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Cancer Epidemiologic Surveillance in the Du Pont Company

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Although various substances have been identified as human carcinogens during the past three centuries, concern over occupational carcinogens has intensified this past decade because of the recent discoveries of the carcinogenic activity of several substances that have been used for many years. Some have been established as human carcinogens (vinyl chloride and bischlormethyl ether), some as experimental animal carcinogens, and others have come under suspicion because of their mutagenic activity.

These discoveries and the fact that many new chemical substances are introduced into the workplace and the environment every year have emphasized the need for more intensive epidemiological investigations to identify human carcinogens as early as possible.

This article will describe the cancer epidemiological surveillance program that was started in the Du Pont Company in 1956. The general objectives of this program have been as follows: to measure cancer incidence and mortality of the company's employees; to identify company installations that have a significant excess of any type of cancer and determine whether the excess could have occurred as a result of exposure to an occupational carcinogen; to measure the cancer incidence or mortality of cohorts of employees who worked with specific substances that are known or suspected human carcinogens; to compare cancer morbidity and mortality of the Du Pont Company employees with that of other populations; to study trends in morbidity and mortality and evaluate their significance; and, to study cancer epidemiology by analyses of rates according to various demographic and personal characteristics.

The article includes a description of the demographic characteristics of the company population, pertinent features of the company medical program, casefinding procedures, the methodology for collecting and analyzing data, the limitations of the data, and a presentation of some morbidity and mortality statistics.

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The Company Population

Demographic Characteristics. — From 1956 through 1974, the company population ranged from about 80,000 to 108,000. About 14% have been female employees. The ages of the active employees do not go beyond 64 years, since retirement is mandatory at age 65.

The company population is divided into two payroll classes, the wage roll and the salary roll. This division is particularly useful for epidemiological studies because it groups employees according to certain occupational and socioeconomic characteristics. Wage roll employees are hourly paid production workers, most of whom are operators, craftsmen, laborers, and service workers. They comprise about 60% of the male population and 43% of the female population. Salaried employees include clerical, technical, professional, and managerial personnel. Some employees start on the wage roll and are later transferred to the salary roll as a result of promotion to a supervisory position.

Employees who retire on a company pension are included in the mortality studies. The number of retirees on the pension roll in 1956 was 5,129, and grew to 21,160 in 1974.

Company installations include manufacturing plants and many offices, laboratories, and warehouses throughout the United States. The largest concentrations of plants are in the middle Atlantic and southeastern states.

The Company Medical Program. — The company's medical program, which was started in 1915, provides preemployment and periodic health examinations to all employees. The examinations are given by company physicians, annually to persons over 40 years of age and biennially to persons 40 years of age and under.

The program is conducted by 67 full-time physicians and 56 part-time physicians, assisted by nurses, technicians, and clerical workers. A medical section is located in all but small installations. Employees not covered by company physicians are examined by private physicians retained by the company.

The routine examination includes blood tests (hematol-

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ogy and blood chemistry), urinalysis, blood pressure measurements, pulse rates, body weights, roentgenograms of the chest, electrocardiograms, pulmonary function tests, audiograms, vision tests, and physical examinations. Additional tests and examinations are often done, either to obtain a diagnosis or to check workers exposed to special hazards.

Employees may also see a company physician by requesting a consultation or for evaluation upon return to work following a disabling illness. For assistance in making an evaluation, company physicians contact private physicians and hospitals. Correspondence to and from these sources is kept in the employees' medical records.

The documents generated by various facets of the medical program (periodic health examinations, special examinations, consultations, and contacts with outside physicians) may be useful in confirming cancer diagnoses and ascertaining the primary site. The medical records, however, are not the primary source of casefinding, but serve as a supplementary source of cancer data.

Casefinding

Any system designed to identify all cancer cases throughout the company would have to take into account the wide dispersion of its 108,000 employees throughout the United States. Some employees are located in small sales offices, laboratories, and warehouses. They are given periodic health examinations by private physicians who usually have no contact with them during the one or two-year interval between examinations, and, therefore, do not know if cancer has subsequently occurred in any of the employees they have examined.

Reporting of cases by company physicians was attempted before the development of the present system, but this method was found to be inadequate for these reasons: (1) as mentioned earlier, some employees are in locations where there is little or no medical surveillance between periodic health examinations; and, (2) analyses of the data indicated underreporting in most plants.

The present system overcomes these obstacles by the automatic reporting of cases through documents generated by two company sponsored insurance plans — one a group accident and health insurance plan, and the other a group life insurance plan.

The accident and health insurance plan provides benefits for nonoccupational injuries and illnesses that cause disability for eight days or longer. To enroll, an employee must have at least six months of service and pay a small monthly premium. The participation rate among eligible employees is about 97%. The claims must show the diagnosis, certified by the attending physician. Copies of each claim are sent from company installations throughout the United States to corporate headquarters in Wilmington, Delaware, for processing. Cancer cases are identified by the diagnosis recorded on the claim.

In addition to the diagnosis, the claims also contain important demographic information, such as the employee's plant or office location, age, sex, social security number, and whether he is on the wage or salary roll.

Reporting of cases by accident and health insurance claims is supplemented by death certificates that must accompany claims filed by beneficiaries of deceased employees and retirees covered by the company's group life insurance plan.

Until 1972, an employee had to have one year of service to be eligible for the life insurance plan. Since then employees have been covered from the first day of employment. The entire premium cost is paid by the company, so that coverage is complete throughout the company. Thus, if an employee who develops cancer is not covered by the accident and health insurance plan, he could be identified as a cancer case if he subsequently died of the disease.

The advantages of using these insurance plans as a means of casefinding are as follows: (1) the diagnosis must be recorded by a physician; (2) complete reporting of cases among participating eligible employees is insured because a claim must be filed to obtain benefits; and, (3) claims from all over the United States must be sent to corporate headquarters in Wilmington for processing, thus providing a complete, convenient, and economical mechanism for case reporting.

Documents generated by the two insurance plans are used to maintain (1) a cancer registry of newly diagnosed cancer cases among active employees, and (2) a cancer mortality file of all cancer deaths occurring among active employees and employees who retire on a company pension. The two files are described in the following sections.

The Cancer Registry

The cancer registry was established in 1956 to study cancer morbidity among company employees. Cases are identified by accident and health insurance claims and death certificates that accompany life insurance claims.

Beginning in 1977, we introduced a cancer registry report to be submitted by company physicians on any employee who develops cancer (Fig 1). This form is not intended as a primary source of casefinding — that function is fulfilled by the insurance claims. The purposes of this form are to report cases that may not have been included among the insurance claims, such as those persons who (1) are not covered by the accident and health insurance plan, or (2) develop basal or squamous cell cancer of the skin that does not result in disability of more than seven days, as required by the insurance plan; and, to provide us with information not always available on other documents, such as histological type, procedures used to establish the diagnosis, smoking history, occupational history, and history of actual or potential exposure to known or suspected carcinogenic agents.

An employee is entered into the registry only once, regardless of the number of claims filed, unless the employee develops cancer of two or more independent primary sites. In these instances, an entry into the registry would be made once for each primary site.

Basal and squamous cell carcinoma of the skin are entered into the registry whenever they are reported, but are not included in the analysis since these cases are rarely fatal. Persons who develop these cancers frequently do not lose time from work and, therefore, many are not reported. The recently implemented cancer registry report form may provide adequate reporting of these cases. Malignant melanoma of the skin, however, is included in the analysis.

The cancer morbidity data are confined to newly diagnosed cases that occur among active employees. The data

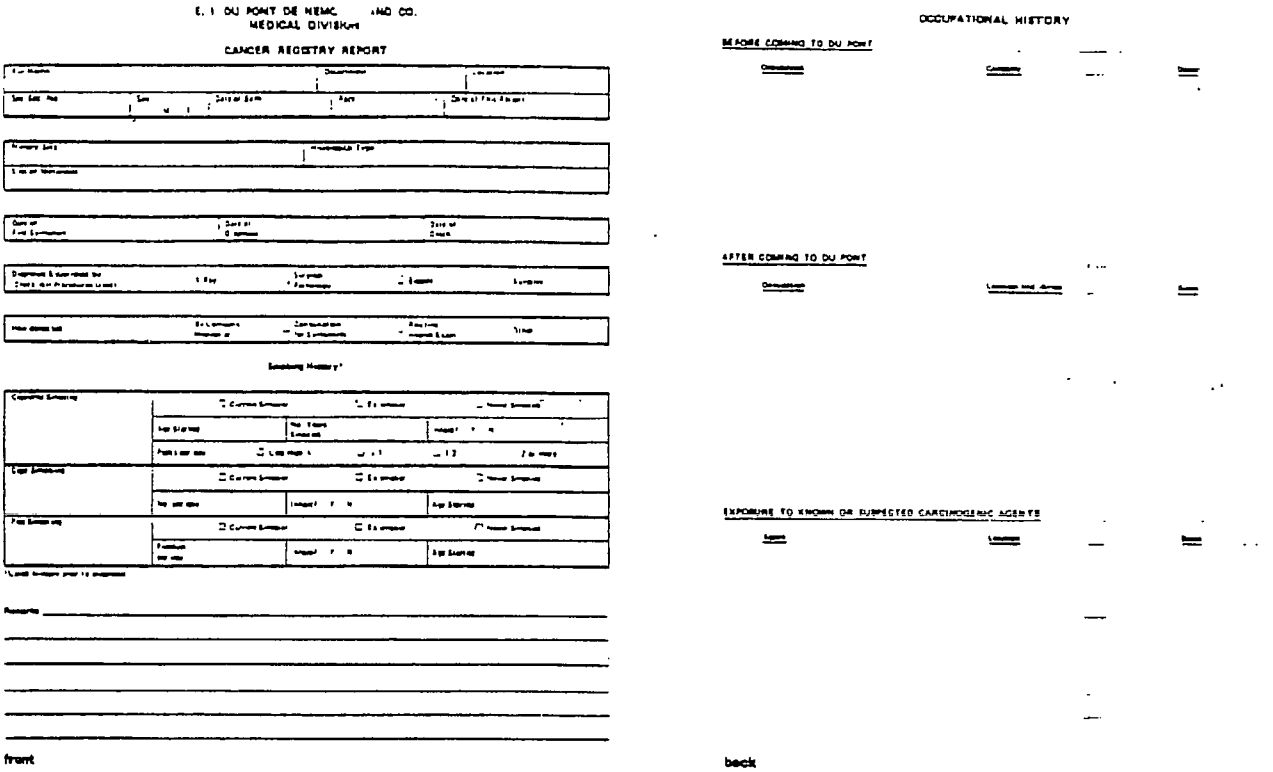


Fig 1. — Cancer registry report.

do not include cases which are first diagnosed after the person's employment is terminated, as a result of either retirement on a company pension, resignation, layoff, or discharge.

Verification of Primary Site. — If, after an employee's first episode of disability from cancer, the primary site shown on subsequent accident and health insurance claims or on a death certificate does not agree with the primary site on the original claim, the company physician at the employee's work location is contacted to ascertain the correct primary site. This is done by the company physician who contacts the employee's personal physician or the hospital where the employee was treated.

The company physician is also contacted whenever the diagnosis on a claim does not specify a primary site or does not indicate whether a tumor is benign or malignant.

Inconsistencies in the designation of a primary site are not uncommon. They usually occur because the attending physician may not have sufficient information to make a correct determination. Occasionally, the corrected primary site is not ascertained until an autopsy is performed.

As a result of these changes in the primary site designation, some of which may not occur until several years after the original diagnosis, corrections are continually made in the cancer registry.

The cancer registry serves two major functions — (1) it is a source of morbidity data for analyzing cancer incidence among various company installations; and, (2) it serves as a means of identifying cancer cases in a cohort study of employees who have worked with a known or suspected carcinogen.

Cancer Mortality File

The company's group life insurance plan, described above, provides the mechanism for the reporting of cancer deaths. Since coverage under the life insurance plan continues after an employee retires on a company pension, cancer death rates can be computed for both active employees and retirees.

If an employee dies, regardless of the cause, his or her company medical records are obtained to abstract that person's medical history. Clinical records are compared with the statement of cause of death for consistency. If the cause of death or the primary site specified in these records does not agree with that specified in other documents, the discrepancy is investigated.

The cancer mortality file serves two functions — (1) it provides the data required to conduct mortality studies; and, (2) it provides a means of identifying cancer deaths in a cohort mortality study of a known or suspected carcinogen.

Limitations of the Cancer Data

The major deficiency of the morbidity statistics is that they do not include persons who develop cancer after retirement or after leaving the company for other reasons. The absence of such information would be important if a certain group of employees were exposed to a carcinogen and, because of a long latent period, the malignancies did not become manifest until after a significant number of exposed employees were no longer on the company payroll.

This deficiency is partially offset by the inclusion of retirees in the mortality statistics, but these data do not in-

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clude employees who developed cancer after they resigned, were laid off, or discharged without qualifying for a company pension.

In cohort studies, however, persons who left the company without retirement benefits are traced through the Social Security Administration to find out which members of the cohort have died, when they died, and where they died. Death certificates are then obtained from state health departments. By this method of tracing personnel lost to follow-up, and by identifying cancer deaths in the company mortality file, almost complete follow-up of the cohort can be achieved.

Cohort studies conducted in this manner could generate data that would indicate mortality differences between those who leave the company after short periods of service and those who stay with the company long enough to be eligible for a retirement pension and thus be included in the company's mortality studies. Such data would indicate the extent and direction of the bias that might be incurred by the omission of persons lost to follow-up.

To what extent currently available cancer morbidity and mortality data in the Du Pont Company are representative of working populations in general awaits the development of cancer data among other employed persons. Differences among various working groups may indicate the effects of work hazards, but may also reflect ethnic, geographic, and socioeconomic differences as well.

Types of Cancer Epidemiological Studies Conducted in the Company

The cancer data that have been collected routinely since 1956 have been used to conduct the following types of studies.

Morbidity Studies. — Cancer incidence data, provided by the cancer registry, are used for two general purposes: (1) to compare cancer incidence among the company's plant, office, and laboratory installations; and, (2) to compare cancer incidence in the company as a whole with that of other populations.

1. Comparisons Among Company Installations. — The cancer incidence at a company installation is assessed by comparing the observed number of cases with the number expected based on age specific incidence rates in a comparison population. These comparisons are made at each installation for male wage, male salaried, female wage and female salaried employees. The identification of high risk groups serves as a warning signal to the company that employees in those groups should be investigated to determine the reason for the excess cancer incidence.

The entire Du Pont Company is used as the comparison population when expected numbers are computed for the following primary site classifications — males: all sites, pancreas, prostate, intestine, lung, leukemia, rectum, bladder; females: all sites, breast, cervix.

For all other forms of cancer, the numbers of cases in the Du Pont Company are not large enough to compute reliable age specific rates. Therefore, for all primary site classifications, other than those listed above, the expected numbers are based on age specific incidence rates reported in the National Cancer Institute's Third National Cancer Survey, 1969-1971.[1]

By making an internal comparison for the primary site categories shown above, we avoid the biases that occur when our data are compared with rates drawn from the general population. Since expected numbers based on company rates are almost always lower than those based on general population rates, the internal comparison provides a more sensitive means of detecting a significant excess number of cancer cases in a plant, office, or laboratory. The statistical methodology used in these studies will be described in a subsequent section.

When a significant excess is seen, an assessment of available data is made to determine whether an intensive, large scale investigation should be undertaken, and, if so, how much priority it should be given. In making this assessment the following factors are taken into consideration.

a. Statistical Considerations. These include the following: (1) The magnitude of the excess as indicated by the ratio of the observed to expected numbers and the absolute difference between the observed and expected numbers. (2) The number of cases. When the number of cases is small, especially when it is less than six, the validity of the test of significance is open to question. Moreover, when the number is small it becomes very difficult, if not impossible, to analyze statistically the many factors that may contribute to the incidence rate. (3) The probability value. A very small value is greater cause for concern than one that is slightly below the 0.05 level of significance.

b. Latency. The average latent period for known human carcinogens is about 20 to 25 years, but in individual cases may be as long as 40 years. Thus, if a plant is less than 15 years old, it is unlikely that a significant excess of cases is due to a carcinogen in the plant. In older plants, the length of time between the date of employment and the date of diagnosis should be taken into consideration.

c. Incidence in Different Occupational Groups. Since wage roll employees usually have greater exposure to chemicals in a plant, a significant excess in this group is greater cause for concern than one which occurs among salaried employees. Nevertheless, an excess among salaried employees should be investigated as thoroughly as one which occurs among wage roll employees, particularly since some salaried employees may have previously been on the wage roll as production workers.

d. Work Histories. A review of the work histories of the affected employees could determine whether there has been any unusual clustering of job assignments and work areas that would indicate a common exposure to a specific chemical.

e. Smoking Histories. These are important when evaluating the incidence of types of cancer known to be related to the use of tobacco, such as cancers of the lung, larynx, oral cavity, esophagus and urinary bladder.

f. Distribution of Cases by Primary Site. If the total cancer incidence in a plant is significantly greater than expected, an unusual clustering of cases for a specific organ would suggest a relationship to an environmental carcinogen. If the distribution is widely scattered, however, such a relation is not suggested, since known human carcinogens generally affect only one or two organ sites.

g. Trends. An increasing trend, not accounted for by an increase in the ages of the plant employees or by an increasing trend in the general population (as has been occurring for lung cancer) would suggest that a plant carcino-

gen is responsible. If the trend ha en erratic, showing a temporary high incidence followed by a declining incidence, there would be less cause for concern. Such a trend may, however, indicate that a carcinogen, no longer in the plant, or still present but at reduced exposure levels, may have been responsible for the previous high incidence.

h. Carcinogenic Potential of Chemicals Used in the Plant. Chemicals proven or suspected to be carcinogens would cause more concern than those not thought to have carcinogenic potential.

i. Cancer Incidence in the Area in which the Plant is Located. An unusually high rate in the area might explain a similar high rate in the plant, but such a finding does not necessarily rule out the existence of a carcinogen in the plant. The plant carcinogen might be partly or entirely responsible for the local high rate.

Although periodic analyses of cancer incidence at company plants could provide an initial lead that might, upon further investigation, identify an occupational carcinogen, the use of cancer morbidity data for this purpose has two important limitations.

First, as mentioned earlier, the data does not include retirees who develop cancer after retirement, nor does it include persons who develop cancer after they leave the company because they resigned or were laid off. Since there is usually a long latent period following exposure to a carcinogen, the cancer may not become manifest until after the affected person leaves active employment.

Second, incidence data for the total plant may not reveal the existence of a carcinogen to which only a small percentage of the plant employees is exposed. Any excess incidence in that group might be too small to be detected when data for the entire plant are examined. Therefore, it is very important to keep in mind that when a plant does not show a statistically significant excess cancer incidence, there may nevertheless be a localized problem at that plant.

2. Comparisons between the Company as a Whole and Other Populations. — Unlike mortality statistics, cancer morbidity data are not available for the total U.S. population, but only for a few isolated segments of the population. Such data are scarce because of the difficulty in identifying all cancer cases in the surveyed population. In a study designed to measure the incidence of newly diagnosed cancer cases over a given time period, it is necessary to identify cancer cases from a variety of sources, such as hospitals, out-patient clinics, private physicians, and death certificates. The time, effort, and expense required to identify all cases has limited the development of morbidity data to small segments of the total population and to limited time periods. Morbidity surveys, therefore, provide data for comparatively small geographical areas whose incidence rates for certain types of cancer may differ considerably from rates in other parts of the country. No morbidity surveys of the general population have been done in areas where there are large concentrations of Du Pont employees.

Because of these limitations, it is difficult to find a body of morbidity data that would be appropriate for comparison with the Du Pont Company. The best available data are those that have been compiled in the three cancer surveys conducted by the National Cancer Institute, the first in 1937, the second ,947, and the third during the period 1969 through 1971. The most recent survey, the Third National Cancer Survey, was based on about 10% of the U.S. population in seven metropolitan areas and two entire states. In a later section, we will present data which compare cancer incidence in the Du Pont Company with that of the Third National Cancer Survey.

Other cancer morbidity data that we found useful for comparative purposes were those that were based on the tumor registries of the State of Connecticut, Alameda County, California, and New York State (exclusive of New York City).

Comparisons between the company and various surveyed populations could be useful in identifying certain types of cancer that may be occurring at an unusually high rate among some company employees. However, interpretations of these comparisons should take into account the following.

a. Working populations usually exhibit lower cancer mortality (as well as lower total mortality) than is found in the general population, probably because of socio-economic and other selection factors that result in a reduced proportion of high risk persons in many segments of the work force. Thus, lower cancer morbidity in the company is to be expected and should be taken into account in drawing inferences from the data.

b. Considerable geographical variation in cancer mortality throughout the United States has been observed.[2] This variation may account for some of the differences in cancer incidence between the company and the surveyed population used for comparisons. This factor could lead to either an overestimate or an underestimate of comparative cancer risks in the company.

c. Usually, only a small percentage of the total employee population works with any one of the many chemical substances used in the company. Thus, if a particular substance does increase the risk of a certain type of cancer, the increased incidence among the exposed workers could go undetected in a company-wide study. As noted earlier, this dilution effect is also a problem in assessing overall incidence in a particular plant.

Mortality Studies. — One important advantage in using mortality, rather than morbidity data to compare the company's experience with that of the general population is that cancer mortality statistics are easily available and can be obtained in great detail. Published data show death rates by age, sex, and race, as well as rates in various geographical subdivisions throughout the United States. Age specific death rates by sex and race for any type of cancer in any county or Standard Metropolitan Statistical Area (SMSA) in the United States can be calculated by extracting the required information from mortality tapes available for purchase from the National Center for Health Statistics' Division of Vital Statistics, and from published population statistics tables available from the Bureau of the Census.

Another important advantage in conducting mortality studies in the company is that, whereas morbidity data for the company are limited to persons who develop cancer while active employees, mortality data include both active employees and retired persons. However, as in the case of the company's morbidity data, the mortality data do not include persons who left company employment before they

had enough service to become eligi. for a pension, and are, therefore, lost to follow-up. Thus, when cancer death rates are computed for active employees and retirees, these rates would significantly understate the cancer risk in the company if two conditions prevailed: (1) employees have an increased risk of cancer because of exposure to a variety of occupational carcinogens, and (2) the cancer mortality rate resulting from such exposure was notably greater among persons lost to follow-up than among active employees and retirees. If the second condition does not prevail, the cancer death rates of the active employees and retirees would not understate the cancer risk in the company, even if the first condition did prevail.

Mortality data, however, have serious shortcomings with respect to their utility in measuring the occurrence of cancer in a given population and in epidemiological studies to determine whether a certain substance is a human carcinogen. These shortcomings are as follows.

1. They do not indicate the total number of persons in the population who have developed cancer, either because the malignancy may not be fatal or, if potentially fatal, a person may die of another cause and the occurrence of cancer may not be recorded on the death certificate.

2. Errors in cause of death statements on death certificates are common. For cancer deaths, such errors include the specification of a metastatic rather than the primary site, failure to specify any site, and the designation of the immediate cause of death without mention of cancer as the underlying cause of death. Morbidity surveys, on the other hand, have as their main objectives the identification of all cancer cases in the surveyed population and the verification of the primary site.

3. Mortality data do not indicate the date of the appearance of the tumor or the date of diagnosis. In epidemiological studies this information is important to measure precisely trends in cancer incidence, and, in cohort studies of carcinogenesis, to take into account latent periods in the analysis of the data. This problem may be of little or no importance in studies of types of cancer that have a short survival time, such as cancers of the lung, liver, and pancreas, and acute leukemia.[3]

In spite of these limitations, mortality studies can, under certain circumstances, be very useful in uncovering an excess cancer risk in a segment of the company population.

Company mortality data have been used to compare the company's experience with that of the U.S. population and to conduct cohort studies of employees who have worked with suspected carcinogens. Mortality comparisons between the company and the U.S. population will be presented in a later section. Cohort studies are discussed in the following section.

Cohort Studies. — The most important type of epidemiological cancer research conducted in the company is the prospective cohort study of employees who have worked with a known or suspected carcinogen. Although not part of the routine surveillance program, these studies depend heavily upon the information and data produced by the program.

In this type of study, the cohort of interest consists of all persons who worked with the substance over a certain minimal period of time from the time the substance was first used. Each person in the cohort is followed from the date of first exposure the date of death, the date lost to follow-up, or to the closing date of the study, if known to be still alive on that date. The cancer experience of the cohort is then compared with that of another population.

Cohort studies may be undertaken under the following circumstances: (1) a significant excess of a certain type of cancer is found in a plant and the work histories of the affected employees suggest that the excess incidence might be related to a substance currently or previously used in the plant; (2) animal or mutagenic studies suggest that a substance may be carcinogenic; (3) epidemiologic studies done elsewhere suggest that a substance may be a human carcinogen; and, (4) data are needed to ascertain the adequacy of employee protection where employees work with a known human or animal carcinogen.

Although a cohort study can be designed to investigate either morbidity or mortality, we have been able, so far, to do only mortality studies because of the difficulties in identifying living cancer cases among persons no longer on the company payroll, such as retirees and those who left the company because they resigned, were laid off, or were discharged. In mortality studies, on the other hand, cancer deaths in the cohort can be ascertained either from the mortality file, when deaths occurred among active employees and retirees, or from a search by the Social Security Administration to determine the vital status of those who left the company and were, therefore, lost to follow-up. Cancer deaths would then be identified from death certificates obtained from the state health departments.

Morbidity studies are preferable, for the reasons cited earlier, especially when the type of cancer under investigation has a comparatively high survival rate, such as chronic forms of leukemia and cancers of the breast, colon, and bladder. To conduct a morbidity study, however, the investigation would have to locate all living members of the cohort who have left the company (often many years prior to the start of the investigation) and then contact those persons to get from them a history of cancer. If such a study were done and a sizeable portion of the group lost to follow-up could not be located, and if among those located and contacted there were difficulties in eliciting a reliable cancer history, the validity of the morbidity data would be in doubt.

Several cohort mortality studies have been completed or are underway. Among these are studies on persons who have worked with dimethylsulfate (DMS), chloroprene, acrylonitrile, benzene, vinylidene chloride, and hexamethylphosphoramide. Preliminary findings of the DMS, chloroprene, and acrylonitrile studies have been reported.[4 5 6]

Summary. — Cancer epidemiological studies done in the company can be divided into two broad categories from the standpoint of what functions they perform. One category comprises screening studies ("hypothesis generating" studies), and the other consists of studies that investigate the cancer risk of employees who work with specific substances (studies to test hypotheses).

Included in the first category are studies of cancer incidence in company plants, offices, and laboratories to detect excess incidence of a particular type of cancer in a company installation, and in subgroups within those installations, characterized by sex and payroll classification (wage or salary). This category also includes mortality

studies in the company as a whol ' detect a particular type of cancer that might be occurring at a greater rate in the company than in the general population.

The second category comprises cohort studies of employees who have worked with known or suspected carcinogens. In design, they are historical prospective studies. While the studies in the first category are intended to provide leads for further investigation, the cohort studies are intended to determine whether a specific substance is carcinogenic at the levels to which the employees are exposed.

Statistical Methodology

The Population Base. — Morbidity and mortality in the company as a whole and in the various company installations have been analyzed either by the computation of age-sex specific rates or by comparing observed with expected numbers, where the expected numbers are based on rates in a comparison population. The computation of rates and of expected numbers requires statistics to define the population at risk.

These statistics have been obtained routinely since 1956. Each year, from that date, the required demographic information has been obtained for every company employee as of June 30 of each year. With this information we have tabulated the population statistics for the company as a whole and for each company installation used in the analyses. The statistics for each unit have been broken down by age (five-year categories), sex, and payroll classification (wage or salary). To compute person-years at risk for a given time period, for the entire company or for a particular plant, office, or laboratory, the mid-year population statistics were cumulated over that time period.

Since 1956, we have also compiled annual tabulations of persons on the company's pension roll. These tabulations show a breakdown of the retiree population by age, sex, and payroll classification for the company as a whole. When combined with population statistics for active employees, we obtain a population data base that enables us to analyze cancer mortality data that include both active employees and retirees. Death rates derived from only active employees would grossly understate the extent of cancer mortality in the company because many persons disabled by cancer receive an early pension for disability and die after they retire.

Computation of Rates. — Incidence rates for morbidity studies are computed by age, sex, and payroll classification. They are computed by dividing the number of newly diagnosed cancer cases in a given age-sex-payroll class category, over the duration of the study period, by the number of person-years in that category during the study period. Since retirement is mandatory at age 65, morbidity data do not go beyond age 64.

Death rates are computed the same way. Since retirees are included in the mortality studies, rates are computed for all age groups above age 64.

Computation of Expected Numbers and Standardized Incidence and Mortality Ratios. — To determine if there is a significant excess risk of a particular type of cancer in the company as a whole or in a segment of the company population, the observed number of cancer cases or deaths is compared to the ber expected based on rates in a comparison popula..on.

The expected number is computed by multiplying the age specific rates in the comparison population by the corresponding person-years in the company as a whole or a particular subgroup within the company.

Standardized incidence and mortality ratios (SIR's and SMR's) are computed to express the incidence or death rate in the company as a percentage of the rate in the comparison population, adjusted for age. These ratios are computed as follows.

$$\text{SIR and SMR} = \frac{\text{Observed Number}}{\text{Expected Number}} \times 100$$

Test of Significance. — The significance of the difference between observed and expected numbers is tested by the Poisson probability distribution. The difference is considered statistically significant when the probability of observing x or more cases when the expected number is e. is less than 0.05.

The tables used for this study are those developed by Molina,[7] but they do not provide probability distributions for expected numbers that exceed 100. In such cases, a "Z" test is done to determine if the observed mortality rate is significantly greater than the expected. The test statistic is

$$Z = \frac{\text{SMR} - 100}{\text{SE}}$$

where SE = standard error of SMR

$$= \sqrt{\frac{\text{SMR} \times 100}{\text{Expected No.}}}$$

$p < 0.05$ (one-tailed), when $Z > 1.645$.

$p < 0.01$ (one-tailed), when $Z > 2.33$.

The same tests are done to determine whether the observed number was significantly less than the expected number, or if the SMR was significantly less than 100. For morbidity data, substitute SIR for SMR.

Choice of Comparison Population. — The most appropriate population with which to compare the Du Pont Company's cancer experience would be employed persons in the United States not exposed to substances that may be carcinogenic. The use of general population data for this purpose is not satisfactory, since employed persons usually exhibit lower morbidity and mortality for most diseases because of selection factors that tend to exclude from the labor force persons who are chronically ill. Estimates of expected numbers of cancer deaths in a group of employed persons based on cancer mortality in the U.S. population would be inflated by the higher rates usually found in the general population. Expected numbers thus computed would more likely obscure than reveal a true excess cancer mortality.

Unfortunately, comprehensive cancer morbidity and mortality statistics in U.S. working populations are not available. Several epidemiological studies of cancer have been done on employed persons, but the study populations were selected because they were thought to be, and often were, high risk groups. Data are needed for an employed population large enough to provide reliable age-sex specific rates for various types of cancer.

In the absence of such data, we have had to compare the cancer experience of the company as a whole with that of the general population. For morbidity data, we have used for comparison the incidence rates provided by the Third

National Cancer Survey, and for mor ' data, death rates in the United States.

In spite of their limitations, cancer data drawn from the general population can be useful in making an assessment of cancer risks in the company. One approach, suggested by Goldsmith,[8] is to apply a correction factor to the general population rates. Another way is by closer examination of subgroups, characterized by age, sex, and payroll class, that shows rates about equal to or in excess of those in the general population.

To assess cancer morbidity in plants, offices and laboratories, we have used the entire company as the comparison population. This internal comparison is preferable to a comparison with the general population, since the internal comparison is less affected by socioeconomic, geographic, and various other selection factors. Since company incidence rates are in almost all instances lower than rates in the general population, the expected numbers for individual company installations, when computed by company rates, would usually be lower than those obtained when U.S. rates are applied. As a result, a significant excess incidence in a particular plant would more likely be detected when the company is used as the comparison population.

Analysis of Cohort Mortality Studies. — Cohort studies are also analyzed by comparing observed and expected numbers. Person-years at risk, by age, are computed by tabulating the age distribution, by each year of age, for each year of the study period. Then, the age distributions are cumulated over the entire study period.

Each person is considered at risk from the first day of the study period to the date of death, the date lost to follow-up, or to the last day of the study period, if still alive on that day, whichever is the earliest.

1. Latency. — To allow for a latent period to elapse, members of the cohort are not tabulated as a person-year at risk from the date of first exposure to the substance under investigation until the end of the assumed latent period. Then they are tabulated until the appropriate endpoint is reached. Tabulations of person-years are prepared for various assumed latent periods. Cancer deaths that occur prior to the end of an assumed latent period are not included in the observed numbers.

Expected numbers are computed as described earlier, i.e., by applying age-sex specific death rates in a comparison population to the person-years at risk.

2. Required Sample Size. — If the number of persons in the cohort is too small and the duration of the study period is too short, the number of person-years at risk may be too small to detect an increased risk of cancer. To determine the number of person-years that would be needed, the following factors must be taken into account. (a) How great an excess the investigator would want to detect. The smaller the excess, the larger the sample size that is required. (b) What probability the investigator selects to be confident that the excess he is looking for will be detected. The greater the probability value he selects the larger the sample size that is required. (c) The level of significance the investigator selects to test the significance of the difference between the observed and expected numbers. (d) The death rate in the comparison population for the type of cancer under investigation. The higher the death rate, the smaller the sample size that is required.

Table 1. — Determi ' of Required Number of Person-Years of Observation to Detect an Excessive Death Rate from Lung Cancer in a Cohort.

Person-Years	Expected No.	Minimum Observed No. that is Significantly Greater than the Expected No.	Probability of Concluding There is an Excess Death Rate when the True Ratio of the Death Rate in the Cohort to the Death Rate in the Comparison Population is: 2.0	3.0	4.0	5.0
500	0 40	3	0 05	0 12	0 22	0 32
800	0 64	3	0 14	0 30	0 48	0 62
1.000	0.80	3	0.22	0 43	0.62	0 76
2.000	1 6	5	0 22	0 52	0-76	0 90
3.000	2.4	6	0 35	0 72	0.92	0 98
4.000	3 2	7	0 46	0 84	0 97	
5.000	4 0	9	0 41	0 84	0 98	
6.000	4 8	10	0 49	0 87	0 99	
8.000	6 4	12	0.63	0.97		
10.000	8.0	14	0.73	0 99		
12.000	9 6	16	0 79			
14.000	11 2	18	0 85			
16.000	12 8	20	0.88			
18.000	14 4	22	0.92			
20.000	16 0	24	0 94			

Conditions and assumptions:

1 Annual lung cancer death rate in the comparison population, adjusted to the age distribution of the cohort, is 80 per 100,000

2. Level of significance = 0 05.

3. Number of deaths follows the Poisson probability distribution

Table 1 shows the number of person-years that would be required in a study of lung cancer mortality, assuming the annual age adjusted death rate in the comparison population is 80 per 100,000.

If, for example, the investigator wants to be confident, with a probability of 0.9, that the study will detect a significant excess rate in the cohort when in fact the rate in the cohort is at least three times that of the comparison group, the study will require between 6,000 and 8,000 person-years of observation. To express this concept another way, if the rate in the cohort was actually three times that in the comparison group, the chances are nine in ten that a sample of that size will yield an observed number of deaths that will be significantly greater than the expected number.

If the investigator wants to be confident that he will detect a significant excess when in fact the rate in the cohort is twice, rather than three times, that in the comparison group, the sample size would have to be considerably higher, i.e., between 16,000 and 18,000 person-years.

In conducting cohort studies, we do not decide in advance what sample size is needed, but try to get into the cohort as many persons as we can. After the study is completed, the data in Table 1 can provide some guidance regarding the inferences that can be drawn, considering the results of the study and the size of the cohort.

To illustrate, suppose a study of lung cancer mortality contained 4,000 person-years of observation and showed five lung cancer deaths. This number is short of the seven required to conclude the mortality in the cohort is significantly greater than expected. It can be seen from the table, however, that with 4,000 person-years the

probability is only 0.46 that the study could have detected an excess if the true rate in the cohort were twice that in the comparison population. One could infer from the data, however, that if the cohort does in fact have the minimum number of cases to indicate an excess risk of lung cancer, the magnitude of that risk is probably not greater than four times that in the comparison population, since the probability is 0.97 that the sample size would have been adequate to detect a significant excess with a risk ratio of that magnitude.

Cancer Morbidity in the Du Pont Company

In this section, data will be presented on the incidence of newly diagnosed cancer cases among Du Pont Company employees from 1956 through 1974. Mortality data will be presented in the next section.

Comparison with Third National Cancer Survey. — Cancer incidence rates in the company were compared with rates obtained in the Third National Cancer Survey, 1969-1971, conducted by the National Cancer Institute (NCI). The regions that comprised the survey population were the entire states of Colorado and Iowa and the following Standard Metropolitan Statistical Areas: Atlanta, Birmingham, Dallas-Forth Worth, Detroit, Minneapolis-St. Paul, Pittsburgh, and San Francisco-Oakland. The majority of Du Pont Company plants, offices, and laboratories are located in the middle Atlantic and southeastern states, and most installations are outside of urbanized areas. These geographic differences between the two populations may account for some of the differences in cancer incidence rates.

Other factors that might produce differences in rates between the two populations are differences in their ethnic composition and socioeconomic patterns. In addition, some of the lower rates in the company may have occurred because of the favorable selection factors that tend to produce comparatively low morbidity and mortality in working populations when they are compared to the general population.

Comparisons with morbidity data reported by various tumor registries, such as those in the states of Connecticut, New York, and California, were not done here because data from these registries are confined to limited geographical areas, whereas the NCI data are more representative of the U.S. population. To our knowledge, there are no cancer morbidity data, other than our own, that were drawn from industrial populations to which the Du Pont Company data can be compared.

Table 2 shows the person-years of observation by age, sex, and payroll class that were used to calculate rates and expected numbers. These person-years were obtained by cumulating the mid-year company population statistics for each year from 1956 through 1974. The total number of person-years for male employees was 1,616,457 and for female employees, 269,497.

From 1956 through 1974, there were 3,598 newly diagnosed cancer cases among Du Pont employees, exclusive of basal and squamous cell carcinomas of the skin. Among men, there were 2,905 cases, of whom 1,706 were wage roll employees and 1,199 salaried employees. Among the 693 female cases, 265 were on the wage roll and 428 were salaried.

As in the general population, lung cancer was the most common type seen in men (643 cases), followed by cancer of the intestine (319 cases). Among women, the most common types were cancers of the breast (231 cases) and uterine cervix (141 cases). These two sites accounted for almost 60% of all the cancers seen in women.

Table 2. — Person-Years of Observation by Age and Payroll Class: Du Pont Company Employees, 1956-1974.

Age	Total	Wage	Salary
Males			
Under 20	10,267	8,998	1,269
20-24	112,610	88,627	23,983
25-29	207,528	137,995	69,533
30-34	224,613	136,075	88,538
35-39	223,901	130,373	93,528
40-44	228,724	128,902	99,822
45-49	215,677	119,119	96,558
50-54	183,294	100,901	82,393
55-59	134,511	74,533	59,978
60-64	75,332	43,318	32,014
Total	1,616,457	968,841	647,616
Females			
Age	Total	Wage	Salary
Under 20	6,886	1,865	5,021
20-24	45,527	14,796	30,731
25-29	37,886	16,395	21,491
30-34	31,595	16,501	15,544
35-39	32,454	16,419	16,035
40-44	32,790	15,503	17,287
45-49	30,595	13,331	17,264
50-54	24,769	10,207	14,562
55-59	17,364	6,723	10,641
60-64	9,631	3,672	5,959
Total	269,497	114,962	154,535

Analysis of bladder cancer data presents a special problem. From 1929 to the present, bladder cancer has been occurring among current employees, retirees, and former employees as a result of exposure to beta-naphthylamine, which was used in the company up to 1956, and to benzidine, which was used up to 1972. Since the accident and health insurance plan does not cover occupational related illness, employees whose bladder cancer was attributed to such exposure would not get into the cancer registry unless they died of bladder cancer while active employees. The omission of these cases, however, does have the advantage of permitting an assessment of the risk of bladder cancer among employees who were not exposed to beta-naphthylamine or benzidine. If the occupational cases were included, they could obscure an excess incidence that might occur as a result of exposure to an unknown bladder carcinogen.

The company has accepted responsibility for all cases of bladder cancer which occurred among Du Pont Company employees and former employees, and were attributed to occupational exposure to beta-naphthylamine or benzidine. Complete records of these occupational cancer cases are maintained elsewhere for administrative purposes, so that data in these records are not part of the company-wide data collection system.

1. Males. — Among male employees, the SIR for all sites combined was 79. Age specific rates presented in Table 3 and Fig 2 show a similar rate of increasing incidence with age in both populations. The data also show that incidence rates in the Du Pont Company were lower than those in the

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Table 3. — Age Specific Incidence s and Average Annual Cancer Incidence Rates Among Du Pon.. employees, 1956-1974, and in Areas Surveyed by the National Cancer Institute (NCI), 1969-1971: All Sites.

Age	No. Du Pont	Males Rate per 100,000 Du Pont	NCI	Incidence Ratio
Under 20	1	9.7	16.8	*
20-24	24	21.3	29.7	72
25-29	64	30.8	34.9	88
30-34	86	38.3	45.7	84
35-39	128	57.2	73.7	78
40-44	220	96.2	128.1	75
45-49	388	179.9	245.5	73
50-54	577	314.8	414.6	76
55-59	748	556.1	692.7	80
60-64	669	888.1	1058.8	84
Total	2905	179.7	227.5†	79

Age	No. Du Pont	Females Rate per 100,000 Du Pont	NCI	Incidence Ratio
Under 20	1	14.5	15.6	*
20-24	15	32.9	30.1	109
25-29	39	102.9	54.2	190
30-34	49	155.1	88.6	175
35-39	51	157.1	146.4	107
40-44	92	280.6	247.8	113
45-49	127	415.1	384.7	108
50-54	113	456.2	507.7	90
55-59	128	737.2	643.6	115
60-64	78	809.9	782.1	104
Total	693	257.1	231.6†	111

*Not computed when number of cases was less than 10.
†Age adjusted to Du Pont Company population.

NCI surveyed population in all groups, and the ratio of these rates, as indicated by the morbidity ratios, did not differ very much among the various age groups.

Observed and expected numbers of cases and SIR's for the most common primary site categories are shown in Table 4 for all male employees and for male wage and male salaried employees. The highest SIR was seen for melanoma of the skin (SIR = 123). A higher incidence in the company was seen for both wage and salaried employees. SMR's greater than 100 were also seen for cancers of the connective tissue (116), brain (107), and intestine (102), and for leukemia (102).

Categories for which Du Pont rates were only slightly below those of the NCI surveyed population were the rectum, liver, lymphosarcoma, and Hodgkin's disease. SIR's were especially low for the category buccal cavity and pharynx (45), for cancer of the thyroid (55), and, among male salaried employees, for cancer of the larynx (30).

For lung cancer, the most common primary site, the SIR was 69 for all male employees, 75 for male wage, and 62 for male salaried employees.

Age specific incidence rates in the Du Pont Company and in the NCI surveyed areas are shown in Figs 3 and 4 for cancers of the lung and intestine, the two most common primary sites for men. The curves for lung cancer indicate lower rates in the company at all ages, but a similar rate of increase with age. For intestinal cancer, the curves show almost identical rates at all ages.

2. Females. — Incidence rates for cancer of all sites com-

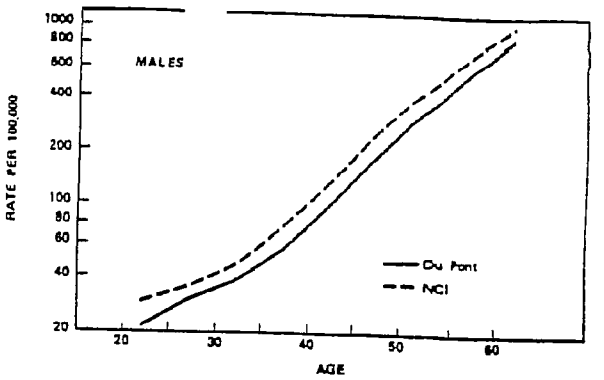


Fig 2. — Average annual age specific cancer incidence rates among Du Pont Company male employees, 1956-1974, and in areas surveyed by the National Cancer Institute (NCI), 1969-1971: all sites. (Age groups omitted where number of Du Pont cases was less than 10.)

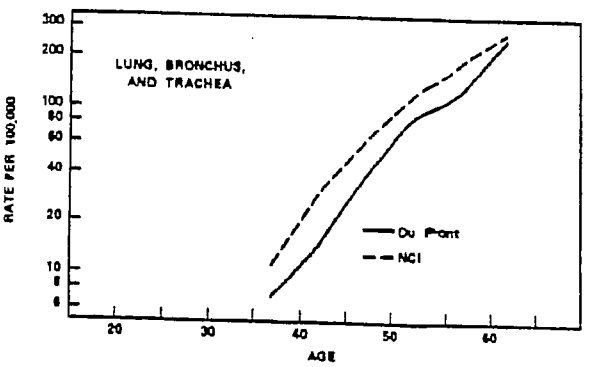


Fig 3. — Average annual age specific incidence rates among Du Pont Company male employees, 1956-1974, and in areas surveyed by the National Cancer Institute (NCI), 1969-1971: cancer of lung, bronchus, and trachea. (Age groups omitted where number of Du Pont cases was less than 10.)

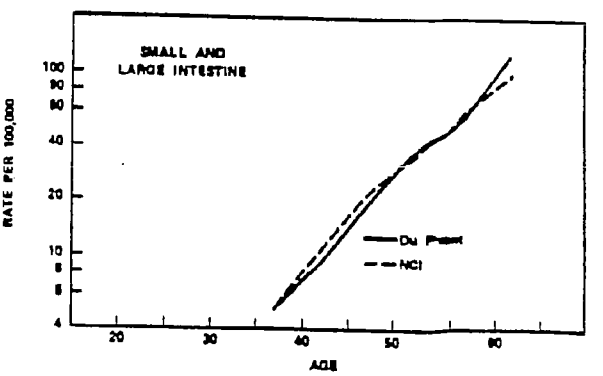


Fig 4. — Average annual age specific cancer incidence rates among Du Pont Company male employees, 1956-1974, and in areas surveyed by the National Cancer Institute (NCI), 1969-1971: cancer of small and large intestine. (Age groups omitted where number of Du Pont cases was less than 10.)

Table 4. — Standardized Incidence Ratios (SIR) and Observed and Expected Numbers of Cancer Cases Among Du Pont Employees for Selected Primary Sites, 1956-1974: Males.

Primary Site	All Males			Male Wage			Male Salary		
	Observed	Expected	SIR	Observed	Expected	SIR	Observed	Expected	SIR
All sites	2905	3691.1	79†	1706	2087.5	82†	1199	1603.6	75†
Buccal cavity and pharynx	120	268.9	45†	77	151.2	51†	43	117.7	37†
Digestive organs									
Esophagus	46	70.0	66†	24	39.2	61†	22	30.8	71
Stomach	109	129.2	84†	75	72.4	104	34	56.8	60†
Intestine	319	312.0	102	160	175.8	91	159	136.2	117*
Rectum	176	184.0	96	109	103.3	106	67	80.7	83
Liver	34	36.7	93	22	20.6	107	12	16.1	75
Pancreas	97	122.3	79	53	68.5	77†	44	53.8	82
Respiratory system									
Larynx	78	128.7	61†	61	71.9	85	17	56.8	30†
Lung, bronchus, and trachea	643	931.5	69†	391	522.0	75†	252	409.5	62†
Genitourinary organs									
Prostate	148	231.8	64†	85	130.6	65†	63	101.2	62†
Testis	66	84.1	79†	33	51.0	65†	33	33.1	100
Kidney	96	113.7	84†	52	63.7	82	44	50.0	88
Bladder	157	202.8	77†	92	114.3	80†	65	88.5	73†
Lymphatic and hematopoietic tissues									
Lymphosarcoma	77	83.7	92	41	48.5	85	36	35.2	102
Hodgkin's disease	72	76.8	94	46	45.9	100	26	30.9	84
Leukemia	115	112.8	102	66	64.9	102	49	47.9	102
Other sites									
Melanoma of skin	118	95.6	123*	67	55.3	121	51	40.3	127
Eye	10	12.3	81	5	6.9	72	5	5.4	93
Brain	109	101.8	107	62	58.4	106	47	43.4	108
Thyroid	25	45.8	55†	14	27.5	51†	11	18.3	60
Connective tissue	45	38.8	116	25	22.5	111	20	16.3	123

*Observed number significantly greater than expected ($p < 0.05$).
†Observed number significantly less than expected ($p < 0.05$).

bined were greater among female than male employees at all ages, except in the 60-64 age group (Table 3). Higher cancer morbidity among women at these ages also occurs in the general population, and is reflected in higher cancer mortality rates in the United States between the ages of 30 and 49.[9]

The total cancer incidence rate among the female employees was also higher than that found among women in the NCI surveyed population, as indicated by an SMR of 111. Age specific rates, presented in Table 3 and Fig 5, show that the rates were higher in all but the 50-54 age group, and were especially high relative to the NCI rates between the ages of 25 and 34.

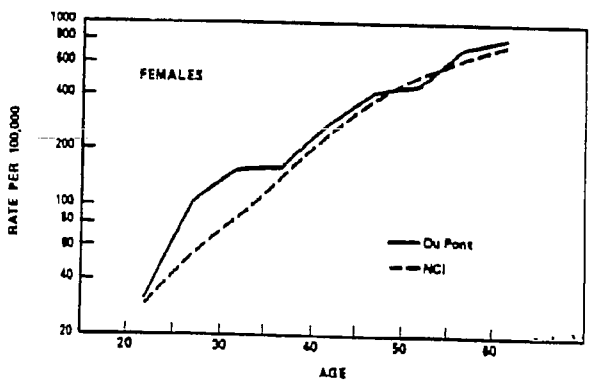


Fig 5. — Average annual age specific cancer incidence rates among Du Pont Company female employees, 1956-1974, and in areas surveyed by the National Cancer Institute (NCI), 1969-1971: all sites. (Age groups omitted where number of Du Pont cases was less than 10.)

Table 5 shows observed and expected numbers and SIR's for major primary sites for all females and for female wage and salaried employees. The data for the various primary sites indicate that the major source of the comparatively high total cancer incidence rate was the very high incidence of cancer of the cervix. There were 141 cases compared to 60.5 expected, an SIR of 233. A significant excess was seen for both wage and salaried employees. The SMR's for these groups were 296 and 183, respectively.

Age-incidence curves for cancer of the cervix, from ages 25 to 54, in the Du Pont Company and in the NCI surveyed population are shown in Fig 6. The NCI curve shows a sharp increase with age from 25 to 40 years, after which the

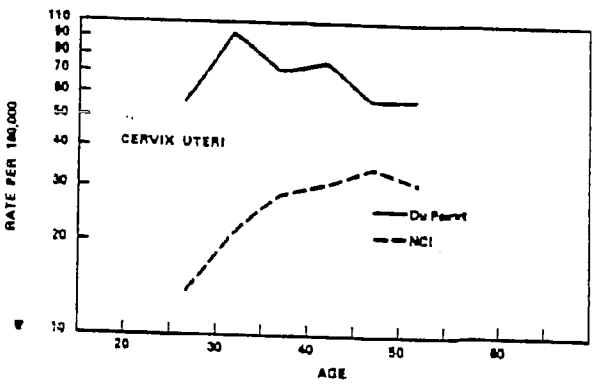


Fig 6. — Average annual age specific incidence rates among Du Pont female employees, 1956-1974, and in areas surveyed by the National Cancer Institute (NCI), 1969-1971: cancer of the cervix uteri. (Age groups omitted where number of Du Pont cases was less than 10.)

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Table 5. — Standardized Incidence Ratios (SIR) and Observed and Expected Numbers of Cancer Cases Among Du Pont Employees for Selected Primary Sites, 1956-1974: Females.

Primary Site	All Females			Female Wage			Female Salary		
	Observed	Expected	SIR	Observed	Expected	SIR	Observed	Expected	SIR
All sites	693	622.8	111*	265	265.5	100	428	357.3	120*
Buccal cavity and pharynx	5	13.9	43	2	5.6	36	4	8.3	48
Digestive organs									
Stomach	9	8.3	108	2	3.4	59	7	4.9	143
Intestine	45	42.5	106	17	17.4	96	28	24.8	113
Rectum	11	15.9	69	3	6.4	47	8	9.5	84
Liver	2	2.3	87	1	1.3	77	1	1.0	100
Pancreas	7	9.6	73	2	4.1	49	5	5.5	91
Respiratory system									
Larynx	1	2.8	36	0	1.2	—	1	1.6	63
Lung, bronchus and trachea	23	34.7	66†	7	14.8	47†	16	19.9	80
Breast	231	205.6	112	72	88.8	81†	159	116.8	136*
Genitourinary organs									
Cervix	141	60.5	233*	79	26.7	296*	62	33.8	183*
Kidney	5	7.7	65	3	3.3	91	2	4.4	45
Bladder	7	7.9	89	3	3.3	91	4	4.6	87
Lymphatic and hematopoietic tissues									
Lymphosarcoma	9	8.1	111	2	3.2	63	7	4.9	143
Hodgkin's disease	10	8.0	125	3	3.4	88	7	4.6	152
Leukemia	16	10.0	160*	5	3.9	128	11	6.1	180*
Other sites									
Melanoma of skin	18	14.5	124	5	6.3	79	13	8.2	159
Eye	3	1.8	167	1	0.8	125	2	1.0	200
Brain	6	9.5	63	3	3.5	86	3	6.0	50
Thyroid	18	19.3	93	7	8.2	85	11	11.1	99
Connective tissue	3	4.6	65	1	2.0	50	2	2.6	77

*Observed number significantly greater than expected ($p < 0.05$)
†Observed number significantly less than expected ($p < 0.05$).

curve tends to level off. The Du Pont curve, on the other hand, shows a peak at age 30 and then declines. These curves indicate that the disparity between the two populations is greatest among younger women. Between the ages of 25 and 34, the rate in the Du Pont Company was about 4 times that in the NCI population; from 35 to 44 years, it was 2.5 times; and from 45 to 54, 1.7 times.

Breast cancer, the most common type of cancer among the women, was also a major contributor to the high total cancer incidence rate, but to a lesser extent than cancer of the cervix. The SIR for breast cancer was 112 for all female employees, but the excess was seen in salaried employees (SIR = 136) and not in wage roll employees (SIR = 81).

Age-incidence curves, presented in Fig 7, show that breast cancer occurred at a higher rate among Du Pont Company women than in the NCI population in all age groups between 40 and 64. Unlike cancer of the cervix, however, the rate of increase with age was about the same in both populations.

Comparisons for other cancer sites are shown in Table 5. Because of the small number of cases found in most primary site categories, it is difficult to draw inferences from these data. Worth noting, however, are the 16 cases of leukemia, compared to 10 expected. The excess was concentrated almost entirely in salaried women, among whom there were 11 cases compared to an expected 6.1.

Cancer Mortality in the Du Pont Company

A major weakness of the morbidity data just presented is that they do not include persons who develop cancer after leaving company employment. Because of this restriction, incidence rates can be computed only up to age 64, and, as a result, the rates computed from the data provide an incomplete measure of cancer risk among company employees. Moreover, the data do not provide an adequate comparison of cancer risk with other populations.

The mortality data presented here have no age limit because they include both active employees and those retired on a company pension. These data, however, do not include persons who leave company employment, as a result of resignation, layoff, or discharge, and, in addition, have not had sufficient service to be eligible for a company pension. The extent to which the omission of these persons biases the data in this study has yet to be determined.

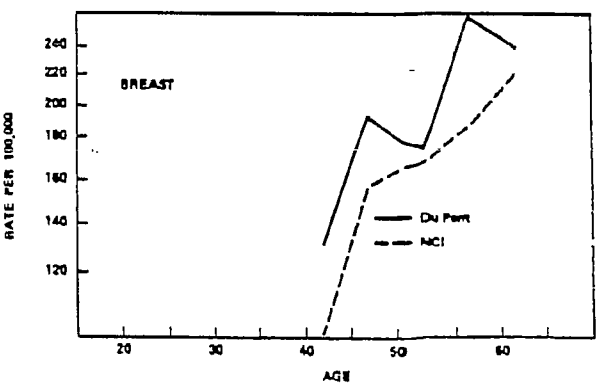


Fig 7. — Average annual age specific cancer incidence rates among Du Pont Company female employees, 1956-1974, and in areas surveyed by the National Cancer Institute (NCI), 1969-1971: cancer of breast. (Age groups omitted where number of Du Pont cases was less than 10.)

Table 6. — Age Specific Mortality Ra , and Average Annual Cancer Death Rates of Du Pont Company Employees and Retirees, 1957-1974, and in the United States, 1966: All Sites.

Age	Males No. Du Pont	Rate Per 100,000 Du Pont	U.S.	Mortality Ratio
Under 25	6	5.6	10.2	*
25-34	45	12.1	17.7	68
35-44	156	38.0	53.3	71
45-54	463	119.1	179.9	66
55-64	996	401.2	485.8	83
65-74	863	856.0	987.5	87
75-84	425	1436.8	1432.5	100
85+	59	1751.8	1812.3	97
Total	3013	181.5	221.3†	82*

Age	Female No. Du Pont	Rate per 100,000 Du Pont	U.S.	Mortality Ratio
Under 25	4	9.1	6.7	*
25-34	8	13.7	19.0	*
35-44	20	33.8	68.4	49
45-54	65	117.8	180.3	65
55-64	119	351.7	334.4	105
65-74	61	442.7	572.5	77
75-84	33	907.1	858.4	106
85+	4	1101.9	1296.3	*
Total	314	117.0	142.7†	82

*Not computed when number of cases was less than 10.
†Age adjusted to Du Pont Company population.

Comparison with United States Mortality. — This study covers the period 1957 through 1974. During that time there were 3,327 cancer deaths among Du Pont employees and retirees. Of these, 3,013 were men and 314 were women. Death rates during this period were compared with rates in the United States in 1966, which is about midway in the range of the study period.[10]

1. Males. — The average annual cancer death rate for Du Pont Company males was 181.5 per 100,000, compared to 221.3, the rate for U.S males in 1966 adjusted to the age distribution of the Du Pont Company population. The SMR was 82. Age specific death rates and mortality ratios, shown in Table 6 and Fig 8, indicate that relative differences in rates were greatest among younger men and that such differences tended to decrease with increasing age. Beyond the age of 75, the cancer death rates in the two populations were essentially the same.

Table 7 shows observed and expected numbers and SMR's for the most common primary site categories for all male, male wage, and male salaried employees. The data show no statistically significant excess mortality for any primary site. Among wage roll employees, the observed number of deaths was greater than expected only for cancer of the bladder, but it was only slightly greater (69 compared to 65.9). Mortality from cancer of the rectum was about the same as in the U.S. population.

In the salaried group, mortality was greater than in the U.S. only for cancer of the brain (SMR = 118), and about the same as in the U.S. for cancer of the large intestine. Types of cancer for which mortality was only slightly below that in the U.S. were leukemia, Hodgkin's disease, and cancers of the bladder and prostate.

2. Females. — For all sites combined, the SMR for women was 82, the same as that for men. As in men, there

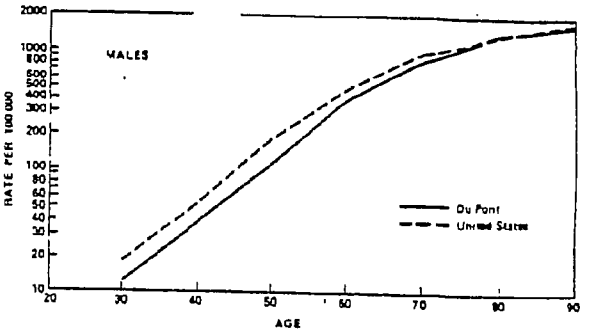


Fig 8. — Average annual age specific cancer death rates among Du Pont Company male employees and retirees, 1957-1974, and in the United States, 1966: all sites. (Age groups omitted where number of Du Pont deaths was less than 10.)

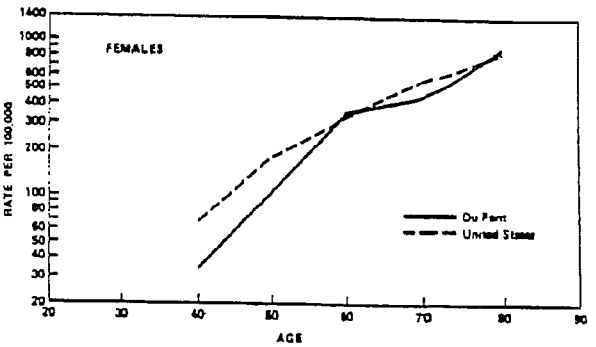


Fig 9. — Average annual age specific cancer death rates among Du Pont Company female employees and retirees, 1957-1974, and in the United States, 1966: all sites. (Age groups omitted where number of Du Pont deaths was less than 10.)

was a tendency for relative differences in rates between the Du Pont Company and the U.S. to decrease with increasing age (Table 6 and Fig 9). This tendency in women, however, was not as strong or consistent as that found in men.

Table 8 shows observed and expected numbers and SMR's for the most common primary sites in women. It is difficult to draw inferences from these data because of the small numbers in most categories. It is noteworthy, however, that the highest SMR, 134, was seen for leukemia among salaried employees (11 deaths compared to an expected 8.2). These data are consistent with the high incidence noted in the analysis of morbidity data.

The SMR for breast cancer was 84. Thus, in contrast to the high incidence rates that were seen when they were compared to rates in the NCI surveyed population, mortality from breast cancer in women was lower than in the U.S. population.

Mortality from cancer of the cervix was especially low, i.e., 9 deaths compared to an expected 26.5. This finding contrasts sharply with the unusually high incidence compared to that of the NCI surveyed population (Table 5). This apparent inconsistency could have occurred as a result of one or both of the following: (a) Since cancer of the cervix

Table 7. — Standardized Mortality Ratios (SMR) and Observed and Expected Numbers of Cancer Deaths Among Du Pont Employees for Selected Primary Sites, 1957-1974: Males.

Primary Site	All Males Observed	All Males Expected	All Males SMR	Male Wage Observed	Male Wage Expected	Male Wage SMR	Male Salary Observed	Male Salary Expected	Male Salary SMR
All sites	3013	3680.9	82†	1797	2153.8	83†	1218	1527.1	80†
Digestive organs									
Esophagus	65	102.1	64†	40	59.2	68†	25	42.9	58†
Stomach	164	226.9	72†	114	133.3	86†	50	93.6	53†
Large intestine	290	314.8	92	161	185.3	87†	129	129.5	100
Rectum	116	128.6	90	75	75.5	99	41	53.1	77†
Pancreas	167	212.9	78†	105	124.3	84†	62	88.6	70†
Respiratory system									
Larnyx	41	57.6	71†	27	33.4	81	14	24.2	58†
Lung, bronchus, and trachea	867	1069.6	81†	526	620.1	85†	341	449.5	76†
Genitourinary organs									
Prostate	219	263.2	83†	120	158.4	76†	99	104.8	94
Kidney	71	87.2	81†	41	50.6	81	30	36.6	82
Bladder	111	111.2	100	69	65.9	105	42	45.3	93
Lymphatic and hematopoietic tissues									
Lymphosarcoma	66	97.6	68†	42	56.9	74†	24	40.7	59†
Hodgkin's disease	46	54.6	84	25	32.2	78	21	22.4	94
Leukemia	130	150.4	86†	71	89.0	80†	59	61.4	96
Other sites									
Skin	37	64.4	57†	20	37.7	53†	17	26.7	64†
Brain	108	106.4	102	55	61.5	89	53	44.9	118

†Observed number significantly less than expected ($p < 0.05$).

usually develops in comparatively young women, many with the disease may have left employment before becoming eligible for a company pension, and thus would not be included in the mortality data; or, (b) the early detection of many cases may have reduced their mortality from the disease to a level well below that in the general population.

Discussion

With certain exceptions, cancer morbidity and mortality were lower among Du Pont employees than in the general population. For men, the incidence rate for all forms of cancer was 79% of that found in the Third National Cancer Survey, and the death rate was 82% of that in the total United States, after making the appropriate age adjustments. Both incidence and death rates were lower in the Du Pont Company for most primary site categories. Among women, cancer morbidity was generally higher, but mortality lower than in the general population.

These results must be interpreted in light of the generally accepted and frequently observed fact that working populations normally exhibit lower mortality (and probably lower morbidity) than in the general population.[11–15] If the data were available, it would have been more appropriate to compare Du Pont Company rates with those of working populations not exposed to substances that may be carcinogenic.

Table 8. — Standardized Mortality Ratios (SMR) and Observed and Expected Numbers of Cancer Deaths Among Du Pont Employees for Selected Primary Sites, 1957-1974: Females.

Primary Site	All Females Observed	All Females Expected	All Females SMR	Female Wage Observed	Female Wage Expected	Female Wage SMR	Female Salary Observed	Female Salary Expected	Female Salary SMR
All sites	314	382.0	82†	100	156.7	64†	214	225.3	95
Digestive organs									
Large intestine	33	41.5	80	15	16.4	91	18	25.1	72
Rectum	7	11.1	63	3	4.4	68	4	6.7	60
Pancreas	12	16.5	73	3	6.5	46	9	10.0	90
Respiratory system									
Lung, bronchus and trachea	19	25.4	75	6	10.6	57	13	14.8	88
Breast	73	86.8	84	21	36.5	58†	52	50.3	103
Genitourinary organs									
Cervix	9	26.5	34†	6	11.4	53	3	15.1	20†
Lymphatic and hematopoietic tissues									
Lymphosarcoma	9	9.3	97	3	3.8	79	6	5.5	109
Hodgkin's disease	3	4.5	67	2	1.9	105	1	2.6	38
Leukemia	16	13.8	116	5	5.6	89	11	8.2	134
Other sites									
Skin	3	5.4	56	1	2.3	43	2	3.1	65
Brain	10	9.8	102	4	4.2	95	6	5.6	107

†Observed number significantly less than expected ($p < 0.05$).

Nevertheless, the data presented can be useful in making an assessment of cancer risks in the company. One way this can be done is by closer examination of subgroups, characterized by age, sex, and payroll class, that have shown rates in excess of those in the general population. Explanations of these excess rates cannot be obtained from available data. The results can only suggest hypotheses that can be tested only by more intensive investigations. The primary purpose of such studies would be to determine whether the excess rates are work related, but any epidemiological study of cancer must take into account, if possible, the many factors that affect the distribution of cancer in a given population, such as socioeconomic characteristics, ethnic factors, diet, smoking habits, alcohol consumption and genetic factors.

The incidence of malignant melanoma of the skin among men was significantly higher than expected, based on NCI data (SIR = 121). An excess was seen in both wage roll and salaried employees, but the magnitude of the excess was slightly greater in the salaried group. The apparent higher rate in the salaried group is not consistent with the hypothesis that the excess incidence is work related, because if it were, one would expect a higher rate among the wage roll employees, who have greater and more frequent exposure to chemicals. Nevertheless, an intensive investigation of the incidence in the company would have to be undertaken before a work related cause can be ruled out.

One possible explanation of the apparent high incidence in the company is the comparatively high concentration of employees in the southeastern part of the United States, where mortality from malignant melanoma of the skin is especially high. The National Cancer Institute's study of cancer mortality by county, from 1950 through 1969, has shown that counties with significantly high rates are found almost entirely in the South.[2] To what extent this explains the high rate in the company would have to be determined by additional investigation.

Among women, there was an unusually high incidence rate of cancer of the cervix. The SIR was 296 for wage roll employees and 159 for salaried employees. The excess was greatest between the ages of 25 and 34, and the highest incidence rate was seen in the 30-34 age group. The unusually high rate in young Du Pont Company women may reflect a high rate of early casefinding as a result of the company's cancer screening program, which, at many locations, includes a Pap test for the detection of cancer of the cervix in its early stage. A screening program would detect cases of carcinoma *in situ* that would not be recognized or reported in other morbidity surveys. Early detection may have accounted, in part, for the low mortality when compared to the U.S. population.

Breast cancer among women also occurred at a higher rate than in the NCI survey population, but the excess was seen in salaried, and not in wage roll, women. The SIR was 136 in the former and 81 in the latter.

The company's cancer detection program and periodic health examinations include screening for breast cancer by palpation, but the higher incidence rate among salaried women in the company is less likely to be the result of early casefinding than what might be a preponderance of salaried women in the company who are at higher risk of breast cancer than women in the general population, i.e., women who, in general, have had fewer children and are at a higher socioeconomic status. Confirmation of this hypothesis requires further investigation.

Comparisons between wage roll and salaried employees can be useful in leading to occupationally related cancer because of the greater exposure to chemicals in the wage roll group. These comparisons, however, have to take into account socioeconomic factors related to cancer incidence. Strong inverse relationships between socioeconomic class and cancer incidence have been found for cancers of the buccal cavity and pharynx, esophagus, stomach, lung, and cervix, whereas cancer of the breast has been found to occur at a higher rate among women in higher socioeconomic classes.[16]

Among Du Pont Company women, the apparent higher rate of breast cancer among salaried women, when compared to that of wage roll women, and the higher rate of cancer of the cervix in the latter group may reflect socioeconomic differences between the two groups.

A comparatively high rate of leukemia was also found among salaried women, as indicated by both morbidity and mortality data. The reason for the high rate is not apparent from the available data.

Mortality data were not entirely comparable to the morbidity data, since they differed with respect to the ages included in the data, the comparison population, and the classification of primary sites. Moreover, differences in survival time for various primary sites also produce apparent inconsistencies between mortality and morbidity data.

Cancer morbidity and mortality rates for the entire company cannot be relied upon to indicate an increased risk of cancer resulting from exposure to a particular carcinogenic substance used in the company. The number of exposed workers may constitute only a small proportion of the total company population, and the consequent increase in cancer incidence in that group may be too small to have any noticeable effect on cancer incidence in the company as a whole. Even a study of cancer incidence in a specific plant may fail to detect a carcinogen because of the dilution of the incidence rate of the exposed workers with the total plant rate.

In spite of these limitations, however, company-wide studies — when done in conjunction with cohort studies of suspected high risk groups and studies of cancer incidence in various company installations — can make an important contribution to cancer surveillance of company employees.

Summary

This article describes the cancer epidemiologic surveillance program that was started in the Du Pont Company in 1956. The program includes (1) the routine reporting of cancer cases among active employees and of cancer deaths among both active employees and retirees; (2) the maintenance of a cancer registry for morbidity studies and of a file of cancer deaths for mortality studies; (3) follow-up procedures to verify the primary site; (4) the routine collection of population statistics by age, sex and payroll class for the company as a whole and for various company installations to provide a population base for statistical analyses; (5) comparisons of cancer morbidity and mortality between the company and the general population;

(6) periodic analyses of cancer incidence in plants, offices and laboratories; and, (7) cohort studies to investigate cancer mortality among persons who have worked with suspected or known carcinogens.

The article includes a description of casefinding mechanisms, problems in casefinding, limitations of the data, and statistical methodology. It also presents data on cancer morbidity and mortality in the Du Pont Company. Morbidity data cover the period 1956-1974, and include only persons who developed cancer while active employees. Incidence rates were compared with those obtained in the Third National Cancer Survey. Mortality data cover the period 1957-1974, and include both employees and retirees. Death rates were compared with U.S. rates for 1966.

With certain exceptions, cancer morbidity and mortality were generally lower in the company than in the comparison populations. For cancer of all sites combined, the standardized incidence and mortality ratios for men were 79 for incidence and 82 for mortality, and for women, 111 for incidence and 82 for mortality. Mortality differences between Du Pont and the U.S. decreased with increasing age. Generally, lower rates were expected, since morbidity and mortality are usually lower in working populations than in the general population.

Among men, a significant excess in incidence was seen for malignant melanoma of the skin (SIR = 123). The magnitude of the excess was slightly higher in salaried than in wage roll employees. A significant excess of cancer of the intestine was seen in salaried employees (SIR = 117).

Among women, the incidence of cancer of the cervix was significantly higher than expected, and was especially high for wage roll employees (SIR = 296). The incidence of breast cancer was significantly higher in salaried employees (SIR = 136), but was lower than expected in wage roll employees. Among female salaried employees, there were 11 cases of leukemia, which was significantly greater than the expected 6.1.

Primary sites for which the incidence rates were especially low were, for men, the thyroid, larynx, prostate, and buccal cavity and pharynx; and, for women, the lung.

Data to test hypotheses that might explain the differences cited are not available in this study, but would have to be obtained by further investigation.

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