ABSTRACT

Title to Thesis: REPRODUCTIVE AND HORMONAL FACTORS IN RELATION TO LUNG CANCER AMONG NEPALI WOMEN

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Over 50% of global lung cancer incidence occurs in less developed regions (LDRs). Despite this, little is known regarding lung cancer risk factors in LDRs such as Nepal. Using data from a hospital-based case-control study conducted in B. P. Koirala Memorial Cancer Hospital (Nepal, 2009-2012), relationships between reproductive and hormonal factors and lung cancer were examined among women aged 23-85 years. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariable logistic regression. Among postmenopausal women, those with a younger age at menopause (<45years; 45-49years) had an increased odds of lung cancer compared to those with an older (≥50years) age at menopause (OR=2.14, 95%CI=1.09, 4.17; OR=1.93, 95%CI=1.07, 3.51, respectively), after adjusting for age and cumulative active smoking. This is the first study to characterize these relationships among Nepali women. Further research is needed to elucidate the role of age at menopause in lung cancer within this understudied population.

REPRODUCTIVE AND HORMONAL FACTORS IN RELATION TO LUNG CANCER AMONG NEPALI WOMEN

by

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DEDICATION

For my parents Nasir and Sufia Vohra.

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CHAPTER I

INTRODUCTION

1.1 Background of the Study

Lung cancer is the most commonly diagnosed cancer and the primary cause of cancer mortality worldwide[1-4]. Approximately 58% of the global lung cancer incidence and 60% of the global lung cancer mortality, in 2012, occurred in less developed regions (LDRs) [4], which include all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia[5]. These figures are only expected to increase in the next decade. However, epidemiologic data on the risk factors of lung cancer in LDRs such as Nepal is still scarce.

Several studies conducted in more developed regions, which include Europe, Northern America, Australia, New Zealand and Japan[5], have suggested potential gender differences in risk[6-10]. Some investigators have reported that women may be more susceptible to the carcinogenic effects of tobacco[6-8] and that they represent a higher proportion of non-smoking lung cancer patients[9], as compared to men. Kiyohara et al. reviewed the existing literature on gender and lung cancer susceptibility in 2010 and concluded that women may have a greater risk of lung cancer for a given level of tobacco smoke exposure[10]. Thus, the risk of developing lung cancer may vary by gender.

The differential distribution of histological subtypes by gender[11] and the presence of specific hormone receptors on lung cancer cells[12] support a role for

reproductive and hormonal factors in the development of lung cancer. Lung cancer in women is more likely to be classified as adenocarcinoma, whereas among men, squamous cell carcinoma is more commonly diagnosed[11]. In addition, female sex-hormone receptors (estrogen-β and progesterone receptors) have been found on human lung cancer cells[12]. According to Omoto and colleagues, adenocarcinomas exhibited significantly higher expression of estrogen-β receptors than squamous cell carcinomas[13]. Stabile et al. observed that incubation of lung cancer-derived cell lines with β-estradiol significantly increased cellular proliferation and that anti-estrogens or estrogen antagonists inhibited this proliferation, suggesting that estrogen could theoretically promote lung cancer[14]. Taken together, these results provide a mechanistic rationale to investigate the role of reproductive and hormonal factors in the development of lung cancer.

While several studies have investigated the association between reproductive and hormonal factors and lung cancer in more developed regions of the world [15-30], no prior study has assessed this relationship in LDRs such as Nepal. Furthermore, the distributions of reproductive and hormonal characteristics have not been well characterized among Nepali women. Given the increased lung cancer global burden in LDRs, the suggested higher susceptibility among women, and the above mentioned biological rationale, the relationship between reproductive and hormonal factors and lung cancer among Nepali women was examined.

1.2 Specific Aims

The current study addresses the following specific aims:

I. Primary Aim: To investigate reproductive and hormonal factors (such as age at menarche, age at menopause, menstrual duration, number of pregnancies or gravidity, age at first birth, age at first live-birth, and birth control use) in relation to lung cancer among Nepali women.

   Hypothesis: The odds of lung cancer among Nepali women will differ by reproductive and hormonal factors. More specifically, reproductive and hormonal factors, such as younger age at menarche, older age at menopause, longer menstrual duration, lower number of pregnancies or nulligravidity, older age at first birth, older age at first live-birth, and birth control use, will be associated with an increased odds of lung cancer.

II. Secondary Aims: To examine if the relationship between reproductive and hormonal factors and lung cancer among Nepali women varies by smoking status.

   Hypothesis: The relationship between reproductive and hormonal factors and lung cancer will differ by smoking status.

1.3 Significance of the Study

According to the World Bank, Nepal is one of the poorest countries in the world[31]. In 2012, the country had an estimated total population of approximately 27.5 million people, of which 25% were living under the national poverty line at that time[32]. Approximately 120 per 100,000 deaths are estimated to be due to

cancer in Nepal[33]. The B. P. Koirala Memorial Cancer Hospital (BPKMCH), which is the first national cancer center in Nepal, predicts that there are approximately 35,000 to 40,000 prevalent cancer cases in Nepal[33]. However, Nepal's national cancer control program is in its early stages of development and it may encounter major hindrances due to the scarcity of data on cancer risk factors among the Nepali populace[34].

In 2009, Pradhananga and colleagues compiled data from seven major cancer diagnostics and treatment hospitals to assess the cancer burden in Nepal, and reported that cervix uteri, breast and lung were the most cancer common sites among Nepali women[35]. Pradhananga et al. also noted that main cancer sites were different based on age groups, and that lung cancer was the number one cancer site for females seventy years old and above and the third most common cancer among Nepali women overall[35].

In summary, lung cancer is one of the three most common cancers among Nepali women. However, as aforementioned, research on the risk factors of lung cancer in a Nepali population is lacking. More specifically, the relationship between reproductive and hormonal factors and lung cancer among Nepali women has not been examined previously. Thus, the overall objective of the current research is to enhance the understanding of the underlying risk factors associated with lung cancer among Nepali women.

1.4 Literature Review

Several epidemiological studies in more developed regions have investigated the role of female reproductive and hormonal factors in the development of lung cancer[15-30]. These studies have reported mixed findings on the association of lung cancer with reproductive and hormonal factors such as parity[15-23, 25, 27, 29-30], gravidity[21], age at first pregnancy[21, 29], age at first birth[15-21, 23, 25, 30], age at menarche[15-19, 21-23, 25, 29-30], age at menopause[15-19, 21-23, 29-30], use of oral contraceptives[16-19, 22-23, 25, 27, 29], duration of oral contraceptive use[16-19, 22, 25, 27, 29], and use of post-menopausal hormones[16-19, 22-27, 29].

Overall, a majority of the large prospective cohort studies have observed an inverse association between age at menopause and lung cancer[17, 19, 23]. In a prospective analysis of the NIH-AARP Diet and Health study cohort with approximately 185,000 women who were ages 50-71 years, the investigators found that age at natural menopause was inversely associated with lung cancer risk[17]. After stratifying by smoking status, this significant inverse relationship was observed only among former and current smokers[17]. Similarly, Baik et al. [19] and Weiss et al. [23] reported an increased risk of lung cancer among postmenopausal women with younger age at menopause, among the participants of the Nurses' Health Study[19] and the Shanghai Women's Health Study cohort[23], respectively.

Although several studies have found an inverse association between parity and lung cancer[15-16, 18, 20, 22-23], two recent large prospective cohort studies, by Brinton et al. [17] and Baik et al. [19], have reported null associations between parity and lung cancer. Similarly, the majority of studies have reported a null

association between lung cancer and the other reproductive and hormonal factors, such as age at first birth[15-16, 18, 20-21, 23, 30], age at menarche[15-16, 18-19, 21-23, 25, 29], use of oral contraceptives[16-19, 22-23, 25, 27], duration of oral contraceptive use[16-18, 22, 25, 27, 29], and use of post-menopausal hormones[16-19, 22-23, 27].

A detailed review of these studies and their findings, with respect to the independent variables of interest, is provided in Appendices B-J.

CHAPTER II

METHODS

2.1 Case – Control Study Design

This ancillary study utilizes data from a hospital-based case-control study, which was conducted between November 2009 and December 2012, at the B. P. Koirala Memorial Cancer Hospital (BPKMCH) in the city of Bharatpur, Chitwan district[34]. The BPKMCH is the primary cancer referral center in Nepal. About 606 lung cancer cases and 606 frequency-matched controls, based on age (±5 years), sex, ethnicity and residential area (district), were recruited for the main study. Lung cancer was defined according the International Classification of Diseases for Oncology, 2nd Edition (ICD-O2) codes C33 (trachea) and C34 (bronchus and lung). The follow inclusion and exclusion criteria, and data collection methodology were used during the primary study.

Inclusion Criteria: Eligible cases included patients diagnosed with primary lung cancer at the BPKMCH.

Eligible controls included visitors (family and friends) of the non-lung cancer patients, subjects being screened for cancer and subjects accompanying the person being screened, at the BPKMCH hospital during the study period.

Exclusion Criteria: Lung cancer patients were excluded if they were younger than 18 years of age or if they were not residents of Nepal for at least 5 years prior to the study. False positive cases were excluded from the study, once histological,

cytological or X-ray-based diagnoses were performed. Family members of the lung-cancer patient were ineligible to participate as controls.

Data collection: All eligible participants were interviewed in-person by a trained staff member (nurse), who collected detailed information on tobacco and alcohol consumption, occupational history, reproductive and hormonal factors, medical conditions, family history of cancer, dietary habits and other lifestyle factors using a standardized questionnaire. Information from all eligible cases was collected as soon as possible after initial lung cancer diagnosis in order to ensure minimal loss of cases due to death. A target interval of one day and a maximal interval of three months between diagnosis and recruitment were used for data attainment. Informed consent was obtained from the patient and their physician prior to data collection.

2.2 Analytic Population

For the present research, cases were defined as primary incidence of lung cancer diagnosed at the B. P. Koirala Memorial Cancer Hospital between 2009 and 2012. The main case-control study consisted of 268 female lung cancer cases and 226 frequency-matched hospital-based controls. One lung cancer case was excluded from the current analysis due to a previous diagnosis of breast cancer (prior to the lung cancer diagnosis). Thus, the final analytic population for this study included 267 cases and 226 controls.

2.3 Dependent Variable

Lung cancer was the primary outcome of interest. As aforementioned, the primary case-control study classified lung cancer based on the ICD-O2 codes C33 and C34. False positive cases, which were estimated to be around ten to twenty percent, were excluded from the study after final diagnosis. Final lung cancer diagnosis of eligible cases was confirmed by a histological, cytological or X-ray-based diagnosis. For the current analysis, lung cancer was classified as "yes" (cases) or "no" (controls).

2.4 Independent Variables

The main exposures of interest consisted of reproductive and hormonal factors such as:

Menopausal status: Classified as "pre-menopausal", "post-menopausal" or "unknown". Pre-menopausal women were defined as those who reported still menstruating, at the time of questionnaire completion. Post-menopausal women were defined as those who reported to have stopped menstruating.

Age at menarche: Defined as the age at which the participant reported having her first menstrual period (continuous measure). For the current study, this variable was analyzed as a continuous as well as a categorical variable. Categories such as <14, 14 and ≥15 years of age were formed, based on the variable's distribution among the controls; missing values were categorized as "unknown".

Age at menopause: Defined as the age at which the participant reported having her last menstrual period (continuous measure). The present study evaluated this variable as a continuous and a categorical variable, among women who self-reported being post-menopausal. Categories such as <45, 45-49 and ≥50 years of age were used, which were based on the variable distribution among the controls; missing values were categorized as “unknown”.

Menstrual Duration: Defined as the difference between the participant’s reported age at menarche and age at menopause. Menstrual duration was examined as a continuous variable, among post-menopausal women (defined above).

Number of Pregnancies (Gravidity): Defined as the number of times a woman reported being pregnant (continuous measure). For the current analysis, gravidity was evaluated as a continuous and a categorical variable. Based on the distribution of this variable within the population, categories such as ≤2, 3-5 and >5 pregnancies were created.

Age at First Birth: Defined as age reported for the completion of the first pregnancy irrespective of whether it resulted in a live birth, miscarriage, abortion or other outcomes. Age at first birth was measured by the primary study as a continuous variable. It was analyzed by the current study as a continuous and a categorical variable. Based on the distribution of the variable within the population, a combination variable was created with categories such as “unknown”, “never pregnant”, “<18”, “18-20” and “≥21” years of age at first birth; missing values were categorized as “unknown”.

Age at First Live-Birth: Defined as the age reported for the first pregnancy that resulted in a live-birth (continuous measure). Similar to age at first birth, this variable was also categorized, for the current analysis, as “unknown”, “never pregnant”, “<18”, “18-20” and “≥21” years, based on the distribution of this variable in the study population; missing values were categorized as “unknown”.

Birth Control (BC) use: Defined as self-reported use of any birth control by the participant. Birth control use was classified as “ever”, “never” or “unknown”.

2.5 Covariates

Age: Defined as the reported age (in years) of the participant at the time the questionnaire was administered (analyzed as a continuous measure).

Tobacco use: Classified as “ever” and “never”. A participant was assigned to the “ever” category if she reported smoking >100 cigarettes, bidi, kankat or choor, over her lifetime. Otherwise, the subject was categorized as a “never” smoker.

Years of tobacco product use: Defined as the total years of use of individual tobacco product (including filtered and unfiltered cigarettes, bidi, kankat or choor, hookat or pipe and hashish); analyzed as a continuous measure.

Cumulative active smoking: Defined as the sum of the total years of use of each tobacco product. This variable was used as a continuous variable for logistic regression adjustment and as a categorical variable (with categories: <15 year and ≥ 15 years) for the stratified analysis. The categories for the stratified analysis were based on the mean cumulative active smoking years among the controls.

Pack-years of smoking: Calculated by multiplying years of use by frequency of use divided by 20 for each tobacco product (analyzed as a continuous measure).

Body Mass Index (BMI): Generated using the weight of women (self-reported for the year before the questionnaire was administered) in kilograms divided by their height in meters squared. This variable was used as a continuous variable.

Residential area: Defined as the most current self-reported residential area; classified as “Rural” or “Urban”.

Ethnicity: Determined based on the participant’s report of their ethnicity, categorized as Brahmin, Chettri, Rai, Madishe, Limbu, Magar, Tharu or other. Due to the similarities between the Madishe and Tharu ethnicities, the present analysis combined the Madishe and Tharu ethnicity to form a “Madishe/Tharu” group. Rai, Limbu, Magar and others were combined into one group to form the “Other” group.

First degree family history of cancer: Defined on the basis of having at least one first degree relative (father, mother, brothers, sisters, sons or daughters) who have or had cancer (of any site); classified as “yes” or “no” in the analysis.

History of medical conditions (such as tuberculosis, asthma, bronchitis, allergic eczema, emphysema, pneumonia, silicosis, and asbestosis): Participants self-reported history of these medical conditions, indicated by “yes” or “no” on the questionnaire. The dichotomous variables were used in analyses.

Education: Defined as the highest level of education received. Categories such as “None”, “Elementary” and “High school” were formed, based on the distribution of this variable within the population. The “None” category included subjects who reported having no education. “Elementary” included individuals who reported having any education upper to 7^{th} standard. The “High school” category consisted of individuals who reported their highest level of education as 8^{th} standard or above.

Alcohol consumption: Classified as “ever” and “never”. Participants were assigned to the “ever” category if they reported consuming any alcoholic beverage at least once a week for at least six months during their lifetime.

Marital status: Defined as the reported marital status at the time of the study and categorized as “Married” and “Unmarried/Widowed”.

Family Monthly Income: The primary study asked participants to indicate their monthly family income using categories such as <500, 500-999, 1000-1999, 2000-4999 and ≥5000 rupees. For the current analysis, these categories were further reduced to “≤999”, “1000-1999” and “≥2000”.

2.6 Data Analysis

Data management procedures were employed including checking for incorrect or implausible values. Simple descriptive statistics on the independent variables (means, standard deviations, frequencies and cross-tabs) were used to check for extreme values or coding errors. The frequency distributions of each variable of interest were checked and analytic variables were generated as

needed. Continuous variables were categorized as needed, based on the distribution among controls, and the frequency distributions of the newly categorized variables were also checked.

Descriptive characteristics of the cases and controls were compared using the student's t-tests and chi-square tests. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between each exposure and lung cancer were estimated using logistic regression. The following parsimonious models were performed and are presented here in: 1) unadjusted, 2) age adjusted and 3) age and CAS adjusted. Reproductive and hormonal exposures assessed include menstrual duration, menopausal status, age at menopause, age at menarche, number of pregnancies, age at first birth, age at first live-birth and birth control use; unknown categories were retained in the model. Model diagnostics were performed for the final models. Additionally, p-trends for all ordinal categorical exposure variables in each of these models were calculated using logistic regression.

Based on prior literature, potential confounders were identified a priori, including age, smoking history, BMI, residential history, ethnicity, marital status, education, family monthly income, first degree family history of cancer, history of medical condition (including tuberculosis, asthma and pneumonia), and alcohol consumption. After adjusting for CAS, none of the above mentioned potential confounders changed the estimated ORs by more than 10%. Thus, the final parsimonious model included adjustment for age and CAS. Additionally, a final

model that mutually adjusted for all exposure variables of interest was created using logistic regression, and ORs and 95% CIs were estimated.

Lastly, ORs and 95% CIs for the relationship between each exposure variable of interest and lung cancer were calculated by strata of cumulative active smoking years. Individual interaction terms (between each exposure of interest and CAS) were checked for significance by comparing likelihood ratios of the full model (with interaction term) and the reduced model (without interaction term). P-trends related to these stratified associations were also calculated as described above.

The SAS statistical package, version 9.3, was used for all statistical analyses. All p-values were 2-sided.

2.7 Human Subjects

The Institutional Review Board (IRB) committees of the University of Utah, University of Maryland and the Nepal Health Research Council approved the primary case-control study. As the project described herein is a secondary data analysis, the University of Maryland IRB determined that no additional human subject research approvals were required (Appendix A).

CHAPTER III

RESULTS

3.1 Medical History and Socio-Demographic Characteristics (Table 1A)

Compared to controls, cases were slightly older (p-value<0.0001) and less educated (p-value<0.0001), and had lower family income (p-value=0.0002). Additionally, cases were more likely to be unmarried or widowed (p-value=0.0002) and to reside in rural areas (p-value=0.02). Cases and controls also varied in their ethnic background (p-value<0.0001), whereby, the control group had a higher proportion of Brahmins (29.2%) compared to cases (11.6%), and more than fifty percent of cases were included in the “other” ethnic groups.

In terms of lifestyle factors, cases were more likely to have consumed tobacco products (p-value<0.0001) and/or alcohol (p-value<0.0001), to have a slightly lower body mass index (BMI) (p-value<0.0001). When smoking behaviors of the cases and controls were analyzed in more detail, results indicated that cases reported greater cumulative active smoking years (p-value<0.0001) and pack-years of smoking (p-value<0.0001). Closer examination revealed that the difference between cases and controls was not statistically significant for years of filtered cigarette use (p-value=0.1). Nevertheless, these groups were significantly different with respect to years of use of unfiltered cigarette (p-value<0.0001), bidi (p-value<0.0001), choor or kankat (p-value<0.0001), and hooka or hashish (p-value=0.02).

Cases and controls were similar with regards to family history of cancer among first degree relatives (p-value=0.28) and prior diagnosis of asthma (p-value=0.31). However, cases were more likely to report a prior history of tuberculosis (p-value=0.01) and pneumonia diagnosis (fisher's p-value=0.04).

Table 1A: Characteristics of Women Enrolled in the Hospital-Based Lung Cancer Case-Control Study in Bharatpur, Nepal, 2009-2012 (n= 493)

	Cases (n= 267)		Controls (n= 226)		p-value[a]
	Mean ± SD				
Age (years)	59.2 ± 11.6		53.2 ± 9.6		<0.0001
BMI (kg/m²)	20.1 ± 3.5		22.6 ± 4.0		<0.0001
Years of tobacco product use					
Cigarettes with filter	5.5 ± 12.5		3.8 ± 10.2		0.1
Cigarettes without filter	24.9 ± 22.5		7.0 ± 13.6		<0.0001
Bidi	12.3 ± 19.5		2.7 ± 8.9		<0.0001
Choor/Kankat	4.6 ± 13.0		0.9 ± 5.3		<0.0001
Hooka/Pipe & Hashish	2.2 ± 10.8		0.5 ± 3.9		0.02
Cumulative number of active smoking years	49.6 ± 32.5		15.1 ± 23.2		<0.0001
Pack-years of smoking	24.7 ± 28.2		5.5 ± 11.9		<0.0001
	N	%[b]	N	%[b]	p-value[c]
Ethnicity					<0.0001
Brahmin	31	11.6	66	29.2	
Chettri	56	21	37	16.4	
Madishe/Tharu	29	10.9	22	9.7	
Other	151	56.6	101	44.7	
Marital status					0.0002
Married	187	70.0	191	84.5	
Unmarried/Widowed	80	30.0	35	15.5	
Residential area					0.02
Urban	35	13.1	47	20.8	
Rural	232	86.9	179	79.2	
Education					<0.0001
None	242	90.6	157	69.5	
Elementary	15	5.6	42	18.6	
High School	10	3.8	27	12.0	
Family Monthly Income (Rupees)					0.0002
≤ 999	69	25.8	29	12.8	
1000-1999	74	27.7	55	24.3	
≥ 2000	124	46.4	142	62.8	
First Degree Family history of cancer (Yes)	79	29.6	57	25.2	0.28
History of tuberculosis (Yes)	30	11.2	11	4.9	0.01
History of asthma (Yes)	23	8.6	14	6.2	0.3
History of pneumonia (Yes)[d]	13	4.9	3	1.3	0.04
Alcohol consumption (Ever)	94	35.2	42	18.6	<0.0001
Tobacco use (Ever)	234	87.6	97	42.9	<0.0001

Abbreviations: BMI, body mass index; SD, standard deviation; N, number of participants.

[a] P-values generated by t-test.

[b] Percentages may not add up to 100 because of rounding.

[c] P-values generated by chi-square test.

[d] P-value generated by fisher's exact test. There was one missing value, which was not included in the test.

3.2 Reproductive and Hormonal Characteristics (Table 1B)

When reproductive and hormonal characteristics of the study population were evaluated as a continuous variable, the cases and controls were similar with regards to menstrual duration (p-value=0.09) and age at menopause (p-value=0.30) among post-menopausal women. Additionally, the reported age at menarche of all cases and controls were comparable (p-value=0.27). Among those who reported being pregnant, the cases and controls were similar with respect to age at first birth (p-value=0.42) and age at first live-birth (p-value=0.38). Nevertheless, cases were observed (p-value=0.003) to have a slightly higher number of pregnancies (mean=5.1; standard-deviation=2.6) compared to controls (mean=4.4; standard deviation=2.4).

When these reproductive and hormonal characteristics were examined as a categorical variable, the cases and controls remained similar with regards to age at menarche (p-value=0.17) within the entire analytic population, and with regards to age at first birth (p-value=0.83) and age at first live-birth (p-value =0.87) among the women who reported being pregnant. However, cases and controls were significantly different (p-value<0.0001) when the combination categories of age at menopause (including pre-menopausal and post-menopausal women) were considered. Additionally, a greater proportion of controls (31.4%) reported that they were still menstruating compared to cases (9.4%) (p-value<0.0001). Furthermore, cases were less likely to have used birth controls compared to their counterparts (p-value =0.04). Lastly, after

categorization, number of pregnancies remained statistically significantly different between cases and controls (p-value=0.005).

Table 1B: Reproductive and Hormonal Characteristics of Women Enrolled in the Hospital-Based Lung Cancer Case-Control Study, 2009-2012

	Cases (n= 267)		Controls (n= 226)		p-value[a]
	Mean ± SD				
Menstrual Duration[b] (years)	31.2 ± 5.2		32.2 ± 5.1		0.09
Age at Menopause[b] (years)	46.3 ± 5.0		46.9 ± 4.8		0.3
Age at Menarche (years)	14.9 ± 1.7		14.7 ± 1.6		0.3
Number of Pregnancies (gravidity)	5.1 ± 2.6		4.4 ± 2.4		0.003
Age at First Birth[c] (years)	20.0 ± 3.5		19.8 ± 3.3		0.42
Age at First Live Birth[c] (years)	20.1 ± 3.6		19.8 ± 3.4		0.38
	N	%[d]	N	%[d]	p-value[a]
Still Menstruating (Yes)	25	9.4	71	31.4	<0.0001
Age at Menopause (years)					<0.0001
Pre-menopausal	25	9.4	71	31.4	
<45	61	22.9	39	17.3	
45-49	98	36.7	55	24.3	
≥50	71	26.6	52	23.0	
Age at Menarche (years)					0.17
<14	46	17.2	50	22.1	
14	58	21.7	62	27.4	
≥15	134	50.2	101	44.7	
Number of Pregnancies (Gravidity)					0.005
≤2	40	15.0	43	19.0	
3-5	116	43.5	121	53.5	
>5	111	41.6	62	27.4	
Age at First Birth (years)					0.8
Never Pregnant	15	5.6	10	4.4	
<18	50	18.7	47	20.8	
18-20	100	37.5	80	35.4	
≥21	77	28.8	69	30.5	
Age at First Live-Birth (years)					0.9
Never Pregnant	15	5.6	10	4.4	
<18	50	18.7	47	20.8	
18-20	98	36.7	80	35.4	
≥21	79	29.6	69	30.5	
Birth Control Use (Ever)	29	10.9	39	17.3	0.04

Abbreviations: SD, standard deviation; N, number of participants.

[a] P-values generated by t-test or chi-square test; unknown category or missings excluded.

[b] Only among post-menopausal women.

[c] Only among women who reported being pregnant.

[d] Percentages may not add up to 100 because of rounding and due to unknown categories (not shown).

3.3 Multivariable Logistic Regression (Table 2)

Unadjusted multivariable logistic regression indicated an increased odds of lung cancer among women with greater than five pregnancies when compared to those with three to five pregnancies (OR=1.87; 95%CI=1.25, 2.79). Additionally, women who reported to have ever used birth control had a decreased odds of lung cancer (OR=0.58; 95%CI=0.35, 0.97), in this preliminary examination of the data. No statistically significant associations between menstrual duration (among post-menopausal women), menopausal status, age at menopause (among post-menopausal women), age at menarche, age at first birth, and age at first live-birth were observed within this unadjusted model.

After adjusting for age, the relationship between number of pregnancies and lung cancer, as well as that between birth control use and lung cancer, no longer remained statistically significant ($OR_{>5 \text{ vs. } 3\text{-}5}$=1.43; $95\%CI_{>5 \text{ vs. } 3\text{-}5}$=0.94, 2.18 and $OR_{\text{ever vs. never}}$=0.86; $95\%CI_{\text{ever vs. never}}$ =0.50, 1.49, respectively). However, this age-adjusted model, among post-menopausal women, suggested that women with longer menstrual duration had decreased odds of lung cancer compared to those with a shorter menstrual duration (OR=0.94; 95%CI=0.90, 0.99). The relationship between other reproductive and hormonal factors, examined in this analysis, and lung cancer remained statistically non-significant for this model.

Final parsimonious models adjusted for age and CAS are also summarized in Table 2. Among post-menopausal women, women with a younger age at menopause (<45 years and 45-49 years) had an increased odds of lung cancer compared to women who were ≥ 50 years at menopause (OR=2.14; 95%CI=1.09, 4.17 and OR=1.93; 95%CI=1.07, 3.51, respectively), after adjusting for age and cumulative active smoking (CAS) years. The p-trend for age at menopause, with respect to lung cancer, was also statistically significant (p-trend = 0.02) for the age and CAS adjusted model suggesting a dose-response relationship. Furthermore, among post-menopausal women, women with longer menstrual duration continued to have a decreased odds of lung cancer compared to those with a shorter menstrual duration (OR=0.93; 95%CI=0.88, 0.98), for the age and cumulative smoking adjusted model. Lastly, women who reported to be still menstruating had a decreased odds of lung cancer compared to those who had stopped menstruating (OR=0.41; 95%CI=0.20, 0.85). The remaining reproductive and hormonal factors (which were not associated with lung cancer in the previous models) were not associated with lung cancer, after adjusting for age and CAS.

Table 2: Multivariable Odds Ratios and 95% Confidence Intervals for the Relationship between Reproductive and Hormonal Factors and Lung Cancer in the Hospital-Based Lung Cancer Case-Control Study, 2009-2012

	Cases	Controls	Unadjusted	Age-Adjusted	Age & CAS Adjusted[a]
	N	N	OR (95% CI)	OR (95% CI)	OR (95% CI)
Menstrual Duration[b] (years)	213	142	0.97 (0.93, 1.01)	0.94 (0.90, 0.99)	0.93 (0.88, 0.98)
Still Menstruating					
Yes	25	71	0.21 (0.12, 0.34)	0.35 (0.18, 0.65)	0.41 (0.20, 0.85)
No	196	114	1 (referent)	1 (referent)	1 (referent)
Age at Menopause[b] (years)					
<45	61	39	1.15 (0.67, 1.96)	1.70 (0.95, 3.04)	2.14 (1.09, 4.17)
45-49	98	55	1.31 (0.80, 2.12)	1.54 (0.93, 2.55)	1.93 (1.07, 3.51)
≥50	71	52	1 (referent)	1 (referent)	1 (referent)
p-trend[a]			0.58	0.06	0.02
Age at Menarche (years)					
<14	46	50	0.69 (0.43, 1.12)	0.83 (0.50, 1.36)	0.93 (0.53, 1.62)
14	58	62	0.71 (0.45, 1.10)	0.74 (0.47, 1.17)	0.88 (0.52,1.49)
≥15	134	101	1 (referent)	1 (referent)	1 (referent)
p-trend[a]			0.08	0.32	0.77
Number of Pregnancies (Gravidity)					
≤2	40	43	0.97 (0.59, 1.60)	1.00 (0.59, 1.68)	0.87 (0.48, 1.57)
3-5	116	121	1 (referent)	1 (referent)	1 (referent)
>5	111	62	1.87 (1.25, 2.79)	1.43 (0.94, 2.18)	1.27 (0.78, 2.08)
p-trend[a]			0.004	0.13	0.21
Age at First Birth (years)					
Never Pregnant	15	10	1.2 (0.51, 2.81)	1.37 (0.56, 3.3)	1.06 (0.38, 2.97)
<18	50	47	0.85 (0.52, 1.40)	0.88(0.53, 1.47)	0.79 (0.44, 1.42)
18-20	100	80	1 (referent)	1 (referent)	1 (referent)
≥21	77	69	0.89 (0.58, 1.38)	0.89 (0.56, 1.40)	1.74 (0.44, 1.25)
p-trend[a]			0.93	0.96	0.72
Age at First Live-Birth (years)					
Never Pregnant	15	10	1.22 (0.52, 2.87)	1.39 (0.57, 3.39)	1.07 (0.38, 3.00)
<18	50	47	0.87 (0.53, 1.43)	0.90 (0.54, 1.50)	0.80 (0.44, 1.44)
18-20	98	80	1 (referent)	1 (referent)	1 (referent)
≥21	79	69	0.94 (0.60, 1.45)	0.93 (0.59, 1.46)	0.76 (0.45, 1.28)
p-trend[a]			0.83	0.96	0.76
Birth Control Use					
Ever	29	39	0.58 (0.35, 0.97)	0.86 (0.50, 1.49)	0.79 (0.42, 1.50)
Never	227	177	1 (referent)	1 (referent)	1 (referent)

Abbreviations: CAS, Cumulative Active Smoking; N, number of participants; OR, odds ratio; CI, confidence interval.

[a] Estimates were adjusted for age and cumulative active smoking years; one subject with missing cumulative active smoking history was excluded.

[b] Premenopausal women not included.

Unknown categories were retained in all models but not presented here.

3.4 Model Mutually Adjusted for Reproductive & Hormonal Factors (Table 3)

After simultaneously adjusting for reproductive and hormonal factors (including age at menarche, age at menopause, number of pregnancies or gravidity, age at first live-birth, and birth control use) along with adjustment for age and cumulative active smoking history, no significant relationships with lung cancer were observed at $\alpha = 0.05$. However, the increased odds of lung cancer among women with younger age at menopause (<45 years and 45-49 years) was still observed (OR=1.7; 95%CI=0.90, 3.4 and OR=1.7; 95%CI=0.90, 3.2, respectively) within the population of post-menopausal women.

Table 3: Mutually Adjusted Odds Ratios and 95% Confidence Intervals of Reproductive and Hormonal Factors in Relation to Lung Cancer in the Hospital-Based Lung Cancer Case-Control Study

	Age at Menarche (years)			Age at Menopause (years)				Number of Pregnancies			Age at First Live-Birth (years)				Birth Control Use	
	<14	14	≥15	Pre-Menopausal	<45	45-49	≥50	≤2	3-5	>5	Never Pregnant	<18	18-20	≥21	Ever	Never
Cases	46	58	134	25	61	98	71	40	116	111	15	50	98	79	29	227
Controls	50	62	101	71	39	55	52	43	121	62	10	47	80	69	39	177
OR[a]	1.0	0.8	1	0.7	1.7	1.7	1	0.8	1	1.1	2.4	0.7	1	0.8	0.8	1
(95% CI)[a]	(0.6, 1.9)	(0.5, 1.5)		(0.3, 1.7)	(0.9, 3.4)	(0.9, 3.2)		(0.4, 1.7)		(0.7, 1.9)	(0.6, 10.4)	(0.4, 1.4)		(0.4, 1.3)	(0.4, 1.6)	

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Estimates were adjusted for age and cumulative active smoking years, and exposures listed in the above table as applicable; one subject with missing cumulative active smoking history was excluded.

Unknown categories were retained in the model but not presented here.

3.5 Effect Modification by Smoking Status (Table 4)

After stratifying by cumulative active smoking (CAS) years, younger age at menopause (specifically <45 years) remained significantly associated with a higher odds of lung cancer among post-menopausal women with a cumulative active smoking history of at least 15 years (OR=2.27; 95%CI=1.02, 5.04). Similarly, among post-menopausal women, the inverse relationship between menstrual duration and lung cancer only remained significant among those who reported smoking for greater than or equal to 15 cumulative years over their lifetime. On the other hand, women who reported to be still menstruating had decreased odds of lung cancer among both strata (<15 and ≥15 years) of CAS. Lastly, the relationships between all other reproductive and hormonal factors examined (i.e. age at menarche, number of pregnancies, age at first birth, age at first live-birth and birth control use) and lung cancer were not significant within both strata of cumulative active smoking. Interactions terms were statistically significant for the number of pregnancies, age at first birth and age at first live-birth models (at α=0.05).

Table 4: Multivariable Odds Ratios and 95% Confidence Intervals of the Relationship between Reproductive and Hormonal and Lung Cancer by Smoking Status

	< 15 Cumulative Active Smoking Years			≥ 15 Cumulative Active Smoking Years		
	Cases	Controls	OR (95% CI)[a]	Cases	Controls	OR (95% CI)[a]
	n	n		n	n	
Menstrual Duration[b] (years)	18	81	0.95 (0.84, 1.07)	194	61	0.92 (0.87, 0.98)
Still Menstruating						
Yes	17	60	0.30 (0.10, 0.92)	8	11	0.29 (0.09, 0.88)
No	17	61	1 (referent)	179	53	1 (referent)
Age at Menopause[b] (years)						
<45	6	25	2.46 (0.49, 12.24)	55	14	2.27 (1.02, 5.04)
45-49	10	33	3.33 (0.76, 14.60)	88	22	1.81 (0.92, 3.57)
≥50	3	25	1 (referent)	67	27	1 (referent)
p-trend[a]			0.45			0.03
Age at Menarche (years)						
<14	11	32	1.68 (0.65, 4.30)	35	18	0.71 (0.35, 1.44)
14	10	45	1.01 (0.39, 2.61)	48	17	0.89 (0.44, 1.78)
≥15	13	64	1 (referent)	120	37	1 (referent)
p-trend[a]			0.32			0.37
Number of Pregnancies (Gravidity)						
≤2	9	27	1.20 (0.46, 3.13)	31	16	0.62 (0.29, 1.32)
3-5	19	85	1 (referent)	96	36	1 (referent)
>5	10	34	1.88 (0.72, 4.92)	101	28	1.10 (0.60, 2.00)
p-trend[a]			0.48			0.19
Age at First Birth (years)						
Never Pregnant	4	5	3.78 (0.81, 17.62)	11	5	0.44 (0.13, 1.48)
<18	9	27	1.90 (0.67, 5.37)	41	20	0.51 (0.25, 1.08)
18-20	11	58	1 (referent)	89	22	1 (referent)
≥21	9	42	1.06 (0.39, 2.88)	68	27	0.56 (0.29, 1.10)
p-trend[a]			0.35			0.95
Age at First Live-Birth (years)						
Never Pregnant	4	5	3.78 (0.81, 17.62)	11	5	0.45 (0.13, 1.51)
<18	9	27	1.90 (0.67, 5.37)	41	20	0.52(0.25, 1.10)
18-20	11	58	1 (referent)	87	22	1 (referent)
≥21	9	42	1.06 (0.39, 2.88)	70	27	0.58 (0.30, 1.14)
p-trend[a]			0.35			0.99
Birth Control Use						
Ever	9	28	1.07 (0.43, 2.65)	19	11	0.63 (0.26, 1.49)
Never	27	115	1 (referent)	200	62	1 (referent)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Estimates were adjusted for age and cumulative active smoking years, and exposures listed in the above table as applicable; one subject with missing cumulative active smoking history was excluded.

[b] Premenopausal women not included.

CHAPTER IV

DISCUSSION

4.1 Current Findings

Findings from this first analysis of reproductive and hormonal factors in relation to lung cancer among Nepali women suggest a potential role for menopausal factors. More specifically, among post-menopausal women, younger age at menopause was associated with an increased odds of lung cancer, after adjusting for age and cumulative active smoking. Additionally, longer menstrual duration was inversely associated with odds of lung cancer, among post-menopausal women. Premenopausal women (or still menstruating women) had a decreased odds of lung cancer compared to postmenopausal women (or women who had stopped menstruating). Finally, the relationships between age at menarche, number of pregnancies, age at first birth, age at first live-birth and birth control use, and lung cancer were not statistically significant among the analytic population, after controlling for age and cumulative active smoking history.

4.2 Prior Studies

Although some studies have reported null associations between age at menopause and lung cancer[15, 18, 21, 22, 29], others have reported an inverse association between these two variables[17, 19, 23, 30]. Prior to conducting this analysis, it was hypothesized that women with an older age at menopause will have an increased odds of lung cancer. However, results showed that women

with a younger age at menopause had an increased odds of lung cancer, which is consistent with the majority of prospective cohort studies that have examined this relationship[17, 19, 23]. Liu et al. hypothesized that this inverse association may be due to the fact that women with younger age at menopause may be using exogenous hormones for a longer period (compared to those with older age at menopause) [28]. However, this may not be an appropriate explanation for the current study population, as only two cases and one control reported using hormones for the symptoms of menopause.

Parker et al. [36] and Koushik et al. [21] have reported increase lung cancer risk among women with bilateral oophorectomies. Similarly Brinton et al. [17] observed that among women who had bilateral oophorectomies, the risk of lung cancer was significantly higher with younger age at menopause. However, the same relationship between younger age at menopause and lung cancer was not observed among those who had hysterectomies with ovarian conservation[17]. Thus, there is a possibility that the untimely termination of ovarian function might be involved in the observed inverse association between age at menopause and lung cancer[17]. The current study did not have information on the type of menopause, and therefore, this potential explanation could not be explored. However, it is worth noting that the number of Nepali women who may have had bilateral oophorectomies or other surgically assisted menopause is expected to be relatively low. In conclusion, the precise phenomenon behind the observed inverse association between age at menopause and lung cancer within the

analytic population cannot be asserted with total confidence and further studies are needed to better elucidate this relationship.

With respect to the significant associations that were only observed among women who smoked for at least 15 cumulative active smoking years, when data were stratified by smoking status, these results should be interpreted with caution due to the small cell numbers among the strata. This was due the fact that very few cases within the analytic population had reported smoking for <15 CAS years. Nevertheless, Brinton et al. [17], also observed differences in associations when stratifying by smoking status, whereby the statistically significant inverse associations between age at menopause and lung cancer only remained significant among former and/or current smokers (but not among never smokers). One suggested explanation for these findings is that the stronger binding of estrogen to estrogen receptors may inhibit the carcinogenic effects of polycyclic aromatic hydrocarbons that bind to these receptors, among smokers[17, 37]. Thus, women with younger age at menopause (who have lower levels of endogenous estrogens) may be more susceptible to the carcinogenic effects of tobacco smoke. Further research is needed to understand the underlying mechanisms of this relationship.

The current analysis also observed that women who were still menstruating had decreased odds of lung cancer compared to those who had stopped. It is possible that the observed association may be due to selection bias as the controls included a higher percentage of still menstruating women compared to cases. It is possible that the menopausal status of participants may

have been affected by case status as self-reported data was collected after diagnosis of lung cancer. Additionally, cases were slightly older compared to the controls in the analytic population (Table 1), which may have contributed to the observed association even after adjusting for age, due to residual confounding. Moreover, the temporal trend between these two variables is a little unclear due to the retrospective nature of this study. Thus, future studies, particularly among Nepali or similar populations, should execute a more rigorous analysis of this relationship.

To date, the majority of prior studies have not observed significant associations between age at menarche and lung cancer[15-16, 18-19, 21-23, 25, 29-30]. Our findings are consistent with the observations made in various case-control and prospective studies conducted among Chinese[15-16, 22-23, 30], Canadian, [21, 25] American[18-19], and German[29] women populations. Inverse associations between age at menarche and lung cancer has been noted by Brinton et al.[17]and Brenner et al.[30] among the participants of the NIH-AARP Diet and Health study cohort and a population-based frequency matched Chinese women case-control study, respectively. Brinton et al. reported that after stratifying by smoking status, the inverse association between age at menarche and lung cancer was only significant among never smokers[17]. Due to the limited distribution of the smoking variable in the current study population (never smokers=12.4% case and 42.9% controls), we were unable to examine associations among never smokers.

Additionally, Brinton and colleagues reported a reduced risk of adenocarcinoma and undifferentiated/large cell lung cancer with later age at

menarche, after stratifying by histological subtypes[17]. This finding may be an indication that difference in lung cancer histology among the participants of the various studies may be a key factor leading to the inconsistences noted in findings across studies. The null findings observed in our study may be specific to the histologic distribution of lung cancer among the Nepali women population. However, we were unable to conduct analyses by histologic type as this information was not available.

Number of pregnancies (gravidity) and number of births (parity) are closely related variables that may be associated with lung cancer among women. Only one study has examined the relationship between number of pregnancies or gravidity and lung cancer[21]. The investigators of this previous analysis, which was a population-based case-control study conducted among 422 women with lung cancer and 577 population-based controls from Montreal, Canada, reported no significant association between gravidity and lung cancer[21]. On the other hand several studies that have examined the relationship between number of births or parity and lung cancer have reported an inverse association between these variables[15-16, 18, 20, 22-23]. Earlier studies conducted by Kabat et al. [25] and Elliott et al. [27] among British and Canadian women, respectively, found a positive association between parity and lung cancer. However, two recent large prospective cohort studies, by Brinton et al. [17] and Baik et al., [19] have reported null associations between parity and lung cancer (among the NIH-AARP Diet and Health study cohort and the Nurses' Health Study cohort, respectively). Among

the Nepali female population investigated, the current study observed results that were similar to these cohort findings.

With respect to age at first birth, our results were consistent with several studies that have reported no association between age at first birth and lung cancer[15-16, 18, 20-21, 23, 30]. However, two previous studies, Brinton et al. [17] and Kabat et al. [25], have reported an inverse association between age at first birth and lung cancer among the NIH-AARP Diet and Health study cohort and the Canadian National Breast Screening Study (NBSS) cohort, respectively. The inverse association among the NIH-AARP cohort only remained significant among current smokers after stratification by smoking status[17], whereas this association was significant among both the "never" and "ever" smokers in the study by Kabat et al. [25]. More importantly, when stratified by lung cancer histology, Kabat and coworkers found no significant association between age at first birth and adenocarcinoma, whereas those with other lung cancer cell types (other than adenocarcinoma) continued to demonstrate an inverse association with age at first birth[25]. This difference in the relationship between age at first birth and lung cancer based on histology may explain the varied findings reported by investigators using different study designs and studying different populations.

To our knowledge, no prior study has examined the association between age at live-birth and lung cancer. However, the results of the current analysis are similar to the findings reported in the above mentioned studies which examined the relationship between age at first birth and lung cancer.

Lastly, no significant associations between oral contraceptive (OC) use (never and ever use) and lung cancer have been reported by the majority of studies using both case-control and cohort study designs among different populations of women[16-19, 22-23, 25, 27]. Only one study, a population-based case-control study conducted in Germany, has reported a decreased odds of lung cancer among ever OC users compared to never users[29]. This association was reported to be significant only among smokers, after stratification by smoking status[29]. After stratifying by histological subtypes, the investigators reported that this association remained significant among those with small cell lung cancer and squamous cell carcinoma, but not among those with adenocarcinoma[29]. Our findings showed reduced odds of lung cancer among ever birth control user compared to never user. However, it may not be ideal to compare these findings with the previous study, as definitions of birth control type may vary by study. Thus, no major conclusions may be drawn from the findings on birth control use, as detailed information on the form of birth control use was not available.

4.3 Strengths and Limitations

Generally, case-control studies are more susceptive to selection bias (the exposure status of the subjects may influence the differential selection of cases and controls) and recall bias (controls may have recalled exposures differently than the lung cancer patients). However, this is unlikely with respect to the current analysis, where factors such as number of pregnancies and menopausal age constitute the independent variables. Moreover, although temporal ambiguity is normally implicated in retrospective study designs, it is not suspected to be a

hindrance in the current research due to the low likelihood that a participant experienced reproductive or hormonal events (such as menarche and pregnancy) due to lung cancer. However, the temporal trend with respect to menopausal variables (such as menopausal status and age at menopause) is unclear in this retrospective analysis. Additionally, the definition of menopausal status was based on self-reported menstrual status, and thus, exposure misclassification is also a potential limitation of this analysis.

Another potential limitation of this study is that the controls in this analysis included subjects being screened at the cancer hospital, and thus, it is possible that some of these controls might have cancer of some other type (participants' prior history of cancer were limited to self-report and not confirmed). This might have biased the odds towards the null, given that some of these cancers (e.g. breast cancer) may share the same risk factors under study.

The current analysis was unable to examine associations among never smokers, due to the distribution of the smoking variable in the study population. Additionally, these associations were also not analyzed by strata of menopausal status, due to the limited number of premenopausal women in the study. Moreover, data on the type of menopause (natural, surgical, or due to radiation or chemotherapy) would have been helpful in discerning if the associations between age at menopause and lung cancer were specific to any particular type of menopause. Finally, information on lung cancer histology and specific types of birth control use may have been more informative in clarifying these associations further within this population.

Despite these limitations, this is the first study to examine the relationship between reproductive and hormonal factors and lung cancer among Nepali women, which is an understudied population. Additionally, the current analysis is one of the few studies to access the effects of gravidity (number of pregnancies) and age at first live-birth in relation to lung cancer. Moreover, due to the long latency period of lung cancer, the case-control study design of our study made it time and financially efficient. Lastly, the use of trained nurses and standardized questionnaire, and detailed data collection through in-person interviews were some additional strengths of this study. In addition to contributing to the epidemiological body of evidence surrounding potential associations between reproductive and hormonal factors and lung cancer, this study contributes much needed information on the distribution of these risk factors among Nepali women.

4.4 Recommendations for Future Studies

Based on prior studies and the current findings, future research should focus on understanding the relationships between these risk factors and the specific histological types of lung cancer. Additionally, considering the type of menopause (i.e. natural, surgical, or due to radiation or chemotherapy) may be important for clarifying the relationship between these factors and lung cancer (or particular histological subtypes of lung cancer). Large sample sizes should be utilized wherever possible to support adequate cell numbers among strata formed by effect modifiers (e.g. smoking status). In summary, more studies are needed to understand the relationship between reproductive and hormonal factor

and lung cancer with respect to type of menopause and lung cancer histology overall and specifically among the understudied Nepali population.

4.5 Conclusion

To our knowledge, this was the first study to examine the relationship between reproductive and hormonal factors and lung cancer among Nepali women. The current analysis, found that cases and controls were significantly different with respect to age, ethnicity, education, family monthly income, smoking behaviors, menstrual status, age at menopause, number of pregnancies and birth control use. This study also observed that women who were still menstruating (premenopausal) had a reduced odds of lung cancer compared to those who had stopped (postmenopausal). Our results support increased odds of lung cancer with younger age at menopause, after adjustment for age and cumulative active smoking years. After stratifying by cumulative active smoking years, younger age at menopause remained significantly associated with higher odds of lung cancer only among those with a cumulative active smoking history of at least 15 years. These results are consistence with a majority of the recent large prospective cohort studies. Future studies should pay close attention to the histological types of lung cancer, type of menopause and type of oral contraceptives used by the study participants. Findings from this analysis support a potential role of menopausal factors in relation to lung cancer among Nepali women but further research is needed to better clarify these relationships.

APPENDICE

A. **University of Maryland IRB: Human Subject Research Determination**

B. **Supplementary Table 1: Age at Menarche**

C. **Supplementary Table 2: Age at Menopause**

D. **Supplementary Table 3: Gravidity**

E. **Supplementary Table 4: Parity**

F. **Supplementary Table 5: Age at First Pregnancy**

G. **Supplementary Table 6: Age at First Birth**

H. **Supplementary Table 7: Oral Contraceptive (OC) use**

I. **Supplementary Table 8: Duration of Oral Contraceptive(OC) use**

J. **Supplementary Table 9: Post-Menopausal Hormone use**

APPENDIX A: University of Maryland IRB: Human Subject Research Determination

INSTITUTIONAL REVIEW BOARD

DATE: February 12, 2015

TO: Sanah Vohra
FROM: University of Maryland College Park (UMCP) IRB

1204 Marie Mount Hall College Park, MD 20742-5125 TEL 301.405.4212
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PROJECT TITLE: [719834-1] Reproductive and Hormonal Factors in Relation to Lung Cancer among Nepali Women

SUBMISSION TYPE: New Project

ACTION: DETERMINATION OF NOT HUMAN SUBJECT RESEARCH
DECISION DATE: February 12, 2015

Thank you for your submission of New Project materials for this project. The University of Maryland College Park (UMCP) IRB has determined this project does not meet the definition of human subject research under the purview of the IRB according to federal regulations.

We will retain a copy of this correspondence within our records.

If you have any questions, please contact the IRB Office at 301-405-4212 or irb@umd.edu. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within University of Maryland College Park (UMCP) IRB's records.

APPENDIX B: Supplementary Table 1: Age at Menarche

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brenner et al. (2003) [30]	**Case-Control** Variable Type: *Categorical*; 1) <15, 15-16 and ≥17years Confounder Adjustment: Age and prefectures (Pingliang and Qingyang).	109 incident female lung cancer cases and 435 population-based frequency matched (on gender and age) controls recruited from hospitals in two rural prefectures (Pingliang and Qingyang) in Eastern Gansu Province, China, between January 1994 and April 1998.	There is an inverse association between age at menarche and lung cancer (P for trend =0.015).	Not analyzed
Kreuzer et al. (2003) [29]	**Case-Control** Variable Type: *Categorical*; 1) <13, 13-14 and ≥15 years Confounder Adjustment: Age, region, pack years of smoking, smoking status, and education.	811 women with lung cancer and 912 population controls enrolled between 1990 and 1996 in Germany.	There was no significant association between age at menarche and lung cancer.	Smoking status: There was no significant association between age at menarche and lung cancer after stratifying by smoking status (non-smokers and smokers). Histological subtypes: There was no significant association between age at menarche and lung cancer after stratifying by histology (adenocarcinoma, small cell carcinoma and squamous carcinoma).
Kabat et al. (2007) [25]	**Cohort** Variable Type: *Categorical*; 1) <12, 12, 13, 14 and >14years Confounder Adjustment: Body mass index, education, smoking status, pack-years of smoking, study center and randomization group (intervention versus control), other exposure variables.	89,835 Canadian women aged 40–59 years recruitment in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer, between 1980 and 1985.	The association between age at menarche and lung cancer was not statistically significant.	Smoking status: There was no significant association between age at menarche and lung cancer after stratifying by smoking status (never and ever). Histological subtypes: There was no significant association between age at menarche and lung cancer after stratifying by histology (Adenocarcinoma and other cell types). Age: There was no significant association between age at menarche and lung cancer after stratifying by age (40-49 and 50-59 years).

APPENDIX B: Supplementary Table 1: Age at Menarche (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Weiss et al. (2008) [23]	**Cohort** Variable Type: *Categorical*; 1)<15, 15-16, and ≥17 years Confounder Adjustment: Passive smoking	71,314 non-smoking Chinese women aged 40-70 with no history of cancer at baseline from the prospective Shanghai Women's Health Study conducted between 1996 and 2000.	There was no significant association between age at menarche and lung cancer.	Histological subtypes: There was no significant association between age at menarche and lung cancer among women with adenocarcinoma; this relationship was not examined among women with other histologic types of lung cancer. Passive smoking: The association between age at menarche and lung cancer is not significant among women with or without passive smoking exposure.
Koushik et al. (2009) [21]	**Case-Control** Variable Type: *Categorical*; 1) <13, 13, 14, and ≥15years Confounder Adjustment: Age, respondent status, ethnicity, education, family income, and smoking status.	422 women with lung cancer and 577 population-based controls from Montreal, Canada recruited between January 1996 and December 1997.	There was no significant association between age at menarche and lung cancer.	Histological subtypes: There was no significant association between age at menarche and adenocarcinoma; other histological subtypes were not analyzed.

APPENDIX B: Supplementary Table 1: Age at Menarche (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Seow et al. (2009) [22]	**Cohort** Variable Type: *Categorical*; 1) <15 and ≥15 years Confounder Adjustment: Age, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level, body mass index (BMI), total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, and duration of smoking (years), cigarettes per day, and number of years since quitting among current or former smokers.	35,298 women aged 45 to 78 years recruited into the Singapore Chinese Health Study between April 1993 and December 1998.	There was no significant association between age at menarche and lung cancer.	Smoking status: There was no significant association between age at menarche and lung cancer, when stratified by smoking status. Histological subtypes: There was no significant association between age at menarche and lung cancer, when stratified by histology.
Baik et al. (2010) [19]	**Cohort** Variable Type: *Categorical*; 1) <11, 12, 13, 14 and ≥15years Confounder Adjustment: Smoking, fruit/vegetable in-take, BMI, environmental smoking exposure, and other exposure variables.	107,171 postmenopausal women aged 30-55 years enrolled in the Nurse's Health Study, collected between 1984 and 2006.	There was no significant association between age at menarche and lung cancer.	Smoking status: There was not significant association between age at menarche and lung cancer in the various strata based on smoking status. Histological subtypes: There was not significant association between lung cancer and age a menarche, based on histological subgroups.

APPENDIX B: Supplementary Table 1: Age at Menarche (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brinton et al. (2011) [17]	**Cohort** Variable Type: Categorical; 1) <11, 11-12, 13-14 and ≥15 years Confounder Adjustment: Age, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menopause and type of menopause.	185,017 women between the ages of 50 and71 years were recruited into the NIH-AARP (American Association of Retired Persons) Diet and Health Study during 1995 and 1996.	Younger age at menarche is associated with an increased risk for lung cancer (P for trend = 0.01).	Smoking status: The inverse association between age at menarche and lung cancer was only significant among never smokers (P for trend=- 0.03). Histological subtypes: There was a reduced risk of adenocarcinoma and undifferentiated/large cell was observed with later age at menarche (P for trend = <0.01 and 0.02, respectively).
Meinhold et al. (2011) [18]	**Case-Control** Variable Type: *Categorical*; 1) <12, 12-13, 14-15 and ≥16years Confounder Adjustment: Age, education, smoking, number of smoking adults in household and current household income.	430 women diagnosed with non-small cell lung cancer, 316 hospital controls and 295 population controls recruited in the multi-center Maryland Lung Cancer Study between 1998 and 2008.	There was no significant association between age at menarche and non-small cell lung cancer, when using hospital, population or combined controls.	Smoking status: The association between age at menarche and non-small cell lung cancer was not significant when stratified by smoking status.

APPENDIX B: Supplementary Table 1: Age at Menarche (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Lim et al. (2012) [16]	**Case-Control** Variable Type: *Categorical*; 1) ≤12, 13-15 and ≥16years Confounder Adjustment: Age, fruit and vegetable consumption, country of origin, dwelling type, years of education, history of cancer in first-degree relatives, smoking status , secondhand smoke exposure at home, and study set.	702 Chinese female lung cancer cases and 1,578 hospital controls from 2 hospital-based case-control studies, which recruited from the 5 major public-sector hospitals in Singapore during 1996–1998 and 2005–2008.	There was no significant association between age at menarche and lung cancer.	Smoking status: There was no significant association between age at menarche and lung cancer by smoking status (never and ever smokers).
Gallagher et al. (2013) [15]	**Cohort** Variable Type: *Categorical*; 1) ≤13, 14, 15, 16 and ≥17 years Confounder Adjustment: Age and smoking.	267,400 female textile workers in Shanghai, China, enrolled between 1989 and 1991 and followed until 2000 for incidence of lung cancer.	There was no significant association between age at menarche and lung cancer.	Not analyzed

APPENDIX C: Supplementary Table 2: Age at Menopause

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brenner et al. (2003) [30]	**Case-Control** Variable Type: *Categorical*; 1) Natural menopause: <45, 45-49 and ≥50 years Confounder Adjustment: Age and prefectures (Pingliang and Qingyang).	109 incident female lung cancer cases and 435 population-based frequency matched (on gender and age) controls recruited from hospitals in two rural prefectures (Pingliang and Qingyang) in Eastern Gansu Province, China, between January 1994 and April 1998.	There is an inverse association between age at menopause and lung cancer (P for trend =0.074).	Not analyzed
Kreuzer et al. (2003) [29]	**Case-Control** Variable Type: *Categorical*; 1) ≤49, 50-51 and ≥53 years Confounder Adjustment: Age, region, pack years of smoking, smoking status, and education.	811 women with lung cancer and 912 population controls enrolled between 1990 and 1996 in Germany.	There was no significant association between age at menopause and lung cancer.	Smoking status: There was no significant association between age at menopause and lung cancer after stratifying by smoking status (non-smokers and smokers). Histological subtypes: There was no significant association between age at menopause and lung cancer after stratifying by histology (adenocarcinoma, small cell carcinoma and squamous carcinoma).
Weiss et al. (2008) [23]	**Cohort** Variable Type: *Categorical*; 1)<46, 46-48, 49-50 and ≥51 years Confounder Adjustment: Passive smoking	71,314 non-smoking Chinese women aged 40-70 with no history of cancer at baseline from the prospective Shanghai Women's Health Study conducted between 1996 and 2000.	Age at menopause was inversely associated with lung cancer risk (P for trend = 0.03).	Histological subtypes: Age at menopause was inversely associated with adenocarcinoma; this relationship was not examined among women with other histologic types of lung cancer. Passive smoking: The association between age at menopause and lung cancer is not significant among women with or without passive smoking exposure.

APPENDIX C: Supplementary Table 2: Age at Menopause (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Koushik et al. (2009) [21]	**Case-Control** Variable Type: *Categorical*; 1) <45, 45-<51 and ≥51years Confounder Adjustment: Age, respondent status, ethnicity, education, family income, and smoking status.	422 women with lung cancer and 577 population-based controls from Montreal, Canada recruited between January 1996 and December 1997.	There was no significant association between age at menopause and lung cancer.	Histological subtypes: There was no significant association between age at menopause and adenocarcinoma; other histological subtypes were not analyzed. Types of Menopause: There was no significant association between age at natural or non-natural menopause and lung cancer (or adenocarcinoma).
Seow et al. (2009) [22]	**Cohort** Variable Type: *Categorical*; 1) <50 and ≥50 years Confounder Adjustment: Age, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level, body mass index (BMI), total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, and duration of smoking (years), cigarettes per day, and number of years since quitting among current or former smokers.	35,298 women aged 45 to 78 years recruited into the Singapore Chinese Health Study between April 1993 and December 1998.	There was no significant association between age at menopause and lung cancer.	Smoking status: There was no significant association between age at menopause and lung cancer, when stratified by smoking status. Histological subtypes: There was no significant association between age at menopause and lung cancer, when stratified by histology.

APPENDIX C: Supplementary Table 2: Age at Menopause (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Baik et al. (2010) [19]	**Cohort** Variable Type: *Categorical*; 1) <44, 44-47, 48-49, 50-51 and ≥52 years Confounder Adjustment: Smoking, fruit/vegetable intake, BMI, environmental smoking exposure, and other exposure variables.	107,171 postmenopausal women aged 30-55 years enrolled in the Nurse's Health Study, collected between 1984 and 2006.	Age at menopause was inversely associated with lung cancer risk (P for trend =0.0004).	Smoking status: When stratified by smoking status, the increase lung cancer risk with younger age at menopause only remained significant among current smokers (P for trend = 0.001); there was no significant association between age at menopause and lung cancer among never and former smokers. Histological subtypes: Small cell carcinoma is inversely associated with age at menopause, whereas the relationship between age at menopause and adenocarcinoma or squamous carcinoma is not statistically significant.
Brinton et al. (2011) [17]	**Cohort** Variable Type: *Categorical*; 1) <45, 45-49, 50-54, and ≥55 years Confounder Adjustment: Age, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche.	185,017 women between the ages of 50 and71 years were recruited into the NIH-AARP (American Association of Retired Persons) Diet and Health Study during 1995 and 1996.	There was an inverse relationship between age at menopause and lung cancer risk (P for trend <0.0001).	Smoking status & Type of Menopause: For women that had a natural menopause, age at menopause was inversely associated with lung cancer risk among current and former smokers (P for trend <0.01 and <0.0001). For women that had an unnatural menopause, age at menopause was inversely associated with lung cancer only among former smokers (P for trend <0.001). Histological Subtypes: Among women that had a natural menopause, the risk of adenocarcinoma and squamous cell carcinoma increase with younger age at menopause (P for trend < 0.01 and < 0.001, respectively). Among women that had an unnatural menopause, the risk of small cell carcinoma increased with younger age at menopause (P for trend = 0.04)

APPENDIX C: Supplementary Table 2: Age at Menopause (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Meinhold et al. (2011) [18]	**Case-Control** Variable Type: *Categorical*; 1) Natural menopause <50, natural menopause 50-54, and natural menopause ≥55years Confounder Adjustment: Age, education, smoking, number of smoking adults in household and current household income.	430 women diagnosed with non-small cell lung cancer, 316 hospital controls and 295 population controls recruited in the multi-center Maryland Lung Cancer Study between 1998 and 2008.	There was no significant association between age at natural menopause and non-small cell lung cancer, when using hospital, population or combined controls.	Smoking status: The association between age at natural menopause and non-small cell lung cancer was not significant when stratified by smoking status.
Lim et al. (2012) [16]	**Case-Control** Variable Type: *Categorical*; 1) ≤48, 49-51 and ≥52years Confounder Adjustment: Age, fruit and vegetable consumption, country of origin, dwelling type, years of education, history of cancer in first-degree relatives, smoking status , secondhand smoke exposure at home, and study set.	702 Chinese female lung cancer cases and 1,578 hospital controls from 2 hospital-based case-control studies, which recruited from the 5 major public-sector hospitals in Singapore during 1996–1998 and 2005–2008.	There was positive association between age at menopause and lung cancer (P for trend = 0.027).	Smoking status: There was a positive association between age at menopause and lung cancer among never smoking status (P for trend = 0.003); however, this relationship was not significant among ever smokers.
Gallagher et al. (2013) [15]	**Cohort** Variable Type: *Categorical*; 1) ≤48, 49-51 and ≥52 years Confounder Adjustment: Age and smoking.	267,400 female textile workers in Shanghai, China, enrolled between 1989 and 1991 and followed until 2000 for incidence of lung cancer.	There was no significant association between age at menopause and lung cancer.	Not analyzed

APPENDIX D: Supplementary Table 3: Gravidity

Authors	Study Design	Population	Key Findings	Effect Modifiers
Koushik et al. (2009) [21]	**Case-Control** Variable Type: *Categorical*; 1) Nulligravid, 1, 2, 3 and ≥4 pregnancies Confounder Adjustment: Age, respondent status, ethnicity, education, family income, and smoking status.	422 women with lung cancer and 577 population-based controls from Montreal, Canada recruited between January 1996 and December 1997.	There is no significant association between gravidity and lung cancer.	Histological subtypes: There is no significant association between gravidity and adenocarcinoma; other histological subtypes were not analyzed.

APPENDIX E: Supplementary Table 4: Parity

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kreuzer et al. (2003) [29]	**Case-Control** Variable Type: *Categorical*; 1) 0, 1, 2-3 and ≥4 full-term pregnancies Confounder Adjustment: Age, region, pack years of smoking, smoking status, and education.	811 women with lung cancer and 912 population controls enrolled between 1990 and 1996 in Germany.	There was no significant association between parity and lung cancer.	Smoking status: There was no significant association between parity and lung cancer among strata based on smoking status (non-smokers and smokers). Histological subtypes: There was no significant association between parity and lung cancer among strata based on histology (adenocarcinoma, small cell carcinoma and squamous carcinoma).
Brenner et al. (2003) [30]	**Case-Control** Variable Type: *Categorical*; 1) 1-2, 3-4, 5-6, ≥7children Confounder Adjustment: Age and prefectures (Pingliang and Qingyang).	109 incident female lung cancer cases and 435 population-based frequency matched (on gender and age) controls recruited from hospitals in two rural prefectures (Pingliang and Qingyang) in Eastern Gansu Province, China, between January 1994 and April 1998.	There is no significant association between parity and lung cancer.	Not analyzed
Elliott et al. (2006) [27]	**Nested Case-Control** Variable Type: *Categorical*; 1) 0, 1, 2 and ≥3 children Confounder Adjustment: Smoking and social class.	162 incident cases of lung cancer, among women, recorded by the Royal College of General Practitioners' Oral Contraception Study (OCS)database by August 2004, and age and length of follow-up matched controls (n=3*162) from the same cohort.	There was a positive association between parity and lung cancer (P for trend = 0.01).	Not analyzed

APPENDIX E: Supplementary Table 4: Parity (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kabat et al. (2007) [25]	**Cohort** Variable Type: *Categorical*; 1) Nulliparous and Parous 2) Nulliparous, 1, 2, 3, 4 and ≥5 children Confounder Adjustment: Body mass index, education, smoking status, pack-years of smoking, study center and randomization group (intervention versus control), and other exposure variables.	89,835 Canadian women aged 40–59 years recruitment in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer, between 1980 and 1985.	There was no significant difference in the odds of lung cancer between nulliparous and parous women. However, when the parous was further divided into 1, 2, 3, 4 and ≥5 children, the odds of lung cancer increased with the number of children (P for trend = 0.02).	Smoking status: The odd of lung cancer increased with the number of children among never smokers (P for trend = 0.02); however, this association was not significant among ever smokers. Histological subtypes: There was no significant association between parity and lung cancer after stratifying by histology. Age: The association between parity and lung cancer was no longer significant after stratification by age (40-49 and 50-59 years).
Weiss et al. (2008) [23]	**Cohort** Variable Type: *Categorical*; 1) 0, 1- 3 and ≥4 children Confounder Adjustment: Passive smoking	71,314 non-smoking Chinese women aged 40-70 with no history of cancer at baseline from the prospective Shanghai Women's Health Study conducted between 1996 and 2000.	As parity increases, the risk of lung cancer decreases (P for trend <0.01).	Histological subtypes: The association between parity and lung cancer was not significant among women with adenocarcinoma; this relationship was not examined among women with other histologic types of lung cancer.

APPENDIX E: Supplementary Table 4: Parity (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Koushik et al. (2009) [21]	**Case-Control** Variable Type: *Categorical*; 1) Nulliparous, 1, 2, 3 and ≥4 children Confounder Adjustment: Age, respondent status, ethnicity, education, family income, and smoking status.	422 women with lung cancer and 577 population-based controls from Montreal, Canada recruited between January 1996 and December 1997.	There was no significant association between parity and lung cancer.	Histological subtypes: There was no significant association between parity and adenocarcinoma; other histological subtypes were not analyzed.
Seow et al. (2009) [22]	**Cohort** Variable Type: *Categorical*; 1) Measured as number of live births: 0, 1-2, 3-4 and ≥5 Confounder Adjustment: Age, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level, body mass index (BMI), total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, and duration of smoking (years), cigarettes per day, and number of years since quitting among current or former smokers.	35,298 women aged 45 to 78 years recruited into the Singapore Chinese Health Study between April 1993 and December 1998.	As the number of live births increased the risk of lung cancer decrease (P for trend = < 0.01).	Smoking status: When stratified by smoking status, the association between parity and lung cancer was no longer significant. Histological subtypes: Only divided into two categories, adenocarcinoma and other histological subtypes. Number of live births was inversely associated with adenocarcinoma risk (P for trend <0.01); however, no significant association was found between number of live births and other histological subtypes.

APPENDIX E: Supplementary Table 4: Parity (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Paulus et al. (2010) [20]	**Case-Control** Variable Type: *Categorical*; 1) Nulliparous and Parous 2) Nulliparous, 1, 2, 3 and ≥4 children Confounder Adjustment: Age, smoking status, pack-years of smoking, and years since quitting smoking.	1,004 cases and 848 controls (friends and non-blood relatives) enrolled in the Lung Cancer Susceptibility Study (LCSS) at Massachusetts General Hospital (Boston, Massachusetts) between December 1992 and December 2003.	1) The odds of lung cancer was significantly lower among parous women compared nulliparous women. 2) Lung cancer odds decrease with increasing number of children; the linear trend was significant.	Smoking status: The inverse association between lung cancer and parity remained significant among never-smokers; however, the association was not statistically significant among ever-smokers. Age at diagnosis: The inverse association was statistically significant among women diagnosed at ≥50 years of age, but not among those diagnosed before 50. Histological subtypes: The relationship between lung cancer and parity were similar among all subgroups based on histology.
Baik et al. (2010) [19]	**Cohort** Variable Type: *Categorical*; 1) Nulliparous and Parous 2) 1-2, 3-4 and ≥5 children Confounder Adjustment: Smoking, fruit/vegetable in-take, BMI, environmental smoking exposure, and other exposure variables.	107,171 postmenopausal women aged 30-55 years enrolled in the Nurse's Health Study, collected between 1984 and 2006.	The association between parity and lung cancer is not significant.	Smoking status: Among parous women, increased number of children was associated with decreased lung cancer risk in never smokers (P for trend = 0.03). However, this association was not significant among former and current smokers. Histological subtypes: There is an inverse relationship between parity and lung cancer among women with small cell carcinoma. This association is not significant among women with adenocarcinoma and squamous carcinoma.

APPENDIX E: Supplementary Table 4: Parity (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brinton et al. (2011) [17]	**Cohort** Variable Type: *Categorical*; 1) Nulliparous and Parous 2) Nulliparous, 1, 2, 3-4 and ≥5 children Confounder Adjustment: Age, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche, age at menopause and type of menopause.	185,017 women between the ages of 50 and 71 years were recruited into the NIH-AARP (American Association of Retired Persons) Diet and Health Study during 1995 and 1996.	There was no significant association between parity and lung cancer.	Not analyzed
Meinhold et al. (2011) [18]	**Case-Control** Variable Type: *Categorical*; 1) Nulliparous, 1-2, 3-4 and ≥5 children Confounder Adjustment: Age, education, smoking, number of smoking adults in household and current household income.	430 women diagnosed with non-small cell lung cancer, 316 hospital controls and 295 population controls recruited in the multi-center Maryland Lung Cancer Study between 1998 and 2008.	Parity was inversely associated with risk of non-small cell lung cancer, when comparing cases to hospital-controls, population-controls or both controls together (P for trend = 0.003, 0.01 and 0.002, respectively).	Smoking status: The association between parity and non-small cell lung cancer became insignificant when stratified by smoking status.

APPENDIX E: Supplementary Table 4: Parity (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Lim et al. (2012) [16]	**Case-Control** Variable Type: *Categorical*; 1) 0, 1-2, 3-4 and ≥5 children Confounder Adjustment: Age, fruit and vegetable consumption, country of origin, dwelling type, years of education, history of cancer in first-degree relatives, smoking status, secondhand smoke exposure at home, and study set.	702 Chinese female lung cancer cases and 1,578 hospital controls from 2 hospital-based case-control studies, which recruited from the 5 major public-sector hospitals in Singapore during 1996–1998 and 2005–2008.	There was an inverse association between parity and lung cancer (P for trend = 0.001).	Smoking status: The association between parity and lung cancer was no longer significant after stratifying by smoking status (never and ever smokers). Age: The inverse association remained significant among women older than 65 years (P for trend = 0.001), but it was not significant among women 65 and younger.
Gallagher et al. (2013) [15]	**Cohort** Variable Type: *Categorical*; 1)0, 1, 2, 3, 4 and ≥5 children Confounder Adjustment: Age and smoking.	267,400 female textile workers in Shanghai, China, enrolled between 1989 and 1991 and followed until 2000 for incidence of lung cancer.	Women with 4 and 5 or more children had a significant reduced risk of lung cancer compared to women without children; however, the p for trend (0.15) was not significant.	Not analyzed

APPENDIX F: Supplementary Table 5: Age at First Pregnancy

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kreuzer et al. (2003) [29]	**Case-Control** Variable Type: *Categorical*; 1) <22, 22-25 and ≥26 years Confounder Adjustment: Age, region, pack years of smoking, smoking status, and education.	811 women with lung cancer and 912 population controls enrolled between 1990 and 1996 in Germany.	The odds of lung cancer decreased with older age at first pregnancy (P for trend = 0.007).	Smoking status: The odds of lung cancer decreased with older age at first pregnancy among smokers; however, no significant association between age at first pregnancy with lung cancer was reported among non-smokers. Histological subtypes: The odds of lung cancer decreased with older age at first pregnancy for all histological subgroups (adenocarcinoma, small cell carcinoma and squamous carcinoma).
Koushik et al. (2009) [21]	**Case-Control** Variable Type: *Categorical*; 1) <22, 22-<25, 25-<29 and ≥29years Confounder Adjustment: Age, respondent status, ethnicity, education, family income, and smoking status.	422 women with lung cancer and 577 population-based controls from Montreal, Canada recruited between January 1996 and December 1997.	There was no significant association between age at first pregnancy and lung cancer.	Histological subtypes: There was no significant association between age at first pregnancy and adenocarcinoma; other histological subtypes were not analyzed.

APPENDIX G: Supplementary Table 6: Age at First Birth

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brenner et al. (2003) [30]	**Case-Control** Variable Type: *Categorical*; 1) ≤18, 19-22 and ≥23years Confounder Adjustment: Age and prefectures (Pingliang and Qingyang).	109 incident female lung cancer cases and 435 population-based frequency matched (on gender and age) controls recruited from hospitals in two rural prefectures (Pingliang and Qingyang) in Eastern Gansu Province, China, between January 1994 and April 1998.	There is no significant association between age at first birth and lung cancer.	Not analyzed
Kabat et al. (2007) [25]	**Cohort** Variable Type: *Categorical*; 1) <23, 23-25, 26-29 and ≥30 years Confounder Adjustment: Body mass index, education, smoking status, pack-years of smoking, study center and randomization group (intervention versus control), and other exposure variables.	89,835 Canadian women aged 40–59 years recruitment in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer, between 1980 and 1985.	The odds of lung cancer decreased with older age at first birth (P for trend = 0.004).	Smoking status: This inverse association remained significant after stratifying by never and ever smokers (P for trend = 0.01 and 0.02, respectively). Histological subtypes: The association between age at first birth and adenocarcinoma was not statistically significant; however, the odds of lung cancer of other cell types decreased with increasing age at first birth (P for trend = 0.004). Age: The inverse association between age at first birth and lung cancer remained significant after stratifying by age (P for trend (40-49 years) = 0.007 and P for trend (50-59 years) = 0.07).
Weiss et al. (2008) [23]	**Cohort** Variable Type: *Categorical*; 1) <23, 23-25, 26-27 and ≥28 years Confounder Adjustment: Passive smoking.	71,314 non-smoking Chinese women aged 40-70 with no history of cancer at baseline from the prospective Shanghai Women's Health Study conducted between 1996 and 2000.	There was no significant association between age at first birth and lung cancer.	Histological subtypes: There was no significant association between age at first birth and lung cancer among women with adenocarcinoma; this relationship was not examined among women with other histologic types of lung cancer.

APPENDIX G: Supplementary Table 6: Age at First Birth (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Koushik et al. (2009) [21]	**Case-Control** Variable Type: *Categorical*; 1) <23, 23-<26, 26-<30 and ≥30 years Confounder Adjustment: Age, respondent status, ethnicity, education, family income, and smoking status.	422 women with lung cancer and 577 population-based controls from Montreal, Canada recruited between January 1996 and December 1997.	There was no significant association between age at first birth and lung cancer.	Histological subtypes: There was no significant association between age at first birth and adenocarcinoma; other histological subtypes were not analyzed.
Paulus et al. (2010) [20]	**Case-Control** Variable Type: *Categorical*; 1) <20, 20-24, 25-29 and ≥30 years Confounder Adjustment: Age, smoking status, pack-years of smoking, and years since quitting smoking.	1,004 cases and 848 controls (friends and non-blood relatives) enrolled in the Lung Cancer Susceptibility Study (LCSS) at Massachusetts General Hospital (Boston, Massachusetts) between December 1992 and December 2003.	1) Lung cancer risk was not associated with age at first birth, among parous women.	Not analyzed
Baik et al. (2010) [19]	**Cohort** Variable Type: *Categorical*; 1) <26, 26-30 and ≥30 years Confounder Adjustment: Smoking, fruit/vegetable in-take, BMI, environmental smoking exposure, and other exposure variables	107,171 postmenopausal women aged 30-55 years enrolled in the Nurse's Health Study, collected between 1984 and 2006.	There was no significant association between age at first birth and lung cancer.	Smoking status: Age at first birth was positively associated with lung cancer among current smokers (P for trend=0.02). However, this association was not significant among never and former smokers. Histological subtypes: There is no significant association between age at first birth and lung cancer, when stratified by histological subgroups.

APPENDIX G: Supplementary Table 6: Age at First Birth (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brinton et al. (2011) [17]	**Cohort** Variable Type: *Categorical*; 1) <20, 20-24, 25-29 and ≥30 years Confounder Adjustment: Age, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche, age at menopause and type of menopause.	185,017 women between the ages of 50 and71 years were recruited into the NIH-AARP (American Association of Retired Persons) Diet and Health Study during 1995 and 1996.	There was an inverse relationship between age at first birth and lung cancer risk among parous women (P for trend = 0.03).	Smoking status: The inverse relationship between age at first birth and lung cancer was only observed among current smoker (P for trend = 0.04), after stratifying my smoking status; this association was not statistically significant among never and former smokers. Histological subtypes: The association between age at first birth and lung cancer was not significant after stratifying by histological subgroups.
Meinhold et al. (2011) [18]	**Case-Control** Variable Type: *Categorical*; 1) <20, 20-24, ≥25 years Confounder Adjustment: Age, education, smoking, number of smoking adults in household and current household income.	430 women diagnosed with non-small cell lung cancer, 316 hospital controls and 295 population controls recruited in the multi-center Maryland Lung Cancer Study between 1998 and 2008.	There was no significant association between age at first birth and non-small cell lung cancer, when using hospital, population or combined controls.	Smoking status: The association between age at first birth and non-small cell lung cancer was not significant when stratified by smoking status.

APPENDIX G: Supplementary Table 6: Age at First Birth (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Lim et al. (2012) [16]	**Case-Control** Variable Type: *Categorical*; 1) 20, 21-25, 26-30 and ≥31years Confounder Adjustment: Age, fruit and vegetable consumption, country of origin, dwelling type, years of education, history of cancer in first-degree relatives, smoking status , secondhand smoke exposure at home, and study set.	702 Chinese female lung cancer cases and 1,578 hospital controls from 2 hospital-based case-control studies, which recruited from the 5 major public-sector hospitals in Singapore during 1996–1998 and 2005–2008.	There was no significant association between age at first birth and lung cancer.	Smoking status: There was no significant association between age at first birth and lung cancer by smoking status (never and ever smokers).
Gallagher et al. (2013) [15]	**Cohort** Variable Type: *Categorical*; 1)<19, 20-24, 25-29 and ≥30 years Confounder Adjustment: Age and smoking.	267,400 female textile workers in Shanghai, China, enrolled between 1989 and 1991 and followed until 2000 for incidence of lung cancer.	There was no significant association between age at first birth and lung cancer.	Not analyzed

APPENDIX H: Supplementary Table 7: Oral Contraceptive (OC) use

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kreuzer et al. (2003) [29]	**Case-Control** Variable Type: *Categorical*; 1) Never and ever Confounder Adjustment: Age, region, pack years of smoking, smoking status, and education.	811 women with lung cancer and 912 population controls enrolled between 1990 and 1996 in Germany.	There was a decreased odds of lung cancer among ever OC users compared to never users.	Smoking status: Among smokers, the odds of lung cancer was reduced among women that ever used OC compared to those at never used OC. However, no significant association between OC use and lung cancer was report among non-smokers. Histological subtypes: There was a significant reduction in the odds of small cell lung cancer and squamous cell carcinoma among OC ever users compared to never users; however the association between adenocarcinoma and OC use was not statistically significant.
Elliott et al. (2006) [27]	**Nested Case-Control** Variable Type: *Categorical*; 1) Never and ever 2) Never, current and former Confounder Adjustment: Smoking, social class and parity.	162 incident cases of lung cancer, among women, recorded by the Royal College of General Practitioners' Oral Contraception Study (OCS)database by August 2004, and age and length of follow-up matched controls (n=3*162) from the same cohort.	There was no significant association between OC use and lung cancer.	Not analyzed

APPENDIX H: Supplementary Table 7: Oral Contraceptive (OC) use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kabat et al. (2007) [25]	**Cohort** Variable Type: *Categorical*; 1) Never and ever Confounder Adjustment: Body mass index, education, smoking status, pack-years of smoking, study center and randomization group (intervention versus control), and other exposure variables.	89,835 Canadian women aged 40–59 years recruitment in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer, between 1980 and 1985.	The association between OC use and lung cancer was not statistically significant.	Smoking status: There was no significant association between OC use and lung cancer after stratifying by smoking status (never and ever). Histological subtypes: There was no significant association between OC use and lung cancer after stratifying by histology (Adenocarcinoma and other cell types). Age: There was no significant association between OC use and lung cancer after stratifying by age (40-49 and 50-59 years).
Weiss et al. (2008) [23]	**Cohort** Variable Type: *Categorical*; 1) Never and ever Confounder Adjustment: Passive smoking.	71,314 non-smoking Chinese women aged 40-70 with no history of cancer at baseline from the prospective Shanghai Women's Health Study conducted between 1996 and 2000.	There was no significant association between OC use and lung cancer.	Histological subtypes: There was no significant association between OC use and lung cancer among women with adenocarcinoma; this relationship was not examined among women with other histologic types of lung cancer.

APPENDIX H: Supplementary Table 7: Oral Contraceptive (OC) use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Seow et al. (2009) [22]	**Cohort** Variable Type: *Categorical*; 1) Never, <10years and ≥10years Confounder Adjustment: Age, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level, body mass index (BMI), total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, and duration of smoking (years), cigarettes per day, and number of years since quitting among current or former smokers.	35,298 women aged 45 to 78 years recruited into the Singapore Chinese Health Study between April 1993 and December 1998.	There was no significant association between OC use and lung cancer.	Histological subtypes: There was no significant association between OC use and lung cancer, when stratified by histology.
Baik et al. (2010) [19]	**Cohort** Variable Type: *Categorical*; 1) Never and Ever Confounder Adjustment: Smoking, fruit/vegetable intake, BMI, environmental smoking exposure, and other exposure variables.	107,171 postmenopausal women aged 30-55 years enrolled in the Nurse's Health Study, collected between 1984 and 2006.	There was no significant association between OC use and lung cancer.	Smoking status: The association between OC use and lung cancer remained insignificant when stratified by smoking status. Histological subtypes: There was no significant association between OC use and lung cancer when stratified by histological subgroups.

APPENDIX H: Supplementary Table 7: Oral Contraceptive (OC) use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brinton et al. (2011) [17]	**Cohort** Variable Type: *Categorical*; 1) Never used/use <1 year and Use ≥ 1 year Confounder Adjustment: Age, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche, age at menopause and type of menopause.	185,017 women between the ages of 50 and71 years were recruited into the NIH-AARP (American Association of Retired Persons) Diet and Health Study during 1995 and 1996.	There was no significant association between OC use and lung cancer.	Not analyzed
Meinhold et al. (2011) [18]	**Case-Control** Variable Type: *Categorical*; 1)Never and ever Confounder Adjustment: Age, education, smoking, number of smoking adults in household and current household income.	430 women diagnosed with non-small cell lung cancer, 316 hospital controls and 295 population controls recruited in the multi-center Maryland Lung Cancer Study between 1998 and 2008.	There was no significant association between OC use and non-small cell lung cancer, when using hospital, population or combined controls.	Smoking status: The association between OC use and non-small cell lung cancer was not significant when stratified by smoking status.

APPENDIX H: Supplementary Table 7: Oral Contraceptive (OC) use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Lim et al. (2012) [16]	**Case-Control** Variable Type: *Categorical*; 1) exogenous hormone use (combined OC and menopausal hormone use): Never, ≤5 years and ≥5years Confounder Adjustment: Age, fruit and vegetable consumption, country of origin, dwelling type, years of education, history of cancer in first-degree relatives, smoking status , secondhand smoke exposure at home, and study set.	702 Chinese female lung cancer cases and 1,578 hospital controls from 2 hospital-based case-control studies, which recruited from the 5 major public-sector hospitals in Singapore during 1996–1998 and 2005–2008.	There was no significant association between exogenous hormone use and lung cancer.	Smoking status: There was no significant association between exogenous hormone use and lung cancer by smoking status (never and ever smokers).

APPENDIX I: Supplementary Table 8: Duration of Oral Contraceptive (OC) use

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kreuzer et al. (2003) [29]	**Case-Control** Variable Type: *Categorical*; 1) Non-user, <5, 5-11 and ≥12 years Confounder Adjustment: Age, region, pack years of smoking, smoking status, and education.	811 women with lung cancer and 912 population controls enrolled between 1990 and 1996 in Germany.	There was no significant association between duration of OC use and lung cancer.	Smoking status: There was no significant association between duration of OC use and lung cancer after stratifying by smoking status (non-smokers and smokers). Histological subtypes: There was no significant association between duration of OC use and lung cancer after stratifying by histology (adenocarcinoma, small cell carcinoma and squamous carcinoma).
Elliott et al. (2006) [27]	**Nested Case-Control** Variable Type: *Categorical*; 1) No use, <5, 5-9 and ≥10years Confounder Adjustment: Smoking, social class and parity.	162 incident cases of lung cancer, among women, recorded by the Royal College of General Practitioners' Oral Contraception Study (OCS)database by August 2004, and age and length of follow-up matched controls (n=3*162) from the same cohort.	There was no significant association between duration of OC use and lung cancer.	Not analyzed
Kabat et al. (2007) [25]	**Cohort** Variable Type: *Categorical*; 1) Never, 1-11, 12-35, 36-71 and ≥72 months Confounder Adjustment: Body mass index, education, smoking status, pack-years of smoking, study center and randomization group (intervention versus control), and other exposure variables.	89,835 Canadian women aged 40–59 years recruitment in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer, between 1980 and 1985.	The association between duration of OC use and lung cancer was not statistically significant.	Smoking status: There was no significant association between duration of OC use and lung cancer after stratifying by smoking status (never and ever). Histological subtypes: There was no significant association between duration of OC use and lung cancer after stratifying by histology (Adenocarcinoma and other cell types). Age: There was no significant association between duration of OC use and lung cancer after stratifying by age (40-49 and 50-59 years).

APPENDIX I: Supplementary Table 8: Duration of Oral Contraceptive (OC) use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Seow et al. (2009) [22]	**Cohort** Variable Type: *Categorical*; 1) Never, <10years and ≥10years Confounder Adjustment: Age, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level, body mass index (BMI), total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, and duration of smoking (years), cigarettes per day, and number of years since quitting among current or former smokers.	35,298 women aged 45 to 78 years recruited into the Singapore Chinese Health Study between April 1993 and December 1998.	There was no significant association between OC use and lung cancer.	Histological subtypes: There was no significant association between OC use and lung cancer, when stratified by histology.
Baik et al. (2010) [19]	**Cohort** Variable Type: *Categorical*; 1) <5 and >5 years Confounder Adjustment: Smoking, fruit/vegetable in-take, BMI, environmental smoking exposure, and other exposure variables.	107,171 postmenopausal women aged 30-55 years enrolled in the Nurse's Health Study, collected between 1984 and 2006.	Women that used oral contraceptives for more than 5 years had and increased risk of lung cancer compared those that used OC for less than 5 years.	Smoking status: When stratified by smoking status, the increased lung cancer risk among women that use oral contraceptives for more than 5 years was observed among current smoker, but the relationship was not statistically significant among never and former smokers. Histological subtypes: When stratified by histological subtypes, there was an increased risk of small cell carcinoma with greater than 5 years of OC use. However, there was no significant association between adenocarcinoma or squamous carcinoma and lung cancer.

APPENDIX I: Supplementary Table 8: Duration of Oral Contraceptive (OC) use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Brinton et al. (2011) [17]	**Cohort** Variable Type: *Categorical*; 1) Never used/use <1 year, 1-4, 5-9, ≥10 years Confounder Adjustment: Age, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche, age at menopause and type of menopause.	185,017 women between the ages of 50 and 71 years were recruited into the NIH-AARP (American Association of Retired Persons) Diet and Health Study during 1995 and 1996.	There was no significant association between duration of OC use and lung cancer.	Not analyzed
Meinhold et al. (2011) [18]	**Case-Control** Variable Type: *Categorical*; 1) <5years and ≥5years Confounder Adjustment: Age, education, smoking, number of smoking adults in household and current household income.	430 women diagnosed with non-small cell lung cancer, 316 hospital controls and 295 population controls recruited in the multi-center Maryland Lung Cancer Study between 1998 and 2008.	There was no significant association between duration of OC use and non-small cell lung cancer, when using hospital, population or combined controls.	Not analyzed

APPENDIX I: Supplementary Table 8: Duration of Oral Contraceptive (OC) use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Lim et al. (2012) [16]	**Case-Control** Variable Type: *Categorical*; 1) exogenous hormone use (combined OC and menopausal hormone use): Never, ≤5 years and ≥5 years Confounder Adjustment: Age, fruit and vegetable consumption, country of origin, dwelling type, years of education, history of cancer in first-degree relatives, smoking status , secondhand smoke exposure at home, and study set.	702 Chinese female lung cancer cases and 1,578 hospital controls from 2 hospital-based case-control studies, which recruited from the 5 major public-sector hospitals in Singapore during 1996–1998 and 2005–2008.	There was no significant association between exogenous hormone use and lung cancer.	Smoking status: There was no significant association between exogenous hormone use and lung cancer by smoking status (never and ever smokers).

APPENDIX J: Supplementary Table 9: Post-Menopausal Hormone use

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kreuzer et al. (2003) [29]	**Case-Control** Variable Type: *Categorical*; 1) Never and ever 2) Nonusers, <3, 3-6 and ≥7years 3) Use after surgical menopause: ever, never, <3, 3-6, ≥7 years Confounder Adjustment: Age, region, pack years of smoking, smoking status, and education.	811 women with lung cancer and 912 population controls enrolled between 1990 and 1996 in Germany.	There was no significant association between menopausal hormone use and lung cancer. However, the odds of lung cancer decrease among women that used menopausal hormone for 7 years or more, compared to never users (OR=0.59; 95% CI=0.37-0.93). Among women that use menopausal hormone after surgical menopause, reduced odds of lung cancer was also observed with increased duration of menopausal hormone use.	Smoking status: There was no significant association between menopausal hormone use and lung cancer among smokers and non-smokers that had surgical menopause. Histological subtypes: There was no significant association between menopausal hormone use and lung cancer women that had surgical menopause, after stratification by histological subgroups.

APPENDIX J: Supplementary Table 9: Post-Menopausal Hormone use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Elliott et al. (2006) [27]	**Nested Case-Control** Variable Type: *Categorical*; 1) Never and ever 2) Never, current and former Confounder Adjustment: Smoking, social class and parity.	162 incident cases of lung cancer, among women, recorded by the Royal College of General Practitioners' Oral Contraception Study (OCS)database by August 2004, and age and length of follow-up matched controls (n=3*162) from the same cohort.	There was no significant association between menopausal hormone use and lung cancer.	Not analyzed
Chen et al. (2007) [26]	**Case-Control** Variable Type: *Categorical*; 1) Yes and No Confounder Adjustment: Age, ethnicity, smoking, education, BMI, menopause, cooking, motorcycle riding, passive smoking, incense burning, family history.	826 lung cancer cases and 531 healthy controls enrolled in the Genetic Epidemiological Study of Female Lung Adenocarcinoma (GEFLAC) in Taiwan form September 2002 to February 2006.	Women that receive hormone replacement therapy had reduced odds of lung cancer.	Smoking status: The odds of lung cancer reduced with hormone replacement therapy use among female never smoker; however, this association was not significant among ever smokers. Histological subtypes: The odds of non-small cell carcinoma and large cell lung cancer were lower among hormone replacement therapy (HRT) users; however, the associations between HRT and adenocarcinoma, squamous cell carcinoma and small cell lung cancer were not significant. * This study also investigated effect modification by active and passive cigarette smoking, BMI, history of incense burning, cooking, and motorcycle riding, as well as family history of cancer. Reduced odds ratios of lung cancer were reported in all these subset analyses.

APPENDIX J: Supplementary Table 9: Post-Menopausal Hormone use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Kabat et al. (2007) [25]	**Cohort** Variable Type: *Categorical*; 1) Never and ever 2) Never, 1-12, 13-59, 60-119 and ≥120 months Confounder Adjustment: Body mass index, education, smoking status, pack-years of smoking, study center and randomization group (intervention versus control), and other exposure variables.	89,835 Canadian women aged 40–59 years recruitment in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer, between 1980 and 1985.	There was not significant difference between women that never used menopausal hormones and those that ever used menopausal hormone. However, the risk of lung cancer increase among women that used menopausal hormone for 120months or more, compared to never users (HR=1.51; 95% CI=1.14-1.99).	Smoking status: There was no significant association between menopausal hormone use (of duration of use) and lung cancer after stratifying by smoking status (never and ever). Histological subtypes: There was no significant association between menopausal hormone use (of duration of use) and lung cancer after stratifying by histology (Adenocarcinoma and other cell types). Age: When only women between the age of 50-59years were analyzed, there was an inverse association between duration of menopausal hormone use and lung cancer (P for trend = 0.01); nevertheless, there was no significant difference between never and ever users of menopausal hormone.
Weiss et al. (2008) [23]	**Cohort** Variable Type: *Categorical*; 1) Never and ever Confounder Adjustment: Passive smoking.	71,314 non-smoking Chinese women aged 40-70 with no history of cancer at baseline from the prospective Shanghai Women's Health Study conducted between 1996 and 2000.	There was no significant association between menopausal hormone use and lung cancer.	Histological subtypes: There was no significant association between menopausal hormone use and lung cancer among women with adenocarcinoma; this relationship was not examined among women with other histologic types of lung cancer.

APPENDIX J: Supplementary Table 9: Post-Menopausal Hormone use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Rodriguez et al. (2008) [24]	**Cohort** Variable Type: *Categorical*; 1) Never, current and former Confounder Adjustment: Age, smoking status, spousal tobacco exposure in 1992, body mass index in 1992, age at menopause, education, weekly servings of fruit, physical activity, total β-carotene intake, and oral contraceptive use.	97,786 female participants of the Cancer Prevention Study II (CPS-II) Nutrition Cohort followed-up from 1992 to 2003.	There was an increased risk of lung cancer among current users of menopausal hormones compared to never users.	Smoking status: There was no significant association between menopausal hormone use and lung cancer after stratification by smoking status (never, current and former).
Seow et al. (2009) [22]	**Cohort** Variable Type: *Categorical*; 1) Yes and No Confounder Adjustment: Age, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level, body mass index (BMI), total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, and duration of smoking (years), cigarettes per day, and number of years since quitting among current or former smokers.	35,298 women aged 45 to 78 years recruited into the Singapore Chinese Health Study between April 1993 and December 1998.	There was no significant association between menopausal hormone use and lung cancer.	Histological subtypes: There was no significant association between menopausal hormone use and lung cancer, when stratified by histology.

APPENDIX J: Supplementary Table 9: Post-Menopausal Hormone use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Baik et al. (2010) [19]	**Cohort** Variable Type: *Categorical*; 1) Never, past and current Confounder Adjustment: Smoking, fruit/vegetable in-take, BMI, environmental smoking exposure, and other exposure variables.	107,171 postmenopausal women aged 30-55 years enrolled in the Nurse's Health Study, collected between 1984 and 2006.	There was no significant association between menopausal hormone use and lung cancer.	Smoking status: There was no significant association between menopausal hormone use and lung cancer, among the strata formed by smoking status. Histological subtypes: The association between menopausal hormone use and lung cancer were not significant when stratified by histology.
Brinton et al. (2011) [17]	**Cohort** Variable Type: *Categorical*; 1) Never, Current, Former Confounder Adjustment: Age, race/ethnicity, education, BMI, emphysema, smoking status and dose, age at menarche.	185,017 women between the ages of 50 and 71 years were recruited into the NIH-AARP (American Association of Retired Persons) Diet and Health Study during 1995 and 1996.	There was no significant association between menopausal hormone use and lung cancer.	Not analyzed
Meinhold et al. (2011) [18]	**Case-Control** Variable Type: *Categorical*; 1) Never and ever 2) <5years and ≥5years of use 3) <5years and ≥5years since last use Confounder Adjustment: Age, education, smoking, number of smoking adults in household and current household income.	430 women diagnosed with non-small cell lung cancer, 316 hospital controls and 295 population controls recruited in the multi-center Maryland Lung Cancer Study between 1998 and 2008.	There was no significant association between menopausal hormone use and non-small cell lung cancer, when using hospital, population or combined controls.	Smoking status: The association between menopausal hormone use and non-small cell lung cancer was not significant when stratified by smoking status.

APPENDIX J: Supplementary Table 9: Post-Menopausal Hormone use (Cont'd)

Authors	Study Design	Population	Key Findings	Effect Modifiers
Lim et al. (2012) [16]	**Case-Control** Variable Type: *Categorical*; 1) exogenous hormone use (combined OC and menopausal hormone use): Never, ≤5 years and ≥5 years Confounder Adjustment: Age, fruit and vegetable consumption, country of origin, dwelling type, years of education, history of cancer in first-degree relatives, smoking status, secondhand smoke exposure at home, and study set.	702 Chinese female lung cancer cases and 1,578 hospital controls from 2 hospital-based case-control studies, which recruited from the 5 major public-sector hospitals in Singapore during 1996–1998 and 2005–2008.	There was no significant association between exogenous hormone use and lung cancer.	Smoking status: There was no significant association between exogenous hormone use and lung cancer by smoking status (never and ever smokers).

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