

**ENVIRONMENTAL
TOBACCO SMOKE (ETS)
AND
RISK OF LUNG CANCER—**

**HOW CONVINCING IS THE
EVIDENCE?**

Alan W. Katzenstein

HOW CONVINCING IS THE EVIDENCE?

Does exposure to environmental tobacco smoke (ETS) increase the non-smoker's risk of developing lung cancer? The scientific evidence does not support such a claim, even though press releases and statements in the popular media have tended to create that impression.

THE NATURE OF THE EVIDENCE

Despite statements that nonsmokers exposed to ETS incur increased risk of lung cancer, there appears to be not a single scientific study that has assessed the risk to nonsmokers by actual measurement of exposure to ETS in the home, in the workplace or in public. The 1986 report of the National Academy of Sciences on ETS commented: "The studies do not directly address chronic health effects in individuals who are exposed at work or have occasional exposures in the home or elsewhere."

Two studies have attempted to estimate total exposure through questionnaires, but neither study found a statistically significant increased risk of lung cancer on the basis of total ETS exposure.

Except for the two studies noted above, all the studies listed by Surgeon General C. E. Koop in Congressional testimony in 1985 and 1986 and the studies cited in the 1986 reports of the Office of Technology Assessment (OTA), the National Academy of Sciences (NAS), and the Surgeon General pertain only to the risk of lung cancer for nonsmokers married to smokers in relation to the risk for nonsmokers with nonsmoking spouses. In other words, the risks have been estimated primarily in relation to the spouses' smoking habits.

THE QUALITY OF THE EVIDENCE

All of the reports in the literature have been reviewed by independent investigators, as is customary and appropriate in the scientific process. Most of the studies have been criticized for one or more significant flaws in methodology, such as too few subjects to permit statistically reliable findings, failure to provide appropriate controls

against which comparisons can be made, failure to verify the origin of the primary cancer in all subjects, and failure to account for life style factors that might influence the results.

Numerous reviewers have commented on the possibility of inaccurate classification of smokers and of spouses in terms of their smoking habits, which could result in significant errors in the risk statistics. The NAS report comments at length on this weakness in the evidence, going so far as to revise its calculations downward to account for possible bias or misclassification.

All of the reports said to find increased risk for the exposed nonsmoker have been found to be significantly flawed and have been widely criticized.

In 1985, the International Agency for Research on Cancer reviewed the quality of the evidence in the eight reports then available and concluded that "each is compatible either with an increase or with an absence of risk." In other words, none established increased risk with any certainty.

The 1986 report of the Office of Technology Assessment noted that "all the lung cancer studies have some methodologic weaknesses."

Highlights of the critical comments by various reviewers of the studies listed in Surgeon General Koop's congressional testimony of June, 1986, are summarized in Appendix 2.

THE QUANTITY OF THE EVIDENCE

More than 30 reports covering 19 separate studies have been listed in the various reviews and testimony on the risk of lung cancer in relation to ETS.

- 2 studies have been so severely criticized for inappropriateness that they were excluded from the data base in the OTA study and were not even listed in the NAS report.
- 3 studies were mentioned and discounted by NAS because of technical weaknesses.
- 13 studies survived critical assessment by NAS, 12 of which are included also in the Surgeon General's Report.

- The Surgeon General's Report inexplicably fails to cite one of the studies in the NAS report but includes another that was excluded by NAS because raw data were not provided to permit critical assessment.

Considered by the populations studied:

- 6 studies were based on U.S. subjects.
- 5 studies were based on European subjects.
- 3 studies were based on Asian subjects, including one study based on atomic bomb survivors now averaging more than 70 years of age.

The 13 studies listed by NAS cover a total of 677 cancer subjects, with studies ranging from as few as 10 subjects to as many as 146.

OVERALL RISK ESTIMATES

NAS concluded, "the risk of lung cancer is roughly 30% higher for nonsmoking spouses of smokers than it is for nonsmoking spouses of nonsmokers." Then, recognizing the likelihood of bias or misclassification of subjects, NAS lowered the overall estimate to about 25% higher risk for exposed nonsmokers.

However, the lack of statistically significant risk findings for all but two of the studies, along with the flaws identified in each of the individual studies, as summarized in Appendix 2, makes it highly questionable whether an increase in overall risk has really been established.

NAS further noted that "the estimate of the increased risk from the American studies is lower than the average for all the studies. . . ."

RISKS FOR AMERICANS

When considering only the studies of American subjects, NAS concluded that the risk for nonsmokers with a spouse who smokes is only 14% higher than the risk for a nonsmoker with a nonsmoking spouse. (*There is no indication whether NAS made adjustments for possible bias or misclassification in the American studies.*) However, individually and as a group, the risk levels from these studies

are not statistically significant; that is, statisticians consider the results might well arise by chance alone.

Of the 5 studies of American subjects included in the NAS report, 3 provide data separately for males and females, yielding 8 data sets. (*See Table 1.*)

- In 4 of those data sets, the risk for nonsmokers is increased.
- In 1 set, there is neither increased nor decreased risk.
- In 3 sets, the risk is decreased.

This 4-1-3 pattern is remarkably consistent with what statisticians would expect from a series of studies where no real difference in risk actually exists.

The study excluded from the NAS list but included in the Surgeon General's report similarly shows an increased risk that is not statistically significant.

CONCLUSION

A total of 14 studies on lung cancer risk for the nonsmoker in relation to spousal smoking survive critical assessment despite their technical flaws. Of the 6 studies based on American subjects, none shows a statistically significant increase in risk for the nonsmoker with a spouse who smokes.

Based on the evidence to date, the concern about the risk of lung cancer for nonsmoking Americans appears to be overstated and unsupported.

Katzenstein Associates
Larchmont, NY 10538

March 1987

Table 1

LUNG CANCER RISK ESTIMATES AND CONFIDENCE LIMITS FOR STUDIES WITH AMERICAN SUBJECTS AS CITED BY NATIONAL ACADEMY OF SCIENCES AND SURGEON GENERAL'S REPORT

Study	Females			Males		
	N	Risk	Confidence Limits	N	Risk	Confidence Limits
From NAS Report¹						
Kabat & Wynder	13	0.79	0.26 2.43	5	1.00	0.20 4.40
Buffler	33	0.80	0.32 1.99	5	0.50	0.14 1.79
Garfinkel (1985)	92	1.12	0.74 1.69			
Garfinkel (1981)	88	1.18	0.90 1.54			
Correa	14	2.03	0.83 5.03	2	2.29	0.31 16.50
Overall risk ratio for American studies ² 1.14 0.92 1.40						
From Surgeon General's Report³						
Wu	29					
Smoked 1-20 yrs.		1.4	0.4 4.9			
Smoked 21+ yrs.		1.2	0.4 3.7			

- References: 1. *Environmental Tobacco Smoke—Measuring and Assessing Health Effects*. 1986. National Academy of Sciences. Table 12.4
 2. *Ibid.*, p. 231
 3. *The Health Consequences of Involuntary Smoking—A report of the Surgeon General*. 1986. Tables 8 and 9

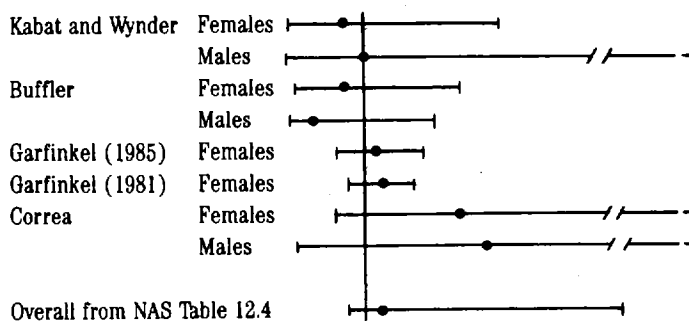
Notes:

- *"Risk" value is the ratio of lung cancer risk for nonsmokers whose spouses smoke in relation to the risk for nonsmokers married to nonsmokers.
 ***"Confidence limits" are the values between which the risk value can be expected to fall 95% of the time based on the variability of the underlying data. When the 95% confidence limits are both greater and less than 1.00, the risk value is considered not statistically significant, i.e., the results are likely to be due to chance and do not support a causal relationship.

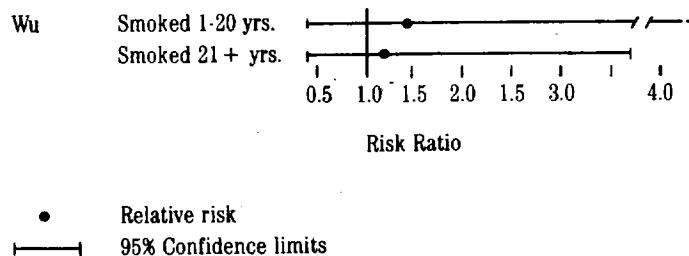
Figure 1

LUNG CANCER RISK AND CONFIDENCE LIMITS FOR STUDIES WITH AMERICAN SUBJECTS AS CITED BY NATIONAL ACADEMY OF SCIENCES AND SURGEON GENERAL'S REPORT

From NAS Report



From Surgeon General's Report



Data and sources from Table 1

Appendix 1

In Congressional testimony in June, 1986, Surgeon General C. E. Koop cited 14 studies on the link between risk of lung cancer and non-smokers' exposure to spouses who smoke. (See below.) Three of the studies were characterized as not showing positive correlation between lung cancer risk and exposure to spousal smoking. Of the 11 studies said to show "positive correlation," all have been reviewed by independent investigators and found flawed as noted in Appendix 2.

RR values are "risk ratios," reflecting the risk of lung cancer for non-smokers whose spouses smoke compared to the risk for nonsmokers married to nonsmokers. For example, an RR = 1.25 would represent a 25% increase in risk for the exposed nonsmokers, while an RR = 0.80 would represent a risk 20% less than that of a nonsmoker with nonsmoking spouse.

SUMMARY OF STUDIES ON PASSIVE SMOKING AND CANCER LISTED BY U.S. SURGEON GENERAL C. E. KOOP (JUNE 17, 1986)

Worker	Country	Risk Ratio	Statistically Significant	Size	Type of Study
Chan (1979)	Hong Kong	0.85	—	223 F	Case control
Phillips (1980)	USA	2.4F, 1.5M	F	52,000 F, 17,000 M	Prospective
Garfinkel (1981)	USA	1.2	NO	180,000 F	Prospective
Hirayama (1981)	Japan	1.8F, 2.9M	F, M	90,000 F, 20,000 M	Prospective
Trichopoulos (1981)	Greece	2.4	F	302 F	Case control
Correa (1983)	USA	2.0M, 2.1F	F	188 M, 155 F	Case control
Gillis (1983)	Scotland	3.2M, 1.0F	NO	6 M, 8 F	Case control
Hirayama (1983)	Japan	2.3-3.4	—	28 F	Prospective
Hirayama (1983)	Japan	1.4-1.9	—	200 F	Prospective
Knoth (1983)	Germany	3.0	—	39 F	Case control
Koo (1983)	Hong Kong	—	—	120 F	Case control
Kabat (1984)	USA	1.4M, 0.9F	M	37 M, 97 F	Case control
Miller (1984)	USA	1.9	F	438 F	Case control
Repace (1984)	USA	1.7	—	180,000 F	Reanalysis
Sandler (1985)	USA	1.7-4.6	M, F	420 M, F	Case control
Sandler (1985)	USA	2.0	M, F	466 M, F	Case control
Garfinkel (1985)	USA	2.1	F	134 F	Case control

Source: Statement of C. Everett Koop, M.D., Surgeon General, before the Subcommittee on Health and the Environment, Committee on Energy and Commerce, U.S. House of Representatives (June 12, 1986)

Appendix 2

**COMMENTS FROM THE LITERATURE ON
THE STUDIES CITED BY SURGEON
GENERAL KOOP**

*Abbreviations: SG = Surgeon General
OTA = Office of Technology Assessment report
NAS = National Academy of Sciences report

†Sources are identified in the reference list.

Cited in Surgeon General Testimony*	Comments From the Literature†
<i>Koo (1983)</i> —SG cites no RR, no significance indicated.	OTA noted RR = 1.28 for cases exposed less than 35,000 hours, and RR = 0.96 for cases exposed more than 35,000 hours. Balter noted no significant difference in lung cancer incidence for cases exposed at home, in the workplace, or both, nor by degree of exposure. NAS mentions and excludes this study. SG Report shows results not statistically significant.
<i>Correa (1983)</i> —SG lists RR = 2.0 for males, 2.1 for females; statistically significant for females	OTA and Weiss note small number of cases. Balter and OTA note statistically significant relationship was only for nonsmokers whose husbands smoked more than 41 pack-years. Lebowitz notes possible error or bias in estimating degree of exposure; also notes anomalous finding of "increased risk in smokers whose mothers smoked ... but no elevated risk for nonsmokers."
<i>Sandler (1985)</i> —SG lists RR = 1.7-4.6, significant for males and females.	Weiss notes "almost certain misclassification of exposure." OTA and Balter note too few cases to evaluate. Lebowitz notes that there was "no significant increase in lung cancer risk ... but increases in non-tobacco related cancers." NAS mentions and excludes. Excluded in SG Report.
<i>Knott (1983)</i> —SG lists RR = 3.0; no indication of significance	OTA and Balter noted lack of control groups. Weiss noted "possible misclassification of exposure; no control group." Lebowitz noted "a high likelihood of misclassification/bias in this study." NAS mentions and excludes. Excluded in SG Report.
<i>Miller (1984)</i> —SG lists RR = 1.9, statistically significant.	Results cited pertain only to women not employed outside the home. For women employed outside, RR = 0.80; for all women in the study, RR = 1.4, not statistically significant. OTA noted failure to control for age differences between cases and controls. NAS mentions and excludes. Excluded in SG Report.

Cited in Surgeon General Testimony	Comments From the Literature
<i>Phillips (1980)</i> —SG lists RR = 2.4 for females, 1.5 for males; statistically significant for females.	Study pertains entirely to Seventh Day Adventists (SDA). Environmental Protection Agency's Carcinogen Assessment Group noted: "SDAs are a very unique group and may differ from the general population with regard to lung cancer risk by more than just their lack of exposure to passive smoking. In addition to not smoking, SDAs do not drink, and they maintain rather strict diets." OTA also considered SDAs inappropriate for assessing risks of ETS exposure. NAS does not mention Phillips study. Excluded in SG Report.
<i>Repace (1985)</i> —SG lists RR = 1.7, not statistically significant.	Calculations are based on data from Phillips (1980) study. Repace is an analyst at EPA. EPA Carcinogen Assessment Group criticized study based on SDAs as noted above and faulted the Repace study for unsupported age-adjustments to lung cancer rates. OTA noted that some of the assumptions are "inappropriate" because of SDA lifestyle differences; excluded Repace report from further consideration. NAS does not mention Repace study at all. Excluded from SG Report.
<i>Kabat (1984)</i> —SG lists RR = 1.4 for males, 0.9 for females; statistically significant for males.	OTA found RR = 1.0 for males and 0.8 for females based on spousal smoking. For exposure at home, RR = 1.3 for males and 0.9 for females. For exposure at work, RR = 3.3 for males and 0.7 for females. OTA noted "authors consider data on passive smoking 'preliminary.'" NAS found RR = 0.79 for females, 1.00 for males. SG Report lists RR = 0.9 overall.

Cited in Surgeon General Testimony	Comments From the Literature
<i>Trichopoulos (1981)</i> —SG lists RR = 2.4 for females, statistically significant.	Numerous reviewers have noted that many of the lung cancer cases were not histologically confirmed; SG Report states 65% histologically confirmed. Lebowitz states "only about one-fourth of the lung cancer cases had histological confirmation." Lebowitz also notes that cases and controls were matched on some factors but not on others. Balter noted a dose-response trend is significant when data are analyzed based on husbands smoking 1-20 and 21+ cigarettes/day, but trend is not significant when based on 1-10, 11-20, 21-30 and 31+ cigarettes/day; RR = 2.9 for 31+ cigarettes/day but RR = 4.3 for 21-30 cigarettes/day, creating doubt about the significance of pooling data. SG Report cites RR only for pooled data.
<i>Hirayama (1981, 1983)</i> —SG lists RR = 1.8 for females and 2.9 for males, both statistically significant.	Study has been widely criticized. EPA memo on Repace notes that Hirayama report had been "severely criticized" in letters in British Medical Journal where it was published. Rylander noted wide criticism "from the point of view of questionnaire reliability, absence of histological diagnosis, statistical treatment, grouping of smoking habits among husbands, and confounding factors such as air pollution from heating and/or cooking" as well as anomalous results among subgroups and possible changes in classification of subjects and spouses over time. Lebowitz points up numerous inconsistencies in the findings as well as other weaknesses in the treatment of data.
<i>Garfinkel (1985)</i> —SG lists RR = 2.1 for females, statistically significant.	Garfinkel et al. stated "elevated risk ... ranging from 13 to 31% ... not statistically significant. ... No consistently higher risk for certain age groups or by histological types or by exposure at home or at work. Exposure in other areas carried a higher OR [odds ratios], but this finding is difficult to interpret." Data show smaller RR for 7+ hours/day exposure to spouse's smoking than for 3-5 hours/day, as well as smaller RR for 25 years of exposure than for 5 years of exposure. NAS listed RR = 1.12 for females, not significant on basis of confidence limits.

References:

Arundel, A., T. Irwin, and T. Sterling. Nonsmoker lung cancer risk from tobacco smoke exposure: An evaluation of Repace and Lowrey's phenomenological model. *Journal of Environmental Science and Health C4(1)*: 93-118 (1986)

Balter, N. J., S. J. Kilpatrick, P. Witorsch, and S. S. Schwartz. Causal relationship between environmental tobacco smoke and lung cancer in non-smokers: A critical review of the literature. To be published, *Proceedings of the Air Pollution Control Association* (1986)

Burch, P. R. J. Health risks of passive smoking: Problems of interpretation. *Environment International* 12:23-28 (1986)

Environmental Protection Agency, Carcinogen Assessment Group. H. J. Gibb. Repace and Lowrey's estimate of the nonsmoker's lung cancer risk from passive smoking. (Undated memorandum)

Johnson, C. Letter. *Environment International* 12:21 (1986)

Kilpatrick, S. J. Letter. *Environment International* 23:29-31 (1986)

Lebowitz, M. D. The potential association of lung cancer with passive smoking. *Environment International* 21:3-9 (1986)

Office of Technology Assessment, U.S. Congress. Passive Smoking in the Workplace: Selected Issues. Staff paper. (May, 1986)

Rylander, R. Environmental tobacco smoke and lung cancer. *European Journal of Respiratory Diseases*. Supp. No. 133, 65:127-133 (1984)

Weiss, S. T. Passive smoking and lung cancer (Editorial). *American Review of Respiratory Diseases* 133:1-3 (1986)

Katzenstein Associates
51 Rockwood Drive
Larchmont, N.Y. 10538



TINY 0009815