Intramural Activities

October 1, 1989–September 31, 1990

Intramural report

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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NATIONAL CANCER INSTITUTE (U.S.)

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Intramural Project Summaries
(Forms 6040)

DIRECTOR'S REPORT

Intramural research is one of the foundation stones of the National Cancer Institute. This report describes the intramural research activities 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 the DCPC encompasses basic research on cancer prevention, cancer control research, public health applications research including technology transfer, and cancer surveillance—all aimed at the overall goal of the NCI: to reduce the incidence, mortality, and morbidity of cancer.

The Division of Cancer Prevention and Control conducts an array of cancer control research and applications encompassing the earliest stages of hypothesis development through clinical studies, clinical trials, defined population studies, and demonstration and evaluation studies. The Division's activities include research on prevention, evaluation of screening and early detection regimens, research on cancer among special populations, and research on rehabilitation and continuing care. One of the major emphases is cancer prevention research, with significant efforts (particularly in the intramural program) devoted to research on diet, nutrition, and chemoprevention. As outlined below, the DCPC's intramural program, housed in two Branches and a Laboratory, is rapidly expanding. The Division is committed to the concept that a strong intramural research program is essential to the conduct of highest quality extramural research.

ORGANIZATION

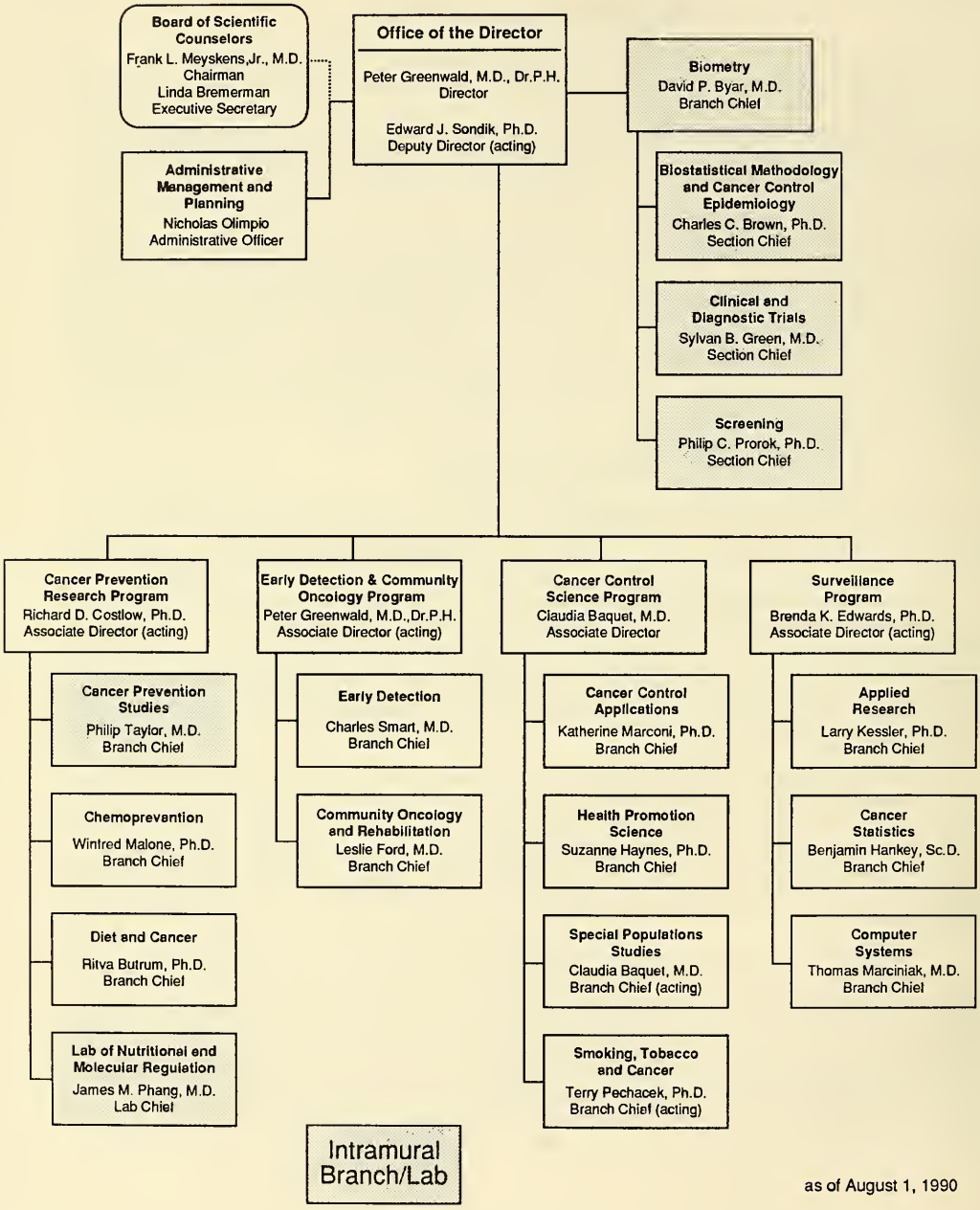
Figure 1 outlines the DCPC organization. The Division consists of four major programs, each led by an Associate Director. The Office of the Division Director provides overall coordination and direction as well as analytic program support. Each program is described briefly below.

The **Cancer Prevention Research Program** 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 of Nutritional and Molecular Regulation, two of the three intramural components in the Division. The Laboratory is located at the Frederick Cancer Research and Development Center (FCRDC) in Frederick, MD.

The **Early Detection and Community Oncology Program** supports the community-based clinical research programs, as well as early detection and rehabilitation research. These programs are designed to improve the delivery and application of state-of-the-art cancer regimens. The Program includes the Community Clinical Oncology Program (CCOP), which links community-based physicians with Cancer Centers and the Cooperative Groups to conduct clinical treatment research and cancer prevention and control research in community settings. Currently there are 53 funded CCOPs.

The **Cancer Control Science Program** 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 that suffer disproportionately from cancer, figure prominently in the Program's activities. The Program also directs a number of cancer control resource activities, including the National Black Leadership Initiative. The Program's Smoking, Tobacco, and Cancer Branch operates as a focus for NCI-wide research on smoking.

Figure 1. DCPC Organization Chart



as of August 1, 1990

The **Surveillance Program** is responsible for tracking and evaluating trends in cancer and for 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. Related efforts 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 two branches: the Biometry Branch and the Administrative Management and Planning Branch. The Biometry Branch conducts and supports intramural research using SEER and other epidemiologic data bases, intramural research in biostatistical methodology, and clinical trials research. The Administrative Management and Planning Branch assists in the management of the Division's budget and administrative matters. The Office of the Director also 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.

INTRAMURAL ACTIVITIES

Intramural research is an important component 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 the DCPC, the intramural research program is conducted through the Cancer Prevention Studies Branch (CPSB), the Biometry Branch, and the recently established Laboratory of Nutritional and Molecular Regulation. 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 **Laboratory of Nutritional and Molecular Regulation** (LNMR), also located in the Cancer Prevention Studies Branch, is now equipped and functional in space allocated at the NCI-Frederick Cancer Research and Development Center (NCI-FCRDC). It is anticipated that by the end of FY 90, a core of research staff will be aboard after a vigorous recruiting period. The LNMR's research will include drug-resistance as a model for cellular defense, nutrient-dependent modulation of signalling mechanisms in cell proliferation, and dietary perturbation of nutrient and carcinogen metabolism.

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.

One of the factors behind the strong research programs at the National Institutes of Health is the use of peer review in the development 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 Prevention and Control is no exception to that tradition and a vigorous, high-quality, peer-reviewed intramural program is anticipated to provide the necessary leadership.

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 intramural projects which were active during FY90.

Etiologic Studies:

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

The purpose of the NHANES (National Health and Examination Survey) Epidemiologic Follow-up Study (NHEFS) was to investigate prospectively morbidity and mortality outcomes among the 14,407 adults originally examined in 1971-75. The specific objective of this intramural project was to investigate a number of nutrition and cancer and cancer chemoprevention hypotheses in the NHEFS.

The NHEFS is a prospective cohort study created through a systematic follow-up of persons examined in the First National Health and Nutrition Examination Survey (NHANES I). NHANES I intended to investigate the health and nutritional status of the United States population, and was particularly targeted toward those population groups hypothesized to be at greatest risk of poor health and nutritional deficiency. The survey was carried out on a probability sample of the civilian noninstitutional population of the United States from 1971-75. NHANES I included a sociodemographic and medical history, a standardized medical examination, a dietary questionnaire (24-hour recall, with a crude 18-question food frequency questionnaire), hematologic and biochemical tests, and anthropometry.

A total of 14,407 men and women aged 25-74 were eligible for inclusion in the NHEFS cohort. Subjects were first traced and interviewed again for the NHEFS in 1981-84. Approximately 93% of the subjects were successfully traced and interviewed. The follow-up consisted of personal interviews with the subjects or proxies, weight and blood pressure measurements, and the acquisition of hospital and nursing home records and death certificates. The 1981-84 follow-up originated as a joint project between NCHS and the National Institute on Aging. Subsequently several institutes at NIH provided financial support, including the NCI's DCPC and DCE.

Results from NHEFS studies that have been published or in press include:

Dietary fat was not (or, for some analyses, was even slightly inversely) associated with breast cancer. This finding was derived from the 24-hour recall data and was based on 99 cases of breast cancer.

Moderate alcohol consumption (3 or more drinks per week) was positively associated with breast cancer. The association was stronger in younger, leaner, and premenopausal women. No data were available on beverage type or age of drinking.

Serum total cholesterol was inversely related to both cancer incidence and mortality in men and women, with the inverse relation being largely confined to smoking-related cancers. This inverse relation persisted six or more years after cholesterol determination, suggesting that the preclinical cancer hypothesis could not account fully for these findings.

Men and women in the lowest quartile of body stature were at reduced risk of cancer relative to those in the upper three quartiles. This association was present especially for cancers of the large bowel in men and women and breast in women.

In a study of self-reported physical activity and cancer, the risk of cancer was elevated in men and women who were very inactive compared to those who were active. Those sites demonstrating the strongest inactivity-cancer relations were large bowel and lung in men, and breast and cervix in women.

Mean total iron-binding capacity was significantly lower and transferrin saturation was higher among men who remained free of cancer. Similar but weaker (and nonsignificant) relations were found for women. Serum albumin was also found to be inversely related to cancer in both men and women

An excess risk of breast cancer was observed in relation to both stature and frame size in the NHEFS women. Body size defined by weight, relative weight, or skin fold measurements was not associated with an increased risk of breast cancer.

The relative risks for standard breast cancer reproductive risk factors were in general agreement with those observed in other studies. Family history and higher education were also found to be associated with an increased breast cancer risk.

In an investigation of a hypothesized association between constipation and breast cancer, breast cancer risk was found to be slightly increased in women with decreased frequency of bowel movements and firm stool consistency.

A small inverse relation was observed between both education and income and all-sites cancer in men and women. This inverse relation largely disappeared when adjustments were made for cigarette smoking.

Adult weight gain in women, as reflected in answers to questions on the lowest and highest adult weights, was found to be positively associated with breast cancer.

Serum retinol was inversely related to the risk of prostate cancer among men in the NHEFS cohort.

Follow-up of this cohort has continued. The 1986 follow-up of the elderly focused on the 3,850 subjects from NHANES I who were over 75 at the time of the 1981-84 follow-up. The 1987 follow-up was directed at all 12,385 members of the cohort who were still alive regardless of age. Interviews were completed in approximately 91% of subjects. Follow-ups are also proposed for 1991 and 1994 which would extend the period of observation of this cohort to an average of over 20 years.

Preliminary estimates indicate that the yield of cancer cases will increase by approximately 50% through the end of the 1987 follow-up, relative to the number of cases identified through 1984. Data from this follow-up should be available to us in early 1990. Since the 1981-84 follow-up interview ascertained information on drinking during 10-year age periods over a woman's life, the additional cases will enable us to examine the relation between alcohol consumption at various ages and subsequent breast cancer risk. Moreover, the food frequency questionnaire administered in 1981-84 can now be used in prospective fashion for subsequent cases so that the relation of, say, dietary fat to various cancers can be analyzed.

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.

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 in September 1986 in all centers, an initial continued follow-up of the LTF subcohorts was completed in 1990, and further follow-up is being planned.

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.

Nutritional Factors and Cancer in the Framingham Heart Study (Z01 CN 00146-02 CPSB)

The objective of this project was to develop a cancer data base within the Framingham Heart Study data set in order to carry out etiologic studies of nutrition-related factors and cancer.

The Framingham Heart Study was begun in 1948 to investigate risk factors for cardiovascular disease. The original cohort consisted of 5,209 men and women aged 30-62 at baseline who received biennial examinations consisting of medical histories, physical examinations, and a variety of laboratory tests.

CPSB collaborated with Boston University and NHLBI investigators to develop a Framingham Cancer file consisting of all incident malignancies developing during the lifetime of each of the cohort members. Over one thousand malignancies have been identified in this cohort, including over 150 breast cancers in women and nearly 200 large bowel cancers in men and women combined.

The initial impetus for investigating cancer as an endpoint in the Framingham Study was the alcohol-breast cancer hypothesis. Five epidemiologic cohort studies and a majority of case-control studies had demonstrated a positive association between moderate alcohol consumption and breast cancer, with relative risks in the range of 1.5-2.0. Framingham provided an opportunity to investigate this finding in another cohort study.

No association between alcohol consumption and breast cancer was observed in this cohort. It was not possible to exclude an excess breast cancer risk among women consuming more than one drink per day. It has been noted that the Framingham women were in their teenage years or 20's during Prohibition in the U.S. If alcohol were to affect breast carcinogenesis only when consumed during early life, then it is plausible that recent/later life consumption is a poorer proxy for early life consumption in the Framingham study than in other cohorts. The fact remains that this is the only null cohort study of alcohol and breast cancer to date. We are especially interested in examining this hypothesis in the Framingham Offspring Study.

The availability of cancer data for this cohort has made it possible to examine the relation between other nutrition-related factors and cancer. We have shown positive associations between body fat distribution (ratio of the sum of central/peripheral skinfold thicknesses) and breast cancer in women and between physical activity and large bowel cancer in men.

We are currently analyzing the relation of body size to large bowel cancer and serum lipoproteins to cancer. This latter study is an update, with specific lipoprotein fraction data, of earlier work in Framingham which showed an inverse cholesterol-cancer relation that persisted even several years or more after cholesterol measurement.

This study is being conducted collaboratively with investigators from Boston University and the National Heart, Lung and Blood Institute.

Nutritional Factors and Cancer in the Framingham Offspring Study (Z01 CN 00147-02 CPSB)

The objective of this project was to develop a cancer data base within the Framingham Offspring Study data set in order to carry out etiologic studies of nutrition-related factors and cancer.

The Framingham Offspring Study, begun in 1971, comprised 5,135 children (2,489 men, 2,646 women) of the original Framingham Heart Study cohort. The Cycle 1 (baseline) examination was carried out from 1971-77; the Cycles 2 and 3 examinations were conducted, respectively, in 1979-82 and 1984-85. The Cycle 4 examination is ongoing.

Interest in the alcohol-breast cancer hypothesis was again the primary rationale for collaborating with Boston University and NHLBI investigators in developing a cancer file in this cohort.

Two hundred forty-six (246) cancers, including 43 breast cancers in women, have been identified through Cycle 3. Case identification based on information from Cycle 4 is ongoing; this Cycle is expected to be completed over the next one to two years.

In addition to analyzing alcohol and breast cancer, it will be possible to examine the cholesterol-cancer relation in this cohort. Data on body size, diet (an intensive dietary history was administered at Cycle 3), physical exercise, and serum hormones (estrogen and testosterone—laboratory analyses are completed) will also be available for future analysis.

This study is being conducted collaboratively with investigators from Boston University and the National Heart, Lung, and Blood Institute.

Finland Studies of Nutrition and Cancer (Z01 CN 00148-02 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 also being explored. To date, basic hormonal and reproductive risk factors have been analyzed. Results support several of the established risk associations, and specifically identify total lifetime duration of menstrual activity as a determinant of breast cancer risk. 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 are being assessed. Analyses to date have revealed a significant inverse association between energy intake and breast cancer risk, and a significant positive association for energy-adjusted total fat intake and breast cancer. The fat association was more strongly associated with intake of mono- and polyunsaturated fats than saturated fats.

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 00149-02 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. Analysis of the case-control data on tobacco and radon exposure among the initial 107 cases indicated that there was a modest increase in risk with smoking, primarily for water pipe use; workers in the highest quarter of radon exposure had a 10-fold increase in risk compared to nonexposed workers; higher risk was associated with long duration as opposed to high rate of exposure; and risk was greater for radon as opposed to tobacco exposure. Analysis of the arsenic exposure data in these cases and controls found a strong linear dose response relation with a risk in excess of 20-fold for the highest quarter of arsenic exposure. When compared with tobacco, arsenic exposure was the greater risk in these data. Workers whose sole arsenic exposure came from underground mining had nearly the same risk of lung cancer as did

those with exclusively smelter exposure. Detailed quantitative modeling of a subset of these data found no modification of risk among workers with early age at first exposure. Analyses of risk by dietary and other variables in 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, the Labor Protection Institute of the Yunnan Tin Corporation, and the Division of Cancer Etiology at the NCI.

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, conducted collaboratively with scientists at the University of California at Berkeley and Louisiana State University, concluded this year.

Esophageal Cancer Genetics Studies (Z01 CN 00150-02 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 at the NCI.

Fels Early Nutrition and Growth Study (Z01 CN 00152-01 CPSB)

This project is designed to investigate the relation of childhood nutrition to breast cancer risk factors, including age at menarche, adult height, weight, and fatness. Secondary purposes include tracking the development of overweight and obesity from birth through young adulthood, identification of possible "sensitive" or high-risk periods (with respect to obesity) in childhood and, more important, to identify the contribution of diet to the development of childhood and adult obesity.

Detailed anthropometric data (height, weight, skinfold thickness, etc.) and demographic characteristics are currently available on a computer data base from the Fels Study and the Division of Human Biology of the Wright State School of Medicine. Up to 18 annual dietary and anthropometric assessments are available for "index" girls. Calorie, macro- and micronutrient data will be linked to an existing anthropometry computer file, including later adult height and weight. Nutrient composition will be calculated using the latest version of the USDA Handbook series. Nutrients will include the following: total energy (kilocalories); total fat, protein, and carbohydrate; saturated, polyunsaturated, and monounsaturated fat; cholesterol; dietary fiber; and vitamins and minerals (from food and supplementary sources).

This study is being conducted collaboratively with scientists at the Wright State School of Medicine in Yellow Springs, Ohio.

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 in this collaboration focused on three nutrients which have shown the most promise for cancer prevention selenium, fat, and beta-carotene. More recently, studies have examined alcohol, omega-3 fatty acids, and vitamin C.

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 was conducted to investigate the pharmacokinetics of selenium. Two distinct, complex, multicompartmental models have been developed to explain the kinetics of selenite and 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. In spite of the high selenium intake and serum levels in subjects from these areas, physical findings characteristic of selenium toxicity were not seen, and no association was observed between the various indices of selenium status and frequency of self-reported symptoms, hematologic or biochemical parameters, or abnormalities seen on photographs of nails. The relation of selenium status to age, gender, and current smoking has also been evaluated. Men and women had similar mean values of serum, whole blood, and toenail selenium despite higher intake among men. Smokers had lower tissue selenium levels than did nonsmokers due, at least in part, to lower selenium intake. Age was not associated with tissue selenium content in these subjects.

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 lengthening of menstrual cycle; 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. Results of lipid determinations indicate that total cholesterol, LDL cholesterol, and HDL cholesterol were 17-20% lower in men on the experimental as compared to the reference diet. The percent reductions in lipids were similar whether the men initially had total cholesterol levels of 200 or more or less than 200, suggesting that the cholesterol-lowering effect of the low fat/high fiber diet is not confined to men with markedly elevated cholesterol levels. Cholesterol was lowered on the experimental diet in all but one of the subjects, raising the possibility that cholesterol could be a valuable adherence marker in intervention studies involving a combined low fat/high fiber diet. The experimental diet, with 6.6% of calories from polyunsaturated fat, was associated with a 14% reduction in prostaglandin synthesis as measured by the urinary excretion of 7-alpha-hydroxy-5,11-dioxo-tetranorprostaten-1,16-dioic acid. These results support the hypothesis that dietary lipid changes can substantially alter the in vivo production of E-series prostaglandins.

Results from other aspects of this study can be be summarized as follows: Lipid phase fluidity, determined by DPH fluorescence polarization, increased significantly in VLDL, LDL, and HDL on the experimental, as opposed to the reference, diet. Intake and fecal excretion of calcium, magnesium, manganese, iron, zinc and copper were significantly higher on the experimental compared to the reference diet. Moreover, calcium, magnesium, zinc, and copper showed significantly higher apparent retention on the experimental diet, suggesting that a low fat/high fiber diet containing mineral levels above the recommended dietary allowance can result in positive mineral balance. A validation study that involved the administration of several physical activity questionnaires and the measurement of resting energy expenditure indicated that the estimates of individual energy expenditure was suboptimal for the questionnaires, but the questionnaires did provide reasonable group means for the various physical activity parameters. Results from analyses of fecal mutagenicity (especially the SOS test), hormones, bile acids, and cheek cell fatty acids (a potential marker of qualitative dietary fat intake) are still pending. Preliminary analyses indicate a small reduction in serum testosterone and more substantial significant reductions in urinary E2 and E3 on the experimental as opposed to the reference diet.

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.

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.

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.

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.

Vitamin C Study

There have been numerous epidemiologic studies of the relation between cancer and fruits, vegetables, or indices derived from them, and the vast majority have found significant protective effect for one or more fruits or vegetables. Despite the clear evidence regarding fruits and vegetables themselves, it cannot be said definitively which constituents of fruits and vegetables are protective. At least part of the difficulty in ascribing protective effect to specific nutrients is due to uncertainty about the nutrient content of foods as actually consumed. Vitamin C is one of prime candidates among the potentially protective nutrients found in fruits and vegetables. To better understand the bioavailability of vitamin C administered in different forms, including tablets, fruits, and vegetables, a controlled feeding study has been initiated.

Evaluation of the Effects of a Fat-Modified Diet on Hormones During Adolescence
(Z01 CN 00153-01 CPSB)

This study is ancillary to the Diet Intervention Study in Children (DISC), sponsored by the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute (NHLBI). DISC is a multicenter, randomized clinical trial designed to evaluate the feasibility, safety and efficacy of a fat modified diet during adolescence to lower LDL-cholesterol. The NCI sponsored ancillary study will evaluate the effect of this fat modified diet on sex hormones during adolescence. The effect of the diet on total concentrations of hormones and bioavailable fractions of hormones will be determined. The NCI sponsored ancillary study will also identify characteristics of adolescents that affect sex hormone levels and bioavailability of sex hormones; these include age, Tanner stage, anthropometric measures, physical activity, and dietary intake. Since a family intervention is being used, the effect of the intervention on sex hormone levels of parents of participants will also be assessed.

DISC is being conducted as a cooperative agreement between NHLBI, six clinical centers, and a coordinating center. The first participants were randomized into the feasibility study in the spring of 1988 and recruitment will be completed by the summer of 1990.

Five of the six DISC clinical centers have agreed to participate in the NCI sponsored ancillary study on hormones. This will yield approximately 540 participants equally divided between the intervention and control groups. Children enrolled in the trial must be girls 7.8-10.1 years old or boys 8.6-10.8 years old who have LDL-cholesterol levels between the 80th and 98th percentile but who are otherwise healthy. Dietary goals for the intervention group are to limit fat intake to 28 percent of calories and increase the ratio of polyunsaturated to saturated fats to approximately 1. Cholesterol intake will be restricted to 75mg/1000 calories. Children in the control group follow their usual diets.

Currently, DISC is funded through 1993 which will allow a minimum of three years of follow-up. Additional follow-up beyond 1993 is also being considered.

This study is being conducted collaboratively with scientists from the National Heart, Lung, and Blood Institute in Bethesda, MD; Children's Hospital in New Orleans, LA; Johns Hopkins University in Baltimore, MD; Kaiser Center for Health Research in Portland, OR; Maryland Medical Research Institute in Baltimore, MD; Medical College of New Jersey in Newark, NJ; Northwestern University in Chicago, IL; and University of Pittsburgh in Pittsburgh, PA.

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 13 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 less than 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 (through 1988), 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 atrophic 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.

The 3-year intervention phase of the study ended on June 30, 1990. Major statistical analyses are underway with public release of findings expected in early 1991.

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.

The active intervention phase of these two trials will conclude in the spring of 1991 at which time additional cytologic and histologic surveys are planned. An additional 5 years of post-intervention follow-up is also being planned for trial participants.

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 00151-02 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:

Many studies of diet and cancer demonstrate inconsistent results. Reasons for these inconsistencies include both difficulties in assessing exposure due to the complexity and variation of our diets, as well as the relatively small increases in risk being estimated. Although dietary assessment methods will continue to be refined, it seems desirable to attempt to deal with the problem of measurement error in studies of small relative risks by prospectively studying very large groups. We are presently evaluating the possibility of assembling a large cohort for studying diet-cancer relations, especially in men.

While it is clear that certain malignancies are hormone dependent, the role of hormones in the development of cancer has not been conclusively demonstrated. The development of assays which focus on bioavailable (as opposed to total) hormone levels have opened up new opportunities for evaluating the hormone-cancer relation. We are considering ways to use prospectively collected blood samples from extant cohorts to study this relation.

New, more specific data on carotenoids in foods are now becoming available. These data (and additional more detailed data of this type that may become available in the future) will be used in conjunction with dietary and biochemical assessment and cancer incidence data from existing epidemiologic data bases to reexamine the role of individual carotenoids in the etiology of cancer.

A large number of studies have shown that increased body size is associated with an increased risk for cancer, especially cancer of the breast. The direct relation of height to cancer suggests a role for remote nutrition, particularly total caloric intake during growth, in carcinogenesis. We plan to further explore the hypothesis that body size is related to cancer in other study groups and look at potential mechanisms of action. We also plan to examine in detail the relation of diet to body size among children and potentially address some methodologic questions about the assessment of dietary intake in youth via questionnaires administered to adults.

Obesity, weight gain, and the central location of body fat (as opposed to peripheral) have also been associated with increased risk for breast cancer. Further work is planned to evaluate these observations in other groups and to examine potential mechanisms of action.

The alcohol-breast cancer relation is still unresolved. Results from our own studies have been inconsistent, but the majority of epidemiologic evidence still supports the hypothesis. Further, more refined epidemiologic investigations of the question are warranted. The questions of timing of exposure and type of alcohol used need additional study, and plausible mechanisms of action need to be further explored.

Clinical Nutrition Studies:

In addition to assays of bioavailable hormone fractions, other new assays have been developed for metabolic products of estradiol, such as 16-hydroxyestrone. Measurement of these metabolites among subjects participating in controlled dietary studies should allow us to draw conclusions about dietary-induced changes in metabolic pathways that may affect carcinogenesis. Such evaluations can be done in new as well as previously conducted studies.

The effect of diet on hormone levels has been a major theme in our studies of fat reduction among adults, but an area of equal concern is what effect diet has on hormone levels in children. The proposed ancillary study to the DISC study is the first intervention among children in which we have participated. It should offer a number of useful scientific insights on this subject as well as provide us with information on the logistics of handling such studies in children.

There are a number of questions about carotenoids that need to be answered and can best be addressed using clinical nutrition studies. Serum alpha- and beta-carotene levels have consistently been found to be lower in men, smokers, and drinkers, and it is unknown whether this is due to differences in dietary intake or whether there are also metabolic differences. There appear to be some individuals whose blood levels of carotenoids do not rise appreciably in response to single doses of carotenoids given either in food or pills, and the reasons for this nonresponse are unknown. Little is known of the kinetics of any of the individual carotenoid components other than beta-carotene. In a number of the clinical nutrition studies that have been completed, assessment of carotenoid status will be undertaken in relation to prestudy dietary intake and response to the intervention. Additionally, the components of variation in plasma carotenoids among individuals will be examined. Finally, exploration of the absorption and metabolism of carotenoids in humans using carbon-13 stable isotopes is being planned.

Controlled dietary studies offer unique opportunities to evaluate potential markers of compliance that can subsequently be applied to large intervention studies with cancer or a premalignant condition as an endpoint. We have evaluated several such markers already and expect to explore other potential markers using both new and old samples. Specific carotenoids might, for example, be good markers of vegetable intake in general or specific vegetables in particular.

Prevention Studies:

The ATBC Trial is not scheduled to complete active intervention until March of 1993. While the primary endpoint of the trial is lung cancer incidence, other cancer and noncancer endpoints will be examined in relation to the intervention. This study also can be viewed as a large, prospective study of diet and cancer in which baseline and at least one interval serum sample have been collected. Other cancer sites of particular interest in this cohort are prostate and stomach. We will continue at least passive follow-up of this cohort through the Finnish cancer registry after the intervention has been completed. Some form of active follow-up is also under consideration at this time.

The ISO-BCC Study will conclude active intervention this June (1990) and an average of two years non-intervention observation follows. In addition to evaluating the primary objective of the trial, the effect of isotretinoin on incidence and multiplicity of basal cell tumors among participants, we should also be able to describe the natural history of basal cell and squamous cell skin cancer, the effect of isotretinoin on squamous cell skin cancer, the potential skeletal toxicity and lipid effects of long-term, low-dose isotretinoin therapy, the natural history and evolution of skeletal hyperostosis in the control population, as well as further elucidating the risk factors (including diet) for basal and squamous cell skin cancers.

The Linxian nutrition intervention studies will conclude active intervention in March and April of 1991 and a 5-year post-intervention follow-up is being planned. The large number of evaluations of intermediate endpoints already in process or planned will continue to keep us very busy analytically with these trials for several years to come. Pre-trial sera and dietary assessments were collected and offer the opportunity to examine micronutrients and other variables prospectively in the trial cohorts.

The polyp trial is just getting underway and is planned to run through 1997.

As a group, the synthetic retinoids remain one of the most promising group of cancer chemopreventive compounds. We expect to continue to explore various potential opportunities for testing these compounds in very high risk groups such as the tin miners in China, or among patients with recurrent bladder tumors.

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CANCER PREVENTION STUDIES BRANCH BIBLIOGRAPHY

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LABORATORY OF NUTRITIONAL AND MOLECULAR REGULATION

OBJECTIVES

With the addition of a new Laboratory Chief, the Laboratory for Nutrition and Cancer Research was changed to the Laboratory of Nutritional and Molecular Regulation. The objectives of the Laboratory of Nutritional and Molecular Regulation, currently being established at the Frederick Cancer Research and Development Center, are summarized in the functional statements below:

The overall objectives of the Laboratory of Nutritional and Molecular Regulation:

- Plans, develops and conducts intramural basic research on cellular and molecular regulation relevant to nutrition and cancer.

- Performs research studies in biochemistry, cell biology and molecular biology relevant to nutrition and cancer emphasizing the mechanisms by which nutrients, directly or indirectly, augment or inhibit tumorigenesis.

- Formulates and tests heuristic models on nutrition and cancer by studying the absorption and conversion of dietary substances in metabolic studies in animals.

- Investigates the applicability of these models to cancer prevention in humans by measuring plasma or cellular levels of metabolic intermediates, nutrient-derived effector molecules, circulating hormones and/or growth factors in healthy humans undergoing dietary manipulations.

- Contributes scientific back-up to the Institute's programs in research on diet, nutrition and cancer, and serves as a focal point for new information pertaining to nutrition research.

Areas of research emphasis and specific objectives of the Laboratory of Nutritional and Molecular Regulation:

- Studies on cellular resistance to carcinogens; modulation by nutrients and hormones. The mechanisms demonstrated for drug resistance with the efflux pump mediated by P-gp 170 encoded by the mdr gene serve as a useful model. Preliminary results indicate that carcinogens and certain nutrients are processed by this mechanism. Activation and detoxification mechanisms dependent on NADPH generation by glucose-6-phosphate dehydrogenase also are being studied.

- Studies on effects of nutrients on cell signaling mechanisms modulated by metal-dependent redox mechanisms, retinoids and metabolic intermediates, e.g. pyrroline 5-carboxylate, the intermediate in the interconversion of proline, ornithine and glutamate. Ongoing studies show that pyrroline 5-carboxylate participates in cell-cell communication modulated by certain growth factors.

- Studies on physiologic metabolism of retinol using multicompartmental analysis of radioretinol kinetics perturbed by dietary levels of vitamin A and by analogues, e.g. N-(4-hydroxyphenyl)retinamide.

- Studies on physiologic processing of dietary carcinogens. Formation of DNA-adducts in animals fed low-dose carcinogens and modulation by dietary fat and fiber will be investigated.

- Studies on metabolic regulation of post-translational modification of oncoproteins. Regulation of the cholesterol biosynthetic pathway and its effects on farnesylation of $p21^{ras}$ are of special interest.

- Identification and characterization of fiber components and fermentation products as agonists or antagonists of colonic mucosa cell proliferation.

Progress in establishment of the Laboratory and recruitment of scientific staff:

- A component of the Laboratory of Nutritional and Molecular Regulation moved from Bethesda to Frederick in late January 1990 and recruitment of scientific personnel was assigned high priority. The LNMR has recruited a Senior Investigator and a complement of Senior Staff Fellows and Postdoctoral Fellows. Arrival of this scientific staff is expected by October 1990. Planning and renovating the laboratory space at the Frederick Cancer Research and Development Center and acquiring the necessary equipment and facilities should complete this phase for establishing the LNMR.

LABORATORY OF NUTRITIONAL AND MOLECULAR REGULATION STAFF

Branch Chief	James M. Phang, M.D.
Senior Investigator	Grace C. Yeh, Ph.D.
Biological Lab Technician	Charles M. Poore
Chemist	Sylvia J. Downing
Medical Staff Fellow	Bruce A. Semon, Ph.D., M.D.
IRTA	Kevin C. Lewis, Ph.D.
Senior Staff Fellow	Thomas T.Y. Wang, Ph.D.
Visiting Fellow	Joanna R. Lopaczynska, M.D.
Secretary	Iva C. DeArmon

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:

Screening Trial for Prostate, Lung, and Colorectal Cancer in Males (PLC Trial)

During the past year the staff of the Biometry Branch has been in continual collaboration with the Early Detection Branch and the Research Contracts Branch in developing the Project Plans and RFPs for the three major components of the PLC Trial, namely the Study Coordinating and Data Management Center (CC), the Screening Centers (SCs), and the Laboratory to perform blood testing and storage. This is 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—lung, prostate, and colorectal cancer. The trial design calls for a total sample size of 100,000 males between the ages of 60 and 74 who are to be divided at random into two groups. One group will be screened for prostate, lung, and colorectal cancers while the other group will serve as a control. The screening techniques to be used are annual digital rectal examination and prostate specific antigen for prostate cancer, annual chest film for lung cancer, and annual digital rectal examination and three-yearly flexible sigmoidoscopy for colorectal cancer. The concept for this trial was approved at the October 12, 1989 meeting of the DCPC Board of Scientific Counselors. The RFP for the CC was issued on May 24, 1990 and the RFP for the SCs is scheduled to be issued on August 11, 1990. The RFP for the lab will be issued about three months later. Award of the CC contract and initiation of the trial is planned for January, 1991.

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.

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 a first version has been completed. One hundred and twenty 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).

The task of continuing the Inventory and its regular updating is being undertaken by staff in the Surveillance Program.

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 (J Natl Cancer Inst 1989;80:1442-4) 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.

Validation of Intermediate Endpoints for Cancer Research

Because of the long duration from initiation to development of overt malignancy and the relative rarity of malignant disease, primary and secondary cancer prevention trials involve large numbers of subjects followed over many years. There is considerable interest in finding biomarkers which are intermediate endpoints for cancer and which may be reliably used as a surrogate for the cancer endpoint in a prevention trial. Statistical methods for developing and validating potential surrogates are being formulated, drawing together previous work on causal inference in epidemiology, attributable proportion, and surrogate endpoints in cancer treatment trials. This work is being done in conjunction with other staff of DCPC and also from NCI's Division of Cancer Etiology.

Trial Designs for Investigating More Than One Treatment

Efficiency in clinical trial design is becoming increasingly important in view of funding limitations. In this project, three types of design have been identified which enable investigators to investigate more than one treatment in the same trial—the factorial design, the reciprocal-control design, and the all-or-none design. The possible uses of the designs in cancer prevention research have been described and examples have been given.

Sample Size for Cohort Studies

Cohort studies for investigating the relationship between dietary intake and cancer depend upon the measurement of intake of nutrients by simple methods such as a food frequency questionnaire. It is known that such ascertainment methods give imperfect measures of the long-term average intake. A method to calculate the sample size for such a study has been developed and takes into account the case where the range of intakes in the cohort has been estimated in a baseline survey using the same imperfect measure of intake. This method is being used for the planning of a proposed cohort study in an elderly population to be conducted through the American Association of Retired People.

AIDS Research

Staff of the Biometry Branch are collaborating with staff of the National Institute of Allergy and Infectious Disease on several AIDS-related projects including development of an observational database covering 42 centers belonging to the Community Based Clinical Trials Network (composed of members of the Community Program for Clinical Research on AIDS and the American Foundation for AIDS Research.) Dataforms have been developed and are currently being tested in a pilot study before development of final versions.

Cancer Control Objectives and Cancer Mortality Projections (Z01 CN 00142-06 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 conversion of the program from the DEC-10 to the Convex computer (NIH's replacement for the DEC-10), calculation of rates to different standard populations, calculations of expected cases for individual tumor registries, and detailed analyses for several sites such as breast and ovarian 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 U.S. Department of Agriculture, data from a series of feeding studies are being evaluated. These studies include 1) plasma cholesterol in men eating high fat, low fiber or low fat, high fiber diets; 2) the influence of dietary fat on fecal mutagenicity in premenopausal women; 3) plasma and urinary hormones in men eating high fat, low fiber or low fat, high fiber diets; and 4) the effect of alcohol ingestion on hormonal status in women.

In collaboration with the Applied Research Branch (ARB), the association between prostate cancer incidence rates and the rate of transurethral prostatectomy was examined in order to explore reasons for the dramatic increase in incidence rates from 1973-1986. The analyses suggest that the increase in use of this surgical procedure, commonly used to relieve urinary obstruction due to benign enlargement of the prostate, is the primary reason for the reported increase in prostate cancer incidence.

A second project with the ARB (described in more detail on the next page) involves designing a methodology to periodically evaluate the accuracy and responsiveness of the nationwide network of the Cancer Information Service by using sham telephone inquiries. False scenarios are currently being developed and will be evaluated for their ability to test reliability and validity.

In a third collaboration, 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. A computer program for fitting regression models to repeated Poisson count data has been developed for this analysis. Early tentative results show a positive effect in a subset of the study group who are at particularly high risk.

In consultation with the Health Promotion Science Branch, statistical sampling design guidance is being given to the two initiatives, Cancer Control in Primary Health Care and Worksite Health Promotion Intervention. Two-stage cluster sampling methods are being proposed for both studies. The first stage clusters are defined as physician practice and worksite, while the second stage sample involves patients and employees, respectively.

Research in Biostatistical Methodology and Mathematical Modeling (Z01 CN 00121-06 BB)

Evaluating the Effect of Heterogeneity in Survival Analysis

The assumption of "proportional hazards" is commonly made when analyzing the effects of different factors which may be related to survival in a cohort of patients treated for cancer. Parametric models such as the Exponential or Weibull, and semi-parametric methods such as Cox regression are often used for these analyses. Variability in patient mortality is commonly modeled by assuming the scale parameter in the parametric models and the underlying hazard function in the semi-parametric models to be functions of risk factors being studied. However, unexplained extraneous hazard rate heterogeneity among these patients can produce substantial deviations from this proportional hazards assumption. This research will fit Gamma-mixtures of individual Weibull survival models to survival data from the Surveillance, Epidemiology and End Results Program in order to estimate the degree of heterogeneity and its effect on the hazard ratio over time.

Evaluating the Proper Time Metric for Cox Regression of Follow-up Studies

Cox regression methods are commonly used for the analysis of cancer incidence and mortality in a defined cohort of individuals such as the follow-up of the National Health and Nutrition Study. Follow-up time since the start of the study is often used as the underlying time metric. However, because carcinogenesis theory implies that age at risk is often a more valid metric, this research will evaluate any bias induced by using the incorrect metric. Simulation methods will be used to estimate the bias as a function of the true relative hazard and the length of the follow-up period. Adjusting for age at start of the study will also be examined. In addition, the bias induced by incorrect age-adjustment for an age-related risk factor, such as many different dietary components, will also be evaluated by simulation.

Using the Kappa Statistic to Estimate Required Sample Sizes for Measuring Reliability

The Kappa statistic, $\kappa = \frac{P_o - P_e}{1 - P_e}$, is commonly used to gauge the ability of two different categorical measuring devices to give equal measurements when applied to the same item (P_o and P_e are the observed and expected proportions, under random agreement, of items on which the two devices give the same measurement). This is a project to develop methodology for estimating the necessary sample size n,m (n is the number of measuring devices and m is the number of items being measured) of a reliability study to test the hypothesis that the true kappa, κ, is at least as large as κ_0 with specified errors α and $1-\beta$. The results of this research will be used to develop sampling methods to evaluate the accuracy of information available through the national Cancer Information Service.

Descriptive Cancer Epidemiology (Z01 CN 00115-07 BB)

Age-Period-Cohort Analysis of Brain Cancer Incidence in SEER Areas

A marked increase in brain and central nervous system cancer incidence rates during the 15-year period 1973-1987 in Surveillance, Epidemiology and End Results (SEER) Program areas was investigated using age-period-cohort models. Separate analyses for white males and white females aged 15-84 at diagnosis show similar patterns: little effect of period (year of diagnosis) and a significant effect of cohort (year of birth). The age-cohort model provides an excellent fit to the data for both sexes. After adjustment for cohort effects, there is no marked downward curvature in age effects for those over age 65, a phenomenon that is often seen using age-period models. Whether or not improvement in the diagnosis of these cancers over time, especially among the elderly, accounts for the observed pattern in incidence rates is being investigated.

HHV Antibodies in Hodgkin's Disease Patients

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 Hodgkin's disease patients were evaluated. Serum samples were taken from each of 37 patients with Hodgkin's disease at the time of diagnosis and at 1-, 3-, and 5-years of follow-up whenever possible. Due to some missing observations, classical analytic methods for repeated-measures experiments could not be used. Maximum likelihood methods were employed and showed a declining HHV-6 antibody pattern for patients who responded to therapy and went into long-term remission, whereas patients with more severe disease had increasing antibody titers.

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.

The risk for early menopause among female members of this cohort was determined and compared to the risk found among sisters of the childhood cancer survivors. Survival analysis methodology was used to estimate the proportion still menstruating as a function of age and to examine other factors affecting the hazard of menopause under the proportional hazards model. Survivors were found to be at an increased risk for early menopause. The risk was primarily a function of age and the type of treatment received for cancer. Women treated with radiation below the diaphragm and alkylating-agent chemotherapy had a 25 fold excess risk over sibling controls during ages 21-25. This excess risk decreased later in their lives but still remained high compared to their sisters.

In another study based on this cohort, development of the cigarette smoking habit among 1,406 survivors who were nonsmokers when their cancer was diagnosed was compared to that among 2,236 sibling controls. Using conditional maximum likelihood methods, the smoking rate at last follow-up among survivors was found to be 79% of the rate among controls, a statistically significant deficit. The sex, time period of diagnosis, and type of cancer of the survivors were shown to have a strong influence on their smoking rate. It is suggested that even more innovative approaches should be used to educate young cancer patients not to smoke.

Cancer in Oriental Populations (Z01 CN 00113-07 BB)

Mainland China - 65 County Study

An in-depth diet, lifestyle, and mortality study of 65 mostly rural counties is being carried out by researchers in China and elsewhere. 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 were made available to us, together with 1975 mortality data, for an analysis on selected causes of death.

Initially, we have correlated various measures (nutritional status, reproductive history, etc.) with several components of cardiovascular diseases. We noted several statistically significant relationships among the mainland Chinese that have also been observed in the U.S., such as negative associations of cardiovascular disease with oleic acid (unsaturated fat), liquor (at lower or moderate levels), and legumes, and positive associations with salt, triglycerides, and herpes virus infection. Other associations not previously noted were negative correlations of molybdenum and age at first pregnancy, both also negatively related to certain neoplasms.

Migrants to Taiwan from Fujian Province

Analysis of mortality data for the Taiwan population (originating in Fujian province on mainland China) has been completed. 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.

Histologic and Sub-Site Distributions of Asian-American Cancer Cases

While site-specific cancer rates are the primary method of cancer epidemiologic study, histologic and sub-site analysis within sites is an important additional tool that may reveal other information useful in examining the etiologic significance of risk factors. Such differences have been documented for some sites, particularly lung. With 15 years of data accumulated in the Surveillance, Epidemiology and End Results (SEER) Program, we are reviewing these distributions for Chinese, Japanese and Filipino populations, and comparing them to whites.

Our analysis so far had indicated major differences for cancers of the esophagus, stomach, colon-rectum, lung, and breast. Esophageal cancer rates, for example, which remain high in Asia, are similar to those of U.S. whites. Yet, despite this similarity, substantial histologic and site-specific differences exist between the two groups. As a corollary to the Asian-American analysis, data for the black population are being analyzed in detail as well.

Asian Resource Data

A statistical file of age-specific and age-adjusted (using several different standards) 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, with the exception of homicide, the trend is downward for both nativity groups and sexes. 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 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 when 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, when 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, *Selected Abstracts on Recent Epidemiologic Studies of Neoplasms Among Asians* was published. 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 15-20% of the time. We will explore the possibility of improving reporting of this important variable.

2. Upon completion of our correlation analysis of mainland Chinese cardiovascular disease mortality with diet and lifestyle measurements, we hope to follow up with studies of selected cancer sites.

3. 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.

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 00116-07 BB)

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

In analyzing data such as that obtained from the National Health and Nutrition Examination Survey (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. Development has continued on measurement error techniques to apply to this problem,

including investigating the use of validation datasets. Analyses of four-day dietary data from the Continuing Survey of Food Intakes by Individuals for 1985 and 1986 have begun in collaboration with investigators at the Food and Drug Administration. These data will be used to investigate the measurement error inherent in the 24-hour recall data used in the NHANES-I follow-up.

Methods for Analyzing Complex Survey Data

Data from household surveys such as NHANES-I follow-up and the National Health Interview Survey (NHIS) derive from clustered samples of persons that are usually selected at differential rates. These aspects of the sampling result in nonindependence and unequal weighting of the observations that should be considered during the analysis stage. Survey data are used extensively in three types of study designs: 1) cohort studies through long term follow-up of the sample, 2) case-control studies by providing population controls, and 3) cross-sectional studies. Work has proceeded in developing and studying ways of incorporating the clustering and weighting of the observations from surveys into the statistical methods for analyzing these three types of studies. Modified methods for stratified and logistic regression analysis are being developed for analyzing case-control data. A general approach which utilizes jackknife methods and eigenvalue estimation is being developed to perform inferences about multiple regression models for cohort and cross-sectional studies. The effect of the weighting and clustering on the analysis of cohort studies is being empirically studied using data on iron levels and cancer from the NHANES-I follow-up.

Models of Food Purchasing Behavior

Several methodologic issues related to the use of a cross-sectional time series model in a quasi-experimental situation are being considered. These methods are being applied to data from the Giant Food Study (see also Z01 CN 00119-07 BB). Bootstrap estimates of standard errors are being compared to asymptotic estimates. Two alternative methods of obtaining a null distribution of the intervention effects are also being implemented: a pair permutation approach and simulations in which stores are randomly paired and assigned to control or intervention status within each region. Results are being assessed in relation to the differing underlying assumptions of each method.

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.

Consultation on Clinical Trials and Other Studies (Z01 CN 00119-07 BB)

Community Intervention Trial for Smoking Cessation (COMMIT)

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. 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. Data from an Evaluation Cohort of 400 adults from each of the 22 communities were examined to assess the

population-wide impact of COMMIT on intervention awareness, participation, and the decline of the social acceptability of smoking. The full cohorts of heavy and light-to-moderate smokers were contacted for tracking purposes only. Surveys of worksites, religious organizations, and health care providers were conducted. A survey to assess the level of cessation resources in both the COMMIT comparison and intervention communities was conducted. These surveys were designed to measure the level of smoking cessation activities currently available in the COMMIT communities. These surveys provide a baseline against which to measure the impact of the COMMIT intervention.

Brain Tumor Clinical Trials

The Section provides full support for the Brain Tumor Cooperative Group (BTCG), a multi-center 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 continued to accrue patients to a phase III trial, BTCG 87-01, investigating interstitial radiation (seed implants) as an addition to the customary external beam radiation and chemotherapy. A randomized study for low-grade glioma patients, BTCG 87-30, is comparing immediate versus delayed radiotherapy; for the delayed arm, radiotherapy is only given at the time of documented tumor progression. This trial is an intergroup study with two other cooperative groups, the Radiation Therapy Oncology Group and the Southwest Oncology Group.

A new randomized trial, BTCG 89-01, has been designed and has begun accrual of patients. This trial compares two phase III chemotherapy regimens to be given in addition to surgery and radiotherapy. One regimen is the standard intravenous BCNU, the second is the combination of intravenous BCNU with intra-arterial Cisplatin. The trial also includes a third regimen in the randomization. This arm will be used to investigate, successively, new investigational phase II drugs; the initial agent is 10-EDAM.

Follow-up has continued for previous BTCG studies. 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. During the past year, one blinded panel was sent to evaluate an isoenzyme (CK-BB), two mucin-type glycoproteins (M-26 and M-29) and one isoform (M 26-2) as potential markers for breast cancer. 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.

Issues in the Design of Clinical Trials for AIDS

In collaboration with other clinical trialists, work has been done on re-evaluating principles of clinical trial design to expedite progress in investigating new interventions for patients with HIV infection and AIDS. A document summarizing important issues and suggestions, based on discussions of a statistical design working group, has been created and published. The issues addressed include 1) progression of clinical trials through phases; 2) choices of outcomes; 3) breadth and complexity of clinical trials (eligibility criteria and "low-tech" trials); 4) alternative designs to be used in randomized trials; and 5) the concept of randomized clinical trials as a desirable option, both for patients and for science.

In addition, collaboration has been provided on design of an innovative community-based randomized trial of simultaneous prophylaxis against multiple distinct opportunistic infections associated with HIV infection.

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.

Another aspect of this project is a review of national survey data on fruit and vegetable consumption. The four surveys included are the Second National Health and Nutrition Examination Survey—NHANES II (1976-80), the National Health Interview Survey—HIS (1987), the Nationwide Food Consumption Survey (1977-78), and the Continuing Survey of Food Intakes by Individuals (1985 and 1986). The NHANES II and HIS surveys were conducted by the National Center for Health Statistics; the other two by the U.S. Department of Agriculture. Twenty-four hour recall, food record, food frequency and diet history data have been reviewed. The data are striking in their consistency: On any given day, large numbers of U.S. adults did not include fruit and vegetables in their diet. In a three-day consecutive period, 31 percent of whites and 41 percent of blacks did not have even a single serving of fruit or fruit juice; less than one half had any citrus fruit or juice. Potatoes were the single most popular vegetable, and were eaten about four times per week. HIS respondents reported eating yellow and green vegetables about six times per week. Available data suggests little change in either fruit or vegetable consumption from the late 1970's through the mid 1980's.

Study of Food Purchasing Behavior and Consumer Nutrition Education

The Section is providing extensive 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 of the intervention was to increase the purchase (and the consumption) of foods high in fiber. The data 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 cross-sectional time series model which accounts for both the cross-sectional correlation between purchases at different stores in the same week, and the autocorrelation between purchases in adjacent weeks at the same store, has been fitted to sales data for each food category. The model controlled for the possible confounding effect of price, seasonal monthly effect on purchases, and baseline differences between the stores in the target and control areas. The magnitude of the intervention effects and their significance are being investigated.

In addition, a simplified analysis is being conducted which compares sales that are aggregated for the pre-intervention January-March period with sales from the same period in each of the two years of post-intervention. Matched t-tests, that maintain the store pairing, are used to test for a difference between Baltimore and Washington, DC stores in the change in sales between pre- and post-intervention periods.

Evaluation of the Primary Care Nutrition Guide

The Section has provided statistical consultation to the Health Promotion Science Branch on the design of an evaluation of the Physician Primary Care Nutrition Guide among internal medicine primary care physicians. A cluster randomized design, in which physician practices will be randomly assigned either to an intervention arm or to a control arm, will be used to evaluate the guide. The physicians assigned to intervention will be given the guide and training on how to apply the guide to their practice. The control arm physicians will be given the guide with training withheld

until after the study. Before intervention, baseline data will be collected from the physicians and a sample of their patients. About two months after intervention these same physicians and patients will be interviewed to determine if their knowledge and behavior about nutrition had changed. The Section is planning to conduct the data analysis for this study.

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 report has now been prepared, based on inventories of trials in the several Divisions of the NCI and discussions with investigators in the field, giving estimates for the cost of developing and maintaining a system to implement this policy.

Design and Analysis of Pharmacokinetic Studies of Selenium (Z01 CN 00107-08 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 two 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, has been 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 there is no biologically significant difference in absorption between fasting and nonfasting states, there is a greater first pass effect in nonfasters, probably in response to eating. Many parameters (e.g. delay time in the liver) change with fasting state, while others (e.g. proportions of material passing into the bile) do not change. Such information is important in deciding on an optimal dosing regimen. A model for the metabolism of selenomethionine has also been 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 Working Group 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 NCI. 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 World Health Organization and the International Union Against Cancer (UICC). 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 at the Workshop have been edited and compiled into a proceedings volume which will be published by Hogrefe and Huber Press. 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. Screening Section staff are collaborating with members of the Applied Research Branch, and investigators at FDA and Johns Hopkins University in this Working Group. An initial data base questionnaire has been circulated to Group members, and the next step required to develop the data base will be discussed at a Working Group meeting in Hamburg, Germany in August, 1990.

Studies in Cancer Screening (Z01 CN 00106-08 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 Health Insurance Plan 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 monoclonal antibody 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 may have a reasonable specificity and predictive value in post menopausal women. 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 metabolites vanillylmandelic acid and homovanillic acid in specimens from infants in Quebec, Canada. Control populations will be drawn from the state of Minnesota, the Greater Delaware Valley, and the province of Ontario. In collaboration with a visiting investigator from the People's Republic of China, study designs and data analysis methods are being examined to evaluate screening for stomach cancer in Shandong Province.

Research in Cancer Screening and Statistical Methodology (Z01 CN 00105-08 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 controlled trial (RCT) in which there is appreciable follow-up after the trial's screening intervention has stopped is difficult because the effect is diluted after screening ceases. This project considers the usual analysis involving all the individuals randomized and a limited analysis based on subgroups of those with cancer diagnosed during defined periods from entry into the study. Statistical testing procedures are compared for these two analyses. It is seen that the determination of comparable groups is critical to the validity of the limited analysis. Procedures to assess comparability of subgroups of cancers are investigated. These include investigation of the cancer incidence and the covariates that reflect the natural history of the cancers. Procedures are proposed for use both with the cancers in the subgroups thought to be comparable and with the cancers that arise after these groups are defined.

Case-Control Studies

In recent years, case-control methodology has been suggested for evaluating screening programs and several 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. This project has focused on the ability of the case-control study to provide estimates of the efficacy of screening for those screened where efficacy is defined to be the mortality reduction of those screened relative to their mortality in the absence of screening. In the usual setting the case-control approach provides an estimate of the mortality reduction of those offered screening and being screened relative to those offered screening and not being screened. It is demonstrated that this, in general, is a biased estimate of the efficacy, and may overestimate or underestimate the true impact of screening, depending upon the direction of selection bias among individuals not screened. The findings of case-control studies of screening must therefore be interpreted with caution. Data from the Health Insurance Plan (HIP) breast cancer screening trial were used in this analysis.

Stage-Shift Screening Model

The stage-shift screening model previously developed was used to examine the breast cancer mortality in the HIP Study for women aged 40 to 49 at entry and for women aged 50 to 64 at entry. There appears to be a difference in these two groups. The application of the model suggests that the younger age group had a beneficial shift of cancers within stage one and that the older age group had a beneficial shift of usual stage II cancers to stage I as well as a shift within stage I cancers.

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. Sample size estimation procedures for this methodology are under development.

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. Simple techniques have been developed for obtaining closed-form maximum likelihood estimates and their asymptotic variances for many important cases of missing categorical data.

Capture-Recapture Methodology Applied to the Analysis of Screening Data

The method of capture-recapture has been traditionally used to estimate the size of animal populations based on samples of animals captured and tagged. New methodology has been developed for applying the method of capture-recapture to estimate sensitivity of a screening test and duration of preclinical sojourn time. An important innovation is the use of the EM algorithm to obtain maximum likelihood estimates and the use of the bootstrap to obtain estimates of the variance.

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.

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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 00100-08 CPSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

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)*

National Public Health Institute, Helsinki, Finland
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:
2.5	2.25	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.)*

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 13 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 less than 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 (through 1988) 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 00101-08 CPSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

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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	C. A. Swanson	Staff Fellow	CPSB, DCPC, NCI
	E. Lanza	Nutritionist	DCB, DCPC, NCI
	B. H. Patterson	Math. Statistician	BB, DCPC, NCI
	B. K. Edwards	Biostatistician	SP, DCPC, NCI
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI
	R. Ballard-Barbash	Staff Fellow	CPSB, DCPC, NCI
	G. Block	Epidemiologist	ARB, DCPC, NCI
	M. Forman	Nutritional Epidemiologist	CPSB, DCPC, NCI
	W. Campbell	Research Study Coordinator	CPSB, DCPC, NCI
	M. Maher	Nurse Specialist	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*

U.S. Dept 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

Cancer Prevention Studies Branch, DCPC

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892

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

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 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 and the bioavailability of vitamin C are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00103-08 CPSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

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)*

PI:	J. A. Tangrea	Deputy Branch Chief	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
	G. Peck	Senior Investigator	DB, DCT, NCI

COOPERATING UNITS *(if any)*

Walter Reed Army Med Ctr; Fitzsimmons Army Med Ctr; Brooke Army Med Ctr; Eisenhower Army Med Ctr; Portsmouth Naval Med Ctr; Northwestern U; U of Arkansas; Roswell Park Med Inst; Dermatology Br, NCI; Radiology Dept, Clinical Ctr; 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:
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.)*

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 00104-08 CPSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

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)*

PI:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
Others:	D. Albanes	Staff Fellow	CPSB, DCPC, NCI
	G. Block	Epidemiologist	ARB, DCPC, NCI
	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
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI
	A. Kant	Prevention Fellow	CPSB, DCPC, NCI
	J. Dorgan	Prevention 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

SECTION

INSTITUTE AND LOCATION

National Cancer Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	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 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 initial 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 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.

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

PROJECT NUMBER
Z01 CN 00112-07 CPSB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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)*

PIs:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
	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

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.)*

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 00143-06 CPSB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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)*

PIs:	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 00145-05 CPSB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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	0.0

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 00146-02 CPSB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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
	J. Dorgan	Prevention Fellow	CPSP, DCPC, NCI

COOPERATING UNITS *(if any)*
Boston University and the National Heart, Lung and Blood Institute (NHLBI).

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 00147-02 CPSB) is being conducted on children of the original cohort.

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

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

PROJECT NUMBER
Z01 CN 00147-02 CPSB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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
	J. Dorgan	Prevention Fellow	CPSP, DCPC, NCI

COOPERATING UNITS *(if any)*
Boston University and the National Heart, Lung and Blood Institute (NHLBI).

LAB/BRANCH
Cancer Prevention Studies Branch, DCPC

SECTION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.50	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.)*

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 00146-02 CPSB) is being conducted on the original cohort.

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

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

PROJECT NUMBER
Z01 CN 00148-02 CPSB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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 00149-02 CPSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

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
	M. Forman	Nutritional Epidemiologist	CPSP, 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:
0.50	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 00150-02 CPSB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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 00151-02 CPSB

PERIOD COVERED

October 1, 1989 to September 30, 1990

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)*

PIs:	A. Schatzkin	Senior Investigator	CPSB, DCPC, NCI
	E. Lanza	Nutritionist	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	Nurse Specialist	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 00152-01 CPSB

PERIOD COVERED
October 1, 1989 - September 30, 1990

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

COOPERATING UNITS *(if any)*
Wright State School of Medicine

LAB/BRANCH
Cancer Prevention Studies Branch

SECTION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	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.)*

This project is designed to investigate the relation of childhood nutrition to breast cancer risk factors, including age at menarche, adult height, weight, and fatness. Secondary purposes include tracking the development of overweight and obesity from birth through young adulthood, identification of possible "sensitive" or high-risk periods (with respect to obesity) in childhood and, more important, to identify the contribution of diet to the development of childhood and adult obesity.

Detailed anthropometric data (height, weight, skinfold thickness, etc.) and demographic characteristics are currently available on a computer data base from the Fels Study and the Division of Human Biology of the Wright State School of Medicine. Up to 18 annual dietary and anthropometric assessments are available for "index" girls. Calorie, macro- and micronutrient data will be linked to an existing anthropometry computer file, including later adult height and weight. Nutrient composition will be calculated using the latest version of the USDA Handbook series. Nutrients will include the following: total energy (kilocalories); total fat, protein, and carbohydrate; saturated, polyunsaturated, and monounsaturated fat; cholesterol; dietary fiber; and vitamins and minerals (from food and supplementary sources).

This study is being conducted collaboratively with scientists at the Wright State School of Medicine in Yellow Springs, Ohio.

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

PROJECT NUMBER
Z01 CN 00153-01 CPSB

PERIOD COVERED
October 1, 1989 - September 30, 1990

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Evaluation of the Effects of a Fat-Modified Diet on Hormones During Adolescence

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

PI:	J. Dorgan	Prevention Fellow	CPSB, DCPC, NCI
Others:	A. Schatzkin	Medical Officer	CPSB, DCPC, NCI
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)* National Heart, Lung, & Blood Institute; Children's Hospital (New Orleans, LA); Johns Hopkins U (Baltimore, MD); Kaiser Center for Health Res (Portland, OR); Maryland Med Res Inst (Baltimore, MD); Med College of New Jersey (Newark, NJ); Northwestern U (Chicago, IL); U of Pittsburgh (Pittsburgh, PA)

LAB/BRANCH
Cancer Prevention Studies Branch

SECTION

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.25	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.)*

This study is ancillary to the Diet Intervention Study in Children (DISC), sponsored by the Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute (NHLBI). DISC is a multicenter, randomized clinical trial designed to evaluate the feasibility, safety and efficacy of a fat modified diet during adolescence to lower LDL-cholesterol. The NCI sponsored ancillary study will evaluate the effect of this fat modified diet on sex hormones during adolescence. The effect of the diet on total concentrations of hormones and bioavailable fractions of hormones will be determined. The NCI sponsored ancillary study will also identify characteristics of adolescents, including age, Tanner stage, anthropometric measures, physical activity and dietary intake, that affect sex hormone levels and bioavailability of sex hormones. Since a family intervention is being used, the effect of the intervention on sex hormone levels of parents of participants will also be assessed.

Dietary goals for the intervention group are to limit fat intake to 28 percent of calories and increase the ratio of polyunsaturated to saturated fats to approximately 1. Cholesterol intake will be restricted to 75mg/1000 calories. Children in the control group follow their usual diets.

This study is being conducted collaboratively with scientists from the National Heart, Lung, and Blood Institute in Bethesda, MD; Children's Hospital in New Orleans, LA; Johns Hopkins University in Baltimore, MD; Kaiser Center for Health Research in Portland, OR; Maryland Medical Research Institute in Baltimore, MD; Medical College of New Jersey in Newark, NJ; Northwestern University in Chicago, IL; and University of Pittsburgh in Pittsburgh, PA.

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

PROJECT NUMBER
Z01 CN 00105-08 BB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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

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. 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. The model was used to investigate age-specific breast cancer mortality in the HIP study. Screening impact appeared to be restricted to stage one disease in women less than 50, but both stage two and one cancers were affected by screening in older women. A novel application of capture-recapture methodology was developed to estimate screening test sensitivity and preclinical sojourn time. The EM algorithm was used to estimate parameters while variances were obtained using the bootstrap. 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 00106-08 BB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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 Co. (V. Zurawski); Harvard U. (D. Schoenfeld); Duke U. (R. Bast); U. of Minnesota (W. Woods); Karolinska Hospital (K. Sjovall); Beijing Medical U. (R. Wang)

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 have a reasonable specificity and predictive value in post menopausal women. Study designs are under consideration to assess sensitivity and evaluate the impact of screening on ovarian cancer mortality. 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. An additional collaborative effort involves examination of study design and data analysis approaches for evaluating screening for stomach cancer in Shandong Province, People's Republic of China.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00107-08 BB

PERIOD COVERED

October 1, 1989 to September 30, 1990

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 00101-08 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. Models of selenite and selenomethionine have been developed and are 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.

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 00113-07 BB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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:	F. B. Locke	Statistician	BMCCES, BB, DCPC, NCI
Others:	H. King	Adjunct Scientist	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:
1.4	1.2	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. Histologic and sub-site analyses of Asian-American cancer cases compared to whites and blacks, has been underway, revealing major differences, possibly useful in etiologic studies.

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. These data are the basis for a time-trend study on cancer/non-cancer mortality 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).

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

5. As consulting reviewers of an Oncology Overview of "Selected Abstracts on Recent Epidemiologic Studies of Neoplasms Among Asians", an editorial was prepared covering a site-specific commentary on cancer epidemiology among Orientals.

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

PROJECT NUMBER
Z01 CN 00115-07 BB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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)
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.

A marked increase in brain cancer incidence rates during the 15-year period 1973-1987 in SEER program areas was investigated using age-period-cohort models. Analyses for white males and white females aged 15-84 at diagnosis showed little effect of period (year of diagnosis) and a significant effect of cohort (year of birth).

In collaboration with researchers in the Environmental Epidemiology Branch, HHV-6 antibodies in Hodgkin's disease patients were evaluated. Serum samples were taken from each of 37 patients with Hodgkin's disease at the time of diagnosis and at 1-, 3-, and 5-years of follow-up. Repeated-measures methods showed a declining HHV-6 antibody pattern for patients who responded to therapy, whereas patients with more severe disease had increasing antibody titers.

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. The risk for early menopause among female members of this cohort was determined and compared to the risk among sisters of the survivors. Survival analysis methodology was used to estimate the proportion still menstruating as a function of age and to examine other factors affecting the hazard of menopause under the proportional hazards model. Survivors were found to be at an increased risk for early menopause. The risk was primarily a function of age and the type of treatment received for cancer. In another study based on this cohort, development of the cigarette smoking habit among 1,406 survivors who were nonsmokers when their cancer was diagnosed was compared to that among 2,236 sibling controls. Using conditional maximum likelihood methods, the smoking rate at last follow-up among survivors was found to be 79% of the rate among controls.

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

PROJECT NUMBER
Z01 CN 00116-07 BB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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	Section 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
	B. Graubard	Mathematical Statistician	CDTS, BB, DCPC, NCI
	R. Carroll	Guest Researcher	CDTS, BB, 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 accounting for the effect of measurement error and intra-individual variation in analyzing the relation of diet to breast cancer; investigating methods for analyzing complex sample survey data (including ways of incorporating the clustering and weighting of the observations into regression analyses of epidemiologic studies); and developing and investigating cross- sectional time series models of food purchasing behavior.

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 00119-07 BB

PERIOD COVERED

October 1, 1989 to September 30,1990

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	Section 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
	B. Graubard	Mathematical Statistician	CDTS, BB, DCPC, NCI

COOPERATING UNITS *(if any)*

Surveillance Program, DCPC; Smoking, Tobacco, and Cancer Branch, DCPC; Health Promotion Science 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 the Evaluation Cohort survey and surveys of worksites, religious organizations, health care providers, and community cessation resources. 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; collaborating on re-evaluation of issues in the design of clinical trials for AIDS and on the specific design of a randomized trial for simultaneous prophylaxis of multiple opportunistic infections; investigating the consumption of fruit and vegetables in the American diet; collaborating on a study of food purchasing behavior and consumer nutrition education, involving a supermarket-based intervention; and designing an evaluation, using a cluster randomized design, of the Physician Primary Care Nutrition Guide.

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

PROJECT NUMBER
Z01 CN 00121-06 BB

PERIOD COVERED
October 1, 1989 to September 30, 1990

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
	Y. Wax	Guest Researcher	ARB, 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:
1.0	0.8	0.2

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 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.

The proper time metric to be used when applying Cox regression techniques to analyze a cohort's cancer incidence over time is being studied by simulation methods. Data are being generated according to known cancer age-specific incidence and known mortality from all causes. The time metrics being studied are follow-up time from study initiation and age at risk. Different study durations are also being evaluated. In addition, different methods to properly estimate the effect of risk factors which are related to age at ascertainment are being evaluated.

The assumption of "proportional hazards" is commonly made when analyzing survival in patients treated for cancer. The scale parameter in parametric models and the underlying hazard function in semi-parametric models are assumed to vary between patients only because of the risk factors included in the model. However, extraneous hazard rate heterogeneity can produce substantial deviations from this assumption. This research will fit a Gamma-mixture of Weibull models to estimate the degree of heterogeneity and its biasing effect on estimated parameters and on the hazard ratio.

Methodology is being developed to calculate the necessary sample size n,m (n is the number of measuring devices and m is the number of items being measured) to test the hypothesis that the accuracy of a measuring device is acceptably large. The results will be used to develop sampling methods to evaluate the accuracy of the CIS.

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, 1989 to September 30, 1990

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 Research 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:
1.0	0.9	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 continued updating of the basic underlying database used by the program, conversion from the DEC-10 to the Convex computer (DCRT's replacement for the DEC-10), calculation of rates to different standard populations, calculation of expected cases for individual tumor registries, and detailed analyses for several sites such as breast and ovarian cancer.