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PROJECT TITLE: *Anti*-estrogen Use, Estrogen Receptor Expression, Smoking Patterns, and Survival of Women with Non-Small-Cell Lung Cancer: A Manitoba Perspective

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BACKGROUND: Lung cancer is the leading cause of cancer death worldwide. Gender differences in lung cancer outcomes are known. When compared to men, women have significantly better survival and women are more likely to develop lung cancer when non-smokers. Research suggests estrogen plays a key role in the risk of development and outcomes of lung cancer. Accordingly, *anti*-estrogen use should also influence survival in female non-small cell lung cancer (NSCLC) patients. In this study we compared mortality among *anti*-estrogen users and non-users. **METHODS**: This population-based study had a retrospective study design. Using the Manitoba Cancer Registry (MCR) we identified all women diagnosed with NSCLC from 2000-2007. The Drug Program Information Network (DPIN) was accessed to establish patients that received *anti*-estrogens. Demographic data (e.g. smoking patterns, stage, histology) was gathered by chart review. Mortality rates for *anti*-estrogen users and non-users were compared using Kaplan-Meier survival functions and Cox regression models. **RESULTS**: 2320 women fit our patient criteria, of which 156 had received prior *anti*-estrogens. A positive smoking history was documented in 88%, 62% being former vs. 26% current smokers. A history of 30+ pack-years was seen in 55%. Exposure to *anti*-estrogen was associated with a significantly decreased mortality (HR 0.718, $p = 0.0031$). Overall survival with *anti*-estrogen vs. none resulted in median survival of 1.89 vs. 0.93 years, respectively ($p < 0.0001$). **CONCLUSIONS**: Our results demonstrate that *anti*-estrogens are associated with decreased mortality from NSCLC. These findings supplement and reinforce past evidence that estrogen plays a key factor in the biology and outcomes of NSCLC.

ACKNOWLEDGEMENTS:

Dr. Gary Harding's Grant funding from The Manitoba Medical Service Foundation (MMSF) and the Winnipeg Foundation (WF)
The Thoracic Oncology Research Group at CancerCare Manitoba.
The Manitoba Health Research Council (MHRC) and CancerCare Manitoba (CCMB) provided stipendiary support

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Anti-estrogen Use, Estrogen Receptor Expression, Smoking Patterns, and Survival of Women with Non-Small-Cell Lung Cancer: A Manitoba Perspective

Lung cancer is the leading cause of cancer death worldwide. Despite advances in treatment, age adjusted 5-year survival rates remain poor at 15% (1). The Canadian Cancer Society estimates that 25,300 Canadians will be diagnosed with lung cancer in 2011 while 20,500 will die from it. Women account for as many as 12,200 of these new cases and 9,300 deaths (2). Since the 1990s, there has been an increasing trend in the incidence of lung cancer cases. Despite a recent decline in incidence and mortality among men in the United States, this epidemic continues to follow an unfortunate rising trend among women in Western Countries (3). While tobacco exposure is a well-established major risk factor for the development of lung cancer, other factors contribute to the differing degree of risk in incidence and death for women in comparison to men (4,5). For example, studies have shown that women were at an increased susceptibility to lung cancer development with a lower overall exposure to tobacco than men. Women and men with equivalent tobacco exposure were also shown to have significantly higher odds for different histological types of lung cancer. Finally, the lifetime occurrence of lung cancer in non-smoking women has been shown to be 2.5 times greater than in non-smoking men (4). Gender differences in survival have also been reported. Females with non-small cell lung cancer (NSCLC) have significantly better survival than males with the same disease, in all stages, histology, and methods of treatment (6,7). These studies suggest that lung cancer is a different disease in women than in men. The reasons for these gender differences remain unclear, but are most likely multifactorial. The aim of this study is to investigate if a relationship exists between *anti*-estrogen use and clinical outcomes in female NSCLC patients in Manitoba.

Biological evidence that sex-specific hormones such as estrogen have a key role to play in the risk and development of NSCLC was provided when steroid receptors were found in lung tumors. Prior research suggests that estrogen increases the risk of lung cancer in women by either directly promoting cell proliferation in the lung, or by influencing lung tumor metabolism or other effects on lung diseases with potential predispositions to lung cancer development (8). These mechanisms may act independently or simultaneously. Estrogen status may be a risk factor for lung cancer development in women. Serum estrogen levels are dependent on endogenous and exogenous factors. These can be modified by factors such as exogenous use of oral contraceptives (OC), hormone replacement therapy (HRT), *anti*-estrogen therapy, or the endogenous occurrence of menopause (8). A recent sub-group analysis of a randomized control trial from the Women's Health Initiative research project, where women were randomly and blindly assigned to estrogen/progesterone use vs. placebo, demonstrated that there was no statistical difference in the incidence of lung cancer between the two arms ($p = 0.16$). However, there was a significant increase in death from lung cancer (mainly due to NSCLC) in the combined hormone group (Hazard Ratio (HR) of death 1.71, 95% CI, 1.16-2.52, $p = 0.01$) (9). Several retrospective studies have attempted to determine the link between NSCLC risk and exogenous hormone use as well. In these studies, conflicting observations, small sample sizes, poor study design, and incomplete analyses have made it difficult to determine a uniform consensus (8,10-12). For this reason, further studies in this field will be required to uncover the potential link between estrogen and NSCLC.

Far less attention has been paid to investigating the blockade of estrogen effects as it relates to NSCLC. Very recently, unique research has offered a different perspective on estrogen status in NSCLC patients. Preliminary research by Bouchardy *et al* (2010) investigated the use of *anti*-estrogens in breast cancer patients as it relates to future NSCLC development and mortality. In this study, 6655 women were diagnosed with breast cancer between 1980-2003 in the Geneva Cancer Registry. Of these, 46% had received some form of oral *anti*-estrogens. Patients with and without *anti*-estrogen use were then followed until December 2007 for occurrence and clinical outcome from lung cancer. These findings were compared with rates expected in the general population by Standardized Incidence Ratios (SIRs) and Standardized Mortality Ratios (SMRs). Analyses included sub-group comparisons based on period of diagnosis and smoking status. The results demonstrated a nonsignificant lower risk of developing lung cancer (SIRs per 100,000 person-years: 0.63 95% CI, 0.33-1.10), and a significantly decreased risk of death from lung cancer among women who received *anti*-estrogen therapy (SMRs per 100,000 person-years: 0.13 95% CI, 0.02-0.47) (13). These findings are consistent with those from previous studies that showed an increased risk of death with exogenous hormone use, as mentioned above.

While studies have reported the presence of estrogen receptors (ERs) in lung tumors (14,15), its role in normal lung tissue and carcinogenesis has yet to be determined. To date, research has focused on two types of estrogen receptors, ERα and ERβ. ERβ has been identified in both normal lung as well as tumour tissue (16,17). Although, ERα mRNA has been detected in lung tumors, there are conflicting reports of immunohistochemical detection of ERα protein in lung tumors (15,16,18,19). Moreover, few studies have investigated any potential correlation between hormone use, ER expression, and the risk of NSCLC. Schwartz *et al* (2007) recently examined 278 paraffin embedded lung tumour samples from men and women and found that there was no significant difference in ERβ status with HRT, OC use, or menopausal status (20). Multivariable analysis determined that there was a nonsignificant increased risk of mortality in women with ERβ -positive tumors. The same authors in a subsequent study identified a significantly decreased risk of NSCLC among HRT users when one or both ERs were expressed (21).

The paucity of research in this area in combination with the conflicting and inconsistent results from previous exogenous hormone and ER biomarker studies exemplifies an evident need for further research on this topic. If exogenous estrogen exposure increases a woman's risk of dying from NSCLC, than *anti*-estrogens may reduce this risk. In this retrospective population based study, we sought to evaluate NSCLC mortality amongst women previously treated with *anti*-estrogen therapy to examine its impact on lung cancer outcome.

Materials and Methods

This is a population-based study with a retrospective study design to determine the relationship that may exist between *anti*-estrogen use and clinical outcomes in female NSCLC patients in Manitoba.

Databases

The International Classification of Diseases (ICD) diagnostic codes have been recorded in a Physician Claims Database since the early 1970s. Personal Health Identification Numbers

(PHIN) were added for every citizen in Manitoba since 1984. The Manitoba Cancer Registry (MCR), a database with a mandatory reporting system, has a collection of all neoplastic diagnoses established in Manitoba (catchment population of approximately 1.2 million) from 1956 onward. The MCR is about 95-98% complete for case ascertainment (22) with positive diagnoses being confirmed with histology and/or cytology.

CancerCare Manitoba (CCMB) has recorded most patient information with the ARIA electronic charting system since 1990. These records were accessed manually to determine demographic information through individual patient chart review not recorded by the MCR. The Drug Program Information Network (DPIN) was also used to determine the type and duration of *anti*-estrogen use by patients, with available records dating back to 1995.

Study Population

All female patients diagnosed with NSCLC from January 1, 2000 to December 31, 2007 were identified from the Manitoba Cancer Registry (MCR) using the International Statistical Classification of Disease Codes (ICD-9 and ICD-10). These were linked to Manitoba Health's DPIN Database using individual patient PHIN numbers. Patients with small cell lung cancer, pleural-based malignancies, other thoracic neoplasms, and unspecified lung cancer were excluded from the study. The final study cohort excluded males. The remaining 2320 females with NSCLC formed the main study cohort, of which 2375 NSCLC tumors were available from multiple primary cancers within the study period. This cohort was categorized based upon never or ever use of *anti*-estrogen as identified using the DPIN database. A positive history for *anti*-estrogen use was defined as a prescription for any *anti*-estrogen (Table 1) issued between 1995-2007. The time horizon chosen is sufficient to determine outcomes such as mortality since the median survival rate of NSCLC patients is less than one year.

Data Collection

Data extracted from the MCR for our patient population included the number of primary lung cancers (NSCLC), date of diagnosis, date of birth, date of death, sex, histology, and treatment modalities. Multiple primary NSCLCs (sequential diagnoses) were considered separate events, with demographic information recorded until the diagnosis date of the subsequent primary lung cancer. The date of diagnosis as recorded by the MCR is the date of first sample collection that pathologically confirmed NSCLC and the date of death were followed until May 31, 2011. Staging data was available from the MCR from January 2004 – December 2007 as determined by the Cancer Registry Collaborative Staging Group. The staging system used at this time was the 6^{th} edition of the American Joint Committee on Cancer (AJCC) TNM staging system. Earlier Physician based staging was compiled manually through ARIA electronic individual chart review for the rest of the cohort from January 2000 – December 2004. The overlapping physician based working stage data from 2004 was compared to the gold standard Cancer Registry Collaborative Staging and was found to be similar. Therefore all staging information was compiled together for the entire cohort.

Demographic data was manually collected from the ARIA electronic charting system. Individual patient Cancer Registry ID numbers were manually entered into the ARIA system to gain access

to physician notes such as history and physical examination documentation and progress notes, as well as pathology reports and other staging investigations. Information was available for roughly two thirds of our patient cohort who presented to CCMB following diagnosis, however those with pathologically proven NSCLC as reported by the MCR that were never seen at CCMB had no available information. All available notes were thoroughly read and analyzed, compiling data such as proportion of documented smoking histories, never or ever smoker, past or present smoker, and amount of smoking exposure. This is the first time smoking data has ever been compiled among our lung cancer population in Manitoba, and was critical to our study to rule out its potential confounding impact on our survival analysis. Also, staging information was missing for roughly half of our patient population. In order to retain a large sample size for multivariable analysis it was imperative to accumulate data on physician working based stage, as described above. This data was also compiled meticulously from information within physician notes, as well as pathology reports and staging investigations.

Research Ethics Board (REB) approval was obtained by the University of Manitoba REB. CancerCare Manitoba's Research Impact Committee also approved the study.

Statistical Methods

The primary goal of this analysis was to determine the effects of *anti*-estrogen use on survival and quantify this effect over time. Our main cohort was divided into two groups: those patients that received *anti*-estrogen therapy and those patients that did not receive *anti*-estrogen therapy. These cohorts were further subdivided based on smoking histories explored or not explored. This smoking data was included in our multivariable Cox regression model to evaluate differences in smoking patterns as they relate to the effects of *anti*-estrogen use on survival, based on groups of ever smokers (past and current) vs. never smoker. These Cox regression models were also run for both our full cohort and a sub-cohort of patients with smoking data, and compared for their impact on survival. Differences in survival patterns were quantified by comparing *anti*-estrogen users' survival to non-users. Survival was measured from the date of diagnosis to the date of death or end of study (May 31, 2011). Survival analysis was performed using Kaplan-Meier survival functions, log rank testing, and a multivariable Cox proportional hazards survival model using SAS statistical software. We also performed exploratory analyses, where *anti*-estrogen users were further stratified into users of the selective estrogen receptor modulators (SERMs) tamoxifen and/or raloxifene, vs. users of other *anti*-estrogens such as aromatase inhibitors and/or non-users.

Results

We identified 2,320 women diagnosed with NSCLC that fit our patient criteria of which 156 received *anti*-estrogen therapy and 2,164 did not. Demographic characteristics and the distribution of potential confounders were analyzed via a retrospective chart study and are summarized in Table 2. Mean age at diagnosis for both *anti*-estrogen and no *anti*-estrogen groups was 69. Of our 2,320-person cohort, we accessed 1,594 electronic charts to gather smoking data (Table 3). Smoking history was explored and documented by physicians in 83% (n = 1,317) of cases. As with most lung cancer populations, a considerably larger number of patients reported a positive smoking history (88%, n = 1,154) than never smokers (12%, n = 163). The

proportion of smokers was very similar in those treated with *anti*-estrogen therapy (83%) vs. those who were not (88%). Of those who were smokers, 62% were documented as a former smoker (n = 845) and 26% (n = 346) as current smokers at the time of diagnosis. Furthermore, amount of tobacco exposure was recorded in 64% (n = 860) of cases and identified less than 1% (n = 6) whom had fewer than 5 pack-year history of smoking, 25% (n = 214) had a 5-29 pack-year history, and 55% (n = 477) had a 30+ pack-year history.

Univariate analysis of overall survival by *anti*-estrogen use revealed a median, mean, and 5-year survival of 1.89 years, 3.38 years, and 33%, respectively, among our *anti*-estrogen cohort. These rates were significantly higher than those without *anti*-estrogen use, with median, mean, and 5-year survival rates of 0.93 years, 2.78 years, and 22%, respectively ($p < 0.0001$) (Figure 1). *Anti*-estrogen users, as validated by our Cox Regression model, illustrated a protective effect on mortality (HR 0.718, $p = 0.0031$) as shown in Figure 2. In this regression model, mortality was adjusted for age (<70, 70+), histology (adenocarcinoma, non-adenocarcinoma), stage 3 vs. stage 1 and 2 and stage 4 vs. stage 1 and 2 separately. All these variables had significant impact on survival as summarized in Table 4.

Anti-estrogen use was further stratified into use of selective estrogen receptor modulators (SERMs) vs. other or no *anti*-estrogen use (i.e. aromatase inhibitors (AIs), AIs in combination with SERMs, or no *anti*-estrogen use) and this regression analysis controlled for the same aforementioned variables. This resulted in a slightly less protective role with SERM use, however it did not maintain statistical significance (HR 0.830, $p = 0.1930$).

A separate sensitivity analysis looking at patients with smoking histories (n = 1184) revealed that smoking did not change the effect of *anti*-estrogen use on survival. Overall, smoking as a predictor of survival was found to be non-significant (HR 1.103, p = 0.3248). Additionally, *anti*-estrogens were found to have similar protective effects in smokers (HR 0.745, p = 0.0179) as our final Cox regression model.

Discussion

When comparing mortality differences among *anti*-estrogen users and non-users, we found that its effects were associated with a significantly decreased risk of death from all causes in female NSCLC patients. Multivariable analyses additionally demonstrated *anti*-estrogens association with decreased mortality when controlling for age, histology, and stage. A similar Manitoban population (1995-2004) consisting of males and females was previously investigated in a recent study by Pitz *et al* (2009), which demonstrated gender differences in survival among NSCLC patients (23), thus this patient population was appropriate to examine. Therefore our findings further support the building evidence that estrogen, estrogen receptors, and estrogen signaling pathways play a contributory role in the biology of lung carcinogenesis and progression.

Since smoking is the greatest established risk factor for lung cancer, it is important to account for smoking differences and trends in both cohorts. We found similar smoking patterns within these cohorts: 82.9% ever smokers within the *anti*-estrogen group, and 88.4% ever smokers in the no *anti*-estrogen group. These rates are consistent with those reported in previous studies (24,25). Additionally, smoking was explored as a predictor of survival in our Cox regression model and

shown to have a non-significant impact. After stratifying our cohort based on smoking histories explored, we found nearly identical significant impacts on survival when compared to our entire cohort. While smoking histories were available for roughly one half of our patient population, the consistency of smoking percentages with past studies implies a likely similarity among patients for which we were unable to obtain smoking information. Therefore the protective effects of *anti*-estrogens demonstrated in our study are unlikely attributable to smoking differences in both populations.

A potential explanation for the survival benefits illustrated in our *anti*-estrogen cohort lies in the nature of our study design. Since most women receiving *anti*-estrogen therapy had a previous history of breast cancer, it is possible that these patients received more routine follow up examinations and physician visits, leading to earlier detection of new NSCLC primaries as compared to the general population. In fact, women within the *anti*-estrogen cohort presented with an earlier stage of disease as compared to the non-users (Stage I 26.3% and 20.5% respectively; Stage II 5.8% and 4.5% respectively). *Anti*-estrogen users also presented with surgically resectable disease more frequently than non-users (41.7% and 31.6% respectively).

Our findings that *anti*-estrogen users are associated with a decreased risk of mortality are consistent with past studies investigating estrogen levels and its effect on incidence and mortality for lung cancer (9,10,13,26). A recent study by Bouchardy *et al* (2010) followed a cohort of breast cancer patients receiving *anti*-estrogen therapy for risk of development and outcomes of future lung cancer. While their results showed no difference in *anti*-estrogens effect on incidence of lung cancer, they demonstrated a significant benefit in mortality among women with *anti*-estrogen (Standardized Mortality Ratio (SMR) 0.13 95% CI, 0.02 – 0.47, $p < 0.001$) but not for women without *anti*-estrogen (SMR 0.76, 95% CI, 0.43 – 1.23) (13).

While this study as well as ours demonstrated the protective nature of low estrogen states, it is also in accordance with studies investigating high levels of estrogen, such as with HRT, which was associated with a greater risk of mortality. The Women's Health Initiative Trial (WHI) is the only randomized control trial to date that investigates the effects of hormones in lung cancer outcomes. This trial was also consistent with our results, in that the trial was ended early since more women died from NSCLC in the combined hormone group vs. the placebo group (62 vs. 31 deaths; 0.09% vs. 0.04%; HR 1.87, 95% CI, 1.22 – 2.88, $p = 0.004$) (9). A study by Ganti *et al* (2006) determined worse survival in women with HRT as compared to no HRT (survival 39 vs. 79 months, HR 1.97, 95% CI, 1.14 – 3.39) (10). A more recent publication by Slatore *et al* (2010) illustrated an increased risk of incident lung cancer with estrogen + progestin (E + P) formulations of HRT in a dose dependent manner (HR 1.27 for E + P use 1 – 9 years, 95% CI, 0.91 – 1.78 and HR 1.48 for E + P use 10+ years, 95% CI, 1.03 – 2.12, p for trend 0.03) (26). Interestingly, there was no association with duration of unopposed conjugated equine estrogen use in this study, as well as in a post hoc analysis of the WHI trial (HR 1.07, 95% CI, 0.66 – 1.72, $p = 0.79$) (26,27).

These studies, along with our findings, suggest that high estrogen states lead to worse clinical outcomes, however these trends have not always been observed. Past studies found a lack of association between HRT and clinical outcomes (11,27,28) whereas protective effects have been reported in others (8,29,30). In a case control study by Ettinger *et al* (1996), HRT use resulted in

significant decreased all cause mortality (age adjusted relative risk (RR) 0.54, 95% CI, 0.38 – 0.76) (30). Schabath *et al* (2004) similarly reported a decreased risk of death and improved survival with HRT use, and a decreased incidence of lung cancer by 34% (odds ratio (OR) 0.66, 95% CI, 0.51 – 0.89) (29).

Although these inconsistencies among studies may be due to several factors, evidence suggests that they may be primarily due to differences in study designs. First, differences in smoking patterns within patient populations may account for large variations in survival outcomes. For example, HRT was found to only significantly reduce lung CA incidence in current smokers, and its protective nature in former and non-smokers was not significant in the study by Schabath *et al* mentioned above. Additionally, as tobacco exposure increased, its protective effects diminished substantially, suggesting DNA damage is required to alter estrogens protective nature, but as DNA adducts accumulate from increasing tobacco exposure, estrogens effects are diminished or lost (29). Thus limitations in availability of smoking information, as well as its complex interaction with the biology of lung cancer and estrogen status, make it difficult to interpret these results. Second, most of the studies done to date report death as all cause mortality. Since estrogen is known to affect many physiological systems and alter clinical outcomes in diseases other than cancer, its specific mortality effects on lung cancer remain unclear. For example, the strongest available evidence is in estrogen's protective role in heart disease (9,30). While median survival for NSCLC patients is less than one year, prevention of co-morbidities related to estrogen status prior to development of NSCLC may alter their clinical outcomes.

Despite the fact that estrogens exact biological mechanisms in both normal lung and lung tumors have yet to be deciphered, studies have shown the presence of estrogen receptors (ERs) alpha and beta in normal lungs (17,19) and the overwhelming majority of NSCLCs (18,20,28,31,32). This strongly suggests that estrogens are involved in lung cancer via ER-mediated cell signaling pathways. Experiments have demonstrated stimulatory effects via the ER-mediated pathways on NSCLC cell proliferation (31,32). When exposed to the SERMs tamoxifen or raloxifene, cell proliferation and tumor growth was inhibited by estrogen (33,34). As well, high levels of aromatase expression, an enzyme responsible for the biosynthesis of estrogens, were associated with a worse prognosis in NSCLC patients with early stage disease (35). While further research is necessary to outline the exact signaling pathways involved, these molecular studies help explain a potential biological mechanism behind the protective effects of *anti*-estrogen on lung cancer outcomes as demonstrated in our study.

Our study had inherent strengths and limitations. Access to the MCR captured all NSCLC cases, which provided us with a large population based cohort, eliminating selection bias. Fortunately, access to the DPIN database provided us with a reliable method of accessing *anti*-estrogen data. Information on type of *anti*-estrogen and whether or not the prescription was filled eliminated the potential for biases that result from patient questionnaires and patient recall. However, DPIN information was limited to prescriptions issued only as far back as 1995 and thus any prior *anti*-estrogen use was not discovered. Duration and dosage of *anti*-estrogen use was not assessed. Further limitations included the retrospective nature of our study, the small number of *anti*-estrogen users, limited smoking data, missing chart information, and incomplete staging data for a portion of our cohort. While previous studies have commented on estrogens effect on incidence

and development of lung cancer, we could not comment on such phenomena based on the nature of our population.

The biological mechanisms of estrogen in lung tissues and tumors remain understudied. In order for us to fully elicit the role of estrogen in lung carcinogenesis and survival outcomes, future molecular studies are required via well designed hypothesis driven studies to determine the physiologic role of estrogen in ER-mediated cell signaling. Furthermore, there is a need to collaborate with other institutions to develop a large database of female NSCLC patients, who have been treated with *anti*-estrogens and have available tumor sections that can be utilized for immunohistochemical (IHC) scoring for ERs, and correlated to clinical outcomes. These would be compared to female NSCLC patients whom have not received *anti*-estrogens and analyzed for benefits in survival. Results from these studies will allow for more evidence-based patient discussions with regards to counseling on the risks and benefits of hormone replacement therapy, oral contraceptive use, and *anti*-estrogen therapy. Randomized control trials of *anti*-estrogens vs. placebo in lung cancer may also provide useful insights in its effect in lung cancer biology as it relates to survival outcome. Moreover, molecular based testing such as IHC could provide a predictive and prognostic value on prognosis from NSCLC. Available tissue samples would be a requirement to the study and survival should be analyzed and stratified by ER expression.

In conclusion, our study demonstrates that exposure to *anti*-estrogen therapy is associated with decreased mortality from NSCLC. These findings supplement and reinforce past evidence suggesting that estrogen plays a key factor in the biology of NSCLC and its progression. ;.

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Tables and Figures

Table 1: *Anti*-estrogens searched for in the Drug Program Information Network (DPIN)

Anti-estrogen	Drug Name	Trade Name
	Tamoxifen	
	Anastrazole	Arimidex
	Letrozole	Femara
	Exemestane	Aromasin
	Raloxifene	Evista
	Aminoglutethimide	
	Toremifene	Fareston
	Fulvestrant	Faslodex
	Formestane	Lenatron
	Fadrozole	
	Megestrol Acetate	Megace
	Mifepristone	Mifeprex
	Afimoxifene	
	Levonorgestrel	Mirena, Next Choice, Plan B, Plan B One-Step
	Lasofoxifene	Fablyn
	Goserelin	Zoladex
	Leuprolide	Lupron

Table 2: Demographic characteristics of female NSCLC patients, Manitoba, 2000-2007

	Anti-estrogen Therapy			
	Yes (n = 156)		No (n = 2,164)	
Age				
<55	9	5.7	228	10.3
55 -74	96	61.5	1,152	51.8
75+	51	32.7	842	37.9
Mean	69		69	
Median	70		71	
Range	46-89		25-99	
Smoking Status				
Not Explored	45	28.8	979	44.1
Explored	111	71.2	1,243	55.9
Never	19	17.1	144	11.6
Ever	92	82.9	1099	88.4
Past	66	71.7	779	70.9
Current	26	28.3	320	29.1
Amount (pack-years)	65		795	
0	19	29.2	144	18.1
<5	0	0	6	0.7
5-29	14	21.5	200	25.2
30+	32	49.2	445	56.0
Staging				
I	41	26.3	455	20.5
II	9	5.8	101	4.5
III	36	23.1	459	20.7
IV	37	23.7	684	30.8
Unknown	33	21.1	523	23.5
Treatment				
Surgery				
Yes	65	41.7	702	31.6
No	91	58.3	1,520	68.4
Radiotherapy				
Yes	63	40.4	947	42.6
No	93	59.6	1,275	57.4
Chemotherapy				
Yes	46	29.5	493	22.2
No	110	70.5	1,729	77.8

Table 3: Smoking patterns in women with NSCLC in Manitoba, 2000-2007

	Frequency	Percentage
Smoking Status		
Not Explored & Documented	240	15
Explored & Documented	1354	85
Never	163	12
Ever	1191	88
Past	845	62
Current	346	26
Pack-years of smoking		
Never smoker	163	12
<5	6	1
5-29	214	16
30+	477	35
Unknown	494	36

Table 4: Multivariable Cox proportional hazards model of all female NSCLC patients in Manitoba, 2000-2007

Parameter	Hazard Ratio (95% CI)	p value
Anti-Estrogen Use vs. Non-Use	0.718	0.0031
Stage 3 vs. Stage 1 & 2	3.503	<0.0001
Stage 4 vs. Stage 1 & 2	6.391	<0.0001
Adenocarcinoma vs. Non-Adenocarcinoma	0.663	<0.0001
Age <70 vs. 70+	1.358	<0.0001

Figure 1: Kaplan-Meier survival function for *anti*-estrogen users vs. non-users

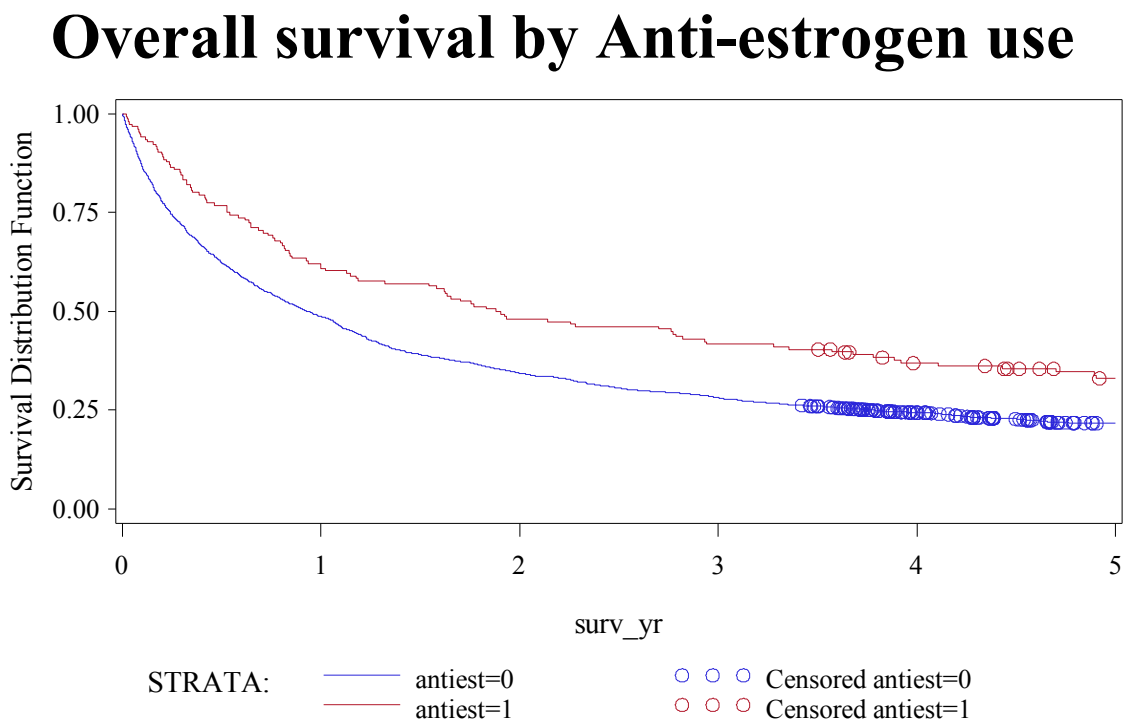

Figure 2: Adjusted Kaplan-Meier survival function for all female NSCLC patients in Manitoba, 2000-2007 by *anti*-estrogen use vs. non-use.

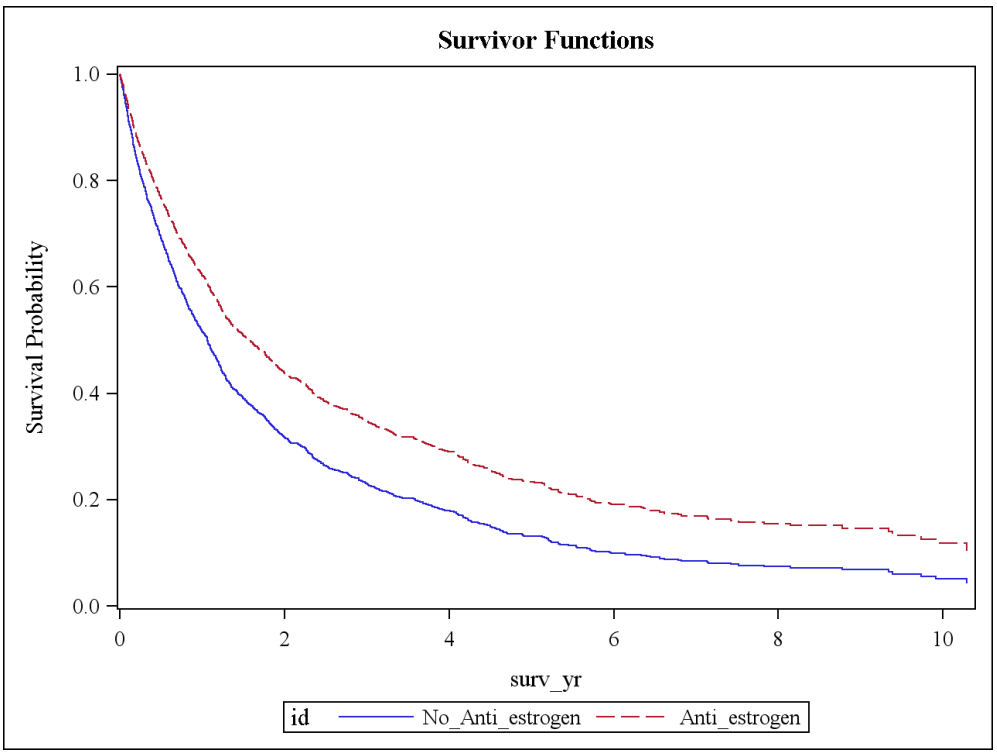

Figure 3: Adjusted Kaplan-Meier survival function for all female NSCLC patients in Manitoba, 2000-20007 by use of SERMs only (tamoxifen/raloxifene) vs. other type or no *anti*-estrogen