Reproductive Variables, Soy Intake, and Lung Cancer Risk among Nonsmoking Women in the Singapore Chinese Health Study

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Abstract

Lung cancer among nonsmokers has emerged as a distinct clinicopathologic entity for which the etiology is still poorly understood, but which accounts for a significant proportion of the lung cancers among women. Although estrogens have been shown to have mitogenic effects in lung cells and interact with growth factor pathways in tumorigenesis, epidemiologic evidence for a link between reproductive hormones and lung cancer is sparse and inconsistent. We examined the effect of parity, age at menarche/menopause, cycle length and use of exogenous hormones, and dietary soy and soy isoflavonoid intake on lung cancer risk in a prospective cohort of middle-aged and elderly Chinese women in Singapore among whom 91% were lifetime nonsmokers. Among 35,298 women (mean follow-up time, 9.6 years), 298 cases of incident lung cancer were recorded, of which 189 (63.4%) occurred in nonsmokers. Compared with nulliparous women, those with one to two, three to four, and more than five livebirths had relative risks of between 0.49 and 0.59 (P for trend < 0.01) for all lung cancers, and between 0.32 and 0.42 (P for trend < 0.001) for adenocarcinomas. This relationship was observed in both smokers and nonsmokers. Age at menarche and menopause did not seem to influence risk. Dietary soy isoflavonoid intake was associated with a statistically significant inverse trend among nonsmokers only (relative risks, 0.59 for highest versus lower quartile; P for trend, 0.021). These findings add support for the role of hormonal factors in the etiology of lung cancer among nonsmoking women, and are consistent with emerging experimental evidence in this regard. (Cancer Epidemiol Biomarkers Prev 2009;18(3):821–7)

Introduction

Factors other than smoking account for 25% of all lung cancers worldwide (1). There is growing evidence that lung cancer among nonsmokers is a distinct clinicopathologic entity (2). The most prominent histologic type linked with this form is adenocarcinoma, which in itself has been increasing in incidence over the last few decades. Among the more consistent risk factors that have emerged include occupational factors, previous infection, exposure to environmental tobacco smoke, and other forms of indoor air pollution (3, 4). Genetic susceptibility is also believed to be important, and although recent work on the growth factor receptor pathways is a promising step towards a unifying hypothesis, there are still many questions that remain to be answered before the major causes of this disease entity can be clearly understood.

Across geographic regions, there is a consistent gender difference in the proportion of lung cancers not attributable to smoking. Never smokers comprise 53% of individuals with lung cancer among women, and 15% among men (1, 4). The first direct evidence that this may be a reflection of a higher risk among women was the report by Wakelee et al. (5), which showed that within each of three large prospective cohorts, the incidence of lung cancer among nonsmokers was higher in women than in men; a similar finding was reported by Freedman et al. (6) among men and women in the United States. Mortality from lung cancer among nonsmokers, however, remains higher among men than among women (7). Currently, comparable data from populations in Asia is sparse.

Estrogens are known to promote tumor growth by a variety of mechanisms and this could be relevant for lung carcinogenesis among women. The association between hormonal factors and nonsmoking lung cancer was first observed by Taioli and Wynder (8), who reported a lower risk of adenocarcinoma with an early age at menopause and a higher risk with use of hormone replacement therapy. Several subsequent studies seem to point to a risk-enhancing effect of exogenous or endogenous estrogens, but overall, the results are still inconsistent (8-17). The observation that estrogen receptors are expressed in lung tumors, particularly adenocarcinomas, and that these cells are responsive to estrogen (18, 19), has provided an impetus for investigating the etiologic and potential therapeutic significance of these hormones in lung cancer.

Based on case-control data, we earlier reported a protective effect of parity and of longer menstrual cycles on lung cancer in Singapore Chinese women (20). In this report, we describe our observations on the association

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between female reproductive factors and lung cancer risk in the context of a large prospective study among Singapore Chinese women. In addition, we examine the hypothesis that soy isoflavonoids, which are the primary source of phytoestrogens in this population, influence risk in a manner consistent with their known capacity to competitively inhibit estrogen receptor pathways.

Materials and Methods

The Singapore Chinese Health Study is a prospective cohort study which recruited 63,257 Chinese men and women who are Singapore citizens or permanent residents, aged between 45 and 74 years and residing in public housing estates. Of these, 35,298 were women. Participants were restricted to the two major dialect groups, the Hokkien and Cantonese, and were enrolled between April 1993 and December 1998. The present study has been approved by the Institutional Review Boards of the University of Minnesota and the National University of Singapore.

Baseline Interview. At recruitment, an in-person interview was conducted at home by a trained interviewer using a structured questionnaire. This instrument elicited information on demographics, lifetime use of tobacco, and medical history. For women, a reproductive history was obtained and this included age at menarche and menopause, number of livebirths, and use of exogenous hormones. Dietary information was obtained via a validated 165-item food frequency questionnaire which assessed usual pattern of intake over the last 12 months. The questionnaire included seven commonly consumed soy items (tofu, tau pok, tau kwa, yong tau foo, foojook, tofu far, and soy milk). Details of the development and validation of the food frequency questionnaire, and dietary soy intake in particular, are given elsewhere (21, 22).

Case Ascertainment. Incident cancer cases were identified by record linkage with the Singapore Cancer Registry and the Registry of Births and Deaths. The Singapore Cancer Registry maintains an accurate and complete database of incident cases in the population, with more than 85% of cases microscopically verified and a death certificate–only rate of <1.0% in 1998 to 2002 (23). As of December 31, 2005, 298 women cohort participants who were free of cancer at baseline had developed lung cancer.

Data Analysis. For each member of the cohort, person-years of follow-up were computed from date of recruitment to date of death, diagnosis of lung cancer or December 31, 2005, whichever occurred first. The person-year distribution of the entire cohort was used as an internal standard in the computation of age-adjusted incidence rates of lung cancer by gender and smoking status.

Total soy isoflavonoid intake was computed based on the food frequency questionnaire and the nutrient content recorded in the Singaporean Food Composition Database (21). Energy-adjustment was carried out by expressing this in milligrams per 1,000 kcal.

We used the proportional hazards method to calculate the hazard ratios and corresponding 95% confidence intervals (CI) for the association between reproductive variables, soy isoflavonoid intake, and lung cancer. Quartiles were based on the distribution from the entire cohort, and linear trend tests for exposure-disease associations were based on median values within each quartile. Analyses reported here are for women only, and are adjusted for potential confounders (see footnote to table). The SAS statistical package (SAS Institute, Inc.) was used for analysis and all P values quoted are two-sided.

Results

Incidence of Lung Cancer by Smoking Status and Gender. Between April 1993 and December 2005, with an average follow-up of 9.6 years, a total of 298 incident cases of lung cancer occurred among women in the cohort. The age-adjusted incidence rate was 87.3 per 100,000 person-years, which is about one-third that in men (251.2/100,000). Approximately two-thirds (63.4%, 189 cases) of the lung cancers in women occurred in nonsmokers. Among smokers (ex-smokers or current smokers at recruitment), the age-adjusted rate was 385.5 per 100,000 and among lifetime nonsmokers, it was 60.5 per 100,000 person-years. The gender difference was greatest among those who were current smokers at recruitment (280.2/100,000 and 505.4/100,000 in women and men, respectively) and least among lifetime nonsmokers (62.7/100,000 and 73.5/100,000 in women and men, respectively).

Reproductive Variables, Body Mass Index, and Risk of Lung Cancer. When stratified by parity, women with fewer than three livebirths differed from multiparous (more than three livebirths) women in several ways. The former were more likely to be younger, Cantonese in dialectal origin, more highly educated, and to consume higher levels of fruits and vegetables, with correspondingly higher intake of carotenoids (Table 1).

The relative risk (RR) for lung cancer was inversely related to parity: women who had five or more livebirths had a RR of 0.49 (95% CI, 0.33-0.72) for all lung cancers, and the reduction in risk was greater (RR, 0.32; 95% CI, 0.19-0.55) for adenocarcinomas (Table 2). This protective effect was evident among women with at least one livebirth, and differences between categories of parous women were small. Additionally, after excluding nulliparous women, age at first birth did not impose any additional effect on risk (data not shown). Information on environmental tobacco smoke exposure was available for a subset of women who provided this data as part of the follow-up interview. Adjustment for this variable did not materially affect the relative risk estimates.

When we examined the effect of age at menarche and menopause, there was no consistent relationship observed with age of menarche or of menopause (Table 2). Although there was a suggestion of an increase in risk of adenocarcinoma among women with a later age at menarche, this was not evident upon closer examination in smaller age intervals.

Use of oral contraceptives and use of replacement hormones were both rare in this study population. Thus, relative risk estimates for both exposures are highly

Table 1. Singapore Chinese Health Study: characteristics of study participants (women only) in relation to parity and dietary soy intake

	All women	Isoflavonoid intake lower than the median	Isoflavonoid intake higher than the median	0-2 livebirths	3+ livebirths
No. of subjects	34,028	17,015	17,013	11,975	22,053
Age at recruitment (y)	56.2 (8.0)	57.1 (8.2)	55.4 (7.8)	53.3 (7.4)	57.8 (7.9)
Dialect group (%)					
Cantonese	47.9	48.1	47.6	57.7	42.5
Hokkien	52.1	51.9	52.4	42.3	57.5
Educational level (%)					
No formal	40.3	43.9	36.6	23.5	49.4
Primary	39.0	38.0	40.0	39.6	38.7
Secondary and higher	20.7	18.0	23.4	36.9	11.9
BMI (kg/m^2)	23.2 (3.3)	23.2 (3.3)	23.3 (3.3)	22.8 (3.3)	23.5 (3.3)
Dietary intake (per day)					
Mean, SD					
Total vegetables (g)	109.9 (61.9)	96.2 (53.3)	123.6 (66.6)	114.5 (64.3)	107.5 (60.4)
Total fruit and juices (g)	194.0 (162.1)	170.9 (150.7)	217.1 (169.5)	223.8 (174.2)	177.8 (152.6)
β-Cryptoxanthin (μg)	240.4 (328.6)	212.2 (313.4)	268.6 (340.8)	281.5 (352.3)	218.1 (312.8)
Total isothiocyanates (μmol)	9.1 (6.9)	7.9 (6.0)	10.3 (7.4)	9.5 (7.1)	8.9 (6.7)
Smokers only					
No. of cigarettes/d (mean, SD)	11.0 (8.9)	11.0 (8.8)	10.9 (9.0)	10.6 (8.6)	11.1 (9.0)
Years of smoking (mean, SD)	33.2 (12.8)	33.7 (12.6)	32.6 (13.0)	32.4 (12.8)	33.5 (12.7)

unstable due to the small number of subjects in the exposed categories. Nonetheless, statistically nonsignificant increased risks were associated with use of both types of exogenous estrogenic compounds.

Dietary Soy Foods and Isoflavonoid Intake, and Lung Cancer Risk. We observed an inverse relationship between intake of soy foods (tofu products and soybean drinks) and lung cancer among women. The RR for the highest versus lowest quartile of intake for soy foods was 0.75 (95% CI, 0.53-1.05; *P* for trend, 0.048). For total isoflavonoid intake, the corresponding RR was 0.74 (95% CI, 0.53-1.04; *P* for trend, 0.059). This relationship was stronger among nonsmokers (RR, 0.59; *P* for trend, 0.021), and for histologic types other than adenocarcinomas. There was no association observed among women who smoked (Table 3). Furthermore, we did not see any relationship between dietary isoflavonoids and lung cancer among men in the cohort, either in smokers (RR for highest versus lowest quartile 0.98; 95% CI, 0.77-1.25; *P* for trend, 0.93) or among nonsmokers (RR, 1.39; 95% CI, 0.71-2.73; *P* for trend, 0.51).

Discussion

The Singapore Chinese Health Study offers an opportunity to prospectively examine the influence of hormone-related factors on lung cancer risk in a study population with comprehensive dietary and other relevant information, and a high proportion of nonsmoking women. Among all the women enrolled in the cohort, 91.27% were lifetime nonsmokers, consistent with the low smoking prevalence in the general female population, and two-thirds (63%) of the 298 incident lung cancers occurred among lifetime nonsmokers. There is no evidence from this study population that women nonsmokers are at a higher risk of lung cancer than men—this is consistent with emerging data from Western populations, although there remains a need for observations in other Asian populations to further support this.

In this population, we observed a significant inverse association between lung cancer risk and increasing parity. The reduction in risk was substantial, applied to both smokers and nonsmokers, and when stratified by histologic type, seemed to be specific to adenocarcinomas. A second notable finding was an inverse association with dietary intake of soy isoflavonoids, the major source of phytoestrogens in this population, among women nonsmokers but not in smokers. Our findings are consistent with earlier case-control data demonstrating that parity and soy intake are inversely related to lung cancer risk in nonsmoking Chinese women in Singapore (18). Taken together, they suggest a role for hormonal factors, specifically estrogens, in lung cancer among women, particularly in those who do not smoke.

Investigations into the role of female hormones in lung cancer have led to varying conclusions, and there has been no consistent line of evidence to provide guidance for more focused study. The pattern of effects points to a more complex relationship than has been shown for breast cancer. For example, hormone replacement therapy has been consistently shown to be a risk factor for the latter (24). In contrast, findings from studies on hormone replacement therapy and lung cancer variously report an elevation in risk (8, 9), a reduction in risk (10-13), or no demonstrable effect (14, 15). Our finding that being parous seems to be a key protective factor but that subsequent pregnancies have little effect on risk, and that among parous women, age at first birth is unrelated to risk also suggest a different mechanism from that which operates in breast carcinogenesis. Few studies of lung cancer have examined the effect of other reproductive factors that could modulate cumulative or cyclical exposure to endogenous estrogens. Two early studies in Chinese women reported increased risks of lung adenocarcinomas among women with shorter menstrual cycles (16, 17). A case-control study in Germany (11) found no association with age at menarche or menopause

Table 2. Risk of lung cancer in relation to reproductive characteristics and body mass index (Singapore Chinese Health Study 1993-2005, women only)

	Person-years	All lung cancers		Adenocarcinomas only		Other histologic types	
		No. of cases	RR* (95% CI)	No. of cases	RR* (95% CI)	No. of cases	RR* (95% CI)
No. of livebirths							
All women							
0	23,290	36	1.00	23	1.00	13	1.00
1-2	95,025	55	0.52 (0.34-0.79)	26	0.35 (0.20-0.62)	29	0.81 (0.42-1.56)
3-4	128,103	90	0.59 (0.40-0.87)	45	0.42 (0.25-0.70)	45	0.90 (0.48-1.67)
5+	94,104	117	0.49 (0.33-0.72)	44	0.32 (0.19-0.55)	73	0.77 (0.42-1.41)
P for trend			<0.01		<0.01		0.48
Ever smokers							
0	2,070	15	1.00	7	1.00	8	1.00
1-2	5,259	14	0.40 (0.19-0.84)	3	0.18 (0.05-0.71)	11	0.59 (0.23-1.46)
3-4	8,041	28	0.65 (0.34-1.23)	9	0.41 (0.15-1.12)	19	0.85 (0.37-1.97)
5+	12,902	52	0.45 (0.25-0.82)	11	0.21 (0.08-0.57)	41	0.65 (0.30-1.42)
P for trend			0.089		0.027		0.53
Lifetime nonsmokers							
0	21,220	21	1.00	16	1.00	5	1.00
1-2	89,767	41	0.58 (0.34-0.99)	23	0.42 (0.22-0.79)	18	1.11 (0.41-3.00)
3-4	120,062	62	0.58 (0.35-0.96)	36	0.44 (0.24-0.81)	26	1.03 (0.39-2.68)
5+	81,202	65	0.51 (0.30-0.86)	33	0.37 (0.19-0.70)	32	0.95 (0.36-2.50)
P for trend			0.045		0.020		0.71
Age at menarche							
All							
<15 y	178,463	119	1.00	53	1.00	66	1.00
15+ y	161,990	179	1.22 (0.96-1.55)	85	1.44 (1.01-2.05)	94	1.07 (0.78-1.48)
			0.10		0.046		0.67
Ever smokers							
<15 y	13,041	42	1.00	12	1.00	30	1.00
15+ y	15,207	67	1.16 (0.78-1.72)	18	1.14 (0.54-2.40)	49	1.18 (0.74-1.87)
			0.45		0.74		0.49
Lifetime nonsmokers							
<15 y	165,423	77	1.00	41	1.00	36	1.00
15+y	146,782	112	1.27 (0.94-1.72)	67	1.54 (1.03-2.31)	45	0.99 (0.63-1.56)
			0.12		0.037		0.98
Age at menopause (y) †							
All							
<50	88,404	125	1.00	48	1.00	77	1.00
50+	137,303	143	0.83 (0.65-1.06)	69	0.97 (0.67-1.41)	74	0.73 (0.53-1.01)
P value			0.13		0.88		0.06
Ever smokers							
<50	11,438	56	1.00	16	1.00	40	1.00
50+	13,637	49	0.81 (0.55-1.18)	12	0.69 (0.32-1.45)	37	0.85 (0.54-1.33)
P value			0.27		0.32		0.47
Lifetime nonsmokers							
<50	76,965	69	1.00	32	1.00	37	1.00
50+	123,666	94	0.85 (0.62-1.16)	57	1.11 (0.72-1.70)	37	0.62 (0.40-0.99)
P value			0.30		0.65		0.04
Use of hormonal contraceptives ‡							
All							
Never	250,674	255	1.00	120	1.00	135	1.00
<10 y	79,083	33	0.73 (0.50-1.07)	13	0.49 (0.27-0.88)	20	1.07 (0.65-1.76)
10+ y	10,696	10	1.33 (0.70-2.52)	5	1.23 (0.5-3.03)	5	1.47 (0.60-3.63)
P for trend			0.56		0.15		0.45
Use of hormone replacement therapy ‡							
All							
No	322,797	286	1.00	132	1.00	154	1.00
Yes	17,656	12	1.38 (0.76-2.49)	6	1.11 (0.48-2.56)	6	1.75 (0.75-4.06)
P value			0.29		0.81		0.19

*Adjusted for age at interview, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level (none, primary, secondary, or higher), body mass index, total vegetable intake, total fruit/juice intake, β-cryptoxanthin, total isothiocyanates, and (except for nonsmokers) duration of smoking (years), cigarettes per day, and number of years since quitting. Adjustment for number of livebirths did not alter results for menarche/menopause materially.

†Women aged 50+ only.

‡The number of cases was too small for meaningful analysis by smoking status.

or with cycle length among nonsmokers, and a prospective study among Japanese nonsmoking women did not find any association between incidence of lung cancer and age at menarche/menopause or use of exogenous hormones (9). There was no association with parity from two studies in nonsmoking women (9, 11), and data from the Canadian National Breast Screening study revealed that having five or more livebirths

was associated with a 2-fold increase in risk; an effect that was stronger in nonsmokers (15). The most recent study to address this question found that among nonsmoking women in Shanghai (25), higher parity (four or more livebirths) was associated with an almost 2-fold reduction in risk; length of reproductive period was also associated with risk, supporting a role for hormonal factors in lung carcinogenesis via mechanisms yet unclear.

Estrogens are known to promote cell division at the target tissue level, and exposure to these mitogenic effects is considered to explain much of their role in promoting carcinogenesis in hormone-responsive tissue such as the breast. In addition, catechol estrogens, which are metabolic intermediates formed via hydroxylation of estradiol and estrone, are capable of directly damaging DNA and are carcinogenic *in vivo* (24, 26). However, the effect of these hormones is likely to be tissue-specific and dependent to some extent on the relative expression of the two types of estrogen receptors (ERα and ERβ), as evidence from the colon suggests. In contrast to breast cancer, epidemiologic and laboratory data point to a protective effect of estrogens on the development of colorectal cancer, and to ERβ-mediated enhancement of apoptosis and reduction in cell proliferation as possible mechanisms (27). Furthermore, alternative mechanisms, including protein-protein interactions involving other transcription factors are actively being investigated (28) and may explain the complex role of these hormones in carcinogenesis in various tissues.

In keeping with the breast cancer model, a protective effect of parity on risk of lung cancer potentially could be attributed to lower plasma estrogen levels among women with a greater number of livebirths (29, 30). Our findings, that dietary isoflavonoids are protective, are similar to others' (31, 32) but not all (33), and are consistent with this understanding. It has been known that lung cells are responsive to steroid hormones (19),

Table 3. Risk of lung cancer in relation to dietary soybean products and isoflavonoids (Singapore Chinese Health Study 1993-2005, women only)

	Person-years	All lung cancers		Adenocarcinomas only		Other histologic types	
		No. of cases	RR* (95% CI)	No. of cases	RR* (95% CI)	No. of cases	RR* (95% CI)
Tofu products and soybean drink (g/d)							
All women							
Q1[†]	83,220	103	1.00	40	1.00	63	1.00
Q2	85,656	81	0.93 (0.69-1.24)	39	1.10 (070-1.71)	42	0.82 (0.55-1.21)
Q3	86,141	59	0.77 (0.55-1.06)	28	0.85 (0.52-1.40)	31	0.71 (0.46-1.10)
Q4	85,504	55	0.75 (0.53-1.05)	31	0.99 (0.61-1.60)	24	0.58 (0.36-0.94)
P for trend			0.048		0.72		0.019
Never smokers							
Q1	73,952	63	1.00	30	1.00	33	1.00
Q2	78,842	49	0.81 (0.56-1.81)	31	1.07 (0.65-1.77)	18	0.58 (0.33-1.04)
Q3	80,204	39	0.69 (0.46-1.03)	22	0.79 (0.45-1.38)	17	0.60 (0.33-1.08)
Q4	79,252	38	0.71 (0.47-1.07)	25	0.94 (0.55-1.63)	13	0.49 (0.26-0.95)
P for trend			0.060		0.59		0.028
Ever smokers							
Q1	9,268	40	1.00	10	1.00	30	1.00
Q2	6,814	32	1.16 (0.72-1.86)	8	1.26 (0.49-3.23)	24	1.15 (0.67-1.98)
Q3	5,937	20	0.94 (0.54-1.62)	6	1.21 (0.43-3.39)	14	0.86 (0.45-1.64)
Q4	6,252	17	0.81 (0.45-1.46)	6	1.26 (0.44-3.59)	11	0.68 (0.33-1.38)
P for trend			0.46		0.66		0.26
Total isoflavonoids (mg/1,000 kcal/d)							
All women							
Q1[‡]	82,897	94	1.00	39	1.00	55	1.00
Q2	85,599	82	0.97 (0.72-1.3)	38	1.03 (0.66-1.62)	44	0.92 (0.62-1.38)
Q3	86,223	66	0.83 (0.6-1.14)	31	0.90 (0.55-1.44)	35	0.78 (0.51-1.21)
Q4	85,803	56	0.74 (0.53-1.04)	30	0.90 (0.55-1.47)	26	0.62 (0.38-1.00)
P for trend			0.059		0.57		0.042
Never smokers							
Q1	74,103	58	1.00	29	1.00	29	1.00
Q2	78,933	53	0.90 (0.62-1.31)	30	1.02 (0.61-1.70)	23	0.80 (0.46-1.38)
Q3	79,794	46	0.83 (0.56-1.23)	27	0.96 (0.56-1.63)	19	0.71 (0.39-1.27)
Q4	79,421	32	0.59 (0.38-0.91)	22	0.79 (0.45-1.39)	10	0.38 (0.18-0.80)
P for trend			0.021		0.41		0.011
Ever smokers							
Q1	8,793	36	1.00	10	1.00	26	1.00
Q2	6,666	29	1.12 (0.68-1.84)	8	1.21 (0.47-3.10)	21	1.11 (0.62-1.99)
Q3	6,429	20	0.82 (0.47-1.43)	4	0.68 (0.21-2.20)	16	0.87 (0.46-1.64)
Q4	6,383	24	1.10 (0.64-1.89)	8	1.53 (0.58-4.01)	16	0.97 (0.50-1.85)
P for trend			0.99		0.63		0.75

*Adjusted for age at interview, year of interview (1993-1995, 1996-1998), dialect group (Cantonese, Hokkien), educational level (none, primary, secondary, or higher), body mass index, total vegetable intake, total fruit /juice intake, β-cryptoxanthin, total isothiocyanates, and (except for nonsmokers) duration of smoking (years), cigarettes per day, and number of years since quitting.

[†]Median values for quartiles of tofu products and soybean drink intake: Q1, 30.7 g/d; Q2, 66.1 g/d; Q3, 108.8 g/d; Q4, 197.7 g/d.

[‡]Median values for quartiles of total isoflavonoid intake (expressed as nutrient densities): Q1, 4.0 mg/1,000 kcal/d; Q2, 8.4 mg/1,000 kcal/d; Q3, 13.1 mg/1,000 kcal/d; Q4, 22.0 mg/1,000 kcal/d.

and that these weakly estrogenic compounds may bind competitively with the estrogen receptor and interrupt signaling pathways or modulate the activity of enzymes involved in the synthesis of these hormones (34). Although there is some indication from our data that exogenous estrogens increase risk, interpretation is limited by the low prevalence of hormone use. Although the overall picture that emerges from Table 3 is that of a protective effect among nonsmokers, it is also interesting that the effect is not evident among adenocarcinomas, which is the histologic type most common in this subgroup.

However, in contrast to the well-established inverse association between breast cancer risk and length of exposure to cyclical estrogens, the present study failed to observe any association between lung cancer risk and age at menarche and menopause. The effect of hormones on breast cancer is also contrary to that for lung cancer among nonsmoking women in Shanghai (25), for whom a statistically significant reduction in risk of the disease was observed with a later age at menopause and a longer reproductive period. We can offer no credible biological explanations for the unexpected findings between menstrual factors and lung cancer risk in these two prospective studies.

In summary, this study adds support for the role of hormonal factors in the etiology of lung cancer. The overall picture that emerges is of an effect that is stronger and more consistent among nonsmoking women, but does not seem to be specific to any one cell type. The strengths of this study include its prospective nature, the detailed information on diet and nutrient intake, and the comprehensive system of cancer registration in the country. Emigration among subjects in the cohort is likely to be negligible, as evidenced by recent follow-up interviews conducted between 1999 and 2004. Contact was made with 61,685 subjects (97.5% of the original cohort), of whom only 17 individuals (0.03%) were found to have emigrated and would not have had cancer outcomes ascertained through our follow-up methods.

Although we recognize that a consistent pattern in the effect of estrogens at different points in the reproductive life cycle has yet to emerge from epidemiologic studies, these data corroborate emerging evidence from the laboratory that estrogens acting on lung tissue, either via direct effects on the target genes or via complex interactions with other pathways, are involved in processes that enhance the risk of lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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