ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER MORTALITY IN THE AMERICAN CANCER SOCIATY'S CANCER PREVENTION STUDY II

by

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An Abstract of
A dissertation submitted to the Faculty of the Graduate School of
Emory University in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

Division of Epidemiology

1994

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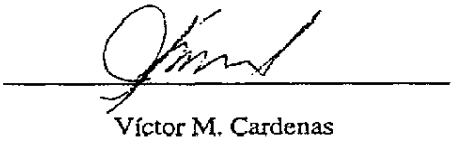

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Abstract

Background Evidence from epidemiologic studies and animal and genotoxicity assays leads to the conclusion that environmental tobacco smoke (ETS) causes lung cancer. *Objectives* The hypothesis of a causal relationship between exposure to ETS during adulthood and risk of death from lung cancer was tested using seven years of follow-up data of the American Cancer Society's Cancer Prevention Study II. *Methods* Three analytic cohorts of life-time nonsmokers were assembled for ETS analyses based upon: 1) self-reported current hours of exposure to ETS, 2) exposure from spousal smoking, and 3) dose of exposure to ETS from cigarette smoking of spouses. These cohorts included 362, 265, and 127 lung cancer deaths, respectively. Mantel-Haenszel rate ratio analyses by ETS exposure variables, followed by Cox regression modeling controlled for age, gender, race, education, intake of vegetables, fruits and fat, occupational exposure to asbestos and history of chronic lung diseases. *Results* Lung cancer risk among nonsmokers was not associated with current self-reported number of hours of exposure to ETS. Nonsmokers reportedly exposed to ETS for 6+ hours a day had a 20% statistically not significant increased risk: the multivariate rate ratio (RR) was 1.2, [95% Confidence Interval (CI)=0.8-1.7]. Nonsmoking women married to current smokers had also a statistically not significant 30 percent greater risk of developing lung cancer (multivariate RR=1.3, 95% CI=0.8-1.9). Women married to current cigar/pipe smokers had a 50% increased risk, but again the finding was not statistically significant (multivariate RR=1.5, 95% CI=0.8-2.7). After adjusting for all covariates, we found among nonsmoking women an increasing risk of lung cancer with increasing pack-years of cigarettes smoked by their husbands which was not statistically significant (p=0.14). *Discussion* Missing data on self-reported ETS could have resulted in considerable misclassification and thus biased the study findings towards an absent of an effect. Self-reported hours of ETS exposure does not measure intensity of exposure and referred only to current, rather than lifelong ETS exposure. Assessment of exposure to ETS using spousal smoking habits is better, but still has considerable limitations and at best is an imperfect measurement. The study also has limited statistical power and its generally null findings are still consistent with the positive association reported from other

studies. *Conclusions* This study found no evidence of an association between self-reported ETS and lung cancer risk among nonsmokers. However, using spousal smoking habits to assess exposure, we found ETS is only weakly, and not statistically significantly, related to lung cancer risk among nonsmoking women in seven years of follow-up of the CPS II cohort.

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Dedicated to dearest Carmen and Angela whose

love has been a constant source of support, always!

Acknowledgments

Without the support, encouragement and help of many individuals the completion of this dissertation and academic degree would have been an impossible task. I am indebted to my mentors, Drs. John Boring, Jonathan Liff, Ira Longini, Ray Greenberg, Ralph Coates, Harland Austin and Dana Flanders for their patient instruction, the learning opportunities they provided me, and for their insistence on excellence in epidemiologic research. The vision and encouragement of Dr. Ray Greenberg was largely instrumental in my involvement in this program.

Our program advisor, Dollie Daniels, deserves special mention for her support throughout the past four years has been much appreciated. I also wish to acknowledge the excellent proofreading of Ms. Daniels and Dr. Louis Escobedo of several versions of this manuscript.

I am especially grateful to each member of my doctoral dissertation committee, Drs. Harland Austin, Michael Thun, Clark Heath, Scott Clark, and Ray Greenberg for their support, patience and encouragement throughout this experience.

I have been especially fortunate to have Harland Austin as advisor in the area of cancer epidemiology and epidemiologic methods. He was always there to guide me through the different stages of this study.

At Emory Universtiy I have had the privilege to use the American Cancer Society Cancer Prevention Study II data base and facilities for my research. It has been a pleasure to work and receive advice on a daily basis from Drs. Michael Thun, and Clark Heath. The programming guidance of Mohan Namboodiri first, and then brilliantly embraced by Cathy Lally and Heidi Miracle, was decisive. I also acknowledge the advice of Dena Myers, Dr. Eugenia Calle, and Diane Terrell for their valuable suggestions throughout the study conduct.

To develop a definition of different categories of jobs/trades with potential occupational exposure to asbestos, I was fortunate to count on with the advice of an expert in the field such as Dr. Howard Frumkin, and I also want to express my gratitude to him.

I thank Dr. Christina Park, from the National Center for Health Statistics, for providing unpublished data from the 1988 NHIS-OH supplement on the extent of ETS exposure.

I thank the following persons, principal investigators of the National Cancer Institute SEER program, who promptly replied to our inquiry to confirm the diagnoses of lung cancer among nonsmoking CPS II participants who resided in the Cancer Registries areas: Mrs. Kathleen M. McKeen; Director of the State Health Registry of Iowa; Mr. J.T. Flannery, Director of the Connecticut Tumor Registry; Dr. David B. Thomas, from the Cancer Surveillance System of Western Washington; Dr. Dee West, Director of the San Francisco Bay Area Cancer Registry; Dr. Charles R. Key, Medical Director of the New Mexico Tumor Registry; to my professor, Dr. Jonathan M. Liff, Director of the Georgia Center for Cancer Statistics; Dr. G. Marie Swanson Director, and Sherry Enoex, Data Manager from the Michigan Cancer Foundation; Dr. L.N. Kolonel, Director and Ruth D. Mertz, administrator from the Cancer Research Center of Hawaii; and to Dr. W.P. McWhorter Director of the Utah Cancer Registry.

Finally, I acknowledge the generous support of the W.K. Kellogg Foundation and Emory University for providing me with scholarships to complete my studies.

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Chapter 1: Introduction

1.1. Background

Epidemiologic studies, along with collateral evidence from experimental studies in animals and genotoxicity assays, indicate that tobacco smoking causes: 1) lung cancer, 2) other cancers (oral, laryngeal, esophageal, bladder, renal, pancreatic, stomach, cervical and leukemia); 3) acute and other chronic conditions such as hypertension, coronary heart disease, peripheral arterial occlusive disease, cerebrovascular disease, chronic obstructive pulmonary disease, gastrointestinal disease, disease of the mouth; 4) that parental smoking is associated with major reproductive disorders such as low birthweight, birth defects, and the fetal tobacco syndrome; and 5) an increase in overall mortality (US DHHS Surgeon General 1989).

Three decades after the publication of three seminal reports of case-control studies on the association of active smoking and lung cancer (Wynder 1950, Doll 1950, Levine 1950), the first two reports from epidemiologic studies on the effect of passive smoking and lung cancer among nonsmokers were published (Hirayama 1981,Trichopoulos 1981). In the 12 years since those reports were published, the scientific evidence accumulated on the effects of environmental tobacco smoke (ETS) on health, is not as strong as for active smoking. However, with respect to the potential health hazards from ETS, it seems that in recent years, a consensus is forming that passive smoking is injurious to health, although to a lesser degree than smoking.

In particular, a report from the US National Research Council concluded after reviewing 13 published epidemiologic studies, that "a summary estimate from epidemiologic studies places the increased risk of lung cancer in nonsmokers married to smokers compared with nonsmokers married to non-smokers at about 34 percent" (NRC 1986). The International Agency for Research on Cancer concluded: "knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during 'passive smoking', and of quantitative relationships

between dose and effect that are commonly observed from exposure to carcinogens leads to the conclusion that passive smoking gives rise to some risk of cancer" (O'Neill 1987). A recently published report from the US Environmental Protection Agency, included evidence from a total of 29 epidemiologic studies on the effect of ETS on lung cancer risk and concluded that "ETS is a Group A human carcinogen, the classification used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer" (EPA 1992).

Since the late 1980's smoking in many public places, as well as on local and international airplane flights, has been banned. As the wave of anti-smoking campaigns rises, banning of smoking in public places and workplaces will further contribute to the goal of a tobacco-free world. Epidemiologic research on this subject is needed since there is still controversy over the size of the effect of exposure to ETS on the risk of cancer and other diseases, and whether the observed modest increased risk is causal or an artifact due to: 1) misclassification of smoking status, described by Mantel and Lee (Mantel 1983, Lee 1984); 2) a publication bias (Mantel 1990, Vandenbroucke 1988), or 3) confounding by socioeconomic status or other unspecified/unknown factors (Mantel 1992). The EPA report (1992) and a study and paper by Fontham et al. (1991) offer reasonable rebuttal of these critiques.

1.2. Specific Aim

The purpose of this study is to assess, in a large prospective study, whether ETS exposure in adulthood causes lung cancer.

The objective of this study is to quantify the effect, if any, of adult ETS exposure on lung cancer mortality among lifelong nonsmokers in the American Cancer Society's Cancer Prevention Study II (CPS II).

1.3. Hypotheses

The specific research questions that were tested in this study can be stated, in the alternative form, as follows:

1. Non-smokers exposed to ETS (either spousal or self-reported exposure) are at higher risk of fatal lung cancer than are non-smokers not exposed to ETS.

2. The risk increases in a dose-response relationship with: 1) hours (per day) of self-reported ETS exposure (cumulative at home, work or other places), and 2) pack-years of cigarettes smoked by spouses (married once and that had complete smoking data).

3. The relative risk of lung cancer among nonsmokers exposed both to ETS and occupationally exposed to asbestos, is greater than the risk of those exposed to ETS only.

4. The association remains after adjustment for relevant potential confounders, and is not attributable entirely to misclassification of smoking status (i.e, misclassified smokers are included into a study restricted to nonsmokers).

1.4. Definitions of ETS, Lung Cancer, and Analytical Cohorts

ETS in General

The term ETS refers to "aged exhaled mainstream smoke (MS) from the smoker, diluted sidestream smoke (SS) emitted from the smoldering tobacco between puffs, contaminants emitted into the air during the puff, and contaminants that diffuse through the cigarette paper" (EPA 1992). In addition, it has been pointed out that ETS from pipe and cigar smoking should be considered in assessing the effect of ETS (Lychou 1986, Pershagen 1986). Few studies

(e.g., Garfinkel 1985, Fontham 1991), have assessed the risk of lung cancer among nonsmokers by type of smoking of spouses. Although both smokers and nonsmokers are exposed to ETS, the effect of active smoking on lung cancer risk would overshadow any small effect of ETS among smokers, and hence most studies, as is this one, are restricted to the nonsmoking population.

Passive smoking is a term that refers to inhalation of ETS by a non-smoker exposed to a smoking environment. The term "involuntary smoking" has the same connotation as passive smoking. These terms, along with "inhalation of second-hand smoke", are no longer in wide use in the recent literature, and we will only refer hereafter to ETS.

ETS Exposure in CPS II

The information on ETS in the CPS II cohort includes:

A. Self reported number of hours exposed to ETS: the average number of hours subjects were reportedly exposed to "the smoke of others" at home, work, and other places, separately, for each of these settings and in total (all settings combined).

B. Spousal ETS exposure: Smoking history as reported by the spouses of nonsmoking subjects, including the type of smoking habits (cigarettes, cigars, pipes), if current or former smokers, and the cumulative exposure to ETS from spousal cigarette-smoking during marriage.

Lung Cancer in General

Lung cancer is a group of malignant neoplasms that arise from: 1) the bronchial or bronchioloalveolar surface epithelium, 2) the bronchial mucous glands, or 3) a combination of the previous. According to the International Classification of

Diseases Ninth revision (ICD-9 WHO 1975), primary cancers of trachea, bronchus, and lung are grouped under the ICD-9 code N 162.0 to N 162.9.

Lung Cancer in CPS II

This is a study of mortality from lung cancer. Therefore, the outcomes refer to deaths for which the underlying cause of death selected by nosologist was coded N 162.

Self-reported and Spousal Exposure to ETS

This terminology distinguishes the study population for which self-reported average number of hours of ETS exposure is used as exposure variable (self-reported ETS) from the population of nonsmoking wives and husbands in CPS II (spousal ETS) that uses spousal exposure data.

Throughout the text other standard epidemiologic nomenclature is used (Last 1988). The glossary at the end of the text contains an exhaustive list of abbreviations used below.

1.5. Significance and Relevance of the Study

CPS II provides a good opportunity to test the ETS-lung cancer hypothesis, with numerous advantages over existing epidemiologic evidence. First, the study provides information on 392,226 non-smokers, on 362 deaths from lung cancer among nonsmokers for analyses of self-reported ETS and 265 lung cancer deaths for analyses of spousal ETS, and 127 lung cancer deaths for dose-response analyses, numbers nearly as large as those of the largest case-control studies (Gao, 1987, Fontham 1991, Brownson 1992) or any other cohort study, including the CPS I (Garfinkel 1983), on this issue. Only four other cohort studies (Hirayama 1981, Hole 1989, Butler 1988) have addressed this issue; of

them only the CPS I study (Garfinkel 1983) had a statistical power greater than 80 percent of detecting a 1.5 increased rate.

Second, the prospective nature of the study limits the possibility of recall bias, since information on exposure was obtained at the beginning of the follow-up. Prevalent cancer cases (i.e., persons with cancer at baseline) were also excluded, limiting the possibility of recall bias.

Third, the information on both active smoking and ETS is unusually detailed and includes both: 1) self-reported average number of hours a person is exposed to the smoke of others (at home, work and elsewhere) and 2) smoking habits of spouses. Spousal smoking provides an important cross-check of the validity of self-reported smoking data. In most cases the spousal smoking information was provided directly by the respondents, unlike many case-control studies which rely on surrogate respondents. CPS II shares this advantage with four smaller cohort studies (Garfinkel 1983, Hirayama 1981, Hole 1989, Butler 1988).

Also, this study provided information to assess the effect of potential bias by active smoking status misclassification (Mantel 1983, Lee 1984). To set the limits of a reasonable bias by misclassification of active smoking status, we needed to obtain estimates of: 1) the concordance of smoking status among spouses (i.e., smoking status as reported by spouses and by study subjects themselves); 2) the association of smoking status, especially of former smoking, a group over-represented among misclassified nonsmokers, and lung cancer; and 3) of the validity of the classification of smoking status. CPS II provides information on smoking habits of members of the same household therefore, the concordance of smoking status among spouse-pairs can be estimated. This along with published estimates of misclassification of active smoking in CPS I and of the association of different cell-types of lung cancer with active smoking provided the necessary data to set limits to potential bias from misclassification of active smoking status.

At the same time, this study assessed potential confounders of the relationship of interest such as age, diet, history of chronic lung disease, and exposure to occupational risk factors such as asbestos exposure, as well as concomitants of socioeconomic status such as education and 'race'.

Finally, this is an important scientific issue and is a subject of ongoing epidemiologic research projects (Coleman 1992). Some ongoing projects on this topic are: 1) a large international collaborative study being conducted in Western Europe and the US; 2) a study planned to collect data from 400 lung cancer cases among nonsmokers in Russia; 3) in the US, two studies, one in Michigan and the other in New York, are in progress.

1.6. Extent of ETS Exposure

Estimates of prevalence of exposure were not available until very recently. The 1988 National Health Interview Survey (NCHS 1988) included a set of questions for adults about their lifetime working status and their work experience in the year before the interview. ETS exposure information was obtained from 44, 233 respondents. Interviewees were asked: "Do you live with a smoker?" and "Do they smoke at home?". According to the 1988 NHIS, about one quarter of adults live with at least one smoker at home, and almost 90 percent of smokers smoke at home. Some of the data obtained in this survey are presented in Table 1.

Preliminary results from the ongoing National Health and Nutrition Examination Survey III (NHANES III), in which serum levels of cotinine are measured to assess exposure to tobacco smoke by persons in the US aged ≥ 4 years, are available. The first 800 samples were tested with a highly specific test for serum cotinine, and all of them had measurable levels of cotinine. Results showed a bimodal distribution, with its antimode around 10-15 ng/mL (MMWR 1993), the cutoff most often used to distinguish smokers from nonsmokers. These data showed the ubiquitious nature of ETS exposure in the US. These preliminary results from NHANES III agree with a previous report by Wald on levels of

serum cotinine among 101 nonsmoking men, who had a mean of 8.5 ng/mL (with a standard deviation of 1.3) (Wald 1984).

A study of 380 nonsmoking participants in a cancer screening program in Buffalo, New York, conducted in 1986, showed that 24.3 percent of men were exposed to the ETS of their wives, whereas 66.0 of the women were married to smoking men. About 70 percent of the participants reported some exposure at home, and exposure at work was reported by 87 percent of subjects (Cummings 1989).

Also, the 1988 NHIS included questions about policies at worksites and exposure to ETS at work, on which a report has been published (MMWR 1992). Half of the smokers in the 1988 NHIS reported some discomfort at work because of the smoke of others, whereas 84 percent of the nonsmokers reported some discomfort from ETS at their workplace.

Thus, from a broad public health perspective, this study has important implications. First, exposure to ETS is preventable by means of regulations at work sites and public places, as has been shown in the US (Fielding 1992). Smoking control measures are implemented by the government and the private sector in the US, and increasingly in the rest of the world. By 1987, in the US, restrictions were in place in more than 42 States and the District of Columbia, for smoking in transportation facilities, hospitals, schools, elevators, government buildings, and recreational facilities. According to the 1988 NHIS data, 40.3 percent of the 114.1 million employed adults in 1988 (who reported that their workplace was not their home), worked in locations where smoking was allowed only in designated areas. This estimate is consistent with results from the 1986 Adult Use of Tobacco Survey, which reported that 42 percent of worksites had restrictive policies (MMWR 1988). An estimate derived from the National Survey of Worksite Health Promotions, showed that 76 percent of work sites with smoking cessation activities had a smoking policy in effect (Fielding 1992).

Table 1. Percent distribution of persons 18 years of age and over by cohabitees smoking status, according to gender, education, occupation, race, and age; United States, 1988.

Characteristics	Live with smoker Yes %	No %	Unknown %	Sample Size
Total	26.6	71.5	1.8	44,233
Gender				
Male	26.2	71.9	1.9	18,562
Female	27.0	71.2	1.8	25,671
Years of education				
≤12	30.6	67.6	1.8	25,671
13-15	28.3	70.0	1.7	9,808
16+	17.8	80.3	1.9	10,990
Occupation				
White collar	22.8	75.3	1.9	22,505
Blue collar/service	33.1	65.2	1.6	6,535
Blue collar/other	30.1	68.3	1.6	13,169
Other	26.2	70.2	3.6	2,024
Race				
White	26.5	71.8	1.7	36,864
Black	28.3	69.3	2.4	6,186
Other	25.2	72.6	2.2	1,183
Age				
18-29	33.6	64.6	1.8	10,516
30-44	27.2	71.1	1.7	13,987
45-64	27.4	70.9	1.8	10,747
65+	13.0	85.0	2.0	8,983

Source: CDC NCHS: Occupational Health supplement to the 1988, NHIS.

The US Public Health Service Centers for Disease Control and Prevention's National Institute for Occupational Safety and Health has recently released a recommendation to reduce ETS in the workplace to the lowest feasible concentration, and suggested to employers "to minimize the occupational exposure to ETS by all available preventive measures" (MMWR 1991).

1.7 Organization of Thesis

In this chapter, we described the aims, specific objectives, and relevance of this study. Definitions of ETS exposure and lung cancer were provided. Chapter 2, deals with the epidemiology of lung cancer, and the role of smoking as a

cause of cancer, as well as other risk factors. The biological plausibility of the carcinogenicity of ETS is reviewed. Special emphasis is placed on reviewing the literature on ETS and lung cancer; a summary estimate of 36 studies is presented and compared with that of the 1992 EPA report. These data are used to illustrate a funneling of estimates by sample size and to assess the potential of publication bias in studies of ETS and lung cancer. The limitations of existing studies on this issue are reviewed. Chapter 3 narrates the methods used in this study, with special reference to the selection of the analytic cohort, specification of exposure and outcome variables, and rationale and description of the statistical modeling used. Also a brief description of the CPS II design is given. The steps followed to validate death certificate data on lung cancer, as well as self-reported exposure to ETS are presented in a separate section of that Chapter. Chapter 4 gives demographic descriptive information for the CPS II entire cohort, the analytic cohort based on self-reported ETS and the analytic cohort based upon spousal ETS and gives a comparison with the entire US population. Chapter 5 presents the results of the validation studies to use lung cancer as underlying cause of death from death certificates as diagnosis of lung cancer, as well as the validity of self-reported exposure to ETS. Chapter 6 provides a description of the exposure variables in the entire CPS II population, and analytical cohorts. Chapter 7 presents the main results of the study based upon the self-reported exposure to ETS at home, work, and other places, and ETS spousal exposure. The relationship of ETS with potential confounders and effect modifiers is also presented. Chapter 8 includes the general discussion and conclusions of the study. The reader will find tables and figures incorporated into the text. Detailed tabular data of existing studies on ETS and lung cancer are given in Appendices, along with the CPS II questionnaires.

Chapter 2: Literature Review and Metanalysis

2.1. Descriptive Lung Cancer Epidemiology

Lung cancers account for 15 percent (or 168,000) of all new cancer cases, and 28 percent of all cancer deaths (or 149,000) in the US (ACS 1993). According to most recently published US mortality statistics, the lung cancer epidemic may have reached its peak among older men (Boring 1993) and is declining among young men and young women (Devesa 1989, Glass 1991). The overall incidence rate based on the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) data was 57 per 100,000 in 1984-1988 (NCI SEER 1991). Whereas both incidence and mortality rates from lung cancer have begun to decrease in men, they continue to increase in women (all ages combined), and lung cancer has now surpassed breast cancer as the most comon cause of death from cancer in women. These changes in the epidemiology of lung cancer are reflected in the male to female ratio among new cases; it was 2:1 in 1984-1988 , but it was 6:1 in the 1960's (Schottenfeld 1975). Age-specific incidence rates of lung cancer increase exponentially with age. This observation has been considered a function of duration of smoking (Doll 1978), although it is argued that there is an independent effect of age at uptake of smoking habits (Molgaavkar 1989). Cohort analysis of lung cancer indicates that incidence peaked among men born between 1925-1930 and among women born between 1935-1940 and declined in subsequent birth cohorts, a pattern that mirrors the changes in the prevalence of cigarette smoking (Devesa 1984, 1989).

In the SEER Cancer Registries data, lung cancer incidence in 1984-1988 was 37 percent greater among blacks (both males and females) than whites (SEER 1991). The race difference has widened since 1969 when the Third National Cancer Survey (Wynder 1975) reported an 11 percent excess for black men compared to white men and no excess for black women in relation to white women, a difference that reflects changes in smoking patterns.

According to the same sources, an increase in the 5-year survival of lung cancer patients from 4 percent to 13 percent among whites and from 5 percent to 11 percent among blacks, was observed between 1950 and 1987 (SEER 1991). However, the overall survival of these cancers remains poor, with a median survival of less than a year from diagnosis (Wetzel 1989). Few reports exist on specific survival rates by stage at diagnosis; in one of them, comprising 999 registered cases at the Northwestern Memorial Hospital from 1976 to 1985, 48.7 percent of the cases had distant spread at the time of diagnosis. Even among patients with localized disease, median survival was only 22 months (Wetzel 1989). This poor survival, in conjunction with secular changes in smoking prevalence and better breast cancer survival rates, explains why, among US women, lung cancer has surpassed breast cancer as the leading cause of cancer mortality among women (Boring 1992).

2.2 Smoking and Lung Cancer

The earliest observations of the association of tobacco and cancer can be traced to 1761 in a report by John Hill, who described cancer of the nose among users of tobacco snuff (Redmond 1970). A literature review by Adler, reported in 1912, could document only 374 lung cancer cases worldwide, and the author suspected that cancer of the lung was decidedly on the increase. In 1918, Yamagiwa and Ichikawa reported on the experimental induction of squamous cell skin cancer by application of coal tar in the rabbit model (Yamagiwa 1918), confirming the early observations of Percival Pott upon scrotal cancer among chimney-sweepers (Shimkin 1975), and thus lending plausibility to the cigarette smoking-lung cancer hypothesis. Specifically the association between tobacco smoking and lung cancer was first reported in Germany based upon clinical and autopsy evidence by Lickint and Hanf in 1928, (Vincent, 1986) and further confirmed by Müller in 1939 (Wynder , 1975). However, it was not until the early 1950's that the major link was established through epidemiologic studies. Following the publication in 1950 of reports from case-control studies describing a strong positive association of smoking and lung cancer (Wynder 1950, Doll 1950, Levine 1950), numerous other epidemiologic studies have consistently

reported increased incidence and mortality from lung cancer among smokers compared with non-smokers, with a "best" estimate of the relative risk of 22 in men and 12 in women (US Surgeon General 1989). Tobacco smoking also is associated with cancer of five other sites (larynx, buccal cavity, pharynx, esophagus, and bladder), and though not firmly established, it may be a cause of cancers of the pancreas, kidney, stomach, cervix and leukemia (Thomas 1992, Garfinkel 1990). More than 50 independent case-control studies and eight cohort studies consistently reported associations between smoking habits and overall, lung cancer, other upper respiratory and digestive cancers, chronic bronchitis, coronary disease, and peptic ulcer mortality. Smoking is also responsible for an excess of deaths from cardiovascular diseases that until recently, surpassed the magnitude of smoking-attributable lung cancer mortality in the US (Shopland 1991). Smoking also increases blood pressure. Also, parental smoking is associated with major reproductive disorders such as low birthweight, including the so-called fetal tobacco syndrome (Thomas 1992), and birth defects (Kelsey 1978). Last, smoking is a cause of several gastrointestinal and mouth diseases, such as peptic ulcer disease and gingivitis (Thomas 1992).

2.3. Biological Plausibility

More than 4000 chemical compounds have been identified in ETS (Surgeon General 1986, IARC 1987, NRC 1986, EPA 1992, O'Neill 1987, Löfroth 1989, Claxton 1989), of which eighteen are known carcinogens: benzene, formaldehyde, hydrazine, N-nitrosodimethylamine, N-nitrosopyrrolidine, 2-toluidine, 2-naphtylamine, 4-aminobiphenyl, benz[α]anthracene, benz[α]pyrene, γ-butyrolactone, quinoline, N'-nitrosonornicotine, NNK [or 4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone], N-nitrosodiethanolamine, cadmium, nickel, and ^{210} Polonium. Five studies measuring personal exposure to particulate matter associated with ETS for nonsmokers, and another five on exposure to airborne nicotine associated with ETS, were reviewed in a recently published report of the Environmental Protection Agency (EPA 1992). Accordingly, particle mass due to ETS in the respiration zone of nonsmokers ranges from 18.4 to 64 $\mu g/m^3$, and 0.1 to 40 $\mu g/m^3$ of nicotine.

The size of the SS particles is smaller and dilutes more rapidly in air, than MS particles. Some carcinogens, like nitrosamines, benzo[a]pyrene, benzene, cadmium, nickel and aromatic amines, are found in larger quantities in SS than in MS. The NRC reports pointed out that "constituents of the vapor phase such as N-nitrosamines would be more likely to remain in the ambient air for longer spans of time ". For instance, two constituents of the vapor phase are N-nitrosodimethylamine and benza[a]pyrene. They are found at a 20 to 100 SS /MS ratio (range in SS: 200-4000 ng), and a 2-4 ratio (range in SS: 40-280 ng), respectively.

Smoke of cigars and pipes carries more carcinogens than do cigarettes, in addition to the obvious observation that they produce smoke in larger volumes than do cigarettes. In particular, the smoke of cigars contains more benz[a]pyrene and pyridine, whereas that of pipes has more tar (Shephard1982, Appel 1990).

A model-based approach (Repace 1980, Repace 1982) was used in a report of the National Research Council (NRC 1986) to describe ETS exposures. As illustration of this model, the NRC report presented a range of 10 to 100 total respirable particulate matter emitted ($\mu g/m^3$) "in a residence with one smoker smoking at a rate of either 1 or 2 cigarettes per hour for the range of mixing, ventilation, and removal rates occurring in residences under steady-state conditions" (NRC, 1986).

2.4 Epidemiological Evidence

Two seminal reports (Hirayama, 1981, Trichopoulos 1981) implicated ETS as a risk factor for lung cancer among non-smokers. These two, along with 34 other reports are summarized in Table 2. A detailed review of most of these studies can be found in the Appendix of the 1992 EPA report, but it is worth summarizing their key features: 1) without exception they are restricted to nonsmokers, 2) most of them have concentrated on women, 3) 32 are case-

control studies, 4) ETS exposure has been measured in terms of spousal smoking history reported by cases or next-of-kin, most of them have relied on exposure information from proxy respondents, and 5) most of them had little statistical power for detecting a weak association.

The original reports from 36 studies were reviewed and we abstracted information on the association between having a smoking spouse and the occurrence of lung cancer. Confidence limits for the studies in Table 2 are shown in Figure 1, arranged by sample size. Nine of these 36 studies reported a positive, statistically significant association; in three other instances a positive and borderline significant association was found (i.e., point estimate above one and lower 95% confidence limit=0.9). A negative point estimate was reported in eight studies, but none of these negative studies was statistically significant. Only twelve studies had at least a 50 percent statistical power (i.e., information on at least 100 lung cancer cases or deaths among nonsmokers) of detecting a risk ratio of 1.34, the hypothesized size of the ETS effect on lung cancer risk in the NRC meta-analysis.

A summary estimate over these 36 studies was obtained using precision-based estimators (i.e., weighting each study by the inverse of the variance of the RR on the logarithmic scale): ETS during adulthood (i.e., married to smoking spouse) increases the risk of lung cancer among nonsmokers by 20 percent (95 percent confidence interval (95% CI)= 1.1-1.3) (See Appendix A, for 2x2 tables of these studies and calculations). Moreover, in most studies, even in those who did not find an overall association, there was evidence of a dose-response relationship between ETS exposure and the risk of lung cancer among nonsmokers.

The funnel plot in figure 2, shows the inverse relationship between precision and sample size. Vandenbroucke and Mantel have argued that there is some evidence of a publication bias, since there is a deficit of small negative studies, depicted in figure 2 in the lower left of the funnel plot (i.e., the non-significant small negative studies) (Mantel 1990, Vandenbroucke 1988). However, four small negative studies are shown in this plot. Even if this deficit exists it would be

largely overwhelmed by the number of both positive and negative large studies in the right section of the plot. A closer examination of studies by country, as reported in the 1992 EPA report, shows that two large studies in China (Wu-Williams 1990, and Gao 1987) reported statistically significant inverse associations, whereas those in Japan and Europe were more likely to be positive and to report stronger associations as compared to US studies.

Our metanalysis summary estimate of the RR is remarkably close to that of the EPA report on US studies, which is 1.19. The EPA report made a downward adjustment by misclassification bias and reduced the observed associations. Since on average that adjustment represented less than 10 percent of the point estimates, ours and those of the EPA report are approximately the same.

2.5 Collateral Evidence

In support of the role of ETS as cause of lung cancer among nonsmokers, a recently published autopsy-based study (Trichopoulos 1992) documented an increase of pre-cancerous lesions due to ETS, opening a new research avenue on this issue. Another piece of epidemiological evidence that supports the claim that ETS causes lung cancer derives from a study of lung cancer among dogs in relation to the smoking habits of their owners. The authors found an association of magnitude similar to that reported in humans for ETS and lung cancer risk. Interestingly, also the authors noted that the association held for brachicephalic/mesocephalic dogs but not for dolicocephalic dogs, a fact interpreted by the researchers consistent with an effect from exposure to volatile smoke particles as those of ETS (Reif 1992). This study reinforces the findings of experimental studies of lung tumors among male beagles trained to smoke through a tracheostomy: the authors concluded that smoking of cigarettes greatly increased the development of such tumors (Auerbach 1970).

Table 2
Summary of 36 epidemiologic studies on ETS and lung cancer risk, from 1981 to 1993. Point estimates and 95% confidence intervals of the association of lung cancer and spouse'smoking habits

No	Author	Design	Study Size[1]	Weight [2]	Estimated RR	Source
1.	Hirayama	Cohort	174 deaths	142.0	1.5 (1.1-2.1)	Lancet 1981
2.	Garfinkel	Cohort	153 deaths	88.0	1.2 (0.9-1.4)	JNCI 1983
3.	Hole et al.	Cohort	9 deaths	7.0	2.1(0.5-14.7)	BMJ 1989
4.	Butler	Cohort	8 deaths	2.0	2.0(0.6-6.7)	UCLA 1988
5.	Trichopoulos et al	Case-control	77 cases	12.7	2.1(1.2-3.7)	Lancet 1983
6.	Chan & Fung	Case-control	86 cases	12.8	0.8(0.4-1.3)	Grundmann, 1982
7.	Correa et al.	Case-control	32 cases	6.8	3.1(1.5-6.8)	Lancet 1983
8.	Buffler et al.	Case-control	52 cases	8.5	0.8(0.4-1.6)	Mizell 1983
9.	Dahlager et al.	Case-control	48 cases	8.3	1.5(0.8-2.8)	Cancer Res 1986
10.	Kabat & Wynder	Case-control	36 cases	4.5	0.9(0.3-2.2)	Cancer 1984
11.	Garfinkel et al.	Case-control	134 cases	22.2	1.2(0.8-1.9)	JNCI 1985
12.	Wu et al.	Case-control	31 cases	7.1	1.2(0.6-2.5)	JNCI 1985
13.	Akiba et al.	Case-control	113 cases	19.7	1.9(1.2-3.0)	Cancer Res 1986
14.	Lee et al.	Case-control	47 cases	7.3	1.1(0.5-2.3)	BJC 1986
15.	Gao et al.	Case-control	436 cases	61.2	0.8(0.6-1.0)	IJC 1987
16.	Koo et al.	Case-control	86 cases	12.9	1.5(0.9-2.7)	IJC 1987
17.	Pershagen et al.	Case-control	77 cases	16.4	1.2(0.7-2.1)	AJE 1987
18.	Humble et al.	Case-control	28 cases	5.3	3.2(1.4-7.9)	AJPH 1987
19.	Browson et al.	Case-control	19 cases	2.0	1.8(0.4-7.5)	AJE 1987
20.	Lam et al.	Case-control	199 cases	30.6	1.6(1.2-2.3)	BJC 1987
21	Lam & Cheng	Case-control	60 cases	10.1	2.0(1.1-3.8)	Lee, 1992
22.	Shimizu et al.	Case-control	90 cases	14.1	1.1(0.7-1.9)	TJEM 1988
23.	Inoue	Case-control	22 cases	2.9	2.6(0.8-9.9)	Smk& Hlth 1987
24.	Geng et al.	Case-control	54 cases	8.1	2.2(1.1-4.3)	Smk& Hlth 1987
25.	Svensson et al.	Case-control	34 cases	6.0	1.3(0.6-2.9)	Acta Oncol 1989
26.	Janerich et al.	Case-control	191 cases	14.0	0.9(0.6-1.6)	NEJM 1990
27.	Stockwell et al.	Case-control	210 cases	9.6	1.6(0.8-3.0)	JNCI,1992
28.	Kalandidi et al.	Case-control	91 cases	11.2	1.6(0.9-2.8)	Can Ca Cil 1991
29.	Sobue et al	Case-control	144 cases	29.6	1.1(0.8-1.6)	Ga No Rin 1990
30.	Katada et al.	Case-control	17 cases	0.4	NC(0.6- NC)	Ga No Rin 1988
31.	Wu -Williams	Case-control	417 cases	61.3	0.8(0.6-1.0)	BJC,1990
32.	Kabat et al.	Case-control	89 cases	16.0	1.0(0.6-1.7)	Lee 1992
33.	Liu et al.	Case-control	54 cases	5.6	0.7(0.3-1.8)	IJE 1991
34.	Fontham et al.	Case-control	420 cases	59.4	1.4(1.1-1.8)	Cancer Epid 1991
35.	Browson et al.	Case-control	451 cases	78.6	1.0(0.8-1.2)	AJPH 1992
36.	Liu et al.	Case-control	38 cases	5.7	1.7(0.7-3.8)	AJE 1993
	Total		4,227	802.6	1.2(1.1-1.3)	

[1]Number of lung cancer cases; [2] Inverse of the variance of the logarithm of the RR estimate

Figure 1. Relative risk of lung cancer from 36 studies of nonsmokers exposed to ETS, 1981 to 1993

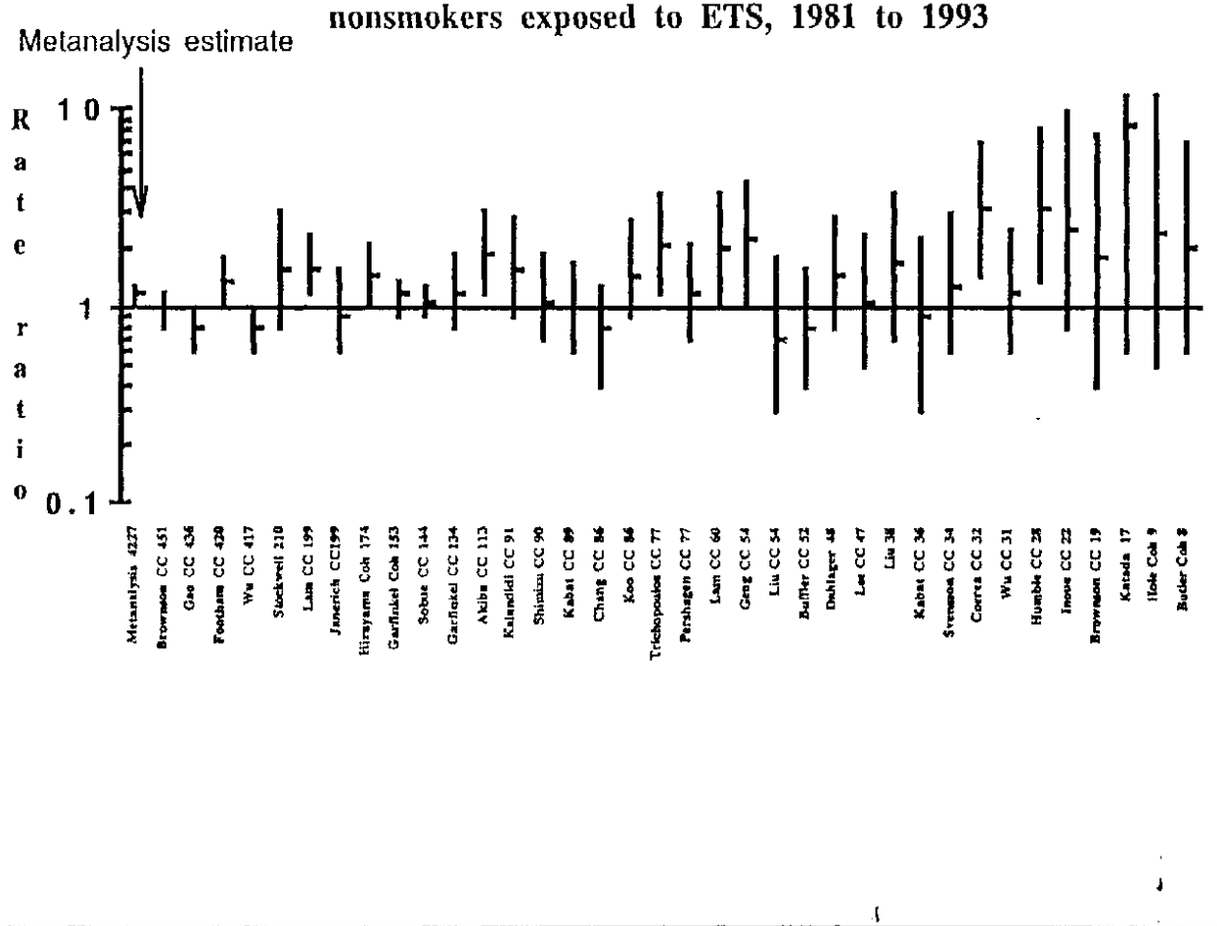


Figure 2. Funnel plot of relative risk (on log scale) according to the size of SD (ln RR) of 36 studies of lung cancer and ETS spousal exposure

2.5 Collateral Evidence

In support of the role of ETS as cause of lung cancer among nonsmokers, a recently published autopsy-based study (Trichopoulos 1992) documented an increase of pre-cancerous lesions due to ETS, opening a new research avenue on this issue. Another piece of epidemiological evidence that supports the claim that ETS causes lung cancer derives from a study of lung cancer among dogs in relation to the smoking habits of their owners. The authors found an association of magnitude similar to that reported in humans for ETS and lung cancer risk. Interestingly, also the authors noted that the association held for brachicephalic/mesocephalic dogs but not for dolicocephalic dogs, a fact interpreted by the researchers consistent with an effect from exposure to volatile smoke particles as those of ETS (Reif 1992). This study reinforces the findings of experimental studies of lung tumors among male beagles trained to smoke through a tracheostomy: the authors concluded that smoking of cigarettes greatly increased the development of such tumors (Auerbach 1970).

Figure 3. Hypothetical cohort study of nonsmokers to show the effect of misclassification of smoking status on lung cancer rates by spousal ETS (adapted from NCR 1986).

A.
True distribution

1,000,000 population

62% ever smokers and 38% never smokers

		Gold standard +	-	Total
Questionnaire	+	595,000	5,000	600,000
	-	25,000	375,000	400,000
Total		620,000	380,000	1,000,000

Observed distribution under 3% misclassification: 60 % ever smokers and 40 % never smokers

B.

1,000,000 population

smokers: 620,000 — 375,000 non smokers

smokers misclassified as nonsmokers: 25,000

CPS II estimates of concordance of smoking:

64% of smokers are married to smokers → 16,000 smokers; 9,000 nonsmokers

46% of nonsmokers are married to nonsmokers → 202,500 smokers; 172,500 nonsmokers

C.
RR of 5 cancer of the lung for active smoking assumming most misclassified smokers are truly former smokers

Rate of lung cancer death: (per year)	5.0 0.0004	5.0 0.0004	1.0 0.00009	1.0 0.00009
Number of deaths: (in six years)	38.4	21.6	109.4	93.2

D.
Observed study

	Spouse smoking status: Smoker	Nonsmoker	
Cases	148	115	RR=1.07
Person-Years	1,310,926	1,088,943	

nonsmokers: in CPS II sixty-four percent of the smokers were married to smokers, and 46 percent of nonsmokers were married to nonsmokers. Another key factor for this misclassification bias to take place is a strong relationship of the outcome under study with active smoking: in this example, we assume a five-fold increased risk of death from lung cancer among smokers due to the fact that 70% of those deaths would be adenocarcinomas, hence an estimate of the relative risk of 4 for adenocarcinomas was used (Cfr. Brownson 1986), and weighted for 50% as former smokers, since most misclassified smokers would be actually former smokers (Cfr. Lee 1988). A reasonable estimate of the effect of smoking among misclassified smokers would be 5, because most of them would be former smokers. The rates of lung cancer death among nonsmokers in CPS II is 11 deaths per 100,000 (Garfinkel 1991). Knowing that only 3 percent of the population in this study is formed by smokers., using the relationship of total incidence, in this case mortality, to calculate the rates among the unexposed* : $M_0 = \frac{M_t}{(OR * P_e) + P_0}$ (Hennekens and Buring 1987) we arrived at the rates among truly classified nonsmokers. Therefore, the observed 7 percent increase is only due to misclassification of smoking status.

The argument of bias from misclassification of active smoking status assumes that smoking spouses would have the same survival as nonsmokers. Indeed, subjects with a history of regular cigarette smoking have 24% (95% CI= 1.20-1.28) increased risk of deaths from all causes as compared to never smokers (US DHHS: Surgeon General 1989). This assumption would work in the opposite direction of the misclassification bias. For instance, history of current ETS exposure among nonsmokers who were exposed in the past, might bias study results towards the null because of poorer survival of heavy smokers.

* Notation M_0=mortality among the unexposed; M_1=mortality among the exposed; P_e=proportion of the population exposed and P_0=proportion of the population unexposed.

same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposure to ETS lead to the conclusion that involuntary smoking is a cause of lung cancer."
Blot and Fraumeni published a general review of the available epidemiologic evidence about the time of the publication of the NRC report, and provided a relative risk summary estimate of 1.3 (95% CI=1.1-1.5) (Blot and Fraumeni 1986).

Fleiss and Gross found the conclusions in the NRC report "unwarranted given the poor quality of the studies on which it (was) based." However, their assessment of nine US studies in the NRC meta-analysis, found no evidence of study-to-study heterogeneity, and is consistent with a small, although not statistically significant, increased risk (Fleiss 1991).

The effect of ETS on other diseases and adverse outcomes, is beyond the scope of this document, but it has been reviewed in detail in Working Group on Passive Smoking (Spitzer 1990). Risk assessment of ETS is a subject of many letters, editorials, articles and monographs in the scientific and medical literature (Mantel 1992, Steenland 1992, Glantz 1991, Vandenbroucke 1988, Wells 1988, Glantz 1992, Lee 1992a, Heath 1993).

2.7 Other Risk Factors

Ionizing radiation, including both α-rays, emitted by radon dust particles, and x-rays, asbestos, arsenic and nickel compounds, polycyclic aromatic hydrocarbons, hexavalent chromium, mustard gas, and other environmental and occupational exposures have been documented as risk factors for lung cancer (Blot 1984). A study by Selikoff, Hammond, and Churg showed that smoking and asbestos exposure have more than additive joint effects on the risk of lung cancer (Selikoff 1968). Previous lung diseases such as pneumonia, chronic bronchitis, asthma, and tuberculosis are known risk factors for lung cancer among nonsmokers (Alavanja 1992). Studies conducted in the 1980's using

In addition to the argument of bias from misclassification of active smoking, there are two other validity issues that have been brought into the discussion of the ETS-lung cancer hypothesis. Figure 2, presented a funnel plot that shows little indication of a publication bias. A similar plot based upont the published studies by 1988 led to argue that there was a publication bias on this issue (Vandenbroucke 1988). However, based upon the available information by 1994, it seems unlikely that those unpublished studies would have outnumberedbthe large positive studies, and even less likely, that they would have outweighed the summary estimates such as those presented in reports by NRC, Fleiss, EPA and before in 2.4.

Finally, some researchers have suggested that the potential of confounding by some unspecified potential confounder such as socioeconomic status has been overlooked. For instance, it is argued that low socioeconomic status is associated with increased risk of cancer, and at the same time, smoking is more prevalent among the poor. This led Mantel to formulate the following hypothesis to explain the ETS-lung cancer association: (nonsmoking) "wives of smoking husbands would be affected by the concomitants of socioeconomic levels" (Mantel 1992). Most studies, however, have controlled for socioeconomic status or proxy variables of socioeconomic level, such as 'race' and education, and have still found an association between lung cancer and ETS.

A recent review by Lee (1992b), concluded that: "Taken as a whole, the evidence reviewed does not demonstrate that exposure to environmental tobacco smoke increases risk of cancer, heart disease or other diseases among adult non-smokers." Four of the other major six reviews, however, agree that ETS is causally related to lung cancer, and we excerpted the following conclusions.

The NRC report (NCR 1986) stated the misclassification bias pointed out by Lee "is not likely to account for all the increased risk." The Surgeon General's report (US DHHS Surgeon General 1986) concluded "The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the

stronger association with smoking. Kreyberg type II included adenocarcinomas and mucous-gland tumors, frequently diagnosed among non-smokers and women. A so-called third Kreyberg group, showing intermediate strength of association with active smoking, includes adenosquamous, anaplastic, and undifferentiated carcinomas. A recently published large multicenter case-control study of lung cancer in non-smoking women included histologically confirmation, and reported a more specific association of ETS with adenocarcinomas (78 percent of all cases) than with the other histologic types (Fontham 1991). Some previous studies, such as those by Kabat and Wynder, and CPS I (Garfinkel 1981), had found a smaller proportion of adenocarcinomas (i.e., 55% and 56%, respectively) (Kabat 1984). However, the validity of the Kreyberg dichotomy has been increasingly questioned given the recent trends in lung cancer histopathology.

2.9 Measurement of ETS Exposure

Ideally ETS should be measured directly using 1) air samples of ETS pollutants in various settings (home, work, and other places) or 2) highly specific biomarkers such as cotinine in saliva, blood and urine. Measurements of cotinine (a nicotine metabolite) in serum, urine and saliva have been used effectively to quantify exposure to tobacco smoke (Wall 1988). A highly specific technique for serum cotinine has been developed recently to measure levels as low as 0.03 ng/mL (MMWR 1993). Today, questionnaires are the most commonly used method, and have unique advantages over direct measurements. The most important advatage is that questionnaires can describe past exposure that is relevant for diseases of long latency such as cancer. However, the extent of misclassification of self-reported ETS exposure may be extensive (Pron 1988). Questionnaires are also an inexpensive method that can be used in large studies.

Studies conducted to assess sources of ETS have consistently reported that ETS was ubiquitous at settings such as the workplace (Cummings 1989) and therefore

sera banks from prospective studies explored the effect of different nutrients on the subsequent risk of cancer (i.e., nested case-control studies). Lower levels of serum β-carotene were found among persons who subsequently became cases than among controls as recently reviewed by Comstock et al. (Comstock 1992). Fontham reviewed dietary studies on this issue and reported that they have been notably consistent in finding an approximate 50% reduction in risk associated with high, compared with low consumption of carotene containing fruits and vegetables (Fontham 1990). Dietary fat intake has been implicated as a risk factor for lung cancer in one large case-control study (Alavanja, 1993). Empirical evidence coming from case-control studies reporting an apparent effect of family history of cancer; pedigree studies, variations in carcinogen-metabolizing enzymes and chromosomal markers are also consistent with the hypothesis of inherited susceptibility (Mulvihill 1984, Kellerman et al. 1973, Weston et al. 1991, Caporaso et al. 1990). Three studies of twins have shown a familial proclivity to smoking (Mulvihill 1984).

2.8 Lung Cancer Classification

Tumors of the respiratory tract include neoplasms of the oropharynx, larynx, trachea, lungs, and pleura. Epithelial malignant tumors comprise, according to the World Health Organization, the following major histological types of lung tumors: 1) squamous cell carcinoma, formerly called epidermoid carcinomas, 2) adenocarcinomas, 3) small cell carcinoma, including oat cell carcinoma, and 4) large cell carcinoma (Sobin, 1981). Estimates of the proportion each type represents vary depending on the source data (i.e., biopsy cytology, surgical specimens, autopsy), and range from 33-64 percent, 16-26 percent, 9-20 percent and 19-25 percent respectively, of all malignant pulmonary neoplasms (Minna 1989, NCI SEER 1991). In 1962, Kreyberg divided lung cancer into two groups according to the strength of its association with active smoking (Kreyberg 1962). This classification was based upon observation recorded in the cohort study of British physicians (Doll 1957). Squamous cell, small cell carcinomas, and large cell carcinomas fell into the Kreyberg type I for those who had a

Chapter 3: Methods

3.1 The Cancer Prevention Study II

Study Population: The Cancer Prevention Study II

a) Recruitment

CPS II is a cohort study of 1,185,124 men and women whose mortality experience has been ascertained since 1982. CPS II is the third large prospective study sponsored by ACS. A key feature of the ACS studies is that volunteers invite family groups among their relatives, friends, and neighbors to participate in the study. The volunteers then assist in follow-up. The first study, often referred to as the Hammond-Horn study (Hammond 1958), was comprised of 188,000 white men 59-69 years-old living in 394 counties in nine states, recruited by 22,000 volunteers, and followed for 44 months, from 1952 to 1955. That study was a landmark in epidemiologic studies of cancer and provided compelling evidence for the causal role of active smoking on lung cancer and other diseases. In the next study, the Cancer Prevention Study I (CPS I), 68,116 ACS volunteers recruited a cohort of 1,078,894 men and women, aged 35-84 at enrollment and followed them over a 12-year period (Hammond 1966).

Enrollment in CPS II began in September 1982 and was essentially completed by the end of November 1982. Approximately 77,000 ACS volunteers enrolled consenting families if at least one household member was 45 years or older, enrolled all family members who were 30 years or older. Enrollment of subjects was carried out in all 50 states, the District of Columbia, and Puerto Rico. Volunteers were asked to include families they thought would remain in the local area for the next six years (Stellman 1986).

exposure sustained in the workplace makes an important contribution to lifelong exposure. Two studies have reported that spouses are a very important source of ETS exposure and that by itself explains most of the total exposure (Becher 1992, Emmons 1992). Moreover, the validity and reproducibility of spousal ETS exposure assessment is greater than that of self reported ETS (Pron 1988, Gann 1988). Another large study among ex-smokers and nonsmokers who were under the Kaiser-Permanente Medical Care Program was conducted to estimate and identify the frequency and determinants of ETS exposure: age was found inversely related to ETS exposure, as was education to duration of self-reported ETS exposure (Friedman 1983). Evidence of denying of ETS exposure by subjects with less schooling was also found, leading the authors to suggest that "further effort be devoted to improving methods for assessing passive smoking by questionnaire". . Nonsmokers with history of atopy or any respiratory illness were found more likely to report ETS exposure than subjects with no such history (Cummings 1991), implying that these subjects "are more likely to experience adverse acute reactions to ETS than people without such a medical history", suggesting individual differences in sensitivity to ETS.

A study of the correlation of urine cotinine of infants with the smoking status of household members showed that this marker of tobacco exposure had a median of 1.6 μg/L for infants unexposed at home, that it was lower among infants living with smoking cohabitees but whose mothers were nonsmokers (median 8.9μg/L) as compared to the levels of those infants whose mothers were the only smokers in the households (median 28 μg/L). In turn, the level of urinary cotinine among infants of smoking mothers who also had other smokers among the household members was even higher: 43 μg/L (Chilmonczyk 1990). This study result underscores the importance of: 1) the number of smokers among cohabitees as source of exposure to ETS, and 2) of the relationship between family members who smoke and nonsmokers in determining the intensity of exposure to ETS in households.

cigarettes, cigars or pipes per day and duration of smoking habits was elicited for both current and former smokers.

3.2. Published Results from CPS II

CPS II has already provided important information published in 32 papers in journals and book chapters, on different issues such as: 1) smoking trends and projected mortality from lung cancer in the US (US Surgeon General 1989, Stellman 1988, Garfinkel 1991) and in economically developed countries (Peto 1992); 2) a protective effect of regular aspirin use on the risk of fatal colon cancer (Thun 1991), as well as the effect of dietary fiber (from vegetables and grains), physical activity, obesity and dietary fat on the risk of fatal colon cancer (Thun 1992); 3) the assessment of the risk of exposure to diesel exhaust (Boffetta 1988); 4) artificial sweetener use (Stellman 1988); 5) estrogen-related cancers and smoking (Garfinkel 1990); 6) leukemia and smoking (Garfinkel 1990); 7) the validation of follow-up procedures in CPS II through the National Death Index (Calle 1993), and 8) the relationship between hair dye use and fatal cancers (Thun 1994).

3.3 Main Design Features

This is an ongoing prospective cohort study. By design, no new enrollees were allowed after 1982; therefore, CPS II is a closed cohort study. Individuals leave the cohort either because they die or because they are lost to follow-up. The mortality rate ratio is the parameter of interest (i.e., the measure of association of choice in this study), given the absence of incidence data in this study. In a cohort study, individuals contribute varying amounts of time under observation. Therefore, the statistical analysis for cohort studies with time-to-event-data is based upon survival techniques. In survival analysis the variable under observation becomes time to event (death from lung cancer or censoring). In our analyses, we considered as censored observations those individuals who

b) Follow-up

The participants' vital status was determined using two approaches from the month of enrollment in the Fall of 1982 through December 31, 1989. All volunteers made personal inquiries in September of 1984, 1986, and 1988 to determine whether their enrollees were alive or deceased and to record the date and place of all deaths. Since 1988 a new approach was used: automated linkage through the National Death Index (NDI) to extend follow-up through December 1989 (Calle 1993) and to identify deaths among 21,704 (1.8%) persons lost to follow-up between 1982 and 1988. By December 1989, 101,541 participants (8.6%) had died, 1,080,689 (91.2%) were considered alive, and 2,894 (0.2%) had follow-up truncated on September 30, 1988. Specifically this group comprises persons who were followed by ACS volunteers through that point in time but who had insufficient data on names and date of birth to be sent to NDI for matching using the linkage system. Death certificates were obtained for 96.8 percent of persons known to have died. Using the system described in the International Classification of Diseases, 9th Revision (ICD-9), a nosologist coded lung cancer deaths according to the ICD-9 code (WHO 1979).

c) Baseline Questionnaire

Persons enrolled in the study completed and returned a self-administered, four-page confidential questionnaire that covered 400 items. Appendix C includes a copy of the CPS II questionnaires for men and women. Baseline questions included personal identifiers, height, weight, demographic characteristics, personal and family history of cancer and other diseases; use of medicines and vitamins; occupational exposures; menstrual and reproductive history; diet and drinking habits; and other habits, including active and passive smoking (See below). To classify the active smoking status, participants were asked the standard question: "Do you now or have you ever smoked cigarettes at least one a day for one year's time?". The questionnaire for men also inquired about cigar and pipe smoking. For every type of active smoking, information on number of

c) Persons of 30 years and more.
d) Persons of all races.
e) Period of follow-up: September 1, 1982, through December 31, 1989.

b) Exclusion Criteria

We will exclude from analysis the following persons:
a) Current and former active smokers.
b) Persons with incomplete or unclassifiable data on smoking habits.
c) Persons who had cancer (except non-malignant melanoma skin cancer) at the time of the interview, or whose cancer status was unknown.
d) For the analyses of self-reported ETS exposure, we will exclude nonsmoking participants with unclassifiable information on self-reported ETS exposure in any of the following settings: home, work or elsewhere.
d) For the analyses of spousal ETS exposure, we will also exclude nonsmoking participants whose spouses are not in the study.
e) persons whose spouses have incomplete or unclassifiable data on smoking habits.
f) Analyses of intensity, duration and a combined measure of intensity and duration of ETS from spousal smoking will be restricted to cigarette smoking spouses (current and former) with complete data, and who were married only once (both the nonsmokers and their spouses) at time of interview, and who had complete information on age at first marriage (both for the nonsmokers and their spouses).

The analyses of self-reported ETS exposure include 392,226 subjects and 362 deaths from lung cancer. Three people, two women and one men, died shortly after enrollment, and thus did not contribute person-time, and hence were excluded from analyses, bringing the number of subjects down to 392,223 subjects and 362 deaths for most analyses using person-time. The cohort of nonsmokers for ETS from spousal smoking includes 314,108 participants and 265 lung cancer deaths. One of those persons who died promptly after enrollment was a nonsmoking husband and thus did not contribute person-time either, and hence was excluded from analyses: for analyses based upon person-

remained alive at the end of the study period (i.e., seven years of follow-up), as well as those with truncated follow-up or who died from causes other than lung cancer. Failure times are computed for all individuals to date of death of subjects who died from lung cancer, our event of interest, or from the remaining causes of death, and time to end of the study for all others.

As with any observational study, cohort studies are subject to potential confounding. In cohort studies, stratification and multivariate analyses can be used to control for confounding. In addition, statistical modeling (i.e., proportional hazards (Cox 1972) regression model or Poisson regression) can be used to estimate the ratio of incidence or mortality rates. Cox regression analysis can provide estimates of the effect of both continuous and discrete variables and for time varying covariates (Breslow 1987). Cox proportional hazard modeling was the primary analytic method used in this study.

3.4. Sub Cohort of Interest: Definition and Source Population

As mentioned above, the study population is restricted to non-institutionalized individuals 30 years and older of households in which at least one household member was 45 years old. This study will concentrate on nonsmoking participants and their spouses, after applying the inclusion and exclusion criteria described below. A nonsmoker in CPS II is defined as someone who never smoked cigarettes, pipes or cigars or who smoked or smoked less than one of these tobacco products a day for one year's time. The distribution of smoking habits in the CPS II at time of enrollment is shown in Table 3.

3.5. Eligibility

a) Inclusion Criteria

We will include:

a) Never smokers.

b) Both men and women.

Table 3. Smoking habits at time of enrollment* of the CPS II population according to gender

Smoking Habits	Males	Females	Total
Never smoked regularly	127,165 (25.0)	355,519 (52.6)	482, 684 (40.7)
Current cigarette smokers	105,954 (20.8)	135,092 (20.0)	241,046 (20.3)
Former cigarette smokers	157,734 (31.0)	138,957 (20.5)	296,691(25.0)
Current pipe/cigar and cigarette	14,120 (2.8)	–	14,120 (1.2)
Pipe/cigar smokers never smoked cigarette	22,529 (4.4)	–	22,529 (1.9)
Ex-cigarette, ex-pipe/cigar	34,649 (6.8)	–	34,649 (2.9)
Ex-pipe/cigar, current cigarette	19,031 (3.7)	–	19,031 (1.6)
Ex-cigarette, current pipe/cigar	11,272 (2.2)	–	11,272 (0.9)
Uncertain whether current or former cigarette smoker	–	12,822 (1.9)	12,822 (1.1)
Unclassifiable	16,140 (3.2)	34,140 (5.0)	50,280 (4.2)
Total	508,594 (100.0)	676,530 (100.0)	1,185,124 (100.0)

Source: ACS, CPS II documentation codebook.
*–18 study participants died shortly after enrollment and did not contribute person-time, and four had less than 28 years of age at enrollment.

time data there were 314,107 subjects and 265 lung cancer deaths. Table 4 gives the details of the application of the exclusion criteria to select the major analytic cohorts.

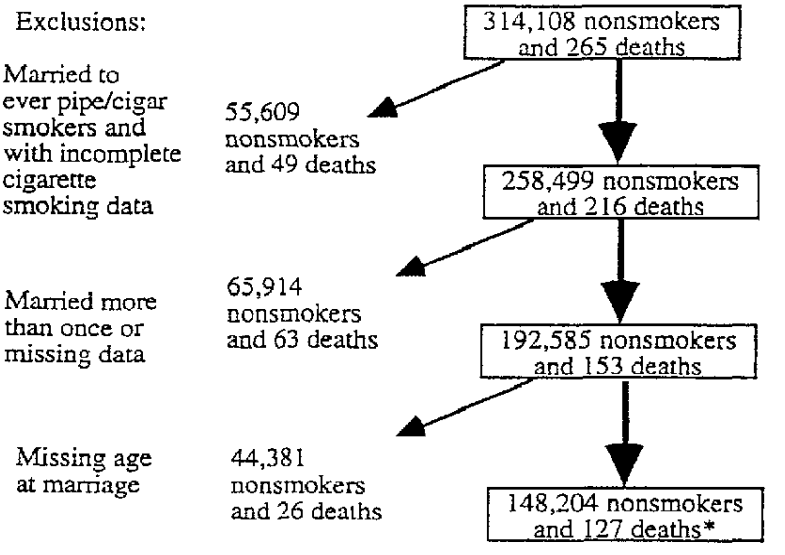
Another subset of nonsmokers was used as analytic cohort for dose-response analyses of cigarette smoking of the spouses. The time they were married to spouses was estimated, to assess the effect of this variable as well as that of the pack-years smoked during marriage by smoking spouses. Therefore, we excluded those spouses married more than once, since the information available on age at marriage in the CPS II questionnaire referred to age at first marriage. In addition to these missing values, there were also missing values (i.e., blanks) for the number of times married. Figure 4 shows the sequential application of theses exclusion criteria for analyses of dose-response of ETS from spousal smoking.

3.6. Variables

Status

The vital status as of December 31, 1989 is a variable assumed one of the following values: 1) alive, 2) dead, 3) those who had follow-up truncated on September 1, 1988. The length of follow-up was the difference between date of entry, and date of follow-up truncation (i.e., September 1, 1988), date of death, or December 31, 1989, otherwise. Informative events were deaths from lung cancer; if subjects died from other causes, they were censored observations, as were losses to follow-up and subjects alive at the end of the follow-up period.

Figure 4. Exclusions for analyses on dose-response of ETS from spousal cigarette smoking



*Population of 148,204 comprises study group for tables 23, 38-40

Main Outcome

Death from lung cancer: Subject reported as deceased as of December 31, 1989, from cancer of the trachea, bronchus and lung (ICD-9 codes 162.0 to 162.9) as the underlying cause of death.

Table 4
Number of CPS II persons and deaths from lung cancer (ICD-9 162) at baseline and number of eligible for analyses of self-reported and spousal ETS exposure

	Women				Men				Total			
	Persons	(%)	Deaths	(%)	Persons	(%)	Deaths	(%)	Persons	(%)	Deaths	(%)
Total Cohort	676,530	(100.0)	2,686	(100.0)	508,594	(100.0)	5,470	(100.0)	1,185,124	(100.0)	8,156	(100.0)
Exclusions												
1) Ever smoked	286,871	(42.4)	2,190	(81.5)	365,289	(71.8)	5,174	(94.6)	652,160	(55.0)	7,364	(90.3)
2)Unclassifiable smoking	34,140	(5.0)	95	(3.5)	16,140	(3.2)	137	(2.5)	50,280	(4.2)	232	(2.8)
3) With cancer at baseline:												
a) lung	154	(0.0)	38	(1.4)	28	(0.0)	10	(0.2)	182	(0.0)	48	(0.6)
b) other*												
and missing data on cancer at interview	31,172	(4.6)	74	(2.7)	6,014	(1.2)	22	(0.4)	37,186	(3.1)	96	(1.2)
4 a) Self-reported ETS exposure unclassifiable§	42,655	(6.3)	43	(1.6)	10,435	(2.0)	11	(0.2)	53,090	(4.5)	54	(0.7)
For the spousal cohort:												
4 b) Spouse not in CPS II	103,774	(15.3)	113	(4.2)	15,510	(3.0)	18	(0.3)	119,284	(10.1)	131	(1.6)
5) Spouse had unclassifiable active smoking	7,265	(1.1)	12	(0.4)	4,659	(0.9)	8	(0.1)	11,924	(1.0)	20	(0.2)
Analytic cohort for Self-reported ETS exposure	281,538	(41.6)	246	(9.2)	110,688	(21.8)	116	(2.1)	392,226	(33.1)	362	(4.4)
Analytic cohort for Spousal ETS exposure	213,154	(31.5)	164	(6.1)	100,954	(19.8)	101	(1.8)	314,108	(26.5)	265	(3.2)

* All other except non-melanoma skin cancer.
§ Hours per day coded as unclassifiable for any of home, work or other

exposure variables for a subset of the spousal cohort described above. Pack-years of cigarette smoking during marriage were grouped by quintiles of the distribution of ETS exposure from spousal cigarette smoking.

Covariates

Potential confounders and effect modifiers included in the analyses were : 1) age, 2) gender, 3) socioeconomic status, as measured by schooling, and race; 4) exposure to asbestos, 5) frequency of consumption of six groups of fruits/juices and vegetables, as major sources of carotenoids, 6) total dietary fat as nutrient index, and 7) a history of tuberculosis and other chronic diseases of the lung. All these variables were examined as independent risk factors and controlled for in the analyses. A complete discussion of potential confounders of the ETS-lung cancer link can be found elsewhere (Butler 1990, Mantel 1992).

The analysis of these covariates in the CPS II cohort is complicated by missing data on some of these variables. As will be discussed below for ETS data in CPS II (Sections 3.8 and Chapter 5), a large proportion of CPS II participants left blank the relevant spaces provided in the questionnaire. CPS II participants were not instructed to record zeros for no consumption/exposure. Regarding demographic data (i.e., age, and gender) and schooling and race as proxies of socio-economic status, there are few subjects with missing data. For two of these four covariates: 'race' (1,393 subjects, or 0.4 percent) and schooling (5,413 subjects or 1.4 percent), subjects will be treated as a separate strata in multivariate analyses, when blocking on them. Only when obtaining estimates for covariates with missing data (i.e., included in the model instead of blocking for them), an indicator variable of missing data will be set up, and hence we did not block for them (Table 30). However, there are many more subjects with missing or blank data on items in the food frequency, history of chronic lung diseases and occupational history sections, from which the other set of covariates was derived. The approach we used to deal with these missing data for food frequency is similar to that followed by Thun et al. in a nested case-control study of colon cancer in CPS II (Thun et al., 1992). Missing values

Exposure Variables

Main Exposure Variable (ETS)

i. Self-reported ETS exposure

The average number of hours per day a person reported being presently exposed to ETS at home, work and other places will be used as one exposure variable (i.e., self-reported ETS exposure at time of enrollment). We will use the number of hours a person is exposed at home, work and other places, as well as the sum of the exposures in the three settings, as exposure variables. Dichotomous ETS exposures will be examined (none versus any), and we will then examine the number of hours of exposed individuals, grouped in tertiles, and then treated as ordinal variables for dose-response hypothesis testing.

ii. Spousal Smoking Habits

A second source of information on ETS exposure involves linking non-smokers with the active smoking habits of their spouses. The questions on active smoking previously described, plus the information on times married and age at marriage, and age at interview (both for the index subjects and their spouses), and age at uptake and cessation of smoking for smoking spouses, were used to estimate the intensity and duration of ETS exposure from spousal smoking. Smoking status (ever and never) as well as cigarettes usually smoked per day by current and former smokers will be considered. Pack-years of cigarette exposure from the spouse will also be calculated by multiplying the number of cigarettes smoked per day, by the number of years the spouse smoked cigarettes while married to the study subjects. For the quantitative analyses dealing with intensity, duration and the combination of these two dimensions of ETS exposure from spousal smoking, we will restrict the analysis to subjects with valid information on these variables above mentioned, as needed to estimate time in marriage exposed to ETS from spousal smoking. These will be the other main

The same variable derived in a recently published analysis of CPS II data (Thun et al., 1992) to assess fat intake from the food frequency section will be used. Briefly, this variable represents a nutrient index calculated for each person by summing the products of consumption frequency of each food item by the fat content of a medium-portion size for that food (specific to age and sex as estimated for US adults from the NHANES II survey). Total fat consumption was divided into quintiles, and CPS II nonsmokers in lowest quintile were the referent group. As for total frequency of foods and vegetables containing carotenoids, subjects who insufficiently filled the CPS II questionnaire in the diet section were coded as missing for total amount of dietary fat.

Denominator Information

Person-years denominators were summed over five-year age intervals for the time each person was observed. This procedure provided the appropriate denominators for mortality rates. Person-years accumulated during follow-up were stratified by specific characteristics (i.e., exposure variables and covariates), such as age and smoking history of cohabitees. A data step 'macro' procedure for the Statistical Analysis System was developed by the ACS Division of Epidemiology and Statistics that provided person-year stratification. The follow-up period of a study subject was subdivided into segments of months and, for each segment, age was evaluated at its midpoint.

3.7. Validation of ETS exposure data

Self-reported data on current exposure to ETS were validated using two approaches:

Because the CPS II questionnaires did not require respondents to complete all fields, many questionnaires contained blanks. To determine whether these blanks should be considered negative responses or incomplete questionnaires,

were considered to represent infrequent consumption and a 0.25 times per week value was imputed. Thun et al. validated their approach by comparing the prevalence of reported consumption of several food items in CPS II with data from the National Health and Nutrition Examination Survey epidemiologic study. The consumption patterns in the two datasets were similar when missing values were grouped with the categories of 0 or <1 time a week in CPS II. Thus, for analytic purposes we let blanks be zeros and assigned a frequency of once a month (i.e., 0.25 in a weekly scale ranging from 0, none, to 7, everyday) to answers of < 1 time per week. Our approach also follows that of Thun et al., in excluding from the multivariate analyses of diet, persons who completed fewer than five food items or who left blank an entire column of the questionnaire. For the purposes of adjusting for this covariate and providing an estimate of other variables such as ETS, these subjects with incomplete data in the diet section were treated as having missing values, but considered valid values of these covariates and allowed to form strata as such and will not be excluded.

Following the same rationale, blanks in data on medical history of tuberculosis and chronic obstructive pulmonary disease and occupational exposures were considered to represent a negative history of such disease and no exposure, respectively. As an alternative source to self-reported occupational exposure to asbestos, any mention of having ever held any of occupations likely to involve exposure to asbestos (i.e., shipbuilders, pipefitters, as high-dose exposed, and plumber, construction, duckworker, autorepair, and electrician, as low-dose), or possibly exposed (i.e., janitor, railroadworker, foreman, machinist, painter, assembler, welder, miner, sewer, factory worker, firemen, engineers, steel mill workers, aides, laborers, refinery workers, and military) was used to compare the mortality experience with that of those who had occupations unlikely exposed. We followed the approach of Hinds et al. (1985) to rate these trades: two raters independently classified the list of occupational codes in CPS II (VMC and Howard Frumkin, M.D., Dr. P.H.), agreeing in most of the cases. The final list was completed with the instructions of Dr. Frumkin. The classification here presented closely agrees with that of Hinds et al. (1985), under the circumstances of sketchy data on occupations available in CPS II.

$$\hat{k} = \frac{P_O - P_e}{1 - P_e}$$

the agreement by chance P_e is given by

$$P_e = (p_{1.}p_{.1} + p_{2.}p_{.2})$$

and the observed agreement P_O by

$$P_O = \sum_{i=1}^{k} p_{ii}$$

where k denotes the observers (two in our example).

In our example: $\hat{k} = \dfrac{\frac{p11 + p22}{n} - [(p1 \bullet * p \bullet 1) + (p2 \bullet * p \bullet 2)]}{1 - \frac{p11 + p22}{n}}$

The standard error of k, letting p_{ij} be the proportion of subjects assigned to category i by rater 1 and category j by rater 2,

$$SE(\hat{k}) = \frac{\sqrt{(a + b - c)}}{1 - P_e\sqrt{n}}$$

where

$$a = \sum_{i=1}^{k} p_{ii}[1 - (p_{i.} + p_{.i})(1 - \hat{k})]^2$$

$$b = (1-k)^2 \sum \sum_{i \neq j} p_{ij}(p_{.i} + p_{j.})^2$$

and

$c = [\hat{k} - p_e(1 - \hat{k})]^2$.

(Cfr. Brilliant et al.,1983).

Interpretation of estimates of k follows the criterion outlined by Landis and Koch: "values greater then 0.75 or so may be taken to represent excellent agreement beyond chance, values below 0.40 or so may be taken to represent poor agreement beyond chance, and values between 0.40 and 0.75 may be taken to represent fair or good agreement beyond chance " (Fleiss 1981).

we compared CPS-II data on ETS exposure at home with data from the 1988 National Health Interview Survey (MMWR 1992, NCHS 1988). No previous population based surveys inquired about ETS exposure. The 1988 NHIS included a set of questions for adults about their lifetime working status and their work experience in the year before the interview. The 1988 NHIS included information about ETS exposure for 44,233 respondents, based on the questions: "Do you live with a smoker?", and "Do they smoke at home?". Comparisons were made using direct standardization for age, race and gender, and taking the weights from the 1980 US Population (US Census Bureau 1983).

A second validation study involved a comparison within CPS II, comparing self-reported ETS exposure with the smoking status of cohabitees and spouses enrolled in the CPS II cohort. Persons living with or married to nonsmokers or former smokers should be less likely to report any current exposure to ETS at home than persons living with or married to current smokers. We tested the agreement between these two independent measures of exposure to ETS.

Thus, the number of current smokers among household members in CPS II was estimated and compared with the self-reported number of hours of ETS exposure at home. The smoking status of spouses was also compared with the self-reported number of hours of ETS exposure at home (e.g., smoking status of spouse versus number of hours exposed to ETS, and packs of cigarettes smoked by current cigarette smoking husbands). The agreement correcting for chance was measured using the k statistic (Fleiss 1981).

For the most simple case of the agreement between two observers, a two by two table analysis is displayed as illustration of the method:

Observer 1	Observer 2		
	Present	Absent	Total
Present	p11	p12	p1•
Absent	p21	p22	p2•
Total	p•1	p•2	n

where p_{ij} are expressed as fractions of n (i.e., total sample size), and . denote marginals.

National Cancer Survey (TNCS), the underlying cause of cancer deaths as determined from death certificates was compared to the hospital diagnoses for 48,826 resident cases of single primary cancers. The death certificate diagnosis was confirmed by the hospital diagnosis in 9,560 (93.9%) out of 10,178 lung cancer deaths (Percy 1981).

To validate the use of information on lung cancer diagnoses from death certificates, we conducted a validation study. In particular, we assessed whether deaths coded as "lung cancer" in nonsmokers were truly primary lung cancer or metastatic from other sites.

For 30 deaths for which lung cancer was considered the underlying cause of death in CPS II nonsmoking participants who resided in SEER registry areas, we compared SEER diagnosis with underlying cause of death on death certificates. These 30 deaths represent 9.7 percent of all deaths from lung cancer as of August, 1988, among never smokers free of cancer at the beginning of the follow-up (i.e., 296 deaths of "incident cases" that had occurred as of August 1988). The NCI-SEER Program cancer registries cover approximately 9.5 percent of the US population (NCI SEER 1991).

Finally, we reviewed each one of the death certificates in the analytic cohorts, and checked for inconsistencies in the selection or coding of the underlying cause of death. In doing so, our assumption is that the most critical parameter for the purpose of the study validity is in its specificity rather than sensitivity (Kleinbaum 1982).

3.10. Statistical Analysis

Outline of the Analytic Approach

The analytic approach to be used is outlined in Figure 5. After checking and editing the main exposure variables and covariates described below, the analyses followed these steps :

poor agreement beyond chance, and values between 0.40 and 0.75 may be taken to represent fair or good agreement beyond chance " (Fleiss 1981).

3.8. Exposure Criteria Used In Analysis

i. Self-reported ETS Exposure

Persons with blank spaces in the questionnaire for ETS at home, work and other places were considered unexposed (i.e., 0 hours of exposure). Persons with unclassifiable information on ETS exposure were excluded. The three fields (hours of ETS exposure at home, work and other places) were added to obtain a cumulative exposure variable.

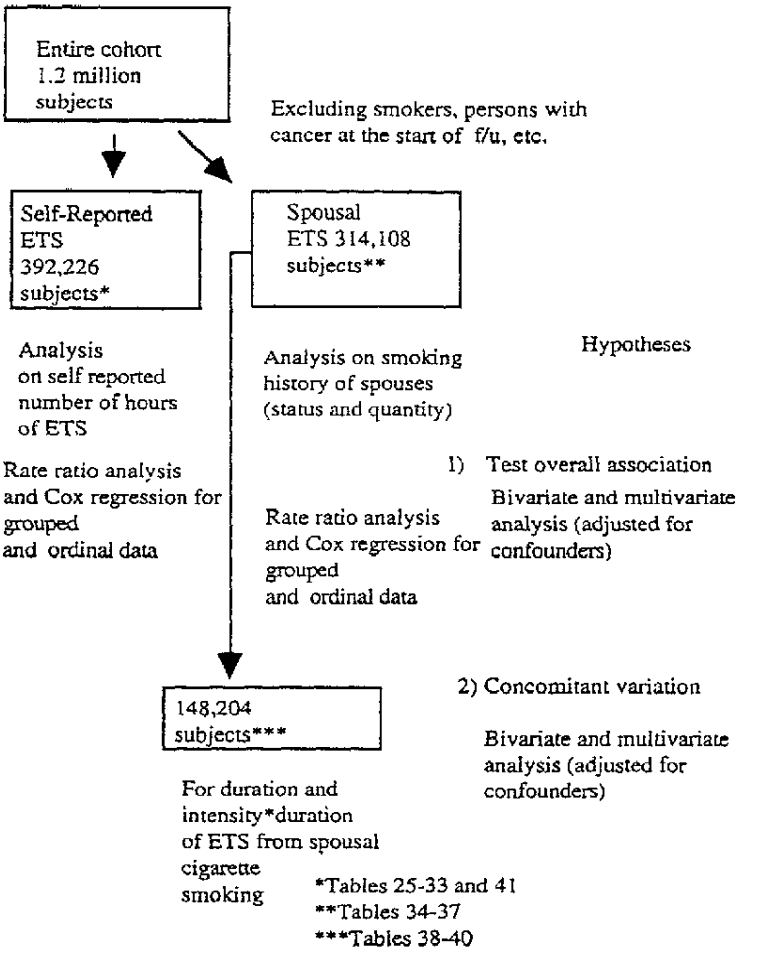
ii. Spousal ETS Exposure

Most published epidemiologic studies have relied on spousal smoking history, rather than on self-reported exposure. Indeed, as shown in the meta-analysis presented above, the strongest evidence of a causal relationship derives from spousal smoking. Spouses generally have a closer and longer relationship with the study subjects than do other adult household members. Therefore, we will use information on the smoking status of spouses, number of cigarettes, pipes and cigars smoked and for spouse-pairs married once in their lifetime, we computed time in marriage nonsmokers were exposed to ETS from spousal cigarette smoking as described before combined with the information on the quantity usually smoked by spouses to estimate pack-years.

3.9. Validation of Information from Death Certificates

Metastatic cancers to the lung may comprise a larger proportion of "lung cancers" in non-smokers than among smokers. A number of authors have studied the accuracy of cancer death certificates by comparing the specified underlying cause of death to autopsy diagnosis and more specific hospital and pathologic data. In one of those studies, using data from eight of the nine areas included in the Third

Figure 5. Outline of Analytic Approach



Using the methods described below under the sections of simple and stratified analyses and Cox regression for both the self-reported ETS and spouse-pairs cohorts, the null hypothesis of no association between exposure to ETS and lung cancer was tested comparing the rates of lung cancer among nonsmokers according to self-reported hours of exposure to ETS and the smoking status of

1) For the self-reported ETS cohort:

a) Simple and stratified analyses using rate ratios of any versus no ETS exposure, followed by multivariate analysis using Cox regression to adjust for potential confounding.

b) Rate ratios of hours of ETS exposure per day (summed over the three settings: home, work and other places) grouped by tertiles, and using this varibles as categorical first, and then as ordinal in Cox regression analysis, controlling for potential confounders.

2) Spousal ETS cohort:

a) Simple and stratified analysis using rate ratios of the smoking status and type of smoking habits of spouses (ever versus never, any cigarette, pipe/cigar versus never), followed by multivariate analysis using Cox regression to control for potential confounders. Additionally, the amount of cigarette smoked during marriage was grouped into quintiles and compared using the rates of nonsmoking participants married to nonsmoking spouses as the reference.

Also we assessed the strength of the association of potential confounders with the risk of lung cancer, as well as the distribution of covariates among the exposed and unexposed to ETS (both self-reported and from spousal smoking).

We used the binomial distribution in the statistical analyses of simple 2x2 tables and stratified analyses. Under the null hypothesis, the number of exposed cases **a**, is unrelated to that among the unexposed, using the theorem of conditional probability, and given that the total number of cases **M1** is fixed, **a** is a variable that follows a binomial distribution (Breslow 1987). Also, it has been shown that given the distribution of one of those binomial variates conditional on the total number of cases, **a** follows the hypergeometric distribution; and if the conditions $\frac{M_1}{T} \Rightarrow 0, \frac{N_1}{T} \Rightarrow 0$ are met, the limit is a Poisson distribution with parameter $\frac{M_1 N_1}{T}$ (Miettinen 1985).

Exact binomial 95 percent confidence intervals around rate ratios were calculated. Simple analyses were followed by a stratified analyses. A basic feature of the method used to estimate age-time-specific mortality rates consists of determining for each subject the amount of follow-up time contributed to a given age times calendar period category and to sum up those contributions for all the members of the CPS II cohort to obtain the total number of person-years of observation in a given category.

Since ratios of age-specific cancer incidence are more constant, the measure of choice was ratio of rates rather than rate differences. Age-adjusted rates were calculated using the entire CPS II person-years population as standard. The formula for a standardized rate is:

$$SR = \frac{\sum w_i R_i}{\sum w_i}$$

Weighted averages of stratum-specific effect measure estimates were obtained using as weights the product of the weight from the standard and the rate among the unexposed:

$$SRR = \frac{\sum \frac{w_i R_{1i}}{\sum w_i}}{\sum \frac{w_i R_{0i}}{\sum w_i}} = \frac{\sum w_i R_{0i} RR_i}{\sum w_i R_{0i}}$$

Precision-based variance estimate for this expression has two terms using approximate variance estimates of the rates to substitute then in the formula:

$$Var[\ln(SRR)] \approx \frac{\sum w_i^2 Var(RR_{1i})}{(\sum w_i R_{1i})^2} + \frac{\sum w_i^2 Var(RR_{0i})}{(\sum w_i R_{0i})^2}$$

Comparison groups were each one of the self-reported ETS and spousal smoking categories taking the unexposed categories (i.e., never smokers) as referent. Categorical variables were formed using the unexposed as referent and dividing exposed into tertiles or quartiles. For the stratified analysis the Mantel-Haenszel method (Mantel 1959) was used. This method uses as weights the contribution of unexposed cases times the number of exposed person-years to the total of each stratum: it is a simple noniterative estimator for a uniform rate ratio and is nearly as efficient as the maximum likelihood estimator (Rothman, 1986):

$$IDR_{(m-h)} = \frac{\sum_i a_i N_{0i} / T_i}{\sum_i b_i N_{1i} / T_i}$$

where a_i and b_i are exposed and unexposed cases, N_{1i} and N_{0i} are exposed and unexposed person-time denominators, and T_i are the totals for the i stratum. Rothman (1986) reviewed variance estimators of the above point estimator of the Mantel Haenszel approach. A stable formula for the variance that considers each a_i to be an independent binomial variate conditional on N_{1i} is:

$$Var[\ln(IDR_{mh})] = \frac{\sum_{i=1}^{N} \frac{M_{1i}N_{1i}N_{0i}}{T_i^2}}{\sum_{i=1}^{N} \frac{a_i N_{0i}}{T_i} \sum_{i=1}^{N} \frac{b_i N_{1i}}{T_i}}$$

Both the Mantel-Haenzsel and the maximum likelihood summary rate ratio estimators were computed using a "rapidly converging network" algorithm (Guess and Thomas 1990), which in turn uses an F-distribution algorithm developed by Brownlee as used in programs #12 and #15 of Rothman and Boice (Rothman 1982). A program that uses these algorithms and developed by Simons, Campos-Filho and Nechi (IDR-E) which provides mid-p values for exact binomial confidence limits, was used.

Confounding and effect modification were assessed following standard criteria (Miettinen 1981, Greenland 1989), and the stratified analysis led to select variables for statistical modeling. After reviewing the published literature comprising more than 30 reports of epidemiologic studies which found no evidence of confounding, it was anticipated that confounding in this study was unlikely to occur. Confounding by age, marital status, and education (as an indicator of socioeconomic status) was assessed. Even if no change in estimate by these potential confounders was found, we obtained and reported, at least, age-adjusted rate ratios, or age-gender adjusted RR when appropriate given that age is the major determinant of the risk of lung cancer among nonsmokers. Assessment of confounding by other well established risk factors such as SES (i.e., 'race', and schooling), dietary intake of foods containing carotenoids, dietary fat, and asbestos exposure was also conducted, because we assess the ETS-lung cancer hypothesis only when other factors known *a priori* to be causally related to lung cancer are taken into account. Effect modification was predicted to occur by asbestos occupational exposure. It is known that active

smoking acts synergistically with asbestos exposure to account for excess risks among those exposed to both asbestos and active smoking (Selikoff 1968).

Multivariate Analysis

Multivariate analyses using Cox regression analysis (Cox 1972) were used as the major analytic tool in this research. The general form of the stratified model which uses a partial likelihood function is:

$$\lambda_g(t,\mathbf{X}) = \lambda_{0g}(t)e^{b_1x_1+b_2x_2+...+b_px_p}$$

where t represents a continuous variable (i.e., length of follow-up, age); $\lambda(t)$ is the mortality rate of persons with specified values of variables $X_1, X_2, ...X_p$; and $\lambda_0(t)$ is the baseline mortality rate (i.e., of unexposed persons) at the t level of the continuous variable, and the g subscript indicates the g-th stratum of categories of the covariates in the model.

The choice of the model is based upon the type of data. In order to obtain the greatest control over confounding by age and other covariates, the proportional hazards model takes into account the contribution of the set of person-time "at risk" and provides adjustment for covariates to simultaneously estimate their effects or to block those covariates for which the proportional hazard assumption might not hold. In addition, this model has fewer assumptions (i.e., assumes no parametric distribution, only that the rates have the same ratio over time, a multiplicative model takes place, and that the occurrence of disease in each subject is independent of the occurrence of disease in other subjects).

Hypothesis testing was carried out using the likelihood ratio statistic [-2lnL reduced model minus - 2lnL full model], via maximum likelihood estimation procedures available in the PHREG Procedure of SAS (SAS 1991). A formal test of heterogeneity was provided by the likelihood ratio test for fitting the proportional hazards model. The change in estimate criterion and allowing for *a*

priori knowledge of potential confounders (i.e., by age even if it had not shown up as confounder in the data) (Greenland 1989) were used in model building.

Concomitant variation in the stratified analysis step was assessed contrasting the rates of lung cancer among ETS unexposed non-smokers to k categories of ETS exposed non-smokers. Ordinal variables were created from categories of dummy variables to test the hypothesis of increasing rates by increasing levels of exposure to ETS using the likelihood ratio test. We treated k number of categories of cumulative exposure (i. e., k categories of number of hours exposed to ETS, or pack-years of cigarettes smoked by spouses), as continuous variables. Adjustment for covariates was allowed in testing this hypothesis by blocking for them.

Regression diagnostics used include plotting survival curves [log -log ($S_1(t)$) and log -log($S_0(t)$] and checked for a pattern of parallelism (a constant ratio). For most analyses the estimates were obtained by blocking for them, rather than including them in the model. However, when estimates were obtained for the covariates, all of them along with the main exposure were included in the model. Kaplan-Meier survival estimates were computed for the main exposure variables, as well as the covariates and the above mentioned graphic approach was used to check for the proportional hazard assumption.

3.11. Sample Size and Power Considerations

The statistical power attained by the sample size of this study to detect different values of the rate ratio, including the point estimates from this study, was computed using the following estimator that assumes the rate ratio is a binomial parameter (Breslow 1987):

$$1-\beta = 1-\Phi(A) =$$

$$\Pr(x \geq X_A) = \sum_{x=X_A}^{M_1} \binom{M_1}{x} \frac{N_1 RR}{N_1 RR + N_0}^{x} 1 - \frac{N_1 RR}{N_1 RR + N_0}^{M_1 - x}$$

where X_A is the most extreme value in the acceptance zone under the the null hypothesis. One way of estimating X_A is by using the beta distribution with parameters 1- α and the expected number of exposed and unexposed cases under the null.

Chapter 4: Comparisons of Demographics and Smoking Habits in the US, CPS II, and the Study Populations

Rationale

A comparison of the 1980 US population with the CPS II population and specifically with the two analytic cohorts (i.e., 1) self-reported ETS and 2) spousal ETS by gender, age, race, occupation, education, geographic residence and smoking habits, is presented below. We used the population figures from the 1980 US Census as standard for age-adjustment, unless specified otherwise, because it was the Census closer in time to the cohort at the time of enrollment. Therefore, we excluded for the purpose of these comparisons those CPS II participants who resided in Puerto Rico, since they were not included in the 1980 US Census. Comparisons with the 1983 National Health Interview Survey (US DHHS Surgeon General 1989) figures are also presented.

These comparisons lend a general perspective to better understand the analytic cohorts, and particularly to generate a profile of the demographics and smoking habits of the subjects in the study cohorts.

Race

Demographic information in the US is available by 'race'. Race is a proxy of socioeconomic status and was used here for the purpose of demographic comparisons. Twelve percent (or 26 million) in the US are blacks. In CPS II they represent 4.4 percent (or 52,038) of the participants. For these reasons, further comparisons of demographics were restricted to whites.

Gender and Age Structure

The ratio of males to females (or gender ratio) in CPS II is considerably lower (0.75) than that among persons 30 years and older in the 1980 US Census

(0.88). Participants in this large cohort were more likely to be in their 50's and 60's at enrollment (Tables 5 and 6). Nonsmoking men and women (i.e., in our analytic cohorts) did not differ in their age distribution from the entire cohort (median 57 years in both groups).

Table 5. Comparison of age distributions of white males 30 years and over, in the US population in 1980, with CPS II participants*, and analytic cohorts*

			Men					
Age Group	1980 Census	%	Entire CPS II	%	Self-reported ETS	%	Husbands (spousal ETS)	%
30-34	7,386,562	16.1	7,610	1.6	3,078	3.0	1,126	1.2
35-39	5,848,891	12.7	9,270	1.9	2,890	2.8	1,875	2.0
40-44	4,862,473	10.6	15,052	3.2	3,890	3.7	3,.286	3.4
45-49	4,616,347	10.1	68,776	14.4	17,079	16.4	16,003	16.8
50-54	4,925,489	10.7	87,030	18.2	19,141	18.4	18,480	19.4
55-59	4,877,635	10.6	91,236	19.1	17,647	16.9	16,893	17.7
60-64	4,199,446	9.1	79,344	16.6	15,804	15.2	15,306	16.0
65-69	3,470,295	7.6	58,162	12.2	11,861	11.4	11,406	11.9
70-74	2,565,929	5.6	35,487	7.4	7,069	6.8	6,534	6.8
75-79	1,652,668	3.6	17,045	3.6	3,687	3.5	3,206	3.4
80-84	918,166	2.0	5,909	1.2	1,361	1.3	1,029	1.1
85+	603,663	1.3	2,419	0.5	624	0.6	330	0.3
Total	45,927,564	100	477,340	100	104,131	100	95,474	100

*Excludes CPS II participants who resided in Puerto Rico

Table 6. Comparison of age distributions of white females 30 years and over, in the US population in 1980, with CPS II participants*, and analytic cohorts*

Age Group	1980 Census	%	Women: Entire CPS II	%	Women: Self-reported ETS	%	Women: Wives (spousal ETS)	%
30-34	7,411,223	14.2	11,764	1.9	5,591	2.1	2,971	1.5
35-39	5,949,670	11.4	18,831	3.0	7,579	2.9	5,753	2.8
40-44	4,981,237	9.5	44,595	7.1	18,241	6.9	16,858	8.3
45-49	4,807,473	9.2	91,972	14.7	37,349	14.2	34,006	16.8
50-54	5,249,428	10.0	106,175	17.0	43,434	16.5	38,805	19.2
55-59	5,409,320	10.3	107,900	17.2	43,756	16.7	38,098	18.8
60-64	4,826,403	9.2	92,102	14.7	38,274	14.6	30,949	15.3
65-69	4,344,316	8.3	68,889	11.0	28,367	10.8	19,637	9.7
70-74	3,562,454	6.8	44,568	7.1	19,731	7.5	10,295	5.1
75-79	2,667,233	5.1	23,892	3.8	11,736	4.5	3,866	1.9
80-84	1,756,793	3.4	9,916	1.6	5,366	2.0	881	0.4
85+	1,400,053	2.7	5,350	0.9	3,165	1.2	160	0.1
Total	52,365,603	100	625,954	100	262,589	100.0	202,279	100

*Excludes CPS II participants who resided in Puerto Rico

Occupation

The types of occupations presently held by CPS II employed white participants were categorized into white and blue collar occupations. Managerial and professional specialty occupations, technicians and related support occupations, sales occupations, and administrative support occupations including clerical represented white collar occupations. Precision production, craft, and repair occupations, operators, fabricators, and laborers were classified as blue collar occupations. For these comparisons we excluded subjects with the following occupational codes in CPS II: housewives, disabled, retired, and subjects with none or unspecified data on occupations.

CPS II participants were more likely to be engaged in white collar occupations (Table 7). White women in CPS II were more likely to hold white collar jobs than white men, in a higher proportion than their counterparts in the entire US population do. Nonsmokers did not differ from the entire cohort with respect to their occupations.

Table 7. Comparison of occupations of employed white persons 30 years and over, in the US population in 1980, in CPS II participants*, and analytic cohorts*

a. Men

Type of Jobs	1980 Census (%)	Entire CPS II (%)	Self-reported ETS (%)	Husbands (spousal ETS) (%)
White Collar	18,165,788 (55.8)	200,612 (73.7)	47,889 (74.3)	43,901 (73.7)
Blue Collar	14,409,714 (44.2)	71,718 (26.3)	16,573 (25.7)	15,684 (26.3)
Total	32,575,502 (100.0)	272,330 (100.0)	64,462 (100.0)	59,585 (100.0)

b. Women

Type of Jobs	1980 Census (%)	Entire CPS II (%)	Self-reported ETS (%)	Wives (spousal ETS) (%)
White Collar	18,464,642 (84.8)	221,093 (94.6)	91,700 (94.3)	70,404 (94.5)
Blue Collar	3,299,972 (15.2)	12,553 (5.4)	5,518 (5.7)	4,137 (5.5)
Total	21,764,614 (100.0)	233,646 (100.0)	97,218 (100.0)	74,541 (100.0)

*Excludes CPS II participants who resided in Puerto Rico

Schooling

Nonsmoking CPS II men and women were more educated than smokers in CPS II as is also true for the rest of the US population, as reflected by their considerably higher rates of college graduates (Table 8). The entire CPS II cohort, after adjustment for age is also more educated than the US population as a whole (28% of college graduates in CPS II women versus 12% in the US populations over 30 years of age). Nonsmoking men in the analytic cohorts (in the cohort for analyses of self-reported ETS and among nonsmoking husbands for analyses of ETS from spousal smoking) were more educated than the rest of the CPS II men.

Table 8. Comparison of the proportion (%) of college graduates among whites in the US population in 1980, CPS II participants§, and analytic cohorts§

	Men				Women			
Age group	US Census	CPS II	SRETS ¶	Husbands	US Census	CPS II	SRETS ¶	Wives
30-34	31.5	49.6	62.5	66.0	21.4	40.4	47.1	43.7
35-39	27.7	48.4	61.1	64.3	17.2	34.9	39.9	37.9
40-44	23.6	43.8	56.7	56.6	13.6	30.8	32.0	31.3
45-49	22.6	46.2	56.9	56.5	11.6	28.9	28.8	28.4
50-54	19.7	43.1	53.1	52.4	10.3	26.6	25.3	25.0
55-59	17.0	39.0	47.6	47.1	8.5	23.0	21.7	21.4
60-64	13.2	32.6	40.0	39.8	8.2	21.1	20.3	20.6
65-69	11.4	27.1	32.9	33.2	8.0	20.8	20.0	20.5
70-74	11.1	26.1	30.2	30.9	8.5	22.4	21.1	22.2
75+	9.1	24.8	27.8	30.0	6.7	21.2	13.0	20.3
Age Adjusted	20.6	40.4	50.1	51.0	12.0	27.9	28.1	28.2

§ Excludes CPS II participants who resided in Puerto Rico
¶ SRETS: Self-reported ETS cohorts
* The standards are taken from 1980 US Census race-gender specific populations

Marital Status

As shown in table 9, CPS II participants were more likely to be married than the rest of the US population, a fact that may be related to their more affluent status and the way they were enrolled. There were more unmarried women, and particularly single women in CPS II than unmarried men. This difference may be explained by a more active participation of women in recruiting people (i.e., ACS volunteers), whereas the men were more likely to get enrolled in CPS II as members of family groups.

Table 9. Comparison of the proportion (%) of married whites in the US population in 1980, white CPS II participants§, and analytic cohorts§

	Men			Women		
Age group	US Census	CPS II	SRETS ¶	US Census	CPS II	SRETS¶
30-34	77.4	62.4	60.6	79.4	67.4	67.6
35-39	83.5	80.7	77.2	82.0	82.3	82.4
40-44	85.8	91.3	90.4	82.8	91.4	92.4
45-49	86.6	95.9	95.7	82.2	88.6	90.9
50-54	86.5	96.4	96.5	79.6	87.0	89.1
55-59	86.8	96.8	96.6	75.1	83.3	85.9
60-64	86.3	96.7	96.8	67.2	77.0	79.9
65-69	84.2	95.9	96.2	56.2	65.7	68.4
70-74	80.8	94.2	94.3	43.6	51.7	54.3
75-79	74.8	90.8	91.7	30.1	35.3	36.2
80-84	65.3	83.2	83.6	17.9	19.8	19.9
85+	48.8	62.0	60.8	8.3	7.9	7.7
Age Adjusted*	82.8	87.3	86.5	67.9	71.8	73.3

§Excludes CPS II participants who resided in Puerto Rico
¶ SRETS: Self-reported ETS cohorts
* The standards are taken from the 1980 US Census race-gender specific populations

Residence

The distribution of the CPS II by territory in general resembles the distribution of the US population (Table 10). A few States in the South (e.g., Texas, Oklahoma), the Mid-West (e.g., Missouri) and the North-East (e.g., New York) showed a deficit with respect to the distribution of the US population. Two States, Minnesota and Utah, had an outstanding participation rate, reflecting the activities of the ACS Divisions and perhaps the advancement of public health in those communities.

Smoking Habits

The age-adjusted prevalence of smoking habits in CPS II and the 1983 HIS is shown in Table 11. Prevalence figures of smoking habits in CPS II are similar to those of the US population by 1982.

Table 10. US population in 1980, and CPS II participants* by State of residence

State	US	CPS II Men	CPS II Women	State	US	CPS II Men	CPS II Women
Alabama	1.7	1.7	1.8	Montana	0.4	0.4	0.4
Alaska	0.2	0.1	0.1	Nebraska	0.7	1.1	1.0
Arizona	1.2	1.4	1.4	Nevada	0.4	0.2	0.2
Arkansas	1.0	1.3	1.3	N Hamp.	0.4	0.4	0.4
California	10.5	8.7	8.9	New Jersey	3.3	3.7	3.7
Colorado	1.3	1.2	1.2	New Mex	0.6	0.5	0.5
Connecticut	1.4	1.7	1.7	New York	7.8	5.8	6.0
Delaware	0.3	0.3	0.3	NCarolina	2.6	1.8	1.8
D.C.	0.3	0.1	0.1	N Dakota	0.3	0.6	0.5
Florida	4.3	4.8	4.9	Ohio	4.8	4.5	4.5
Georgia	2.4	2.6	2.6	Oklahoma	1.3	0.0	0.0
Hawaii	0.4	0.2	0.2	Oregon	1.2	1.3	1.4
Idaho	0.4	0.6	0.5	Penn	5.2	6.4	6.5
Illinois	5.0	5.6	5.6	R Island	0.4	0.7	0.7
Indiana	2.4	2.8	2.8	S Carolina	1.4	1.2	1.3
Iowa	1.3	1.5	1.4	S Dakota	0.3	0.6	0.5
Kansas	1.0	1.5	1.5	Tennessee	2.0	2.6	2.7
Kentucky	1.6	1.5	1.6	Texas	6.3	4.6	4.5
Lousiana	1.9	0.9	1.0	Utah	0.6	2.0	1.9
Maine	0.5	0.6	0.6	Vermont	0.2	0.2	0.2
Maryland	1.9	2.8	2.7	Virginia	2.4	2.7	2.8
Masss	2.5	2.0	2.0	Washington	1.8	1.8	1.8
Michigan	4.1	3.8	3.7	W Virginia	0.9	1.0	1.1
Minnesota	1.8	3.2	3.0	Wisconsin	2.1	2.7	2.6
Mississippi	1.1	0.9	0.9	Wyoming	0.2	0.2	0.2
Missouri	2.2	1.3	1.3				

*Excludes CPS II participants who resided in Puerto Rico

Table 11. Age-adjusted prevalence* of current, former, and never cigarette smoking, CPS II and NHIS-83

	Current		Former		Never	
	CPS II	HIS	CPS II	HIS	CPS II	HIS
Men						
White	30.1	31.1	44.4	43.5	25.5	25.4
Black	42.5	41.8	31.6	32.1	25.9	26.1
Women						
White	20.4	26.0	22.5	19.7	57.1	54.3
Black	26.2	27.4	15.8	14.4	58.0	58.2

*(Percent). Standard population: CPS II

Chapter 5: Validity and Completeness of the Information

On the Outcome Variable

i. Follow-up Procedures

A validation study of the CPS II automated follow-up procedure has been conducted previously using the National Death Index (NDI) (Calle, 1993). In a linkage of over 15,000 persons whose vital status through 1988 had been traced through manual follow-up, 4,686 out of 5,046 (or 92.9 percent) of all deaths known to ACS volunteers were identified by the National Death Index . Since the use of automated follow-up in CPS II started in 1988, when there were 340 deaths from lung cancer ascertained by volunteers, another 22 have been ascertained by the use of the NDI. At a false-negative rate of 7% for the automated procedure, less than two deaths would have been missed in our study (i.e. 0.07*22=1.54) , by using the automated procedure instead of ascertaining deaths by ACS volunteers . As noted earlier, follow-up of vital status is complete for 99.8 % of all enrolled subjects, and of those 101,541 deceased subjects only 3,258 (3.2%) did not have a death certificate (ACS: Update of the CPS-II Master Index Vital Status report, April 12, 1993).

ii. Results of Validation Study of Death Certificate Diagnoses of Lung Cancer

For 30 deaths for which lung cancer was considered the underlying cause of death in CPS II nonsmoking participants who resided in SEER registry areas, SEER diagnosis was compared with the underlying cause of death on death certificates.

In 29 subjects classified as primary lung cancer by death certificates, SEER Cancer Registries also diagnosed primary lung cancer in 27, and for two, the primary site was listed unknown in the SEER database. For no cases was the

disease known to be metastatic from other sites to the lung. In 25 of these 29 lung cancers (86.2 percent), the specific histologic type was known to the SEER Cancer Registries, and in 64 percent they were adenocarcinomas.

From this small validation study we conclude that lung cancers coded from death certificates generally correctly classify deaths from primary lung cancer. The confirmation rate was 93.1 percent (27/29), similar to that found in the TNCS study (Percy 1981). Even in the two instances in our validation study in which the primary site of cancer was unknown, the diagnosis of lung cancer was not ruled out.

Main Exposure Variables

i. Self Reported ETS Exposure in CPS II and NHIS

As mentioned above, because the CPS II questionnaires did not require respondents to complete all fields, many questionnaires contained blanks (Table 12). Twenty-three percent of the questionnaires filled by men and thirteen percent of those filled by women were left blank in the three spaces provided for self-reported number of hours exposed to ETS (i.e., at home, work and other places). Table 13 displays in detail the patterns of answers from CPS II enrollees to the questions: " Whether or not you smoke, on the average, how many hours a day are you exposed to cigarette smoke of others? At home? (hours); At work (hours); In other areas? (hours)". As shown in this table, most times a space was left blank when valid answers were provided for at least one of the three environments.

Table 12. Answers to question in CPS II on reported hours of ETS exposure at different settings
a. All Men in CPS II

Hours	Home	%	Work	%	Other Places	%
0	196,031	38.5	124,114	24.4	101,533	20.0
1	15,107	3.0	52,856	10.4	71,040	14.0
2	12,258	2.4	24,834	4.9	26,533	5.2
3	8,649	1.7	9,089	1.8	6,979	1.4
4	18,363	3.6	13,359	2.6	6,240	1.2
5	8,678	1.7	5,059	1.0	1,714	0.3
6	11,904	2.3	8,527	1.7	1,384	0.3
7	2,621	0.5	3,985	0.8	280	0.1
8+	37,827	7.4	80,478	15.8	4,710	0.9
Blank	180,924	35.6	163,357	32.1	261,885	51.5
Unclass	16,232	3.2	22,936	4.5	26,296	5.2
Total	508,594	100.0	508,594	100.0	508,594	100.0

All three fields left blank	65,999 (13.0%)
All three fields with unclassifiable data	5,006 (1.0%)

b. All Women in CPS II

Hours	Home	%	Work	%	Other Places	%
0	208,404	30.8	154,373	22.8	99,953	14.8
1	16,103	2.4	40,117	5.9	46,088	6.8
2	14,029	2.1	16,636	2.5	20,148	3.0
3	10,952	1.6	6,243	0.9	7,061	1.0
4	20,430	3.0	8,937	1.3	4,726	0.7
5	13,642	2.0	4,766	0.7	1,385	0.2
6	15,753	2.3	7,204	1.1	928	0.1
7	4,097	0.6	6,630	1.0	181	0.0
8+	59,412	8.8	59,133	8.7	4,393	0.6
Blank	282,326	41.7	345,165	51.0	433,178	64.0
Unclass	31,382	4.6	27,326	4.0	58,489	8.6
Total	676,530	100.0	676,530	100.0	676,530	100.0

All three fields left blank	156,249 (23.1%)
All three fields with unclass data	6,285 (0.9%)

Table 13. Patterns of answers given by CPS II participants to self-assessment of number of hours exposed to ETS

Setting			Men		Women	
Home hours	Work hours	Other hours		%		%
.	.	.	65,999	12.98	156,249	23.10
.	.	0	5,732	1.13	8,565	1.27
.	.	1 to 8	26,097	5.13	24,543	3.63
.	.	9*	8,993	1.77	22,486	3.32
.	0	.	4,422	0.87	5,434	0.80
.	0	0	186	0.04	173	0.03
.	0	1 to 8	130	0.03	100	0.01
.	0	9	30	0.01	80	0.01
.	1 to 8	.	50,206	9.87	47,135	6.97
.	1 to 8	0	319	0.06	186	0.03
.	1 to 8	1 to 8	7,361	1.45	4,265	0.63
.	1 to 8	9	373	0.07	745	0.11
.	9	.	9,208	1.81	9,946	1.47
.	9	0	25	0.00	18	0.00
.	9	1 to 8	110	0.02	119	0.02
.	9	9	1,733	0.34	2,282	0.34
0	.	.	7,704	1.51	18,908	2.79
0	.	0	2,334	0.46	4,372	0.65
0	.	1 to 8	2,216	0.44	3,743	0.55
0	.	9	431	0.08	2,613	0.39
0	0	.	11,190	2.20	27,148	4.01
0	0	0	65,314	12.84	72,162	10.67
0	0	1 to 8	28,323	5.57	22,997	3.40
0	0	9	4,791	0.94	13,632	2.01
0	1 to 8	.	21,994	4.32	19,751	2.92
0	1 to 8	0	19,818	3.90	8,292	1.23
0	1 to 8	1 to 8	28,225	5.55	10,249	1.51
0	1 to 8	9	1,284	0.25	1,871	0.28
0	9	.	654	0.13	841	0.12
0	9	0	522	0.10	354	0.05
0	9	1 to 8	299	0.06	265	0.04
0	9	9	932	0.18	1,206	0.18
1 to 8	.	.	31,703	6.23	77,326	11.43
1 to 8	.	0	145	0.03	142	0.02
1 to 8	.	1 to 8	5,311	1.04	6,890	1.02
1 to 8	.	9	167	0.03	876	0.13
1 to 8	0	.	2,244	0.44	5,009	0.74
1 to 8	0	0	4,146	0.82	4,022	0.59

1 to 8	0	1 to 8	3,050	0.60	2,810	0.42
1 to 8	0	9	174	0.03	505	0.07
1 to 8	1 to 8	.	46,980	9.24	44,622	6.60
1 to 8	1 to 8	0	2,897	0.57	1,518	0.22
1 to 8	1 to 8	1 to 8	17,191	3.38	8,415	1.24
1 to 8	1 to 8	9	791	0.16	1,316	0.19
1 to 8	9	.	206	0.04	432	0.06
1 to 8	9	0	17	0.00	19	0.00
1 to 8	9	1 to 8	123	0.02	96	0.01
1 to 8	9	9	262	0.05	420	0.06
9	.	.	5,362	1.05	14,569	2.15
9	.	0	15	0.00	15	0.00
9	.	1 to 8	69	0.01	133	0.02
9	.	9	1,079	0.21	3,735	0.55
9	0	.	37	0.01	71	0.01
9	0	0	27	0.01	76	0.01
9	0	1 to 8	11	0.00	23	0.00
9	0	9	39	0.01	131	0.02
9	1 to 8	.	390	0.08	922	0.14
9	1 to 8	0	10	0.00	11	0.00
9	1 to 8	1 to 8	137	0.03	62	0.01
9	1 to 8	9	211	0.04	306	0.05
9	9	.	3,586	0.71	4,815	0.71
9	9	0	26	0.01	28	0.00
9	9	1 to 8	227	0.04	200	0.03
9	9	9	5,006	0.98	6,285	0.93
		Total	508,594	100.00	676,530	100.00

*a 9 code means that unquantifiable answers (wording like a "lot" or "little"), as well as question marks, were answered.

The comparisons of CPS-II data on ETS exposure at home, with data from the 1988 National Health Interview Survey (NCHS NHIS 1988) is presented in table 14, stratified by age, race and gender. If spaces left blank for number of hours exposed to ETS at home in CPS II are considered to represent zero hours (i.e., unexposed), and persons with "unclassifiable" ETS information are excluded, then the prevalence figures from self reported data on ETS exposure at home in CPS II resemble the prevalence in NHIS . Indeed, all age-adjusted comparisons of gender and racial specific prevalence figures agree within 3.3 percent. The category of "unclassifiable" ETS represent vague wording (e.g., a question mark, 'little') that could not be converted into hours during coding of questionnaires. We concluded that when self-reported ETS exposure in CPS II

was left blank, persons should be considered unexposed, and that "unclassifiable" data on ETS exposure in the three blanks should be excluded from the analyses.

Table 14. Percentage of nonsmokers reportedly exposed to ETS at home* in CPS II ** and NHIS * by age, race and gender.**

	White Men			Black Men			White Women			Black Women		
Age	CPS II	NHIS	±Diff	CPS II	NHIS	± Diff	CPS II	NHIS	± Diff	CPS II	NHIS	± Diff
30-34	12.8	10.2	2.6	12.9	11.6	1.3	21.2	15.9	5.3	22.9	21.8	1.1
35-39	10.5	9.2	1.3	12.7	12.4	0.3	19.9	14.9	5.0	20.1	18.1	2.0
40-44	8.7	7.7	1.0	14.4	9.4	5.0	19.3	15.3	4.0	22.4	20.7	1.7
45-49	9.1	7.3	1.8	9.6	18.1	-8.5	18.9	17.6	1.3	21.1	18.4	2.7
50-54	8.7	15.5	-6.8	11.0	14.2	-3.2	18.3	18.6	-0.3	19.4	30.0	-10.6
55-59	8.3	14.4	-6.1	12.0	17.9	-5.9	16.4	11.5	4.9	17.1	22.8	-5.7
60-64	7.3	11.4	-4.1	10.3	25.0	-14.7	13.1	13.0	0.1	15.5	24.0	-8.5
65+	5.2	5.9	-0.7	5.4	12.0	-6.6	8.4	7.2	1.2	11.7	11.7	0.0
Total	7.8	9.4	-1.6	9.9	13.4	-3.5	14.7	12.8	1.9	17.0	19.2	-2.2
	8.8§	9.8	-1.0	10.9	14.2	-3.3	15.8	13.2	2.6	18.5	19.9	-1.4

* ETS exposure as self-reported number of hours of exposure to ETS at home in CPS II, and as living with a smoking person who smokes at home in NHIS.
** Excludes "unclassifiable" ETS exposure at home. Considers 1-8 hours as exposed, and blanks in spaces provided to write ETS exposure at home, as well as 0's as unexposed.
*** Weighted percentages (i.e., weights are inverse of selection probabilities)
§Age adjusted prevalence figures using the 1980 US Census sub-populations as standards

Comparisons of CPS II participants in the analytic cohort for self-reported ETS analyses were conducted to contrast characteristics such as age, schooling and 'race', for individuals who filled all three spaces and those who left spaces blank. Those who left any space blank were more likely to be older, and less educated, and more likely to be non-whites than those who filled the three spaces (Table 15). However, persons who filled all three fields for hours of exposure at home, work and other places and who reportedly had zero hours of exposure to ETS, were similar to those who left any blank space for ETS in CPS II questionnaires. As will be discussed in Chapter 8, a possible implication of this distribution of missing data is that perhaps blanks might not represent ETS unexposed subjects.

Table 15. Characteristics of CPS II nonsmokers in analytic cohort for self-reported ETS by completeness of the information provided for ETS

Characteristic	Left any ETS field blank (Column percent)	Completed all ETS fields (Column percent)	Cross-product ratio
Age group			
65 +	25.4	20.5	1.4
30-64	74.6	79.5	
Schooling			
<12 years	15.6	8.1	2.1
12+	84.4	91.9	
'Race'			
Non-whites	8.3	5.5	1.7
Whites	91.7	94.5	

ii. CPS II Self-reported Exposure to ETS and Spousal Smoking Habits

Results of the second validation study that compared self-reported ETS exposure with the smoking status of cohabitees and spouses are presented in table16. Table 16.a. and 16.b show that self-reported exposure to ETS at home by CPS II nonsmoking women and men, respectively, agreed with having at least one current smoker among cohabitees: the observed agreement was 88.4% for women, and 94.5% of men (k=56.0%; 95% CI=55.6-56.45 for women, and k=63.5%; 95% CI=62.7-64.3 for men). Self reported ETS (hours of exposure at home) agreed better with the smoking status of spouses (Table 16.c. and 16.d.) than with the number of smoking cohabitees (Table 16.a. and 16.b.); the observed agreement was 87.8% and 95.4% for wives (Table 16.c.) and husbands, respectively (k=62.6%; 95% CI=62.2-62.9 for nonsmoking wives, and k=69.8%; CI=69.0-70.6, for nonsmoking husbands). We concluded that self-reported ETS exposure in CPS II was internally consistent with the smoking habits reported by spouses. We also concluded that self-reported ETS is closer to spousal ETS than to smoking of cohabitees. Using current smoking status of spouses as standard, self-reported ETS would misclassify 4.6% of the subjects, with a specificity of 98%.

Table 16.a. Comparison of self-reported exposure to ETS at home by CPS II nonsmoking women and the number of current smokers among cohabitees.

Self-reported ETS	Cohabitees status: At least one current smoker	Nonsmoker and former smokers only	Total
Yes	33,951 (9.8)	17,250 (5.0)	51,201(14.8)
No	22,850 (6.6)	271,947 (78.6)	294,797 (85.2)
Total	56,801 (16.4)	289,197 (83.6)	345,998 (100.0)

k=56.0% (95% CI=55.6-56.4)

Table 16.b. Comparison of self-reported exposure to ETS at home by CPS II nonsmoking men and the number of current smokers among cohabitees

Self-reported ETS	Cohabitees status: At least one current smoker	Nonsmoker and former smokers only	Total
Yes	6,981 (5.6)	2,814 (2.2)	9,795 (7.8)
No	4,204 (3.3)	111,622 (88.9)	115,826 (92.2)
Total	11,185 (8.9)	114,436 (91.1)	125,621 (100.0)

k=63.5% (95% CI=62.7-64.3)

Table 16.c. Comparison of self-reported exposure to ETS at home by CPS II nonsmoking wives and the smoking status of their husbands

Self-reported ETS	Husband status: Current smoker	Nonsmoker and former smoker	Total
Yes	31,945 (14.2)	5,463 (2.4)	37,408 (16.6)
No	22,047 (9.8)	165,781 (73.6)	187,828 (83.4)
Total	53,992 (24.0)	171,244 (76.0)	225,236 (100.0)

k=62.6% (95% CI=62.2-62.9)

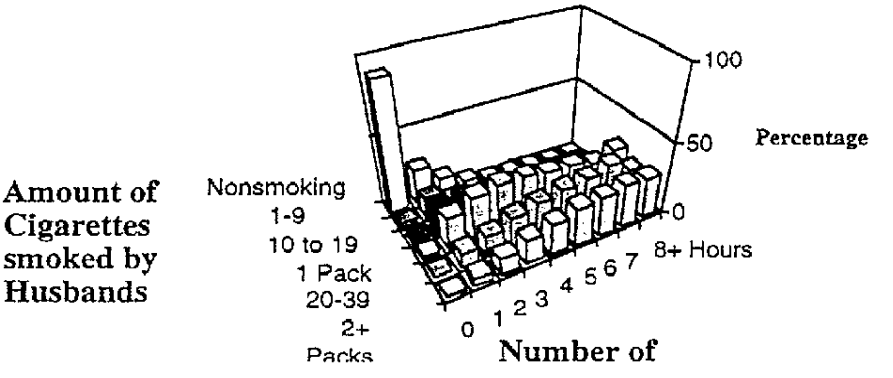
Table 16.d. Comparison of self-reported exposure to ETS at home by CPS II nonsmoking husbands and the smoking status of their wives

Self-reported ETS	Wife status: Current smoker	Nonsmoker and former smoker	Total
Yes	6,266 (6.0)	1,741 (1.7)	8,007 (7.6)
No	3,058 (2.9)	93,549 (89.4)	96,607 (92.4)
Total	9,334 (8.9)	95,290 (91.1)	104,614 (100.0)

k=69.8% (95% CI=69.0-70.6)

Among nonsmoking women, we also compared the amount of cigarettes smoked by their male cohabitees and the self-reported number of hours exposed to ETS at home. As shown in table 17 and figure 6, there is a concomitant variation of more hours of exposure to ETS and the number of cigarettes and pack of cigarettes reportedly smoked by their husbands.

Figure 6. Percentage of nonsmoking women exposed to specified self-reported number of hours of ETS at home and number of cigarettes smoked by their husbands



*Restricted to nonsmoking women whose spouses were current cigarette smoking

Table 17. Distribution of reported hours of exposure to ETS at home by nonsmoking women, according to number of cigarettes smoked by their husbands.

	Number of Hours of ETS at home									
Cigarettes husband smoked	0	%	1	%	2	%	3	%	4	%
Non smoking	75299	89.9	691	26.3	334	13.1	135	5.91	121	2.84
1 to 9	2211	2.64	388	14.8	235	9.24	139	6.09	160	3.75
10 to 19	2081	2.49	520	19.8	500	19.7	368	16.1	550	12.9
1 pack	2484	2.97	620	23.6	792	31.2	775	33.9	1430	33.5
20-39	905	1.08	268	10.2	397	15.6	485	21.2	1065	25
2+ packs	745	0.89	140	5.33	284	11.2	382	16.7	939	22
	83725	100	2627	100	2542	100	2284	100	4265	100

	5	%	6	%	7	%	8	%	Total	%
Non smoking	56	1.79	58	1.72	13	1.52	146	2.19	76853	70.2
1 to 9	77	2.46	85	2.52	11	1.29	203	3.05	3509	3.21
10 to 19	325	10.4	291	8.62	62	7.24	626	9.4	5323	4.86
1 pack	966	30.9	999	29.6	227	26.5	2094	31.4	10387	9.49
20-39	892	28.5	1015	30.1	288	33.6	1720	25.8	7035	6.43
2+ packs	809	25.9	927	27.5	255	29.8	1874	28.1	6355	5.81
Total	3125	100	3375	100	856	100	6663	100	109462	100

Chapter 6: Descriptive Statistics of Exposure Variables

Frequency of Self-reported and Spousal ETS

Forty-eight percent of the nonsmoking population in our analytic cohort reported ETS exposure at home, work or other places. Table 18 presents the distribution of self-reported number of hours of ETS exposure at home, work and other places, and combined in the three settings, according to the definitions presented in Section 3.9. Fourteen percent reported any exposure at home, 26 percent at work and 18 percent from elsewhere. Among those exposed to any ETS, one third was exposed to ETS for one or two hours, another third was exposed for two to five hours, and the rest to six and more hours of ETS. Accordingly, cutoffs of ETS were used at 3, and 5 hours of self-reported exposure at home, 1, 2 and 6 hours of self-reported exposure at work, and 1, 2, and 3 for self-reported exposure elsewhere, to create categorical variables and conduct further analyses. Up to 9.7 percent of nonsmokers had 3 and more hours of ETS exposure at home, but only 2.6 percent obtained that amount of exposure to ETS in places other than work or home.

More than half of the nonsmoking spouses, or 53.6 percent, in the analytic cohort for spousal ETS were married to smoking spouses. As mentioned before, smoking of tobacco products other than cigarettes were not collected in the questionnaires sent to women, and thus all the spousal smoking of nonsmoking husbands comprised exclusively cigarette smoking. On the other hand, 33.7 percent of nonsmoking wives (or 71, 891) were married to nonsmokers, and two-thirds, or 66.3 percent, were married to ever smoking husbands. The latter group could be further divided according to the following types of smoking: 15.8 percent (or 33,705) were married to current cigarette smokers; 30.1 percent (or 64,230) to former cigarette smokers; 2.5 percent (or 5, 487) to smokers of both cigarettes and pipes or cigars; 4.6 percent (or 9,794) to current pipe and or cigar smokers who formerly smoked cigarettes; 6.7 percent

or (14,306) to former smokers of both cigarettes and pipe/cigars; 4.3 percent (or 9,253) to former pipe/cigar smokers who never smoked cigarettes; and 2.1 percent (or 4,487) to former cigarette smokers who then smoked pipe or cigars.

Correlates of ETS exposure

However, the contributions of each ETS exposure setting to the overall exposure varied greatly by gender. More men more than women reported exposure at work, whereas women reported most of their exposure at home.

Table 18. Hours of exposure to ETS reported by nonsmoking CPS II participants at different settings, 1982

a. Both Men and Women

Hours	Home	%	Work	%	Other Places	%	Total ETS	%
None	337,144	86.0	288,832	73.6	321,012	81.8	205,433	52.4
1	9,855	2.5	37,737	9.6	46,554	11.9	61,490	15.7
2	7,324	1.9	14,039	3.6	14,379	3.7	31,140	7.9
3	8,679	1.4	4,911	1.3	4,202	1.1	13,116	3.3
4	5,367	1.4	6,376	1.6	2,512	0.6	13,366	3.4
5	5,748	2.2	2,914	0.7	745	0.2	8,074	2.1
6	5,748	1.5	4,355	1.1	433	0.1	9,051	2.3
7	1,290	0.3	3,349	0.9	102	0.0	5,010	1.3
8+	11,484	2.9	29,713	7.6	2,287	0.6	45,546	11.6
Total	392,226	100	392,226	100	392,226	100	392,226	100

b. Men

Hours	Home	%	Work	%	Other Places	%	Total ETS	%
None	101,481	91.7	69,973	63.2	81,912	74.0	48,175	43.5
1	2,641	2.4	16,909	15.3	20,758	18.8	24,272	21.9
2	1,488	1.3	6,363	5.7	4,990	4.5	12,548	11.3
3	933	0.8	2,072	1.9	1,144	1.0	4,355	3.9
4	1,380	1.2	2,724	2.5	783	0.7	3,937	3.6
5	606	0.5	989	0.9	289	0.3	2,009	1.8
6	726	0.7	1,513	1.4	135	0.1	2,192	2.0
7	93	0.1	704	0.6	39	0.0	1,042	0.9
8+	1,340	1.2	9,486	8.6	638	0.6	12,158	11.0
Total	110,688	100	110,688	100	110,688	100	110,688	100

c. Women

Hours	Home	%	Work	%	Other Places	%	Total ETS	%
None	235,663	83.7	218,859	77.7	239,100	84.9	157,258	55.9
1	7,214	2.6	20,828	7.4	25,796	9.2	37,218	13.2
2	5,836	2.1	7,703	2.7	9,389	3.3	18,592	6.6
3	4,402	1.6	2,839	1.0	3,058	1.1	8,761	6.6
4	7,299	2.6	3,652	1.3	1,729	0.6	9,429	3.3
5	4,761	1.7	1,925	0.7	456	0.2	6,065	2.2
6	5,022	1.8	2,842	1.0	298	0.1	6,859	2.4
7	1,197	0.4	2,645	0.9	63	0.0	3,968	1.4
8+	10,144	3.6	20,245	7.2	1,649	0.6	33,388	11.9
Total	281,538	100	281,538	100	281,538	100	281,538	100

As shown in table 19, self-reported exposure to ETS decreased from 70 percent to 16 percent with increasing age. Spousal smoking exposure, however, did not show this trend, except for current smokers (Table 20). One implication of this

difference, as will be discussed in Chapter 8, may be that self-reported ETS does not reflect long-term, but rather current ETS exposure.

Table 19. Proportion of nonsmoking CPS II participants in analytic cohorts who reported any ETS exposure by age at interview, 1982

Age Group	Men and Women	Women	Men
30-34	70.1	67.5	75.1
35-39	66.5	64.5	71.9
40-44	61.0	58.9	70.6
45-49	61.6	57.5	70.7
50-54	58.6	54.7	67.5
55-59	52.9	49.1	62.3
60-64	43.3	39.5	52.6
65-69	29.6	26.7	36.6
70-74	20.7	18.7	26.2
75+ years	15.5	14.7	18.1
Total	52.4	55.9	43.5

Table 20 presents the proportion of participants with spouses also in the study and whose spouses were ever smokers (i.e., spousal smoking). Almost two-thirds of nonsmoking women lived with ever smoker husbands whereas only 27 percent of men were married to ever smoker wives.

Table 20. Proportion of nonsmoking participants married to ever-smoking spouse by age at interview, 1982

Age Group	Men and Women	Women	Men
30-34	46.5	53.9	27.2
35-39	52.7	60.7	29.2
40-44	57.4	62.7	31.3
45-49	52.8	63.7	29.8
50-54	54.8	67.1	29.0
55-59	56.7	69.4	28.1
60-64	54.3	68.3	26.1
65-69	51.2	67.4	23.4
70-74	49.0	66.6	21.4
75+ years	40.5	63.0	16.1
Total	53.6	66.3	26.8

Important correlates of ETS exposure were schooling and race, both of which can be taken as surrogates of social class. Non-white men and women were slightly less self-reportedly exposed than whites: the ratio of the proportion of exposed nonwhites to exposed whites was 0.8. Married women were 5.8 percent more likely to be self-reportedly exposed to ETS than unmarried women. More educated men and women were more likely to report ETS exposure, or to have an ever-smoker spouse than less educated men and women: the ratio of self-reported ETS exposure among the most formally educated, to that among the least formally educated was 2.8 and 2.0 for men and women, respectively. However, among husbands and wives, the ratio of smoking spouse among the most educated the least educated was 0.6 for men and women. Unlike self-reported ETS exposure, assessment of ETS exposure based on the smoking history provided by spouses in the study shows a picture consistent with the demography of ETS exposure in the US population at large that was described in Chapter 1. Therefore, the assessment of ETS exposure based upon spousal ETS might reflect better true ETS exposure, than self-reported ETS.

People reporting exposure to asbestos, chemicals, coal dust or tar, formaldehyde and ionizing radiation, were more likely to report ETS exposure but did not differ substantially according to the smoking status of spouses. ETS exposed and unexposed were comparable with respect to medical history of any chronic non-malignant disease. ETS exposed and unexposed groups were also comparable with respect to the consumption of foods considered major sources of carotenoids.

Table 21. Characteristics of nonsmoking participants according to self-reported ETS

	Men		Women	
Characteristic	No ETS	Any ETS	No ETS	Any ETS
Number of subjects	48,175	62,513	157,258	124,280
	(43%)	(57%)	(56%)	(44%)
Age at interview (years)	60.4	53.6	60.2	53.2
(standard deviation)	(11.2)	(9.6)	(11.7)	(10.0)
Race (% white)	92.9	94.3	92.1	93.3
Married (%)	93.7	93.4	74.1	79.9
Education (%)				
<High School	17.7	7.6	18.3	9.9
High School	19.9	17.7	31.1	33.8
Trade School or some College	21.7	24.8	26.7	30.5
≥College	40.7	49.8	23.9	25.8
Occupation (%)				
Any asbestos	4.9	7.1	1.4	2.4
Other lung carcinogens§	20.1	26.6	6.8	11.9
Diet: times/week (standard deviation)				
Green leafy vegetables	4.8	4.7	5.0	5.0
	(2.0)	(2.0)	(2.0)	(1.9)
Fruit/Juices	5.2	5.0	5.5	5.4
	(2.3)	(2.3)	(2.1)	(2.2)
Chronic lung dis. (%)				
Any	7.2	7.2	7.6	8.0
Tuberculosis	1.1	0.9	1.0	1.0
Chronic bronchitis	1.7	1.7	2.9	3.1
Emphysema	1.0	0.5	0.5	0.3
Asthma	4.4	4.9	4.2	4.6

§ Self-reported occupational exposures to: Chemicals, coal dust or tar, formaldehyde and ionizing radiation.

Table 22. Characteristics of nonsmoking participants according to spousal smoking

Characteristic	Husbands		Wives	
	Non smoker wife	Wife ever smoked	Non smoker husband	Husband ever smoked
Number of subjects	73,914	27,040	71,892	141,262
Age at interview (years)	57.4	55.8	54.5	55.3
(standard deviation)	(10.2)	(9.4)	(10.1)	(9.5)
Race (% white)	94.9	94.7	94.8	95.0
Married (%)	100.0	100.0	100.0	100.0
Education (%)				
<High School	12.6	8.5	9.0	11.5
High School	20.2	16.2	31.3	36.0
Trade School or some College	23.9	23.2	30.1	29.6
≥College	43.2	52.1	29.5	23.0
Occupation (%)				
Any asbestos	6.2	6.6	1.7	1.8
Other lung carcinogens§	24.3	24.2	8.9	9.4
Diet: times/week (standard deviation)				
Green leafy vegetables	4.0	4.0	4.7	4.6
	(2.5)	(2.5)	(2.2)	(2.3)
Fruit/Juices	5.1	5.2	5.4	5.4
	(2.3)	(2.3)	(2.1)	(2.2)
Chronic lung dis. (%)				
Any	7.1	7.1	7.2	7.7
Tuberculosis	1.0	1.0	0.9	1.0
Chronic bronchitis	1.7	1.4	2.6	3.0
Emphysema	0.8	0.6	0.3	0.3
Asthma	4.5	4.9	4.3	4.4

§ Self-reported occupational exposures to: Chemicals, coal dust or tar, formaldehyde and ionizing radiation.

Smoking status, quantity and duration of ETS from spouses

Spouses of subjects in the study comprised the following major categories: 1) nonsmoking spouses (145,806, or 46.4 percent) 2) current and former cigarette smokers with complete data (41,099 or 13.1 percent, and 71,594 or 22.8 percent respectively), 3) former and current smokers with incomplete data (1,764 or 0.6 percent and 6,087 or 1.9 percent, respectively), 4) ever smokers with unclassifiable smoking (4,431 or 1.4 percent) and 5) ever pipe and or cigar smokers which includes a mixture of smoking of the different tobacco products (43,327 or 13.8 percent).

Analysis of dose-response relationships between ETS from spousal smoking and the risk of cancer among nonsmokers is restricted to cigarette smoking spouses with complete data, and the univariate statistics of the variables used in the analyses are presented. The quantity of smoking is based upon frequency (i.e., cigarettes per day) as recalled by the smoking spouses of nonsmoking participants. We set a value of zero for nonsmoking spouses of nonsmokers in the study.

The number of cigarettes smoked by the 41,099 spouses of nonsmoking participants who were current cigarette smokers and had complete smoking information, and who never smoked cigars or pipes, ranged from 1 to 100 a day, with a mean of 22.6 cigarettes per day, a first quartile of 15 cigarettes, a median of 20, and a third quartile of 30 cigarettes. Ninety percent of current smoking spouses smoked up to two packs of cigarettes. The position of the first and second tertiles for the quantity of cigarette smoking among the current cigarette smokers of nonsmokers was 20 (i.e., one pack) and 25 cigarettes per day, respectively.

Among the 71,594 nonsmokers in this analytic cohort whose spouses were former cigarette smokers, had complete smoking information, and did not smoke other tobacco products, the quantity of usual former cigarette smoking were

similar to those previously shown for current cigarette smoking spouses: a range from 1 to 100 cigarettes per day, the mean was in 22.6 cigarettes per day, the median was 20 (i.e. one pack), but the first quartile was lower at 11 cigarettes per day, and the third quartile was 30. Again, ninety percent smoked less up to two packs of cigarettes. The tertiles were 18 and 20 for the lower and upper, respectively.

For those subjects in the analytic cohort of spousal ETS who were married to cigarette smoking spouses with complete data, we computed the time they were married to spouses, to assess the effect of this variable as well as to compute the pack-years smoked during marriage by smoking spouses. As described before, we excluded those subjects married more than once or whose spouse was also married more than once, or with incomplete data on age at marriage., since both were needed to compute time in marriage exposed to smoking spouse (i.e., the difference between age at interview and the age at first marriage yielded the duration of marriage, and is used in combination with the age at uptake and quitting smoking as well as the age at interview of smoking spouses, to compute the time during marriage nonsmokers were exposed to spousal smoking).

Typically nonsmoking husbands and wives who were married to a cigarette smoking spouses, had spent in average 21 years (standard deviation of 12 years, median=21 years) exposed to ETS, and the values of this variable ranged from 1-63 years, and differences between men and women were small. The cutoffs for the tertiles of the distribution of the duration of exposure to ETS from spousal smoking for these group of individuals were 15 and 27 years for exposed men, and 17 and 30 for exposed women.

The distribution of study subjects according to the combination of usual amount of cigarette smoking with the duration of exposure to ETS from spousal cigarette smoking during marriage is presented in Table 23. Among nonsmokers married to smoking spouses pack-years ranged from 1 to 198 with a mean of 24.0 pack-years, and a median of 20 pack-years, and the cutoffs of tertiles the cutoffs were approximately 16, and 35, but men and women differed considerably: the mean

packyears of ETS spousal smoking among nonsmoking men and exposed to any ETS were 19 and 29, respectively. A t-test yielded a p-value <0.0001.

Table 23. Study populations included in spousal analyses for intensity and duration of ETS exposure from spousal cigarette smoking among nonsmoking spouses in CPS II

a. Smoking of current and former cigarette smoking (i.e., nonsmokers =0)

n=258,499. see page 88. Results in table37.

Amount of current smoking	Number	%	Amount of former smoking	Number	%
0	145,806	78.0	0	145,806	67.1
< 1 pack	12,606	6.7	< 1 pack	23,917	11.0
1 - 1.9 packs	21,511	11.6	1 - 1.9 packs	33,878	15.6
2+ packs	6,982	3.7	2+ packs	13,799	6.3
Total	186,905	100.0	Total	217,400	100.0

b. Time in marriage with cigarette smoking spouse, and packs of cigarette-years in marriage, (nonsmoking spouses set to 0), n=148,204. Results in table 39.

Exposed to spousal ETS for:					
Years	Men Number	%	Years	Women Number	%
None	46,039	82.2	None	46,149	50.0
1-15	3,326	5.9	1-17	14,794	16.0
16-26	3,125	5.6	18-29	15,491	16.8
27+	3,492	6.2	30+	15,788	17.1
	Total	148,204		100.0	

c. Packs of cigarette-years in marriage, (nonsmoking spouses set to 0), n=148.204. Results in table 40.

Pack-years	Men Number	%	Pack-years	Women Number	%
0	46,039	82.2	0	76,771	83.2
1-8	3,339	6.0	1-16	15,451	16.7
9-22	3,263	5.8	17-35	15,569	16.9
23+	3,341	6.0	36+	15,053	16.3
	Total	148,204	100.0		

Chapter 7: Main Results

7.1 Deaths from Lung Cancer and Histological Data in Death Certificates

There were 362 deaths from lung cancer among nonsmokers in the study cohort of self-reported ETS exposure. Before the NDI update of follow-up status was completed to include new deaths from lung cancer that occurred between October 1, 1988, and December 31, 1989, we reviewed the death certificates from 284 or 78 percent of the deaths from lung cancer finally included in our analyses. These 284 deaths were the deaths ascertained during the first six years of follow-up. In 169 instances or 59 percent, death certificates only mentioned lung cancer without any reference to histological type. In the remaining 115 lung cancer deaths, or 41 percent, the certificate specifically mentioned histological type. Table 24, shows the frequencies of each major histologic type. Seventy percent of lung cancer among nonsmokers, when their histological types were documented in death certificates, were adenocarcinomas. If the unclassified were excluded, the proportion of adenocarcinomas would be 75 percent. There were no differences by gender in the distribution of histological types mentioned in death certificates.

Table 24. Distribution of hystological types in 115 deaths from lung cancer among nonsmokers in the analytic cohorts in CPS II, 1982-1988, for which this information was readily available from death certificates

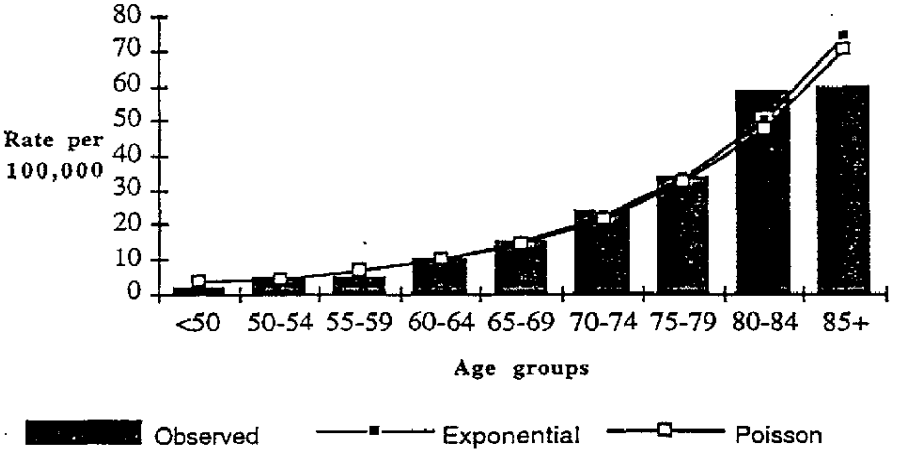
Type	Women	Men	Total
	Number (%)	Number (%)	Number (%)
Adenocarcinomas	59 (71.1)	21 (65.6)	80 (69.6)
Squamous cell	12 (14.4)	7 (21.9)	19 (16.5)
Large cell	1 (1.2)	3 (9.4)	4 (3.5)
Other types	3 (3.6)	1 (3.1)	4 (3.5)
Unclassified	8 (9.6)	0 (0.0)	8 (7.0)
Total	83 (100.0)	32 (100.0)	115 (100.0)

7.2 Potential confounders: age, gender, schooling, race, prexisting lung disease, occupational exposure to lung carcinogens, consumption of foods containing carotenoids, and fat as nutrient index.

Age

The rates of lung cancer increased monotonically with age. Figure 7 depicts this feature of the risk of lung cancer by age: observed values were fitted empirically by Poisson and exponential regression models, both providing an adequate description of the data. As we described earlier, age was also strongly associated with self-reported and ETS exposure from spousal smoking. Thus, age was included in all models.

Figure 7. Death Rates of Lung Cancer among CPS II Nonsmoking participants by Age, 1982-1989



Gender

Nonsmoking men showed an increased risk of lung cancer as compared with nonsmoking women, the crude rate ratio being 1.2 (95% CI=1.0-1.5) (i.e., $RR_{crude} = \frac{116/786,532}{246/2,020,081}$). Men and women were comparable with respect to age, men being slightly younger (Table 25). Thus, the Mantel-Haenszel RR for gender, adjusted for age was 1.3 (95% CI=1.1-1.7). Men had a slightly greater likelihood of being reportedly exposed to ETS than women (56 percent and 53 percent, respectively). Sources of exposures to ETS were different for men than for women (i.e., most for men from work, and women at home). Women were more exposed to ETS from their husbands, than were nonsmoking men from their wives. Thus, gender was included in all the models.

Table 25. Death rates of Lung Cancer among Nonsmokers by Age and Gender, CPS II, 1982-1989

	Men				Women			
Age-group	Deaths	Person-years	%	Rate 10^{-5}	Deaths	Person-years	%	Rate 10^{-5}
<50	3	121,178	15	2	4	341,834	17	1
50-54	4	133,136	17	3	18	303,204	15	6
55-59	4	144,161	18	3	21	338,198	17	6
60-64	16	131,477	17	12	30	329,075	16	9
65-69	27	109,588	14	25	30	270,185	13	11
70-74	26	76,221	10	34	39	196,522	10	20
75-79	14	42,807	5	33	44	129,427	6	34
80-84	17	19,322	2	88	35	69,869	3	50
85+	5	8,643	1	58	25	41,768	2	60
Total	116	786,532	100	15*	246	2,020,081	100	10*

(n=392,226 subjects) *Age-adjusted to the CPS-II population.

Age-SRR=1.4 (95% CI=1.1-1.8)

RR (m-h)=1.3 (95% CI=1.1-1.7)

Race

Only 9.4 percent of the deaths from lung cancer, or 34 occurred among 'nonwhites'. All but three of these deaths occurred among African-Americans. We collapsed all 'races' different from 'whites' into a category of 'nonwhites' for the purpose of the analyses. Table 26 presents deaths rates by this dichotomous variable, and by age. The total row presents age-adjusted rates. Nonwhites had a 44% increased risk of lung cancer, after adjusting for age [RR m-h=1.4 (95% CI=1.0-2.0)] (Table 26). As pointed out before, nonwhites were less likely to report ETS exposure but were comparable in the proportion of spousal ETS. Therefore, we included 'race' in the multivariate analysis of ETS and lung cancer.

Table 26. Death rates of Lung Cancer among Nonsmokers by Age and 'Race', CPS II, 1982-1989

	Whites				Nonwhites			
Age-group	Deaths	Person-years	%	Rate 10^{-5}	Deaths	Person-years	%	Rate 10^{-5}
<50	0	43,513	22	0	7	419,493	16	2
50-54	2	30,306	15	7	20	406,037	16	5
55-59	2	31,258	16	6	23	451,103	17	5
60-64	1	28,440	14	4	45	432,112	17	10
65-69	10	23,123	12	43	47	356,650	14	13
70-74	6	17,487	9	34	59	255,256	10	23
75-79	8	11,458	6	70	48	160,776	6	30
80-84	2	6,306	3	32	50	82,885	3	60
85+	3	4,271	2	70	27	46,140	2	59
Total	34	196,161	100	17*	326	2,610,452	100	11*

(n=390,833 subjects and 360 deaths) *Age-adjusted to the CPS-II population.

Age-SRR=1.6 (95% CI=1.1-2.3)

RR (m-h) age-adjusted=1.4 (95% CI=1.0-2.1)

Schooling

Years of education was both related to ETS exposure in the entire study population and was a risk factor for lung cancer. Younger CPS II nonsmoking participants tended to be more educated than older, as shown in table 27, along with the corresponding number of deaths, person-years under observation, and death rates. The unadjusted comparison of rates of those who did not graduate from high school, as compared to those who did, was 2.2 (95% CI=1.8-2.8). After adjustment by age, the Mantel-Haenszel estimate dropped to 1.2 (95% CI=0.9-1.5). Years of education was positively associated with self-reported ETS, and inversely related with spousal smoking status. Although schooling was not a meaningful confounder based upon the data at hand, it was included in all multivariate analyses based upon *a priori* knowledge of the association between lung cancer and low socioeconomic status.

Table 27. Death rates of Lung Cancer among Nonsmokers by Age and Schooling, CPS II, 1982-1989

	<12 yrs				12 + yrs			
Age-group	Deaths	Person-years	%	Rate 10^{-5}	Deaths	Person-years	%	Rate 10^{-5}
<50	0	20,515	6	0	7	442,497	18	2
50-54	1	27,204	7	4	21	409,136	17	5
55-59	2	41,590	11	5	23	440,769	18	5
60-64	4	52,470	14	8	42	408,081	17	10
65-69	13	60,234	16	22	44	319,539	13	14
70-74	20	61,908	17	32	45	210,835	9	21
75-79	18	50,765	14	35	40	121,468	5	33
80-84	21	31,749	9	66	31	57,442	2	54
85+	13	23,322	6	56	17	27,089	1	63
Total	92	369,758	100	13*	270	2,436,856	100	12*

(n=392,226 subjects) *Age-adjusted to the CPS-II population.

Age-SRR=1.1 (95% CI=0.8-1.4) RR (m-h) age-adj.=1.2 (95% CI=0.9-1.5)

Asbestos

Self-report of being ever occupationally exposed to asbestos was associated with a two-fold higher risk of lung cancer among nonsmokers in CPS II (Table 28) [age-adjusted RR (m-h)=2.0 (95% CI=1.1-3.5)]. The effect estimate associated with asbestos was similar [multivariate RR=1.8 (95% CI=1.1-3.2)], after controlling for age, gender and the indicator of 'race', and schooling, as well as total intake of foods containing carotenoids, history of chronic lung disease and self-reported ETS exposure in Cox multivariate analyses (Table 30). Adjusted rate ratios associated with ever being exposed to asbestos at work were slightly lower for men [1.5 (95% CI=0.7-3.1)] than for women [2.3 (95% CI=1.0-5.3)].

Table 28. Death rates of Lung Cancer among Nonsmokers by Age and self-reported Occupational Exposure to Asbestos, CPS II,1982-1989

	Ever exposed				Unexposed			
Age-group	Deaths	Person-years	%	Rate 10^{-5}	Deaths	Person-years	%	Rate 10^{-5}
<50	0	13,913	20	0	7	449,099	16	2
50-54	2	12,326	18	16	20	424,018	15	5
55-59	0	13,073	19	0	25	469,288	17	5
60-64	2	11,730	17	17	44	448,822	16	10
65-69	5	9,071	13	55	52	370,701	14	14
70-74	1	5,384	8	19	64	267,359	10	24
75-79	0	2,609	4	0	58	169,625	6	34
80-84	2	999	1	200	50	88,192	3	57
85+	2	457	1	437	28	49,953	2	56
Total	14	69,562	100	25*	348	2,737,057	100	11*

(n=392,226 subjects) *Age-adjusted to the CPS-II population.

Age-SRR=2.2 (95% CI=1.2-3.9)

RR (m-h) age-adjusted=2.0 (95% CI=1.1-3.5)

Only 2.5 percent, or 9,664 subjects reported ever having occupational exposure to asbestos. Five percent of men in the analytic cohort for self-reported ETS fell in that category, and only 1.4 percent of women said they had ever been occupationally exposed in their life-time. Among those who said they had ever been exposed to asbestos at work, 65 percent were in the labor force by 1982. The occupations/industries more frequently mentioned by them included professions with presumably low exposure such as teaching (21 percent), management (11 percent), engineering (5 percent), and technicians (2 percent), as well as trades with potentially higher exposures such as automechanics (5 percent), and construction (2 percent). Twenty-five percent of those ever exposed to asbestos had retired from the same occupations.

Sixty percent of CPS II participants had previously held a job different from that currently held or at retirement. The major frequencies were approximately the same (teachers, managers, and salesmen, 10, 4 and 8 percent, respectively). In addition, 2 percent mentioned they also had worked at factories, 4 percent were farmers and fishermen, and 8 percent worked in offices.

Of those nonsmokers ever engaged in occupations known to carry likely high exposure to asbestos (i.e., shipbuilding, pipefitters), or likely low exposure to asbestos (i.e., plumber, construction, duckworker, autorepair, and electrician), or engaged in any occupation which fell in the category of 'possibly exposed' (See the detailed list in the Covariates section in 3.6), only those subjects who were reportedly ever engaged in shipbuilding trades (n=95) had a significant increased risk [multivariate RR=9.7 (95% CI=1.3-71.3)].

The number of years men and women were ever exposed to asbestos were grouped by tertiles of those ever exposed (i.e., the categories being 1-5 years, 6-15 years, and 16+ years of exposure) and compared with those who reportedly were never exposed to asbestos at work. Table 29 shows the deaths, person-years and rate ratios for men and women separately and combined in the last column. Among the 9,664 exposed CPS II participants, 8,316 (or 86 percent)

reported the number of years exposed; out of the 14 deaths among nonsmokers ever exposed to asbestos, only 12 had information on years of exposure. Multivariate rate ratios showed in the third, six and nine columns of table 29, indicate that the rate ratios increase with longer exposure; however, did not follow a consistent increasing trend. The risk of lung cancer among nonsmokers exposed to asbestos in this study increased to 3.1 for those who worked up to five years as compared to nonsmokers unexposed to asbestos and then decreased to 1.2 for those who worked 5 to 16 years and remained at 1.2 among those who worked more than twenty years. Among women there was a non-statistically significant increasing trend of lung cancer risk by years of self-reported exposure to asbestos (p=0.15), but not for men (p=0.66).

Self-reported occupational exposure to asbestos was a potential confounder of the ETS and lung cancer association, so we included asbestos in multivariate analysis.

Preexisting chronic lung disease

Medical history of any obstructive pulmonary disease (asthma, chronic bronchitis, or emphysema) or tuberculosis, or a combination of all of these conditions was not associated with the risk of lung cancer for men and women combined (RR=1.0 (95% CI=0.7-1.5)]. However, among men there was a statistically significant increased risk (RR=2.1, 95%CI=1.3-3.6), whereas among women, there was no association (RR=0.6, 95%CI=0.4-1.2). The interaction term of gender and history of chronic lung disease, when adjusting for all other covariates was statistically significant ($LR\chi^2_{df=1}$=9.2, p=0.002).

This apparent effect of reported medical history of preexisting lung disease on the risk of lung cancer among nonsmokers in CPS II was heavily influenced by the history of chronic bronchitis. There was an increased risk of lung cancer among nonsmoking men with a history of chronic bronchitis [multivariate RR=3.8 (95% CI=1.8-7.8)], and there was none among women [0.6 (95% CI=0.2-1.4)].

Table 29. Lung cancer rate ratios among nonsmokers by years of occupational exposure to asbestos, and gender, CPS II,1982-1989

Years of exposure	Deaths among Men	Men-Years	RR* (95% CI)	Deaths among Women	Women-Years	RR* (95% CI)	Deaths Men and Women	All person-years	RR** (95% CI)
None	108	745,894	1.0	240	1,991,163		356	2,737,057	1.0
Ever	8	40,638	1.5 (0.7-3.1)	6	28,925	2.3 (1.0-5.3)	14	69,562	1.8 (1.1-3.2)
1-5 yrs	6	12,793	3.6 (1.5-8.4)	1	7,456	1.9 (0.3-13.4)	7	20,249	3.1 (1.4-6.8)
6-15 yrs	1	9,708	1.1 (0.2-7.8)	1	9,280	1.3 (0.2-9.5)	2	18,988	1.2 (0.3-4.8)
16+ yrs	1	13,158	0.6 (0.1-4.2)	2	6,890	2.8 (0.7-11.2)	3	20,048	1.2 (0.4-3.9)
p for trend			0.66			0.15			0.23
Missing	0	4,979		2	5,298		2	10,277	

(n=392,058; 168 were exposed but had vague data on number of years exposed)
*Adjusted for age, schooling, 'race', consumption of foods containing carotenoids, total fat as a nutrient index, history of chronic lung disease, and ETS.
** In addition adjusted for gender.

Diet: foods containing carotenoids and total fat

After controlling for other covariates, a reduction in the risk of lung cancer was observed among nonsmokers with the highest reported frequency of consumption of a combination of the following foods containing carotenoids: carrots, squash and corn, green leafy vegetables, cabbage, broccoli and Brussels sprouts, tomato, and fruits and juices. There was a borderline significant trend of decreasing risk of death from lung cancer by increasing frequency of weekly intake of these food items ($LR\chi^2_{df=1}$=3.043, p value for trend=0.0811). Nonsmokers who were in the upper quintile of the distribution of total fat intake (as nutrient index) had a statistically significant increased risk of lung cancer as compared to those in the lowest category, after adjusting for all other covariates (age, 'race', gender, schooling, history of lung disease, frequency of consumption of foods containing carotenoids, and occupational exposure to asbestos). There was a statistically significant dose-response relationship between the risk of lung cancer among nonsmokers by increasing level of total fat intake ($LR\chi^2_{df=1}$=4.695, p value for trend=0.0302). There was a weak positive correlation between the frequency of consumption of foods containing carotenoids and total dietary fat intake (r_{xy}=0.29). The partial correlation coefficient controlling for schooling, age, gender, was essentially unchanged ($r_{xy|z1,z2,..zp}$=0.30).

Other risk factors

Nonsmokers who had ever been occupationally exposed to ionizing radiation showed a non-statistically significant increased risk of lung cancer [multivariate RR=1.6 (95% CI=0.7-3.5)] (Table 30). No evidence was found of an increasing trend of years of self-reported occupational exposure to ionizing radiation, when those ever exposed where grouped by tertiles of years of exposure to ionizing radiation at work: the multivariate RR were 0.9 (95% CI=0.2-3.7), 1.1(95% CI=0.3-4.5), and 0.9 (95% CI=0.2-3.6), for the first, second and third tertiles, respectively. The p value for a test for trend was 0.9.

Other occupational exposures to lung carcinogens such as formaldehyde, coal tar products, and chemicals, as recorded in CPS II questionnaire, were not associated with the risk of lung cancer among nonsmokers [multivariate RR=0.9 (95% CI=0.6-1.3)] (Table 30).

Multivariate rate ratios on the covariates presented in this section are summarized in table 30, and are all included in the model, along with self-reported ETS : age at interview grouped into nine five-year groups, gender, schooling and 'race' and history of chronic lung disease as dichotomous variables, frequency of consumption of foods containing carotenoids grouped into tertiles compared with no consumption of foods and vegetable, and total fat as a nutrient index grouped into quintiles. In addition, indicator variables were included for missing observations on 'race', schooling, and diet.

As shown in table 30, multivariate Cox regression analysis shows that when smokers under 50 years of age were used as referent, the RR estimates increased monotonically by every five-year age period: 1.8, 2.9, 4.4, 6.1, 8.2, 14.6, 14.6, and 22.4 . Men had a 30% increased risk as compared to women [RR=1.3 (95% CI=1.0-1.6)]. Non-whites had a 50% increased risk of lung cancer as compared to whites [RR=1.5 (95% CI=1.1-2.2)]. Asbestos was associated with almost a two-fold increased risk [RR=1.8 (95% CI=1.1-3.2)]. History of chronic lung disease was not associated with the risk of lung cancer among men and women together [RR-1.0 (95% CI= 0.7-1.5)]. Consumption of six groups of vegetables and fruits/juices was associated with a 30% decreased risk of lung cancer but showed no clear pattern of dose-response relationship. Subjects classified in the upper 20% of the distribution of intake of total fat as a nutrient index had a 70% increased risk of lung cancer; the intake of fat showed a statistically significant increasing trend with lung cancer death risk.

Table 30. Risk ratios of lung cancer among nonsmoking CPS II participants by non-ETS known risk factors

Risk Factors	Multivariate § RR (95% C.I.)	Risk Factors	Multivariate § RR (95% C.I.)
Age group		Gender	
<50	1.0		
50-54	1.8 (1.0-3.0)	Women	1.0
55-59	2.9 (1.8-4.7)		
60-64	4.4 (2.7-7.0)	Men	1.3 (1.0-1.6)
65-69	6.1 (3.8-9.9)		
70-74	8.2 (5.0-13.3)	Race	
75-79	14.4 (8.8-23.9)		
80-84	14.6 (8.1-26.6)	Whites	1.0
85+	22.4 (11.6-43.6)	Non-whites	1.5 (1.1-2.2)
Schooling		Frequency of consumption of carotenoid containing foods	
12 yrs. +	1.0		
<12 yrs.	1.2 (0.9-1.5)		
		None	1.0
Asbestos at work		Seldom to 2/ week	0.3 (0.1-0.8)
Never	1.0	3 week	0.3 (0.1-0.7)
Ever	1.8 (1.1-3.2)	>3 week	0.3 (0.1-0.7)
		p for trend	0.08
Ionizing radiation at work		Total fat as nutrient intake in quintiles	
Never	1.0	Least	1.0
Ever	1.5 (0.7-3.5)	2	1.2 (0.8-1.6)
		3	1.3(0.9-1.8)
		4	0.9 (0.6-1.3)
		Most	1.7 (1.2-2.3)
		p for trend	0.03
Other occupational exposures to lung carcinogens*		History of chronic lung disease	
None	1.0	None	1.0
Any	0.9 (0.6-1.3)	Any of these:	1.0 (0.7-1.5)
		Tuberculosis	1.1 (0.4-2.6)
		Emphysema	1.8 (0.8-4.2)
		Asthma	1.7 (0.9-3.6)
		Chronic bronchitis	1.2 (0.7-2.1)

(n=392,226) § Cox regression models included age, gender, 'race', schooling, ETS, frequency of foods containing carotenoids, total fat as a nutrient index, history of chronic lung diseases, and occupational exposure to asbestos. * Self-reported occupational exposure to any of: coal tar, formaldehyde, and chemicals.

7.3 Main exposure variables

7.3 a. Self-reported exposure to ETS

Table 31 shows the deaths from lung cancer among CPS II nonsmokers by any versus none self-reported ETS exposure. There was no indication of an association between self-reported ETS and the risk of lung cancer among nonsmokers when this exposure variable was treated as dichotomous (i.e., any versus 0 hours of exposure to ETS). The rate ratio adjusted for the age-gender distribution of person-time was 0.8 (95%CI=0.6-1.0). The unadjusted (i.e., confounded by age) rate ratio was 0.3. Table 31 displays the lung cancer death rates in persons with no versus any exposure to ETS at home, work or elsewhere.

The age-standardized rate ratio for men was 0.8 (95% CI=0.6-1.2) and for women 0.9 (95% CI=0.7-1.3). The age-adjusted Mantel-Haenszel mortality rate ratios were 0.6 (95% CI=0.4-1.0) and 0.9 (95% CI=0.7-1.2) for men and women respectively. The age-gender adjusted Mantel-Haenszel rate ratio was 0.8 (95%CI=0.6-1.0).

7.3.b Dose-response analyses of self-reported ETS

Table 32 presents the analysis by tertiles of self-reported hours of exposure to ETS (i.e., 1-2 hours, 3-5 hours and 6+ hours). Panel A of table 32 summarizes the information on the total number of persons in each category. This part of the table presents the number of lung cancer deaths, person years, and lung cancer death rates, among men, and women, separately and then combined in the last column. Panel B breaks down the previous numbers by five-year age groups.

Thus, when the comparison of lung cancer mortality rates was made by duration of daily exposure to ETS between nonsmokers unexposed to ETS (i.e., no self-

reported ETS exposure) and nonsmokers most heavily exposed (i.e., those in the upper tertile or exposed for 6 and more hours to ETS), subjects in this exposure category of ETS had a 20% increased risk of lung cancer, after adjustment for age and gender [RR_{m-h}=1.2 95% CI=(0.9-1.7)] Comparisons of the lung cancer death rates by tertile of ETS exposure among men and women are presented in Figure 8.

Further adjustment of the association between ETS exposure and the risk of lung cancer was then conducted *via* Cox regression by blocking for age (12 five-year groups) 'race' (whites versus non-whites), schooling (<12 years of education, vs 12+ years), gender, asbestos exposure (ever versus never), and a history of chronic lung disease (any versus none) as dichotmous variables, 3 indicator variables for the intake of foods containing carotenoids (grouping those who had one or more a week into tertiles), and 4 other indicators for total fat as a nutrient index (grouping all subjects by quintiles). This coding of the covariates is the same used to obtain the estimates presented in table 30. The results of the stratified Cox regression analyses are presented in table 33, and they show that inclusion of the covariates did not materially alter the reported association, once the confounding effect of age was controlled (Cfr. table 32 versus table 33). A multivariate test for dose-response was then conducted using this categorization of self-reported ETS as an ordinal variable, and failed to reject the null hypothesis.

Separate analyses were conducted for the number of hours of exposure to ETS at different settings (home, work and other places), using the approach of simple and stratified analysis by age described for the cumulative hours of exposure to ETS. These results are summarized in table 33, along with the multivariate results for all ETS. The findings were the same as for the cumulative measure.

Table 31. Lung cancer death rates among CPS II nonsmokers by self-reported ETS (any versus none), 1982-1989

Level:	Men						Women					
	0 hours of ETS			Any ETS			0 hours of ETS			Any ETS		
Age group	Deaths	P-Y	Rate	Deaths	P-Y	Rate	Deaths	P-Y	Rate	Deaths	P-Y	Rate
<50	1	33,932	3	2	87,246	2	3	133,717	2	1	208,117	0
50-54	0	40,625	0	4	92,511	4	9	131,105	7	9	172,103	5
55-59	0	48,610	0	4	95,551	4	7	158,650	4	14	179,550	8
60-64	6	52,560	11	10	78,917	13	15	175,460	9	15	153,614	10
65-69	16	56,440	28	11	53,144	21	19	171,875	11	11	98,310	11
70-74	20	49,773	40	6	26,448	23	28	147,678	19	11	48,843	23
75-79	11	31,781	35	3	11,025	27	40	105,983	38	4	23,445	17
80-84	15	15,519	97	2	3,803	53	32	59,479	54	3	10,389	29
85+	5	7,368	68	0	1,273	0	22	35,831	61	3	5,937	51
Total	74	336,614	14*	42	449,918	12*	175	1,119,778	10*	71	900,309	10*

(n=329,226)

*Age-standardized rates to the CPS II population.

RR any versus none both men and women (age-gender adjusted)=0.8 (95% CI=0.6-1.0)

RR any versus none for men (age adj. for men)=0.6 (95% CI=0.4-1.0)

RR any versus none for women (age adj. for women)=0.9 (95% CI=0.7-1.2)

Table 32. A. (Summary) Lung cancer deaths, nonsmokers and person-years and rates by self-reported ETS category among nonsmokers in CPS II

Exposure	Men			Women				Total			
	Deaths	Person-Years	Rate* x10^{-5}	Deaths	Person-Years	Rate* x10^{-5}		Deaths	Person-Years	Rate* x10^{-5}	
All subjects	116	110,688	786,532	16	246	281,538	2,020,081	11	362	392,226	2,806,613	12
0 Hours of ETS	74	48,175	336,614	15	175	157,258	1,119,778	11	249	205,433	1,456,392	12
1-2 Hours of ETS	20	36,820	264,812	9	29	55,810	404,565	8	49	92,630	669,378	9
3-5 Hours of ETS	8	10,301	74,060	18	11	24,255	175,376	9	19	34,556	249,436	11
6+ Hours of ETS	14	15,392	111,046	17	31	44,215	320,362	12	45	59,607	431,408	13

Table 32. B. Age distribution and lung cancer death rates by self-reported ETS category

Age group in years	Unexposed Men (0 hours of ETS exposure)				Unexposed Women (0 hours of ETS exposure)				Unexposed Subjects (0 hours of ETS exposure)			
	Deaths	Person-years at risk	(%)	Rates 10^{-5}	Deaths	Person-years at risk	(%)	Rates 10^{-5}	Deaths	Person-years at risk	(%)	Rates 10^{-5}
<50	1	33,932	10.1	3	3	133,717	11.9	2	4	167,648	11.5	2
50-54	0	40,625	12.1	0	9	131,105	11.7	7	9	171,730	11.8	5
55-59	0	48,610	14.4	0	7	158,650	14.2	4	7	207,260	14.2	3
60-64	6	52,560	15.6	11	15	175,460	15.7	9	21	228,020	15.7	9
65-69	16	56,444	16.8	28	19	171,875	15.3	11	35	228,319	15.7	15
70-74	20	49,774	14.8	40	28	147,678	13.2	19	48	197,452	13.6	24
75-79	11	31,781	9.4	35	40	105,983	9.5	38	51	137,764	9.5	37
80-84	15	15,519	4.6	97	32	59,479	5.3	54	47	74,998	5.1	63
85+	5	7,370	2.2	68	22	35,831	3.2	61	27	43,200	3.0	62
Total	74	336,614	100.0	15*	175	1,119,778	100.0	11*	249	1,456,391	100.0	12*
	m-h age-adj RR=1.0				m-h age-adj RR=1.0				m-h gender-age-adj RR=1.0			

*Age-adjusted to the CPS-II population

Table 32. (continued)

Age group in years	Exposed Men (1-2 hours of ETS exposure) Deaths	Person-years at risk	(%)	Rates 10^{-5}	Exposed Women (1-2 hours of ETS exposure) Deaths	Person-years at risk	(%)	Rates 10^{-5}	Exposed Subjects (1-2 hours of ETS exposure) Deaths	Person-years at risk	(%)	Rates 10^{-5}
<50	2	47,965	18.1	4	1	94,276	23.3	1	3	142,242	21.2	2
50-54	2	52,918	20.0	4	5	76,538	18.9	7	7	129,456	19.3	5
55-59	1	55,079	20.8	2	6	78,929	19.5	8	7	134,008	20.0	5
60-64	5	46,170	17.4	11	5	67,636	16.7	7	10	113,806	17.0	9
65-69	3	33,230	12.5	9	4	44,868	11.1	9	7	78,098	11.7	9
70-74	5	18,087	6.8	28	5	23,309	5.8	21	10	41,397	6.2	24
75-79	2	7,800	2.9	26	2	11,542	2.9	17	4	19,341	2.9	21
80-84	0	2,713	1.0	0	0	4,974	1.2	0	0	7,687	1.1	0
85+	0	851	0.3	0	1	2,494	0.6	40	1	3,345	0.5	30
Total	20	264,812	100.0	9*	29	404,565	100.0	8*	49	669,378	100.0	9*

Men: m-h age-adj. RR=0.6 (95%CI=0.4-1.0) Women:m-h age-adj. RR=0.8 (95%CI=0.5-1.2)

Both: m-h gender-age adj. RR=0.7(95%CI=0.5-1.0)

*Age-adjusted to the CPS-II population

Table 32. (continued)

Age group in years	Exposed Men (3-5 hours of ETS exposure)				Exposed Women (3-5 hours of ETS exposure)				Exposed Subjects (3-5 hours of ETS exposure)			
	Deaths	Person-years at risk	(%)	Rates 10^{-5}	Deaths	Person-years at risk	(%)	Rates 10^{-5}	Deaths	Person-years at risk	(%)	Rates 10^{-5}
<50	0	15,754	21.3	0	0	39,517	22.5	0	0	55,271	22.2	0
50-54	0	15,635	21.1	0	0	33,808	19.3	0	0	49,443	19.8	0
55-59	1	15,840	21.4	6	2	34,675	19.8	6	3	50,515	20.3	6
60-64	3	12,593	17.0	24	1	28,857	16.5	3	4	41,450	16.6	10
65-69	2	7,985	10.8	25	1	18,981	10.8	5	3	26,966	10.8	11
70-74	0	3,840	5.2	0	3	10,302	5.9	29	3	14,143	5.7	21
75-79	0	1,651	2.2	0	0	5,341	3.0	0	0	6,992	2.8	0
80-84	2	528	0.7	379	2	2,440	1.4	82	4	2,968	1.2	135
85+	0	234	0.3	0	2	1,455	0.8	137	2	1,689	0.7	118
Total	8	74,060	100.0	18*	11	175,376	100.0	9*	19	249,436	100.0	11*

m-h age-adj. RR=1.1 (95%CI=0.5-2.3) m-h age-adj. RR=0.7 (95%CI=0.4-1.3)

m-h gender-age adj. RR=0.9(95%CI=0.5-1.4)

*Age-adjusted to the CPS-II population

Table 32. (continued)

Age group in years	Exposed Men (6+ hours of ETS exposure)				Exposed Women (6+ hours of ETS exposure)				Exposed Subjects (6+ hours of ETS exposure)			
	Deaths	Person-years at risk	(%)	Rates 10^{-5}	Deaths	Person-years at risk	(%)	Rates 10^{-5}	Deaths	Person-years at risk	(%)	Rates 10^{-5}
<50	0	23,527	21.2	0	0	74,324	23.2	0	0	97,850	22.7	0
50-54	2	23,958	21.6	8	4	61,754	19.3	6	6	85,712	19.9	7
55-59	2	24,632	22.2	8	6	65,945	20.6	9	8	90,576	21.0	9
60-64	2	20,154	18.1	10	9	57,122	17.8	16	11	77,276	17.9	14
65-69	6	11,929	10.7	50	6	34,462	10.8	17	12	46,390	10.8	26
70-74	1	4,521	4.1	22	3	15,232	4.8	20	4	19,752	4.6	20
75-79	1	1,575	1.4	64	2	6,562	2.0	30	3	8,137	1.9	37
80-84	0	563	0.5	0	1	2,975	0.9	34	1	3,538	0.8	28
85+	0	188	0.2	0	0	1,988	0.6	0	0	2,176	0.5	0
Total	14	111,046	100.0	17*	31	320,362	100.0	12*	45	431,408	100.0	13*

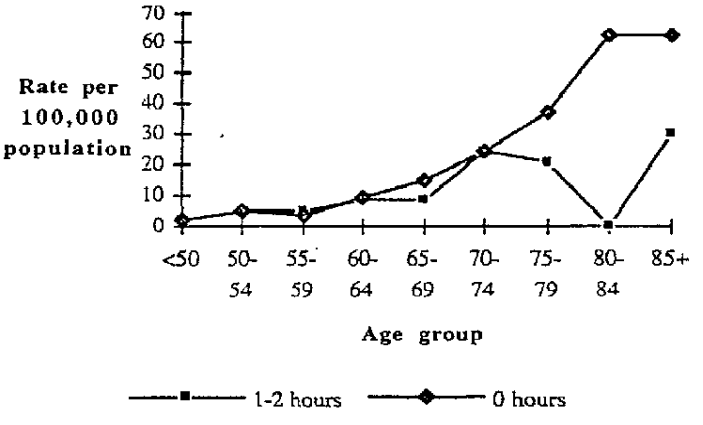
m-h age-adj. RR=1.4 (95%CI=0.7-2.5) m-h age-adj. RR=1.2 (95%CI=0.8-1.8)

m-h gender-age adj. RR=1.2(95%CI=0.9-1.7)

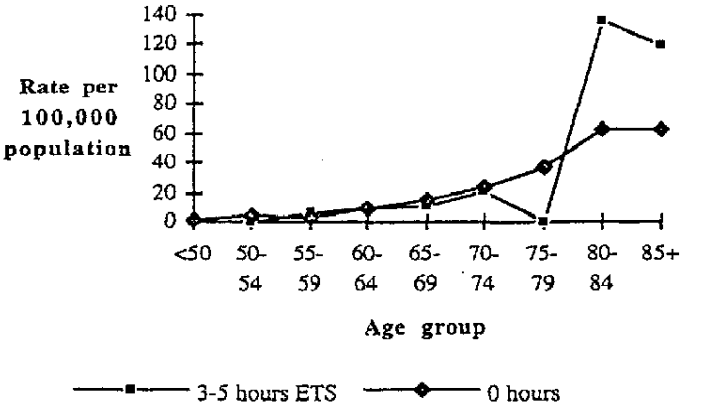
*Age-adjusted to the CPS-II population

Figure 8. Mortality rates from lung cancer among nonsmokers, by tertiles of self-reported ETS exposure and among unexposed, CPS II, 1982-1989

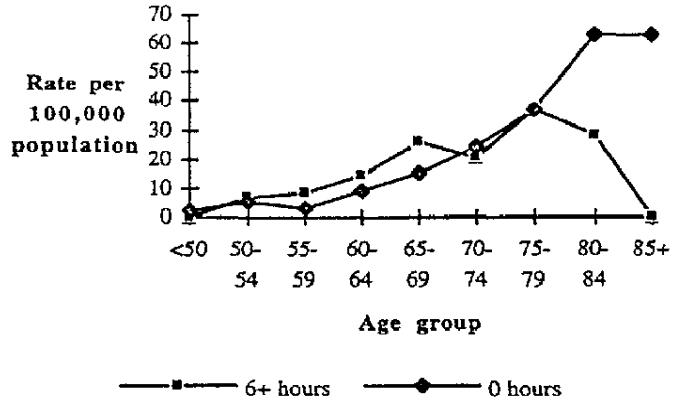
a) 1-2 hours versus 0 hours



b) 3-5 hours versus 0 hours



c) 6+ hours versus 0 hours



None of the rate ratios by increasing amount of hours of self-reported ETS exposure at home, work or elsewhere, displayed in table 33, showed a statistically significant slope of a linear trend using Cox regression analysis. Moreover, there is a consistent pattern of risk deficit for low self-reported ETS exposure categories.

Table 33. Cox regression multivariate lung cancer rate ratios for ETS exposure, cumulative and for specific sites, by gender, among CPS II nonsmoking participants, 1982-1989.

	Men	Women	Total
Hours of exposure by Source	Multivariate Rate Ratio§ (95 % CI)	Multivariate Rate Ratio§ (95 % CI)	Multivariate Rate Ratio§§ (95 % CI)
All ETS			
0	1.0	1.0	1.0
1-2	0.6 (0.4-1.1)	0.8 (0.6-1.3)	0.7 (0.5-1.0)
3-5	1.0 (0.4-2.0)	0.7 (0.4-1.3)	0.8 (0.5-1.3)
6 + hours	1.3 (0.7-2.4)	1.1 (0.8-1.7)	1.2 (0.8-1.7)
Home			
0	1.0	1.0	1.0
1-3	0.7 (0.2-2.0)	0.4 (0.2-1.0)	0.5 (0.2-1.0)
4-5	0.0 (0.0-NC)	0.7 (0.3-1.7)	0.6 (0.2-1.4)
6 + hours	0.5 (0.1-3.9)	1.3 (0.8-2.1)	1.2 (0.7-1.9)
Work			
0	1.0	1.0	1.0
1	0.7 (0.3-1.6)	0.9 (0.5-1.9)	0.8 (0.5-1.4)
2-6	1.0 (0.5-2.1)	1.1 (0.6-2.1)	1.1 (0.6-1.7)
7+ hours	1.8 (0.9-3.6)	1.0 (0.5-1.8)	1.2 (0.8-2.0)
Other places			
0	1.0	1.0	1.0
1	0.5 (0.3-1.0)	1.0 (0.6-1.7)	0.7 (0.5-1.1)
2	0.7 (0.2-2.2)	0.8 (0.3-2.2)	0.7 (0.4-1.6)
3 + hours	1.1 (0.4-3.0)	1.1 (0.5-2.5)	1.1 (0.6-2.0)

§ Adjusted for age, race, education, intake of carotenoid-containing foods, total fat as a nutrient index, occupational exposure to asbestos and history of chronic lung disease.
§§ Additionally adjusted for gender.

7.3.c. Spousal ETS

The relationship between environmental tobacco smoke exposure from spousal smoking and lung cancer mortality among nonsmokers was then assessed. Exposure to ETS based on exposure by a nonsmoking spouse to tobacco smoke from a smoking spouse was further defined based on whether the spouse was a nonsmoker or ever smoked, if the spouse was a current or former smoker (i.e., if the nonsmoker was ever, current or formerly exposed to ETS from the smoking habits of spouse).

Comparisons of lung cancer death rates by ETS exposure from ever versus never smoking spouses showed no indication of an increased risk: the Mantel-Haenszel age-gender adjusted rate ratios were 1.0 (95% CI=0.7-1.4) for all nonsmoking spouses, and 0.9 (95% CI=0.7-1.5) for husbands and 1.1 (95% CI=0.8-1.5) for nonsmoking wives, respectively.

Table 34 shows lung cancer mortality associated with exposure and no exposure to ETS from current smoking spouses for men and women, separately, and by the nine five-year age groups. The first four columns of table 34 present the data for nonsmokers married to current smokers of any type of tobacco product; the last four present the corresponding data for nonsmokers married to nonsmokers.

Examination of lung cancer death rates presented as person-years for spouses, of either gender, shown in Table 34, are not appreciably different whether they were exposed or unexposed to ETS from a current smoking spouse. For example, the death rate columns for these ETS-exposed spouses show no appreciable differences across age groups among men, though a slightly greater mortality was observed among older women, as is graphically presented in figure 9. For nonsmoking spouses married to current smokers of any type of tobacco the RR was slightly above unity [RR(m-h)=1.2 (95% CI=0.8-1.9)] for men and women combined, after adjusting for the age and gender distribution. For men, marriage to a current smoker was not associated with an increased risk [RR(m-

h)=0.9 95% CI=0.4-1.9)]. The corresponding age-adjusted estimate for nonsmoking women married to a current smoker was 1.3 (95% CI=0.8-1.9).

Nonsmokers married to former smokers had no increased risk of lung cancer: the age-adjusted estimate for men and women combined was 1.0 (95% CI=0.7-1.3). This was true both for men and women in our study, with age-adjusted rate ratios of 0.9 (95% CI=0.5-1.6), and 1.0 (95% CI=0.7-1.5), respectively.

Most of smoking spouses smoked cigarettes. The relationships described above regarding current smoking spouses were true also for current cigarette smoking spouses: men married to current cigarette smoking women had an age-adjusted rate ratio of 0.9 (95%CI=0.3-1.9), whereas women married to current cigarette smokers had an age-adjusted rate ratio of 1.2 (95%CI=0.7-2.0). The age-gender adjusted RR was 1.1 (95% CI=0.7-1.7).

Table 34. Age-specific lung cancer rates among nonsmokers by smoking status (current §-any type of tobacco vs. life-long nonsmokers) of the spouses, CPS II, 1982-1989.

a. Men

Age Group	Deaths among married to current smokers	PY among married to current smokers	(%)	Rate 10^5	Deaths among married to never smokers	PY among married to never smokers	(%)	Rate 10^5
<50	0	9,133	14	0	1	64,314	12	2
50-54	1	12,593	20	8	1	88,297	17	1
55-59	0	13,568	21	0	4	97,670	19	4
60-64	4	11,509	18	35	12	91,288	17	13
65-69	2	8,760	14	23	23	78,696	15	29
70-74	0	5,031	8	0	18	55,503	11	32
75-79	0	2,180	3	0	8	30,941	6	26
80-84	0	701	1	0	9	13,672	3	66
85+	0	177	0	0	3	5,083	1	59
Total	7	63,652	100	10*	79	525,464	100	14*

§ Excludes current smoking spouses with incomplete smoking data.
Age adjusted MH RR=0.9 (95% CI=0.3-1.9). *Age-adjusted to the CPS II population

b. Women

Age Group	Deaths among married to current smokers	PY among married to current smokers	(%)	Rate 10^5	Deaths among married to never smokers	PY among married to never smokers	(%)	Rate 10^5
<50	0	77,591	21	0	2	108,378	21	2
50-54	4	72,473	19	6	6	94,967	18	6
55-59	7	76,798	20	9	8	94,598	18	8
60-64	14	66,410	18	21	8	85,095	16	9
65-69	3	45,069	12	7	7	66,320	13	11
70-74	7	24,182	6	29	13	41,303	8	31
75-79	5	10,575	3	47	6	20,762	4	29
80-84	3	3,249	1	92	1	7,534	1	13
85+	0	727	0	0	0	2,105	0	0
Total	43	377,074	100	15*	51	521,062	100	11*

§ Excludes current smoking spouses with incomplete cigarette smoking data
Age adjusted MH RR=1.3 (95% CI=0.8-1.9). *Age-adjusted to the CPS II population

Figure 9. a) Rates of lung cancer among nonsmoking men by smoking status of their wives, CPS II 1982-1989

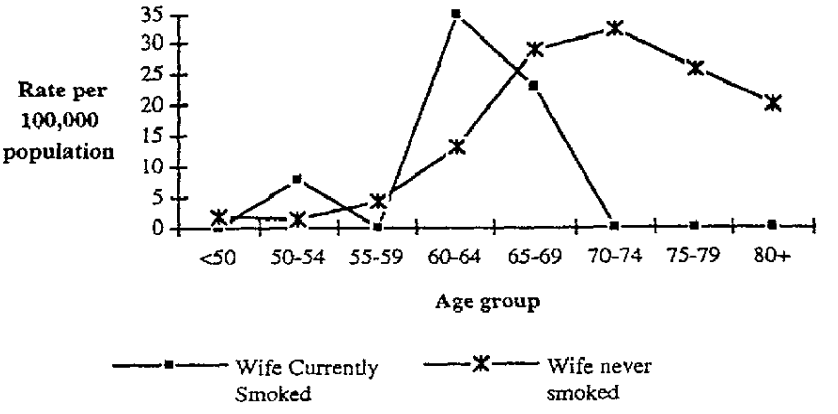


Figure 9. b) Rates of lung cancer among nonsmoking women by smoking status of their husbands, CPS II 1982-1989

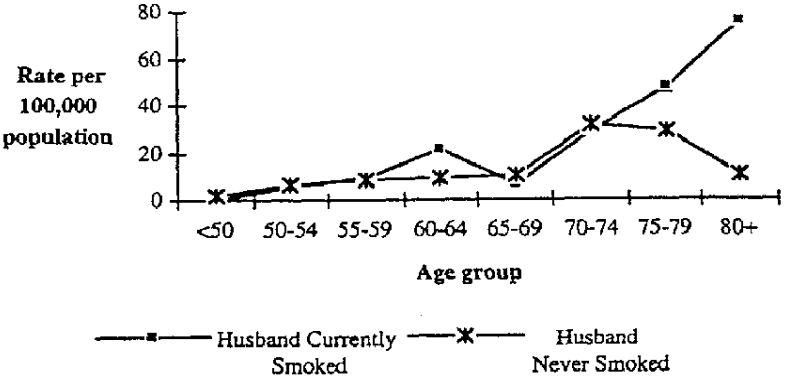


Table 35 presents lung cancer deaths, person-years and lung cancer death rates among nonsmoking women exposed to ETS from pipe/cigar current smoking of their spouses, compared to those among women married to nonsmokers. Death rates for lung cancer among nonsmoking women married to current pipe/cigar smokers increased more rapidly after age 70, than in those married to nonsmoking husbands. However, the small numbers of deaths make age specific estimates unstable. Nevertheless, it seems that exposure to ETS from spousal pipe/cigar has a weak statistically insignificant effect on the risk of lung cancer.

More details on the types of smoking habits of spouses of nonsmoking subjects and their risk of lung cancer is displayed in table 36, along with a summary of the results of spousal ETS analysis described above. The first row of table 36 presents the number of lung cancer deaths and person-years among nonsmokers in the entire cohort. The second row presents those numbers for men and women married to nonsmokers, as the referent category for analyses of the effect of ETS from spousal smoking. Thereafter those numbers for each category of smoking spouses are given along with age and age-gender adjusted Mantel-Haenszel rate ratios, as well as multivariate rate ratios controlling for all relevant covariates included in analyses of self-reported ETS. Nonsmoking wives married to current cigarette, pipe and cigar smokers showed an elevated risk of lung cancer. Nonsmokers married to former smokers, except for cigar/pipe smoking spouses, did not have an increased risk of lung cancer.

Table 35. Age-specific lung cancer rates among nonsmoking women by cigar/pipe smoking status (current vs. life-time nonsmokers) of their husbands, CPS II, 1982-1989.

Age Group	Deaths among married to current pipe/cigar smokers	PY among married to current smokers	(%)	Rate 10^5	Deaths among married to never smokers	PY among married to never smokers	(%)	Rate 10^5
<50	0	24,967	17	0	2	108,378	21	2
50-54	0	25,615	18	0	6	94,967	18	6
55-59	0	28,490	20	0	8	94,598	18	8
60-64	7	26,281	18	27	8	85,095	16	9
65-69	2	18,945	13	11	7	66,320	13	11
70-74	5	11,096	8	45	13	41,303	8	31
75-79	3	5,526	4	54	6	20,762	4	29
80-84	1	1,918	1	52	1	7,534	1	13
85+	0	494	0	0	0	2,105	0	0
Total	18	143,341	100	15*	51	521,062	100	11*

Age adjusted Mantel-Haenszel RR=1.3 (95% CI=0.7-2.2).
*Age-adjusted to the CPS II population

This relationship between current smoking of spouses and the risk of lung cancer did not change when 'race', schooling, history of lung disease, frequency of consumption of foods containing carotenoids, and occupational asbestos exposure were allowed into the Cox regression model, along with age, as shown in table 36, suggesting that there was no confounding by these covariates.

Table 36. Association between smoking status, type of smoking of spouses of nonsmoking CPS II subjects, and lung cancer risk.

Spouse smoked tobacco (by type)	Husbands Deaths	Husbands Person-Years	Wives Deaths	Wives Person-Years	Total Deaths	Total Person-Years
Total	101	719,044	164	1,544,935	265	2,263,979
Never	79	525,464	51	521,062	130	1,046,526
RRm-h*		1.0		1.0		1.0
RRCox§		1.0		1.0		1.0
Ever ** (any type)	22	193,580	113	1,023,873	135	1,217,453
RRm-h*		0.9 (0.5-1.5)		1.1 (0.8-1.5)		1.1 (0.8-1.5)
RRCox§		0.9 (0.6-1.4)		1.1 (0.8-1.6)		1.0 (0.8-1.4)
Current (any type)	8	67,689	44	385,676	52	453,365
RRm-h*		0.9 (0.3-1.9)		1.3 (0.8-1.9)		1.2 (0.8-1.9)
RRCox§		1.0 (0.5-2.0)		1.3 (0.8-1.9)		1.2 (0.8-1.8)
Former (any type)	13	117,462	68	614,961	81	732,423
RRm-h*		0.9 (0.5-1.6)		1.0 (0.7-1.5)		1.0 (0.7-1.3)
RRCox§		1.1 (0.6-2.8)		1.1 (0.7-1.6)		1.0 (0.7-1.4)
Ever Cigarettes	22	193,580	74	709,944	96	903,524
RRm-h*		0.9 (0.5-1.5)		1.0 (0.7-1.5)		1.1 (0.7-1.4)
RRCox§		1.0 (0.5-2.0)		1.1 (0.8-1.6)		1.0 (0.7-1.8)
unclass. ever smoker	1	8,429	1	23,236	2	31,665
Current cigarettes	7	63,652	25	233,743	32	297,395
incomplete	1	4,037	1	8,592	2	12,629
RRm-h*		0.9 (0.4-1.9)		1.3 (0.8-1.9)		1.1 (0.7-1.5)
RRCox§		1.0 (0.5-2.0)		1.3 (0.8-2.0)		1.2 (0.8-1.9)
Former cigarettes	10	103,945	44	414,146	54	518,091
incomplete	3	13,517	3	30,227	6	43,744
RRm-h*		0.9 (0.5-1.6)		1.0 (0.6-1.5)		0.9 (0.7-1.3)
RRCox§		1.1 (0.6-2.8)		1.2 (0.8-1.8)		1.1 (0.7-1.9)
Ever Cigar/Pipes			39	313,929	39	313,929
m-h*				1.2 (0.8-1.8)		
Cox§				1.1 (0.8-1.6)		
Current			18	143,341		
m-h*				1.3 (0.7-2.2)		
Cox				1.5 (0.8-2.9)		
Former			21	170,588		
m-h*				1.1 (0.7-1.9)		
Cox§				1.3 (0.6-2.8)		

(n=314, 108) *M-H: age adjusted using Mantel-Haenszel
§ Cox: multivariate regression using the proportional hazard model to control for age, gender (for estimates listed in last column), 'race' and schooling, asbestos, history of chronic lung disease, consumption of foods containing carotenoids, and total fat as nutrient index.
**Includes 2 ever smokers with unclassifiable smoking (i.e., former or current cigarette smokers).

7.3.d. Relationship between lung cancer death and ETS exposure by amount, duration, and both

The dose-response relationship between lung cancer death and ETS exposure was assessed in a variety of ways. We first examined amount of ETS exposure by measuring the number of packs of cigarettes smoked by current or former cigarette smoking spouses. We also examined the number of years nonsmokers were exposed to ETS from the smoking of their spouses. Finally, we examined both amount and duration using pack-years as a measure of cumulative ETS exposure. For these three analyses, we included data about subjects whose spouses were ever cigarette smokers, as the ETS-exposed group, and subjects whose spouses were never smokers, as the referent group.

Table 37 shows lung cancer deaths per person-years for ETS-exposed spouses and multivariate rate ratios by packs of cigarettes smoked by their spouses compared with the referent group of non ETS-exposed spouses. These estimates are presented by gender and then combined for subjects exposed to a spouse who was either a current or a former smoker. The upper panel of the table presents the data to compare the rates among nonsmokers married to current smoking spouses, and the lower for former smoking spouses; rate ratios are presented by categories of amount of smoking grouped by packs of cigarettes. The risk of lung cancer among men married to current cigarette smokers only increased among those who smoked less than one pack [RR=2.0 (95%CI=0.9-4.4)] but the rate ratios decreased for the categories of heaviest cigarette smoking. Among women there was also an increased risk for those exposed to ETS from less than one pack of cigarette smoking, and declined among those married to current heavy smokers. No consistent linear trend with amount currently smoked by spouses was found.

Table 37. Lung Cancer Adjusted Rate Ratios (95% CI) among nonsmoking spouses according to the amount of cigarette smoked by spouses*, CPS II, 1982-1989.

Exposure	Husbands		Wives		All Nonsmokers
Packs of cigarettes: by current smokers	Deaths/PY	multivariate RR (95% CI)	Deaths/PY	multivariate RR (95% CI)	multivariate RR (95% CI)
Nonsmokers	79/525,464	1.0	51/521,062	1.0	1.0
< 1 pack	7/28,923	2.0	8/61,820	1.4	1.6
		(0.94.4)		(0.6-2.9)	(0.9-2.7)
1 - 1.9 packs	0/29,756	0	15/126,087	1.4	1.0
		(0-NC)		(0.8-2.6)	(0.6-1.8)
2+ packs	0/4.973	0	2/45,836	0.6	0.5
		(0-NC)		(0.1-2.3)	(0.1-2.0)
p test for trend		0.26		0.66	0.90
by former smokers	Deaths/PY	multivariate RR (95% CI)	Deaths/PY	multivariate RR (95% CI)	multivariate RR (95% CI)
Nonsmokers	79/525,464	1.0	51/521,062	1.0	1.0
< 1 pack	5/64,258	0.6	10/108,365	0.8	0.8
		(0.3-1.6)		(0.5-1.8)	(0.5-1.4)
1 - 1.9 packs	4/32,191	1.0	20/213,304	0.8	0.9
		(0.3-2.8)		(0.5-1.4)	(0.6-1.4)
2+ packs	1/7,495	1.2	14/92,462	1.5	1.5
		(0.2-1.9)		(0.8-2.7)	(0.8-2.6)
p test for trend		0.74		0.58	0.72

(n=258,499)

*Only cigarette smokers (current and former) with complete data .

§ Cox regression model stratified for age, gender, 'race', schooling, total intake of foods containing carotenoids, total fat intake, occupational exposure to asbestos and history of chronic lung disease.

A possible problem with the aforementioned analysis is that some ETS-exposed spouses may have been previously married to someone who was not a smoker. Thus, it was decided to re-examine the realtionship between lung cancer mortality and ETS exposure by packs of cigarettes smoked by spouses by restricting to an analysis of spouses married only once in their lifetime.

Table 38 presents lung cancer deaths, person years and multvariate rate ratios by amount of cigarettes smoked by current or former smokers as was presented above for the full data set. The analysis is restricted to the 148,402 spouses married once and who had complete information on age at marriage. The same group of nonsmokers unexposed to ETS is the referent.

Unlike in the previous analysis of the full data set of nonsmokers married to cigarette smokers, in this subset of spouses married once in their life-time, among nonsmokers married to former smokers, there is a slightly increased risk of lung cancer for those married to former smokers who smoked 2+ packs of cigarettes. However, there is no statistically significant trend: the p value of multivariate Cox regression analyses of the packs of cigarettes smoked by former smokers were 0.28 for men -decreasing trend, and 0.29 for women whose risks showed an increasing, but inconsistent trend, and 0.6 for both men and women.

Table 38. Lung Cancer Adjusted Rate Ratios (95% CI) among nonsmoking spouses according to the amount of cigarette smoked by spouses* if married once and with data on age at marriage, CPS II, 1982-1989.

Exposure	Husbands		Wives		All Nonsmokers
Packs of cigarettes: by current smokers	Deaths/PY	multivariate RR (95% CI)	Deaths/PY	multivariate RR (95% CI)	multivariate RR (95% CI)
Nonsmokers	46/314,944	1.0	30/311,333	1.0	1.0
< 1 pack	5/14,310	3.0	5/32,524	1.7	2.1
		(1.1-7.9)		(0.7-4.4)	(1.1-4.1)
1 - 1.9 packs	0/15,054	0.0	10/69,060	1.6	1.2
		(0.0-NC)		(0.8-3.4)	(0.6-2.3)
2+ packs	0/2,308	0.0	2/24,900	0.9	0.8
		(0.0-NC)		(0.2-3.9)	(0.2-3.5)
p test for trend		0.6		0.34	0.55
by former smokers	Deaths/PY	multivariate RR (95% CI)	Deaths/PY	multivariate RR (95% CI)	multivariate RR (95% CI)
Nonsmokers	46/314,944	1.0	30/311,333	1.0	1.0
< 1 pack	1/34,042	0.2	4/61,677	0.6	0.5
		(0.0-1.7)		(0.2-1.8)	(0.2-1.2)
1 - 1.9 packs	0/15,915	0.0	12/120,585	0.8	0.7
		(0.0-NC)		(0.4-1.7)	(0.3-1.4)
2+ packs	1/3,559	2.8	11/49,304	2.0	1.9
		(0.4-21.6)		(1.0-4.0)	(1.0-3.7)
p test for trend		0.28		0.29	0.6

(n=148,204)

* Analyses restricted to nonsmoking spouses married to nonsmoking spouses and those married to cigarette smokers (and not other type of tobacco), with complete smoking data, married once at the time of interview, and with valid data on age at first marriage.

§ Cox regression model stratified for age, gender, 'race', schooling, total intake of foods containing carotenoids, total fat as nutrient index, occupational exposure to asbestos and history of chronic lung disease. NC=not calculable

The hypothesis of this study was submitted to a more severe test to take into account the time these spouses married once in their life-time spent together (i.e., whether or not these nonsmokers were exposed to ETS from the smoking habits of their spouses).

The relationship between lung cancer mortality and ETS exposure by duration was examined. To conduct these analyses, it was necessary to estimate the number of years nonsmokers were exposed to ETS from spousal cigarette smoking. For this variable, the referent groups represented spouses who were not exposed, either because thay were married to nonsmokers or to former smokers who quit smoking before marriage (i.e., in doing so, those nonsmokers were never exposed to the tobacco smoke of their spouses). This resulted in reclassifying from the exposed categories 4 percent of the person-time, and 1 death (0.8 percent) in this analytic cohort, to the unexposed category. Therefore, the specificity of classification of exposure to ETS was increased. Table 39 shows deaths per person-years for ETS-exposed spouses by duration, accounting for the eight covariates presented in table 30. Distribution of time in marriage are gender-specific. For estimates of the RR for both men and women, we used the combined distribution of time in marriage to smokers.

Nonsmoking men married to smokers for 15 or more years did not have an increased risk of lung cancer, although there were fewer persons in these categories. Nonsmokers married up to 15 years to smoking wives had a 30 percent increased risk. We found no evidence that the rate ratios increased among nonsmoking men by time in marriage with smokers. However, rate ratios increased among women as the time in marriage from one to seventeen years to smokers, and then decreased slightly, in an erratic trend shown in table 39.

Table 39. Lung Cancer Adjusted Rate Ratios (95% CI) among nonsmoking spouses according to time in marriage with current cigarette smoking spouses*, CPS II, 1982-1989.

	Husbands			Wives			Both
Years married to smoker	Deaths/PY	multivariate RR (95% CI)	Years married to smoker	Deaths/PY	multivariate RR (95% CI)	Years married to smoker	multivariate RR (95% CI)
0 years (Nonsmokers and quitters before marriage)	46/329,905	1.0	0 years (Nonsmokers and quitters before marriage)	30/334,946	1.0	0 years (Nonsmokers and quitters before marriage)	1.0
1-15	1/22,101	0.4 (0.0-3.1)	1-17	13/107,681	1.5 (0.8-3.0)	1-17	1.2 (0.6-2.2)
16-26	1/29,918	1.2 (0.0-3.7)	18-29	14/112,761	1.3 (0.7-2.6)	18-29	1.2 (0.7-2.2)
27+	5/18,208	0.7 (0.2-2.7)	30+	17/114,002	1.2 (0.6-2.2)	30+	1.0 (0.6-1.8)
test for trend		0.76	test for trend		0.49	test for trend	0.72

(n=148,204)

* Analyses restricted to nonsmoking spouses married to nonsmoking spouses and those married to cigarette smokers (and not other type of tobacco), with complete smoking data, married once at the time of interview, and with valid data on age at first marriage. § Cox regression model stratified for age, gender, 'race', schooling, total intake of foods containing carotenoids, total fat as nutrient index, occupational exposure to asbestos and history of chronic lung disease.

Finally, the relationship between lung cancer deaths and ETS exposure was examined by both amount and duration. Pack-years, the exposure variable for this analysis, was created by multiplying the packs of cigarettes (i.e., amount) by the number of years of exposure (i.e., duration). For example 20 pack-years could have been reached during marriage for 20 years with a smoker who smoked one pack of cigarettes daily . This variable represents cumulative exposure to ETS over time. As mentioned above for time in marriage, for estimates of the RR for both men and women, we used the combined distribution of pack-years of smoking spousal.

Table 40 presents lung cancer deaths, person-years, and rate ratios among nonsmoking men, women and then both men and women, by pack-years according to the quintiles of the distribution of pack-years of smoking of the spouses during marriage with further adjustment for the same confounders in table 30.

Nonsmoking husbands were exposed to considerably less ETS from spousal smoking than nonsmoking wives. As was shown before fewer nonsmoking men fell into any of the categories of heavy spousal ETS from cigarette smoking (i.e., 15+ pack years), whereas, 32 percent of the nonsmoking women experienced such exposure and were evenly divided across the categories of pack-years of cigarette smoking of their cigarette smoking husbands.

The multivariate rate ratios of lung cancer among nonsmoking men increased by cumulative exposure to ETS up to 22 pack-years of cigarette smoking, and then decreased. Thus no consistency in the variation of lung cancer risk and this measure of long-term ETS exposure was found among nonsmoking men.

However, among women, the rate ratios increased consistenly by pack-years of cigarette smoking of their husbands, from 1.1 among slightly ETS exposed women, to 1.1 among women exposed from 17 to 35 pack-years, and then roughly reached a 50% increased risk for women exposed from 36 pack-years and more. The associated p value for the multivariate test of linear trend was 0.14, thus failing to reject the null hypothesis of nolinear trend.

Pack-years of cigarette smoking during marriage, was not statistically significant associated with increasing risk of lung cancer of both nonsmoking husbands and wives (p=0.54) (Table 40).

Table 40. Lung Cancer Adjusted Rate Ratios (95% CI) among nonsmoking spouses according to pack-years of spousal cigarette smoking, CPS II, 1982-1989.

		Husbands			Wives	Both
Pack-years	Deaths/PY	multivariate RR (95% CI)	Pack-years	Deaths/PY	multivariate RR (95% CI)	multivariate RR (95% CI)
0	46/329,905	1.0	0	30/334,946	1.0	1.0
1-8	1/24,018	0.4	1-16	10/112,318	1.1	1.0
		(0.1-2.9)			(0.5-2.2)	(0.6-1 9)
9-22	2/23,438	1.4	17-35	16/113,119	1.3	1.2
		(0.5-4.2)			(0.7-2.5)	(0.7-2.1)
23+	2/23,862	0.5	36+	18/109,006	1.5	1.1
		(0.1-2.2)			(0.8-2.8)	(0.6-1.9)
test for trend		0.54	test for trend		p=0.14	p=0.54

(n=148,204)

* Analyses restricted to nonsmoking spouses married to nonsmoking spouses and those married to cigarette smokers (and not other type of tobacco), with complete smoking data, married once at the time of interview, and with valid data on age at first marriage. § Cox regression model stratified for age, gender, 'race', schooling, total intake of foods containing carotenoids, total fat as nutrient index, occupational exposure to asbestos and history of chronic lung disease.

7.4 Joint effects of ETS and asbestos exposure

Further analyses were conducted to describe the effect of ETS among those subjects exposed to asbestos. Occupational exposure to asbestos was reported by only 2.5 percent of CPS II participants. As shown in Table 21, asbestos exposure was reported three times more frequently by men than women. Using the CPS II cohort for analyses of self-reported ETS, we contrasted lung cancer death rates of grouping subjects by tertiles of self-reported ETS exposure and by ever or never exposed to asbestos. Nonsmokers heavily exposed to ETS (≥6 hours) in 1982, and who had ever been exposed to asbestos at work, experienced a higher risk of lung cancer than expected if the effects of ETS and asbestos were independent. Table 41 shows the results of these analysis. The formal test for interaction in the multiplicative scale using the Cox regression model with both asbestos and ETS exposure variables (reduced model), controlling for age, schooling, gender, 'race', consumption of foods containing carotenoids, total fat as nutrient index, and history of lung disease, yielded a -2 ln likelihood of 4125.88, and that with asbestos and ETS and the three interaction terms of asbestos and tertiles of ETS exposure (full model) was 4121.002, for a $LR\chi_{3df}^2$=4.878 with an associated p value of 0.18. Nonsmoking men and women who reported 6 or more hours of exposure to ETS, and ever being exposed to asbestos had four times the risk of lung cancer [multivariate RR=4.5 (95%CI=0.4-48.7)] compared to those of nonsmoking CPS II participants who had neither of those environmental exposures. The multivariate association with asbestos alone was RR=1.5 (95%CI=0.7-3.2).

Table 41. Rate ratios (95% CI) for lung cancer among CPS II nonsmoking men and women according to exposure to ETS (cumulative at home, work, and elsewhere) and occupational exposure to asbestos.

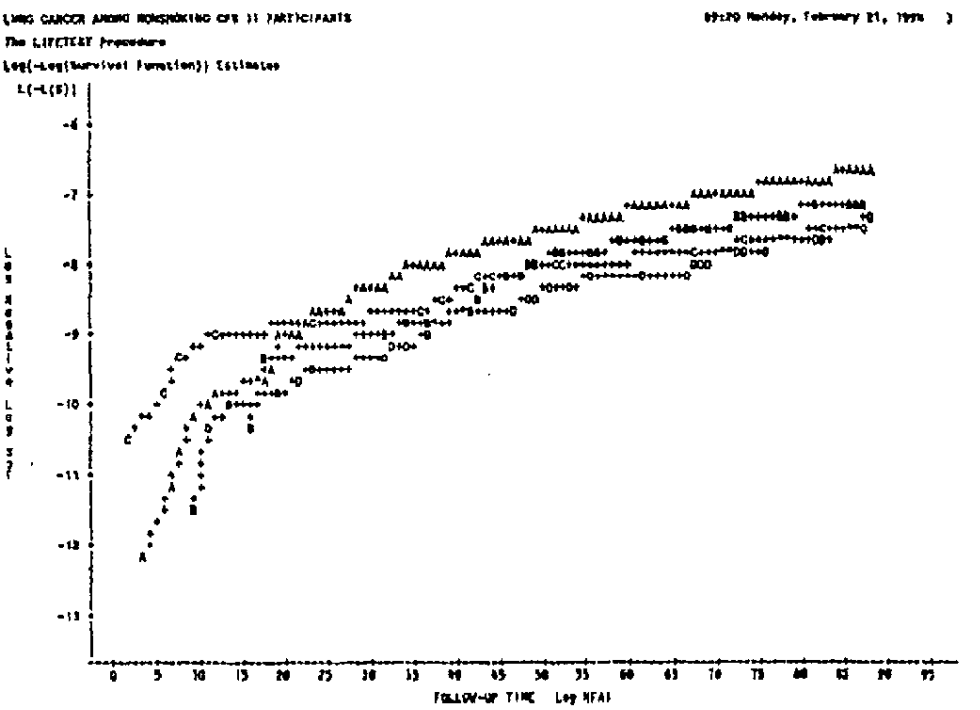
		Exposure to ETS							
		+6 hours		3-5 hours		1-2 hours		0 hours	
		Deaths	Person-Years at risk	Deaths	Person-Years at risk	Deaths	Person-Years at risk	Deaths	Person-Years at risk
Asbestos	Yes	5	14,954	0	7,922	2	22,250	7	24,436
	Rate*		33×10^{-5}		0		11×10^{-5}		16×10^{-5}
	RR Cox§§		4.5 (0.4-48.7)		0		0.9 (0.1-11.1)		1.5 (0.7-3.2)
Asbestos	No	40	416,453	19	241,513	47	647,134	242	1,431,956
	Rate*		13×10^{-5}		11×10^{-5}		9×10^{-5}		11×10^{-5}
	RR Cox§		1.1 (0.8-1.6)		0.8 (0.5-1.4)		0.8 (0.5-1.0)		1.0

* Age adjusted to the distribution of the CPS II population
§ Cox regression model stratified for age, gender, 'race', schooling, history of chronic lung disease, frequency of consumption of foods containing carotenoids, and total fat intake.

7.5 Model Specification

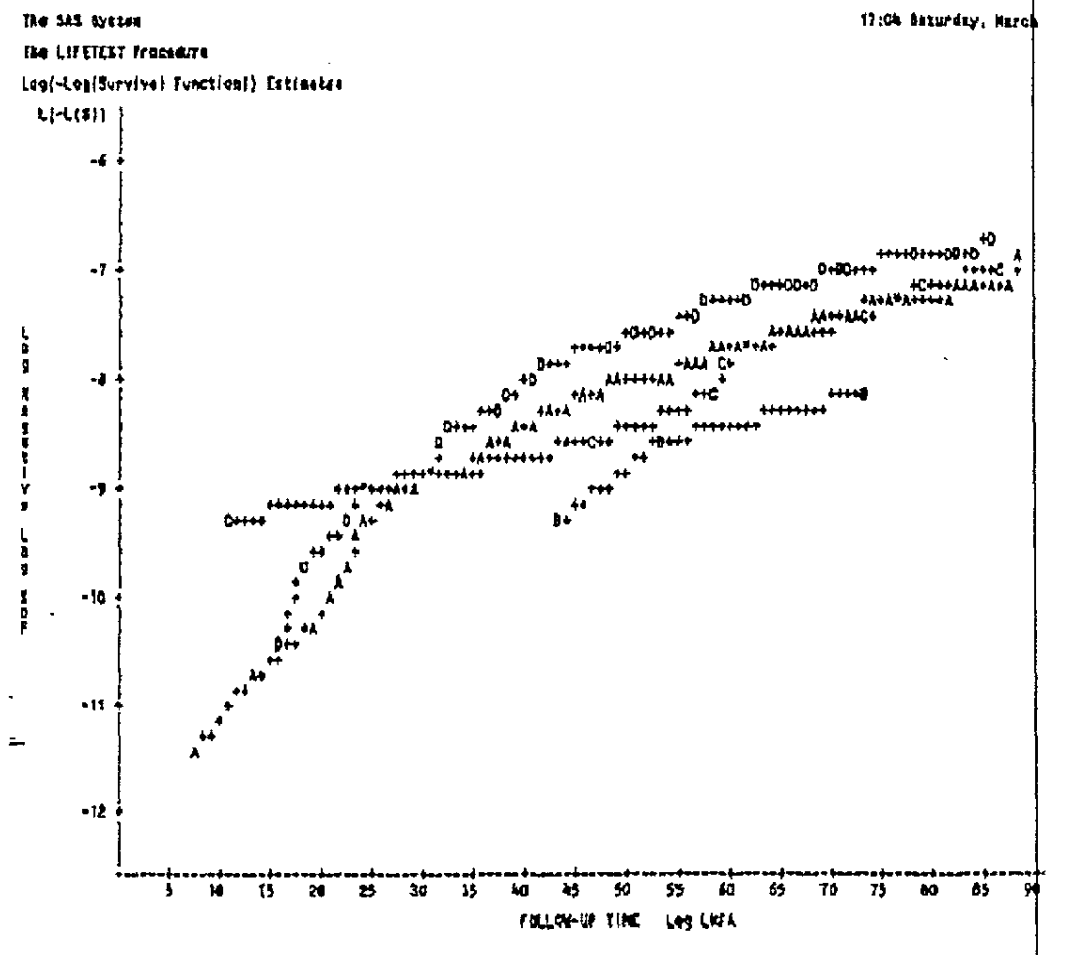
Proportional hazards modeling was the main analytic tool used in this study. Therefore, a valid question to ask is whether the proportional hazard assumption held. Univariate survival curves using Kaplan-Meier estimates for age, gender, schooling, 'race', consumption of foods containing carotenois, and total fat, history of chronic lung disease, and occupational exposure to asbestos, all followed a pattern of parallel curves by follow-up time in CPS II. Since most analyses on ETS (either self-reported exposure or from spousal smoking) were conducted while blocking for the covariates, we present univariate Kaplan-Meier estimates of survival for the main exposure variables themselves, displayed in figure 10.

Figure 10. Log [-log(S)] curves for grouped data analyses of A. self-reported ETS



A=unexposed, B=1-2 hours, C=3-5 hours, and D= 6+ hours of exposure to ETS.

Figure 10 B. ETS from pack-years of spousal smoking



A=0, B=<7 pack-years , C=7-14 pack-years, and D= 15+ pack-years.

We also conducted Poisson regression analyses, an alternative choice of the Cox regression model. RR estimates from the Poisson model for self-reported ETS (upper tertile ≥ 6 hours of ETS) and current spousal ETS from cigarette smokers were 1.2 (95% CI= 0.8-1.6) and 1.2 (95% CI=0.9-1.8), respectively. Thus, the general results from Poisson regression modeling, closely agree with those presented using the Cox regression model.

7.5 Leading causes of death in the cohort

During the same period of follow-up among the 314, 108 nonsmoking participants in the the spousal ETS analytic cohort, there were 12,792 other deaths. Coronary heart disease was the leading cause of death in this group, with 3,742 deaths (29.2 percent). The major causes of death according to ICD-9 codes are displayed in table 42.

Table 42. Number of deaths from major smoking-related causes among nonsmoking spouses in the CPS II, 1982-1989.

Causes of death (ICD-9)	Deaths	%
Ischemic heart disease (410-414)	3,742	29.2
Stroke (430-438)	724	5.6
Upper aerodigestive cancer -mouth, pharynx, larynx, and esophagus (140-150, 161)	36	0.3
Other cancers (140-209)	909	7.1
Lung cancer (162)	265	2.1
Duodenal or gastric ulcer (531-534)	25	0.2
Cirrhosis and alcoholism (571, 291, 303)	116	0.9
Hypertensive heart disease (401-405)	120	0.9
Injuries (E810-E988)	569	4.4
Other medical causes (000-799)	6,286	49.1
All causes	12,792	100.0

Chapter 8: Discussion and Conclusions

8.1 Consistency

Since 1981, when the first study that examined the relationship between ETS and lung cancer death was published (Hirayama, 1981), 35 other studies that have examined this same relationship have beeen published (Appendix A and Table 2). Of these 36 studies, four are cohort studies and 32 case-control. It is known that in case-control studies, in which the "information most times comes from the subject of proxy respondents after disease onset, knowledge of the disease could affect exposure data" (i.e., introducing a recall bias) (Rothman 1986). Cohort studies are less subject to recall bias and therefore lend themselves more than case-control studies to making inferences about cause and effect. Thus, although many published studies are available, only a few can be considered to have assessèd the relationship between ETS and lung cancer risk in such a way that the measurement of ETS exposure preceds the occurrence of lung cancer. Of those four cohort studies on ETS and lung cancer, one included eight lung cancer cases (Butler 1988), another had nine (Hole 1989), a third had 153 (Garfinkel 1981), and the largest had 174 lung cancer deaths (Hirayama 1981). Our study is the largest cohort study to assess the relationship between ETS and lung cancer death. Therefore, in this paper we report findings from the largest cohort study that are consistent with aggregated evidence that supports the existence of a relationship between cumulative ETS exposure and the risk of lung cancer among nonsmokers.

This study makes use of a measure of exposure that combines duration and amount of exposure to ETS that had not been used before in previous cohort studies about the effect of ETS on lung cancer risk. This cumulative exposure to ETS, which is referred to as ETS exposure from pack-years of cigarette smoking of the spouse (Fontham 1991), attempts to estimate ETS long-term exposure. Because 90% of smokers smoke at home (1988 NHIS-OH, Table 1), spouses married to smokers are likely to be exposed to ETS in the home. Our measure of exposure reflects intensity and duration of exposure to ETS during marriage, and may provide a more adequate measure of long-term ETS exposure. Therefore, this measure of exposure enabled us

to estimate lung cancer risks associated with increasingly greater ETS exposure with regard to duration and amount. For example, in this study we found increasing lung cancer risks with increasing ETS exposure, with a 50% increased risk, although not statistically signficant, for the most exposed group versus those who were not exposed.

In this study, we also found that this not statistically signficiant increased lung cancer risks associated with ETS exposure remained even after we adjusted for the effects of potentially confounding variables by means of Cox proportional hazards modeling. Most previously published studies that had examined the relationship between ETS exposure and lung cancer risk had not accounted for the effects of most known potentially confounding variables included in our models. Thus, questions had been raised about the possibility of spurious findings in past studies (Mantel 1992). In our study, we controlled for the effects of age, gender, socioeconomic status, race/ethnicity, fruit and vegetable intake, fat intake, occupational exposure to asbestos, and a history of chronic lung disease, and we still found that ETS exposure from pack-years of spousal smoking increased the risk of lung cancer. Therefore, our findings support the notion that the observed relationship is not the result of known confounding variables.

All cohort studies on this issue have been based on lung cancer diagnosis from death certificates. As previously reported for lung cancer in the US, this approach provides a valid diagnostic tool for epidemiologic research (Percy 1981). None of the previous studies verified their death certificate diagnoses with histopathologic data. Some have reviewed hospital records, and in one large case-control study histopathological slides were reviewed (Fontham 1991). In our study, we verified death certificate diagnoses with cancer registry diagnoses on a 10 percent sample of lung cancer deaths (i.e., those of residents of SEER cancer registries areas). Most SEER cancer registry diagnoses (92%) are histopathologically confirmed (NCI-SEER 1989). The proportion of the study subjects who died from lung cancer and resided in SEER cancer registries' areas, who were histologically confirmed was 86.2 percent. Seventy percent of all lung cancer deaths were adenocarcinomas. Thus, cases in our study are likely to have been primary lung cancer, and most were adenocarcinomas.

Adenocarcinomas are the specific histological type of lung cancer seen most often among nonsmokers. Although the information on specific histologic types was limited in our study, based upon the estimate of seventy percent of adenocarcinomas among the lung cancer deaths of nonsmokers, our findings of this study lend support to the hypothesis that a richer composition of SS in volatile carcinogen components more likely to reach the periphery of the lung would actually be responsible for the higher proportion of adenocarcinomas among nonsmokers (Wynder 1983, Fontham 1991).

Our findings on the association between ETS exposure from spousal smoking and the risk of lung cancer agree with the combined estimate from 36 published studies, reporting a 20% increased risk of lung cancer among nonsmokers associated with this measure of exposure to ETS. In 1981 Garfinkel published the results of the second large prospective cohort study sponsored by the American Cancer Society, the Cancer Prevention Study I. This study,comprised a cohort of 1,078,894 men and women followed from 1960 to 1972. The CPS I analyses based on 153 lung cancer deaths among nonsmoking women found a 20% percent increased risk of lung cancer, although this elevated risk was not statistically significant (95% CI=0.9-1.4) (Garfinkel 1981). Analysis of CPS I and CPS II agree in the magnitude of the effect of spousal smoking.

As in most previous epidemiologic studies of ETS, we found a trend in the risk of lung cancer among nonsmoking wives with increasing levels of smoking by the husbands, although it was not statistically signficant. In contrast, for self-reported ETS we found no statistically significant evidence of an elevated risk among the ETS exposed individuals at interview. A case-control study by Kabat and Wynder found an association for self-reported ETS at work among men [3.1 (95% CI=1.1-11.0)], but not women. In another case-control study that used self-reported ETS as one measure of exposure, Garfinkel et al. found no increasing trend with increasing exposure to ETS measured as number of hours of exposed to the smoke of others in the past, and the risk of lung cancer among nonsmoking women. This fact led the authors to conclude that "the lack of relationship when exposure was classified by

hours exposed to smoke of others may have occurred because this variable does not accurately measure intensity of exposure". In this study, however, a two-fold increased risk was found for women whose husbands in the past smoked 20 or more cigarettes at home (Garfinkel 1985). Brownson et al. reported a 1.7 odds ratio for lung cancer for nonsmokers who had four or more hours of self-reported exposure to ETS in a small study of adenocarcinomas (Brownson 1987) but were unable to replicate their findings in a larger study (Brownson 1992).

The negative findings of this study with respect to self-reported ETS exposure may well be due to misclassification of exposure since the questionnaire data on self-reported number of hours of exposure to ETS may reflect only current exposure and not the more biologically relevant past exposure. An important evidence of the possibility of such misclassification can be found in the decreased risk of persons in low self-reported ETS exposure categories. This might be due to the inclusion in the referent category (i.e., "0" hours or unexposed) of false negative unexposed persons particularly among those with missing data on self-reported ETS exposure.

Exposure to tobacco smoke from the spouse, as was measured in our study (i.e., self-reported smoking history of the spouse) probably provides a more reliable index of long-term and meaningful ETS exposure than current self-report ETS. This measure is not affected by dramatic changes in the prevalence of smoking seen since the 1960's in the US. It ensures that the smoker has a close relationship with the nonsmoker (i.e., spouse). Moreover, our measure of time in marriage takes into account the effective time spent with the smoker during marriage in such a way that if a smoker had quit smoking before marriage, nonsmokers were classified as unexposed to spousal smoking. By the same token, the time smoking spouses smoked in marriage was estimated to take into account the time since quitters stopped smoking.

Our findings are generally consistent with those of other epidemiologic studies. Some case-control studies found an association with number of cigarettes or other measures of quantity usually smoked by husbands, but not with duration of spousal smoking (i.e., time living with a smoking spouse) (Hirayama 1984, Akiba 1986, Dalager 1986, Lam 1987, Inoue 1988), while the reverse was observed in some other epidemiologic

studies (Gao 1987, Kalandidi 1990). The use of a combination of quantity and duration has been found associated in at least one other epidemiologic study (Fontham 1991). That study conducted by Fontham et al., is by far the best in this regard.

The observations regarding the effect of ETS among nonsmokers exposed to asbestos are consistent with those of other large epidemiologic studies which concluded that active smoking and asbestos act synergistically (Selikoff 1968). This finding provides additional evidence in support of a causal relationship between ETS and lung cancer.

Some limitations of this study, such as statistical power and misclassification bias, are reviewed.

8.2 Study power

The most obvious limitation of this study, shared with most other epidemiologic studies which have addressed this hypothesis, is limited power to detect with sufficient precision a RR on the order of 1.2 (i.e., the summary effect of ETS from 36 other studies). The power of the CPS II was approximately 50 percent for detecting this magnitude of association, as shown in table 43. If indeed ETS increases the risk of lung cancer among nonsmokers by less than 20 percent (e.g., 10 percent), then the power of this study to detect such association with sufficient precision would be only 20 percent.

Table 43. Results of power calculations (binomial parameter p=0.5, the proportion of CPS II nonsmoking participants exposed to ETS, by M_1 the total number of lung cancer deaths among nonsmokers

Mortality Rate Ratio	Power) Self-reported ETS M_1=362	Spousal ETS M_1=265
1.4	94.1	87.1
1.3	80.5	70.3
1.2	54.1	45.4
1.1	23.5	20.5

Thus, the lack of statistical significance in most analyses may reflect low statistical power.

8.3 Misclassification of self-reported ETS

Misclassification of both self-reported and spousal ETS exposure might have affected the results of our study yielding a bias towards the null. A dilution of the effect from non-differential misclassification would obscure a weak association between ETS and lung cancer.

If any misclassification occurred, probably it was non-differential (i.e., subjects who died from lung cancer were as likely to have misclassified themselves with respect to ETS exposure, as those who did not). Table 44 displays the results of using values in the range of 0.75-0.95 for specificity and sensitivity of classification of outcome or exposure variables in standard formulas (Kleinbaum 1982) to correct for misclassification of an observed association of 1.2 as observed in this study (Cf. Table 34, for nonsmoking wives comparing those married to nonsmokers versus those married to current smoking spouses) . Each one of the parameters assumes the values in the x axis, while the others are assumed to have perfect validity. A meaningful adjustment for misclassification of ETS exposure would be necessary in the likely case of having classified exposure with a specificity below 90 percent.

Table 44. Corrected RR from an observed value of 1.2 (using data from table 34, nonsmoking wives exposed to ETS from current spousal smoking), by degree of misclassification of ETS exposure§

Value of Parameter	Specificity of Exposure	Sensitivity of Exposure
0.95	1.2	1.2
0.9	1.2	1.2
0.85	1.2	1.2
0.8	1.3	1.2
0.75	1.3	1.2

§ Each parameter changes, while the other is held constant at 1 (i.e., perfect classification).

In general subjects may have misclassified themselves with respect to their exposure status for the reasons discussed in 8.1. In addition, both refer to exposure during adulthood and thus do not take into account exposure during childhood. However, Fontham et al. study findings (1991) suggest that this source of bias probably is unimportant. Misclassification of relevant exposure to ETS, however, is more likely to have occurred for self-reported ETS than for spousal smoking for the following five reasons.

First, a large proportion of blanks in the CPS II ETS questionnaire section were interpreted as unexposed; this assumption may be unrealistic and therefore, augmented a dilution bias. Results of analyses restricted to those who had filled the three spaces provided for self-reported hours of ETS exposure (Table 45) showed that such dilution bias existed: the point estimate of the rate ratio of subjects with 6 and more hours of ETS exposure was 1.8 (95% CI=0.9-3.6). The rate ratio was found to be diluted upon inclusion of people with any blank for ETS, because when only those who left the three spaces blank were excluded, the rate ratio was 1.2 for those who were exposed for 6 or more hours to ETS. However, in that case the study had been conducted based on fewer deaths (i.e., 104, or 243, respectively), and therefore, would have had even less power. Those who left any space blank in the spaces provided to write down

the number of hours exposed to ETS (and grouped with those who annotated zero hours) or had unquantifiable ETS data (and excluded from analysis) had a multivariate RR of 1.0 (95% CI=0.8-1.3) and 1.0 (95% CI=0.8-1.4), respectively, when compared with the rates of those who annotated zero hours in the three spaces.

Table 45. Rate ratios § from ETS by different approaches in dealing with missing information on ETS

Exposure to ETS	Missings are Unexposed (n=362 deaths)	Excludes missings in all three fields (n=243 deaths)	Excludes missings in any of three fields (n=104 deaths)
0	1.0	1.0	1.0
1-2	0.7	0.7	0.7
	(0.5-1.0)	(0.5-1.1)	(0.4-1.2)
3-5	0.8	0.7	0.3
	(0.5-1.2)	(0.5-1.3)	(0.1-1.9)
6+ hours	1.2	1.2	1.8
	(0.8-1.7)	(0.8-1.8)	(0.9-3.6)

§ Adjusted for age, gender, race, education, intake of carotenoid-containing foods, total fat as a nutrient index, occupational exposure to asbestos and history of chronic lung disease.

Second, a positive association between schooling with self-reported ETS, could be interpreted as proof of 'increased sensitivity' to the smoke of others among nonsmokers of higher SES. Based upon data from the 1988 NHIS-OH, and most other smaller surveys and studies of ETS, we expected to find that CPS II participants of relatively lower SES would have reported more ETS than those in higher SES. Tables 21 and 22 show that there was a direct relationship between any self-reported exposure to ETS and years of education (i.e., higher educated participants reporting more exposure), whereas the opposite occurred with any spousal ETS. In table 46 we compared formal education with self-reported ETS status, and spousal smoking status (any versus none). For simplicity we restricted the comparison to the extremes of less than high school and college

graduates and graduate school. The results of this comparison clearly indicate that nonsmokers with higher education were more likely to report any ETS exposure, but less likely to be married to ever smokers, and suggests that self-reported ETS does not accurately reflect ETS exposure.

Table 46. Comparison of any ETS exposure (self-reported or from spousal smoking) by years of education among CPS II nonsmokers, 1982.

Years of	Self reported ETS		Ratio of exposed	Spousal ETS		Ratio of exposed
education	Any	None		Any	None	
16+	62,731	56,101	1.3	46,036	52,621	0.9
<12	16,922	36,681	(95% CI=1.3-1.3)	18,331	15,688	(95% CI=0.9-0.9)

Third, self-reported number of hours of ETS exposure does not necessarily reflect the intensity of ETS exposure, but duration to an undetermined amount of ETS. This limitation might contribute considerable misclassification of self-reported ETS.

Fourth, as mentioned in 8.1, an indication that suggests such misclassification of ETS exposure is found in the results of self-reported ETS exposure itself. Unlike most spousal smoking analyses, there is a consistent pattern of deficit in the risk of lung cancer for the first and second tertile of self-reported ETS exposed, whether it is cumulative in the three settings, ETS at home, work or other places separately. These results are compatible with misclassification of an undetermined proportion of exposed who left blank spaces for hours of ETS exposure blank in the CPS II questionnaire.

Last, the classification by self-reported ETS in 1982 has another inherent source of misclassification: that from the changing patterns of smoking (e.g., unexposed subjects in 1982 might have been exposed before if married to former smokers). Therefore, self-reported current ETS exposure does not assess long-term exposure, whereas smoking status of spouses might reflect exposure for many

years, although it may still have limited validity (Garfinkel 1981, Friedman 1983).

An estimate of the RR of lung cancer from ETS corrected for this downward misclassification bias, using the data available in NRC 1987 report which was RR=1.9 (Gann 1988). The EPA report included a correction for this bias (EPA 1992), and the pooled estimates were in the order of our metanalysis estimate (i.e., 1.2). Correcting for this downward bias would result in estimates of 1.2.

Garfinkel et al. pointed out, when reporting the findings of CPS I, that "Long-term effects of passive smoking are difficult to establish because of the problems of classification. It may be misleading to classify a woman as a passive smoker or not on the basis of her husband's smoking habit. Wives of nonsmokers may be more exposed to cigarette smoke of others than wives of cigarette smoking men; wives of smokers may be very little exposed to the cigarette smoke of their husbands or other" (Garfinkel 1981).
In the hypothetical situation of randomly misclassifying 10-25 percent of the study participants, any bias is towards the null: the true effect of ETS would be at least as great as the point estimate, and the size of the bias would range from -0.03 to -0.4. Notice that in the typical stituation the bias would have been around -0.06 (i.e., the true parameter 1.2), and that the bias is more sensitive to misclassification of exposure (i.e., nonsmoking spouses being truly smokers). If classification of subjects in this study had been 5 percent imperfect by the four parameters, the corrected RR would have been 1.2.

8.4 Confounding

The decline of smoking in the US since the late 60's is reflected in the age distribution of either spousal ETS (particularly the prevalence of current smoking spouses), and self-reported ETS. Younger nonsmoking study subjects were more likely to have any ETS exposure than older persons in the analytic cohort of self-reported ETS. Since lung cancer rates increase exponentially with age, confounding by this variable occurred in the analyses of self-reported ETS. Data-based confounding (i.e., change in estimate) by SES and gender was not

detected across the different analyses conducted in this study. However, estimates presented in this report are simultaneously adjusted for age, gender, 'race' and schooling as a proxy of SES. Uncontrolled confounding by age is unlikely to have occurred given the fact that in most analyses we grouped age by quinquennia, thus allowing variation within age levels.

Inclusion of other variables in the Cox regression models did not affect the adjusted results reported in the previous chapter. No evidence of confounding by other risk factors such as the intake of foods containing carotenoids, dietary fat, marital status, or history of chronic lung disease, was found.

8.5 ETS-CHD association is unexplained by misclassification of smoking status

At the core of the Mantel-Lee bias argument against the scientific case for an ETS lung cancer and cardiovascular diseases association, is the contention that a very strong association of active smoking with those outcomes would be reflected by the misclassification of some smokers, more likely former smokers, among those selected into a study population of nonsmokers. As shown in the NCR report and reproduced in an illustrative example above, the Mantel-Lee argument may be reasonable when discussing the ETS and lung cancer association, given the fact that the size of the effect (i.e., odds ratio) of active smoking on lung cancer risk is considerably large (22 among men in CPS II). This argument, however, cannot explain the association of CHD and ETS, as shown below.

A review of the evidence from major cohort studies on active smoking and coronary heart mortality provides estimates of the RR that range from 1.58 to 2.55 for current cigarette smokers (Fielding 1992).

To set limits to the possible effect of the Mantel-Lee bias, we will follow the same approach illustrated in figure 3, but for the case of the ETS-coronary heart disease association. The same simplifying assumptions are used to provide the

figures: a closed cohort of 1 million subjects with all observations except deaths from CHD, are censored at the end of the six-year follow-up, and deaths occurred at the mid-period. We assumed also a 3 percent misclassification of active smokers (Lee 1988). In addition, we assumed a CHD mortality rate of 4.8 per 1000 subjects, with a 20 percent prevalence of current smokers, and a two-fold increased CHD death rate among smokers. It was found that misclassification of smoking status would not have a meaningful effect on the estimates of a such study (i.e., biasing the study from 1.0 to 1.03). The hypothesis of bias from misclassification of active smoking to explain the ETS lung cancer hypothesis as set forth by Mantel and Lee (Lee 1985) necessarily implies it should also explain the ETS-CHD association. The number of reports on ETS and CHD has increased since this argument was first presented in 1985 (Steenland 1992), and by refuting this statement, these studies further reduce the credibility of the argument of bias by misclassification of active smoking to explain the observed effects of ETS on lung cancer risk or any other major ETS-related disease.

There is another major weakness of the Mantel-Lee or "active smoking misclassification bias", namely that most misclassified smokers are actually former smokers. The CHD-active-smoking relationship holds for current smokers and the increased risk is reduced by more than half by the end of the first year of cessation. Also, the risk of former smokers slowly approaches the risk of never smokers (Fielding 1992, US DHHS 1982). Therefore, the net effect of the potential bias argued by Mantel and Lee is negligible on the observed relationship between CHD and ETS. Steenland made this point in a review of the ETS -CHD association, noting that the effect of such bias would be about 2% (Steenland 1992).

8.6 Causal Inference

The research hypotheses outlined in the Introduction, cannot be rejected or verified on the basis of the results of a single study. The results of this study seem to support the hypothesis of a weak association of cumulative exposure to ETS with the risk of lung cancer among nonsmokers, increasing such risk by 20-30 percent. The lack of statistical significance of the estimates of the effect should not be confused with a null effect, because statistical significance depends heavily on numbers, and it has been shown that our study had little power to detect a RR of 1.2. In addition, a misclassification bias towards the null is likely to have taken place in this study, in an amount enough to dilute the RR estimate from 1.3 to 1.2 (specificity <90%). It is not in the strength of the association that the ETS-lung cancer hypothesis finds support, but in other major criteria for causal inference in epidemiology.

The time order of the observed association is a particular advantage of this study: the assessment of ETS exposure preceded the ascertainment of deaths. This criterion for causal inference is assured by the prospective nature of the study design. As discussed before, this design prevents the occurrence of recall bias.

Consistency is the persistence of an association upon repeated test, and has two domains: survivability and replication (Susser 1991). Survivability stresses the number and severity of tests. This study adds survivability to the ETS and lung cancer hypothesis in at least the following ways. First, this study, controls more rigorously for age by using proportional hazards modeling and thus "stratifying" more finely for age, and at the same time it adjusted for SES, and many other potential confounders. Second, this study avoided the potential of recall bias more likely to occur in case-control studies. Last, this study also provided estimates for two independent sources of assessing ETS exposure: self-reported ETS and exposure from spousal smoking status, and the smoking status of spouses was doubly checked.

Regarding replicability, most epidemiologic studies of lung cancer and ETS have consisted of non-smoking lung cancer cases among wives according to the smoking of

their husbands. The summary estimate from 37 epidemiologic studies, including this one, contrasting the risk of lung cancer of women according to their ETS exposure on the basis of their husband smoking status is still 1.2 (95% CI=1.1-1.3). This study is consistent with a weak effect of ETS on the risk of lung cancer among nonsmokers.

Based on previous knowledge of the joint effects of asbestos and tobacco smoke upon the risk of lung cancer, this study is a confirmation of the prediction that tobacco smoke involuntarily inhaled by nonsmokers exposed to asbestos will increase the risk of lung cancer above that of those exposed to either asbestos or ETS alone. Although based on few numbers, this study found suggestive evidence that this synergism might occur for both active smoking and ETS.

It is important to note, at this point, that smoking spouses of CPS II nonsmokers smoked less than their counterparts of other US nationwide studies (e.g., Fontham 1991). The distribution of pack-years indicates that only 1 percent of the entire cohort was exposed to 80+ pack years. The distribution of pack-years of CPS II smoking spouses of nonsmokers is skewed to the left with respect with to the SEER based case-control study population . Thus, the overall effect of ETS on lung cancer risk among nonsmokers is likely to be somewhat small because of the low level of ETS exposure in the cohort.

Finally, the findings of this study are plausible in terms of pre-existing knowledge about the carcinogenicity of tobacco smoke components, *in vitro* and *in vivo* models, as well as from epidemiologic studies of active smoking.

The biological plausibility of the ETS-lung cancer association is also well founded and it is based upon the evidence of harmful effects of ETS constituents leading to: 1) an increased incidence of lower respiratory tract infections, additional episodes of asthma in children, reduced lung function, increased prevalence of middle ear infections and symptoms of upper respiratory tract infection in children (EPA 1992); and 2) an increased risk of CHD in adults in a similar pattern followed by active smoking (Steenland 1992). Also, asbestos fibers increase cell proliferation and the occurrence of tumors (Kilburn 1992). Thus, this property of asbestos fibers added to the

genotoxicity properties of tobacco smoke are beneath the observed synergism of those two environmental hazards.

In summary, the following scientific facts lend biologic plausibility to the conclusion in epidemiologic studies like this that ETS causes lung cancer: 1) tobacco smoke from active smoking causes lung cancer as shown in epidemiologic studies, genotoxicity and animal data, 2) the same carcinogens found in MS and some other carcinogens perhaps more likely to reach the peripheral parts of the lung are present in ETS, 3) the levels at which ETS is present are consistent with those at which a risk is expected, 4) ETS is absorbed by nonsmokers in amounts at which a risk would be predicted, and 5) that the collective findings of epidemiologic studies like this one, strongly support a cause-effect relationship.

8.7 Conclusions

1. With respect to our first hypothesis, our study found that non-smokers exposed to ETS from current spousal smoking are at higher risk of fatal lung cancer than are non-smokers not exposed to ETS. However, we failed to provide precise estimates, and the 95% CI included the null value. Current spousal smoking increased the risk of lung cancer of non-smokers (both men and women) by 30% (0.8-1.9). Our study did not find an overall association with self-reported ETS exposure. However, we found indication that missing data on reported hours of exposure to ETS may have introduced misclassification, thus biasing the results towards the null.

2. Our study found a weak dose-response relationship with pack-years of cigarettes smoked during marriage by husbands of nonsmoking women, but also this relationship was not statistically signficant (test for trend p=0.14). This relationship was not found for nonsmoking men. There was an 50 percent increased risk of of lung cancer among nonsmoking wives married to cigarette smoking husbands who smoked heavily during their marriage (36+ pack- years) [RR=1.5 (95% CI=0.8-2.8)]; these women represent the upper 17 percent of those married to ever cigarette smokers.

3. Consistent with the summary estimate of 1.2 (95%CI=1.1-1.3) for the risk of nonsmoking women married to ever smokers from 36 published epidemiologic studies reviewed for this paper, this study reports an estimate of 1.3 for the risk of lung cancer among nonsmoking women married to current smokers (any type) (95% CI=0.8-1.9).

4. This study among nonsmoking CPS II participants suggests that there are greater than expected joint effects of ETS and occupational exposure to asbestos (p=0.18). If this relationship exists, it would resemble the known synergism between active smoking and asbestos.

5. The nonstatistically significant association between ETS exposure from spousal smoking and the risk of lung cancer remained unchanged after adjustment for relevant potential confounders, and is not attributable entirely to misclassification of smoking status (i.e, misclassified smokers are included in a study restricted to nonsmokers).

6. Consistent with larger studies, a small validation study found that diagnosis of lung cancer from death certificates correctly classifies lung cancer deaths. Therefore, epidemiologic studies of lung cancer which rely on diagnosis from death certificates may still yield valid estimates of effect.

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APPENDICES

A References and Tables of published studies and Metanalysis of ETS-Lung Cancer

B Abbreviations

C CPS II Questionnaires and Instructions

Appendix A — Meta-analysis of 36 studies on ETS-lung cancer — ETS-Lung Cancer in CPS II

1		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Trichopoulos et al.	Cases	53	24	77	2.075	0.73	0.07833	12.7666	9.31954	
Source: Lancet, 1983	Controls	116	109	225						
Country: Greece	Total	169	133	302						

2		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Chang &Fung	Cases	34	50	84	0.752	-0.285	0.078262	12.7776	-3.639801	
Source: Grundmann, 1982	Controls	66	73	139						
Country:Hong Kong	Total	100	123	223						

3		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Correa et al.	Cases	17	14	31	3.154	1.1488	0.146171	6.8413	7.859164	
Source: Lancet 1983	Controls	87	226	313						
Country: USA	Total	104	240	344						

4		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Kabat & Wynder	Cases	18	18	36	0.85	-0.163	0.219935	4.54681	-0.738942	
Source: Cancer 1984	Controls	20	17	37						
Country: USA	Total	38	35	73						

5		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Buffler et al.	Cases	38	14	52	0.814	-0.205	0.117441	8.51489	-1.749333	
Source: Mizell 1983	Controls	220	66	286						
Country:USA	Total	258	80	338						

6		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Garfinkel et al.	Cases	91	43	134	1.233	0.2095	0.044939		22.2526	4.6627498
Source: JNCI 1985	Controls	254	148	402						
Country:USA	Total	345	191	536						

7		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Wu et al.	Cases	?	?	29	1.2	0.1823	0.140231		7.1311	1.3001532
Source: JNCI 1985	Controls	?	?	62						
Country: USA	Total	?	?	91	(CI=0.6-2.5)					

8		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Akiba et al.	Cases	76	37	113	1.908	0.6461	0.050726		19.7139	12.73713
Source: Can Res 1986	Controls	197	183	380						
Country: Japan	Total	273	220	493						

9		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Dahlager et al.	Cases	?	?	48	1.47	0.3853	0.11947		8.3703	3.2247627
Source: Can Res 1986	Controls	?	?	466	(95% CI=0.76-2.83)					
Country: USA	Total	?	?	514						

10		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Lee et al.	Cases	30	17	47	1.107	0.1014	0.136133		7.34576	0.7445988
Source: BJC 1986	Controls	59	37	96						
Country: UK	Total	89	54	143						

11		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Gao et al.	Cases	246	190	436	0.794	-0.231	0.016343	61.1894	-14.10657	
Source: IJC 1987	Controls	375	230	605						
Country: China	Total	621	420	1041						

12		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Brownson et al.	Cases	4	15	19	1.822	0.6001	0.507724	1.96958	1.1818572	
Source: AJE 1987	Controls	6	41	47						
Country: USA	Total	10	56	66						

13		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Koo et al.	Cases	51	35	86	1.545	0.4353	0.077617	12.8839	5.6085763	
Source: IJC 1987	Controls	66	70	135						
Country: Hong Kong	Total	117	105	222						

14		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Pershagen et al.	Cases	37	44	81	1.182	0.1669	0.060941	16.4092	2.7391618	
Source: AJE 1987	Controls	153	215	368						
Country: Sweden	Total	190	259	449						

15		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Humble et al.	Cases	20	8	28	3.203	1.1641	0.18891	5.29352	6.162334	
Source: AJPH 1987	Controls	128	164	292						
Country: USA	Total	148	172	320						

16		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Lam et al, 1987	Cases	115	84	199	1.648	0.4997	0.032644	30.6338	15.308276	
Source: BJC, 1987	Controls	152	183	335						
Country: Hong Kong	Total	267	267	534						

17		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Lam & Cheng	Cases	37	23	60	2.011	0.6986	0.09863	10.1389	7.0826849	
Source: Smoking and Health 1987	Controls	64	80	144						
Country: Hong Kong	Total	101	103	204						

18		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Shimizu, 1988	Cases	53	37	90	1.133	0.1252	0.070773	14.1297	1.768766	
Source: Toh J Exp Med 1988	Controls	91	72	163						
Country: Japan	Total	144	109	253						

19		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Inoue 1988	Cases	18	4	22	2.25	0.8109	0.343758	2.90903	2.3590176	
Source: Smoking and Health,1988	Controls	30	17	47						
Cell numbers from Lee, 1992	Total	48	21	69	CI=(0.91-7.1)					

20		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total						
Authors: Geng, 1987	Cases	34	20	54	2.156	0.7683	0.123033	8.12792	6.2446768	
Source: Smoking and Health 1987	Controls	41	52	93						
Country: China	Total	75	72	147						

21		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)I
Case-control study		Smoker	Nonsmoker	Total					
Authors: Kalada, 1988	Cases	17.5	0.5	17	8.448	2.134	2.411823	0.41462	0.8847924
Source: Gan No Rinsho 1988	Controls	14.5	3.5	17		177.3			
Country: Japan	Total	32	4	34		0.4026			

22		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)I
Case-control study		Smoker	Nonsmoker	Total					
Authors: Svensson, 1989	Cases	24	10	34	1.263	0.2336	0.167105	5.98425	1.3980101
Source: Acta Oncol 1989	Controls	114	60	174					
Country: Sweden	Total	138	70	208					

23		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)I
Case-control study		Smoker	Nonsmoker	Total					
Authors: Sobue et al. 1990	Cases	80	64	144	1.063	0.0614	0.033633	29.7328	1.8246736
Source: Gan No Rinsho 1990	Controls	395	336	731					
Country: Japan	Total	475	400	875	UppOR	1.2773			
					LowOR	0.8851			

24		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)I
Case-control study		Smoker	Nonsmoker	Total					
Authors: Janerich et al. 1990	Cases	147	44	191	0.93	-0.073	0.071378	14.0099	-1.016711
Source: IJE 1991	Controls	153	38	191					
Cells estimated from EPA, 1992	Total	300	82	382	(CI=0.55-1.57)				
CI from authors, p. 634									
Country: USA									

25		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)I
Case-control study		Smoker	Nonsmoker	Total					
Authors: Wu-Williams 1990	Cases	205	212	417	0.792	-0.234	0.016306	61.3263	-14.32435
Source: BJC1990	Controls	331	271	602					
Country: China	Total	536	483	1019					

26		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total					
Authors: Kabat et al. 1990	Cases	48	41	89	1.026	0.0252	0.061825	16.1747	0.4076721
Source: Toxicology Forum 1990	Controls	129	113	242					
Country: USA	Total	177	154	331					

27		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total					
Authors: Kalandidi et al. 1991	Cases	64	26	90	1.573	0.4528	0.089715	11.1465	5.0466929
Source: EPA 1992, Lee 1992	Controls	72	46	118					
Country: Greece	Total	136	72	208					

28		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total					
Authors: Liu et al. 1991	Cases	45	9	54	0.739	-0.303	0.177477	5.63454	-1.706982
Source: IJE 1991	Controls	176	26	202					
Country: China	Total	221	35	256					

29		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total					
Authors: Fontham et al. 1991	Cases	294	126	420	1.366	0.3118	0.016843	59.3732	18.511359
Source: Can Epid Biom Prev 1991	Controls	492	288	780					
Country: USA	Total	786	414	1200					

30		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)1/V	ln(OR)	Wi*ln(OR)i
Case-control study		Smoker	Nonsmoker	Total					
Authors: Brownsonet al.1992	Cases	218	213	431	0.972	-0.028	0.012715	78.6485	-2.223114
Source: AJPH 1992	Controls	598	568	1166					
	Total	816	781	1597					

Appendix A Meta-analysis of 35 studies on ETS-lung cancer Proposal ETS-Lung Cancer in CPS II

31		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)I
Case-control study		Smoker	Nonsmoker	Total						
Authors: Stockwell, 1992	Cases	?	?	210	1.60	0.47	0.104496	9.56974	4.4978146	
Source:JNCI, 1992	Controls	?	?	301						
	Total	?	?	511	(95% CI=0.8-3.0)					
					Var=	-0.015				

32		Smoking habits of spouse			OR	ln (OR)	Var ln (OR)	1/V	ln(OR)	Wi*ln(OR)I
Case-control study		Smoker	Nonsmoker	Total						
Authors: Liu, 1993	Cases	25	13	38	1.663	0.5087	0.1752	5.70776	2.9037908	
Source: AJE 1993	Controls	37	32	69						
	Total	62	45	107	UL	3.7778				
					LL	0.7322				

			Total	Total	Total
Summary estimates of 32 case-control studies	Summary ln OR (Precision-based)=	0.147	5.990523	571.669	84.272461
	Summary OR (Precision-based)=	1.159			
	Summary Var (ln OR) (Precision-based)=	0.002			
	Summary SD (ln OR) (Precision-based)=	0.042			
	Summary Lower 95% OR (Precision-based)=	1.068			
	Summary Upper 95% OR (Precision-based)=	1.258			

Appendix A — Meta-analysis of 36 studies on ETS-lung cancer — Proposal ETS-Lung Cancer in CPS II

33		Smoking habits of spouse			SMR	ln(SMR)	weights	Wi*ln(RR)i	
Cohort study		Smoker	Nonsmoker	Total					
Authors: Hirayama, 1981	Cases	142	32	174	1.5	0.4055	142	57.576	0.0382923
Source: Lancet 1981	Total	69645	21695	91540	Var (SMR)				
					0.047				
		Smoking habits of spouse							
34		Smoker	Nonsmoker	Total	SMR	ln(SMR)	weights	Wi*ln(RR)i	
Cohort study	Cases	88	65	153					
Authors: Garfinkel, 1981	Total	49487	127252	176739	1.17	0.157	88	13.8163	0.0267483
Source: JNCI, 1983					Var (SMR)				
					0.018				
		Smoking habits of spouse							
		Smoker	Nonsmoker	Total	RR	ln(RR)	weights	Wi*ln(RR)i	
35	Cases	7	2	9	2.1	0.7419	7	5.19356	0.6428571
Cohort study	Total	1538	917	2455					
Authors: Hole et al., 1989									
Source: BMJ 1989		Smoking habits of spouse			RR				
		Smoker	Nonsmoker	Total		ln(RR)	weights	Wi*ln(RR)i	
	Cases	2	6	8	2.01	0.6981	2	1.39627	0.6666667
36	Noncases	3128	6071	9199					
Cohort study	Total	3130	6077	9207					
Authors: Butler 1989									
Source: Dissertation UCLA, 1988							Total		Total
							239		1.3745643

Summary estimates of four cohort studies

Overall ln(RR)= 0.326285 Overall RR= 1.3858

Sum of weights= 239 verall Variance= 0.0042

Overall SD= 0.0647

Summary Lower 95% RR (Precision-based)= 1.221

Summary Upper 95% RR (Precision-based)= 1.573

Summary over 36 studies

Overall ln (RR) of 36 studies=	0.200149
Overall (RR) of 36 studies=	1.221585
Summary Var (ln RR) (Precision-based)=	0.001234
Summary SD (ln RR) (Precision-based)=	0.035122
Summary Lower 95% RR (Precision-based)=	1.140321
Summary Upper 95% RR (Precision-based)=	1.30864

Appendix B

Abbreviations

ACS	American Cancer Society
CHD	Coronary heart disease
CI	Confidence Interval
CPS I	Cancer Prevention Study I
CPS II	Cancer Prevention Study II
EPA	Environmental Protection Agency
ETS	Environmental tobacco smoke
IARC	International Agency for Research on Cancer
ICD-9	International Classification of Disease, 9th revision (1975)
MMWR	Morbidity and Mortality Weekly Review
MS	Mainstream (tobacco) smoke
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NRC	National Research Council
RR	Rate ratio, otherwise relative risk
SEER	Surveillance, Epidemiology and End Results program
SES	Socioeconomic status
SS	Sidestream tobacco smoke
TNCS	Third National Cancer Survey
US DHHS	United States Department of Human and Health Services
WHO	World Health Organization

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY II QUESTIONNAIRE FOR MEN	Division No.	Unit No.	Group No.
	Researcher No.	Family No.	Person No.

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother or Sister)	IS THIS PERSON? (Circle One)	IF ALIVE, GIVE AGE	IF DEAD, GIVE AGE AT DEATH	DID THIS PERSON EVER HAVE CANCER? (Circle One)	IF "YES," SPECIFY TYPE OF CANCER	AT WHAT AGE?
Father	Alive Dead			Yes No		
Mother	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes," a) What type? _____ b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:

☐ High Blood Pressure	☐ Emphysema
☐ Heart Disease	☐ Hay Fever
☐ Stroke	☐ Asthma
☐ Diabetes	☐ Stomach Ulcer
☐ Gall Stones	☐ Duodenal Ulcer
☐ Chronic Indigestion	☐ Diverticulosis
☐ Kidney Disease	☐ Rectal Polyps
☐ Kidney Stones	☐ Colon Polyps
☐ Bladder Disease	☐ Thyroid Condition
☐ Cirrhosis of the Liver	☐ Arthritis
☐ Tuberculosis	☐ Prostate Trouble
☐ Chronic Bronchitis	☐ Hepatitis

☐ Any other serious disease (specify) _____

3. Have you ever had an operation? ☐ Yes ☐ No
If "yes," specify type and date(s) of operation(s):

4. How many x-ray or fluoroscopic examinations (GI series, barium enema, etc.) have you ever had of:

	0	1-5	6 or More		0	1-5	6 or More
Stomach	☐	☐	☐	Chest	☐	☐	☐
Intestine	☐	☐	☐	Arms/Legs	☐	☐	☐
Back	☐	☐	☐	Head/Neck	☐	☐	☐

5. Have you ever been treated with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
If "yes," when? _____
For what disease? _____
What part of your body? _____
6. How many times have you had colds or flu in the past twelve months? _____

DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

Beef		Raw vegetables	
Pork		Carrots	
Chicken		Squash/Corn	
Liver		Citrus fruits/Juices	
Ham		Spaghetti/Macaroni/ White rice	
Fish			
Smoked meats		White bread/Rolls/ Biscuits	
Frankfurters/ Sausage		Brown rice/Whole wheat/Barley	
Butter		Bran/Corn muffins	
Margarine		Potatoes	
Cheese		Oatmeal/Shredded wheat/Bran cereals	
Eggs		Cold (Dry) cereals	
Green leafy vegetables		Ice cream	
Tomatoes		Chocolate	
Cabbage/Broccoli/ Brussels sprouts			

2. How many days a week do you eat the following fried foods?

Fried eggs	Fried hamburgers or beef
Fried bacon	Other fried foods
Fried chicken/fish	
French fries	

DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
   If "yes," what type and for how many years?

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
   If "yes," what was the change?

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
   ☐ Yes, currently ☐ Formerly ☐ Never
   b) If ever used artificial sweeteners, indicate amount per day and for how long.
   Packets: No. per day____ Years____
   Drops: No. per day____ Years____
   Tablets: No. per day____ Years____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify)____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2.)

Beverages	Currently		Previously	
	Amount	Years	Amount	Years
Whole milk (not skim milk)				
Caffeinated coffee				
Decaffeinated coffee				
Tea				
Diet soda or diet iced tea				
Non-diet colas				
Other non-diet soft drinks				
Beer				
Wine				
Hard liquor				

MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

Medications and Vitamins	Times	Years
Aspirin, Bufferin, Anacin		
Tylenol		
Vitamin A		
Vitamin C		
Vitamin E		
Multi-Vitamins		
Blood Pressure pills		
Diuretics (water pills)		
Thyroid medications		
Heart medications		
Anti-Acid medications		
Valium		
Librium		
Prescription sleeping pills		
Tagamet (for ulcers)		
Other:		

CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night? _____
3. On the average, how many times a month do you have insomnia? _____ ☐ None
4. Within the last month, have you noticed:
   a) Painful or frequent urination? ☐ Yes ☐ No
   b) An unusual discharge from your penis? ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains? _____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition? _____

HABITS:

1. Whether or not you smoke, on the average, how many hours a day are you exposed to cigarette smoke of others:
   At home_____, At work_____, In other areas_____
2. Do you now or have you ever smoked cigarettes, cigars or pipes, at least one a day for one year's time? ☐ Yes ☐ No
   If never smoked, skip to question 8.
3. If you currently smoke cigarettes, cigars or pipes, fill in the information below:

Current Smokers	Cigarettes	Cigars	Pipes
Average number smoked per day			
Age began smoking			
INHALATION:			
Do not inhale			
Inhale slightly			
Inhale moderately			
Inhale deeply			
Total years of smoking			
Years smoked filtered cigarettes			
Years smoked non-filtered cigarettes			

4. Current brand of cigarette: _____
   a) Size: ☐ Regular ☐ King ☐ 100 mm ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand: _____

5. If you have quit smoking cigarettes, cigars or pipes, fill in the information below:

Ex-Smokers	Cigarettes	Cigars	Pipes
Average number smoked per day			
Age began smoking			
Age quit			
INHALATION:			
Did not inhale			
Inhaled slightly			
Inhaled moderately			
Inhaled deeply			
Total years smoked			
Years smoked filtered cigarettes			
Years smoked non-filtered cigarettes			

6. Last brand of cigarette smoked: _____
   a) Size: ☐ Regular ☐ King ☐ 100 mm ☐ 120 mm
   b) ☐ Non-filter ☐ Filter ☐ Menthol
   c) Years smoked this brand: _____
7. Current and ex-cigarette smokers, fill in the following information for:
   1) The first brand smoked regularly; and
   2) The brand of cigarette smoked for the longest period of time.

Brand Name	Size	Filter Yes	Filter No	Menthol Yes	Menthol No	Number Per Day	Years
1.							
2.							

8. Have you ever chewed tobacco at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to question 9.
   a) Age began chewing tobacco: _____
   b) How many times a week? _____
   c) For how many years? _____
   d) Do you still chew tobacco? ☐ Yes ☐ No
9. Have you ever used snuff at least once a week for at least one year? ☐ Yes ☐ No
   If "no," skip to "Diet."
   a) Age began using snuff: _____
   b) How many times a week? _____
   c) For how many years? _____
   d) Do you still use snuff? ☐ Yes ☐ No

OCCUPATIONS:

1. What is your current occupation and what are your duties?_____
   How many years: _____
2. If retired, what was your last occupation?_____
   Year retired: _____
3. What other job have you held for the longest period of time?_____
   How many years: _____
4. What time of day do you start working?_____
   Do you work rotating shifts? ☐ Yes ☐ No
5. How many hours a week do you work on:
   paid jobs _____ volunteer work _____
   housework _____
6. In your work or daily life, are (were) you regularly exposed to any of the following? If "yes," indicate the number of years exposed.

Exposure to:	Check One Yes	No	Number of Years
Asbestos			
Chemicals/Acids/Solvents			
Coal or Stone Dusts			
Coal Tar/Pitch/Asphalt			
Diesel Engine Exhaust			
Dyes			
Formaldehyde			
Gasoline Exhaust			
Pesticides/Herbicides			
Textile Fibers/Dusts			
Wood Dust			
X-rays/Radioactive Materials			

REMARKS:

MISCELLANEOUS:

1. Where were you born?_____
2. Where were your parents born?
   Father:_____
   Mother:_____
3. Religion: ☐ Protestant ☐ Catholic ☐ Jewish ☐ LDS ☐ Other _____ ☐ None
   If Protestant, what denomination?_____
4. Education:
   ☐ 8th Grade or Less ☐ Some College
   ☐ Some High School ☐ College Graduate
   ☐ High School Graduate ☐ Graduate School
   ☐ Vocational/Trade School
5. How many years have you lived in your present neighborhood?_____
6. How many friends or relatives do you feel close to?_____
7. How many times a month do you:
   a) Go to church or temple?_____
   b) Attend club meetings?_____
   c) Participate in group activities?_____
8. Were you in the U.S. Armed Services? ☐ Yes ☐ No
   If "yes,"
   a) What branch of the service were you in?_____
   b) What were your dates of service?
   _____ to _____
   _____ to _____
   c) Where did you serve?_____
9. What is the most upsetting event that happened to you in about the last five years?_____
   ☐ None
10. Do you now or have you ever used mouthwash? ☐ Yes ☐ No
    If "yes,"
    a) What brand?_____
    b) How many times a week is it used?_____
    c) For how many years have you used it?_____

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY II QUESTIONNAIRE FOR WOMEN	Division No.	Unit No.	Group No.
	Researcher No.	Family No.	Person No.

Date: _____

1. Name: _____
2. Date of birth: Month _____ Year _____
3. How old are you now? _____
4. Current weight with indoor clothing: _____ lbs.
5. Weight 1 year ago: _____ lbs.
6. Height (without shoes): _____ ft. _____ in.
7. ☐ White ☐ Black ☐ Hispanic ☐ Oriental ☐ Other _____ (specify)
8. Marital status: ☐ Single ☐ Separated ☐ Widowed ☐ Married ☐ Divorced
9. If ever married, age at first marriage: _____
10. Number of times married: _____
11. Social Security No.: _____ (optional)

FAMILY HISTORY (IN RELATION TO CANCER):

1. Fill in the following table as completely as possible for parents, brothers and sisters.

LIST ONE BLOOD RELATIVE PER LINE: (Circle Brother or Sister)	IS THIS PERSON? (Circle One)	IF ALIVE, GIVE AGE	IF DEAD, GIVE AGE AT DEATH	DID THIS PERSON EVER HAVE CANCER? (Circle One)	IF "YES," SPECIFY TYPE OF CANCER	AT WHAT AGE?
Father	Alive Dead			Yes No		
Mother	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		
Brother or Sister	Alive Dead			Yes No		

2. When you were born, a) How old was your mother? _____ b) How old was your father? _____

HISTORY OF DISEASES:

1. Have you ever had cancer? ☐ Yes ☐ No. If "yes,"
   a) What type? _____
   b) Date of first treatment: _____
2. Place a check-mark by the following diseases or conditions for which you have ever been diagnosed by a doctor:
   - ☐ High Blood Pressure
   - ☐ Heart Disease
   - ☐ Stroke
   - ☐ Diabetes
   - ☐ Gall Stones
   - ☐ Chronic Indigestion
   - ☐ Kidney Disease
   - ☐ Kidney Stones
   - ☐ Bladder Disease
   - ☐ Cirrhosis of the Liver
   - ☐ Tuberculosis
   - ☐ Chronic Bronchitis
   - ☐ Emphysema
   - ☐ Hay Fever
   - ☐ Asthma
   - ☐ Stomach Ulcer
   - ☐ Duodenal Ulcer
   - ☐ Diverticulosis
   - ☐ Rectal Polyps
   - ☐ Colon Polyps
   - ☐ Thyroid Condition
   - ☐ Arthritis
   - ☐ Breast Cysts
   - ☐ Gynecological Problems
   - ☐ Hepatitis
   - ☐ Any other serious disease (specify) _____
3. Have you ever had an operation? ☐ Yes ☐ No
   If "yes," specify type and date(s) of operation(s):
   _____
   _____
   _____
   _____
4. How many x-ray or fluoroscopic examinations (GI series, barium enema, etc.) have you ever had of:

	0	1-5	6 or More		0	1-5	6 or More
Stomach	☐	☐	☐	Chest	☐	☐	☐
Intestine	☐	☐	☐	Breast	☐	☐	☐
Back	☐	☐	☐	Head/Neck	☐	☐	☐

5. Have you ever been treated with radium, x-rays, or radioactive isotopes? ☐ Yes ☐ No
   If "yes," when? _____
   For what disease? _____
   What part of your body? _____
6. How many times have you had colds or flu in the past twelve months? _____

CURRENT PHYSICAL CONDITION:

1. How much exercise do you get (work or play)?
   ☐ None ☐ Slight ☐ Moderate ☐ Heavy
2. On the average, how many hours do you sleep each night? _____
3. On the average, how many times a month do you have insomnia? _____ ☐ None
4. Within the last twelve months, have you noticed:
   a) A lump or thickening in your breast?
   ☐ Yes ☐ No
   b) An unusual discharge from your breast?
   ☐ Yes ☐ No
5. Do you notice pains in your legs when you walk which go away when you rest? ☐ Yes ☐ No
   If "yes," how many years have you had these pains? _____
6. Are you sick at the present time? ☐ Yes ☐ No
   If "yes," with what disease or condition? _____

MENSTRUAL AND REPRODUCTIVE HISTORY:

1. How old were you when menstruation began? _____
2. What is your current menopausal status?
   ☐ Still regularly menstruating
   ☐ In menopause ☐ Past menopause
3. During your menstrual history:
   a) Are (were) your periods: ☐ Regular ☐ Irregular
   b) What is (was) the usual number of days of flow? _____
4. If **past menopause:**
   a) Was your menopause: ☐ Natural ☐ Artificial
   b) Age when periods stopped completely? _____
   c) Did you have excessive bleeding during menopause? ☐ Yes ☐ No
5. Have you ever had or tried to have children?
   ☐ Yes ☐ No
   If "no," skip to question 9.
6. Have you ever had difficulty becoming pregnant?
   ☐ Yes ☐ No
   If "yes," what was the reason? _____
7. How many times have you been pregnant? _____
   a) Your age at your first pregnancy? _____
   b) Your age at your first live birth? _____
   c) Number of children born alive? _____
   d) Number of stillbirths (carried 5 months or more)? _____
   e) Number of miscarriages (carried less than 5 months)? _____
8. Were you ever given DES (Diethyistilbestrol) to prevent miscarriage? ☐ Yes ☐ No
   If "yes,"
   a) At what age did you take it? _____
   b) For how many months did you take it? _____
9. Birth control methods: Indicate your age when first used and number of years of use.

Method Used	Age	Years
Rhythm		
Diaphragm		
Cream/Foam/Jelly		
Tubal Ligation		
Intrauterine Device (IUD)		
Condom (partner)		
Vasectomy (partner)		
NONE OF THE ABOVE ☐		

10. Have you **ever** taken oral contraceptives (birth control pills)? ☐ Yes ☐ No
    If "no," skip to question 11.
    a) Age when you first took them? _____
    b) How many years did you take them? _____
    c) What brand(s) do (did) you take? _____
    d) If you stopped taking them, what was the reason? _____
    e) Did you have irregular or painful periods when you stopped? ☐ Yes ☐ No
11. Have you **ever** used female hormones (estrogens) other than oral contraceptives? ☐ Yes ☐ No
    a) Why do (did) you take estrogens?
    ☐ Menopausal symptoms ☐ Hysterectomy
    ☐ Bone problems ☐ Cancer
    ☐ Other (specify) _____
    b) Age first took estrogens? _____
    c) For how many years did you take them? _____
    d) How did you take them? ☐ Injection ☐ Cream ☐ Pill (brand): _____

HABITS:

1. Whether or not you smoke, on the average, how many hours a day are you exposed to cigarette smoke of others:
   At home _____, At work _____, In other areas _____
2. Do you now or have you ever smoked cigarettes, at least one a day for one year's time? ☐ Yes ☐ No

Smoking History	Current Smokers	Ex-Smokers
Number smoked a day		
Age began smoking		
Age quit smoking		
Most recent (last) brand		
Years smoked this brand		
Total years smoked filtered cigarettes		
Total years smoked non-filtered cigarettes		
Total years of smoking (filtered + non-filtered)		

3. Current and ex-smokers:
   a) Do (did) you inhale? ☐ No, never ☐ Slightly ☐ Moderately ☐ Deeply
   b) Fill in the following information for:
      1) The first brand smoked regularly; and
      2) The brand of cigarette smoked for the longest period of time.

Brand Name	Size	Filter Yes	Filter No	Menthol Yes	Menthol No	Number Per Day	Years
1.							
2.							

DIET:

1. On the average, how many days per week do you eat the following foods? (If less than once a week, but at least twice a month, write 1/2.)

Beef	Raw vegetables
Pork	Carrots
Chicken	Squash/Corn
Liver	Citrus fruits/Juices
Ham	Spaghetti/Macaroni/ White rice
Fish	
Smoked meats	White bread/Rolls/ Biscuits
Frankfurters/ Sausage	Brown rice/Whole wheat/Barley
Butter	Bran/Corn muffins
Margarine	Potatoes
Cheese	Oatmeal/Shredded wheat/Bran cereals
Eggs	
Green leafy vegetables	Cold (Dry) cereals
Tomatoes	Ice cream
Cabbage/Broccoli/ Brussels sprouts	Chocolate

2. How many days a week do you eat the following fried foods?

Fried eggs	Fried hamburgers or beef
Fried bacon	
Fried chicken/fish	Other fried foods
French fries	

DO NOT EAT FRIED FOODS ☐

3. Do you eat a vegetarian diet? ☐ Yes ☐ No
   If "yes," what type and for how many years?

4. Has there been a major change in your diet in the last 10 years? ☐ Yes ☐ No
   If "yes," what was the change?

5. a) Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?
   ☐ Yes, currently ☐ Formerly ☐ Never
   b) If ever used artificial sweeteners, indicate amount per day and for how long.
   Packets: No. per day____ Years____
   Drops: No. per day____ Years____
   Tablets: No. per day____ Years____

6. Do you get your drinking water from: ☐ City supply ☐ Private well ☐ Other (specify)____

7. Do you add any substances to soften your drinking water? ☐ Yes ☐ No

8. How many cups, glasses, or drinks of these beverages do you usually drink a day, and for how many years? (If you no longer drink a listed beverage, or your pattern has changed in the last ten years, indicate previous and current amounts. If less than once a day, but at least three times a week, write 1/2).

Beverages	Currently Amount	Currently Years	Previously Amount	Previously Years
Whole milk (not skim milk)				
Caffeinated coffee				
Decaffeinated coffee				
Tea				
Diet soda or diet iced tea				
Non-diet colas				
Other non-diet soft drinks				
Beer				
Wine				
Hard liquor				

MEDICATIONS AND VITAMINS:

1. How many times in the last month have you used the following and how long have you used them? (If none, write 0; if used only occasionally, write 1/2.)

Medications and Vitamins	Times	Years
Aspirin, Bufferin, Anacin		
Tylenol		
Vitamin A		
Vitamin C		
Vitamin E		
Multi-Vitamins		
Blood Pressure pills		
Diuretics (water pills)		
Thyroid medications		
Heart medications		
Anti-Acid medications		
Valium		
Librium		
Prescription sleeping pills		
Tagamet (for ulcers)		
Other:		

OCCUPATIONS:

1. What is your current occupation and what are your duties? _____
   _____
   _____ How many years: _____
2. If retired, what was your last occupation? _____
   _____
   _____
   _____ Year retired: _____
3. What other job have you held for the longest period of time? _____
   _____
   _____ How many years: _____
4. What time of day do you start working? _____
   Do you work rotating shifts? ☐ Yes ☐ No
5. How many hours a week do you work on:
   paid jobs _____ volunteer work _____
   housework _____
6. In your work or daily life, are (were) you regularly exposed to any of the following? If "yes," indicate the number of years exposed.

Exposure to:	Check One: Yes	No	Number of Years
Asbestos			
Chemicals/Acids/Solvents			
Coal or Stone Dusts			
Coal Tar/Pitch/Asphalt			
Diesel Engine Exhaust			
Dyes			
Formaldehyde			
Gasoline Exhaust			
Pesticides/Herbicides			
Textile Fibers/Dusts			
Wood Dust			
X-rays/Radioactive Materials			

REMARKS:

MISCELLANEOUS:

1. Where were you born? _____ (city) _____ (state/country)
2. Where were your parents born?
   Father: _____
   Mother: _____
3. Religion: ☐ Protestant ☐ Catholic ☐ Jewish
   ☐ LDS ☐ Other _____ ☐ None
   If Protestant, what denomination? _____
4. Education:
   ☐ 8th Grade or Less ☐ Some College
   ☐ Some High School ☐ College Graduate
   ☐ High School Graduate ☐ Graduate School
   ☐ Vocational/Trade School
5. How many years have you lived in your present neighborhood? _____
6. How many friends or relatives do you feel close to? _____
7. How many times a month do you:
   a) Go to church or temple? _____
   b) Attend club meetings? _____
   c) Participate in group activities? _____
8. What is the most upsetting event that happened to you in about the last five years? _____
   _____ ☐ None
9. How many people do you take care of in your household? (Include yourself) _____
10. Do you now or have you ever used a permanent hair dye? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) What color? _____
    c) How often applied? _____
    d) How many years have you used it? _____
11. Do you now or have you ever used mouthwash? ☐ Yes ☐ No
    If "yes,"
    a) What brand? _____
    b) How many times a week is it used? _____
    c) For how many years have you used it? _____

AMERICAN CANCER SOCIETY
CANCER PREVENTION STUDY II
INSTRUCCIONES PARA LOS ENTREVISTADORES

INSTRUCCIONES GENERALES:

Inscriba a alrededor de diez familias: Por familias se entiende hogares donde hay más de una persona viviendo juntos como una familia. Cada familia debe tener por **lo menos una persona que tenga más de 45 años.** Por favor haga un esfuerzo por encontrar familias con personas entre las edades de 50 a 60 años. Inscriba solamente aquellas familias las cuales usted está bastante seguro que van a permanecer en el mismo vecindario durante los próximos seis años. Si usted puede inscribir más de diez familias, por favor hágalo.

Para ayudar a explicar el propósito y el plan de este estudio deje el panfleto "Cancer Prevention Study II—Hoja Informativa" con cada familia que usted inscriba.

En cada una de las familias que usted inscriba, pida que cada miembro que sea **mayor de 30 años** llene o conteste el cuestionario, los coloque en un "Sobre Confidencial," lo cierre y se lo devuelva a usted. Debido a lo extenso de este estudio es necesario identificar cada cuestionario con una serie de números. Esto se explica en el párrafo número 3, abajo indicado. Por favor siga las instrucciones cuidadosamente.

Después de recoger los cuestionarios, llene el folleto de cuatro páginas "Lista de Familias y Personas Inscritas." Incluya en éste el nombre y la dirección de una persona que conozca a la mayoría de las familias inscritas y que pueda **reemplazarlo** durante los próximos seis años, si fuera necesario. Cuando ésto esté terminado meta los "Sobres Confidenciales" (con los cuestionarios completos) en el folleto "Lista de Familias y Personas Inscritas," asegúrelo con una goma elástica y colóquelo en el sobre grande. Entregue todo el material terminado según las instrucciones que se le han dado.

INSTRUCCIONES DETALLADAS:

1. Revise el paquete para asegurarse de que contiene lo siguiente:
   a) suficientes cuestionarios para hombres (impreso en color azul);
   b) suficientes cuestionarios para mujeres (impreso en color blanco);
   c) suficientes "Sobres Confidenciales;"
   d) un folleto de cuatro páginas "Lista de Familias y Personas Inscritas;" y
   e) suficientes "Hojas Informativas."
2. En la última página de este folleto de instrucciones, enumere las familias (hogares) en las que usted sabe hay por lo menos una persona mayor de 45 años. El término "hogar" incluye a las personas que viven juntas como una familia y también incluye a personas solteras que viven solas.

   Visite a cada familia en su lista e inscriba solamente aquellas que usted piensa estarán en el área durante los próximos seis años. Pida que cada miembro **mayor de treinta años** llene el cuestionario. No excluya a una familia si uno o dos miembros se niegan a llenar o no llenan el cuestionario después que otros miembros de la familia lo hayan llenado.
3. Para facilitar la identificación a usted se le ha asignado un Número de División, un Número de Unidad, un Número de Grupo y un Número de Entrevistador. Copie todos esos números en todos los cuestionarios y sobres confidenciales que use. Además, asegúrese de escribir todos estos números de identificación, su nombre y dirección, y el nombre y dirección de un substituto que conozca a la mayoría de las familias que usted ha inscrito, en la parte de arriba del folleto "Lista de Familias y Personas Inscritas."

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Asígnele un Número de Familia, a cada familia que inscriba, siendo la primera Familia No. 1, la segunda Familia No. 2, etc. Además asígnele un Número de Persona, a cada persona que inscriba en cada familia, siendo un miembro de la familia Persona No. 1, otro siendo Persona No. 2, etc.

Por ejemplo, la primera familia (Familia No. 1) puede componerse del Señor y Señora López, su hijo de 35 años Jorge López, la suegra del Señor López, la Señora Rivera y un amigo, el Señor Ricardo Martínez. Entonces, para la Familia No. 1, el Señor López es Persona No. 1, La Señora López es Persona No. 2, Jorge López es Persona No. 3, La Señora Rivera es Persona No. 4, y el Señor Martínez es Persona No. 5. Después, el Señor y Señora Brown pueden ser la Familia No. 2; siendo el Señor Brown Persona No. 1 y la Señora Brown Persona No. 2 en la familia.

4. Cuando una persona acepte llenar el cuestionario, escriba el nombre de él o ella y todos los números de identificación (incluyendo el Número de Familia y el Número de Persona) en la parte de arriba del cuestionario. También escriba el nombre de él o ella y la dirección y todos los números de identificación en el "Sobre Confidencial."

   Entréguele el cuestionario y el "Sobre Confidencial" al participante. El cuestionario está diseñado para ser llenado por la persona y las contestaciones son confidenciales. Pida que el participante llene el cuestionario y luego lo meta en un sobre y lo selle. Usted es responsable de recoger los sobres sellados. Usted puede esperar mientras el participante complete el cuestionario o, si usted lo prefiere, puede dejar el cuestionario y regresar más tarde a recogerlo.

5. Trate de inscribir a todas sus familias y de recoger los cuestionarios completados en un periodo de dos semanas.

6. Después de que usted haya recogido los cuestionarios de todos las personas que usted ha inscrito, ya terminados, llene la "Lista de Familias y Personas Inscritas," según las instrucciones dadas en este folleto azul.

7. Después de que haya completado todo, meta "Los Sobres Confidenciales" junto con el folleto "Lista de Familias y Personas Inscritas," asegure todo con una goma elástica y póngalo en el sobre grande y devuélvalos según las instrucciones recibidas.

OBJECTIVO Y PLAN DEL ESTUDIO:

El primer Estudio Sobre la Prevención de la Sociedad Americana Contra el Cáncer se llevó a cabo durante un período de 13 años, desde 1959–1972, y nos ayudó a identificar un número de factores relacionados con el desarrollo del cáncer. De hecho, mucho de lo que conocemos hoy sobre las causas del cáncer ha surgido de éstos estudios epidemiológicos. El Estudio Número 1 de la Prevención del Cáncer, por ejemplo, estableció que el fumar cigarrillos es una de las principales causas del cáncer del pulmón e implicó al uso del tabaco en el desarrollo de otros tipos de cáncer y en las enfermedades del corazón y vías respiratorias. Otros estudios epidemiológicos han vinculado al cáncer de la piel a demasiada exposición a los Rayos-X, arsénico o ciertos tipos de breas y aceites, el cáncer de la vejiga, a trabajadores expuestos a ciertos productos químicos y el cáncer del pulmón a la exposición durante largo tiempo a las fibras de asbestos. Estos son algunos de los factores ambientales que pueden causar cáncer. Es solamente a través de la observación de un amplio número de personas durante un largo periodo de tiempo, como planeamos hacer en el Estudio Número II Para la Prevención del Cáncer, que podemos descubrir muchos otros factores y determinar cuáles son perjudiciales para la salud y cuáles no.

En el Estudio II Para la Prevención del Cáncer, vamos a enfocar nuestra atención hacia los cambios que han ocurrido desde nuestro primer estudio en nuestra estilo de vida, los productos que usamos y en el ambiente de nuestro hogar y lugar de empleo. Recientemente, ha habido un gran interés en determinar el efecto de la sacarina, tintes para el cabello, contraceptivos orales, tranquilizantes y otras drogas y medicamentos. El efecto de la exposición durante largo tiempo a los Rayos-X, la

contaminación del aire y del agua, y los carcinógenos en los lugares de empleo también necesitan ser cuestionados. El público y la comunidad científica desea encontrar la razón para el aumento en los casos de cáncer en la población negra y señalar los especiales riesgos de cáncer entre otras minorías.

El plan del nuevo Estudio Sobre la Prevención del Cáncer de la Sociedad Americana Contra el Cáncer es inscribir a más de 1.000.000 de personas y darles seguimiento durante seis años, o tal vez más tiempo. Como entrevistador voluntario, usted será de gran ayuda en recopilar información investigativa vital. Manteniéndose en contacto con las personas que ha inscrito e informando sobre ellos cada dos años, habrá suministrado a nuestros estadísticos de salud con información sobre cómo los estilos de vida afectan la salud y qué factores aumentan o disminuyen las oportunidades de adquirir cáncer y otras enfermedades.

Este tipo de estudio aumentará nuestro conocimiento sobre el cáncer y nos permitirá identificar aquellos factores que causan cáncer y que pueden ser controlados, así como aquellos que no parecen aumentar el riesgo de desarrollar cáncer. El objetivo final, por supuesto, es prevenir el cáncer y salvar miles de vidas.

ALGUNAS PREGUNTAS QUE LE PODRAN HACER LAS PERSONAS QUE USTED INSCRIBA:

P. ¿Por qué fuí escogido para este estudio?

R. Necesitamos inscribir una amplia muestra de diferente público: personas de diferentes edades, áreas geográficas, razas, religiones, hábitos, exposiciones y estilos de vida. De esta forma encontraremos cuáles grupos tienen riesgos más altos de contraer cáncer y cuáles los más bajos.

P. ¿Está interesado mayormente en personas con cáncer?

R. No, estamos interesados en todas las personas, aquellas que están en buena salud, así como aquellas que tienen o han tenido cáncer.

P. Mi hijo de 25 años vive conmigo. ¿Por qué usted no desea que él conteste el cuestionario?

R. Estamos excluyendo a personas menores de 30 años porque ellos no han sido expuestos a los factores bajo estudio por tan largo tiempo como lo han estado las personas mayores. Además, la frecuencia del cáncer generalmente aumenta con la edad y no habría suficiente información para estudiar si inscribimos personas menores de 30 años.

P. Nosotros sabemos ya que el fumar cigarrillos causa cáncer. ¿Por qué necesitamos otro estudio?

R. Los cigarrillos fumados ahora por más de cincuenta millones de personas son considerablemente diferentes de los fumados en la época de nuestro primer estudio. Necesitamos determinar si cigarrillos bajos en brea y nicotina han afectado substancialmente los riesgos de salud. También estamos investigando los efectos del fumar cigarrillos en el ambiente de lugares de empleo y los posibles efectos de salud del fumador de "segunda-mano," ésto es, el humo inhalado por personas que no fuman.

P. ¿Porqué me preguntó por mi número de Seguro Social? ¿No es eso ilegal?

R. Damos su número de Seguro Social es extrictamente voluntario. Al hacerlo, nos ahorrará usted mucho tiempo, esfuerzo y dinero al verificar nuestros archivos más tarde (especialmente para personas con los mismos nombres). Casualmente, no es ilegal pedir su número, es ilegal **exigírselo.**

P. ¿Se mantendrá confidencial la información en el cuestionario?

R. Sí. Será utilizada solamente para los propósitos de la investigación. Nunca daremos información sobre ninguna persona en particular y no daremos direcciones a ninguna agencia por ningún propósito, cualquiera que éste sea.

LISTA DE FAMILIAS:

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Appendix E.

Bibliography of Epidemiologic Studies of Lung Cancer and ETS

Listed by chronologic order.

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