*Cohort Studies*

*Prologue*

The *Cohort Studies* laboratory exercise continues the investigation of the association between smoking and lung cancer by assessing the bronchogenic carcinoma incidence and risk of death among groups exhibiting different levels of smoking. This exercise contrasts the characteristics of case‑control and cohort investigations and identifies methods used to maximize the cost‑effectiveness of the inherently expensive follow‑up investigation.

Epidemiologic terms and concepts illustrated in the *Cohort Studies* exercise include: *cost containment of cohort investigations, the requirement for confirmation of disease diagnosis, misclassification, statistical significance, chi‑squared, p‑value, measurement of the magnitude of an association using the relative risk, dose‑response, representativeness versus comparability, the standardized mortality ratio (SMR), effects of intervention, risk difference (excess risk), age‑standardization, philosophy regarding causation and use of person‑time (person‑years) in the denominator of the relative risk measurement*.

COHORT STUDIES

*Cigarette Smoking and Lung Cancer*

Edited by John Morgan and Raymond Knutsen

Several case‑control investigations of lung cancer and smoking were considered in an earlier laboratory session. By 1964, more than 29 case‑control studies showing this relationship had been published. Widely varied research methods and study settings were used, yet all of the investigations demonstrated a strong association between smoking and pulmonary malignancy.

In spite of the consistent finding of a relationship between tobacco use and lung cancer, case‑control findings were criticized on the following grounds:

1. Studies limited to hospitalized lung cancer patients may not represent the total group of lung cancer patients and may over‑represent reporting of past tobacco use.

2. Controls chosen from among hospital patients may systematically over‑represent persons reporting a lower past use of tobacco when compared to the population from which lung cancer cases were identified.

3. The retrospective methods used to ascertain past smoking habits among lung cancer cases and controls are prone to systematic error and may provide invalid results.

4. Numerous variables other than smoking were not considered in the case‑control investigations.

5. The retrospective studies do not provide information regarding the *incidence* of lung cancer among smokers and non‑smokers.

These criticisms were not unique to the hypothesized association between smoking and lung cancer; most could be generally extended to all case‑control studies. In spite of the expense involved, the criticisms identified the need for confirmation of case‑control findings using cohort investigations. By the end of 1964, seven cohort (prospective) studies evaluating the relationship between smoking and lung cancer had been completed. Results from selected prospective investigations are presented below.

**Doll and Hill** (1) sent questionnaires on smoking habits to all of the 59,600 physicians in the United Kingdom in October, 1951. Usable replies were received from 40,701 physicians, 34,494 men and 6,207 women. Each participant was followed for a period of approximately 4 1/2 years. Doll and Hill obtained notification of death of participants from several sources. These included the Registrars General, the General Medical Council and the British Medical Association. Deaths listing lung cancer as the underlying cause were confirmed by either the physician certifying the death or by a representative from the hospital where the patient had been diagnosed. Summary results for bronchogenic carcinomas (ICD‑9 162) deaths and other selected diseases are presented in Table 1.

**Hammond and Horn** (2) used 22,000 American Cancer Society (ACS) volunteers as the field staff for a prospective study that began in 1952. Each volunteer was asked to administer a questionnaire on smoking habits to approximately 10 acquainted Caucasian men between the ages 50 and 69 years. The volunteers were asked to exclude men considered to be difficult to trace and those known to be seriously ill. A total of 187,783 men were enrolled in the investigation.

After enrollment, the volunteers were asked to report, on an annual basis, the most recent address and living/dead status for each of the men selected. Status categories included "alive," "dead" and "unknown." A copy of the death certificate was obtained for each death reported. Whenever cancer was mentioned on the certificate, further information was sought from either the attending physician, hospital records, or tumor registry.

The study area included 394 counties in California, Illinois, Iowa, Michigan, Minnesota, New Jersey, New York, Pennsylvania and Wisconsin. The data presented in Tables 2 through 4 include a summary of results derived from the first 44 months of follow‑up; representing 688,538 person‑years of risk.

*Veterans Insurance Study*

In 1954, **Dorn** (3) mailed questionnaires to military veterans holding U.S. Government life insurance policies. This coverage was available to men who had served in the armed forces between 1917 and 1940. These WWI and post WWI veterans represented a group of Americans having the highest prevalence of smoking in the history of the Nation.

The Dorn questionnaire included information regarding the use of tobacco, occupation, and place of residence. Usable replies were received from 198,926 persons; 68 percent of the total policyholders available.

A second questionnaire was mailed to non‑respondents during the first half of 1957. This mailing was followed by more than 50,000 additional replies. A total of nearly 249,000 usable questionnaires were received in the investigation. This number included approximately 85% of the population targeted for study.

Subsequent deaths in the initial target population were assessed for both questionnaire respondents and non‑respondents. Early assessment and confirmation of deaths was conducted by the insurance carrier prior to payment of claims. This investigation included procurement of death certificates and notification of the Veterans Administration. A copy of the claim and death certificate was mailed to the U.S. Public Health Service and forwarded to Dorn's staff.

Confirmation of cause of death was sought for all fatalities, regardless of cause. This process included verification of the underlying cause listed on the death certificate, procedures used to establish clinical diagnosis, mention of cancer in recent medical history and histologic type of cancer where appropriate. Data were requested from either the physician who had signed the death certificate or from the hospital where the death had occurred. Replies were received for more than 99% of the letters of inquiry.

In response to this new information, the reported *underlying cause of death* listed on the death certificate was changed for 6% of the deaths reported. An additional 12% were changed regarding the contributory role of cancer to the death (intermediate cause). Of the deaths for which diagnostic information was obtained, an autopsy had been performed in 31%. Diagnoses were established by use of surgical procedures, endoscopy, radiography or laboratory tests in 47%, and in 22% of the cancer deaths, diagnoses were based upon clinical history and physical examination.

The results obtained in the first 2 1/2 years of follow‑up (July 1954 through December 1956) in the Dorn study are summarized in Table 5. Deaths included only those occurring in study participants who had completed the 1954 questionnaire.

Although true experimental investigations of the association between smoking and lung cancer have not been conducted with human subjects, several "natural experiments" have been described. One of the most convincing was reported by **Doll and Hill** (4). In this observational study, one‑third of the British physicians reported as smokers in 1951 had quit smoking by 1961. During the same ten‑year period, per capita cigarette consumption in the general population of the United Kingdom had continued to rise.

*References*

1. Doll R, Hill A.B. The mortality of doctors in relation to their smoking habits; a preliminary report. British Journal of Medicine 1(4877): 1451‑55, June, 1954.

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4. Doll R, Hill A.B. Lung cancer and other causes of death in relation to smoking. A second report on the mortality of British doctors. British Journal of Medicine 2: 1071‑81, 1956.

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