Hormone Use, Reproductive History, and Risk of Lung Cancer

The Women's Health Initiative Studies

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Introduction: Results from the Women's Health Initiative clinical trials demonstrated no increase in the risk of lung cancer in postmenopausal women treated with hormone therapy (HT). We conducted a joint analysis of the Women's Health Initiative observational study data and clinical trials data to further explore the association between estrogen and estrogen-related reproductive factors and lung cancer risk.

Methods: Reproductive history, oral contraceptive use, and postmenopausal HT were evaluated in 160,855 women with known HT exposures. Follow-up for lung cancer was through September 17, 2012; 2467 incident lung cancer cases were ascertained, with median follow-up of 14 years.

Results: For all lung cancers, women with previous use of estrogen plus progestin of less than 5 years (hazard ratio = 0.84; 95% confidence interval = 0.71–0.99) were at reduced risk. A limited number of reproductive factors demonstrated associations with risk. There was a trend toward decreased risk with increasing age at menopause (p_{trend} = 0.04) and a trend toward increased risk with increasing number of live births (p_{trend} = 0.03). Reduced risk of non–small-cell lung cancer was associated with age 20–29 years at first live birth. Risk estimates varied with smoking history, years of HT use and previous bilateral oophorectomy.

Conclusions: Indirect measures of estrogen exposure to lung tissue, as used in this study, provide only weak evidence for an association between reproductive history or HT use and risk of lung cancer. More detailed mechanistic studies and evaluation of risk factors in conjunction with estrogen receptor expression in the lung should continue as a role for estrogen cannot be ruled out and may hold potential for prevention and treatment strategies.

Key Words: Lung cancer, Hormone therapy, Reproductive history.

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In 2013, an estimated 110,110 women in the US were diagnosed with lung cancer and 72,220 died from this disease.[1] There remains a gender gap in incidence rates with men having higher rates than women, but with the declining incidence among men and the leveling off of incidence among women only recently, this gender difference is narrowing. The lifetime risk of developing lung cancer is 6.9% in both men and women.[1]

While approximately 90% of lung cancer deaths are attributable to cigarette smoking in men, only 75–80% of lung

cancer deaths in women are attributable to smoking.[2] There has been considerable debate about differences in lung cancer occurrence and characteristics between men and women. Women are more likely to have adenocarcinomas of the lung (45.0%) than men (37.2%) and are more likely to have tumors with *EGFR* mutations.[3] Women who never smoked are also more likely to develop lung cancer than men who have never smoked.[4–7] However, the 5-year relative survival after a lung cancer diagnosis is better for women than for men (20.0% and 15.4%, respectively).[1] Taken together, male–female differences in lung cancer risk, tumor characteristics and outcome have fueled investigations into the role of estrogens in lung cancer risk and prognosis.

Epidemiologic studies of estrogen as a risk factor for lung cancer have focused on reproductive and estrogen use history. Findings have been inconsistent, with reports of increased and decreased risk associated with postmenopausal hormone therapy (HT), oral contraceptive (OC) use, pregnancy, and menstrual history.[8–31] The Women's Health Initiative (WHI) clinical trials (CTs) data demonstrated that neither the use of estrogen plus progestin or estrogen alone was associated with lung cancer incidence.[18,19] Taken as a whole, inconsistent findings across studies are likely due to a number of factors including variations in HT dosing over time and potential misclassification of exposures, however, they suggest a possible role for exogenous estrogens (i.e., HT, OCs) in the development of lung cancer.

We evaluated the role of reproductive factors and hormone use in determining risk of lung cancer in women from both the Women's Health Initiative Observational Study and CTs.

METHODS

The Women's Health Initiative

The WHI enrolled a geographically and ethnically diverse cohort of 161,808 postmenopausal women age 50–79 years between October 1, 1993 and December 31, 1998 at 40 centers across the United States. All participants provided informed consent. Women were enrolled in one of four randomized CTs testing use of estrogen alone or estrogen plus progestin, calcium plus vitamin D (CaD), or low fat diet (dietary modification—DM) on several outcomes. In addition, the observational study (OS) enrolled women who provided detailed lifestyle and medical history and were followed for disease outcomes. Details of recruitment[32] and baseline characteristics of study participants[33] have been published previously. Reproductive history (age at first birth, number of pregnancies, age at menarche, age at menopause, bilateral oophorectomy), use of unopposed estrogens, estrogen plus progesterone, and/or OCs (never used, duration of use <5, 5–9, 10–14, 15+ years) were collected at the baseline clinic visit by self-report. Current users of HT were defined as women using HT at baseline in the OS, or women using HT at baseline in the DM or CaD trials (who were not participating in the HT trial) or women assigned to HT use in the HT CT. Past users of HT were defined as women not using HT at baseline in the OS, DM, or CaD CTs but who had used HT in the past, women receiving placebo in the HT CT but who had used HT in the past, or women randomized to HT who used HT in the past and completed a wash out period before going on trial. Never users of HT were defined as women never using HT in the OS or non-HT CTs or women on the placebo arm of the HT CT who had never used HT before trial initiation. Therefore, any of the participants, even those enrolled in the HT CT and randomized to HT, could have been defined as past users of HT.

The type of HT was classified as that reported at baseline for all women except for those on the intervention arm of the HT CT, for whom the assigned HT was used. Duration of use was calculated from start of use to before baseline or randomization. Self-report of age at enrollment, education, income, smoking status (never smoked more than 100 cigarettes, ever smoked more than 100 cigarettes), number of cigarettes smoked per day (<5, 5–14, 15–24, 25–34, 35–44, 45+), years smoked (<5, 1–9, 10–19, 20–29, 30–39, 40–49, 50+), age started smoking in 5-year intervals, age quit smoking in 5-year intervals, passive smoke exposure as a child and as an adult (home and work), alcohol intake, physical activity, diet and medical history were obtained at baseline.

Study participants were followed annually in the OS, and biannually through 2005 and annually thereafter in the CTs. At each follow-up, additional questionnaire data were obtained including self-report of cancer. Self-reports of cancer were confirmed by review of medical records and pathology reports. As of September 17, 2012, 2467 lung cancers had been reported and centrally adjudicated. Of these, 2220 were classified as non–small-cell lung cancers (NSCLC), 236 were classified as small-cell lung cancers (SCLC) and 11 had missing histology.

Statistical Approach

The baseline subject questionnaire data, supplemented with data on lung cancer incidence, were used in the analysis. The primary objective of this study was to assess the association of reproductive history and use of OCs and HT, after adjustment for tobacco use and other known lung cancer risk factors, with risk of lung cancer among women. Two hundred fifty-seven women who reported a history of lung cancer on the baseline questionnaire were excluded. In addition, 696 women who were enrolled in the WHI studies but for whom there was no follow-up information were also excluded, leaving 160,855 women in this analysis, with 2467 incident cases of lung cancer.

Associations between reproductive and hormonal factors and lung cancer incidence were assessed using Cox regression models to compute adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Time to incident lung cancer was computed as days from randomization in the CTs or enrollment in the OS to the first diagnosis of lung cancer during follow-up. Otherwise, follow-up was censored at the last documented follow-up contact, death, or September 17, 2012, whichever came first. Additional analyses were conducted, stratified by baseline smoking status (never, former, current) and in relation to risk by lung cancer histology (SCLC, NSCLC, and specific NSCLC subtypes). For the analyses of histology subtype, each subtype was treated as a

separate outcome and lung cancer cases of a different subtype were censored at the time of diagnosis.

Each baseline hormonal or reproductive factor was modeled separately in relation to disease outcome. Tests for trend were performed by modeling the continuous form of the variable if it was originally collected; otherwise, a linear trend was evaluated by modeling the integer-scored categorical variable as a continuous variable. A set of covariates was selected, a priori, for adjustment of potential confounding, including age at enrollment/recruitment (continuous), race/ethnicity (white, black, other), education (less than high school, high school degree or equivalent, education after high school, college degree or higher), US region (Northeast, South, Midwest, West), pack-years of smoking (never smoked, <5, 5 to <20, ≥20), family history of cancer, personal history of asthma or emphysema, and body mass index (<25, 25 to <30, ≥30). The baseline hazard function in the Cox model was stratified by age (5-year groups); HT trial randomization assignment or study enrollment (active conjugated equine estrogen [CEE] plus medroxyprogesterone acetate, placebo CEE and medroxyprogesterone acetate, active CEE, placebo CEE, or not randomized), DM trial randomization (intervention, control, or not randomized), CaD trial, or OS enrollment; hysterectomy status at baseline; and extension study participation.

Associations were evaluated in a multivariable model that included statistically significant covariates and risk factors. Several variables were not retained in the final multivariable model because their inclusion made no important changes to risk estimates or their interpretation. These included age at menarche, number of births, history of asthma, age at menopause, years since menopause, duration of past OC use, and duration of prior unopposed estrogen use.

Statistical tests were two-sided, and p values less than 0.05 were considered statistically significant. All analyses were performed using the SAS system, version 9.3 (SAS Institute, Cary, NC).

RESULTS

Table 1 presents the baseline characteristics of the 160,855 women included in the analysis stratified by lung cancer status. In the entire cohort, 2467 lung cancers were diagnosed during follow-up. After adjustment for multiple factors (see "Methods" and footnote of Table 2), the only variables in which there was a statistically significant relation with lung cancer risk overall, and NSCLC specifically, included later age at first live birth and later age at menopause, both of which were associated with a reduced risk. Increasing time since menopause was associated with an increased risk (Table 2).

The only statistically significant findings with regard to hormone use were a reduction in risk associated with previous use of estrogen plus progestin of less than 5 years for all lung cancers (HR = 0.84; 95% CI = 0.72–0.98) and a similar reduction in risk associated with 5 to less than 10 years of any previous hormone use for NSCLC (HR = 0.84; 95% CI = 0.71–0.99). Little variation in risk in association with hormone use was seen for subtypes of NSCLC including adenocarcinomas, squamous cell carcinomas, large cell and associated subtypes, and other NSCLC or unspecified NSCLC

TABLE 1. Baseline Characteristics of WHI Participants by Lung Cancer Status

	Noncases (N = 158,388)	Lung Cancer Cases (N = 2467)	
	n (%)	n (%)	p
Age group at screening (5 yr intervals)			
50–54	21,258 (13.4)	161 (6.5)	<0.001
55–59	31,470 (19.9)	330 (13.4)	-
60–64	36,432 (23.0)	567 (23.0)	-
65–69	34,456 (21.8)	745 (30.2)	-
70–74	24,284 (15.3)	485 (19.7)	-
75–79	10,488 (6.6)	179 (7.3)	-
Race/ethnicity			
White	130,738 (82.5)	2198 (89.1)	<0.001
Black	14,328 (9.0)	152 (6.2)	-
Hispanic	6306 (4.0)	35 (1.4)	-
American Indian	692 (0.4)	10 (0.4)	-
Asian/Pacific Islander	4119 (2.6)	38 (1.5)	-
Unknown	2205 (1.4)	34 (1.4)	-
Education			
Less than high school	8362 (5.3)	137 (5.6)	<0.001
High school diploma/GED	27,003 (17.0)	457 (18.5)	-
School after high school	59,552 (37.6)	1017 (41.2)	-
College degree or higher	62,280 (39.3)	841 (34.1)	-
Missing	1191 (0.8)	15 (0.6)	-
US region			
Northeast	36,109 (22.8)	658 (26.7)	<0.001
South	41,024 (25.9)	582 (23.6)	-
Midwest	34,863 (22.0)	492 (19.9)	-
West	46,392 (29.3)	735 (29.8)	-
Smoking status			
Never	80,649 (50.9)	382 (15.5)	<0.001
Past	65,320 (41.2)	1359 (55.1)	-
Current	10,363 (6.5)	691 (28.0)	-
Missing	2056 (1.3)	35 (1.4)	-
Pack years of smoking (categorical)			
Never smoker	80,649 (50.9)	382 (15.5)	<0.001
<5	22,374 (14.1)	133 (5.4)	-
5 to <20	21,940 (13.9)	346 (14.0)	-
≥20	27,791 (17.5)	1506 (61.0)	-
Missing	5634 (3.6)	100 (4.1)	-
History of emphysema			
No	143,852 (90.8)	2090 (84.7)	<0.001
Yes	5363 (3.4)	220 (8.9)	-
Missing	9173 (5.8)	157 (6.4)	-
History of asthma			
No	144,044 (90.9)	2193 (88.9)	<.001
Yes	12,224 (7.7)	245 (9.9)	-
Missing	2120 (1.3)	29 (1.2)	-
Age at menarche			
<12	34,607 (21.8)	552 (22.4)	0.686
12	41,186 (26.0)	632 (25.6)	-

(*Continued*)

TABLE 1. (*Continued*)

	Noncases (*N* = 158,388)	Lung Cancer Cases (*N* = 2467)	
	n (%)	*n* (%)	*p*
13	45,625 (28.8)	685 (27.8)	-
>13	36,342 (22.9)	587 (23.8)	-
Missing	628 (0.4)	11 (0.4)	-
Number of pregnancies			
None	14,596 (9.2)	211 (8.6)	0.002
1	11,069 (7.0)	162 (6.6)	-
2	30,475 (19.2)	438 (17.8)	-
3	35,280 (22.3)	517 (21.0)	-
4	27,310 (17.2)	435 (17.6)	-
≥5	38,895 (24.6)	695 (28.2)	-
Missing	763 (0.5)	9 (0.4)	-
Number of live births			
None	18,803 (11.9)	286 (11.6)	0.103
≥5	23,204 (14.7)	396 (16.1)	-
1–2	53,367 (33.7)	777 (31.5)	-
3–4	62,062 (39.2)	994 (40.3)	-
Missing	952 (0.6)	14 (0.6)	-
Age at first birth, yr (categories)			
Never preg/no term preg	18,803 (11.9)	286 (11.6)	0.003
<20	20,065 (12.7)	379 (15.4)	-
20–29	92,716 (58.5)	1408 (57.1)	-
30+	11,728 (7.4)	173 (7.0)	-
Missing	15,076 (9.5)	221 (9.0)	-
Age at menopause			
<40	14,193 (9.0)	290 (11.8)	<0.001
40–50	51,635 (32.6)	918 (37.2)	-
50+	76,655 (48.4)	1020 (41.3)	-
Missing	15,905 (10.0)	239 (9.7)	-
Years since menopause			
<5 yrs	20,239 (12.8)	151 (6.1)	<0.001
5–9 yrs	26,996 (17.0)	278 (11.3)	-
10–14 yrs	29,424 (18.6)	441 (17.9)	-
15–19 yrs	25,464 (16.1)	441 (17.9)	-
≥20 yrs	47,031 (29.7)	1007 (40.8)	-
Missing	9234 (5.8)	149 (6.0)	-
Oral contraceptive use ever			
No	92,686 (58.5)	1521 (61.7)	0.007
Yes	65,699 (41.5)	946 (38.3)	-
Missing	3 (0.0)	0 (0.0)	-
Duration of OC use			
Nonuser	92,732 (58.5)	1524 (61.8)	0.023
<5 years	36,324 (22.9)	512 (20.8)	-
5 to <10 years	14,922 (9.4)	212 (8.6)	-
10+ years	14,407 (9.1)	219 (8.9)	-
Missing	3 (0.0)	0 (0.0)	-
Unopposed estrogen use ever			
No	101,910 (64.3)	1555 (63.0)	0.393
Yes	56,475 (35.7)	912 (37.0)	-
Missing	3 (0.0)	0 (0.0)	-
Duration of previous unopposed estrogen use			
Nonuser	101,910 (64.3)	1555 (63.0)	0.055
<5 years	20,931 (13.2)	361 (14.6)	-
5 to <10 years	11,168 (7.1)	149 (6.0)	-
10+ years	24,374 (15.4)	402 (16.3)	-
Missing	5 (0.0)	0 (0.0)	-
Estrogen + progesterone use ever			
No	116,991 (73.9)	1937 (78.5)	<0.001
Yes	41,394 (26.1)	530 (21.5)	-
Missing	3 (0.0)	0 (0.0)	-
Duration of previous estrogen + progestin use			
Nonuser	116,991 (73.9)	1937 (78.5)	<0.001
<5 years	20,921 (13.2)	237 (9.6)	-
5 to <10 years	11,239 (7.1)	129 (5.2)	-
10+ years	9232 (5.8)	164 (6.6)	-
Missing	5 (0.0)	0 (0.0)	-
Body-mass index (kg/m^2), baseline			
<25	55,070 (34.8)	974 (39.5)	<0.001
25 to <30	54,547 (34.4)	836 (33.9)	-
≥30	47,386 (29.9)	632 (25.6)	-
Missing	1385 (0.9)	25 (1.0)	-
Family history of cancer			
No	50,859 (32.1)	671 (27.2)	<0.001
Yes	100,480 (63.4)	1678 (68.0)	-
Missing	7049 (4.5)	118 (4.8)	-

OC, oral contraceptive.

(data not shown). There were no significant relations to risk of SCLC.

Table 3 reports the relation between reproductive factors and lung cancer risk after additional adjustment for all other reproductive and hormone use variables that were significant in any of the lung cancer analyses detailed in Table 2. The results by lung cancer histology are also presented in Table 3. This analysis showed that less than 5 years of previous use of estrogen plus progestin was associated with decreased risk of lung cancer (HR = 0.84; 95% CI = 0.71–0.99). A similar risk estimate was noted for NSCLC and SCLC, although these findings did not reach statistical significance. There was also a statistically significant decrease in NSCLC incidence among women with a later age at first birth (HR = 0.84; 95% CI = 0.73–0.98), and for all lung cancers, a trend toward decreased risk with increasing age at menopause (p_{trend} = 0.04) and a trend toward increased risk with increasing number of live births (p_{trend} = 0.03) was observed.

Multivariable modeling was conducted for smoking status strata as described above (Table 4). Bilateral oophorectomy before enrollment was differentially associated with lung cancer risk; risk was increased in never smokers who

TABLE 2. Risk of Developing Lung Cancer in Relationship to Baseline Reproductive and Hormonal Factors in WHI Participants

	All Lung Cancer (*N* = 2467)			NSCLC (*N* = 2220)			SCLC (*N* = 236)		
	Cases	HR (LCI–UCI)	*p*	Cases	HR (LCI–UCI)	*p*	Cases	HR (LCI–UCI)	*p*
Age at menarche									
<12	478	1.00	0.334	431	1.00	0.290	46	1.00	0.931
12	518	0.91(0.80–1.03)	-	466	0.90 (0.79–1.03)	-	49	0.94 (0.62–1.41)	-
13	590	0.92 (0.82–1.04)	-	532	0.92 (0.81–1.04)	-	57	0.98 (0.66–1.45)	-
>13	501	0.96 (0.85–1.09)	-	447	0.95 (0.83–1.09)	-	50	1.03 (0.69–1.54)	-
Parity									
Parous	1841	1.00	0.674	1647	1.00	0.958	185	1.00	0.202
Nulliparous	240	0.97 (0.85–1.11)	-	224	1.00 (0.87–1.16)	-	16	0.71 (0.43–1.20)	-
Number of live births[a]									
1–2	659	1.00	0.052	596	1.00	0.130	60	1.00	0.157
3–4	842	1.06 (0.96–1.18)	-	755	1.06 (0.95–1.18)	-	83	1.09 (0.78–1.53)	-
≥5	340	1.14 (1.00–1.31)	-	296	1.11 (0.96–1.29)	-	42	1.36 (0.91–2.03)	-
Age at first birth, yr (categories)[a]									
<20	317	1.00	0.064	289	1.00	0.030	27	1.00	0.524
20–29	1212	0.87 (0.76–0.99)	-	1071	0.81 (0.70–0.93)	-	136	1.55 (1.00–2.42)	-
30+	141	0.85 (0.69–1.05)	-	133	0.83 (0.67–1.03)	-	8	0.87 (0.39–1.98)	-
Age at menopause									
<40	253	1.00	<0.001	224	1.00	<0.001	28	1.00	0.482
40–50	795	0.90 (0.77–1.04)	-	706	0.89 (0.76–1.04)	-	84	0.93 (0.59–1.45)	-
50+	875	0.73 (0.62–0.85)	-	795	0.73 (0.62–0.86)	-	77	0.68 (0.42–1.10)	-
Years since menopause									
<5 yrs	128	1.00	<0.001	120	1.00	<0.001	8	1.00	0.256
5–9 yrs	245	1.05 (0.83–1.32)	-	219	1.01 (0.79–1.28)	-	25	1.59 (0.68–3.70)	-
10–14 yrs	374	1.17 (0.92–1.49)	-	334	1.14 (0.89–1.47)	-	40	1.62 (0.68–3.87)	-
15–19 yrs	378	1.24 (0.97–1.60)	-	343	1.25 (0.96–1.62)	-	32	1.29 (0.52–3.22)	-
≥20 yrs	882	1.54 (1.20–1.98)	-	785	1.52 (1.17–1.97)	-	92	1.90 (0.77–4.68)	-
Bilateral oophorectomy									
No	1636	1.00	0.185	1474	1.00	0.229	159	1.00	0.281
Yes	409	0.91 (0.80–1.04)	-	369	0.92 (0.80–1.06)	-	36	0.79 (0.51–1.22)	-
Duration of OC use									
Nonuser	1297	1.00	0.934	1170	1.00	0.908	122	1.00	0.407
<5 years	433	0.98 (0.87–1.10)	-	386	0.96 (0.85–1.09)	-	43	1.06 (0.74–1.52)	-
5 to <10 years	183	1.05 (0.89–1.23)	-	165	1.04 (0.87–1.23)	-	18	1.23 (0.74–2.07)	-
10+ years	178	0.98 (0.84–1.16)	-	159	0.96 (0.81–1.14)	-	19	1.25 (0.76–2.07)	-
Duration of previous hormone use									
Nonuser	969	1.00	0.503	864	1.00	0.589	100	1.00	0.663
<5 years	421	1.00 (0.89–1.12)	-	378	0.99 (0.88–1.12)	-	43	1.09 (0.76–1.58)	-
5 to <10 years	212	0.86 (0.74–1.01)	-	188	0.84 (0.71–0.99)	-	23	1.12 (0.69–1.80)	-
10+ years	489	0.93 (0.82–1.05)	-	450	0.95 (0.83–1.08)	-	36	0.76 (0.49–1.17)	-
Duration of previous unopposed estrogen use									
Nonuser	1311	1.00	0.634	1178	1.00	0.768	127	1.00	0.510
<5 years	306	1.08 (0.94–1.23)	-	270	1.06 (0.92–1.23)	-	36	1.27 (0.85–1.89)	-
5 to <10 years	127	0.88 (0.72–1.07)	-	112	0.86 (0.70–1.06)	-	14	1.05 (0.58–1.91)	-
10+ years	347	0.94 (0.82–1.09)	-	320	0.97 (0.83–1.13)	-	25	0.72 (0.43–1.20)	-

(*Continued*)

TABLE 2. (*Continued*)

	All Lung Cancer (*N* = 2467)			NSCLC (*N* = 2220)			SCLC (*N* = 236)		
	Cases	HR (LCI–UCI)	*p*	Cases	HR (LCI–UCI)	*p*	Cases	HR (LCI–UCI)	*p*
Duration of previous estrogen + progestin use									
Nonuser	1643	1.00	0.728	1470	1.00	0.643	165	1.00	0.809
<5 years	199	0.84 (0.72–0.98)	-	184	0.85 (0.72–1.00)	-	15	0.76 (0.44–1.32)	-
5 to <10 years	112	0.84 (0.69–1.03)	-	100	0.81 (0.66–1.01)	-	12	1.22 (0.66–2.26)	-
10+ years	137	1.01 (0.85–1.22)	-	126	1.02 (0.84–1.23)	-	10	0.93 (0.48–1.80)	-
Use of postmenopausal hormone therapy									
None	812	1.00	0.142	731	1.00	0.133	76	1.00	0.963
Past users only	350	1.02 (0.90–1.16)	-	313	1.01 (0.89–1.16)	-	37	1.16 (0.77–1.75)	-
Current users[b]	928	0.91 (0.81–1.03)	-	835	0.91 (0.80–1.02)	-	89	0.97 (0.66–1.45)	-

Numbers in the body of the table are for women with no missing values for the covariate of interest and the adjustment variables. Histology information was missing for 11 patients. Risk estimates were adjusted for age at screening (continuous), race/ethnicity, pack-years of smoking (categories), education, US region, history of emphysema, history of asthma, BMI, and family history of cancer; models were stratified by 5-year age group, baseline hysterectomy status, study type (OS or trial arm for clinical trial participants), and WHI extension study participation. *P* value is for trend if greater than two categories. Trend tests were based on the continuous form of the variable if originally collected as such.

[a]Among parous women only

[b]Includes hormone trial participants who had been nonusers or past users but were randomized to active E-alone or active E + P.

NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; HR, hazard ratio; LCI, 95% confidence interval lower limit; UCI, 95% confidence interval upper limit; BMI, body mass index; OC, oral contraceptive; WHI, Women's Health Initiative.

had undergone bilateral oophorectomy (HR = 1.47; 95% CI = 1.00–2.16; $p = 0.049$) and decreased in current smokers who had undergone the same procedure (HR = 0.68; 95% CI = 0.51–0.90). The risk associated with this procedure was intermediate in former smokers (HR = 0.92; 95% CI = 0.76–1.1; $p_{trend} = 0.098$). In addition, among current smokers only, women with five or more live births were at 34% increased risk and women with 10 or more years of previous use of estrogen plus progestin were at 62% increased risk, but this trend in risk associated with duration of use was not statistically significant.

DISCUSSION

This study found no consistent contributions to lung cancer risk for a wide range of reproductive history measures. This is an area in which the epidemiologic literature has been inconsistent. Decades ago, studies of adenocarcinoma of the lung reported that early age at menopause was associated with decreased risk,[8] and nonsignificant increases in risk were associated with later age at menarche, surgical menopause or early menopause and hormone use.[22] Other studies have reported no association between lung cancer risk and reproductive factors,[12,27] increased risk associated with increased parity,[28] or decreased risk with increasing age at first live birth.[10] In cohort studies, adenocarcinoma risk was reduced with late menarche and increased with early age at menopause (including that resulting from bilateral oophorectomy particularly before age 40 years),[16] and overall lung cancer risk was increased in women having five or more children, a finding we replicated only among current smokers, while decreased for women giving birth for the first time after age 30 years.[31] Boggs et al.[34] report nonsignificant increased risk of lung cancer in African American women with a history of bilateral oophorectomy before age 40 years and fewer than 2 years of hormone use. We found that bilateral oophorectomy was differentially associated with lung cancer risk; risk was increased in never smokers (HR = 1.47; 95% CI = 1.00–2.16; $p = 0.049$) and decreased in smokers (HR = 0.68; 95% CI = 0.51–0.90). These findings need further exploration to untangle contributions from the underlying reason for bilateral oophorectomy, age at surgery, hormone use before and after surgery, and timing of cigarette exposure. Overall, however, published work, like our study, does not support the idea that reproductive history independently contributes to lung cancer risk.

The epidemiologic literature is also inconsistent with regard to the role of hormone use (both HT and OCs) in lung cancer risk. The overall results presented here suggest that OC and HT use are not associated with risk of lung cancer. Only in current smokers do we find increased risk associated with 10 or more years of estrogen plus progestin use. There have been several pooled or meta-analyses of menopausal HT and risk of lung cancer that included many of the same studies.[14,15,21,35] Of the 11 studies and over 220,000 participants included in the analysis by Oh et al.[14], the pooled estimate of relative risk for lung cancer associated with HT use was 0.87 (95% CI = 0.74–1.02), a nonstatistically significant reduction in risk. Among cohort studies, the estimated relative risk was 1.01 (95% CI = 0.74–1.38), while among case–control studies the estimate was 0.81 (95% CI = 0.68–0.97). Of the 11 studies included, one study reported increased risk,[8] four studies reported no association,[10,12,23,36] and three studies reported decreased risk[11,37,38] associated with HT use. Another meta-analysis of 25 studies showed an odds ratio (OR) of 0.91 (95% CI = 0.83–0.99) for the association between HT use and lung cancer risk,[35] while a pooled analysis of six case–control studies reported an OR

TABLE 3. Multivariable Model for Lung Cancer Risk in WHI Participants

	Lung Cancer (*N* = 1713)		NSCLC (*N* = 1541)		SCLC (*N* = 167)	
	HR (LCI–UCI)	***p*[a]**	**HR (LCI–UCI)**	***p*[a]**	**HR (LCI–UCI)**	***p*[a]**
Parity						
Nulliparous	0.95 (0.77–1.16)	0.589	0.92 (0.75–1.14)	0.465	1.10 (0.53–2.28)	0.804
Number of live births						
1 - 2	1.00 (reference)	0.030	1.00 (reference)	0.094	1.00 (reference)	0.091
3 - 4	1.10 (0.98–1.24)	-	1.08 (0.96–1.23)	-	1.25 (0.85–1.82)	-
≥5	1.17 (1.00–1.36)	-	1.13 (0.96–1.33)	-	1.52 (0.95–2.41)	-
Age at first birth						
<20	1.00 (reference)	0.426	1.00 (reference)	0.287	1.00 (reference)	0.521
20–29	0.89 (0.77–1.03)	-	0.84 (0.73–0.98)	-	1.40 (0.88–2.23)	-
30+	0.96 (0.77–1.20)	-	0.94 (0.75–1.19)	-	0.97 (0.42–2.26)	-
Age at menopause						
<40	1.00 (reference)	0.042	1.00 (reference)	0.058	1.00 (reference)	0.435
40–50	0.91 (0.77–1.08)	-	0.91 (0.76–1.08)	-	0.95 (0.57–1.61)	-
50+	0.80 (0.64–1.00)	-	0.80 (0.63–1.02)	-	0.76 (0.37–1.58)	-
Years since menopause						
<5 yrs	1.00 (reference)	0.275	1.00 (reference)	0.311	1.00 (reference)	0.705
5–9 yrs	0.99 (0.76–1.27)	-	0.97 (0.74–1.27)	-	1.23 (0.48–3.15)	-
10–14 yrs	1.06 (0.80–1.39)	-	1.03 (0.78–1.38)	-	1.44 (0.53–3.87)	-
15–19 yrs	1.03 (0.76–1.40)	-	1.04 (0.76–1.43)	-	1.02 (0.34–3.09)	-
≥20 yrs	1.19 (0.83–1.69)	-	1.16 (0.80–1.68)	-	1.54 (0.45–5.28)	-
Bilateral oophorectomy						
Yes	0.90 (0.77–1.04)	0.147	0.91 (0.78–1.06)	0.211	0.73 (0.45–1.19)	0.210
Duration of previous estrogen + progestin use						
Nonuser	1.00 (reference)	0.174	1.00 (reference)	0.146	1.00 (reference)	0.713
<5 years	0.84 (0.71–0.99)	-	0.85 (0.71–1.02)	-	0.73 (0.40–1.36)	-
5 to <10 years	0.89 (0.71–1.10)	-	0.85 (0.68–1.08)	-	1.40 (0.72–2.71)	-
10+ years	0.93 (0.76–1.14)	-	0.92 (0.75–1.14)	-	1.07 (0.54–2.10)	-

Full model includes parity, number of live births, age at first live birth, age at menopause, years since menopause, bilateral oophorectomy, and duration of previous estrogen + progestin use. Risk estimates were further adjusted for age at screening (continuous), race/ethnicity, pack-years of smoking (categories), education, US region, history of emphysema, history of asthma, BMI, and family history of cancer; stratified by age group, baseline hysterectomy status, trial, and WHI extension study participation. Women missing any of these data were excluded from the model.

[a]*p* value is for trend if greater than two categories. Trend tests were based on the continuous form of the variable if originally collected. Trends for number of live births and age at first birth are among parous women only.

BMI, body mass index; WHI, Women's Health Initiative.

of 0.77 (95% CI = 0.66–0.90).[21] Several large cohort studies, including the WHI CTs, have reported no association between HT use and incidence of lung cancer.[16–19] The study by Schwartz et al.[12] is the only one to evaluate risk by estrogen receptor (ER) expression in the lung tumors. Decreased risk of ER-positive NSCLC was reported in postmenopausal women taking HT (OR = 0.42; 95% CI = 0.24–0.74), with no association seen for ER-negative tumors.[12] The WHI did not include a determination of lung tumor ER receptor expression so it was not possible to evaluate differential effects of hormone use in ER-positive versus ER-negative lung cancer.

While not a primary analysis topic for this study, an important note is that 55% of the lung cancers were diagnosed among former smokers. We estimated, based on the data available, that 69% of these former smokers had quit smoking more than 15 years before lung cancer diagnosis. This suggests that there is a large population of longer term women former smokers at risk.

This study has several strengths including its prospective nature and large sample size. The prospective design allowed for collection of exposure data before lung cancer diagnosis. However, there were also some limitations. While the CT data provide the best opportunity for understanding the relation between HT use and lung cancer risk, only a small number of lung cancer cases developed in the CT arms. All study arms collected smoking dose and duration as categorical variables, and therefore did not allow for specific pack-years of exposure to be calculated. This may have resulted in residual confounding within smoking category. The other limitation is not having tumor ER expression data. Estrogen exposure may

TABLE 4. Multivariable Model for Lung Cancer Risk in WHI Participants, by Smoking Status at Baseline

	Never-Smokers (58,171 Women, 273 Cases)		Past Smokers (46,795 Women, 955 Cases)		Current Smokers (7684 Women, 485 Cases)	
	HR (LCI–UCI)	p^a	HR (LCI–UCI)	p^a	HR (LCI–UCI)	p^a
Parity						
Nulliparous	1.13 (0.67–1.90)	0.650	0.83 (0.63–1.10)	0.204	1.09 (0.75–1.60)	0.652
Number of live births						
1–2	1.00 (reference)	0.209	1.00 (reference)	0.603	1.00 (reference)	0.049
3–4	1.13 (0.83–1.53)	-	1.08 (0.93–1.26)	-	1.10 (0.88–1.39)	
≥5	1.26 (0.85–1.88)	-	1.03 (0.84–1.27)	-	1.34 (1.01–1.78)	-
Age at first birth						
<20	1.00 (reference)	0.218	1.00 (reference)	0.705	1.00 (reference)	0.784
20–29	0.72 (0.48–1.07)	-	0.94 (0.77–1.14)	-	0.99 (0.77–1.27)	-
30+	0.76 (0.43–1.34)	-	0.97 (0.72–1.31)	-	1.10 (0.71–1.70)	-
Age at menopause						
<40	1.00 (reference)	0.735	1.00 (reference)	0.088	1.00 (reference)	0.345
40–50	1.43 (0.85–2.41)	-	0.84 (0.67–1.05)	-	0.95 (0.70–1.30)	-
50+	1.11 (0.59–2.10)	-	0.76 (0.57–1.03)	-	0.82 (0.52–1.28)	-
Years since menopause						
<5 yrs	1.00 (reference)	0.275	1.00 (reference)	0.311	1.00 (reference)	0.705
5–9 yrs	1.03 (0.57–1.86)	-	0.96 (0.66–1.39)	-	0.87 (0.55–1.39)	-
10–14 yrs	0.89 (0.46–1.73)	-	1.06 (0.72–1.56)	-	0.90 (0.55–1.48)	-
15–19 yrs	0.82 (0.39–1.74)	-	1.03 (0.67–1.57)	-	0.87 (0.49–1.53)	-
≥20 yrs	0.86 (0.36–2.06)	-	1.07 (0.66–1.74)	-	1.23 (0.63–2.38)	-
Bilateral oophorectomy						
Yes	1.47 (1.00–2.16)	0.049	0.92 (0.76–1.12)	0.425	0.68 (0.51–0.90)	0.008
Duration of previous estrogen + progestin use						
Nonuser	1.00 (reference)	0.445	1.00 (reference)	0.098	1.00 (reference)	0.159
<5 years	0.93 (0.62–1.40)	-	0.86 (0.69–1.08)	-	0.86 (0.61–1.21)	-
5 to <10 years	0.97 (0.57–1.63)	-	0.96 (0.73–1.27)	-	0.87 (0.53–1.46)	-
10+ years	1.31 (0.82–2.10)	-	0.79 (0.60–1.04)	-	1.62 (1.09–2.41)	-

Full model includes parity, number of live births, age at first live birth, age at menopause, years since menopause, bilateral oophorectomy, and duration of previous estrogen + progestin use. Risk estimates were further adjusted for age at screening (continuous), race/ethnicity, pack-years of smoking (categories), education, US region, history of emphysema, history of asthma, BMI, and family history of cancer; stratified by age group, baseline hysterectomy status, trial, and WHI extension study participation. Women missing any of these data were excluded from the model.

[a] *p* value is for trend if greater than two categories. Trend tests were based on the continuous form of the variable if originally collected. Trends for number of live births and age at first birth are among parous women only.

BMI, body mass index; WHI, Women's Health Initiative.

differentially affect development and/or progression of tumors with specific characteristics. Hormone use data also may not accurately reflect local estrogen level in the lung and therefore null associations between hormone use and lung cancer risk should not rule out the potential for a role of estrogen in lung carcinogenesis. Multiple pathways of estrogen action exist[39–48] and estrogen levels in lung tissue, both from endogenous and exogenous estrogens, have never been measured, so the role of estrogen in lung cancer risk is still an open question.

In conclusion, this large, prospective study of lung cancer in women did not find strong associations with specific reproductive variables and risk, and provided only weak support for a role of hormone use in the etiology of lung cancer. There remain questions about estrogen and lung cancer risk that will not easily be answered by studies focusing on hormone use. The interplay among cigarette smoking, estrogen, genetic susceptibility, and lung cancer is complex and continued study is necessary to tease apart these relationships.

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