Rising Lung Cancer Mortality Among Nonsmokers

James E. Enstrom, Ph.D.

ABSTRACT—On the basis of data available from two representative samples of lung cancer deaths in the United States as well as national mortality statistics and other epidemiologic studies, the lung cancer mortality rate has risen substantially between 1914 and 1959 among persons who have never smoked cigarettes. For white males the relative increase for ages 35-64 years has been about 1.6-fold; the relative increase for ages 65-84 years has been about 2.4-fold. For white females the relative increase for ages 35-64 years has been about 1.7-fold. Most of the relative increase occurred before 1935 and was probably due to changes in diagnostic criteria. However, increases have continued up to the present for male nonsmokers, who now apparently have an annual age-adjusted lung cancer death rate of about 25 per 100,000 persons between the ages 35-64 years. The rising lung cancer rate among nonsmokers indicates that factors in addition to personal cigarette smoking have had a significant effect on the mortality rate from this disease. In spite of the limited quality of these data, they suggest that a more complete understanding of lung cancer etiology is needed.—J Natl Cancer Inst 62: 755-760, 1979.

Much effort over the past 30 years has gone into the collection of epidemiologic evidence establishing and confirming a statistical relationship between lung cancer and cigarette smoking. To date the evidence appears so overwhelming that there is general acceptance of the conclusion in the 1964 Surgeon General's report. "Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, although less extensive, point in the same direction." (1) Nevertheless, the conclusion of causality is still subjected to criticism (2). Indeed, no mechanism for human tobacco carcinogenesis has yet been successfully formulated and tested and no randomized human trial has ever been conducted to measure the specific effect of either the initiation or the cessation of smoking on subsequent lung cancer mortality. Also, many factors other than personal cigarette smoking have not been examined in great detail in their relationship to lung cancer. In view of this, it is useful to examine lung cancer mortality among nonsmokers who are subject only to factors other than their own cigarette smoking. (3, 4)

With this brief introduction, an analysis will be made of existing data on lung cancer mortality trends among nonsmokers as well as among the total population in the United States. One probable reason that this analysis has not been done previously is that data on nonsmokers are limited. Because of the low lung cancer rates of nonsmokers, large groups of nonsmokers must be studied for long periods before sufficient deaths from lung cancer occur. Fortunately, however, two large representative surveys of the smoking histories of Americans who died of lung cancer are available. These surveys and concurrent surveys of the smoking status of living Americans allow the calculation of estimated age-specific mortality rates for nonsmokers in the entire U.S. population. These rates can then be compared with early data on U.S. lung cancer mortality when cigarette smoking was a relatively rare habit and with other lung cancer data from epidemiologic studies of nonsmokers. In this paper, nonsmokers are defined as persons who have never smoked cigarettes. Although nonsmokers here do not include former cigarette smokers, they may include present or former cigar and/or pipe smokers.

MATERIALS AND METHODS

The earliest available national lung cancer data are for 1914, based on a death registration system composed of 24 States with 62% of the total U.S. population (1, 5, 6). Only 185 white male and 143 white female lung cancer deaths were recorded in 1914, and problems with the accuracy and representativeness of these data have been discussed in detail elsewhere (6-8). For instance, in recent years these 24 registration States have had significantly higher lung cancer mortality rates than the other States (7). More serious are the difficulties that existed in 1914 in correctly diagnosing and classifying lung cancer (8), as discussed later. Beginning in 1935 the death registration system included all States and 100% of the U.S. population, and age-specific death rates have since been available on an annual basis (9, 10).

National Mortality Survey, 1938-1959.—The Current Mortality sample, a representative 10% sample of all deaths in the United States, provides the records of lung cancer deaths for 2.381 white males 35 years old and over during 1958 (11) and 749 white females 35 years old and over during 1958 and 1959 (12). A questionnaire on the residence and smoking history of each decedent was sent to the family informant listed on the death certificate, and the overall response rate was 90%. The Bureau of the Census collected comparable information on the U.S. population as a supplement to the Current Population Survey for May 1958. From a representative national sample of approximately 35,000 households, histories were obtained from 31,516 white males and 51,939 white females at least 35 years of age (11, 12).

National Mortality Survey, 1966-68.—This survey was conducted in a manner similar to that for the 1958-59 survey. Information on deceased persons 35-84 years old in the United States in 1956-68 comes from:

ABBREVIATION AND ACG = American Cancer Society

1 Received May 19, 1978. Accepted September 3, 1978
2 School of Public Health, University of California, Los Angeles, Calif. 90024
the National Mortality Survey, a follow-back survey of a representative sample of 19,526 death registration records, including 1,464 white males and 319 white female lung cancer deaths. By mail questionnaire, surviving family members and others named on the death certificate provided smoking histories and social characteristics of the deceased person; the overall response rate was 92%. Then, through the Current Population Survey conducted by the Bureau of the Census in August 1967, smoking and socioeconomic information comparable to that for the decedents was obtained for a representative national sample of 61,000 adults 35-84 years old, including 25,266 white males and 29,308 white females. (13, 14). The ACS "cancer prevention study" prospectively followed a cohort of 286,195 U.S. veterans who held active U.S. Government life insurance policies in 1953 (15). Most of the enrollees were healthy white male veterans of World War I; 82% were white-collar or skilled workers. Mortality data are available on 54,344 men 35-84 years old who never smoked regularly and who were followed from July 1, 1954, to December 31, 1962 (15). Other epidemiologic studies of nonsmokers.—The Dorn U.S. veterans study prospectively followed a cohort of 286,195 U.S. veterans who held active U.S. Government life insurance policies in 1953 (15). Most of the enrollees were healthy white male veterans of World War I, 82% were white-collar or skilled workers. Mortality data are available on 54,344 men 35-84 years old who never smoked regularly and who were followed from July 1, 1954, to December 31, 1962 (15).

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They can be effectively considered to be a cohort of males who never smoked; this assumption has been tentatively confirmed by actual survey data on a small sample of High Priests and Seventies (19). Using Mormon Church records, we obtained data on both the deaths and the population at risk, as described elsewhere (18). The lung cancer mortality rates have been calculated for an average 13,500 California High Priests and Seventies during 1968-75 and 50,000 Utah High Priests and Seventies during 1970 and 1975. A total of 63 lung cancer deaths have occurred among 208,000 person-years of mortality experience for ages 35 to 84 years. These data are detailed elsewhere (19); Enstrom JE. Unpublished data). Active Mormons are not a representative sample of all U.S. white males who have never smoked, but they are similar in total mortality to the U.S. veteran and ACS cohorts of nonsmokers, as will be discussed later.

RESULTS

Lung Cancer Mortality Rates

The age-specific U.S. lung cancer mortality rates for nonsmokers and the total population are shown in table 1 for white males and in table 2 for white females. Table 3 shows lung cancer mortality rates from U.S. epidemiologic studies for white male nonsmokers who are not necessarily representative of the nation but who provide additional data on nonsmokers. The rates are given in 10-year intervals from ages 35 to 84 years, with an overall age-adjusted rate standardized to the 1960 U.S. population. Several comments below explain the data.

The 1914 age-specific rates are for all U.S. whites in the death registration area. As much as no breakdown is available by smoking status, the assumption will be made that in 1914 nonsmokers made up the total population. This probably overestimates the true nonsmoker rates, but is reasonable on the basis that cigarette smoking was a relatively rare and minor habit in 1914: only a small percentage of men and essentially no women had ever smoked cigarettes, and the annual cigarette consumption was 500 per person at least 15 years of age (20, 21). By comparison, in 1935 about 70% of the men and 40% of the women had ever smoked cigarettes (20), and the annual cigarette consumption was 3,500 per person at least 15 years of age (21). Use of cigars, pipes, and other tobacco products has declined greatly since 1914 (21) and hence has no major influence on recent lung cancer rates compared with the influence of cigarette smoking.

Rapid changes in nonsmoker rates after 1914 can be seen by a comparison of the 1914 and 1935 age-specific rates for all U.S. whites. In 1935, males 65 years old and above and females 45 years old and above can effectively be considered to have never smoked cigarettes on the basis of the 1935 surveys (20). The relative increases between 1914 and 1935 are approximately a factor of 10 for ages 65 years and above.

Age-specific lung cancer rates are published for 1938.
Rising Lung Cancer Mortality Among Nonsmokers

Table 1—Annual age-specific lung cancer mortality rates for U.S. white males in 1914, 1935, 1955, and 1966-68 according to smoking status (deaths/100,000 persons)

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Never smoked cigarettes</th>
<th>Never smoked</th>
<th>Never smoked cigarettes</th>
<th>Total U.S. population</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-44</td>
<td>0.0 (30)</td>
<td>—</td>
<td>1.6 (3)</td>
<td>1.6 (3)</td>
</tr>
<tr>
<td>45-54</td>
<td>2.6 (43)</td>
<td>5.8 (45)</td>
<td>2.4 (15)</td>
<td>1.5 (2)</td>
</tr>
<tr>
<td>55-64</td>
<td>2.0 (15)</td>
<td>11.7 (18)</td>
<td>14.6 (13)</td>
<td>22.7 (24)</td>
</tr>
<tr>
<td>65-74</td>
<td>2.6 (10)</td>
<td>26.7</td>
<td>22.0 (25)</td>
<td>32.7 (23)</td>
</tr>
<tr>
<td>75-84</td>
<td>1.2 (4)</td>
<td>23.3</td>
<td>5.0 (32)</td>
<td>69.7 (32)</td>
</tr>
<tr>
<td>85-89+</td>
<td>1.6 (14)</td>
<td>10.8 (80)</td>
<td>10.3 (80)</td>
<td>22.5 (100)</td>
</tr>
</tbody>
</table>

References: (1, 3) (9) (12), see text footnotes 3 and 4

* Based on 1914 U.S. death registration area (43), rates for males who never smoked cigarettes have been assumed to be the same as those for all males (see text). Numbers in parentheses are the No. of deaths on which rate is based.
* For ages 65 and above, rates for males who never smoked cigarettes have been assumed to be the same as those for all males (see text).

Table 2—Annual age-specific lung cancer mortality rates for U.S. white females in 1914, 1935, 1955, 1958-59, and 1966-68 according to smoking status (deaths/100,000 persons)

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Never smoked cigarettes</th>
<th>Never smoked</th>
<th>Never smoked cigarettes</th>
<th>Total U.S. population</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-44</td>
<td>0.5 (19)</td>
<td>—</td>
<td>0.7 (7)</td>
<td>0.5 (1)</td>
</tr>
<tr>
<td>45-54</td>
<td>1.6 (31)</td>
<td>6.0 (315)</td>
<td>2.7 (42)</td>
<td>1.2 (31)</td>
</tr>
<tr>
<td>55-64</td>
<td>2.2 (41)</td>
<td>9.2 (419)</td>
<td>3.0 (101)</td>
<td>1.1 (31)</td>
</tr>
<tr>
<td>65-74</td>
<td>2.5 (25)</td>
<td>14.3 (372)</td>
<td>9.6 (21)</td>
<td>2.2 (25)</td>
</tr>
<tr>
<td>75-84</td>
<td>1.0 (8)</td>
<td>14.5 (136)</td>
<td>14.0 (134)</td>
<td>15.9 (50)</td>
</tr>
<tr>
<td>85-89+</td>
<td>1.3 (12)</td>
<td>6.5 (456)</td>
<td>8.5 (122)</td>
<td>1.3 (124)</td>
</tr>
</tbody>
</table>

References: (1, 5) (9) (12) (13), see text footnotes 3 and 4

* Based on 1914 U.S. death registration area (43), rates for females who never smoked cigarettes have been assumed to be the same as those for all females (see text). Numbers in parentheses are the No. of deaths on which rate is based.
* For ages 65 and above, rates for females who never smoked cigarettes have been assumed to be the same as those for all females (see text).

U.S. white males and 1958-59 U.S. white females who "never smoked" (11, 12). The age-specific rates for ages 75-84 years were assumed to be the same as the published rates for ages 75 years and above, inasmuch as 85% of the population over 75 years is between ages 75-84 years; the error in this assumption is less than 5% (9, 10).

Age-specific lung cancer mortality rates for 1966-68 U.S. white males and white females who never smoked cigarettes were calculated from unpublished national survey data. We obtained age-specific rates by dividing the weighted sample of lung cancer deaths among white non-smokers and the total white population, as procured from the 1966-68 National Mortality Survey, by the appropriate number of U.S. white non-smokers and total white population as determined from 1966 Current Population Survey of cigarette smoking habits (13, 14). Finally, each non-smoker rate was adjusted slightly when we multiplied the ratio of non-smoker rate to total population rate as determined from the survey by the respective age and race corresponding 1966-68 U.S. age-specific mortality rate. A somewhat similar adjustment procedure was used on the 1958-59 survey data (12). Lung cancer deaths in both the 1958-59 and 1966-68 surveys are defined as...
Table 3—Annual age-specific lung cancer mortality rates and total mortality rates among selected nonsmoking white male populations in the United States (deaths/100,000 persons)

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Never smoked or occasional only</th>
<th>Never smoked</th>
<th>Never smoked regularly</th>
<th>Never smoked cigarettes</th>
<th>Never smoked</th>
<th>Never smoked cigarettes</th>
<th>1958-75 active Mormons*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer death rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>45-54</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (9)</td>
<td>5 (13)</td>
<td>6 (9)</td>
<td>6 (14)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>55-64</td>
<td>10 (25)</td>
<td>12 (49)</td>
<td>15 (19)</td>
<td>14 (35)</td>
<td>12 (14)</td>
<td>14 (64)</td>
<td>28 (14)</td>
</tr>
<tr>
<td>65-74</td>
<td>22 (48)</td>
<td>28 (97)</td>
<td>29 (84)</td>
<td>26 (59)</td>
<td>35 (131)</td>
<td>34 (39)</td>
<td>54 (19)</td>
</tr>
<tr>
<td>75-84</td>
<td>50 (4)</td>
<td>60 (9)</td>
<td>44 (9)</td>
<td>56 (20)</td>
<td>45 (13)</td>
<td>57 (23)</td>
<td>145 (24)</td>
</tr>
<tr>
<td>84+</td>
<td>94 (78)</td>
<td>127 (156)</td>
<td>104 (49)</td>
<td>134 (104)</td>
<td>108 (127)</td>
<td>131 (250)</td>
<td>244 (65)</td>
</tr>
</tbody>
</table>

| Total death rates | 1.028 (8.332) | 1.064 (11.727) | 1.125 (1.184) | 1.165 (8.797) | 1.085 (12.116) | 1.120 (10.524) | 1.029 (12.629) |

Ratio of lung cancer to total death rate, %

References [(15), appendix A, tables 19, 22, appendix table 2a, see text footnote 4, table A-1).

Note: *Never smoked cigarettes* is defined as the combination of "never smoked or occasionally only" and "current smokers and ex-smokers of pipes and/or cigars only" (15). Numbers in parentheses are the No. of deaths on which rate is based. "Never smoked cigarettes" is defined as the combination of "never smoked regularly", "cigarette only", and "pipe and cigar" (11). Published data, given according to age at start of study, have been modified with a life table correction (see text footnote 4) to give them according to age at death like results from the other studies in this table. Numbers in parentheses are the No. of deaths on which age is based. *Pooled cohort* is defined by a combination of the deaths and person-years of observation in the U.S. veteran and ACS cohorts, this cohort consists almost entirely of white males. Numbers in parentheses are the No. of deaths on which rate is based. *Active Mormons* are defined by the State of Utah residents of age 35-84 years old.

Age-adjusted by the direct method to the 1960 U.S. population 35-84 yr old.

Those with International Classification of Disease numbers 162 and 165 (15). Lung cancer death rates for the earlier years were derived by the international classification in effect in 1914 and 1955 (5, 9).

Because the 1966-68 mortality survey did not have a "never smoked" classification, lung cancer mortality rates are presented for males who "never smoked cigarettes." For females, there is no difference between "never smoked" and "never smoked cigarettes." Because the use of cigar and pipes by females is negligible. To estimate the effect of the male smoking classification differences, data from the U.S. veteran and ACS prospective cohort studies are presented in table 3. The U.S. veteran lung cancer death rates are given for the two categories "never smoked or occasionally only" and "never smoked cigarettes," the latter being defined as the combination of "never smoked or occasionally only" and "current smokers and ex-smokers of pipes and cigars only" (15). The ACS lung cancer death rates are given for the two categories "never smoked regularly" and "never smoked cigarettes," the latter being defined as the combination of "never smoked regularly," "pipe only," "cigarette only," and "pipe and cigar." (17). The deaths and person-years at risk from the two cohorts are pooled and presented for the categories "never smoked" and "never smoked cigarettes." The age-adjusted rate for "never smoked cigarettes" of 133 per 100,000 persons is about 29% higher than the rate for "never smoked" of 108 per 100,000 persons. Note that the "never smoked" rates for the 1954-63 pooled cohorts and for 1958 U.S. white males are identical. Also, the "never smoked" rates for the pooled cohort in table 3 agree with a previous pooling calculation (22). With the use of the ratio of cohort rates the rate for 1958 U.S. white males who "never smoked cigarettes" is estimated to be 13.3 per 100,000 persons as explained in table 1. Age-specific lung cancer mortality rates for active Mormons from California and Utah from 1968 to 1977 are also given in table 3. These results are included for comparison with the U.S. veteran and ACS cohorts in lieu of recent national mortality data on nonsmokers Active Mormons and the two nonsmoking cohorts have nearly identical total death rates, which suggests that these groups are similar in overall health. However the active Mormons have a lower cancer death rate of 22 per 100,000 persons, which is about double the cancer rates. The ratio of lung cancer to total death rate is shown in table 3 to facilitate comparison of the various cohorts.

Table 1 indicates that between 1933-37 and 1966-68 the lung cancer death rate for white males who "never smoked cigarettes" increased by about 30-fold for age 65-84 years and by about 15-fold for ages 35-64 years.

Most of the relative increase occurred before 1955, but there appears to be a continued increase up to the present.
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The results for women are similar, but the changes are less dramatic. Table II indicates that between 1914 and 1966, the lung cancer death rate for white females who "never smoked" increased by about 15-fold for ages 65-84 years and by about sevenfold for ages 35-44 years. Most of the relative increase occurred before 1955, but some increases continued in the older age groups up to 1956-59. However, since 1958-59 no further increase has been noted.

Sources of Error

From the data presented in tables I-3, only the gross changes should be considered definitive, because smaller changes possibly are due to various types of error that may be present. For instance, no claim is being made that the lung cancer death rate for U.S. white male non-smokers was precisely 1.7 times as high in 1966-68 as in 1958, only that the 1966-68 rate is much greater than the 1914 and 1935 rates and appears to be somewhat greater than the 1958 rate.

First, there is the statistical error associated with surveys. An example of this is the small number of lung cancer deaths in the 1914 data among persons over 75 years of age and the 1958-59 and 1966-68 "never smoked" categories among persons between the ages of 35 and 44 years. Second, there is respondent error in the surveys due to the fact that the smoking habits of all the deceased and many of the living were determined from proxies, usually the spouses, and not from the affected individuals themselves (27). This error may be greater for older women, who are usually not survived by their husbands. However, the error has been shown to be quite small among non-smokers in one study (71); and it is reasonable to assume that whatever error might be present is similar in the 1958-59 and 1966-68 surveys. Third, smoker classification varies. For instance, the 1966-68 survey classified persons as "never smoked cigarettes" whereas the 1958-59 survey used "never smoked." However, the 1958 rates for males who "never smoked cigarettes" have been estimated by use of results from the 1954-63 cohort studies in table 2. Fourth, there may be undisclosed biases or errors in the 1958-59 and 1966-68 mortality and population surveys that make them unrepresentative of the U.S. population and that could affect the death rates in either direction. But the remarkably good agreement in non-smoker lung cancer death rates for 1958 U.S. white males and the 1946-65 pooled cohorts tends to diminish the likelihood of any large-scale errors in the 1958 survey. The 1966-68 survey data have been examined in great detail elsewhere and have been found to be quite reliable. Furthermore, the total male- and white female lung cancer death rates estimated from the two surveys agreed within a small percentage with the corresponding rates obtained from U.S. vital statistics.

Finally, and probably most importantly, there have been changes in the diagnosis and certification of death due to lung cancer. These developments took place primarily between 1920 and 1950, with increasing use of chest radiology, bronchoscopy, and cytology and referral of patients to hospitals for diagnosis (1, 24). For instance, if 5% of the deaths certified to respiration tuberculosis in 1914 were really due to lung cancer, the reported 1914 lung cancer rates would be increased by a factor of 7 for males and a factor of 5 for females; larger errors would further increase the 1914 rates (8). Recent estimates indicate that diagnostic improvements may have accounted for up to a tenfold increase in the lung cancer death rates in the United Kingdom since 1916 (24). The precise effect of diagnostic improvements on the U.S. lung cancer death rates is unknown.

DISCUSSION

By use of the data available on the U.S. population from 1914 to 1968, it appears that the relative increase in the lung cancer mortality rate for non-smokers has been large. The increase has occurred in all age groups from 35 to 84 years, but it is concentrated in those over 65 years. The increase for white males 65-84 years old has been about 30-fold, whereas the increase for all white males 35-84 years old has been about 15-fold, on the basis of the reasonable assumption that the rates in 1914 describe non-smokers. The sevenfold increase for white females 35-84 years old follows the same pattern as that for white males, though it has been less dramatic. Most of the relative increases apparently have occurred before 1955, but significant increases have occurred since then, particularly in persons 65 years old and above. As seen in tables 1 and 2, the 1966-68 age-adjusted lung cancer death rate for white male non-smokers (22.8/100,000 persons) is about one-third the 1958 rate for all white males (77.6/100,000 persons) and the 1966-68 rate for white female non-smokers (8.3/100,000 persons) is only slightly less than the 1958-59 rate for all white females (11.7/100,000 persons). These comparisons indicate the current magnitude of lung cancer in persons who never smoked cigarettes.

Furthermore, the rising lung cancer rate among non-smokers implies that other factors must have a substantial influence on lung cancer mortality in addition to personal cigarette smoking. Among the influences that could be affecting both smokers and non-smokers are changes in diagnostic criteria, increases in environmental carcinogens, and certain constitutional factors (2). No rigorous data are available on the effects of diagnostic changes, but various estimates suggest that the true 1914 rates could be much larger than the reported rates (1, 2). As mentioned earlier, if 5% of the deaths certified to respiration tuberculosis in 1914 were really due to lung cancer, the reported 1914 lung cancer rates would be increased by a factor of 5-7. The early mortality data may also have been influenced by other relationships between tuberculosis and lung cancer, which are explored in detail elsewhere (24). Before 1955, diagnostic changes probably had the most impact on increasing lung cancer rates. More remote, environmental carcinogens and constitutional factors...
may have had a significant effect. Environmental carcinogens encompass occupational carcinogens like asbestos (26, 27) and environmental pollution including environmental tobacco smoke (28, 29). Constitutional factors include genetics and general host susceptibility (1, 2).

Before any final conclusions can be drawn, the lung cancer rates among nonsmokers, especially since 1950, should be confirmed with further analysis of the existing national surveys and cohort studies, as well as with another national survey to measure nonsmoker lung cancer rates in the current decade. But if one takes the available data as a whole, apparently lung cancer rates among nonsmokers have now reached significant levels. Indeed, the 1950-58 national and 1960-75 active Mormon survey indicate that the annual age-adjusted lung cancer death rate among white males who never smoked cigarettes is now approximately 25 per 100,000 persons for ages 35-84 years. If one assumes that these findings are accurate, then additional understanding of lung cancer etiology is necessary to supplement the well-established knowledge involving cigarette smoking. Further study of nonsmokers could provide an important means of ascertaining the non-smoking-related aspects of lung cancer etiology.

REFERENCES

(2) Blum PR. The Biology of Cancer A New Approach Baltimoge: Litton Park Press 1976