CORRESPONDENCE

Re: You Say Tomato and I Say Tomahto: Getting a Handle on Pronouncing Apoptosis

I am writing about the item in the News section (*1*) in which Bob Kuska attempted to lay to rest the controversy over the pronunciation of ''apoptosis.'' Although it is true that a proper name can be pronounced any way at all (e.g., Tagliaferro is often pronounced ''Tol-liv-er''), there are rules for Greek pronunciation and they do not include silencing the ''p'' in ''pt'' when it occurs in the middle of the word. Following the author's recommendation, helicopter would be ''hel-i-cot-er,'' proptosis would be ''prot-osis,'' and lepidoptera would be ''lep-i-dot-era.'' With all due respect to Kerr et al. (*2*), it would not seem necessary to change the rules of Greek pronunciation simply to accommodate the process they observed. By the way, pathologists have been recognizing this process for many years on light microscopic examination, but they called it ''karyorrhexis'' from karyon for nucleus or nut and rhexis, a breaking. A new word to describe the process may not have been necessary in the first place; making up new rules for pronouncing it seems even less justified.

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Note

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Re: Second Cancers After Adjuvant Tamoxifen Therapy for Breast Cancer

Curtis et al. (*1*) used the Surveillance, Epidemiology, and End Results (SEER)[1] Program data to evaluate the impact of tamoxifen therapy on the incidence of second primary tumors by comparing the rates of these tumors in patients with breast cancer who did and did not receive ''hormonal therapy'' as part of their first course of cancer therapy. However, other hormones and steroids (which often accompany chemotherapy) are also included as hormonal therapy in the SEER data. Realizing these limitations, Curtis et al. (*1*) restricted their analyses to patients with breast cancer for whom the registry statement of hormone use would most likely represent tamoxifen use, i.e., women 50 years of age or older who had not received chemotherapy. We sought to determine if these restrictions improved the sensitivity and specificity of the SEER-recorded hormonal therapy in identifying patients with breast cancer who received tamoxifen by comparing SEER-recorded hormonal therapy with independently obtained data on tamoxifen use.

We compared hormonal therapy recorded in the western Washington component of the SEER program (the Cancer Surveillance System [CSS]) to data on the same women collected in a population-based study of second primary cancer following a diagnosis of breast cancer between 1978 and 1990 (*2*) (the ''Tamoxifen Study''). The 860 women from the Tamoxifen Study were followed for a median of 36 months (range, 6-155 months) through inpatient and outpatient medical records to establish receipt of adjuvant therapy. Tamoxifen given as a first-course therapy and tamoxifen given for a subsequent diagnosis of a recurrence but prior to any second primary cancer diagnosis were recorded separately. Information on tamoxifen therapy from the Tamoxifen Study is used as the standard against which information from the CSS registry is compared.

The CSS registry recorded that 139 (16.2%) women received hormonal therapy and was 59.1% sensitive and 90.5% specific in identifying those women who received tamoxifen as a first course of therapy (Table 1). Restricting the analysis to the 460 women 50 years of age or more who did not receive chemotherapy increased the specificity but had little impact on the low sensitivity. The sensitivity was lower still when we added the women who received tamoxifen therapy for a diagnosis of a recurrence but prior to a second primary cancer diagnosis (information not routinely collected by SEER registries).

These results imply that only 40%-60% of patients with breast cancer who use tamoxifen are identified by using hormonal therapy from the SEER registries as a proxy for tamoxifen therapy. This low sensitivity would have had but a modest impact on the results of the study by Curtis et al. (*1*) since the number of tamoxifen users falsely labeled as nonusers was small relative to the number of true nonusers because of the relatively low prevalence of tamoxifen use (16.4%) during the study time period (1980 through 1992). Use of hormonal therapy as a surrogate for tamoxifen therapy among women diagnosed with breast cancer today, when tamoxifen is widely used, will lead to a larger absolute number of misclassified individuals and thus a larger reduction of the accuracy of SEER data to assess the consequences of taking this drug.

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References

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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Response

We appreciate the insights provided by Cook et al. on the sensitivity and specificity of the hormone treatment classification in the SEER Program, which we used as a surrogate to identify patients with breast cancer initially treated with tamoxifen (*1*). Although caution may be needed in generalizing results from one SEER registry to the entire SEER Program, the data provided by Cook et al. suggest that the sensitivity of SEER-recorded hormonal therapy in identifying tamoxifen users is likely to be less than 60%, whereas the specificity is high at 99%. The sensitivity of the hormone therapy data is of lesser importance in our study, which was primarily intended to evaluate second cancer risk among women who received tamoxifen. This group was assumed to be a random sample of the entire group of patients with breast cancer initially treated with tamoxifen. Thus, the predictive value (or true positive rate) of the SEER hormone therapy variable in identifying tamoxifen users is especially important. Assuming that data from Table 1 in Cook et al. are representative of the entire SEER Program, we estimate that 90% [34/(34 + 4)] of the patients with breast cancer in our ''tamoxifen'' group (no chemotherapy, age ⩾50 years, 1980 through 1992) were correctly classified as tamoxifen users, and that an estimated 90% [380/(380 + 42)] of the patients in our ''no/unknown tamoxifen'' group were correctly classified as nontamoxifen users. Thus, our conclusions that tamoxifen is linked with a reduction in contralateral breast cancer, an increase in risk of uterine corpus cancer, but no significant elevation in incidence of digestive system cancers are not shaken. Of course, the statistical power of the comparison between the two treatment groups would be improved if all users could be correctly classified.

Cook et al. suggest also that the wider use of tamoxifen in current breast cancer treatment regimens may lead to a larger absolute number of misclassified individuals and thus a larger reduction in the accuracy of SEER data to assess tamoxifen-related late effects. However, data from the SEER Patterns of Care Study covering the period 1987 through 1991 show that the predictive rate of SEER-recorded hormonal therapy for identifying tamoxifen users remains high in the early 1990s. Among patients with breast cancer who were recorded in SEER as initially treated with hormones during 1990 through 1991, 93% were found to have received adjuvant tamoxifen (Hankey B, Harlan L: personal communication). While we agree that misclassification in the ''no/unknown tamoxifen'' group is likely to be substantial in the more recent SEER data, alternative comparison groups exist. The second cancer rate in the tamoxifen group can be compared with the following: 1) SEER general population cancer incidence rates and 2) second cancer rates among patients with breast cancer treated during a period when adjuvant tamoxifen was infrequently used (1973 through 1979). Thus, we believe that the SEER registry database should remain a valuable resource for assessing second cancer risks following tamoxifen treatment, especially among long-term survivors, as it has been for second cancer risk following radiotherapy and chemotherapy (*2-4*).

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Notes

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Table 1. Comparison of hormonal therapy recorded in the Cancer Surveillance System (CSS) with tamoxifen therapy recorded in the Tamoxifen Study among women diagnosed with stage I, II, or III breast cancer between 1978 and 1990: King, Pirece, and Snohomish counties, Washington state

Type of tamoxifen therapy	Tamoxifen users:* hormonal therapy per CSS		Sensitivity: % tamoxifen users identified in CSS	Tamoxifen nonusers:* hormonal therapy per CSS		Specificity: % tamoxifen nonusers identified in CSS
	Yes, No.	No, No.		Yes, No.	No, No.	
Tamoxifen as initial breast cancer therapy						
All women	68	47	59.1	71	674	90.5
Women aged ⩾50 y who did not receive chemotherapy	34	24	58.6	4	398	99.0
Tamoxifen as initial breast cancer therapy or for a breast cancer recurrence:						
Women aged ⩾50 y who did not receive chemotherapy	34	42	44.7	4	380	99.0

*On the basis of the results of the Tamoxifen Study (*2*).

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Re: Randomized Trial of Two Versus Five Years of Adjuvant Tamoxifen for Postmenopausal Early Stage Breast Cancer

The Swedish Breast Cancer Cooperative Group (*1*) concludes that 5 years of adjuvant tamoxifen is more beneficial than 2 years in postmenopausal women with early stage, invasive breast cancer in the subgroup of patients who were estrogen receptor (ER) positive. However, there are several issues that arise that we would like to highlight.

The authors provide an estimate of the trial size based on $\alpha = 0.01$ (two-sided) and a power of 80%. This specification required the observation of 630 ''any first events.'' Despite this, a statistically significant survival benefit is claimed ($P = .03$), implying the use of $\alpha = 0.05$ here (and elsewhere) and an analysis based on only 464 deaths [Table 2 in (*1*)] [Table 3 in (*1*) deaths total 413]. Thus, with so few deaths observed, it is far too early to draw firm conclusions about survival, especially as results at 10 years are quoted. For example, an absolute survival benefit of 6% is claimed at 10 years for patients who had 5 years of adjuvant tamoxifen compared with those who had 2 years of adjuvant tamoxifen, but a confidence interval will, almost certainly, include the possibility of 0% benefit. In any event, such a statement is conditional on being recurrence free after 2 years of therapy and therefore should be adjusted for this probability of surviving those years. Such a calculation may be affected by an imbalance in patient numbers (61 fewer patients who had 5 years of adjuvant tamoxifen compared with those who had 2 years of adjuvant therapy) from those centers that randomized from the start of therapy, and therefore it is essential to report the pattern of recurrences/deaths in this period.

Similarly, a subgroup analysis with respect to distant metastases only appears to establish: ''Five years of adjuvant tamoxifen is more beneficial than 2 years in the treatment of . . . women with estrogen receptor-positive, . . . breast cancer.'' However, this analysis, which tests for the interaction between treatment and ER status, is based on only 338 events (*see also below*). An additional concern here is that ER status is unknown for 23% of the women. A more appropriate analysis, and especially Fig. 3 [in (*1*)], would include the third group of unknown ERs. This will be composed of ER-negative and ER-positive patients in unknown proportions and therefore behave in a manner somewhere between the pure ER-negative and ER-positive groups. This group, which appears to contain relatively few patients with distant metastasis (5% against 15% ER negative and 12% ER positive), could confirm or refute aspects of the ER analysis reported.

In addition, it has been pointed out by Gelman et al. (*2*) that an analysis of any first events, as described in Table 2 [in (*1*)], is based on an incorrect assumption that these events are all independent of each other. They ''. . . propose a solution to the problem of analyzing local failure, which uses a two-step procedure: first analyzing time to first failure (in any site) and then analyzing the distribution of sites of first failure.'' It would be of some interest whether such an analysis would have major impact on the conclusions concerning distant metastasis.

Our major concern is that firm conclusions may be inferred from which, at best, can be regarded as a very preliminary report.

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Response

Machin and Andersen raise three issues in relation to our trial: statistical power, treatment interaction with estrogen receptor (ER) status, and competing risks.

We observed that the benefit with the more prolonged tamoxifen schedule appeared to be restricted to those patients whose primary tumors were classified as ER positive. Information on ER status was not an entry criteria, except in one of the participating trial centers, but such information was still available in 87% of all included patients. In our opinion, the ER-unknown subgroup cannot contribute useful information about the treatment interaction with ER. The ER content could possibly be assayed in some of these patients by use of methods based on paraffin blocks. However, since the assays would not be the same, there would be a possibility of systematic differences in the extent of misclassification between the subgroups. In addition, the potential extra number of events is small, which implies that the overall results and conclusions cannot be expected to be materially different.

Machin and Andersen raise the issue of competing risks in the analysis of the distribution of first events in the two treatment groups. We have done analyses along the lines suggested by Gelman et al. (*1*). However, this approach resulted only in minor differences in terms of the relative hazard for the studied end points. In recent years, new statistical methods have been developed that permit a more detailed analysis of potential problems related to competing risks (*2*,*3*). In future publications of this trial, we aim to include such analyses.

A perhaps more important question is statistical power. The primary end point in the trial was recurrence-free survival, with first events defined as locoregional recurrence, distant metastasis, contralateral breast cancer, or death. This is a fairly standard method in randomized trials of adjuvant therapy in early stage breast cancer. It is self-evident that the power calculation for ''any first event'' does not apply to individual types of

events. However, in our analysis, there was a statistically significant difference between the treatment groups, both in terms of any first event and death, although the 95% confidence interval for the survival benefit obviously was wider. Our results were recently supported by the first publication of a Cancer Research Campaign (CRC) trial that also compared 5 with 2 years of adjuvant tamoxifen. That trial showed hazard rates similar to ours, although their confidence intervals were wider due to fewer events (*4*).

From the Swedish Breast Cancer Cooperative Group and CRC, results have now been published based on a total of about 6500 randomly assigned patients, with 1000 first events and 700 deaths showing that 5 years of adjuvant tamoxifen reduces the risk of disease recurrence by about one fifth and the risk of death by 11%-18% compared with only 2 years of tamoxifen. This illustrates that there is now fairly solid statistical evidence for the benefit with the more prolonged treatment. However, longer follow-up and more events are obviously necessary to permit in-depth analyses of the effect of the more prolonged schedule on, for instance, second cancer incidence and cause-specific mortality.

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Note

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Diabetes Mellitus and Risk of Large Bowel Cancer

High levels of serum triglycerides, plasma glucose, insulin, and insulin resistance—characteristics of patients with non-insulin-dependent diabetes mellitus (NIDDM)—have been hypothesized to increase the risk of colorectal cancer (*1,2*). However, epidemiologic studies (*3-8*) have not consistently supported this theory. We conducted a population-based cohort study to analyze the risk of developing primary colorectal cancer among patients with diabetes mellitus. The methodology used in this study has been described elsewhere (*9*). In brief, 153 852 patients who had diabetes mellitus as a hospital discharge diagnosis in Sweden from 1965 to 1983 were followed-up through 1989 by linkages of nationwide registries. We excluded the first year of follow-up from all analyses to minimize the impact of selection bias. Standardized incidence ratios (SIRs) and standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) were computed based on nationwide colorectal cancer rates. Information was not available to classify diabetes by type, i.e., insulin-dependent diabetes mellitus (IDDM) versus NIDDM.

For colon cancer, an increased incidence was observed in the cohort (SIR = 1.39; 95% CI = 1.31-1.49), with a slightly higher excess risk for right-sided cancers compared with cancers of the transverse or left parts of the colon. The SIRs did not differ significantly between sexes (Table 1). Among patients enrolled in the cohort before age 40 years (probably with IDDM), the SIR was 1.73 (95% CI = 1.04-2.87). Surveillance bias probably does not explain the excess incidence, since mortality was also increased. The overall SMR for colon cancer was 1.63 among men (95%

Table 1. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for primary colon and rectal cancers during 1-24 completed years of follow-up among patients with diabetes mellitus*,†

		Men			Women			Both sexes		
	Cancer site	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
Code ICD-7										
153	All colon sites	417	1.37	1.24-1.50	526	1.42	1.30-1.55	943	1.39	1.31-1.49
153.0	Cecum/ascending colon	172	1.66	1.42-1.93	210	1.48	1.28-1.69	382	1.55	1.40-1.72
153.1	Transverse colon	46	1.19	0.87-1.59	63	1.31	1.00-1.67	109	1.26	1.03-1.51
153.2	Descending colon	18	1.20	0.71-1.90	23	1.38	0.88-2.08	41	1.30	0.93-1.76
153.3	Sigmoid colon	134	1.30	1.09-1.54	140	1.30	1.09-1.53	274	1.30	1.15-1.46
154	Rectal cancer	294	1.36	1.21-1.52	198	1.10	0.95-1.26	492	1.24	1.13-1.35
Completed years of follow-up										
Colon cancer										
1-4		193	1.55	1.35-1.78	226	1.46	1.28-1.66	419	1.50	1.36-1.65
5-9		144	1.16	0.98-1.37	219	1.46	1.28-1.66	363	1.33	1.19-1.47
10-24		80	1.40	1.13-1.74	81	1.22	0.98-1.51	161	1.31	1.11-1.53
Rectal cancer										
1-4		128	1.46	1.23-1.74	82	1.09	0.88-1.35	210	1.29	1.12-1.48
5-9		114	1.30	1.08-1.56	87	1.19	0.97-1.46	201	1.25	1.08-1.44
10-24		52	1.27	0.98-1.65	29	0.89	0.62-1.28	81	1.10	0.88-1.37

*Including only first primary cancers. Excluding cancer cases diagnosed incidentally at autopsy or diagnosed during the first year of follow-up.
†ICD-7 = International Classification of Diseases, 7th Revision; Obs = observed number of cases.

CI = 1.48-1.79) and 1.51 among women (95% CI = 1.38-1.64). For patients with no comorbidity (having diabetes mellitus as their only hospital discharge diagnosis), the SMR was 1.29 (95% CI = 1.08-1.53). The excess mortality persisted 10 or more years after enrollment in the cohort (SMR = 1.33; 95% CI = 1.12-1.58).

For rectal cancer, the increased incidence was more evident among men (SIR = 1.36; 95% CI = 1.21-1.52) than among women (SIR = 1.10; 95% CI = 0.95-1.26) (Table 1). Six cases occurred among patients enrolled in the cohort before age 40 years (SIR = 1.27; 95% CI = 0.46-2.77). The overall SMR was 1.61 among men (95% CI = 1.41-1.82) and 1.36 (95% CI = 1.17-1.57) among women. For patients with no comorbidity, the SMR was 0.98 (95% CI = 0.73-1.29). The SMRs were significantly increased up to 10 years of follow-up but not afterwards (SMR = 1.17; 95% CI = 0.89-1.51).

For both colon and rectal cancers, there was no significant trend with the duration of follow-up in either sex. Thus, selection bias is an unlikely explanation for our findings. We found no appreciable differences in SIRs whether or not the patient was ever hospitalized for complications of diabetes (i.e., neuropathy, nephropathy, or retinopathy). There was also no difference in risk between patients born before 1900 (probably NIDDM) or afterwards (data not shown).

Our results support the hypothesis of a positive association between diabetes mellitus and colorectal cancer, but further studies are needed to assess whether this association is because of diabetes or shared risk factors, such as obesity, body fat distribution, diet, or physical inactivity.

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Notes

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Supported by Public Health Service contract N01CP85636-05 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by grants from the Swedish Cancer Society.

Re: Reversal of Relation Between Body Mass and Endogenous Estrogen Concentrations With Menopausal Status

The brief communication by Potischman et al. (*1*) in a recent issue of the Journal refuted the argument based on anovular cycles to explain the reduced risk of breast cancer in obese premenopausal women. The brief communication also provides the data supporting the hypothesis that I formulated (*2,3*)—that lean premenopausal women showed higher serum estrogen concentrations than their overweight counterparts. Potischman et al. (*1*) suggested, however, that obesity is the cause of low serum estrogen levels in premenopausal women as a result of estradiol uptake by adipocytes and the higher metabolic clearance rate in such women, whereas my hypothesis was that high estrogen levels are the cause of leanness in premenopausal women. This assumption is based on the inverse relationship we demonstrated (*4*) between body mass index (BMI) and high-density lipoprotein (HDL)–cholesterol serum concentrations. HDL–cholesterol serum concentrations parallel serum estrogen levels over a woman's life, with a progressive increase between menarche and menopausal decrease (*5*). The stimulation of hepatic lipoprotein lipase by estrogen (*6*) results in high HDL–cholesterol and low serum triglycerides, hence low BMI. This metabolic link suggests that leanness in premenopausal women is due to high estrogen levels, a risk factor for breast cancer. This mechanism does not prejudge the origin of hyperestrogenemia, although elevated insulin-like growth factor (IGF)-1 levels appear to be an essential factor. Increased levels of IGF-1 result from an elevated secretion of growth hormone, possibly associated with an energy-rich diet during prepuberty and puberty. IGF-1, a growth factor in itself, is also capable of inhibiting hepatic synthesis of sex hormone-binding globulin (SHBG), leading to higher levels of estrogens unbound to SHBG and of up-regulating steroid hormone synthesis. The latter effect might result in a chronic hormone dysregulation (*7*), known as ''functional ovarian hyperandrogenism,'' further aggravating the primary effect of IGF-1.

Obesity in postmenopausal women is generally considered to be the cause of extragonadal estrogen synthesis. However, not only is the estrogen hepatic metabolism different, but also the serum concentrations are much lower than in premenopausal women, reducing the possibility of secondary activation of hepatic lipoprotein lipase. These low estrogen levels raise the likelihood that it

is the estrogens themselves that mediate the risk. Moreover, visceral/abdominal obesity, the specific type of obesity described as a risk factor for breast cancer, is associated with insulin resistance and high levels of IGF-1 and testosterone. This global hormonal dysregulation may be the major effector of increased risk.

To discriminate between the mechanism proposed by Potischman et al. (*1*) and the mechanism that I proposed, larger studies designed to evaluate the influence of BMI and especially the type of fat distribution, as indicated by Potischman et al. (*1*), should include the measurement of insulin, serum lipids, and lipoproteins and of estradiol in adipocytes. Phenotyping of apolipoprotein E may be of interest, since an interaction between visceral obesity and estrogen replacement therapy has been observed only in women with apolipoprotein E4 (Garry PJ: personal communication).

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Note

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Re: Breast Cancer Risk in Rats Fed a Diet High in n-6 Polyunsaturated Fatty Acids During Pregnancy

Hilakivi-Clarke et al. (*1*) reported that consumption of a diet high in corn oil (50% linoleic acid) during pregnancy increases the risk in rats of developing carcinogen-induced mammary tumors, possibly by increasing pregnancy levels of circulating estrogens. Because of the relevance to human breast cancer, the conclusions of this study are of considerable interest to those involved in the study of nutritional carcinogenesis. However, two aspects of this article concern the reader. First, the diet itself, although isocaloric, differs significantly, not only with regard to total fat but also to total fiber. In fact, there is a fourfold difference in fiber intake between animals fed the high-fat versus low-fat diets. This is not a minor difference, particularly in light of our recent article on the role of fiber in carcinogen-induced rat mammary cancer (*2*). Since fiber, even a simple fiber such as purified cellulose, can alter the enterohepatic recirculation of estrogens, it may play a key role in the effects noted. Second, tumor incidence is extremely low, not to mention the total tumor number, suggesting a methodologic problem with either 7,12-dimethylbenz[*a*]anthracene administration or purity.

In light of the above considerations, the authors might well have more accurately described their diets as ''low-fat/high-fiber'' and ''high-fat/low-fiber'' and their tumor data as preliminary at best.

LEONARD A. COHEN

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Note

Correspondence to: Leonard A. Cohen, Ph.D., Division of Nutritional Endocrinology, American Health Foundation, 1 Dana Rd., Valhalla, NY 10595.

Response

We thank Dr. Cohen for his interest in our work and for raising the issue of fiber versus fat in affecting mammary tumorigenesis. Two aspects of our paper concerned Dr. Cohen: 1) the use of fiber to adjust the caloric content of the high- and low-fat diets, and 2) the low 7,12-dimethylbenz[*a*]anthracene (DMBA)-induced mammary tumor incidence. Rodents efficiently regulate their daily caloric intake. If they are fed a diet high in fat and calories compared with a diet low in fat and calories, their feed intake is significantly reduced. This is particularly true during pregnancy. We found that pregnant rats consume 21 g/day of a diet containing 24.6 g corn oil/100 g feed (caloric density, 4.8 kcal/g) and 32 g/day of a diet containing 5 g corn oil/100 g feed (caloric density, 3.8 kcal/g) (34% difference in daily food intake). The daily caloric intake is significantly higher (21%) in the low-fat group (122 kcal/day) than in the high-fat group (101 kcal/day) ($P<.001$) (17% difference in daily caloric intake). Similar findings have been reported by others (*1*). Reflecting the difference in daily caloric intake, the serum estradiol (E_2) levels do not differ in pregnant rats kept on nonisocaloric high- and low-fat diets. These findings may explain the failure to observe a difference in circulating estrogens in adult animals kept on the nonisocaloric high- and low-fat diets. To ensure the same daily caloric intake, we fed pregnant rats isocaloric diets. The high caloric density of the high-fat diet is compensated for by adding noncaloric fiber to the diet. Thus, the high-fat diet is a high-fat/high-fiber diet, not a high-fat/low-fiber diet. Examples of how fiber affects caloric density are given in Table 1. Because fiber increases fecal excretion of estrogens (*2*), we expected the serum E_2 levels to be only moderately different between the pregnant rats kept on the isocaloric high-fat/high-fiber and low-fat/low-fiber diets. We found that the high-fat-fed animals, either pregnant or not, have a 30%-100% higher circulating E_2 content than the low-fat-fed animals (*3,4*). Thus, despite the high fiber content of the high-fat diet (which would reduce serum E_2) and the low fi-

Table 1. Examples of the effect of dietary fat and fiber on caloric density

	Nonisocaloric diets				Isocaloric diets			
	High-fat		Low-fat		High-fat		Low-fat	
Dietary component	g	kcal	g	kcal	g	kcal	g	kcal
Fat, 9 kcal/g	20	180	5	45	20	180	5	45
Fiber, 0 kcal/g	5	0	5	0	25	0	7	0
Vitamins + minerals, 0 kcal/g	5	0	5	0	5	0	5	0
Carbohydrates + protein, 4 kcal/g	70	280	85	340	50	200	83	332
Total feed	100		100		100		100	
Total calories		460 kcal		385 kcal		380 kcal		377 kcal
Caloric density		4.6 kcal/g		3.85 kcal/g		3.8 kcal/g		3.8 kcal/g

ber content of the low-fat diet (which would increase serum E_2), we still detect significantly higher E_2 levels in the rats fed a high-fat diet.

DMBA induces mammary tumors in a substantial proportion of Sprague-Dawley rats. However, tumor incidence is dependent on several factors, the most critical being the number of terminal end-buds (TEBs) in the mammary gland (*5*). The number of TEBs is dependent, for example, on the age of the animal, parity, diet, and early estrogenic environment (*5-7*). Stressors, including handling, also reduce DMBA-induced mammary tumor promotion (*8*). In our hands, the DMBA-induced mammary tumor incidence has been consistently low (*9-11*), probably reflecting differences in handling and diet. Indeed, were the incidence to be 80%-100%, we could not detect a further increase. Therefore, our tumor incidences are appropriate for the experimental design.

Our results indicating that consumption of a high-fat diet during pregnancy increases mammary tumor incidence in rats are very provocative. If the same results are true for humans, pregnant women should not consume a high-fat diet.

LEENA HILAKIVI-CLARKE

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Re: Lung Cancer Risk From Residential Radon: Meta-analysis of Eight Epidemiologic Studies

A meta-analysis of radon and lung cancer was recently presented by Lubin and Boice (*1*). Near the end of the results section, data show that there was no significant increase in lung cancer risk for nonsmokers. There were no significant trends in relative risk either. This is important from a public health viewpoint because the major risk reduction activity for lung cancer is smoking cessation. If there is no increased risk for lung cancer among nonsmokers exposed to radon, then scientists need to look elsewhere for ways of reducing lung cancer in this group. This finding for nonsmokers is not mentioned again in this paper and is not given much prominence.

An analysis focused on females would also appear to have considerable merit. Females are more likely than males to be at home longer and to be exposed to a higher cumulative radon exposure. They also would be less likely to be exposed to occupational carcinogens (*2*). The Finland-I study consists solely of males; if excluded, the overall findings of this meta-analysis are no longer statistically significant [Fig. 4 in (*1*)]. This approach of excluding males in a subset analysis could be applied to practically all of the studies.

The studies cited were quite heterogeneous, as mentioned by the authors. Why then were they combined to give a summary risk estimate? These studies were not designed to be comparable or to be analyzed together (*3*), and the au-

thors do not provide adequate justification for combining them.

The validity of the radon exposure assessment is questionable in several of the individual studies, and, consequently, in the meta-analysis. A number of radon estimates were obtained for homes. Homes lacking valid radon exposure assessment should be excluded from a subset of the analysis (*2*). Field quality assurance/quality control (e.g., duplicates, blanks, spikes, and placement protocols) was not done in some cases. Several studies used less than 1 year's radon measurements, thus not accounting for seasonal variability. Accounting for time on different floors is missing, so that concentration × time cannot be calculated (*4*). Although Figs. 2 and 3 in (*1*) provide a quantitative estimate of uncertainty for relative risk (i.e., 95% confidence intervals), no quantitative information on uncertainty is provided concerning radon exposure.

It is evident from review of the individual case–control studies [Fig. 2 in (*1*)] that dose–response trends generally are not inverse; this is in contrast to the inverse findings in more than one ecologic study. This meta-analysis adds nothing new to this observation. At least one positive ecologic study (*5*) has already pointed out likely confounding effects, including urbanization.

It is recognized that future pooling of data from ongoing studies will take place. Such pooling should be restricted to comparable studies and should provide detailed documentation of comparability and validity before publication in a scientific journal. Analysis should focus on female nonsmokers and should include quantitative information on radon exposure uncertainty.

JOHN NEUBERGER
ACE ALLEN

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Notes

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I am writing in response to the criticisms in the January 1997 issue of the Journal by Lubin and Boice (*1*) and by Samet (*2*) of my article ''Test of the Linear–No Threshold Theory of Radiation Carcinogenesis for Inhaled Radon Decay Products'' (*3*).

Lubin and Boice misinterpreted the purpose and design of my study, which, as implied in the title, was to test the linear–no threshold theory (LNT) of radiation carcinogenesis. A universally accepted and time-honored procedure for testing a scientific theory is to develop it mathematically to derive predictions that can be compared with experimental observations and then to make that comparison. In my paper it was shown, using rigorous mathematics, that LNT predicts that a plot of lung cancer rates in U.S. counties (corrected for smoking prevalence and other confounding factors) versus average radon exposure in those counties should have a positive slope of +0.20 per Bq/m^3; it was shown that this prediction is not in any way affected by ''the ecological fallacy.'' It was then shown that the plot of observational data has a negative slope, −0.21 (±0.02) per Bq/m^3, a 20-standard-deviation discrepancy with the prediction of LNT. My paper gives very extensive treatment of data uncertainties, of potential confounding factors (including elaborate modeling), and of weaknesses in ecologic studies, etc., and finally concludes that LNT fails very badly in the low-dose region of my test; therefore, LNT should not be used in that region.

Lubin and Boice (*1*) and Samet (*2*) did not consider my test of LNT, which is what my article is all about, and interpret my plots of county-average data as risks to individuals, despite my caution against such an interpretation because it is logically invalidated by the ecological fallacy. In fact, Fig. 3 of the Lubin and Boice article (*1*), a plot of their data on relative risk versus radon exposure to an individual, *r*, shows what they identify as my results as a straight line extending to 340 Bq/m^3, at which point there is a large discrepancy with their data. Actually, my largest *r* data point (which is statistically insignificant) is at $r = 230$ Bq/m^3, and the linear portion of my data ends at about $r = 120$ Bq/m^3.

Another problem with their interpretation of my results is that my analysis determined the slope of data points without regard for the intercept at $r = 0$, and hence the line that Lubin and Boice show as my results can be shifted up or down slightly on their plot. If this were done, there would be relatively little discrepancy with their data. To the extent that any discrepancy remains, it is easily explainable by the recognized weaknesses of the meta-analysis technique they use and by the effects of the ecological fallacy on their interpretation of my data. I therefore feel that their criticism of my article was not justified.

BERNARD L. COHEN

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Note

Correspondence to: Bernard L. Cohen, Ph.D., 100 Allen Hall, University of Pittsburgh, Pittsburgh, PA 15260.

Responses

We were bemused by Dr. Cohen's letter regarding our meta-analysis of eight case–control studies of indoor radon and lung cancer, since we did not criticize his ecologic regression analyses (*1*). In the penultimate paragraph of our

discussion, we made the simple observation that his negative regression relationship between age-adjusted lung cancer rates and mean indoor radon levels for counties (*2*) was not consistent with, and indeed contradicted, results from nearly all analytic case–control and cohort studies. Specifically, the relative risks (RRs) from our meta-analysis of eight indoor radon studies, from projections based on a pooled analysis of 11 cohort studies of radon-exposed underground miners, and from miner data restricted to exposures comparable to residential exposures were consistent with a positive exposure–response trend.

Limitations of ecologic studies have been widely discussed in general (*3*) and for radon in particular (*4*). In a telling example, data from a national population survey were used to demonstrate that a regression slope estimated from area means could be biased upward, downward, or even reverse trend, compared with the regression slope estimated from individuals (*3*). Ecologic studies of lung cancer and indoor radon and confounding by cigarette smoking were the topics of a recent exchange in the *American Journal of Epidemiology* (*5-8*), which included a commentary from Cohen (*7*). There is no need to revisit these issues. The RR relationship between radon exposure and lung cancer risk is complex, depending on age, time since exposure, and exposure rate, and smoking is an overwhelming risk factor. The 5%-6% of homes in the United States with radon concentrations over 150 Bq/m^3 are estimated to increase lung cancer risk by 20%-30%. In comparison, the 40%-50% of the population who are current or former smokers incur an estimated 1500% excess lung cancer risk. The complexity of the relationship between lung cancer risk and indoor radon exposure and smoking leads us to concur with the conclusion of Piantadosi (*6*):

> The results of Cohen's analysis will seem biologically implausible to many investigators although it is probably theoretically possible at the individual level. Many epidemiologists will likely attribute the discrepancy between theory and result more to deficiencies in ecologic analyses than to failure of the dose-response theory. . . . Because the result being discussed is at odds with an appealing model, it does more to discredit the (ecologic) analysis than the theory.

The letter by Dr. Neuberger highlights the advantages of pooled analysis of original data over a meta-analysis. We agree that smoking status and sex, as well as attained age, define important subgroups in which to conduct comparative analysis of radon effects; however, we believe that these issues are best addressed in future pooled analyses (which are planned in both North America and Europe), where variables can be defined uniformly across all studies and more complete control of confounding can be achieved. Accordingly, we refrained from over-emphasizing subgroup analyses in our meta-analysis. For completeness, the fitted RR for nonsmokers at 150 Bq/m^3 was 1.18, similar to the 1.24 estimate for the five studies with published details on smoking status. On the basis of data for females presented in only three studies, the fitted RR at 150 Bq/m^3 was 1.10.

JAY H. LUBIN
JOHN D. BOICE, JR.

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Cohen responds to perceived criticisms of his ecologic study of radon and lung cancer in my recent editorial (*1*). Careful reading of the editorial shows, however, that emphasis is placed on the policy implications of his findings in light of the new meta-analysis and not on limitations of his ecologic study itself. With Stidley, I have previously reviewed Cohen's ongoing work as well as other ecologic studies (*2*). The editorial restates the well-known limitations of the ecologic method; Cohen acknowledges the problem of the ''ecologic fallacy'' in interpreting his own findings.

In his letter, Cohen again asserts that the findings of his ecologic study are inconsistent with ''linear-no threshold theory.'' The findings are also inconsistent, however, with the bulk of the epidemiologic data from observations of individuals, including the studies of miners exposed at lower doses and the case–control studies summarized in the new meta-analysis reported by Lubin and Boice (*3*).

JONATHAN SAMET

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