Re: Endocrine Factors and Adenocarcinoma of the Lung in Women

While cigarette smoking is by far the major cause of lung cancer in women, it has been suggested that other factors may act as cocarcinogens, especially with regard to adenocarcinoma, the most common histologic type among women (*1*). Experimental studies (*2-9*) indicate a role of endogenous and exogenous hormones. An association between lung cancer and use of estrogen replacement therapy (ERT) in women has been reported (*10*), although no distinction among histologic types or adjustment for smoking was performed. Some reproductive factors have been associated with lung cancer risk in Chinese women (*11*). Clusters of cancers of the reproductive system and of the lung have been described in some families (*12*).

We analyzed unpublished data collected in a long-standing hospital-based case–control study, described in detail elsewhere (*13*). One hundred and eighty women with newly diagnosed, histologically confirmed primary adenocarcinoma and 303 controls with non-tobacco-, non–hormone-related diseases were included. A standardized questionnaire was administered to both case patients and control patients by a trained interviewer at the time of hospitalization.

Univariate and multivariate analyses were performed using unconditional logistic regression to calculate the odds ratios (ORs) as estimates of the relative risk (*14*) and their 95% confidence intervals (CIs). Adjustment was made for possible confounders.

None of the reproductive variables considered in the analysis was found to be associated with adenocarcinoma (Table 1). An early age at menopause, before or at the age of 40 years, was associated with a decreased risk for adenocarcinoma (OR = 0.3; 95% CI = 0.1-0.8). The use of ERT was significantly associated with adenocarcinoma (OR = 1.7; 95% CI = 1.0-2.5 for ever users versus nonusers). No interaction with body mass was observed, while a statistically significant interaction between smoking and ERT was present. The OR of adenocarcinoma among women who smoke and use ERT was 32.4 (95% CI = 15.9-665.3) and, among women who smoke only, the OR was 13.1 (95% CI = 6.8-25.2) in comparison to women who neither took ERT nor smoked (chi-square for interaction = 22.5; P = .0001). Women who took hormones but never smoked had a OR of adenocarcinoma of 1.0 (95% CI = 0.3-3.8).

The observation of an increased risk of adenocarcinoma with the use of estrogen replacement supports the hypothesis that exogenous steroid hormones play a role in the etiology of lung cancer in women. The predominant use

Table 1. ORs and 95% CIs of adenocarcinoma of the lung with some reproductive and hormonal variables*

Variable	No. of cases (n = 180)	No. of controls (n = 303)	Adjusted OR†	95% CI
Age at menarche, y				
≤12	83	135	1.0	—
13	51	82	1.1	0.6-1.8
≥14	43	83	0.8	0.4-1.2
Age at first pregnancy, y				
<20	30	49	1.0	—
20-23	56	94	1.1	0.6-1.9
24-27	50	67	1.5	0.8-2.7
≥28	27	50	0.9	0.4-1.9
No. of full-term pregnancies				
None	10	39	1.0	—
1	18	43	0.7	0.3-1.8
2	64	67	1.6	0.7-3.7
3	40	73	1.3	0.6-3.1
≥4	41	76	1.0	0.4-2.2
Oral contraceptives				
No	134	229		
Yes	46	74	0.8	0.5-1.5
Estrogen replacement‡				
No	118	227	1.0	—
Yes	62	76	1.7	1.0-2.8
1-12 mo	31	43	1.3	0.7-2.4
13-24 mo	8	11	1.0	0.3-2.8
≥25 mo	18	19	2.0	0.9-4.4§
Breast feeding (parous only)				
No	106	150		
Yes	57	110	0.8	0.5-1.3
Cycle length, d				
28	116	180	1.0	—
<28	16	23	1.5	0.6-3.5
>28	14	35	0.8	0.4-1.7
Irregular	32	60	1.0	0.5-1.7
Period length, d				
4-5	96	170	1.0	—
<4	21	36	0.7	0.3-1.4
≥6	53	75	1.3	0.7-2.2
Irregular	10	21	1.0	0.4-2.6
Age at menopause, y‖				
≥50	67	108	1.0	—
41-49	62	95	0.8	0.5-1.4
≤40	17	45	0.3	0.1-0.8
Type of menopause				
Natural	110	173		
Surgical, radiation	42	84	1.2	0.7-2.1

*Totals may vary because of missing values.

†Adjusted for smoking (never, current [≤14 cigarettes per day], current [≥15 cigarettes per day], ex-smokers), age at diagnosis (continuous), years of education (continuous), body mass index (<21, 21-23.9, 24-26.9, ≥27 Kg/m^2.

‡Adjusted for the previous variables, plus menopausal status (pre/postmenopausal).

§Chi-square for trend: 2.7; P = .09.

‖Adjusted for the previous variables, plus type of menopause (natural or surgical, radiation).

of ERT later in life and the observed interaction with smoking suggest a role of exogenous estrogens in the promotion phase of carcinogenesis. In addition, the contribution of endogenous estrogens cannot be excluded, as suggested by the decreased risk of adenocarcinoma associated with an early age at menopause.

The major limitation of our study is that no information on the composition and the dosage of the ERT was collected at the time of the interview; however, our results demonstrate a significant association between ERT use and adenocarcinoma of the lung in women, after adjustment for smoking, and an interaction between these two factors. Our data have important public health implications because the proportion of female smokers is increasing (*15*), and ERT is becoming a common practice among postmenopausal women (*16*). If our results are confirmed, specific interventions aimed at quitting smoking in women taking ERT should be recommended.

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Notes

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Re: Toxicity of Intrathecal Melphalan

We read with interest the correspondence from Dr. Berg et al. (*1*) reporting toxicity of melphalan administered intrathecally into two adult monkeys. The severe and lethal neurotoxicity observed by these investigators led them to abandon the use of this agent in the clinical setting. However, we have several concerns with their observations based on our current investigations. We have previously demonstrated that melphalan is more cytotoxic in vitro against human medulloblastoma cell lines than other alkylating agents including 4-hydroperoxycyclophosphamide, 4-hydroperoxyiphosphamide, and thiotepa (*2*). Furthermore, we have conducted studies (*3,4*) demonstrating the toxicity and activity of intrathecal melphalan in an athymic rat model of human neoplastic meningitis. Of note, the maximum tolerated dose of melphalan was 40 μL of a 2.0 m*M* concentration of melphalan designed to produce a final cerebrospinal fluid concentration of 200 μ*M*. Compared with the results achieved in the saline-treated controls, treatment at this dose produced no deaths, mild arachnoiditis and demyelination, and an increase in survival of 442% in animals bearing the human rhabdomyosarcoma cell line TE-671 in the subarachnoid space. On the basis of these findings, we successfully completed an Investigation New Drug (IND) application for intrathecal melphalan in patients with neoplastic meningitis and have treated three patients to date with no observed toxicity.

The observation of pronounced and lethal toxicity in monkeys treated with a human equivalent dose of 10 mg may not be predictive of the clinical applicability of intrathecal melphalan in patients. The use of a single large dose of melphalan without consideration of the quantitation of cerebrospinal fluid levels of this drug or the definition of a dose versus toxicity relationship suggests that toxic effects in the primates were simply the result of choosing too high a dose. Furthermore, the investigators have not mentioned if these monkeys were previously treated with any other intrathecal agents that could have rendered them more susceptible to damage from melphalan. We suggest that the results of Dr. Berg and her collaborators may not accurately reflect the potential for intrathecal melphalan in the treatment of patients with neoplastic meningitis.

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