Figures 5a-5e: Stratification by Race/Ethnicity, 2004-2015

Supplemental Figure 5a. Joinpoint analysis for LND use among American Indian/Alaska Native patients (n=575)



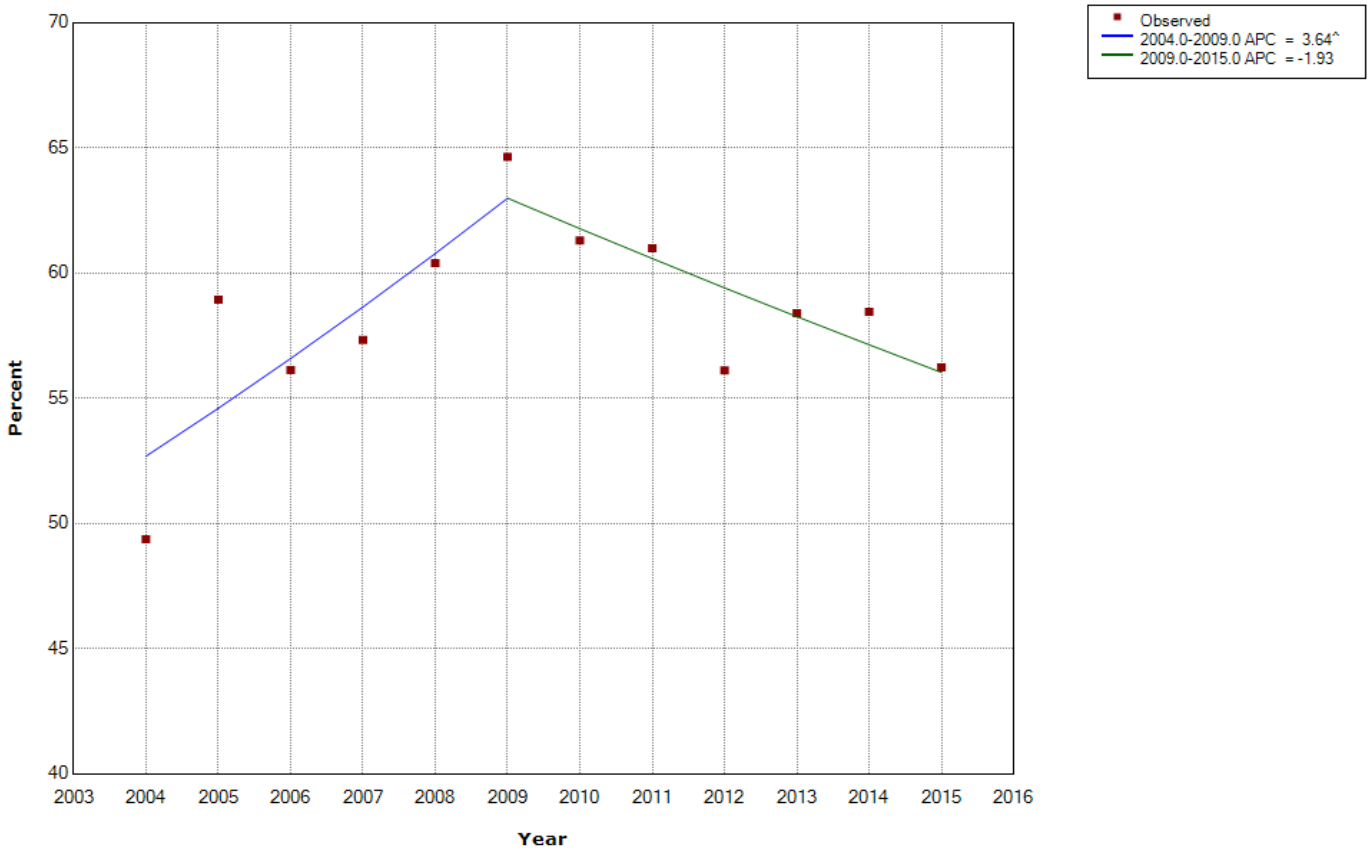
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 5b. Joinpoint analysis for LND use among Asian/Pacific Islander patients (n=7,018)



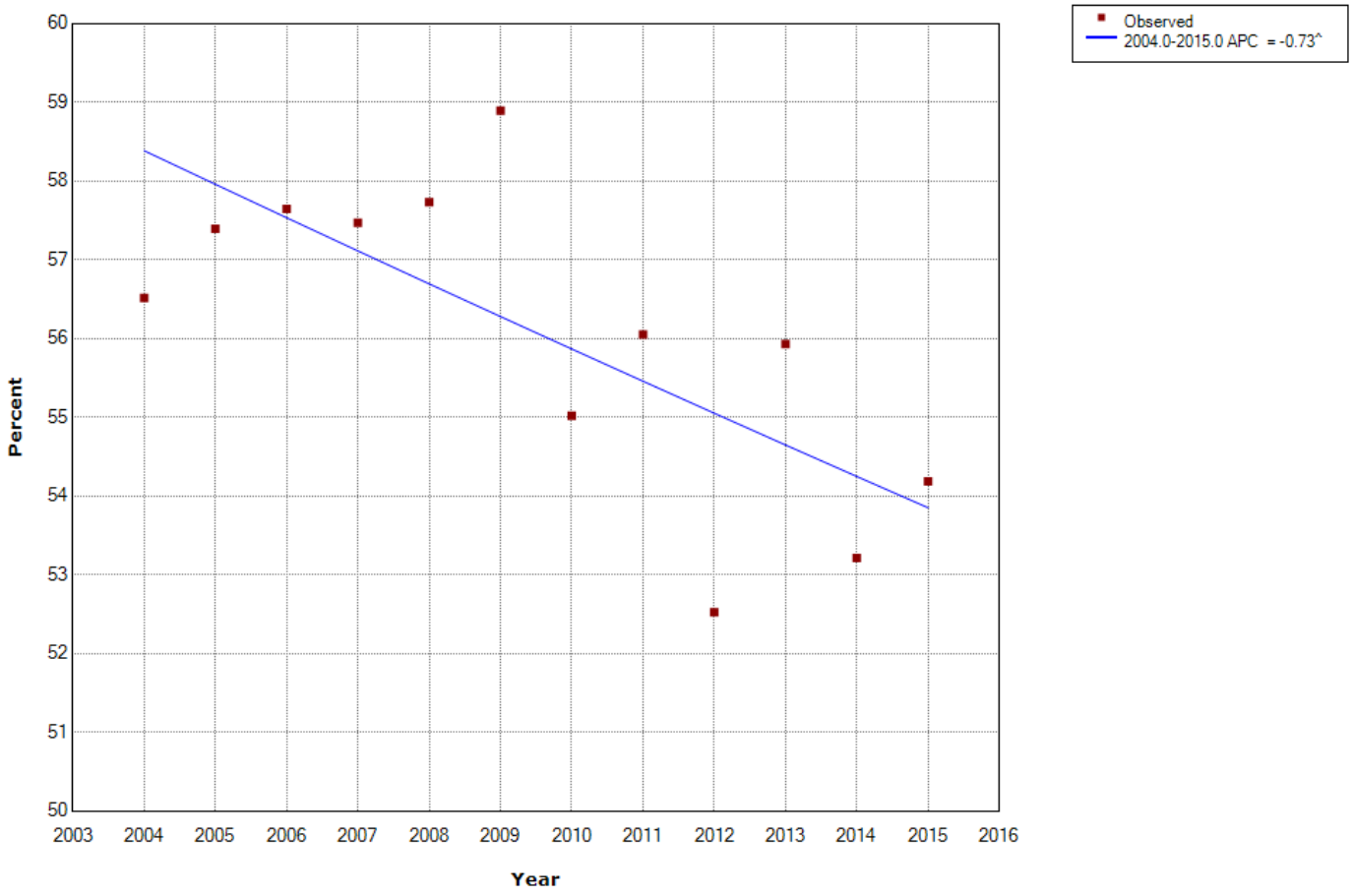
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 5c. Joinpoint analysis for LND use among Black/African American patients (n=5,925)



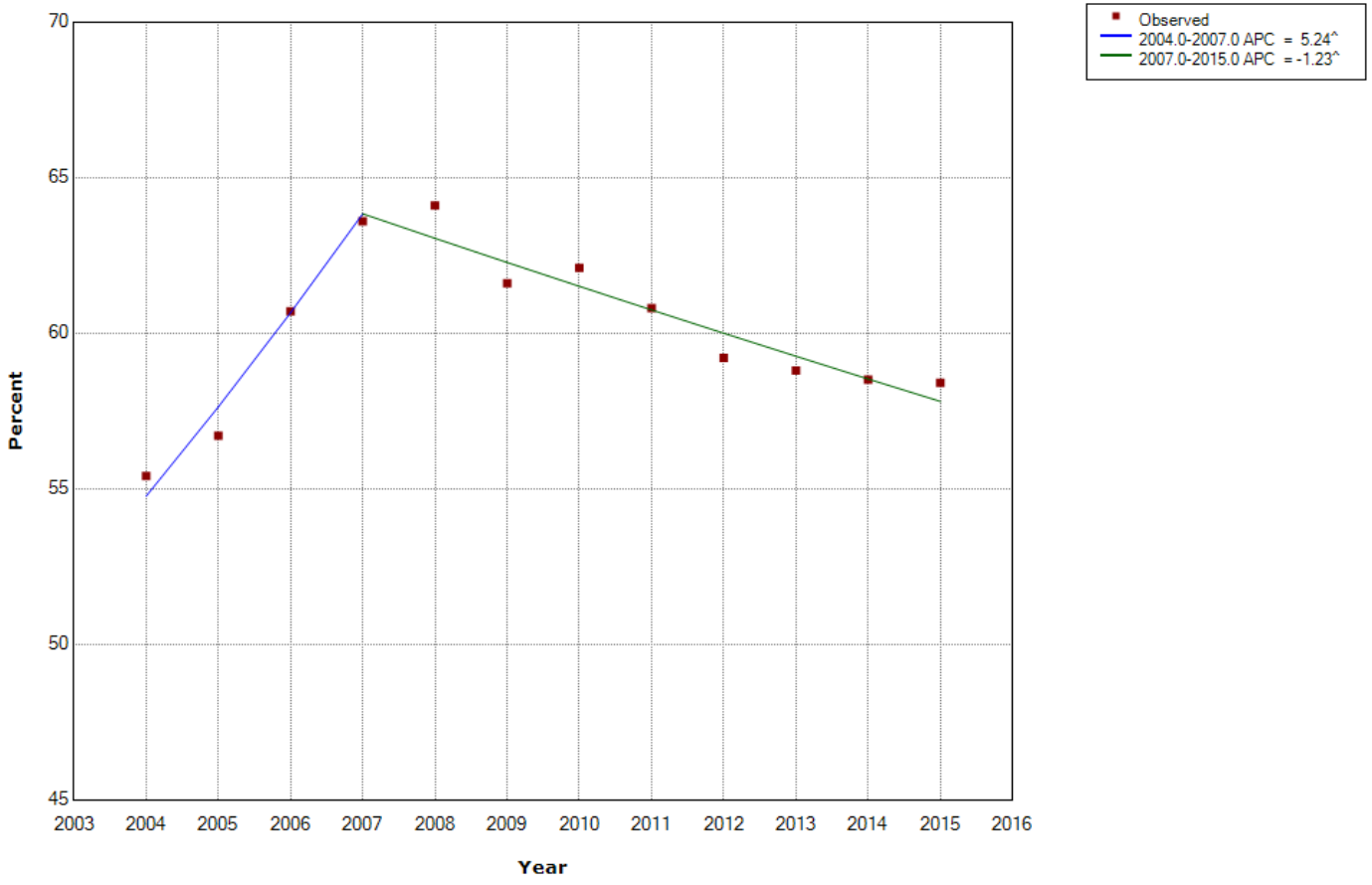
^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

Supplemental Figure 5d. Joinpoint analysis for LND use among Hispanic/Latino patients (n=9,516)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 0 Joinpoints.

Supplemental Figure 5e. Joinpoint analysis for LND use among white patients (n=66,334)



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 1 Joinpoint.

APPENDIX B: ICD-9-CM, ICD-10-CM, ICD-10-PCS, and Healthcare Common Procedure Coding System (HCPCS) codes utilized for identifying outcomes of interest

Condition	Code Type	Code(s)	Description
Lymphedema	ICD-9-CM	457.1	Other lymphedema
	ICD-10-CM	I89.0	Lymphedema, not elsewhere classified
	HCPCS	L8220	Gradient compression stocking, lymphedema
	HCPCS	A6543	Gradient compression stocking, lymphedema
	HCPCS	S8950	Complex lymphedema therapy, each 15 minutes
Hemorrhage	ICD-9-CM	E870.0	Accidental cut, puncture, perforation or hemorrhage during surgical operation
	ICD-9-CM	998.11	Hemorrhage complicating a procedure
	ICD-9-CM	39.3	Suture of vessel
	ICD-9-CM	39.98	Other operations on vessels; control of hemorrhage, not otherwise specified
	ICD-10-CM	R58	Hemorrhage, not elsewhere classified
	ICD-10-CM	N99.61	Intraoperative hemorrhage and hematoma of a genitourinary system organ or structure complicating a genitourinary system procedure
	ICD-10-CM	N99.820	Postprocedural hemorrhage of a genitourinary system organ or structure following a genitourinary system procedure.
	ICD-10-CM	N99.821	Postprocedural hemorrhage of a genitourinary system organ or structure following other procedure
	ICD-10-PCS	0W3J0ZZ	Control Bleeding in Pelvic Cavity, Open Approach
	ICD-10-PCS	0W3J3ZZ	Control Bleeding in Pelvic Cavity, Percutaneous Approach
	ICD-10-PCS	0W3J4ZZ	Control Bleeding in Pelvic Cavity, Percutaneous Endoscopic Approach
	HCPCS	35840	Exploration for postoperative hemorrhage, thrombosis, or infection; abdomen
Ileus	ICD-9-CM	560.1	Paralytic ileus
	ICD-9-CM	560.9	Unspecified intestinal obstruction
	ICD-9-CM	997.4	Surgical complications, digestive system
	ICD-10-CM	K560	Paralytic ileus
	ICD-10-CM	K567	Ileus, unspecified
	ICD-10-CM	K56.600	Partial intestinal obstruction, unspecified as to cause
	ICD-10-CM	K56.601	Complete intestinal obstruction, unspecified as to cause

	ICD-10-CM	K56.609	Unspecified intestinal obstruction, unspecified as to partial versus complete obstruction
Infection	ICD-9-CM	998.5	Postoperative infection
	ICD-9-CM	998.51	Infected postoperative seroma
	ICD-9-CM	998.59	Other postoperative infection
	ICD-10-CM	K68.11	Postprocedural retroperitoneal abscess
Lymphocele	ICD-9-CM	457.8	Other noninfectious disorders of lymphatic channels
	ICD-10-CM	I89.8	Other specified noninfective disorders of lymphatic vessels and lymph nodes
Thrombosis	ICD-9-CM	415.1	Acute pulmonary embolism and infarction
	ICD-9-CM	415.11	Iatrogenic pulmonary embolism and infarction
	ICD-9-CM	415.19	Other pulmonary embolism and infarction
	ICD-9-CM	452	Portal vein thrombosis
	ICD-9-CM	453.8	Venous thrombosis not elsewhere coded
	ICD-9-CM	444	Arterial embolism and thrombosis
	ICD-9-CM	444.0	Arterial embolism and thrombosis; of abdominal aorta
	ICD-9-CM	444.1	Embolism and thrombosis of thoracic aorta
	ICD-9-CM	444.2	Arterial embolism and thrombosis; of arteries of the extremities
	ICD-9-CM	444.8	Arterial embolism and thrombosis; of other specified artery
	ICD-9-CM	444.9	Embolism and thrombosis of unspecified artery
	ICD-9-CM	445	Atheroembolism
	ICD-9-CM	445.0	Atheroembolism; of extremities
	ICD-9-CM	445.01	Atheroembolism of upper extremity
	ICD-9-CM	445.02	Atheroembolism of lower extremity
	ICD-9-CM	445.8	Atheroembolism; of other sites
	ICD-9-CM	445.81	Atheroembolism of kidney
	ICD-9-CM	445.89	Atheroembolism of other site
	ICD-9-CM	410	Acute myocardial infarction
	ICD-9-CM	410.0	Acute myocardial infarction; of anterolateral wall
	ICD-9-CM	410.1	Acute myocardial infarction; of other anterior wall
	ICD-9-CM	410.2	Acute myocardial infarction; of inferolateral wall
	ICD-9-CM	410.3	Acute myocardial infarction; of inferoposterior wall

	ICD-9-CM	410.4	Acute myocardial infarction; of other inferior wall
	ICD-9-CM	410.5	Acute myocardial infarction; of other lateral wall
	ICD-9-CM	410.6	Acute myocardial infarction; true posterial wall infarction
	ICD-9-CM	410.7	Acute myocardial infarction; subendocardial infarction
	ICD-9-CM	410.8	Acute myocardial infarction; of other specified sites
	ICD-9-CM	410.9	Acute myocardial infarction; unspecified site
	ICD-10-CM	I26.90	Septic pulmonary embolism without acute cor pulmonale
	ICD-10-CM	I26.99	Other pulmonary embolism without acute cor pulmonale
	ICD-10-CM	T81718A	Complication of other artery following a procedure, not elsewhere classified, initial encounter
	ICD-10-CM	T8172XA	Complication of vein following a procedure, not elsewhere classified, initial encounter
	ICD-10-CM	I81	Portal vein thrombosis
	ICD-10-CM	I74.11	Embolism and thrombosis of thoracic aorta
	ICD-10-CM	I74.9	Pulmonary embolism
	ICD-10-CM	I75.019	Atheroembolism of unspecified upper extremity
	ICD-10-CM	I75.029	Atheroembolism of unspecified lower extremity
	ICD-10-CM	I75.81	Atheroembolism of kidney
	ICD-10-CM	I75.89	Atheroembolism of other site
	ICD-10-CM	I21.0	Acute myocardial infarction
	ICD-10-CM	I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
	ICD-10-CM	I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
	ICD-10-CM	I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
	ICD-10-CM	I21.1	ST elevation (STEMI) myocardial infarction of inferior wall
	ICD-10-CM	I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
	ICD-10-CM	I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
	ICD-10-CM	I21.2	Acute transmural myocardial infarction of other sites
	ICD-10-CM	I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery

	ICD-10-CM	I21.29	sT elevation (STEMI) myocardial infarction involving other sites
	ICD-10-CM	I21.3	Acute transmural myocardial infarction of unspecified site
	ICD-10-CM	I21.4	Acute subendocardial myocardial infarction
	ICD-10-CM	I21.9	Acute myocardial infarction, unspecified
	ICD-10-CM	I21A	Other type of myocardial infarction
	ICD-10-CM	I21.A1	Myocardial infarction type 2
	ICD-10-CM	I21.A9	Other myocardial infarction type
	HCPCS	34001	Embolectomy or thrombectomy, with or without catheter; carotid, subclavian or innominate artery, by neck incision
	HCPCS	34051	Embolectomy or thrombectomy, with or without catheter; innominate, subclavian artery, by thoracic incision
	HCPCS	34101	Embolectomy or thrombectomy, with or without catheter; axillary, brachial, innominate, subclavian artery, by arm incision
	HCPCS	34111	Embolectomy or thrombectomy, with or without catheter; radial or ulnar artery, by arm incision
	HCPCS	34151	Embolectomy or thrombectomy, with or without catheter; renal, celiac, mesentery, aortoiliac artery, by abdominal incision
	HCPCS	34201	Embolectomy or thrombectomy, with or without catheter; femoropopliteal, aortoiliac artery, by leg incision
	HCPCS	34203	Embolectomy or thrombectomy, with or without catheter; popliteal-tibio-peroneal artery, by leg incision
	HCPCS	34401	Thrombectomy, direct or with catheter; vena cava, iliac vein, by abdominal incision
	HCPCS	34421	Thrombectomy, direct or with catheter; vena cava, iliac, femoropopliteal vein, by leg incision
	HCPCS	34451	Thrombectomy, direct or with catheter; vena cava, iliac, femoropopliteal vein, by abdominal and leg incision
	HCPCS	34471	Thrombectomy, direct or with catheter; subclavian vein, by neck incision
	HCPCS	34490	Thrombectomy, direct or with catheter; axillary and subclavian vein, by arm incision

APPENDIX C: ICD-9-CM, ICD-10-CM, and Healthcare Common Procedure Coding System (HCPCS) codes utilized for identifying date of hysterectomy

Code Type	Code(s)	Description
ICD-9-CM	68.3	Subtotal abdominal hysterectomy
ICD-9-CM	68.4	Total abdominal hysterectomy
ICD-9-CM	68.6	Radical abdominal hysterectomy
ICD-10-CM	0UT90ZZ	Resection of Uterus, Open Approach
ICD-10-CM	0UT9FZZ	Resection of Uterus, Via Natural or Artificial Opening With Percutaneous Endoscopic Assistance
ICD-10-CM	0UT94ZZ	Resection of Uterus, Percutaneous Endoscopic Approach
HCPCS	58150, 58152	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s)
HCPCS	58180	Supracervical abdominal hysterectomy (subtotal hysterectomy), with or without removal of tube(s), with or without removal of ovary(s)
HCPCS	58200	Total abdominal hysterectomy, including partial vaginectomy, with para-aortic and pelvic lymph node sampling, with or without removal of tube(s), with or without removal of ovary(s)
HCPCS	58210	Radical abdominal hysterectomy, with bilateral total pelvic lymphadenectomy and para-aortic lymph node sampling (biopsy), with or without removal of tube(s), with or without removal of ovary(s)
HCPCS	58240	Pelvic exenteration for gynecologic malignancy, with total abdominal hysterectomy or cervicectomy, with or without removal of tube(s), with or without removal of ovary(s), with removal of bladder and ureteral transplantations, and/or abdominoperineal resection of rectum and colon and colostomy, or any combination thereof
HCPCS	58260	Vaginal hysterectomy, for uterus 250 g or less
HCPCS	58262	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s)
HCPCS	58263	Vaginal hysterectomy, for uterus 250 g or less; with removal of tube(s), and/or ovary(s), with repair of enterocele
HCPCS	58270	Vaginal hysterectomy, for uterus 250 g or less; with repair of enterocele
HCPCS	58275	Vaginal hysterectomy, with total or partial vaginectomy

HCPCS	58280	Vaginal hysterectomy, with total or partial vaginectomy; with repair of enterocele
HCPCS	58285	Vaginal hysterectomy, radical (Schauta type operation)
HCPCS	58290	Vaginal hysterectomy, for uterus greater than 250 g
HCPCS	58291	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s)
HCPCS	58292	Vaginal hysterectomy, for uterus greater than 250 g; with removal of tube(s) and/or ovary(s), with repair of enterocele
HCPCS	58293	Vaginal hysterectomy, for uterus greater than 250 g; with colpo-urethrocystopexy (Marshall-Marchetti-Krantz type, Pereyra type) with or without endoscopic control
HCPCS	58294	Vaginal hysterectomy, for uterus greater than 250 g; with repair of enterocele
HCPCS	58570, 58571	Laparoscopy, surgical, with total hysterectomy, for uterus 250 g or less
HCPCS	58572, 58573	Laparoscopy, surgical, with total hysterectomy, for uterus greater than 250 g

APPENDIX D: ICD-9-CM, ICD-10-CM, and Healthcare Common Procedure Coding System (HCPCS) codes utilized for identifying chemotherapy and radiation treatment exposure

Adjuvant Treatment	Code Type	Code	Description
Chemotherapy	ICD-9-CM	V58.11	Encounter for antineoplastic chemotherapy
	ICD-10-CM	Z51.11	Encounter for antineoplastic chemotherapy
	HCPCS	J9000	Injection, doxorubicin hydrochloride, 10 mg
	HCPCS	J9045	Injection, carboplatin, 50 mg
	HCPCS	J9060	Injection, cisplatin, powder or solution, 10 mg
	HCPCS	J9264	Injection, paclitaxel protein-bound particles, 1 mg
	HCPCS	J9999	Not otherwise classified, antineoplastic drugs
	HCPCS	96409	Chemotherapy administration; intravenous, push technique, single or initial substance/drug
	HCPCS	96411	Chemotherapy administration; intravenous, push technique, each additional substance/drug
	HCPCS	96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
	HCPCS	96415	Chemotherapy administration, intravenous infusion technique; each additional hour
	HCPCS	96416	Chemotherapy administration, intravenous infusion technique; initiation of prolonged chemotherapy infusion (more than 8 hours), requiring use of a portable or implantable pump
	HCPCS	96417	Chemotherapy administration, intravenous infusion technique; each additional sequential infusion (different substance/drug), up to 1 hour
	HCPCS	96549	Unlisted chemotherapy procedure
Brachytherapy	HCPCS	77750	Infusion or instillation of radioelement solution (includes 3-month follow-up care)
	HCPCS	77761	Intracavitary radiation source application; simple
	HCPCS	77762	Intracavitary radiation source application; intermediate
	HCPCS	77763	Intracavitary radiation source application; complex

	HCPCS	77767	Remote afterloading high dose rate radionuclide skin surface brachytherapy, includes basic dosimetry, when performed; lesion diameter up to 2.0 cm or 1 channel
	HCPCS	77768	Remote afterloading high dose rate radionuclide skin surface brachytherapy, includes basic dosimetry, when performed; lesion diameter over 2.0 cm and 2 or more channels, or multiple lesions
	HCPCS	77770	Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 1 channel
	HCPCS	77771	Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; 2-12 channels
	HCPCS	77772	Remote afterloading high dose rate radionuclide interstitial or intracavitary brachytherapy, includes basic dosimetry, when performed; over 12 channels
	HCPCS	77776	Interstitial radiation source application; simple
	HCPCS	77777	Interstitial radiation source application; intermediate
	HCPCS	77778	Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed
	HCPCS	77781	Interstitial radiation source application, complex, includes supervision, handling, loading of radiation source, when performed
	HCPCS	77782	Remote afterloading high intensity brachytherapy; 5-8 source positions or catheters
	HCPCS	77783	Remote afterloading high intensity brachytherapy; 9-12 source positions or catheters
	HCPCS	77784	Remote afterloading high intensity brachytherapy; over 12 source positions or catheters
	HCPCS	77785	Remote afterloading high dose rate radionuclide brachytherapy; 1 channel
	HCPCS	77786	Remote afterloading high dose rate radionuclide brachytherapy; 2-12 channels
	HCPCS	77787	Remote afterloading high dose rate radionuclide brachytherapy; over 12 channels
	HCPCS	77789	Surface application of low dose rate radionuclide source
	HCPCS	77790	Supervision, handling, loading of radiation source
	HCPCS	77799	Unlisted procedure, clinical brachytherapy
	HCPCS	C2634	Brachytherapy source, non-stranded, high activity, iodine-125, greater than 1.01 mci (nist), per source

	HCPCS	C2635	Brachytherapy source, non-stranded, high activity, paladium-103, greater than 2.2 mci (nist), per source
	HCPCS	C2636	Brachytherapy linear source, non-stranded, paladium-103, per 1 mm
	HCPCS	C2637	Brachytherapy source, non-stranded, ytterbium-169, per source
	HCPCS	C2638	Brachytherapy source, stranded, iodine-125, per source
	HCPCS	C2639	Brachytherapy source, non-stranded, iodine-125, per source
	HCPCS	C2640	Brachytherapy source, stranded, palladium-103, per source
	HCPCS	C2641	Brachytherapy source, non-stranded, palladium-103, per source
	HCPCS	C2642	Brachytherapy source, stranded, cesium-131, per source
	HCPCS	C2643	Brachytherapy source, non-stranded, cesium-131, per source
	HCPCS	C2644	Brachytherapy source, cesium-131 chloride solution, per millicurie
	HCPCS	C2645	Brachytherapy planar source, palladium-103, per square millimeter
	HCPCS	C2698	Brachytherapy source, stranded, not otherwise specified, per source
	HCPCS	C2699	Brachytherapy source, non-stranded, not otherwise specified, per source
External Beam Radiation Therapy	HCPCS	77385	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
	HCPCS	77386	Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
	HCPCS	77387	Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed
	HCPCS	77399	Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services
	HCPCS	77401	Radiation treatment delivery, superficial and/or ortho voltage, per day
	HCPCS	77402	Radiation treatment delivery, ≥ 1 MeV; simple
	HCPCS	77407	Radiation treatment delivery, ≥ 1 MeV; intermediate
	HCPCS	77412	Radiation treatment delivery, ≥ 1 MeV; complex
	HCPCS	77417	Therapeutic radiology port image(s)
	HCPCS	77424	Intraoperative radiation treatment delivery, x-ray, single treatment session
	HCPCS	77425	Intraoperative radiation treatment delivery, electrons, single treatment session

APPENDIX E: Comparing Imputed and Confirmed Surgery Date Results
All models are adjusted for Age of Diagnosis, Race/Ethnicity, Tumor Grade, Radiation Treatment, Chemotherapy, and NCI Comorbidity Score

Table E1. Imputed vs. Confirmed Surgery Date for Lymphedema

	Imputed Surgery Date (at risk: n=19,041)		Confirmed Surgery Date (at risk: n=11,593)	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Nodes Removed		0.09		0.12
0	Ref		Ref	
1-4	0.70 (0.31, 1.59)		0.93 (0.37, 2.33)	
5-9	1.22 (0.68, 2.18)		1.32 (0.63, 2.76)	
10+	1.53 (0.99, 2.36)		1.81 (1.05, 3.10)	
Age		0.01		0.26
66-69 years	Ref		Ref	
70-74 years	1.50 (0.90, 2.51)		1.35 (0.72, 2.55)	
75-79 years	2.09 (1.24, 3.53)		1.65 (0.86, 3.18)	
80-84 years	2.25 (1.25, 4.04)		2.12 (1.05, 4.26)	
85+ years	2.58 (1.31, 5.08)		1.92 (0.82, 4.51)	
Race/Ethnicity		0.64		0.95
White, Non-Hispanic	Ref		Ref	
Black, Non-Hispanic	1.34 (0.70, 2.58)		1.09 (0.44, 2.72)	
Hispanic/Latino	0.66 (0.27, 1.63)		1.16 (0.47, 2.88)	
Other/Unknown	1.00 (0.41, 2.45)		0.73 (0.18, 3.00)	
FIGO Tumor Grade		0.18		0.20
Grade 1	Ref		Ref	
Grade 2	0.91 (0.57, 1.46)		0.96 (0.53, 1.74)	
Grade 3	1.13 (0.66, 1.95)		1.39 (0.72, 2.68)	
Unknown	1.54 (0.95, 2.52)		1.74 (0.94, 3.23)	
Chemotherapy		0.36		0.87
No	Ref		Ref	
Yes	1.31 (0.74, 2.31)		1.06 (0.52, 2.17)	
Radiation		0.43		0.33
No	Ref		Ref	
Yes	0.99 (0.66, 1.48)		0.97 (0.60, 1.62)	
Unknown	1.94 (0.71, 5.35)		2.40 (0.74, 7.79)	
NCI Comorbidity Score		<0.01		0.02
0	Ref		Ref	
1	2.34 (1.49, 3.68)		2.07 (1.19, 3.60)	
2+	2.35 (1.13, 4.87)		1.98 (0.79, 4.97)	

Table E2. Imputed vs. Confirmed Hysterectomy Date for Hemorrhage

	Imputed Date (at risk: n=19,039)		Confirmed Date (at risk: n=11,588)	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Nodes Removed		0.29		0.52
0	Ref		Ref	
1-4	0.69 (0.44, 1.09)		0.66 (0.38, 1.14)	
5-9	0.76 (0.52, 1.11)		0.92 (0.60, 1.42)	
10+	0.90 (0.69, 1.17)		0.95 (0.69, 1.31)	
Age		0.53		0.55
66-69 years	Ref		Ref	
70-74 years	1.11 (0.83, 1.50)		1.13 (0.78, 1.62)	
75-79 years	1.15 (0.83, 1.50)		1.07 (0.71, 1.61)	
80-84 years	1.39 (0.96, 2.00)		1.45 (0.95, 2.22)	
85+ years	1.10 (0.65, 1.79)		1.16 (0.67, 2.02)	
Race/Ethnicity		0.11		0.19
White, Non-Hispanic	Ref		Ref	
Black, Non-Hispanic	1.31 (0.86, 1.99)		1.27 (0.75, 2.16)	
Hispanic/Latino	0.57 (0.31, 1.05)		0.62 (0.29, 1.32)	
Other/Unknown	0.73 (0.38, 1.42)		0.41 (0.13, 1.29)	
FIGO Tumor Grade		0.57		0.72
Grade 1	Ref		Ref	
Grade 2	0.94 (0.71, 1.25)		0.94 (0.67, 1.31)	
Grade 3	0.93 (0.65, 1.33)		1.06 (0.70, 1.61)	
Unknown	0.77 (0.54, 1.11)		0.81 (0.52, 1.26)	
Chemotherapy		0.02		0.50
No	Ref		Ref	
Yes	1.53 (1.06, 2.20)		1.17 (0.74, 1.85)	
Radiation		0.35		0.50
No	Ref		Ref	
Yes	1.10 (0.85, 1.43)		1.20 (0.88, 1.64)	
Unknown	1.67 (0.78, 3.57)		1.13 (0.36, 3.55)	
NCI Comorbidity Score		0.41		0.99
0	Ref		Ref	
1	1.12 (0.77, 1.63)		0.99 (0.63, 1.54)	
2+	1.42 (0.81, 2.48)		0.96 (0.45, 2.05)	

Table E3. Imputed vs. Confirmed Hysterectomy Date for Ileus

	Imputed Date (at risk: n=19,010)		Confirmed Date (at risk: n=11,560)	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Nodes Removed		<0.01		<0.01
0	Ref		Ref	
1-4	1.49 (1.11, 2.02)		1.63 (1.17, 2.25)	
5-9	1.19 (0.89, 1.59)		1.33 (0.97, 1.84)	
10+	1.50 (1.22, 1.86)		1.76 (1.39, 2.22)	
Age		<0.01		<0.01
66-69 years	Ref		Ref	
70-74 years	1.03 (0.82, 1.31)		0.88 (0.67, 1.16)	
75-79 years	1.49 (1.17, 1.89)		1.30 (0.99, 1.70)	
80-84 years	1.69 (1.29, 2.21)		1.57 (1.17, 2.10)	
85+ years	1.97 (1.45, 2.69)		1.74 (1.24, 2.44)	
Race/Ethnicity		0.21		0.22
White, Non-Hispanic	Ref		Ref	
Black, Non-Hispanic	1.26 (0.92, 1.72)		1.41 (0.99, 2.01)	
Hispanic/Latino	0.84 (0.57, 1.23)		1.02 (0.67, 1.55)	
Other/Unknown	0.74 (0.46, 1.21)		0.79 (0.45, 1.41)	
FIGO Tumor Grade		0.05		0.05
Grade 1	Ref		Ref	
Grade 2	1.09 (0.88, 1.35)		0.88 (0.70, 1.12)	
Grade 3	1.39 (1.08, 1.78)		1.30 (0.99, 1.70)	
Unknown	0.98 (0.75, 1.28)		0.98 (0.722, 1.31)	
Chemotherapy		0.01		0.98
No	Ref		Ref	
Yes	1.44 (1.10, 1.88)		1.01 (0.72, 1.40)	
Radiation		0.01		0.02
No	Ref		Ref	
Yes	0.75 (0.61, 0.92)		0.73 (0.58, 0.91)	
Unknown	1.16 (0.63, 2.11)		1.15 (0.57, 2.32)	
NCI Comorbidity Score		<0.01		0.02
0	Ref		Ref	
1	1.44 (1.12, 1.86)		1.10 (0.82, 1.49)	
2+	1.90 (1.32, 2.74)		1.76 (1.18, 2.63)	

Table E4. Imputed vs. Confirmed Hysterectomy Date for Infection

	Imputed Date (at risk: n=19,036)		Confirmed Date (at risk: n=11,581)	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Nodes Removed		<0.01		<0.01
0	Ref		Ref	
1-4	1.28 (0.96, 1.70)		1.40 (1.02, 1.93)	
5-9	1.40 (1.09, 1.79)		1.46 (1.09, 1.95)	
10+	1.58 (1.31, 1.91)		1.79 (1.44, 2.24)	
Age		0.23		0.09
66-69 years	Ref		Ref	
70-74 years	0.86 (0.71, 1.04)		0.79 (0.63, 0.98)	
75-79 years	0.95 (0.77, 1.17)		0.83 (0.66, 1.06)	
80-84 years	0.95 (0.74, 1.21)		0.85 (0.64, 1.12)	
85+ years	0.69 (0.48, 0.99)			
Race/Ethnicity		<0.01		<0.01
White, Non-Hispanic	Ref		Ref	
Black, Non-Hispanic	1.37 (1.05, 1.79)		1.40 (1.01, 1.93)	
Hispanic/Latino	1.42 (1.09, 1.84)		1.67 (1.23, 2.26)	
Other/Unknown	0.61 (0.38, 0.98)		0.61 (0.34, 1.12)	
FIGO Tumor Grade		<0.01		0.03
Grade 1	Ref		Ref	
Grade 2	1.34 (1.11, 1.62)		1.38 (1.11, 1.72)	
Grade 3	1.43 (1.14, 1.80)		1.35 (1.03, 1.76)	
Unknown	1.12 (0.89, 1.41)		1.19 (0.90, 1.57)	
Chemotherapy		0.11		0.28
No	Ref		Ref	
Yes	1.22 (0.96, 1.56)		1.16 (0.88, 1.53)	
Radiation		<0.01		0.04
No	Ref		Ref	
Yes	0.75 (0.63, 0.90)		0.82 (0.67, 1.00)	
Unknown	1.59 (1.00, 2.52)		1.52 (0.85, 2.70)	
NCI Comorbidity Score		<0.01		<0.01
0	Ref		Ref	
1	1.48 (1.18, 1.84)		1.31 (1.02, 1.70)	
2+	1.57 (1.10, 2.26)		1.86 (1.27, 2.71)	

Table E5. Imputed vs. Confirmed Hysterectomy Date for Thrombosis

	Imputed Date (at risk: n=18,998)		Confirmed Date Only (at risk: n=11,560)	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Nodes Removed		0.01		<0.01
0	Ref		Ref	
1-4	1.13 (0.77, 1.68)		1.25 (0.79, 1.99)	
5-9	0.90 (0.62, 1.30)		0.95 (0.60, 1.51)	
10+	1.42 (1.10, 1.83)		1.70 (1.25, 2.30)	
Age		0.01		0.02
66-69 years	Ref		Ref	
70-74 years	1.12 (0.84, 1.48)		1.05 (0.74, 1.50)	
75-79 years	1.27 (0.94, 1.73)		1.16 (0.79, 1.69)	
80-84 years	1.39 (0.98, 1.96)		1.47 (0.99, 2.30)	
85+ years	1.92 (1.31, 2.80)		1.92 (1.24, 2.99)	
Race/Ethnicity		0.23		0.16
White, Non-Hispanic	Ref		Ref	
Black, Non-Hispanic	1.23 (0.83, 1.83)		1.08 (0.62, 1.45)	
Hispanic/Latino	1.11 (0.73 1.69)		1.23 (0.74, 2.04)	
Other/Unknown	0.54 (0.27, 1.10)		0.23 (0.06, 0.92)	
FIGO Tumor Grade		0.06		0.09
Grade 1	Ref		Ref	
Grade 2	1.19 (0.91, 1.56)		1.16 (0.84, 1.59)	
Grade 3	1.52 (1.11, 2.08)		1.54 (1.06, 2.23)	
Unknown	1.05 (0.76, 1.46)		0.95 (0.62, 1.45)	
Chemotherapy		0.22		0.65
No	Ref		Ref	
Yes	1.25 (0.88, 1.78)		0.90 (0.56, 1.43)	
Radiation		0.01		0.01
No	Ref		Ref	
Yes	0.67 (0.52, 0.87)		0.64 (0.47, 0.88)	
Unknown	1.11 (0.52, 2.37)		0.48 (0.12, 1.95)	
NCI Comorbidity Score		<0.01		<0.01
0	Ref		Ref	
1	1.73 (1.29, 2.33)		1.72 (1.22, 2.43)	
2+	2.20 (1.42, 3.40)		2.39 (1.47, 3.90)	

Table E6. Imputed vs. Confirmed Hysterectomy Date for All-Cause Death

	Imputed Date (at risk: n=19,082)		Confirmed Date Only (at risk: n=11,621)	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Nodes Removed		0.23		0.63
0	Ref		Ref	
1-4	0.82 (0.57, 1.17)		0.82 (0.52, 1.29)	
5-9	0.73 (0.52, 1.02)		0.84 (0.56, 1.27)	
10+	0.84 (0.6, 1.06)		0.84 (0.62, 1.13)	
Age		<0.01		<0.01
66-69 years	Ref		Ref	
70-74 years	1.17 (0.85, 1.63)		1.23 (0.81, 1.86)	
75-79 years	1.83 (1.32, 2.52)		1.62 (1.07, 2.46)	
80-84 years	2.70 (1.96, 3.73)		2.31 (1.52, 3.51)	
85+ years	3.56 (2.54, 5.00)		3.13 (2.03, 4.82)	
Race/Ethnicity		0.11		0.14
White, Non-Hispanic	Ref		Ref	
Black, Non-Hispanic	1.45 (1.01, 2.06)		1.54 (0.98, 2.44)	
Hispanic/Latino	1.34 (0.90, 1.99)		1.46 (0.88, 2.40)	
Other/Unknown	0.90 (0.52, 1.57)		0.89 (0.42, 1.90)	
FIGO Tumor Grade		<0.01		<0.01
Grade 1	Ref		Ref	
Grade 2	1.78 (1.34, 2.38)		1.68 (1.18 2.40)	
Grade 3	4.62 (3.46, 6.17)		4.34 (3.04, 6.19)	
Unknown	1.66 (1.18, 2.34)		1.37 (0.87, 2.16)	
Chemotherapy		0.18		0.07
No	Ref		Ref	
Yes	0.75 (0.50, 1.14)		0.60 (0.35, 1.04)	
Radiation		<0.01		<0.01
No	Ref		Ref	
Yes	0.26 (0.19, 0.36)		0.29 (0.20, 0.43)	
Unknown	1.43 (0.80, 2.56)		1.93 (0.98, 3.78)	
NCI Comorbidity Score		<0.01		<0.01
0	Ref		Ref	
1	2.33 (1.70, 3.03)		2.34 (1.69, 3.24)	
2+	3.70 (2.68, 5.10)		4.39 (3.02, 6.37)	

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PROFESSIONAL EXPERIENCE

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- Collaborated within a multidisciplinary team to design and conduct evaluation strategies for university-wide employee wellness programs
- Co-authored abstracts, presentations, reports, and manuscripts for communication of relevant survey results to employees, university stakeholders, and the public health community
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Consultant Scientist in Benefit-Risk Management, May 2012 – January 2013

Global Patient Safety, Eli Lilly and Company

- Communicated up-to-date knowledge of external pharmacovigilance and benefit-risk regulatory requirements to cross-functional stakeholders through oral and written presentations
- Translated external requirements into efficient internal processes to ensure legislative obligations on benefit-risk assessments were met for pre- and post-marketed pharmaceuticals
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Epidemiologist, January 2010 – May 2012

Global Patient Safety, Eli Lilly and Company via DeLisle Associates LTD

- Provided epidemiological consultation within multidisciplinary teams to evaluate safety issues associated with phase II/III and post-marketed compounds
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Project Coordinator/Research Assistant, September 2008 – December 2009

Bowen Research Center, Department of Family Medicine, Indiana University School of Medicine

- Collaborated with local agencies and community stakeholders in the design, surveillance, and evaluation of community-based health programs
- Co-authored abstracts, presentations, reports, and manuscripts for research findings
- Assisted in protocol design and conducted statistical analyses related to diverse public health topics

Teaching Assistant, May 2008 – August 2008

Indiana University Department of Public Health, Indiana University School of Medicine

- Created weekly study guides to assist students in understanding Environmental Science in Public Health course material
- Conducted twice weekly study sessions to answer student questions regarding the subject matter
- Graded exams and homework assignments

Research Assistant, March 2007 – August 2008

Indiana University Center for Bioethics, Indiana University School of Medicine

- Conducted literature reviews regarding ethical issues that would arise in a pandemic
- Analyzed national, state, and local policies regarding altered standards of care, triage, vaccine allocation, and workforce management in a pandemic
- Composed technical advisory documents in conjunction with bioethics and medical experts that included recommendations to the Indiana State Department of Health for the implementation of ethically sound pandemic response policies
- Participated in working groups to gain feedback on the developed documents and incorporated responses into the final deliverables

HONORS

American Association for the Advancement of Science/Science Program for Excellence in Science, 2016

Delta Omega Honorary Society in Public Health, 2009

SMWC Presidential Scholarship Recipient, Fall 2001 - Spring 2005

Saint Mary-of-the-Woods College Great Honors List, 2005

Kappa Gamma Pi National Women's Honor Society, 2005

CRC Freshman Chemistry Achievement Award, 2002

REPORTS AND PUBLICATIONS

Weathers, T.D., & **Alyea, J.M.** (2019). Gauging progress toward a healthier IU: A comparison of IU workplace health and wellness survey results from 2013 to 2019. (Series of reports covering IU overall and each IU campus location). Available at https://healthy.iu.edu/

Johns, S.A., Brown, L.F., Beck-Coon, K., Talib, T.L., Monahan, P.O., Giesler, R.B., Tong, Y., Wilhelm, L., Carpenter, J.S., Von Ah, D., Wagner, C.D., de Groot, M., Schmidt, K., Monceski, D., Danh, M., **Alyea, J.M.**, Miller, K.D., & Kroenke, K. (2016). Randomized

controlled pilot trial of mindfulness-based stress reduction compared to psychoeducational support for persistently fatigued breast and colorectal cancer survivors. *Supportive Care in Cancer*, *24*(10), 4085-4096.

Johns, S.A., Von Ah, D., Brown, L.F., Beck-Coon, K., Talib, T.L., **Alyea, J.M.**, Monahan, P.O., Tong, Y., Wilhelm, L., & Giesler, R.B. (2016). Randomized controlled pilot trial of mindfulness-based stress reduction for breast and colorectal cancer survivors: Effects on cancer-related cognitive impairment. *Journal of Cancer Survivorship: Research and Practice*, *10*(3), 437-448.

Alyea, J.M., Dixon, B.E., Bowie, J., & Kanter, A.S. (2016). Standardizing health care data across an enterprise. In B.E. Dixon (Ed.), Health Information Exchange: Navigating and Managing a Network of Health Information Systems. Elsevier.

Alyea, J.M., Settle, D., Leitner, C., & Dixon, B.E. (2016). Health worker registries: Managing the health care workforce. In B.E. Dixon (Ed.), Health Information Exchange: Navigating and Managing a Network of Health Information Systems. Elsevier.

Weathers, T.D., **Alyea, J.M.**, Staten, L.K., & Steele, G.K. (2016, February). Gauging progress toward a healthier IU: A comparison of the IU Workplace Health and Wellness Survey results from 2013 and 2015: Series of 8 reports focusing on each IU campus location. Available at: https://fsph.iupui.edu/research-centers/workplace-wellness-survey/index.html

Weathers, T.D., **Alyea, J.M.**, Staten, L.K., & Steele, G.K. (2015, December). Gauging progress toward a Healthier IU: A comparison of the IU Workplace Health and Wellness Survey results from 2013 and 2015. Available at https://fsph.iupui.edu/research-centers/workplace-wellness-survey/index.html

Weathers, T.D., **Alyea, J.M.**, Staten, L.K., & Steele, G.K. (2014, October). The Indiana University Workplace Health & Wellness Survey results, 2013. Available at https://fsph.iupui.edu/research-centers/workplace-wellness-survey/index.html

Weathers, T.D., **Alyea, J.M.**, Steele, G.K., & Staten, L.K. (2013, September). IU Workplace Health & Wellness Survey results (Series of 8 campus-specific reports). Available at https://fsph.iupui.edu/research-centers/workplace-wellness-survey/index.html

Zollinger, T.W., Saywell, R.M., **Alyea, J.M.**, Spitznagle, M., Striebel, E., Jay, S.J., et al. (2010). Trends in adult attitudes toward secondhand smoke in Indiana, 2002-2007: the impact of smoking status. *Journal of Public Health Management and Practice*, *16*(4), 294-303.

Zollinger, T.W., Kochhar, K., & **Alyea, J.M.** (2010, February). Report of responses to the 2004, 2006, and 2008 physician assistant re-licensure surveys. Indianapolis, IN: Indiana Area Health Education Centers Program.

Zollinger, T.W., Kochhar, K., Reger, M.K., & **Alyea, J.M.** (2010, January). Registered nurse re-licensure report. Indianapolis, IN: Indiana Area Health Education Centers Program.

Zollinger, T.W., Kochhar, K., **Alyea, J.M.**, & Ray, D.W. (2009, November). Health professions workforce needs assessment report. Terre Haute, IN: West Central Indiana Area Health Education Center.

Zollinger, T.W., & **Alyea, J.M.** (2009, September). National Center of Excellence in Women's Health 2009 patient satisfaction survey. Indianapolis, IN: Indiana University National Center of Excellence in Women's Health.

Zollinger, T.W., Kochhar, K., & **Alyea, J.M.** (2009, May). Family medicine residency 2008 graduate survey. Indianapolis, IN: Indiana University-Methodist Family Medicine Residency Program.

Meslin, E.M., **Alyea, J.M.**, & Helft, P.R. (2008, August). Pandemic influenza preparedness: Ethical issues and recommendations to the Indiana State Department of Health. Indianapolis, IN: Indiana University Center for Bioethics.

PRESENTATIONS

Weathers, T.D., **Alyea, J.M.**, & Munn, T.J. (2020, February) Gauging progress toward a healthier IU: A comparison of the IU Workplace Health & Wellness Survey Results from 2013 to 2019 – Focus on IUPUI. Presented at the IUPUI Faculty Council Meeting, Indianapolis, Indiana.

Weathers, T.D., **Alyea, J.M.**, & Munn, T. (2019, November). Gauging progress toward a healthier IU: A comparison of IU Workplace Health & Wellness Survey results from 2013 to 2019 – Focus on IU Bloomington. Presented at the Indiana University Bloomington Wellness Coalition Meeting in Bloomington, Indiana.

Weathers, T.D., & **Alyea, J.M.** (2019, September). Gauging progress toward a healthier IU: A comparison of IU Workplace Health & Wellness Survey results from 2013 to 2019. Presented at the Healthy IU Steering Committee and Coalition Meeting in Indianapolis, Indiana.

Alyea, J.M., Hilts, K.E., Osburn, L.L., & Hess, L.M. (2015, November). Evaluation of meditation-based interventions for the treatment of post-traumatic stress disorder in adults: a systematic review and meta-analysis. Poster presented at the American Public Health Association (APHA) Annual Meeting & Exposition, Chicago, IL.

Alyea, J.M., Staten, L.K., Steele, G.K., & Weathers, T.D. (2014, November). Consideration of employee mental health in worksite wellness programs: Findings at a large, Midwestern university. Presented at the American Public Health Association (APHA) Annual Meeting & Exposition, New Orleans, LA.

Weathers, T.D., **Alyea, J.M.**, Staten, L.K., & Steele, G.K. (2014, April). Strategies used by a large Midwestern university to build trust and encourage participation in a survey of workplace health & wellness. Poster presented at the International Association for Worksite Health Promotion (IAWHP) Executive Summit on Worksite Health Promotion, Atlanta, GA.

Weathers, T.D., **Alyea, J.M.**, Staten, L.K., & Steele, G.K. (2013, October). Indiana University Workplace Health & Wellness Survey 2013 results: Focus on IUPUI. Presented at the IUPUI Health and Benefits Fair, Indianapolis, IN.

Staten, L.K., Steele, G.K., Weathers, T.D., & **Alyea, J.M.** (2013, September). Indiana University Workplace Health & Wellness Survey 2013 results. Presented at a workshop of university wellness committees and leaders, Indianapolis, IN.

Alyea, J.M., Zollinger, T.W., Saywell, R.M., & Spitznagle, M. (2009, June). Trends in adult attitudes toward secondhand smoke in Indiana, 2002-2007. Poster presented at the National Conference on Tobacco or Health, Phoenix, AZ.

Zollinger, T.W., Kochhar, K., Reger, M.K., & **Alyea, J.M.** (2009, March). Understanding the puzzle: Shortages of health professionals in Indiana. Presented at the Indiana Area Health Education Center 2nd Annual Meeting, Indianapolis, IN.

Lynch, E.K., **Alyea, J.M.**, Nimry, R., Berry, S., Ketterer, S., & Henkle, J. (2008, October). Understanding and preventing school bullying in depth: Research for Clarian Health of Indiana. Poster presented at the American Public Health Association Annual Meeting & Exposition, San Diego, CA.

Lynch, E.K., **Alyea, J.M.**, Nimry, R., Berry, S., Ketterer, S., & Henkle, J. (2008, October). Comprehending school bullying and current interventions: Research for Clarian Health of Indiana. Presented at the American Public Health Association Annual Meeting & Exposition, San Diego, CA.

Archer, J., **Alyea, J.M.**, & Klopfenstein, M. (2008, February). Ethics and pandemic planning. Presented at the Centers for Disease Control and Prevention Public Health Preparedness Summit, Atlanta, GA.