Intramural Activities

1988- September 31, 1989

Division Of

Cancer Prevention and Control

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

NATIONAL CANCER INSTITUTE

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October 1, 1988- September 31, 1989

89 annual report

Division Of

Cancer Prevention and Control

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NATIONAL CANCER INSTITUTE (U.S.)

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Intramural Project Summaries
(Forms 6040)

DIRECTOR'S REPORT

This report describes the intramural research program of the Division of Cancer Prevention and Control (DCPC), one of the four major program divisions of the National Cancer Institute (NCI). The mission of DCPC couples basic research on cancer prevention with cancer control research, with the application of technology, and with disease surveillance. The goal of these activities is to achieve significant reductions in cancer incidence, mortality and morbidity, with a concomitant increase in survival. The Division conducts a broad array of cancer control research and application activities which emphasize validation, evaluation, and demonstration. The program ranges from research on prevention using screening and early detection to methods for applying the most effective regimens for cancer treatment, rehabilitation and continuing care. Significant emphasis is given to cancer prevention research. In keeping with an increasing priority on prevention, much effort is being devoted to research on diet, nutrition, and chemoprevention. Intramural research is expanding with the establishment of a new laboratory for nutrition and cancer research.

ORGANIZATION

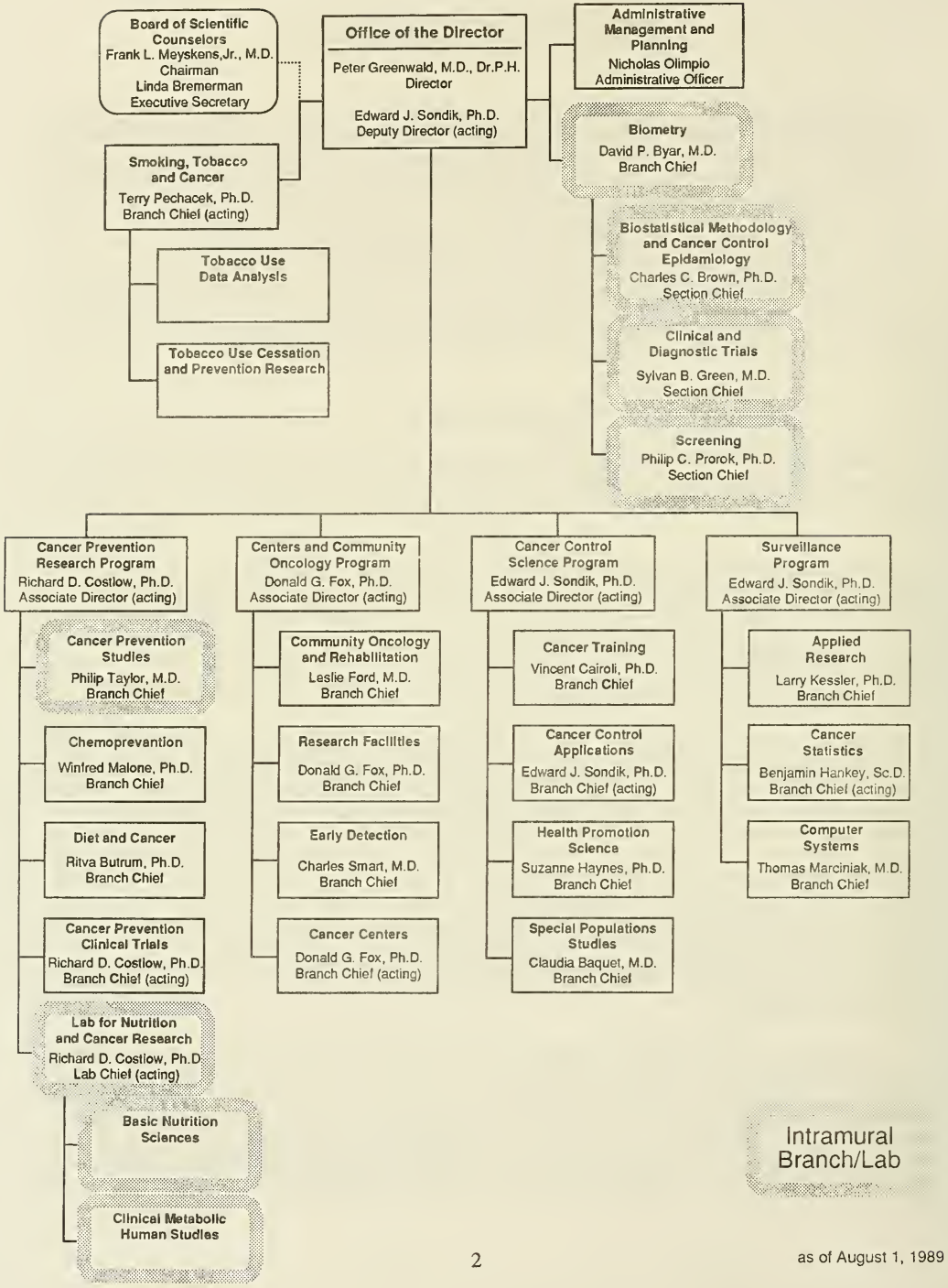
Figure 1 outlines the DCPC organization. The Division consists of four major programs, each led by an Associate Director. The Office of the Division Director provides overall coordination and direction and analytic program support. Each program is described briefly below.

The **Cancer Prevention Research Program (CPRP)** is charged with planning and supporting both intramural and extramural research in diet, nutrition and cancer, and chemoprevention. In addition, this organizational unit serves as the focal point for coordinating diet, nutrition and cancer activities across the NCI divisions. This program houses the Cancer Prevention Studies Branch and a newly-established Laboratory for Nutrition and Cancer Research, two of the three intramural branches in the Division. The intramural Laboratory for Nutrition and Cancer Research will be located at the Frederick Cancer Research Facility (FCRF) in Frederick, MD.

The **Centers and Community Oncology (CCO) Program** supports the nation's network of Cancer Research Centers and community-based clinical research programs. These programs are designed to improve the delivery and application of state-of-the-art cancer treatment, continuing care and rehabilitation. In addition, the CCO is responsible for the integration of cancer center activities with community-based cancer control efforts to develop and disseminate knowledge and technology related to cancer patient management. The Program also conducts research and application activities related to cancer screening and the early detection of cancer. The Community Clinical Oncology Program (CCOP) seeks to link community-based physicians with Cancer Centers and clinical trials research. The CCO had also been responsible for the conduct of the Organ Systems Program, which coordinates basic and clinical research on a number of particular cancers, and for the Research Facilities Program designed to support the construction of cancer research facilities throughout the nation. During this fiscal year, the Organ systems Program was transferred to the Division of Cancer Biology and Diagnosis.

The **Cancer Control Science Program (CCSP)** supports research on ways to effectively transfer cancer control information to the public and to physicians, nurses, and other health professionals. This Program's efforts are directed toward study of a wide variety of cancer control intervention strategies to assess both their impact on populations and the use of proven cancer control methods. Programs that involve State, local and volunteer health groups, and populations with particularly acute cancer problems, figure prominently in the Program's activities. The Program also directs a number of cancer control resource activities, including the nationwide network of

Figure 1. DCPC ORGANIZATION CHART



as of August 1, 1989

cancer information offices accessible through an 800 telephone number. It is responsible for the management of the cancer training program for all Divisions of NCI and directly operates the Cancer Prevention Fellowship Program, developed to provide an opportunity for physicians and scientists to train and to gain experience in the field of cancer prevention and control by working with DCPC preceptors.

The **Surveillance Program** is responsible for tracking and evaluating trends in cancer, a program of research on quantitative methods and statistics designed to monitor progress in cancer control for the United States. An important part of the Surveillance Program is a network of population based cancer reporting systems (the Surveillance, Epidemiology, and End Results [SEER]) Program and related efforts which gather and disseminate information on cancer, cancer risk factors, and other elements of cancer control through a variety of reports. The Program also conducts studies on the organization, delivery, and financing of cancer prevention and control services, as well as on the economics of cancer. The Program includes three branches, the Cancer Statistics Branch, responsible for gathering and disseminating information on cancer incidence, mortality, survival, cancer risk factors, and information on public and professional awareness of cancer; the Applied Research Branch which conducts a variety of analytic and methodological studies and develops methods related to cancer surveillance and the evaluation of cancer control; and the Computer Systems Branch which provides comprehensive computer systems analysis, design, operation, and programming support for the Division.

The **Office of the Director** is responsible for the coordination and direction of the Division programs. It includes three branches: the Biometry Branch, the Smoking, Tobacco and Cancer Branch, and the Administrative Management and Planning Branch. The Biometry Branch supports intramural research using SEER and other epidemiologic data bases, research in biostatistical methodology, and clinical trials research. The Smoking, Tobacco, and Cancer Branch operates as a focus for NCI-wide research on smoking. The Administrative Management and Planning Branch assists in the management of the Division's budget and administrative matters.

Intramural research is an important component of the programs of the Division of Cancer Prevention and Control. The presence of an intramural program provides extramural program directors ready access to technical expertise relevant to scientific decisions. Moreover, an intramural program brings to the Division the resources to take advantage of a number of research and cancer control opportunities unique to, or important to, the Federal Government including international or interagency collaborations and rapid access to specific high risk target populations. The program also enables methodological research to be pursued that is fundamental to developing the technical approach underlying many large-scale cancer control research projects. Traditionally at NIH, a strong intramural program has enhanced extramural support in its research area. Our new intramural nutrition research program is anticipated to stimulate the extramural nutrition research community in this high-priority endeavor.

Within DCPC, the intramural research program is conducted through the Cancer Prevention Studies Branch (CPSB), the Biometry Branch, and a new intramural Laboratory for Nutrition and Cancer Research, the first phase of which is nearly complete. The **Cancer Prevention Studies Branch**, located in the Cancer Prevention Research Program, contributes to the cancer control process by conducting controlled intervention studies. Intervention studies serve the dual purposes of confirming hypotheses about cancer etiology and effecting cancer control, and act as a bridge between these two types of research efforts. The CPSB conducts intramural research in the areas of diet, nutrition and cancer, cancer chemoprevention, occupational cancer studies, and other cancer prevention strategies directed toward methods development and their application to reduce human cancer risk. The **Biometry Branch**, located in the Office of the Director, plans epidemiologic methodology and investigates mathematical modeling of processes relevant to cancer prevention and control activities. The Biometry Branch also provides consultation on statistical methodology and study design within the Division and to other scientists within the NIH. The **Laboratory for**

Nutrition and Cancer Research will plan, develop, implement and conduct intramural research on nutrition and diet as they relate to the prevention of cancer in humans. The Laboratory will also contribute scientific back-up to the National Cancer Institute's programs in research on diet, nutrition and cancer, and serve as a focal point for new information pertaining to nutrition research. The major areas of research will include basic nutrition science and clinical/metabolic nutrition studies. Laboratory space has been acquired at FCRF and a modest amount of space has been committed in the NIH Clinical Center to begin some metabolic research in humans. A Laboratory Chief for the Nutrition Research Laboratory is expected to be named soon.

One of the factors behind the strong research programs at the National Institutes of Health is the use of peer review in the development and evaluation of research programs. The need for peer review applies both to intramural as well as extramural programs. Committees of outstanding scientists representing the various disciplines involved in the intramural research program periodically review the direction and progress of the research program and staff. All of the intramural program is subject to the same critical review, including the concept of new research ideas prior to their implementation.

The committees that review the intramural research address the breadth and depth of each project and its relation to the Division mission. Critiques also address the quality, progress, future directions and an assessment of resources and staff development. Recommendations made at review are monitored and the impact of their outcomes are assessed in subsequent site visits by the Board of Scientific Counselors and its appropriate subcommittees.

Traditionally at NIH, a strong intramural program has provided leadership and focus to stimulate the scientific community in general to respond to important problems and to complement the research needs in a given area. Research in Cancer Control is no exception to that tradition and a vigorous, high-quality, peer-reviewed intramural program is anticipated to provide the necessary leadership.

Division Director:	Peter Greenwald, M.D., Dr.P.H.
Deputy Director (acting):	Edward J. Sondik, Ph.D.

Cancer Prevention Studies Branch

OBJECTIVES

The overall objectives of the Cancer Prevention Studies Branch (CPSB) are to identify, develop, and test hypotheses relevant to cancer control.

OVERVIEW

The CPSB conducts intramural research in the areas of diet, nutrition and cancer, genetics and cancer, cancer chemoprevention, and other cancer prevention strategies aimed at lowering human cancer risk. This specifically involves:

- Analysis of existing dietary, genetic, and lifestyle data in relation to cancer, and the development of new studies and data resources to evaluate these relationships;
- Conducting clinical studies of the metabolic effects of dietary changes in humans; and determining the safety, toxicity, pharmacokinetics, bioavailability, and mechanisms of action of macro- and micronutrients;
- Conducting intervention trials designed to test the effect of nutritional and chemopreventive agents in reducing cancer risk; and
- Conducting applied research in the areas of statistical and epidemiologic methods.

ACCOMPLISHMENTS

The Branch has initiated a number of intramural projects in 3 broad areas, including etiologic studies, clinical nutrition studies, and prevention trials. These projects represent collaborative efforts in investigating dietary, nutritional, and constitutional factors relating to cancer prevention. The following is a brief summary of the major currently active intramural projects, all of which will continue through and beyond FY 89.

Etiologic Studies:

Continued Follow-up of the Breast Cancer Detection and Demonstration Project (BCDDP)
(Z01 CN 00143-06 CPSB)

The BCDDP screening program began in 1973 in 29 centers in 27 widely dispersed geographic areas of the United States. Initial screening was completed on over 280,000 women over a 2-year period. From the original 280,000 participants in the screening phase of the BCDDP, approximately 64,000 were selected for 5 years of long-term follow-up (LTF) beginning in 1978, to assess the biology and natural history of breast disease, and to test hypotheses relating to detection, etiology, and survival. Those selected for LTF included all breast cancer cases found during the screening phase, all benign breast disease cases, all those recommended for biopsy, and a sample of "normals". The LTF data base will facilitate the exploration of important questions regarding the etiology and natural history of breast cancer. The size of the subcohorts and breadth of data available on them makes this population unique. The large number of cases of both breast cancer and benign breast disease with histologic information available should allow particularly useful analyses of several risk factors in relation to these conditions.

The first 5 years of LTF was completed September 1986 in all centers, and a further continued follow-up of the LTF subcohorts is now in progress.

Our analysis of data from the first 5 years of follow-up found that among women with biopsy-proven benign breast disease there was a direct relation between breast cancer risk and degree of epithelial atypia. Our collaborative analysis of the case-control study of breast cancer among BCDDP participants conducted by the Division of Cancer Etiology has confirmed the direct relation between height and breast cancer risk, and has found an increased risk associated with excess weight among older and/or postmenopausal women.

This study is being conducted collaboratively with the Environmental Epidemiology Branch of the Division of Cancer Etiology.

NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects (Z01 CN 00104-08 CPSB)

The purpose of the NHANES (National Health and Nutrition Examination Survey) epidemiologic follow-up survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-75 and to investigate subsequent health and mortality outcomes. Respondents were traced and re-examined. Information was obtained from hospital records, the National Death Index, and death certificates. Several cycles have now been performed. The inital NHANES follow-up survey was completed in 1984. A continued follow-up of the elderly (≥ 75 years old) in this cohort was conducted in 1985-86, while the entire cohort was again followed in 1986-87.

The purpose of this intramural project is to examine the relation of chemopreventive, nutritional, and constitutional factors to cancer in the very large, representative population which NHANES offers. It provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effectiveness of dietary agents which are currently of great interest for cancer prevention. The relation of baseline vitamin use, biochemical or nutritional measures, and subsequent health status will be examined.

A summary of our analyses of data from the initial follow-up indicate a direct relation between breast cancer risk and alcohol consumption, height, frame size, and weight gain; and an inverse association with dietary fat consumption and frequency of bowel movements. All-sites cancer has also been shown to be inversely related to serum cholesterol and level of physical activity, and directly related to height in both sexes and to measures of total body iron in men.

This epidemiologic follow-up study is conducted as a group effort by several of the National Institutes of Health in collaboration with the National Center for Health Statistics.

Nutritional Factors and Cancer in the Framingham Heart Study (Z01 CN 00146-01 CPSB)

In recent years considerable interest has been focused on the possible relation between moderate consumption of alcoholic beverages and breast cancer in women. Five epidemiologic cohort studies and the majority of case-control studies have demonstrated a positive association between moderate alcohol consumption and breast cancer, with relative risks ranging from 1.5 to 2.0. Given the frequency of alcohol consumption among women in this country, even a risk elevation of 50-100% would translate into considerable breast cancer morbidity and mortality that would be attributable to drinking. Further epidemiologic investigation of this question is of high priority.

In prospective cohort studies, exposure (alcohol, in this case) is assessed prior to the onset of disease. The cohort approach, therefore, circumvents the problem of inaccurate assessment of

exposure among persons with existing disease. However, cohort studies can be both expensive and time-consuming. Existing cohort data bases provide a relatively quick and inexpensive means to conduct investigations of research questions of this type.

In this regard, the Division of Cancer Prevention and Control has funded a contract for the procurement of a cancer file based on the original cohort in the Framingham Heart Study. This ongoing prospective cohort study was initially set up to examine risk factors for coronary heart disease, stroke, and other cardiovascular endpoints. Data, including detailed information on alcohol consumption, have been collected for over 30 years. The creation of the cancer file has been successfully completed in the past year. Our analyses indicated no association between alcohol (one drink per day or less) and breast cancer (143 cases) among 2,636 women. This was the first cohort study to show no association.

Additional studies of nutritional and other factors in relation to cancer are underway. In an analysis of the relation between body fat distribution and breast cancer in this cohort, we found a positive relation between central obesity and subsequent breast cancer. Other analyses have shown a positive association between lack of physical exercise and colon cancer in men, and an inverse relation between LDL-cholesterol and colon cancer in men.

This study is being conducted collaboratively with investigators from Boston University.

Nutritional Factors and Cancer in the Framingham Offspring Study (Z01 CN 00147-01 CPSB)

In order to explore further the alcohol-breast cancer relation, a second cohort study, the Framingham Offspring Study, has been undertaken. This cohort study consists of 5,135 children (2,646 female, 2,489 male) of the members of the original Framingham Heart Study Cohort. The baseline examination period was 1972-77 (Cycle 1). Subsequent follow-up periods were 1979-82 (Cycle 2) and 1984-5 (Cycle 3), with Cycle 4 currently ongoing. Alcohol consumption, both frequency and amount by type of beverage, has been ascertained at each cycle. Information on socioeconomic status, and reproductive and family history has been routinely collected. These additional data are important in controlling for variables that might confound an observed association between alcohol and breast cancer.

Six hundred cancers (300 in both men and women) are projected (based on the application of SEER rates to the cohort). This includes approximately 100 breast cancer cases in women, 110 lung cancers (80 in men), and 110 colorectal cancers (60 in men).

This study is being conducted collaboratively with investigators from Boston University.

Finland Studies of Nutrition and Cancer (Z01 CN 00148-01 CPSB)

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory function for various natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels, and cancer incidence. The objectives of these etiologic studies are to: (1) assess the role of fats, selenium, and vitamins A, E, and C in breast cancer development; and (2) evaluate the relation of intake of various nutrients to subsequent cancer, particularly breast, colon, and lung. The project includes two studies. The first is a breast cancer case-control study of fats, total calories, selenium, and vitamins A, E, and C. The role of various anthropometric measurements, genetic markers for breast cancer, and reproductive factors are being explored. The second project is a comparison of nutrient intakes in cases and reference

subjects identified from an existing large cohort with prediagnostic baseline dietary histories. Associations between various dietary components and several cancers will be assessed.

These studies are being conducted collaboratively with the Surveillance Program of the Division of Cancer Prevention and Control and the National Public Health Institute and Social Insurance Institute of Finland.

Yunnan Tin Miners Lung Cancer Studies (Z01 CN 00149 CPSB)

As part of our general collaborative studies in China and the feasibility study for a lung cancer intervention study among Yunnan tin miners, two lung cancer case-control studies have been conducted among the tin miners. The first, a prevalence case-control study, interviewed 107 living cases diagnosed between 1967-1984 and an equal number of matched controls. A second study includes 183 lung cancer cases incident in 1985 and 1986 among miners and an equal number of matched controls. Data concerning smoking, occupational exposures including radon and arsenic exposure, diet and other exposures were collected by personal interview. Analyses of risk by radon, tobacco, and arsenic in the prevalence study have been completed while analyses of the incident case-control study are ongoing.

These studies are being conducted collaboratively with scientists from the Cancer Institute of the Chinese Academy of Medical Sciences and the Labor Protection Institute of the Yunnan Tin Corporation.

Breast Cancer Genetics Studies (Z01 CN 00145-05 CPSB)

The overall goal of this project is to further our understanding of the genetic as well as environmental influences that are involved in the etiology of human breast cancer. The specific aim is to test for genetic linkage between a large array of discrete, polymorphic genetic markers and the gene(s) for breast cancer in family data. The ultimate goal is to localize a gene or genes that predispose women in high-risk families to breast cancer. A sample of women with a strong family history of breast cancer who participated in the Breast Cancer Detection Demonstration Project (BCDDP) have been contacted and pedigree, vital status, health history, and epidemiological data collected from them and their family members. Thirteen families whose pedigree structure were the most informative for use in linkage analysis studies were selected. Blood has been collected from most of these families and analyzed for the presence of a number of genetic markers, including protein markers, oncogenic sequences, and restriction fragment length polymorphisms (RFLPs).

Results thus far indicate that nine oncogenes can be excluded as linkage candidates in twelve of these families. Segregation studies, based on regressive models which can control for important epidemiologic variables, are underway.

This study is being conducted collaboratively with scientists at the University of California at Berkeley and Louisiana State University. In previous Annual Reports, this project was entitled "Linkage of Classical and DNA Markers to the Susceptibility Gene for Breat Cancer."

Esophageal Cancer Genetics Studies (Z01 CN 00150-01 CPSB)

The overall goal of this project is to develop an understanding of the genetic as well as environmental influences that are involved in the etiology of human esophageal cancer. In North Central China where rates of this cancer are highest in the world, a sample of families have been identified with extraordinary familial aggregation for the disease. The specific purpose of the first phase of

these studies is to obtain existing pedigree and epidemiologic information on a limited number of these families, obtain additional data on the base population from which they were drawn, and initiate steps to prospectively follow these families for the development of cancer. Formal genetic and genetic/epidemiologic evaluations will include familial aggregation studies, studies of the transmission or segregation of the disease, and studies that compare lifestyle and dietary aspects between case and control families. Analyses of these data should provide a unique opportunity to understand the genetic and epidemiologic components of esophageal cancer.

This study is being conducted collaboratively by scientists at the Chinese Academy of Medical Sciences as well as scientists from the Division of Cancer Etiology and the Division of Cancer Treatment.

Clinical Nutrition Studies:

Human Studies of Diet and Nutrition (Z01 CN 00101-08 CPSB)

The role of dietary factors in cancer prevention has been assessed in animal experiments, in human epidemiologic studies, and most recently, in prevention trials. For many of these agents, however, information is incomplete concerning their safety, toxicity, dose, form, bioavailability, pharmacokinetics, and mechanisms of action. To further define these parameters in humans, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC), U.S. Department of Agriculture, and the CPSB, DCPC, is being conducted. Initial efforts focused on three nutrients which have shown the most promise for cancer prevention–selenium, fat, and beta-carotene. Current efforts are examining alcohol and omega-3 fatty acids.

1. Selenium Studies

A study examining a single, oral dose of two forms of stable labelled selenium (as selenite and selenomethionine) in the fasting and non-fasting state is being conducted to investigate the pharmacokinetics of selenium. A complex, multicompartmental model has been developed to explain the kinetics of selenite and a similar multicompartmental model is being examined for selenomethionine. To evaluate potential toxicity from long term ingestion of high levels of selenium, interviews, physical examinations, biologic samples, and duplicate meals have been collected for selenium analysis from 142 subjects residing in South Dakota and Wyoming where soil levels (and consequent blood levels) of selenium are the highest found in the U.S.

2. Fat Studies

Studies examining the metabolic effects of changes in dietary fat and fiber have been conducted separately in premenopausal women, postmenopausal women, and men.

The first study of fat examined the metabolic effects of 40% versus 20% of calories from fat in premenopausal women eating controlled diets at two different ratios of polyunsaturated to saturated fats (P:S) for eight menstrual cycles. Study results to date have shown that the low-fat diet was associated with an insignificant reduction in serum cholesterol and a significant increase in serum triglycerides; alterations in lipids measured in exfoliated cheek cells; a shortening of menstrual cycle length; a reduction in the number of insulin receptors in erythrocyte ghosts; lower plasma levels of DHEA-S and cortisol and higher levels of plasma insulin; P:S-ratio-specific changes in bile acid levels; no change in the level of fecapentaene, a potent fecal mutagen; cycle-phase and fat-level specific alterations in lipoprotein and red blood cell fluidity; and alterations in body composition as indicated by a reduction in percent body fat. Menstrual cycle effects on plasma lipids and certain hormones were also observed.

The second study of metabolic parameters associated with fat intake was conducted in healthy men on a controlled high-fat, low-fiber diet. The parameters were compared to measurements on samples collected from the same subjects while on a controlled low-fat, high-fiber diet. Analyses to date have shown a substantial reduction in plasma lipids and urinary prostaglandins on the low-fat, high-fiber diet. Validation of a number of available physical activity questionnaires was also performed in conjunction with this study, an opportunity afforded by the study design because precise information on energy intake was known, and resting energy expenditure could be measured. Studies in progress include examination of changes in plasma lipids and hormones, and fecal bile acids and mutagens.

The third study of fat examined primarily lipid and hormone measures in postmenopausal women, contrasting their free-living uncontrolled diet values with those on a controlled, low-fat (20 percent of calories) diet. Preliminary analyses have not shown significant differences in the lipid and hormone levels examined.

3. Carotenoid Studies

Two human studies have been conducted examining the plasma response to ingestion of selected carotenoids in various forms. The first study involved a single ingestion while the second involved daily prescribed amounts given as part of a controlled diet over a six-week period. Results have shown, for example, that beta-carotene in carrots or broccoli is much less well absorbed than beta-carotene in capsules. In addition, carotenodermia (yellowing of the skin) was observed in all five subjects who took 30 mg but in none of the five who took only 12 mg of purified beta-carotene daily.

4. Alcohol Study

The potential role of alcohol consumption in the etiology of breast cancer has been prominent in several recent studies and is particularly important because it is a risk factor that can be modified. While this hypothesis requires verification in other epidemiologic studies, we have initiated a clinical metabolic study to examine the effect of alcohol ingestion on hormonal status as one potential mechanism of action.

5. Omega-3 Fatty Acid Study

A number of animal and human studies suggest a protective role for omega-3 polyunsaturated fatty acids in carcinogenesis. In order to understand more clearly the underlying mechanisms of this role, we have initiated a controlled feeding study in which a number of metabolic parameters most likely to be affected by feeding omega-3 fatty acids from fish oils are evaluated. Primary among these parameters are effects on prostaglandin biosynthesis, prooxidant stress, and immune function.

Prevention Studies:

Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (Z01 CN 00100-08 CPSB)

The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (ATBC Study) is investigating the efficacy of daily oral alpha-tocopherol (50 mg) and beta-carotene (20 mg) in a double-blind, randomized 2x2 factorial design trial aimed at preventing lung cancer among 50-69 year old male cigarette smokers. The project is based on experimental and epidemiological research which demonstrates a potential preventive role for these agents. Recruitment took place between 1985-1988, and the trial will end in 1993 after an average follow-up of over 6 years. A postal survey

screening for potential trial participants was sent to 291,000 men in southern Finland, and 76% responded. We invited the smokers willing to participate (43,000) to one of 14 study clinics, and over 29,000 were randomized into the study. Compliance to the one capsule daily regimen has remained very high (97% average), and the dropout rate averages 6% per year. Reduction of lung cancer incidence in the active agent groups is the primary study goal; differences in the occurrence of other cancers will also be evaluated. Several pilot studies in support of the trial have also been completed including a feasibility study, validation of study dietary questionnaires, and evaluation of skin yellowing and serum levels following beta-carotene administration.

This study is being conducted in Finland because of their traditionally high lung cancer rate, ready access to a high-risk population, and excellent country-wide cancer registration system. This trial is being conducted collaboratively with the Surveillance Program of the Division of Cancer Prevention and Control and the National Public Health Institute of Finland. In previous Annual Reports, this project was entitled "U.S. Finland Studies of Nutrition and Cancer."

An additional study ancillary to the ATBC Study was initiated this year which will determine the effect of the intervention agents on the development and progression of chronic gastritis, a condition with high prevalence in Finland. This ancillary study is being conducted collaboratively with the Diet and Cancer Branch and the Biometry Branch from the Division of Cancer Prevention and Control and investigators in Finland.

Use of Isotretinoin in Prevention of Basal Cell Carcinoma (Z01 CN 00103-08 CPSB)

This study is a 5-year, randomized, double-blind prevention trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinomas in a high-risk population, and to examine possible side effects associated with long-term administration of low doses of isotretinoin. A total of 981 subjects were entered into the study over a 36-month period at eight participating clinical centers located around the country. At each center, subjects were randomly allocated to intervention (10 mg/day) or control (placebo) groups during the recruitment period which concluded in June 1987.

Vitamin A and its analogs, collectively known as retinoids, have been actively studied for several years in relation to their requirements in normal physiology and health, as well as for their potential in prevention of human disease. This vitamin is necessary for the differentiation of epithelial cells and is essential for the development and function of growth, reproduction, and vision. Deprivation or deficiency of vitamin A promotes tissue metaplasia and neoplasia in various animal and organ culture models. Supplementation with retinoids can reverse these changes and restore functions of cell growth and differentiation in various cell lines.

Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. Since in most of the experiments animals were administered retinoids after their exposure to the carcinogen, the prophylactic effect of the retinoids is believed to be in the post-initiation phase, i.e., during promotion of carcinogenesis. In addition, several epidemiologic studies have shown an association of low dietary intake or serum levels of vitamin A with increased risk of cancer, notably lung cancer and other tumors of epithelial origin. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinomas for 4 years in patients at high risk of developing new tumors.

This study is being conducted collaboratively with the Surveillance Program of the Division of Cancer Prevention and Control.

Nutrition Intervention Studies of Esophageal Cancer in Linxian, China
(Z01 CN 00112-07 CPSB)

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relation between such supplements and esophageal cancer mortality. The Dysplasia Trial includes 3,393 subjects with cytologic evidence of dysplasia who have been taking intervention agents since May of 1985 in a simple multivitamin versus placebo two-arm design. The General Population Trial randomized 30,252 individuals from the general population who begin intervention in March 1986. This trial uses a more complicated fractional factorial design to allow evaluation of four separate factors, including vitamin A + zinc, riboflavin + niacin, vitamin C + molybdenum, and vitamin E + selenium + beta-carotene. In October 1987, as the Dysplasia Trial reached its midpoint, a series of examinations were conducted to evaluate potential endpoints considered to be intermediate in the carcinogenesis process. A repeat balloon cytologic examination was conducted on 2,824 participants and an endoscopic examination and blood collection were performed on 851. Analyses of samples collected during these examinations will include assessment of esophageal cytology, histology, cell proliferation, and DNA-content as well as measures of immune function and other studies.

These two studies are being conducted in Linxian (Henan Province) in the People's Republic of China (PRC). Linxian, a rural county with population of 800,000, was selected because it has the highest rate of esophageal cancer in the world, and because there is suspicion that the population's chronic deficiencies of multiple nutrients may be etiologically involved.

This study is being conducted with the Biostatistics Branch of the Division of Cancer Etiology at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

A Dietary Intervention Study of the Recurrence of Large Bowel Adenomatous Polyps
(Z01 CN 00151-01 CPSB)

Over 60,000 deaths result from large bowel cancer each year, making it the second leading cause of cancer death in the United States. It is estimated that more than 150,000 new cases will occur in 1989. Only about 50% of newly diagnosed cases will survive for more than 5 years. Successful efforts to reduce the incidence of this malignancy would clearly make a major dent in the overall morbidity and mortality due to cancer in the U.S.

Studies of the international variation in large bowel cancer rates, time trends in rates, and changing rates in migrants strongly implicate environmental determinants of this disease. Both epidemiologic and laboratory investigations point to the key role that dietary factors–particularly high fat, low fiber, and low vegetable and fruit intake–play in the development of large bowel cancer.

It is unlikely that any combination of further animal research, clinical investigations employing non-neoplastic endpoints, or observational epidemiologic studies would be sufficiently persuasive to influence public health policy. The Committee on Diet and Health of the National Academy of Sciences has recently concluded that "to obtain definitive information on the role of diet and cancer in humans, it would be desirable to conduct intervention trials in which diets are modified in specific ways...Although intervention trials are likely to be very expensive, the magnitude of the health problem and the lack of satisfactory treatments for many major types of cancer warrant such an investment of human and financial resources."

Large bowel adenomatous polyps present a unique opportunity to conduct an intervention trial because of the high prevalence rate in the general population, the high polyp recurrence rate in those who have undergone polypectomy, and the link between polyps and cancer. It is generally accepted that large bowel adenomas are a requisite precursor lesion for most large bowel cancers. Given the

strong evidence for the polyp-cancer sequence, an intervention that reduces the recurrence of large bowel polyps would have a strong likelihood of reducing the incidence of large bowel cancer.

The major objective of this study is to determine whether an experimental large bowel cancer "risk reduction" diet (low fat, high fiber, vegetable- and fruit-enriched) will decrease the recurrence rate of large bowel adenomatous polyps. This will be a multi-center randomized controlled trial involving 2,000 men and women. Study participants will be randomized into either the experimental diet group or a control group (usual diet). Recruitment will take up to two years, and the follow-up time from randomization is four years.

The study has two secondary objectives: (1) to investigate the relation between the dietary intervention and several putative intermediate endpoints in large bowel carcinogenesis, and (2) to evaluate the correspondence between these intermediate endpoints and subsequent neoplasia (adenoma formation). Particular intermediate endpoints of interest include mucosal cell proliferation, ornithine decarboxylase, and mucins.

PLANS

Etiologic Studies:

Several studies have now shown that increased body size is associated with an increased risk for cancer, particularly cancer of the breast. This result suggests a role for remote nutrition, particularly total caloric intake during youth, in carcinogenesis. Studies are ongoing and/or being planned in both animals and humans to confirm these observations and identify mechanisms of action. Additional studies have also shown that substantial weight gain and greater central as opposed to peripheral distribution of body fat are associated with increased risk of breast cancer. Further work is planned to assess these observations in other groups. Plans are also being developed to follow a large cohort of retired persons to allow better evaluation of the relation of diet, particularly factors with relatively low variability in our U.S. diet, to cancer in the elderly.

Clinical Nutrition Studies:

New clinical nutrition studies are being planned. Such studies will evaluate the kinetics of various forms of ingested vitamin C, both in foods and supplements; the response of hormones to weight loss in overweight women; and the influence of ingestion of putative carcinogens from cooked meats on fecal mutagens.

Prevention Studies:

Experimental studies of cancer such as the ongoing nutrition intervention studies represent a powerful approach in testing the diet-cancer hypothesis. Such studies, however, are long and expensive, typically requiring 5 or more years for completion. The use of intermediate markers is a new and exciting approach in the study of carcinogenesis. The major advantage to studies of intermediate endpoints is that, relative to trials using cancer as the endpoint, they can be conducted with smaller numbers of subjects over shorter periods of time. To date, only a few nutrition intervention studies using intermediate markers have been reported, and none have been conducted in the context of a study with cancer as its final endpoint. Nesting studies of intermediate markers within ongoing intervention studies in which cancer is the final endpoint represents the ideal circumstance in which to determine the relation of the intervention agent to both the intermediate and final endpoints. We are currently examining a number of intermediate endpoints in clinical trial participants. Evaluations

include studies of cytologic and histologic change, studies of cell proliferation and differentiation, examination of cellular DNA content, and immune function.

The four ongoing prevention trials will continue and the dietary intervention study of the recurrence of large bowel adenomatous polyps will be initiated. The feasibility study for a lung cancer intervention study among Yunnan tin miners in China has been evaluated but plans for a full trial are on hold.

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Laboratory for Nutrition and Cancer Research

The objectives of the Laboratory for Nutrition and Cancer Research, currently being established at the Frederick Cancer Research Facility, are summarized in the functional statements below:

The overall objectives of the **Laboratory for Nutrition and Cancer Research:**

- "Plans, develops, implements and conducts intramural research on nutrition and diet as they relate to the prevention of cancer in humans;
- contributes scientific back-up to the National Cancer Institute's programs in research on diet, nutrition and cancer, and serves as a focal point for new information pertaining to nutrition research;
- plans, develops and directs intramural research in the major areas of Basic Nutrition Science and Clinical/Metabolic Nutrition studies;
- identifies new research findings important for cancer prevention and plans, develops and conducts human intervention studies to establish the scientific basis for cancer prevention and public health measures;
- establishes program priorities, integrates research projects in the laboratory to achieve research objectives and goals, evaluates program progress and effectiveness, represents the program area in management, policy and resources to accomplish objectives."

The overall objectives of the **Basic Nutrition Science Section:**

- "Plans, develops and conducts intramural research in basic nutrition science. These studies will explore the basic mechanisms by which food components (nutrient or non-nutrient) may inhibit cancer formation;
- plans, develops and conducts research on nutrition at the molecular level (gene function and expression), cellular (membrane, cytoplasm) and organ (intermediary metabolism, organ-organ interactions) levels;
- plans, develops and conducts research to advance analytical methodology, develop *in vivo* and *in vitro* models for the study of nutrition as it pertains to the prevention of cancer."

The overall objectives of the **Clinical/Metabolic Human Studies Section:**

- "Plans, develops and conducts intramural research on healthy human subjects to ascertain the qualitative and quantitative aspects of the nutrition:diet:cancer relationship with emphasis on cancer prevention;
- plans, develops and conducts clinical research in metabolism, energy utilization or other aspects of human nutrition such as absorption of dietary substances and their metabolic disposition in humans;
- plans, develops and conducts clinical nutrition research leading to more effective and precise public health interventions directed toward the reduction of incidence, morbidity and mortality from cancer."

BIOMETRY BRANCH

OBJECTIVES

The overall objectives of the Biometry Branch are summarized in the functional statement:

- "Plans and conducts independent and cooperative research studies concerning cancer epidemiology, prevention, screening, diagnosis, treatment, and control using methods of mathematical and analytic statistics;
- plans and conducts independent and collaborative studies in biostatistical and epidemiologic methodology and in mathematical modeling of processes relevant to cancer prevention and control activities;
- provides consultation and review of proposed projects concerning biostatistical methodology and study design to staff of the Division and to investigators in other divisions of the NCI and outside;
- provides expertise in statistics and biometry to management and scientific decision-making meetings within the NCI and outside."

OVERVIEW

The work of the Branch is conducted via three Sections and by the Office of the Chief. The principal projects underway in each of these four organizational units will be described separately. The functional statements for each of the three sections will precede the description of their projects. Projects that involve collaboration across Sections or with the Office of the Chief are described only once in this report to avoid duplication.

ACCOMPLISHMENTS AND PLANS

OFFICE OF THE CHIEF

Proposed Screening Trial for Prostate, Lung, and Colorectal Cancer in Males

During the past year the staff of the Biometry Branch has been in continual collaboration with the Early Detection Branch in developing a proposal for a major trial of cancer screening in males for three cancers that comprise more than 50% of the incidence and mortality of cancer in U.S. males. These are lung, prostate, and colorectal cancer. The present proposal calls for a total sample size of 145,000 males between the ages of 55 and 74 who would be divided at random into three groups that would be screened respectively for the three cancer sites according to an innovative reciprocal-control design developed in the Biometry Branch. The screening techniques likely to be proposed are rectal examination, prostate specific antigen, and transrectal ultrasonography for prostate cancer, annual chest film for lung cancer, and flexible sigmoidoscopy for colorectal cancer. This proposal was presented in concept to the January meeting of the DPCP Board of Scientific Counselors which encouraged further work on the idea. The fully developed concept is scheduled to be presented to the Board at their October 1989 meeting.

Workshop on Errors-in-Variables

In last year's Annual Report we described a workshop on errors-in-variables that was held under the sponsorship of the Branch in conjunction with the Epidemiologic Methods Section of the Division of Cancer Etiology. During the past year all the papers presented at the meeting have been reviewed and the taped discussions have been summarized. The proceedings have been sent to the publisher and are expected to appear as the September issue of Statistics in Medicine.

Fatty Acid Profiles as a Marker for a Low Fat Diet

Work has continued on analysis of the NCI-USDA Feeding Study described in previous Annual Reports as well as on samples for 80 women from the Women's Health Trial (WHT). A manuscript was submitted describing the changes observed in the Feeding Study. Reviewers found the presentation difficult, so this paper is currently undergoing a complete revision directed toward simplification. Analyses of fatty acid profiles in the WHT sera permitted some discrimination between women reporting high and low fat intakes, but the separation was not nearly so clear-cut as in the Feeding Study. These same WHT samples are being reanalyzed by the laboratory used for the Feeding Study for fatty acid profiles in the phospholipids and cholesteryl esters rather than in total serum so that WHT results can be compared to those of the Feeding Study.

Analysis of Mammary Carcinogenesis Experiments in Rodents Related to the Effects of Fat

It has recently been suggested that the effect of dietary fat on mammary carcinogenesis in mice and rats can be explained by the effects of calories and that there is not any specific fat effect. Because of dissatisfaction with the published reviews on this subject, a literature search and re-analysis and synthesis of the many experimental reports has been undertaken to re-examine this question. The data have been analyzed using logistic regression techniques for combining information over a number of experiments. The results of these analyses support the view that increased caloric intake promotes mammary tumor development. They also show that there is a specific effect of fat which further enhances the growth of mammary tumors. The magnitude of the fat effect is estimated to be approximately two-thirds of the non-specific calorie effect. These conclusions are important for the design of future prevention trials involving reduction of fat intake in women. The evidence suggests that a low-fat intervention trial should be designed so as to reduce consumption of both fat and total calories.

Further analyses of these data are now being conducted to elucidate the effects of different types of fat: polyunsaturated, monounsaturated, and saturated.

Inventory of Cancer Prevention Trials

The number of cancer prevention trials sponsored by the Division is rapidly increasing. There is a consequent need for an Inventory of Trials to provide a global view of these activities and to help in strategic planning and program development. The compilation of such an Inventory has been undertaken and is now near completion. Thus far 120 trials, 95 randomized and 25 non-randomized, have been identified. The main prevention strategies can be classified as chemoprevention (34 trials), dietary modification (10 trials), screening (29 trials), and reduction of tobacco use (47 trials).

Assessing the Efficiency of the COMMIT Study Design

The Community Intervention Trial (COMMIT) is designed to test the effect of a community-wide smoking cessation program on smoking quit rates. Twenty-two communities, matched into 11 pairs, are involved. Each pair of communities has one member randomly assigned to intervention, while the other member acts as a control. The efficiency of this matched pairs design has been assessed using the baseline quit rates over the previous 5 years as a surrogate for the outcome

variable. The method required use of a linear regression model relating the outcome variable to the surrogate. Using this model it was possible to estimate a lower bound on the efficiency of the design. The results showed an estimated gain of at least 50% in efficiency due to the matched pairs design, i.e., only two-thirds the number of communities was needed to achieve the required power, compared to a conventional two-group randomization scheme.

Effect of Non-Compliance on the Power of Cancer Prevention Trials

A recent paper by Zelen (JNCI 1989;80:1442-44) argues that compliance is such a serious problem that primary prevention trials may not be possible. Both Zelen's contribution and previous papers on this subject were based on the assumption that non-compliance is a binary phenomenon which occurs, if at all, immediately after entry to a trial. Examining the effects of various different patterns of non-compliance has revealed new results. More gradual non-compliance has a considerably smaller impact on power, compared to non-compliance occurring entirely at the beginning of the trial. Patterns of non-compliance which may be encountered in dietary trials are likely to be partial and gradual, so these results provide some assurance that the deleterious effects of incomplete compliance on study power have been exaggerated in such settings.

Cancer Control Objectives and Cancer Mortality Projections (Z01 CN 00142-04 BB)

A comprehensive interactive Fortran program which projects cancer mortality and incidence figures (numbers and rates) from 1980 through 2020 serves as a focus for several projects within the Division. The program incorporates two different survival models (Weibull and mixed exponential), over 40 cancer sites, the ability to begin with or without prevalent cases, temporal trends in underlying cancer incidence and in mortality from other causes, three possible types of intervention (primary prevention, screening, and treatment), age adjustment, calculation of annual incidence and mortality statistics, and comparison of these statistics under changing conditions of trends and interventions. The Biometry Branch staff work closely with the Surveillance Program and other DCPC staff. Work during the past year has included continued refinement of the computer model, updating the basic underlying database, projections of rates for several industrial states in the U.S., and analysis of breast and cervical cancer.

BIOSTATISTICAL METHODOLOGY AND CANCER CONTROL EPIDEMIOLOGY SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Plans and conducts independent and collaborative research concerning biostatistical and epidemiologic methodology related to cancer prevention and control;
- conducts or collaborates in the design and implementation of studies aimed at developing, refining, and testing hypotheses relating to applied cancer prevention and control, community oncology, and diffusion and adaptation of effective prevention, control, and treatment technologies;
- plans and conducts independent and cooperative studies into the theory and analysis of cancer prevention and control;
- provides statistical consultation both within and outside the NCI to researchers concerned with problems related to Section responsibilities and staff expertise."

Consultation and Collaboration in DCPC Studies

In collaboration with the Cancer Prevention Studies Branch and the USDA, data from two high/low-fat controlled-diet feeding studies in males were examined to determine the effect of moderate dietary changes. One study examined the effect on the prostaglandin system. By measuring the urinary output of 7α-hydroxy-5, 11-dioxo-tetranorprostane-1, 16-dioic acid (PGE-M), the low-fat diet compared to the high-fat diet was associated with a significant 14% reduction, supporting the view that dietary lipid changes can alter the in-vivo production of E-series prostaglandins. Another study examined the effect on plasma cholesterol levels. The low-fat diet produced a 16-21% reduction in total-C and LDL-C as compared to the high-fat diet. HDL-C was also reduced so that the LDL/HDL ratio did not change.

Also in collaboration with researchers in the Cancer Prevention Studies Branch, the data from an observational study of South Dakota and Wyoming adults was examined to determine the relationship between dietary selenium intake and different indices (serum, whole blood, toenails) of selenium status in consumers of high levels of selenium. Results of the analysis shows that, adjusted for age, gender, and smoking status, selenium intake is a strong predictor of selenium status while gender is also important (women have higher tissue selenium content than men consuming the same level).

In collaboration with researchers in the Applied Research Branch, the results from two different studies are being examined. Data from a dietary assessment study of Finnish men were analyzed to estimate, for various micro- and macro-nutrients, the components of sampling variability due to differences between persons, differences between sampling periods, and differences between sample days. In addition, seasonal and weekend-weekday effects on nutrient assessment were estimated. These estimated ratios of between- to within-person variation for studies using various combinations of number of sampling periods and number of days within a period can be used to better design future studies of specific nutrients. Preliminary data are being analyzed from a soon-to-be-completed clinical trial of isoretinoin for reducing the incidence of basal cell skin carcinomas in a high risk population. Early tentative results show a positive effect in a subset of the study group who are at particularly high risk.

In collaboration with the Smoking, Tobacco, and Cancer Branch, a study of passive smoking on long-distance commercial airline flights was conducted. In-flight exposures to nicotine were found to be significantly related to post-flight urinary cotinine excretion and symptom self-reports from the flight attendants and passengers being studied. In addition, the type of aircraft ventilation system was found to be an important determinant of in-flight nicotine level.

Research in Biostatistical Methodology and Mathematical Modeling (Z01 CN 00121-05 BB)

Mathematical Models of Drug Resistance to Anti-Tumor Agents

This research expands the simple time-homogeneous Goldie-Coleman model for resistance of tumor cells to the cell-killing effect of chemotherapy. The model is extended in two ways: (1) to include the more general situation of time-varying stochastic birth, death, and mutation of tumor cells; and (2) to include some kind of treatment, such as immunostimulation, which kills cells resistant to conventional chemotherapy so that a "cure" is possible. Formulas for the mean, variance, and probability distribution of the number of sensitive and resistant cells as a function of time have been derived to predict the effect of different schedules under situations involving different time patterns of cellular birth, death, mutation to resistance, and the cell-killing effect of treatment. A further extension to multiple kinds of resistance is planned.

Errors in Variables for General Linear Models

Many biomedical studies involve measurements which are made with error. For example, in the analysis of cancer risk associated with diet, questionnaire studies can measure current and past dietary components only with sizeable error. Most statistical analysis techniques neglect these measurement errors and therefore give biased estimates of the diet-cancer association. The purpose of this research is to develop a General Linear Model (GLIM) regression method for randomized trials which adjusts for this error in measured covariates to give an unbiased estimate of the treatment effect. A computer program has been developed to provide unbiased estimates of the regression coefficients and estimate the magnitude of the measurement error variability. Simulations are being carried out to determine the relationship between the true magnitude of the measurement error, the magnitude of the bias induced by using standard statistical techniques, and the degree of bias-correction using our new techniques.

Comparison of TLVs with Unit Risks in Quantitative Risk Assessments

The Chemical Substances Threshold Limit Value (TLV) Committee of the American Conference of Government Industrial Hygenists is currently reviewing its procedures regarding carcinogens. Our research is directed toward comparing their current TLVs with Unit Risks derived from the Environmental Protection Agency's Carcinogen Assessment Group (CAG) using quantitative carcinogenesis modelling. Based on the 16 chemicals for which both the TLV Committee and the CAG have made quantitative risk assessments, our comparisons show that the two organizations generally put the chemicals in the same rank order of increasing hazard to exposed persons, but that CAG's Unit Risk factors imply that the acceptable TLV worksite levels are often estimated to be associated with substantial cancer risk.

Unbalanced Repeated Measures Linear Regression Procedure

Many sets of data involve repeated measures (e.g. blood samples from the same individual being measured at different times) in which the experimental design is unbalanced (e.g. individuals sometimes skip their scheduled sample collection.) No statistical procedure to correctly analyze data such as this is available in the commonly used packages, SAS, BMDP, or SPSS. A recent paper by Jennrich and Schluchter developed the computational formulas for maximum likelihood normal theory regression in this situation. A computer program using these formulas has been developed which will allow examination of a variety of correlation structures for the repeated measures. An easy to use SAS procedure based on this computer program has also been developed.

Descriptive Cancer Epidemiology (Z01 CN 00115-06 BB)

Age-Period-Cohort Analysis of Lung Cancer Mortality Among World War I Veterans of Known Smoking Status

In collaboration with investigators in the Epidemiology and Biostatistics Program of the Division of Cancer Etiology, age-period-cohort Poisson regression models were used to analyze lung cancer mortality rates for nearly 294,000 World War I veterans of known smoking status. During 1954 through 1979, 7,653 deaths from lung cancer occurred in this cohort. Lung cancer risks, standardized through Poisson regression, increased significantly with the amount of cigarette smoking. There was no evidence of a temporal decrease in mortality as a result of the well documented reduction in smoking among U.S. males since the 1960's decade. When standardized for age and calendar time period, lung cancer risk increased in the more recent birth cohorts as it does in the U.S. population. After smoking was added to the standardization, this cohort trend was not clearly apparent, suggesting that the differences between cohorts in the population are due primarily to differences in smoking habits.

HHV Antibodies, Leukemia and Hodgkin's Disease

In collaboration with the Environmental Epidemiology Branch of the Division of Cancer Etiology, serologic studies of antibodies to human herpes virus 6 (HHV-6) in selected cancer patients and controls were evaluated. Sera from patients with acute lymphocytic leukemia or Hodgkin's disease were obtained from a repository of specimens maintained by the Division. Sera from healthy blood donors were obtained from another repository. Differences in antibody titers between cancer patients and controls, adjusted for sex and age, do not suggest an etiologic role for HHV-6 in either disease. Results do indicate that HHV-6 serology may be of value in identifying individuals with immunologic abnormalities.

Morbidity Among Long-Term Survivors of Childhood Cancer and Their Offspring

This retrospective cohort study, done in collaboration with investigators in the Division of Cancer Etiology, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood, as well as any effects that might have been transmitted to their offspring. Cases selected from five U.S. cancer registries were patients under age 20 with a histologically confirmed malignant neoplasm or brain tumor diagnosed during 1945-1974. Patients must have survived at least 5 years and reached the age of 21 years by December 31, 1979. Up to two sibling controls were selected for each case with sequential priority given to full blood relationship, same sex, closest in age. Interviewer-administered questionnaires were obtained for 2,283 (91%) cases and 3,270 (91%) controls.

In a study of the childhood cancer survivors' knowledge of their diagnosis and treatment, 14% of those with malignancies at sites other than the central nervous system said that they had not had cancer. Among survivors who knew that they had cancer previously, 19% were unable to correctly identify the type of treatment that they received. Logistic regression techniques were used to determine what factors were related to this lack of knowledge. One important factor was race; nonwhite survivors were significantly more likely than white survivors not to know their diagnosis.

In another study, the quality of life in survivors of central nervous system tumors was investigated. Conditional logistic regression analyses of data for 342 survivors and 479 matched sibling controls showed that survivors were significantly more likely to have been unemployed most of their adult life, have a health condition affect their ability to work, and be unable to drive a car. Unfavorable outcomes were more frequent in male survivors than females, in those with supratentorial tumors compared to infratentorial tumors, and in those who received radiation therapy.

In another study, the cigarette smoking habits of 1,650 childhood cancer survivors were compared to those of 2,630 sibling controls. Matched analyses utilized data from 670 families with one survivor and one sibling control and 980 families with one survivor and two sibling controls. At last follow-up, survivors were smoking at nearly the same rate as their siblings. Several demographic factors (sex, education, and income) and the type of treatment received by cancer survivors significantly affected smoking habits. After adjusting for the demographic factors, survivors who were treated with radiation above the diaphragm (with or without chemotherapy) were found to smoke significantly less than their matched controls. This suggests that such treatment may make smoking intolerable.

Cancer in Oriental Populations (Z01 CN 00113-06 BB)

Mainland China - 65 county study

An in-depth diet, lifestyle and mortality study of 65 mostly rural counties is being carried out by other researchers. As part of the study, an ecological survey in 1983 included details on nutrition and lifestyle through use of a questionnaire, food composition analysis, three day diet survey, and blood and urine analysis. In cooperation with researchers in China, the findings are being made available to us, together with 1975 mortality data, for an analysis on selected causes of death. Initially, we are correlating various measures (nutritional status, reproductive history, etc.) with several components of cardiovascular diseases, and expect to follow up with possible relationships to cancer sites.

Migrants to Taiwan from Fujian Province

Analysis of mortality data for the Taiwan population (originating in Fujian province on Mainland China) is approaching the final stage. The site-specific transitional experience is quite similar to earlier findings of the Chinese who migrated to Hong Kong and this country from Guangdong province.

Asian Resource Data

A statistical file of age-specific and age-adjusted incidence and mortality rates for cancer/non-cancer causes since 1960 is being established, covering the Chinese, Japanese, and Filipinos in the U.S. and "home" countries. With continual updating, these figures provide background information on the health status of the Oriental populations in matters of hypothesis formulation and program planning.

Mortality Trends by Nativity among U.S. Chinese and Japanese

The eventual availability of 1980 U.S. Census data on Asians cross-tabulated by age-sex-nativity enabled us to pursue a trend analysis of mortality by nativity among U.S. Chinese around census years from 1960 to 1980. Our review indicates that for almost every major non-cancer cause of death, the trend is downward for both nativity groups and sexes, with the exception of homicide. As for cancer, the picture is mixed. There was a downward trend for such sites as nasopharynx, stomach, and uterus, but upward trend among native-born females for colon, pancreas, and breast. With the number of native-born Chinese aged 45 and over having increased about 2 1/2 times from 1960 to 1980, the new insights thus obtained would complement earlier study results on the Chinese in the U.S., Taiwan, Hong Kong, and Singapore.

While the U.S. Chinese have experienced large increases in immigration during the past 20 years, the Japanese have not, so that the majority of U.S. Japanese are native-born. A preliminary review of mortality indicates that where rates are higher in Japan, the trend is toward lower levels for U.S. Japanese, with transition either partially completed towards the level for whites (stomach and liver cancers), or fully completed (esophageal cancer, suicide, nephritis, cerebrovascular disease). In contrast, where rates in Japan are relatively low, the levels for U.S. Japanese remain low (breast, prostate, and lung cancers, diabetes, cirrhosis), or show only small rises (ischemic heart disease, homicide). Colon cancer, a rare exception, has risen close to white levels.

Oncology Abstracts

For inclusion in a series of oncology overviews, a collection of epidemiologic studies of neoplasms occurring among Orientals is being prepared by others. As consulting reviewers, we prepared an editorial commentary which covered a site-specific overview of cancer epidemiology

among Orientals. Included for U.S. Chinese and Japanese were comments on nativity differences, and significant etiological relationships.

Future Plans

1. With the increasing number of U.S.-born Chinese and Japanese in recent years, cancer risk ascertainment will be extended to making use of nativity information in SEER data for the first time. Nativity, i.e. foreign- or native-born, is included as a code, but in practice is omitted from 15% to 20% of the time. We hope to explore the possibility of improving reporting of this important variable.

2. Realistic population estimates of the post 1980 censal populations of U.S. Asian groups are essential to calculation of disease rates, but the standard methodology used in the past has proved to be inadequate. We will be exploring new approaches to the problem.

3. Histologic and sub-site differences in cancer case distribution between Asians and U.S. whites have been documented, particularly for lung cancer and colorectal cancers. With 14 years of data accumulated in the SEER program, we will be reviewing the histological distribution for all sites with sufficient numbers, and attempting to relate differences or similarities to possible risk factors.

4. A detailed time trend analysis of mortality by cause for Taiwan in the past several decades is being prepared, with emphasis on its comparability to that of U.S. Chinese.

Development of Cancer Control Epidemiologic Methods (Z01 CN 00122-05 BB)

The purpose of this project is to develop the methodology of cancer control epidemiology, with emphasis on its conceptual foundations in biological, epidemiological, statistical, and ethical theory. Research areas include: concepts of cause and prevention, the logic of epidemiologic inference, the structure of causal and preventive models, the relationship of biological models of carcinogenesis to causal and preventive models and to models of interactions, the analysis of epidemiologic reasoning, ethics of cancer control epidemiology, and the design and analysis of cancer control research studies. Specific examples of work underway in this project include:

Studies in Causal and Preventive Inference

Criteria for causal and preventive inference have been improved. Traditional criteria fall into two categories: those dependent upon the specific form of the hypothesis and those independent of the form of the hypothesis. Two general criteria replace all existing criteria and have the added advantage of being equally applicable to causal and preventive inference. These are: predictability and testability. These criteria are currently being applied to these hypotheses: dietary alcohol causes breast cancer, dietary fat causes breast cancer and dietary fiber prevents colon cancer.

Other research underway includes: predicting magnitudes of effect from the sufficient component causes model and a critical examination of the role that the magnitude of association plays in making causal and preventive inferences.

Studies in Causal and Preventive Interactions

A new causal theory (epigenesis theory) has been developed as an elaboration of the sufficient component causes model and is being applied to the evaluation of causal and preventive interactions. The theory defines the following relationships between interacting causal factors: (1) "complementary" causes contribute different causal actions to the sole pathogenic process leading to

disease, (2) "separate process" causes contribute different causal actions to different pathogenic processes, (3) "intermediate" causes contribute different causal actions to the same pathogenic process in the presence of additional pathogenic processes where at most one of them may also participate, and (4) "cooperative-competitive" causes share the same causal action and act within the same pathogenic process. Each of these relationships can be linked to population models of disease distribution. Complementary relationships correspond to multiplicative models; separate process relationships correspond to simple independent action models which are slightly less than the additive model; intermediate relationships lie between multiplicative and simple independent action models; and cooperative-competitive relationships range from greater than multiplicative to less than the simple independent action model.

The Analysis of Epidemiologic Reasoning

A logical method, based upon critical deductive reasoning and therefore suitable for the mega-analysis of epidemiologic reasoning, has been developed and is being applied to: the use of case-control methods for screening, the use of negative results in causal and preventive inference, the debate regarding the use of either p-values, confidence limits, or p-value functions as the best way to report epidemiologic studies, the role of complexity in causal inference, and the links between scientific, technologic, and ethical reasoning when the epidemiologist is faced with the question: "does exposure to alcohol cause breast cancer?"

The Ethics of Prevention

Current literature suggests that epidemiologists should either get directly involved in preventive policy decisions at both the population and individual level, or provide scientific information only without recommendation as to its application. In this effort, the ethics of each choice are described, in order to provide the theoretical justification for personal choices on the part of cancer control epidemiologists.

Phase IV Studies of Cancer Control

Criteria for considering whether a cancer control study qualifies as a Phase IV, defined population study are described and the use of the randomized trial paradigm for the purpose of studies in defined populations is criticized.

CLINICAL AND DIAGNOSTIC TRIALS SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Engages in independent and cooperative research on statistical methodology for design of controlled clinical trials of cancer prevention and treatment and for field testing of diagnostic techniques;
- provides full statistical support in selected trials, including development of the detailed study plan, supervision of data collection, processing, and editing, and analysis of the data as well as preparation of scientific papers;
- develops statistical techniques for analyzing trial results, for identifying prognostic factors and diagnostic determinants, and for analyzing observational data;
- consults and collaborates extensively with other researchers requiring expertise in these and related areas."

Statistical Methodology Research (Z01 CN 00116-06 BB)

The Effect of Age on the Diet-Cancer Relationship in Epidemiological Follow-up Studies

Most nutritional epidemiologic follow-up studies assess the diet-cancer relationship on the basis of dietary data collected at entry into the study. The dependence of the individual's dietary assessment on his age at examination, and the strong dependence of cancer risk on the individual's age, indicate that the confounding effect of age should be controlled along two age scales: age at dietary interview, and age at cancer diagnosis. Most analyses of the diet-cancer association in follow-up studies accumulate person-years at risk according to follow-up time, and treat age at entry into the study as a covariate. In collaboration with the Cancer Prevention Studies Branch and the Biostatistical Methodology and Cancer Control Epidemiology Section, an alternative approach is being investigated using a stratified Cox model with chronological age as the underlying time scale and strata defined by age at entry into the study. The methodology is used to assess the effect of two sets of dietary variables on the development of breast cancer in the first National Health and Nutrition Examination Survey (NHANES-I) cohort, and to examine the possible differential effect of diet between young and old women at age at examination, and between younger and older women at age of breast cancer diagnosis.

Application of Collinearity Diagnostics to Relative Risk Regression Models of the Diet-Cancer Relationship

The general high correlation (collinearity) between intakes of major nutrients, and the relative homogeneity of the Western diet, can result in unstable regression estimates for the effect of diet on cancer risk. Three basic tools for collinearity diagnosis in the standard linear model (the condition indices, the variance decomposition proportions, and the standard error inflation factors) have been extended to relative risk regression models such as the logistic and proportional hazards models. The extension is based on the analogy between the role of the information matrix in relative risk models and the cross-product matrix in the standard linear model. The methodology is applied to assess the magnitude and the sources of collinearity among regression coefficients for three types of relative risk models relating different dietary variables to breast cancer in the NHANES-I epidemiologic follow-up study.

Errors-in-variables and the Analysis of the Relation of Diet to Breast Cancer Risk

In analyzing data such as that obtained from the NHANES-I follow-up cohort investigating the relation of diet to the risk of breast cancer, the problem of large intra-individual variation in the measured daily intake of nutrients must be considered. Work has continued on three aspects of this problem: (1) consideration of methods for determining legitimate standard errors; (2) development of a simple and efficient test statistic for studying effects in measurement error models; and (3) investigation of the design of studies using validation datasets. Work has begun on identifying data available from USDA studies that could be used to investigate the measurement error inherent in the 24-hour recall data used in the NHANES-I follow-up.

A Score Test for Non-Informative Censoring Using Doubly Sampled Grouped Survival Data

Methods for analyzing survival data frequently assume that censoring is noninformative. In some situations, this assumption does not hold and standard methods yield biased estimates of the survival curves. A fundamental problem is that the noninformative censoring assumption generally cannot be tested using the observed data, because the joint distribution of failure and censoring times is not identifiable when censoring is informative. In collaboration with the Screening Section, work has continued on the development of an approach to this problem, based on following a random subsample of subjects to determine post-censoring failure time. Failure and censoring times are treated as interval variables and their joint distribution is assumed to be multinomial. The possible failure-

censoring relationship is characterized by a class of parametric models and a simple closed-form score test for a null hypothesis of noninformative censoring is derived. This methodology has been applied to test the hypothesis of no relationship between time of release from hospital and the occurrence of wound infection, using data collected in Israel in a study of post-operative wound infection.

Nonparametric Estimation of a Bivariate Distribution of Time and a Time-Dependent Variable Subject to Censoring

In some survival studies, the major end point is not the actual survival time but rather a related variable which accumulates events along the time axis. Examples of such variables are the total amount of dollars spent from diagnosis of cancer until death, or the cumulative exposure to a potential hazardous substance. In collaboration with the Applied Research Branch and the Screening Section, a non-parametric estimate of the marginal distribution of the time-dependent variable, when the survival time data may be right censored, is being developed. The joint distribution of survival time and the time-dependent variable is assumed to be multinomial, and the maximum likelihood estimates of a particular parameterization of the joint distribution is derived using the E-M algorithm. The estimates for the marginal distribution for both survival time and the time-dependent variable are compared to the univariate Kaplan-Meier estimates. The methodology is being applied to assess the distribution of the dollars spent on cancer therapy from diagnosis until death for various cancer sites using Medicare data from the Health Care Financing Administration.

Logistic Model for Matched Sets

Results of maximum likelihood estimation in a conditional logistic model for matched sets data were compared with an unconditional logistic model in which the exposure of an individual is "standardized" by subtracting the mean exposure within that individual's matched set. Under the unconditional model the estimate of the regression coefficient, its variance, the Wald statistic and the likelihood ratio statistic are all t/(t-1) times the corresponding values under the conditional model, where t is the size of each matched set. These relationships are exact for matched pairs, and for larger matched sets are approximations. Computer simulations were performed to verify these relationships.

Sample Size Computer Program

Development has continued on a program to compute power and sample size for a variety of experimental design situations. The program operates interactively on the NIH DEC-10 computer system. The program is user-friendly and prompts for answers to design questions. Optional user instructions provide a description of program capabilities as well as citing literature from which equations used in the calculations were adapted.

Interactive Data Analysis Programs

The Section has previously developed and continues to maintain and improve a group of interactive computer programs for efficient analysis of medical data, particularly those dealing with risk factors and prognostic factors using sophisticated multiple regression techniques and survival analysis. These programs have proven useful not only for many projects within the Biometry Branch but also elsewhere in the Division, as well as by other investigators both within the NIH and at outside institutions. During the past year, there has continued to be particular interest in applications for the program for analyzing time-dependent covariates.

Consultation on Clinical Trials and Other Studies (Z01 CN 00119-06 BB)

Community Intervention Trial for Smoking Cessation

Extensive consultation has been provided to the staff of the Smoking, Tobacco, and Cancer Branch concerning statistical issues which have arisen in the planning and implementation of COMMIT, a large-scale community-based study intended to promote smoking cessation among heavy smokers. Staff of the Biometry Branch have devised the basic design for the study, eleven matched pairs of communities with one member of each pair chosen at random for intervention and the other serving as a control. The study was designed to detect a 10% difference in the smoking quit rate between the intervention and control communities. The baseline survey was completed in May of 1988, before randomization. Cohorts of heavy, light-to-moderate, and recent ex-smokers were identified for follow-up. Analysis of demographics showed comparability of community pairs as previously shown by U.S. Census data. In addition to analyses of data from the baseline survey, Biometry Branch staff have been actively involved in all meetings of the Steering Committee and have participated in design of the various surveys that are planned.

An Evaluation Cohort of 400 adults from each of the 22 communities was surveyed to assess the population wide impact of COMMIT on the decline of the social acceptability of smoking and intervention awareness and participation. The remaining members of the cohorts of heavy and light-to-moderate smokers were contacted for tracking purposes only.

Brain Tumor Clinical Trials

The Section provides full support for the Brain Tumor Cooperative Group, a multicenter group of neurosurgeons, neuro-oncologists, radiotherapists, neuro-radiologists and neuro-pathologists conducting randomized trials for patients with primary brain tumors (with emphasis on malignant gliomas). The Group has been accruing patients to a phase III trial, BTCG 87-01, to study interstitial radiation (seed implants) as an addition to the customary external beam radiation and chemotherapy. The Group has also implemented a randomized study for low-grade glioma patients, BTCG 87-30. This study compares immediate versus delayed radiotherapy; for the delayed arm, radiotherapy is only given at the time of documented tumor progression. Planning has proceeded to do this trial as an intergroup study with two other cooperative groups, RTOG and SWOG.

Follow-up has continued for previous BTCG studies. Accrual has continued on BTCG 84-20A, a randomized phase II comparison of intra-arterial cisplatin versus intravenous PCNU for primary brain tumors. Patients were stratified as either progressive (clinically stable) or non-progressive. In general, both regimens have been well tolerated. PCNU led to greater hemato-toxicity, while cisplatin lead to greater renal toxicity, and some cisplatin patients experienced complications associated with IA administration (including encephalopathy). Analyses of results presented in May 1989 showed modestly increased survival for patients randomized to IV PCNU, but this difference was not statistically significant. The Group continues to plan studies to investigate improvements to the multimodality therapy of brain tumors.

Serum Markers for Breast Cancer

Serum and background information have been collected from over 12,000 women for evaluation of biological markers for breast cancer. Shipments of blinded panels of serum were sent on request to qualified researchers. During the course of this project, investigators have evaluated monoclonal antibodies, levels of hyaluronic acid, CEA, lipid bound sialic acid or ductal carcinoma antigen as potential markers. When the results of the assays of blinded sera are completed, the data are returned to the Section for analysis, and these analyses and unblinded data are returned to the investigators.

Fruit and Vegetables in the American Diet

Daily consumption of fruit and vegetables is essential for good health and may be important in cancer prevention. A review of epidemiologic studies examining the association between consumption of these foods and the relative risk of various types of cancer is underway, in collaboration with the Surveillance Program. A strong and consistent inverse relationship is emerging for a number of sites, providing further support for the NCI recommendation that a variety of fruits and vegetables be included in the daily diet.

A second aspect of this project is a study of the number and types of servings and of the nutrient intake, by numbers of servings, of these foods. This study uses twenty-four hour dietary recall data, from the Second National Health and Nutrition Examination Survey. The analysis shows that, on the recall day, 22% had no servings of a vegetable, and 45% had no servings of fruit. Data on types of servings indicate a lack of variety in the choice of vegetables. Mean intake of vitamin A was below the USRDA for those eating fewer than 2 servings of these foods, and mean vitamin C was below the USRDA for those having no servings of fruit (except for those consuming 3 or more servings of a vegetable). The recommended level of fiber intake, (20 or more grams) was achieved on average only by those who had three or more servings of both fruit and vegetables. Regression methods for obtaining means standardized for age, race, and sex for each fruit/vegetable servings category were developed.

Study of Food Purchasing Behavior and Consumer Nutrition Education

The Section is providing statistical support to a project undertaken jointly by the Applied Research Branch and Giant Food to test the effectiveness of several supermarket intervention strategies for changing food purchase behavior. The goal is to increase the purchase (and the consumption) of foods high in fiber. The data that are being collected consist of cross sectional-time series observations on weekly purchases and average prices of the studied food categories at different times in the intervention and control areas, during a baseline year and two years of intervention. A model which assesses the effect of the intervention has been developed. It considers both the spatial correlation between the purchases at different stores at the same week, and the autocorrelation between purchases at adjacent weeks at the same store. It also includes as covariates the following potential confounding variables: the absolute and relative price of the item in the recommended food group, a seasonal monthly effect on purchases, and baseline differences between the target and control areas.

The National Death Index

The National Death Index (NDI) offers an efficient method of ascertaining mortality and subsequently obtaining cause of death for the large numbers of persons involved in studies conducted or funded by the NCI. Efforts to acquaint cancer researchers with the NDI and its uses in treatment and prevention trials and in epidemiologic and occupational studies began in 1984. A Working Group, appointed in September 1985 by the Director of the NCI, has developed an NCI-wide policy concerning use of the NDI. The Group has explored the different requirements for setting policy in intramural research, contracts, grants, and cooperative agreements. A package giving a draft policy and a discussion of problems associated with implementation was reviewed by the NCI Executive Committee, which requested an estimate of costs associated with the policy. A report is being prepared, based on inventories of trials in the several Divisions of the NCI, that gives estimates for the cost of developing and maintaining a system to implement this policy.

Design and Analysis of Pharmacokinetic Studies of Selenium (Z01 CN 00107-07 BB)

Selenium is a possible cancer preventive agent and is being considered for use in intervention trials. A study in collaboration with the Cancer Prevention Studies Branch is in progress which will

provide information on the pharmacokinetics of selenium in its prototype forms–sodium selenite (inorganic form) and selenomethionine (organic form). This information is necessary for the determination of time and manner of administration. In the study, 32 subjects received a single oral tracer dose of selenite or selenomethionine on 2 occasions, 90 days apart, once fasting and once non-fasting.

An objective of the study was the comparison of pharmacokinetic parameters in fasting and non-fasting subjects. A kinetic model of selenite metabolism, developed as part of this project, is being used to analyze tracer data for each subject in both fasting states, taking into account both tracer indigenous in the diet and tracer from the first dose remaining in the body when the second was given. This model includes absorption distributed along the GI tract, transport through four plasma components, a subsystem consisting of the liver and pancreas, and a slowly-turning-over tissue pool. Analysis of selenite tracer data suggests that fasting status modulates the effects of the first plasma component. While absorption is similar in both fasting and nonfasting states, there appears to be a greater first pass effect in nonfasters, probably in response to eating. Such information is important in deciding on an optimal dosing regimen. Based on the introduction of new software, the model was modified to allow for the calculation of fractional standard deviations for each parameter. A model for the metabolism of selenomethionine is currently being developed.

Another aspect of the project is an analysis of variations in total selenium levels in the plasma, urine and feces both within and between individuals, using new software for the analysis of repeated measures when some of the data are missing. This information is important in deciding what measures can be used to determine selenium status.

SCREENING SECTION

The overall objectives of the Section are summarized in its functional statement:

- "Plans, conducts and analyzes independent and cooperative research studies in screening for the early detection of cancer;
- conducts methodologic research in statistics, probability and epidemiology with particular emphasis on techniques appropriate to the design, analysis, and modeling of randomized and observational studies in cancer screening and related areas;
- engages in independent and cooperative research to determine cancer natural history and risk characteristics of populations for application to the design and interpretation of early detection and related studies;
- maintains liaison with other agencies, organizations and professional societies concerned with cancer screening and related methodology in order to coordinate and optimize activities."

International Workshop on Information Systems in Breast Cancer Detection

In December, 1988, an International Workshop on Information Systems in Breast Cancer Detection was held in Rockville, Maryland under the sponsorship of the U.S. Food and Drug Administration (FDA) and the National Cancer Institute. Screening Section staff collaborated with officials at the FDA to organize this workshop. Participants came from Australia, Canada, Finland, Iceland, Italy, Hungary, the Netherlands, Sweden, the U.K., the USSR and the U.S. and included representatives of the WHO and UICC. The rationale for the workshop was the knowledge that a transition was underway in many countries from a preoccupation with efficacy issues related to mammography to the need for information on the organization, effectiveness and costs of screening as it is extended to large proportions of the female population.

Discussion was directed primarily at (1) developing a better understanding of how breast cancer detection is evolving in practice in different countries, and (2) initiating a process for the development of a data base containing key data elements from each country which could be used jointly or individually by the countries for evaluation of breast cancer detection. The papers presented provide a comprehensive overview of the status of breast cancer screening and the potential for generating information needed to assess the effectiveness of programs in action. The proceedings of this workshop will be published by Huber Press. The presentation and discussion of papers were followed by working group meetings aimed at identifying items of information on breast cancer screening that would be useful cross-nationally and within a country. The process that was started at the workshop is being continued through a working group of the participants and focuses on development of a uniform, minimum data set and methods for measuring changes on a national or regional level.

Studies in Cancer Screening (Z01 CN 00106-06 BB)

Data from several cancer screening studies are being collected and analyzed to gain a better understanding of the impact and consequences of such screening in various population settings. Staff are involved in design, monitoring, and data analysis aspects of these studies. The results can be used by the NCI in establishing cancer control policy. These data bases also provide an opportunity for the development and testing of new techniques for data analysis. The studies fall into two main categories: randomized trials and observational studies.

Randomized Trials

Three large-scale randomized trials have been conducted by the NCI to evaluate screening for breast, lung, and colorectal cancer. Staff participate in the analysis of completed studies and conduct of ongoing studies. The data base from the HIP breast cancer screening trial was used to address several scientific and modeling issues. This study demonstrated a 25% reduction in breast cancer mortality after 10 years as a result of screening with physical examination and mammography, and has served as the basis for NCI policy and studies in other countries. Analysis focused on the magnitude and duration of the benefit, age-specific effectiveness, and application to model development and validation. Data from the lung cancer screening trials conducted at Johns Hopkins University, Memorial Sloan Kettering Hospital, and the Mayo Clinic were edited and analyzed. Investigations included assessment of incidence and mortality information. The colorectal cancer screening trial at the University of Minnesota is currently in progress to evaluate testing for occult blood in the stool as an early detection maneuver for colorectal cancer. Staff participate in scientific consultation and ongoing data monitoring for this study.

Observational Studies

In collaboration with researchers from the Centocor Company, Duke University, Harvard University and the Karolinska Hospital in Stockholm, Sweden, the value of using the CA125 assay as a component in the early detection of ovarian malignancy is being studied. At this point serial evaluation of serum CA125 levels over a two year period and a follow-up of four years for 5000 women at least 39 years of age has been completed. The early results indicate the CA125 assay can be valuable for identifying women in a normal population that are at high risk of ovarian malignancy. Neuroblastoma is the most common solid tumor in children under age five, and interest has recently increased in screening for the early detection of this lesion. A consultative effort was initiated with investigators at the University of Minnesota who are coordinating a controlled study to evaluate screening for neuroblastoma. The test procedure involves measuring the urinary catecholamine metabolities vanillylmandelic acid (VMA) and homovanillic acid (HVA) in specimens

from infants in Quebec, Canada. Control populations will be drawn from the state of Minnesota and the Greater Delaware Valley.

Research in Cancer Screening and Statistical Methodology (Z01 CN 00105-06 BB)

The focus of this project is the development and refinement of statistical procedures for the design and analysis of cancer screening and related studies. Problems under investigation include an examination of analysis methods and endpoints for screening studies, assessment of case-control studies for screening evaluation, development of cancer screening models, and derivation of novel approaches to the analysis of categorical data. Each of these problem areas is common to screening and prevention studies in which the Division participates, but the methods for screening studies must address the special lead time and length biases inherent in screening programs.

Limited Mortality Analysis

The analysis of a cancer screening randomized trial (RCT) in which there is appreciable follow-up after the trial's screening intervention has ceased is difficult because the effect is diluted after screening ceases. This project considers the usual analysis of a screening RCT involving all individuals randomized and the problems caused by a long follow-up without screening. A limited mortality analysis based on subgroups of cancers diagnosed during defined periods from entry into the study was investigated. Statistical testing procedures were compared for the limited analysis and the usual population analysis. It was noted that a major issue is the determination of comparable groups of cancers required for the validity of the limited analysis.

Case-Control Studies

In recent years, case-control methodology has been suggested for evaluating screening programs and a few studies using such methods have been carried out for cervical, breast, lung, and stomach cancer screening. At issue are the accuracy and applicability of this design for the evaluation of screening. Initial research to examine case-control studies within randomized trials of screening has been completed. Estimates of the screening effect based on case-control methodology were compared to those based on the randomized trial design. Alternative definitions of cases, controls, and exposure were assessed. Data from the HIP breast cancer screening trial were used in this analysis. The results indicate the case-control methodology can be valuable in assessing the benefits of screening programs when exposure is defined as offered screening.

Current research is focused on the ability of the case-control study methodology to provide estimates of the true impact of screening on those screened. In the usual setting a case-control study of screening provides an estimate of the odds ratio of death for those screened versus those not screened. It was found that this estimate is subject to bias, and may overestimate or underestimate the impact of screening.

Stage-Shift Screening Model

A stage-shift cancer screening model previously developed has been expanded to include estimates of the variance of the stage shifts and the death benefits. The model allows one to estimate both the number of cancers shifted from their usual stage in the absence of screening to a lower stage and the size of the reduction in mortality by stage. Variances for these estimates were derived. Application of the model to the HIP breast cancer screening study indicated that most of the detected breast cancers are usual stage I and II breast cancers that have a poor prognosis, and that almost all of the mortality reduction due to screening is a result of these cancers being detected and treated earlier than usual.

Evaluating Screening for the Early Detection and Treatment of Cancer Without Using Data from a Randomized Control Group

New methodology has been developed for analyzing screening data when no data from a randomized control group are available. The main assumptions are (1) the case-fatality rate in the absence of screening can be estimated from an exogenous population and (2) given age, year of birth is not a predictor of diagnosis. Other methods require more stringent assumptions. As a check on the validity of the methodology, the estimated numbers of cases and deaths in the absence of screening based on data from persons offered screening in the HIP trial were compared with the corresponding observed numbers in a randomized control group. The agreement was good.

Cost-Benefit Analysis of Proposed Prostate, Lung, and Colorectal Screening Trial

An analysis has been undertaken to systematically evaluate the costs and benefits of a proposed trial to screen for prostate, lung, and colorectal cancers. Using priors elicited from experts, the analysis calculates the probability that the trial will indicate a significant benefit, be strongly negative, or be inconclusive. If the trial shows a significant benefit, a large number of people will start receiving screening, and many deaths will be averted. If the trial is strongly negative, a large number of people will stop being screened, and society will save millions of dollars otherwise wasted on an ineffective intervention. If the trial is inconclusive, the number receiving screening is assumed not to change.

Research in the Analysis of Missing Categorical Data

Many problems in the analysis of screening data can be formulated as problems in missing categorical data. Diagnostic tests often yield a categorical outcome and, for various reasons, information on the results of some tests are often not available for some subjects. A simple technique has been developed for obtaining closed-form maximum likelihood estimates for many important cases of missing categorical data.

Regression Models for Grouped Survival Data in the Presence of Possibly Informative Censoring

In many studies with a failure time endpoint, subjects are lost to follow-up for reasons possibly related to their survival time. Such loss to follow-up is called informative censoring. Previous methods for accommodating informative censoring have required strong parametric assumptions about the joint distribution of censoring and failure times. New methodology has been developed which requires many fewer parametric assumptions for the joint distribution of censoring and failure times. Identifiability is ensured by (1) restricting the association between failure and covariates and between removal and covariates, and (2) selecting a random subsample in which censored subjects are followed to determine failure.

Using Replicate Observations in Observer Agreement Studies

Observer agreement studies with categorical variables have not included replicate observations because no methodology was available for analyzing the resulting data. To overcome this problem, methodology has been developed which can handle replicate observer agreement data. This allows investigators to separate between-subject effects from within-subject effects. This, in turn, makes it possible to more easily improve observer agreement. A major application is toward improving agreement among pathologists.

Regression Models with Lag Effect for Cancer Screening Studies

A new regression model to analyze data from screening randomized trials is under development. This model incorporates a lag period before the screening effect begins to emerge, a situation

which has often been observed. The technique is a modification of the multiplicative hazard model used in survival analysis, which allows for an arbitrary time until the beginning of the screening effect and accounts for the impact of covariates. The methodology has the potential to provide a more sensitive statistical test of the screening intervention than other methods, which do not compensate for dilution of the effect. The cause of this dilution is the deaths occurring at roughly equal rates in both the intervention and control groups during the lag period before a screening effect, if there is one, begins to emerge.

Endpoints for Screening Evaluation

The population mortality rate is the only known unbiased endpoint for assessing the impact of cancer screening. Determination of this rate usually requires long term follow-up data. Results of screening studies could be obtained sooner and at less cost if the screening effect could be measured accurately using a short term endpoint which was a valid proxy or predictor of mortality. Suggested early endpoints include case survival and shift in stage distribution, but these are known to be influenced by lead time and length biases. A more promising outcome variable is the incidence rate of advanced stage disease. This research involves a comparison of this rate and other proposed proxy measures with mortality. Data from the HIP breast cancer screening trial and the NCI sponsored lung cancer screening trials are being used to address these comparisons.

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Intramural Project Summaries

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00100-07 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Albanes	Staff Fellow	CPSB, DCPC, NCI
Others:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
	B. K. Edwards	Biostatistician	SP, DCPC, NCI
	A. M. Hartman	Health Statistician	ARB, DCPC, NCI

COOPERATING UNITS *(if any)*
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Surveillance Program, DCPC

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.75	0.25

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (ATBC Study) is investigating the efficacy of daily oral alpha-tocopherol (50 mg) and beta-carotene (20 mg) in a double-blind, randomized 2x2 factorial design trial aimed at preventing lung cancer among 50-69 year old male cigarette smokers. The project is based on experimental and epidemiological research which demonstrates a potential preventive role for these agents. Recruitment took place between 1985-1988, and the trial will end in 1993 after an average follow-up of over 6 years. A postal survey screening for potential trial participants was sent to 291,000 men in southern Finland, and 76% responded. We invited the smokers willing to participate (43,000) to one of 14 study clinics, and over 29,000 were randomized into the study. Compliance to the one capsule daily regimen has remained very high (97% average), and the dropout rate averages 6% per year. Reduction of lung cancer incidence in the active agent groups is the primary study goal; differences in the occurrence of other cancers will also be evaluated. Several pilot studies in support of the trial have also been completed including a feasibility study, validation of study dietary questionnaires, and evaluation of skin yellowing and serum levels following beta-carotene administration.

This trial is being conducted collaboratively with the Surveillance Program of the Division of Cancer Prevention and Control and the National Public Health Institute of Finland. The project was previously entitled "U.S. Finland Studies of Nutrition and Cancer."

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00101-07 CPSB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Human Studies of Diet and Nutrition

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

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	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI
	G. Block	Epidemiologist	ARB, DCPC, NCI

COOPERATING UNITS *(if any)*

U. S. Department of Agriculture, Beltsville Human Nutrition Research Center; Surveillance Program, Biometry Branch, and Diet and Cancer Branch, DCPC; Armed Forces Institute of Pathology (M. Micozzi)

LAB/BRANCH

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.25	0.75

CHECK APPROPRIATE BOX(ES)

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☐ **(a1) Minors**

☐ **(a2) Interviews**

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The role of dietary factors in cancer prevention has been assessed in animal experiments, in human epidemiologic studies, and most recently, in prevention trials. For many of these agents, however, information is incomplete concerning their safety, toxicity, dose, form, bioavailability, pharmacokinetics, and mechanisms of action. To further define these parameters in humans, a cooperative research effort between the Beltsville Human Nutrition Research Center (BHNRC), U.S. Department of Agriculture, and the CPSB, DCPC, is being conducted. Initial efforts have focused on three nutrients which have shown the most promise for cancer prevention--selenium, fat, and beta-carotene.

A study of the kinetics of a single, oral dose of two forms of selenium in the fasting and non-fasting state was conducted in the first year. Current activities include evaluations of the safety/toxicity of selenium and form of ingestion among persons residing in seleniferous areas.

Studies examining the metabolic effects of changes in dietary fat and fiber have been conducted separately in premenopausal women, postmenopausal women, and men. These dietary changes are being related primarily to serum lipids, hormonal status, bile acid metabolism, and fecal mutagenicity.

Beta-carotene studies are examining the plasma carotenoid response to single and long-term ingestion of beta-carotene from either a capsule or from selected vegetables.

Studies of the effects of alcohol on hormonal status and of the influence of omega-3 fatty acids on prostaglandins are in progress, and studies of the kinetics of vitamin C are planned.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00103-07 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Use of Isotretinoin in Prevention of Basal Cell Carcinoma

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

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	A. M. Hartman	Health Statistician	ARB, DCPC, NCI
	G. Peck	Senior Investigator	DB, DCT, NCI

COOPERATING UNITS *(if any)*
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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0.00

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study is a 5-year, randomized, double-blind clinical trial designed to evaluate the effectiveness of low dosage levels of isotretinoin in reducing the incidence of basal cell carcinoma in a high-risk population, and to examine possible side effects associated with long-term administration of low doses of isotretinoin. The recruitment phase of the study has been completed and 981 subjects have been entered over 36 months at 8 participating clinical centers located around the country. At each center, subjects have been randomly allocated to intervention (10 mg/day) or control (placebo) groups.

The rationale for this study includes the following. Laboratory experiments have shown that retinoids administered to animals can prevent chemical carcinogenesis. In the experimental animals, retinoids were effective even if administered after exposure to the carcinogen, and therefore the prophylactic effect of the retinoids is believed to be in the postinitiation phase, i.e., during the promotion phase of carcinogenesis. Recent case reports have shown that isotretinoin can prevent the appearance of new basal cell carcinoma for 4 years in patients at higher risk of developing new tumors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 CN 00104-07 CPSB

PERIOD COVERED: October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: NHANES I Epidemiologic Follow-up Survey: Chemoprevention/Nutrition Aspects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

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	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*: This research developed as a collaborative effort by NCHS and various institutes at NIH: Biometry Branch, DCPC, NCI; NIH; NIMH; NIAAA, NHLBI; NINDS; NIDDK; NIAID; National Center for Health Statistics

LAB/BRANCH: Cancer Prevention Studies Branch, DCPC

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0

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- [x] (a) Human subjects
- [ ] (b) Human tissues
- [ ] (c) Neither
- [ ] (a1) Minors
- [x] (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the NHANES (National Health and Nutrition Examination Survey) epidemiologic follow-up survey was to conduct a longitudinal study of 14,407 adults originally surveyed in 1971-75 and to investigate subsequent health and mortality outcomes. Respondents were traced and re-examined. Information was obtained from hospital records, the National Death Index, and death certificates. Several cycles have now been performed. The inital NHANES follow-up survey was completed in 1984. A continued follow-up of the elderly (75 years of age or older) in this cohort was conducted in 1985-86, while the entire cohort was again followed in 1986-87.

The purpose of this intramural project is to examine the relation of chemopreventive, nutritional, and constitutional factors to cancer in the very large, representative population which NHANES offers. It provides an opportunity to examine these factors and potentially confounding or modifying factors in a prospective fashion, and to examine the effevtiveness of dietary agents which are currently of great interest for cancer prevention. The relation of baseline vitamin use, biochemical or nutritional measures, and subsequent health status will be examined.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00112-06 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Nutrition Intervention Studies of Esophageal Cancer in Linxian, China

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

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	W. Blot	Branch Chief	BB, DCE, NCI
Others:	J. A. Tangrea	Deputy Branch Chief	CPSB, DCPC, NCI
	A. Ershow	Staff Fellow	BB, DCE, NCI
	S. Dawsey	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Cancer Institute, Chinese Academy of Medical Sciences, Beijing, The People's Republic of China; Biostatistics Branch, DCE, NCI

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

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☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct two intervention trials using multiple vitamin-mineral supplements to evaluate the relationship between such supplements and esophageal cancer incidence and mortality. One trial is being conducted in patients diagnosed with esophageal dysplasia (n=3,400) and the other in the general population in a high-risk region (n=30,000). The effect of these supplements on regression/progression of esophageal dysplasia and total cancer incidence, total cancer mortality, and total mortality will be evaluated. These two studies are being conducted in Linxian (Henan Province) in the People's Republic of China (PRC). Linxian, a rural country with population 800,000 was selected because it has the highest rate of esophageal cancer in the world (greater than 100/100,000) and because there is suspicion that the population's chronic deficiencies of multiple nutrients may be etiologically involved.

This study is being conducted jointly by the Biostatistics Branch of the Division of Cancer Etiology and the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control at the NCI in collaboration with the Cancer Institute of the Chinese Academy of Medical Sciences.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00143-05 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Continued Follow-up of the Breast Cancer Detection and Demonstration Project

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI's:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
	R. N. Hoover	Branch Chief	EEB, DCE, NCI
	L. A. Brinton	Section Chief	EEB, DCE, NCI
Others:	C. L. Carter	Expert	CPSB, DCPC, NCI
	A. Schatzkin	Medical Officer	CPSB, DCPC, NCI
	C. A. Swanson	Staff Fellow	CPSB, DCPC, NCI
	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Environmental Epidemiology Branch, DCE
Early Detection Branch, DCPC (C. Smart)
Biometry Branch, DCPC (D. Corle)

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.5	0.5

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Breast Cancer Detection and Demonstration Project (BCDDP) screening program began in 1973 in 29 centers in 27 widely dispersed geographic areas of the United States. Initial screening was complete on over 280,000 women over a 2-year period. From the original 280,000 participants in the screening phase of the BCDDP, approximately 64,000 were selected for 4 years of long-term follow-up (LTF) beginning in 1978, to assess the biology and natural history of breast disease, and to test hypotheses relating to detection, etiology, and survival. Those selected for LTF included all breast cancer cases found during the screening phase, all benign breast cancer cases, all those recommended for biopsy, and a sample of "normals." The LTF database will facilitate the exploration of important questions regarding the etiology and natural history of breast cancer. The size of the subcohorts and breadth of data available on them make this population unique. The large number of cases of both breast cancer and benign breast disease with histologic information available should allow particularly useful analyses of several risk factors in relation to these conditions.

The first 5 years of LTF was completed in all centers in September 1986, and a further continued follow-up has begun.

This project is being conducted jointly by the Cancer Prevention Studies Branch of the Division of Cancer Prevention and Control and the Environmental Epidemiology Branch of the Division of Cancer Etiology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00145-04 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Breast Cancer Genetics Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and Institute affiliation)*

PI:	C. L. Carter	Expert	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
University of California at Berkeley (M-C. King)
Louisiana State University (R. Ellston)

LAB/BRANCH
Cancer Prevention Studies Branch

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.25	0.25	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The overall goal of this project is to further an understanding of the genetic as well as environmental influences that are involved in the etiology of human breast cancer. The specific aim is to test for genetic linkage between a large array of discrete, polymorphic genetic markers and the gene(s) for breast cancer in family data. The ultimate goal is to localize a gene or genes that predispose women in high-risk families to breast cancer. A sample of women with a strong family history of breast cancer who participated in the Breast Cancer Detection Demonstration Project (BCDDP) will be contacted and pedigree, vital status, health history, and epidemiological data will be collected from them and their family members. Fifteen to twenty families whose pedigree structure appears to be the most informative for use in linkage analysis studies will be selected. Blood will be collected from family members and analyzed for the presence of a number of genetic markers, including blood group antigens, red blood cell enzymes, plasma proteins, and restriction fragment length polymorphisms (RFLPs). Marker data results will then be used to perform computer generated linkage analysis.

This project started in September 1986 and will continue for 3 years. This project was previously entitled "Linkage of Classical and DNA Markers to the Susceptibility Gene for Breast Cancer."

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00146-01 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Nutritional Factors and Cancer in the Framingham Heart Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Schatzkin	Medical Officer	CPSB, DCPC, NCI
Others:	C. L. Carter	Expert	CPSB, DCPC, NCI
	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Boston University

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In recent years considerable interest has been focused on the possible relation between moderate consumption of alcoholic beverages and breast cancer in women. Five epidemiologic cohort studies and the majority of case-control studies have demonstrated a positive association between moderate alcohol consumption and breast cancer, with relative risks ranging from 1.5 to 2.0. Given the frequency of alcohol consumption among women in this country, even a risk elevation of 50-100% would translate into considerable breast cancer morbidity and mortality that would be attributable to drinking. Further epidemiologic investigation of this question is of high priority.

In this regard, the Division of Cancer Prevention and Control has funded a contract for the procurement of a cancer file based on the original cohort in the Framingham Heart Study. This ongoing prospective cohort study was initially set up to examine risk factors for coronary heart disease, stroke, and other cardiovascular endpoints. Data, including detailed information on alcohol consumption, have been collected for over 30 years. The creation of the cancer file has been successfully completed in the past year and is being used to examine a number of hypotheses relating nutritional factors to cancer, including alcohol use, body fat distribution, physical activity, and serum cholesterol.

A similar study (Z01 CN 00147-01 CPSB) is being conducted on children of the original cohort.

This study is being conducted collaboratively with investigators from Boston University.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00147-01 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Nutritional Factors and Cancer in the Framingham Offspring Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	A. Schatzkin	Medical Officer	CPSB, DCPC, NCI
Others:	C. L. Carter	Expert	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Boston University

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	0.25

CHECK APPROPRIATE BOX(ES)
- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Framingham Offspring Study has been undertaken in order to explore the relation between alcohol and breast cancer. This cohort study consists of 5,135 children (2,646 female, 2,489 male) of the members of the original Framingham Heart Study Cohort. The baseline examination period was 1972-77 (Cycle 1). Subsequent follow-up periods were 1979-82 (Cycle 2) and 1984-5 (Cycle 3), with Cycle 4 currently ongoing. Alcohol consumption, both frequency and amount by type of beverage, has been ascertained at each cycle. Information on socioeconomic status, and reproductive and family history has been routinely collected. These additional data are important in controlling for variables that might confound an observed association between alcohol and breast cancer.

Six hundred cancers (300 in both men and women) are projected (based on the application of SEER rates to the cohort). This includes approximately 100 breast cancer cases in women, 110 lung cancers (80 in men), and 110 colorectal cancers (60 in men).

A similar study (Z01 CN 00146-01 CPSB) is being conducted on the original cohort.

This study is being conducted collaboratively with investigators from Boston University.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00148-01 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Finland Studies of Nutrition and Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Albanes	Staff Fellow	CPSB, DCPC, NCI
Others:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
	B. K. Edwards	Biostatistician	SP, DCPC, NCI
	A. M. Hartman	Health Statistician	ARB, DCPC, NCI
	C. L. Carter	Expert	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
National Public Health Institute, Finland
Social Insurance Institute, Finland
Applied Research Branch, Surveillance Program, DCPC

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The important relationship of diet and nutrition in the development of cancer has become well known through various research efforts. Laboratory studies have shown cancer inhibitory function for various natural and synthetic nutrients in various models, which have been corroborated by human epidemiologic studies of nutrient intake, tissue levels, and cancer incidence. The objectives of these etiologic studies are to: (1) assess the role of fats, selenium, and vitamins A, E, and C in breast cancer development; and (2) evaluate the relation of intake of various nutrients to subsequent cancer, particularly breast, colon, and lung. The project includes two studies. The first is a breast cancer case-control study of fats, total calories, selenium, and vitamins A, E, and C. The role of various anthropometric measurements, genetic markers for breast cancer, and reproductive factors are being explored. The second project is a comparison of nutrient intakes in cases and reference subjects identified from an existing large cohort with prediagnostic baseline dietary histories. Associations between various dietary components and several cancers will be assessed.

These studies are being conducted collaboratively with the Surveillance Program of the Division of Cancer Prevention and Control and the National Public Health Institute and Social Insurance Institute of Finland.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00149-01 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Yunnan Tin Miners Lung Cancer Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
Others:	A. Schatzkin	Medical Officer	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Yunnan Tin Corporation
Cancer Institute, Chinese Academy of Medical Sciences
Division of Cancer Etiology, NCI

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	0.25

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

As part of our general collaborative studies in China and the feasibility study for a lung cancer intervention study among Yunnan tin miners, two lung cancer case-control studies have been conducted among the tin miners. The first, a prevalence case-control study, interviewed 107 living cases diagnosed between 1967-1984 and an equal number of matched controls. A second study includes 183 lung cancer cases incident in 1985 and 1986 among miners and an equal number of matched controls. Data concerning smoking, occupational exposures including radon and arsenic exposure, diet and other exposures were collected by personal interview. Analyses of risk by radon, tobacco, and arsenic in the prevalence study have been completed while analyses of the incident case-control study are ongoing.

These studies are being conducted collaboratively with scientists from the Cancer Institute of the Chinese Academy of Medical Sciences and the Labor Protection Institute of the Yunnan Tin Corporation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00150-01 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Esophageal Cancer Genetics Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. L. Carter	Expert	CPSB, DCPC, NCI
Others:	S. Dawsey	Staff Fellow	CPSB, DCPC, NCI
	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Chinese Academy of Medical Sciences
Division of Cancer Etiology, NCI
Division of Cancer Treatment, NCI

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The overall goal of this project is to develop an understanding of the genetic as well as environmental influences that are involved in the etiology of human esophageal cancer. In North Central China where rates of this cancer are highest in the world, a sample of families has been identified with extraordinary familial aggregation for the disease. The specific purpose of the first phase of these studies is to obtain existing pedigree and epidemiologic information on a limited number of these families, obtain additional data on the base population from which they were drawn, and initiate steps to prospectively follow these families for the development of cancer. Formal genetic and genetic/epidemiologic evaluations will include familial aggregation studies, studies of the transmission or segregation of the disease, and studies that compare lifestyle and dietary aspects between case and control families. Analyses of these data should provide a unique opportunity to understand the genetic and epidemiologic components of esophageal cancer.

This study is being conducted collaboratively by scientists at the Chinese Academy of Medical Sciences as well as scientists from the Division of Cancer Etiology and the Division of Cancer Treatment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00151-01 CPSB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
A Dietary Intervention Study of the Recurrence of Large Bowel Adenomatous Polyps

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI's:	A. Schatzkin	Senior Investigator	CPSB, DCPC, NCI
	E. Lanza	Senior Chemist	CPSB, DCPC, NCI
Others:	L. Freedman	Expert	BB, DCPC, NCI
	C. Clifford	Health Scientist Administrator	DCB, DCPC, NCI
	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI
	M. Maher	Research Study Coordinator	CPSB, DCPC, NCI
	J. Tangrea	Deputy Branch Chief	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Biometry Branch, DCPC
Diet and Cancer Branch, DCPC

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Large bowel adenomatous polyps present a unique opportunity to conduct an intervention trial because of the high prevalence rate in the general population, the high polyp recurrence rate in those who have undergone polypectomy, and the link between polyps and cancer. It is generally accepted that large bowel adenomas are a requisite precursor lesion for most large bowel cancers. Given the strong evidence for the polyp-cancer sequence, an intervention that reduces the recurrence of large bowel polyps would have a strong likelihood of reducing the incidence of large bowel cancer.

The major objective of this study is to determine whether an experimental large bowel cancer "risk reduction" diet (low fat, high fiber, vegetable- and fruit-enriched) will decrease the recurrence rate of large bowel adenomatous polyps. This will be a multi-center randomized controlled trial involving 2,000 men and women. Study participants will be randomized into either the experimental diet group or a control group (usual diet). Recruitment will take up to two years, and the follow-up time from randomization is four years.

The study has two secondary objectives: 1) to investigate the relation between the dietary intervention and several putative intermediate endpoints in large bowel carcinogenesis, and 2) to evaluate the correspondence between these intermediate endpoints and subsequent neoplasia (adenoma formation). Particular intermediate endpoints of interest include mucosal cell proliferation, ornithine decarboxylase, and mucins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00105-07 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Research in Cancer Screening and Statistical Methodology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. C. Prorok	Chief	SS, BB, DCPC, NCI
Others:	R. J. Connor	Mathematical Statistician	SS, BB, DCPC, NCI
	S. G. Baker	Senior Staff Fellow	SS, BB, DCPC, NCI
	D. L. Weed	Senior Staff Fellow	BMCCES, BB, DCPC, NCI
	K. C. Chu	Health Science Administator	CDB, CCO, DCPC, NCI

COOPERATING UNITS *(if any)*
Cancer Detection Branch, CCO, DCPC, NCI

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Screening Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	1.5	0.4

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

Analysis of data originally obtained from Human Subjects/Human Tissue

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The focus of this project is development and refinement of statistical procedures for the design and analysis of cancer screening and related studies. Problems under investigation include derivation and comparison of data analysis methods, assessment of case-control studies for screening evaluation, development of models of cancer screening, and approaches to the analysis of categorical data. Properties of case-control studies in the context of screening evaluation are being considered. Screening effect as estimated from a case-control study within a randomized trial was compared with the trial result as a standard, initially using data from the HIP study. It was found that the odds ratio from a case control study comparing screened versus not screened individuals is subject to bias and may underestimate or overestimate the impact of screening. Extensions were derived for a stage shift cancer screening model which uses the number of cancers diagnosed by stage in screened and control groups to estimate the number of cases shifted to earlier stages by screening and the mortality impact. Variances for the stage shift and mortality estimates were obtained. New methodology was developed for analyzing screening data when randomized control information is not available. The validity of the method was checked by comparing the estimated numbers of cases and deaths in the absence of screening using data from persons offered screening to the observed numbers in a randomized control group. Good agreement was observed. Regression models were devised to address two particular situations. The first is analysis of grouped survival data in the presence of possibly informative censoring. The new method requires fewer parametric assumptions for the joint distribution of censoring and failure times than previous approaches. The second is the analysis of screening trial data in which a lag period occurs before the effect takes place. The innovation here is a modification of the multiplicative hazard model used in survival analysis which allows for an arbitrary time until the beginning of the screening effect and accounts for the impact of covariates.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00106-07 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies in Cancer Screening

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. C. Prorok	Chief	SS, BB, DCPC, NCI
Others:	R. J. Connor	Mathematical Statistician	SS, BB, DCPC, NCI
	S. G. Baker	Senior Staff Fellow	SS, BB, DCPC, NCI

COOPERATING UNITS *(If any)*
Centocor Company (V. Zurawski); Harvard U. (D. Schoenfeld); Duke U. (R. Bast); U. of Minnesota (W. Woods); Karolinska Hospital (K. Sjovall)

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Screening Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.8	0.4

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Data from several cancer screening studies are being collected and analyzed to gain a better understanding of the impact and consequences of such screening in various population settings, and to develop new techniques for data analysis. Section staff are involved in various aspects of these studies, including design, monitoring, and data analysis.

The data base from the HIP breast cancer screening trial was used to address several scientific and modeling issues. Issues under investigation included the magnitude and duration of benefit, age-specific effectiveness, and application to model development. Data from the NCI sponsored lung cancer screening trials were analyzed. Investigations included assessment of incidence and mortality information. Monitoring continues of a trial to evaluate testing for blood in the stool for the early detection of colorectal cancer.

Staff are also involved in several observational studies of screening procedures. In collaboration with investigators from the Centocor Company, the value of using the CA125 assay as a test for the early detection of ovarian cancer is being studied. Preliminary results indicate that the test may be useful in identifying a population of women at high risk for ovarian malignancy. Evaluation of screening for neuroblastoma in infants is also being addressed in conjunction with investigators at the University of Minnesota. Staff are assisting with the design of a controlled study to assess the measurement of urinary catecholamine metabolites VMA and HVA as screening tests for this tumor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00107-07 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Design and Analysis of Pharmacokinetic Studies of Selenium

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. H. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
Others:	L. A. Zech	Senior Scientist	LMMB, DCBD, NCI

COOPERATING UNITS *(if any)*
Laboratory of Mathematical Biology, DCBD
Cancer Prevention Studies Branch, DCPC

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Selenium is a possible cancer preventive agent, and is being considered for use in intervention trials. A study in collaboration with the Cancer Prevention Studies Branch (Z01 CN 00101-07 CPSB) is in progress which will provide information on the pharmacokinetics of selenium in its prototype forms -- sodium selenite (inorganic form) and selenomethionine (organic form). This information is unavailable for these agents in the dose currently considered optimal, and is necessary to the determination of time and manner of administration. Parameters such as percent absorption, maximum concentration, time to maximum concentration, and mean residence times will be estimated for a single dose and compared in fasting and non-fasting subjects.

Integrated kinetic models are being used to interpret the study data more fully. Such models are useful in making inferences about drug metabolism and about the distribution of the drug in various body pools. A model of selenite has been developed based on pilot study data and is being used to analyze data from the main study. Various body pools have been hypothesized, and rates of exchange between them estimated, as well as mean residence times. Comparisons of rate constants for subjects when fasting and when non-fasting suggests that fasting status modulates the appearance of selenite in the plasma and that there is a greater first pass effect when the dose is given with food. A model for selenomethionine is being developed.

Another aspect of the project is an analysis of variations in total selenium levels in the plasma, urine and feces both within and between individuals. This information is important in deciding what measures can be used to determine selenium status.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00113-06 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cancer in Oriental Populations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. King	Research Sociologist	BMCCES, BB,DCPC,NCI
Others:	F. B. Locke	Statistician	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.8	0.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of Oriental populations represent the Division's continuing interest in the health risk among these minority groups for the mapping out of cancer prevention and control programs:

1. A time-trend study on cancer/non-cancer mortality is being completed of U.S. Chinese and Japanese, by nativity, compared to the host (U.S. white) and homeland populations (PRC, Hong Kong, Singapore, Taiwan for Chinese, and Japan for Japanese).

2. Assembling mortality/incidence figures on Asian populations from various sources, we are establishing an international file of cancer/non-cancer causes since 1960. These Asian resource data, age-adjusted and age-specific rates, also include figures for U.S. and "homeland" populations.

3. A companion mortality study of Chinese migrants to Taiwan and Singapore from Fujian to those who originated in Guangdong and settled in the U.S. and Hong Kong is being completed.

4. An analysis is underway correlating mortality from selected causes of death in 65 mostly rural counties in mainland China with various diet and lifestyle measurements.

5. As consulting reviewers of an oncology overview of abstracts of epidemiological studies of neoplasms among Oriental populations, an editorial was prepared covering a site-specific commentary on cancer epidemiology among Asians.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00115-06 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Descriptive Cancer Epidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. R. Connelly	Statistician	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*
Environmental Epidemiology Branch, DCE (P. H. Levine)
Radiation Epidemiology Branch, DCE (Z. Hrubec)
Clinical Epidemiology Branch, DCE (J. J. Mulvihill)

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The primary purpose of this project is to describe and evaluate the distribution of cancer occurrence in the United States in terms of age, sex, race, place, and time in order to identify subgroups of the population that offer possibilities for mortality reduction through intervention. Cancer incidence, mortality, and survival rates are analyzed using biostatistical techniques.

In collaboration with researchers in the Environmental Epidemiology Branch, serologic studies of HHV-6 antibodies in selected cancer patients and controls were evaluated. Adjusted for age and sex, antibody titers in acute lymphocytic leukemia and Hodgkin's disease do not suggest an etiologic role for HHV-6 in either disease.

In collaboration with investigators in the Radiation Epidemiology Branch, age-period-cohort Poisson regression models were used to analyze lung cancer mortality rates for World War I veterans of known smoking status. There was no evidence of a temporal decrease in lung cancer mortality as a result of the well documented reduction in smoking among U.S. males since the 1960's decade.

A retrospective cohort study, done in collaboration with investigators in the Clinical Epidemiology Branch, was designed to detect the effects of cancer and its treatment on childhood patients who survived to adulthood. Among survivors of malignancies at sites other than the central nervous system, 14% said that they had not had cancer and 19% of those who knew that they had cancer previously were unable to correctly identify the type of treatment they received. In another study based on this cohort, the quality of life in survivors of central nervous system tumors was found to be significantly reduced compared to their sibling controls. In a third study, the cigarette smoking habits of survivors treated by radiation above the diaphragm (with or without chemotherapy) were less likely to be smoking at last follow-up than their sibling controls, but survivors treated by other means smoked at the same rate as their siblings.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00116-06 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Statistical Methodology Research

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. B. Green	Chief	CDTS, BB, DCPC, NCI
Others:	D. K. Corle	Computer Systems Analyst	CDTS, BB, DCPC, NCI
	B. H. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
	Y. Wax	Expert	CDTS, BB, DCPC, NCI
	R. Carroll	Guest Researcher	CDTS, BB, DCPC, NCI
	E. J. Feuer	Operations Research Analyst	ARB, SP, DCPC, NCI

COOPERATING UNITS *(if any)*
Applied Research Branch, SP, DCPC, NCI
Information Management Services, Inc.

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.4	1.9	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to conduct research in statistical methods and computer techniques with particular emphasis on those appropriate for analyzing data from clinical, diagnostic, and prevention trials and epidemiologic studies of cancer. Many of the problems studied under this project arise from the consultative activities of the Section.

Important activities during the past year have included studying the effect of age on the diet-cancer relationship in epidemiologic follow-up studies; applying collinearity diagnostics to correlated dietary variables in relative risk regression models; accounting for the effect of measurement error and intra-individual variation in analyzing the relation of diet to breast cancer; developing a score statistic for non-informative censoring using doubly sampled survival data; nonparametric estimation of a bivariate distribution of time and a time-dependent variable subject to censoring; and comparing the results of maximum likelihood estimation using conditional and unconditional logistic models for matched sets.

Previous work on an interactive computer program for calculating sample size has continued. Finally, the Section has continued to maintain and improve software for interactive analysis of complex medical data using sophisticated multiple regression techniques and survival analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00119-06 BB

PERIOD COVERED
October 1, 1988 to September 30,1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Consultation on Clinical Trials and Other Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. B. Green	Chief	CDTS, BB, DCPC,NCI
Others:	D. K. Corle	Computer Systems Analyst	CDTS, BB, DCPC, NCI
	B. H. Patterson	Mathematical Statistician	CDTS, BB, DCPC, NCI
	Y. Wax	Expert	CDTS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*
Surveillance Program, DCPC; Smoking, Tobacco, and Cancer Branch, DCPC; Division of Cancer Treatment, NCI; Division of Cancer Biology and Diagnosis, NCI; Information Management Services, Inc.

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Clinical and Diagnostic Trials Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.9	0.4

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to provide consultation on statistical and epidemiological methodology in the design, interpretation, and evaluation of clinical trials of diagnosis, treatment, and prevention of cancer, and other studies requiring this kind of expertise. For some studies the Section provides full statistical support, including development of detailed study plans, assistance in the design of appropriate study forms, supervision of randomization (for trials) and collection, processing, and editing of data, performance of interim analyses during the progress of the study, preparation of progress reports, final analysis of study data, and collaboration in the preparation of scientific papers.

During the past year the Section has continued to collaborate extensively on the design and implementation of the Community Intervention Trial for Smoking Cessation; key activities during this year were analysis of data from the baseline survey and design of upcoming surveys. The Section has continued to provide full statistical support for the randomized clinical trials of multimodality treatment conducted by the Brain Tumor Cooperative Group.

Other important activities under this project include monitoring and analyzing results from the use of stored sera to evaluate new markers for breast cancer; investigating the daily consumption of fruit and vegetables in the American diet; and collaborating on a study of food purchasing behavior and consumer nutrition education, involving a supermarket-based intervention.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00121-05 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Research in Biostatistical Methodology and Mathematical Modeling

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. C. Brown	Chief	BMCCES, BB, DCPC, NCI
Others:	R. R. Connelly	Statistician	BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.6	0.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is development of biostatistical methods and mathematical models appropriate for the analysis of epidemiologic and experimental studies related to cancer control and prevention. Many of the statistical problems being studied under this project are derived from the consultation activities of the Section.

A mathematical model of drug resistance to anti-tumor agents has been developed. The model is an extension of the simple Goldie-Coleman model. This extension allows the birth, death and mutation rates of tumor cells to vary with time and also the possibility of additional treatment with an immunostimulant.

Statistical methodology is being developed to give unbiased estimates of the effect of treatment in a randomized clinical trial or cohort study for which important covariates are measured with error. In such a situation, standard statistical techniques give estimated effects which are biased toward zero, erroneously implying no effect.

Development has been completed of an easy to use SAS statistical procedure for normal theory regression of repeated measures data such as multiple blood samples taken from a number of subjects. This type of data is often found in DCPC studies and no computer program which properly handles missing observations had been available until now.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00122-05 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Cancer Control Epidemiologic Methods

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D. L. Weed Senior Staff Fellow BMCCES, BB, DCPC, NCI

COOPERATING UNITS *(if any)*
HPSB, DCPC, NCI (W. Mayer); NIOSH (T. Sinks); Fox Chase Cancer Center (B. Trock); Univ. Michigan (J. Koopman); Office of Protection from Research Risks, NIH (C. McCarthy); Mt. Sinai Medical Center (K. Ringen)

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Biostatistical Methodology and Cancer Control Epidemiology Section

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	0.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The development of the methods of cancer control epidemiology has focused on these areas: 1) studies in causal and preventive inference, 2) studies in interactions, 3) the analysis of epidemiologic reasoning, 4) the ethics of prevention, and 5) design of cancer control research studies.

Criteria for causal and preventive inference have been improved. Previous criteria fall into two categories: those dependent upon the specific form of the hypothesis and those independent of the form of the hypothesis. Two general criteria replace all existing criteria: predictability and testability.

Research underway includes 1) application of general criteria of epidemiologic inference to determine the status of hypotheses that dietary alcohol causes breast cancer, that dietary fat causes cancers, and that dietary fiber prevents colon cancer, 2) predicting magnitudes of effects from the sufficient component causes model and examining the role of magnitude of association in making inferences, 3) application of a new causal theory (epigenesis theory) to the evaluation of causal and preventive interactions, 4) application of a new method of epidemiologic reasoning (mega-analysis) to the use of case-control methods for screening; the use of negative results in causal inference; the debate regarding the use of p-values, confidence limits, and p-value functions; the role of complexity of causal inference; and the links between scientific, technologic and ethical reasoning, 5) a critical study of the ethics of epidemiology in advising for or against preventive interventions, and 6) defining criteria and issues of phase IV (defined population) studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 CN 00142-05 BB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cancer Control Objectives and Cancer Mortality Projections

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. L. Levin	Senior Investigator	BB, DCPC, NCI
Others:	L. G. Kessler	Chief	ARB, SP, DCPC, NCI
	J. Horm	Statistician	SPSB, CCSP, DCPC, NCI
	M. H. Gail	Statistician	BB, FSS, DCE, NCI
	A. Potosky	Operations Research Analyst	ARB, SP, DCPC, NCI
	L. Reis	Statistician	CSB, SP, DCPC, NCI

COOPERATING UNITS *(if any)*
Surveillance Program, DCPC
Cancer Control Science Program, DCPC
Biostatistics Branch, DCE

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Office of the Chief

INSTITUTE AND LOCATION
National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.1	0.1

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Projecting cancer incidence and mortality rates, and relating those projections to the attainment of national cancer control objectives are the goals of this intramural research project. The project includes development and continued refinement of a computer model which projects cancer incidence and mortality, meshing together data from a variety of sources, and adapting quantitative cancer control objectives to fit the modeling framework.

The NCI staff has developed and written a large interactive Fortran program for the NIH DEC-10 computer used to project cancer figures from 1980 through the year 2020. The model incorporates different models for survival from cancer, includes data for a number of cancer sites, the ability to examine temporal trends in underlying cancer incidence and mortality from other causes, adjustment of rates to different populations, and production of annual projections of cancer incidence and mortality. The crux of the model is the flexibility to analyze the effect of cancer prevention, screening, and treatment activities (in any combination) on cancer mortality.

Work in the current year has involved analysis of trials in breast and cervical cancer, projections on a state level, and updating of the basic underlying database used by the program.