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Division Of

Cancer Prevention and Control

NATIONAL CANCER INSTITUTE

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

91 annual report

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NATIONAL CANCER INSTITUTE

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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 and applied 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 three 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

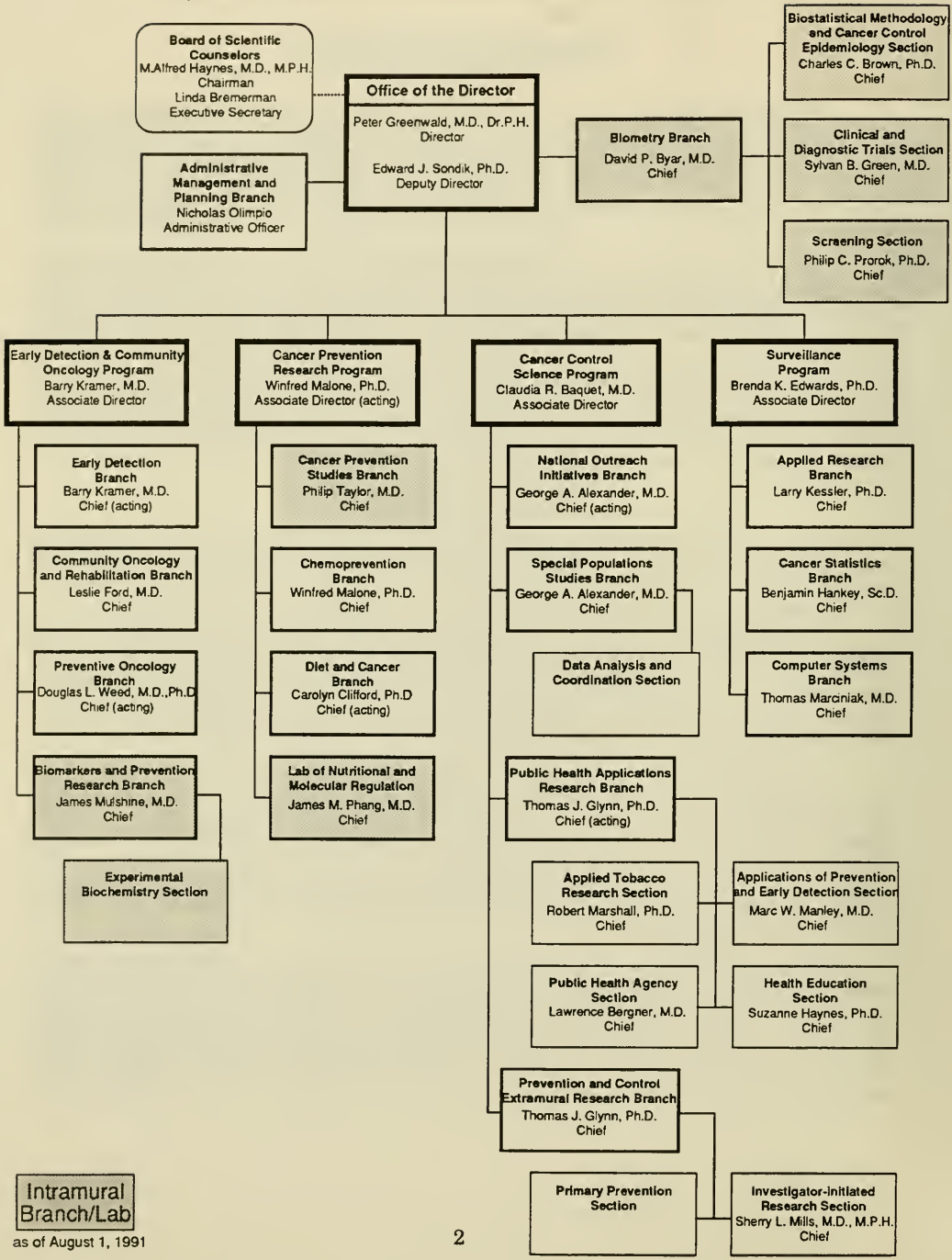
Figure 1 outlines the DCPC organization. The Division consists of four major programs, each led by an Associate Director. The Office of the Division Director provides overall coordination and direction as well as analytic program support. Each program is described briefly below.

The **Office of the Director** is responsible for the coordination and direction of the Division programs. It includes two branches: the Biometry Branch (one of the intramural components) and the Administrative Management and Planning Branch. The Biometry Branch conducts and supports intramural research using epidemiologic data bases, intramural research in biostatistical methodology and aspects of cancer screening, and clinical trials research. The Administrative Management and Planning Branch assists in the management of the Division's budget and administrative matters.

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 the Laboratory of Nutritional and Molecular Regulation, two of the four intramural components of the Division. The Laboratory is located at the Frederick Cancer Research and Development Center (FCRDC) in Frederick, MD. The extramural units of the Program are the Chemoprevention Branch and the Diet and Cancer Branch.

The **Early Detection and Community Oncology Program** (EDCOP) supports the community-based clinical research programs, as well as early detection and rehabilitation research. The Program includes the fourth of the Division's intramural components, the newly established Biomarkers and Prevention Research Branch. The Branch will focus on the use of molecular biological techniques and clinical medicine to develop the biomarker tools to prevent and find cancer early. These programs are designed to improve the delivery and application of state-of-the-art cancer regimens.

Figure 1 - DCPC ORGANIZATION CHART



Intramural Branch/Lab

as of August 1, 1991

EDCOP's extramural units include the Early Detection Branch and the Community Oncology and Rehabilitation Branch, which coordinates the Community Clinical Oncology Program (CCOP) and the minority-based Community Clinical Oncology Program. These CCOPs link 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 52 funded CCOPs and 12 minority-based CCOPs. During the past year the Cancer Prevention Fellowship Program has been moved from the Office of the Director to EDCOP as a new Branch, the Preventive Oncology Branch. The Cancer Prevention Fellowship Program was developed to provide an opportunity for physicians and scientists to train and to gain experience in the field of cancer prevention and control by working with DCPC preceptors.

The **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 Branches (all extramural) are National Outreach Initiatives, Special Populations Studies, Public Health Applications Research, and Prevention and Control Extramural Research.

The **Surveillance Program**, also entirely extramural, 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 as well as the SEER Program; 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.

INTRAMURAL ACTIVITIES

Intramural research is an important and essential 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 expected to stimulate the extramural nutrition research community in this high-priority endeavor.

Within the DCPC, the intramural research program is conducted through the Biometry Branch, the Cancer Prevention Studies Branch, the Laboratory of Nutritional and Molecular Regulation, and the newly established Biomarkers and Prevention Research Branch.

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 both within and outside the NIH.

The **Cancer Prevention Studies Branch** (CPSB), 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), a part of the Cancer Prevention Research Program is located at the NCI-Frederick Cancer Research and Development Center (NCI-FCRDC). The LNMR conducts a broad range of studies including the use of 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 Biomarkers and Prevention Research Branch has been established and will focus on the use of molecular biological techniques and clinical medicine to develop the biomarker tools for prevention and early detection of cancer. These programs are designed to improve the delivery and application of state-of-the-art cancer regimens.

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 DCPC 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.

BIOMETRY BRANCH

OBJECTIVES

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

- "Plans and conducts independent and cooperative research studies on 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 program managers and scientific decision-makers within the NCI and outside."

OVERVIEW

The work of the Branch is conducted by its 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:

Dietary Intervention for Patients with Colorectal Polyps (NCI Polyp Prevention Trial)

The staff has been collaborating with the Cancer Prevention Studies Branch in developing and implementing the NCI Polyp Prevention Trial. This major randomized study is designed to enter 2,000 patients from 10 clinical centers in the USA. Half of the patients will be allocated a dietary counselling program aimed at reducing their intake of fat and increasing their intake of fruits, vegetables, and fiber. The other half will be allocated standard management. The patients will have had a colorectal adenomatous polyp removed shortly before entry to the trial and will be reexamined by colonoscopy at 1 year and 4 years after randomization. The main question to be answered is whether dietary change will reduce the recurrence rate of adenomatous polyps. The trial began at three vanguard centers in May 1991. The other seven centers are scheduled to begin in September 1991.

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. Even more importantly, discovery of such an intermediate endpoint will provide new clues to etiology and may lead to new approaches to prevention. Statistical methods for developing and validating potential intermediate endpoints have been formulated, drawing together previous epidemiological work on causal inference and attributable proportion, and methodological work on surrogate endpoints in clinical trials. Statistical methods of validation have been described and illustrated using data on serum cholesterol and heart disease. Sample size requirements for validating intermediate endpoints in cohort studies or prevention trials have been addressed and the work applied to the assessment of cell proliferation rates within an NCI dietary intervention trial among patients with colorectal polyps.

Geographic Mortality

Geographic analysis has been very useful in the identification of regions of the country whose risk of cancer is high, e.g., New Jersey counties near chemical plants and coastal counties in South Carolina engaged in asbestos industries. In many cases the identification has led to the implementation of a screening program (such as for bladder cancer in the first instance) or even new insights into etiological factors (such as for lung cancer in the second instance). For some sites, geographical effects are more evident after adjustment to the rates has been made for known associations. An adjustment for urbanicity is made to lung cancer mortality rates in U.S. counties for 1970-1979 and 1980-1987 for both white males and white females; choropleth maps of the adjusted rates show some consistently high and low risk for all four sex-decade combinations. For other sites, no obvious associations are known, so prior adjustment is initially unnecessary. This is the situation for prostate cancer, and maps of these rates may well suggest areas for further investigation, both which are high (for implementation of screening programs) and low (for studies of prevention).

Statistical Methodological Research on Two-Dimensional Smoothers

The random variation in data encourages the use of statistical methods to reduce the variation in order to better elucidate underlying patterns. For data that are a function of only one variable, such as number of observed polyps to be modeled by a function of number of fiber servings daily, it is useful to have methods of smoothing the data to reduce the inherent noise in the functional relationship. When data are to be modeled as a function of two variables, such as county mortality rate by geographic location, smoothing is even more important for deciphering patterns in two dimensions. Several two dimensional smoothers are evaluated for their success in capturing underlying patterns, and proposals for other smoothers are being investigated.

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. This reduces the power of the study to detect dietary effects. 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.

The rather narrow range of dietary intakes in Western populations is another major factor for the very large sample sizes required to detect dietary effects. A two-stage sampling scheme has been developed in which a large sample of subjects is asked to complete a dietary questionnaire but only a subsample, selected to include preferentially those with extreme dietary intakes, is followed for disease incidence. This reduces the number of subjects requiring followup.

Analysis of Data from Animal Chemoprevention Experiments

Considerable effort is being made to evaluate chemical compounds which may help to prevent the development of cancer. In an early stage of this evaluation the compounds are tested in animal models. Guidelines for the statistical reporting of such experiments have been developed to help with the rapid assessment of the large volume of experimental data that are now becoming available to NCI.

A statistical model, suggested by Kokoska (Biometrics, 1987), attempts to distinguish between the effect of a compound upon the number of tumors initiated in an animal at the time of carcinogen administration and its effect upon the time to appearance of the tumor. This model is being evaluated on several data sets. Early experience shows that the results obtained are highly dependent upon the assumptions regarding the distribution of the number of tumors per animal. Goodness of fit tests are being developed to help guide the choice of distribution used in the analysis.

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 an Observational DataBase (ODB) covering over 40 centers belonging to the Community Based Clinical Trials Network composed of members of the NIAID Community Program for Clinical Research on AIDS and AmFAR, the American Foundation for AIDS Research. Dataforms have been developed, tested in a pilot study, and modified for study use. Data collection from the AmFAR component of the study began in October 1990 and over 1,000 HIV-positive individuals from have been entered into the study as of June 1991. The database will be used to permit rapid and accurate tabulation of descriptive data about HIV seropositive subjects potentially available for participation in randomized clinical trials and other studies and to generate hypotheses to be tested in randomized clinical trials.

Staff have also collaborated with researchers in Toronto in the design and ongoing analysis of a trial of low dose oral α-interferon for persons with AIDS. This trial will evaluate the short term effect of α-interferon on CD4 counts.

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

An analysis has been conducted previously of the many experiments in the literature investigating the effects of fat, calories, and mammary tumors in rodents. Work is now in progress to evaluate the effect of saturated and polyunsaturated fat in these experiments. Preliminary results indicate that the linoleic acid content of the fat is an important factor in its effect upon mammary tumor development.

Dietary Assessment Using a Food Frequency Questionnaire

Assessment of average dietary intake is a difficult exercise and several different methods are used, each with its own advantages and disadvantages. It is generally felt that the most accurate method is through multiple Food Records completed over the period of study. A method of relating intakes according to a Food Frequency Questionnaire with the "true average intake" has been developed. Of course, true average intake is not actually observed, but use of multiple Food Records allows a mathematical model of this relationship to be estimated. The method was applied to data from the Women's Health Trial Feasibility Study and appeared to reveal a flattened slope phenomenon for the nutrients examined, i.e. a tendency for the Food Frequency Questionnaire to overestimate intake when it is low and to underestimate intake when it is high.

Incomplete Factorial Designs

It is often useful in prevention trials or clinical trials to study more than one intervention in the same study. The most efficient design for this is the complete factorial, in which all combinations of interventions are studied. However, it is sometimes impossible to study all combinations; for example, including a control group with no intervention may be considered unethical. Incomplete factorial designs are those in which a small number of the possible intervention combinations are omitted. Using these designs one may still estimate certain intervention effects and interactions. Different methods of estimation, and their bias and variance, have been studied. In addition, a general method for identifying which sets of effects are estimable has been developed.

Bayesian Methods for Monitoring Trials

In long-term prevention trials or therapeutic trials, data on the effectiveness of an intervention become available before the end of the trial. It is often demanded, by ethical considerations, that data are analyzed to aid in the decision of whether to continue the trial as planned. The most popular statistical methods for aiding this decision are those which preserve the overall Type I error probability; they are known as group sequential tests. However these methods can be rather inflexible in practice, and theoretically suffer from contravening the Likelihood Principle. An alternative method based on Bayesian theory has been developed and has been demonstrated to carry the principle advantages of group sequential methods—avoiding premature stopping—while retaining flexibility and conforming to the Likelihood Principle.

Cancer Control Objectives and Cancer Mortality Projections (Z01 CN 00142-07 BB)

A comprehensive interactive Fortran program which projects cancer mortality and incidence figures (numbers and rates) for forty years 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 the theory and analysis of cancer prevention and control studies;

- 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;

- provides consultation to researchers both within and outside NCI to on problems related to biostatistical methodology and epidemiology."

Consultation and Collaboration in DCPC Studies

In collaboration with the Cancer Prevention Studies Branch and the U.S. Department of Agriculture, data are being analyzed from two feeding studies, 1) plasma lipids and lipoprotein responses in men fed a high-fat/low-fiber diet versus a low-fat/high-fiber diet, and 2) the effect of alcohol ingestion on hormonal status in women.

In consultation with the Cancer Statistics Branch, a method to "age-adjust" the median age at cancer occurrence has been developed in order to compare populations with different age distributions. This methodology is planned to be used to evaluate changes over time in the median age of U.S. incident cancer cases.

In collaboration with the Applied Research Branch, data are being analyzed from a randomized clinical trial of isoretinoin for reducing basal cell skin carcinoma incidence in a high-risk population. Preliminary results show that the subjects have substantially different rates of cancer occurrence and that the treatment appears to have a weak effect in persons with the highest cancer rates.

In consultation with the Prevention and Control Extramural Research Branch, statistical guidance is being given to the Worksite Health Promotion Intervention Study. Initial advice is being given on the sample size calculations and pair-matching of worksites necessary for the two-stage cluster sampling design being employed.

In consultation with the Public Health Applications Research Branch, statistical guidance is being given on designing a study and developing an RFP to evaluate the adoption and use of the NCI Primary Care Nutrition Guide supplied to physicians through professional societies.

In consultation with the Early Detection Branch, statistical guidance is being given on developing PC software for state health departments to map the yearly NCHS county mortality statistics in order to geographically evaluate their state's cancer burden.

In collaboration with the Applied Research Branch and the IMS support contract, a computer program to do Liang-Zeger quasi-likelihood GLM repeated measures analyses is being developed. An early use of this computer program is planned to evaluate the "cost" of assuming unnecessarily general covariance structures.

Research in Biostatistical Methodology and Mathematical Modeling (Z01 CN 00121-07 BB)

Heterogeneity of County Cancer Rates

Regression analysis of cancer mortality rates versus demographic, economic, and ecologic characteristics of U.S. counties is a common method for studying cancer etiology. The number of county deaths is commonly assumed to be a Poisson random variable. However, because of the potentially wide disparity in cancer risks among the county's population (e.g., smokers versus nonsmokers), this heterogeneity should lead to more variability than predicted by the Poisson assumption. This research will study this question by evaluating the degree of intra-county temporal variation for the major cancer sites and the effect of heterogeneity on standard ecologic regression methods.

Heterogeneity in Survival Analysis

The assumption of "proportional hazards" is commonly made when analyzing the effects of prognostic factors in survival of patients treated for cancer. Parametric models such as the Weibull and semi-parametric methods such as Cox regression are often used for these analyses. Variability

in patient mortality is modeled by assuming the scale parameter in the parametric models and the proportionality parameter in the semi-parametric models to be functions of prognostic factors. The study parameter (the shape parameter in the parametric models and the underlying hazard function in the semi-parametric models) is assumed the same for all patients, i.e. the "proportional hazards" assumption. However, unexplained extraneous hazard rate heterogeneity among these patients can produce substantial deviations from this proportional hazards assumption. This research will compare the fits of Weibull and Gamma-mixed-Weibull survival models to 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. Breast cancer will be the first site studied.

Issues in Cox Regression of Followup Studies

Cox regression methods are commonly used for the analysis of prospective followup studies such as the National Health and Nutrition Study. Followup time since the start of the study is often used as the underlying time metric. However, because carcinogenesis theory indicates that age at risk is often a more valid metric, this research will evaluate the 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 followup period. Adjusting for age at start of the study by stratification or by inclusion in the regression model will also be examined.

In addition, the ascertainment age bias induced by a risk factor which has an age-related "measurement error," such as dietary components whose "normal" intake level varies over age, will also be evaluated by simulation.

Descriptive Cancer Epidemiology (Z01 CN 00115-08 BB)

Monitoring Temporal Increases in Kidney Cancer Incidence

Data on kidney cancer diagnosed among 3,980 white residents of Iowa were available for the years 1973-88 from the Surveillance, Epidemiology, and End Results (SEER) Program. Data for 1973-77, the first five years of the study period, were used to compute baseline rates for three major site/type subgroups of kidney cancer within each of the 99 counties in the state. Data from 1978-88 were monitored for increasing incidence over the baseline rates. The principal statistical procedure used (the sets technique) is based on the time ordering of disease occurrences. An alarm is signalled when a certain number of consecutive intervals between diagnoses are all relatively short compared to the expected interval computed from the baseline data.

Alarms signalling an increase in incidence were found in 39 counties for renal parenchyma cancer, in 34 counties for renal pelvis cancer, and in four counties for nephroblastoma. The possibility that the observed number of alarms was a random occurrence was studied by applying a confirmatory analysis to the next five cases diagnosed after the alarm. Twelve alarms were confirmed for renal parenchyma cancer, four for renal pelvis cancer, and none for nephroblastoma. We believe that the observed increases in carcinoma of the kidney seen in some Iowa counties during 1978-88 are real and not due to false alarms.

Ethnic Differences in Human Herpesvirus-6 Antibody Patterns

Human herpesvirus-6 (HHV-6) is a recently discovered virus that has been associated with several human lymphomas. Most reports also indicate a high prevalence of HHV-6 antibody among healthy Europeans and Americans. Little is known about antibody prevalence in African or Asian populations. A study of healthy blood donors from Ghana and Malaysia was conducted in collaboration with the Environmental Epidemiology Branch of the Division of Cancer Etiology.

Sera from 48 Indians and 41 Chinese from Malaysia, 44 Ghanaians, and 25 Americans were obtained from a serum bank maintained by the Tumor Virus Epidemiology Repository. Immunoflorescence tests for antibodies to HHV-6 were performed by standard techniques at one laboratory.

The prevalence of HHV-6 antibody-positive tests was 100% for Ghanaians, 96% for Americans, 54% for Malaysian Indians, and 41% for Malaysian Chinese. The geometric mean titers in antibody-positive donors were 58.4 for Ghanaians, 27.5 for Americans, 16.2 for Malaysian Indians, and 13.3 for Malaysian Chinese. The Ghanaian geometric mean titer is significantly higher than that for the other ethnic groups.

This report documents for the first time that there are differences in HHV-6 antibody patterns among healthy residents of Africa, Asia, and the U.S. The reasons for these differences remain speculative, but the high reactivity among Ghanaians may be due to concurrent malaria.

Human Herpesvirus-6 in Chronic Fatigue Syndrome

In another study done in collaboration with the Environmental Epidemiology Branch, antibodies to human herpesvirus-6 (HHV-6) were evaluated in 27 patients with chronic fatigue syndrome (CFS). These patients had all been diagnosed during 1984-86 in any of four clusters of CFS that occurred in the Lake Tahoe, NV area. Blood samples from 89 other patients from that area with illness other than CFS, or healthy blood donors, served as controls.

The geometric mean antibody titer to HHV-6 was higher among CFS patients (132.6) than for controls (87.9) but the difference was not statistically significant. This and other findings from the study suggest that HHV-6 may be a ubiquitous virus that is reactivated in outbreaks of CFS but is not a cause of the disease.

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 occurrence of 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 incidence 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 27 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 1,289 survivors who were nonsmokers when their cancer was diagnosed was compared to that among 1,930 sibling controls. Using conditional maximum likelihood methods, the current smoking rate at last followup among survivors was found to be 92% of the rate among controls, a non-significant deficit. In a multivariate analysis, gender and time period of diagnosis were shown to have a strong influence on their smoking rate. Survivors were less likely to be current smokers if diagnosed in recent years and quite similar to controls if diagnosed in earlier years.

Cancer in Oriental Populations (Z01 CN 00113-08 BB)

Mainland China – 65 County Study

An in-depth diet, lifestyle, and mortality survey of 65 mostly rural counties has been conducted 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. This study has been completed and submitted for publication.

Migrants to Taiwan from Fujian Province

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

Comparative Study of Histologic and Sub-Site Distributions

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 Asian-Americans (Chinese, Japanese and Filipino populations), Blacks, and Whites.

Currently, our analysis so far had indicated major differences between Asian-Americans and Whites for cancers of the esophagus, stomach, colon-rectum, lung, and breast. For example, Asian-American esophageal cancer rates, 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 racial groups. Analysis of cancer in the U.S. Black population, nearing completion, also shows substantial differences from Whites in both histology and sub-site distributions for cancers of the esophagus and stomach. Other findings include differences, in varying degrees, either in histology or sub-sites for cancers of the buccal cavity, colon-rectum, lung, female breast, and urinary bladder.

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.

Recent availability of cancer mortality rates to 1985 for Japan, Hong Kong, and Singapore will help provide more meaningful analyses.

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 are continuing to 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 plan to follow up with similar 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 00116-08 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. Four-day dietary data from the Continuing Survey of Food Intakes by Individuals (CSFII) for 1985 and 1986 will be used to investigate the measurement error inherent in the 24-hour recall data used in the NHANES-I follow-up. Analyses are underway in this dataset comparing the distribution of intake on the first day, in which a 24-hour recall was obtained, to intake on the remaining three days, when food records were obtained, to average intake over the 4-day period. Nutrient variables from CSFII and NHANES-I are being assessed and compared. To select the appropriate baseline model for the analyses incorporating adjustments for measure error, several logistic regression models are being compared.

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. An estimating equation approach along with robust Taylor linearized variance estimation has been developed for logistic regression of case-control studies when the controls come from a cluster sample. This investigation concludes that under cluster sampling 1) the classical estimating equations are more efficient than other weighted estimating equations when the weights are the inverse of the probability of selecting controls from the population, and 2) the loss in efficiency from cluster sampling will be small if the control to case ratio is greater than one. Research on utilizing replication methods for making inferences about multiple linear regression models with complex survey data has found that 1) the Wald test statistic works well when the number of degrees of freedom for covariance estimation is large relative to the dimension of the parameter being tested, and otherwise 2) a modified jackknife procedure is recommended for testing vectors of means and a procedure based on a

Satherthwaite correction is recommended for testing vectors of linear regression coefficients. The effect of the weighting and clustering on an analysis of iron levels and cancer from the NHANES-I followup was studied. The results of this work suggest that the sample weights should not be used in the analysis because of increased variance caused by the weights and that sample design variables and clustering should be included in the analysis. Research into procedures of trimming sample weights and modeling the complex sample designs of surveys so as to make analysis more efficient is in progress.

Models of Food Purchasing Behavior

A cross-sectional time series model, TSCSREG, was applied to data from the Giant Food Study (see also Z01 CN 00119-08 BB). The standard asymptotic significance tests for the effects of the intervention were judged to be inappropriate for assessing the significance of these effects, because these testing procedures yielded highly significant intervention effects when the control Baltimore stores were randomly allocated to "intervention" and "control" status and the model was applied to assess these pseudo intervention effects. An alternative approach to assessing the significance of the intervention effect was to generate a null distribution by randomly pairing stores within the Baltimore area, allocating one to intervention status and the other to comparison status. "Intervention effects" were estimated for 200 such pairings and the original effect was considered significant if it was larger than 95% of these "pseudo" effects. Alternative methods of obtaining a distribution, including a pair permutation approach in which the original pairing of Baltimore and Washington stores was maintained but status (e.g. intervention or control) was randomly assigned, and simulations in which stores are randomly paired and assigned to control or intervention status in the Washington area, are being compared with the above approach from a methodological viewpoint.

Interactive Data Analysis Programs

The Section has previously developed and continues to maintain and improve a group of interactive computer programs for efficient analysis of medical data, particularly those dealing with risk factors and prognostic factors using sophisticated multiple regression techniques and survival analysis. These programs have proven useful not only for many projects within the Biometry Branch but also elsewhere in the Division, as well as by other investigators both within the NIH and at outside institutions. During the past year, the programs were modified to run on the NIH Convex Computer (which has replaced the older technology DECsystem-10).

During the past year, there has been further development of sample size and power formulas for use in case-control studies when response probabilities are heterogeneous within the control and exposed populations. Three models of the difference in average response probabilities between cases and controls are incorporated into a user friendly, interactive computer program.

Consultation on Clinical Trials and Other Studies (Z01 CN 00119-08 BB)

Community Intervention Trial for Smoking Cessation (COMMIT)

Extensive consultation has been provided to the staff of the Prevention and Control Extramural Research 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. The second survey of the Evaluation Cohort of 400 adults from each of the 22 communities designed to assess the

population-wide impact of COMMIT on intervention awareness, participation, and the decline of the social acceptability of smoking was completed in the summer of 1991. The full cohorts of heavy and light-to-moderate smokers were contacted for tracking purposes only. Biometry Branch staff have been actively involved in the analysis of COMMIT baseline data to characterize the smoking behavior of the minority populations in COMMIT and the attitudes regarding limits on public smoking and regulation of tobacco sales and advertising. A random sample of approximately 400 ninth grade students was surveyed in each of the 22 COMMIT communities in November, 1990. The survey was designed to measure the smoking knowledge, attitudes, and behavior of the ninth graders. Preliminary tables were distributed to the various school districts in May of 1991.

Additional analysis has focused on the cohort members who have been lost to followup or moved from the community to assess the potential biasing of the estimates of smoking cessation at the end of the trial. Branch staff have begun specifications for the design and content of the final cohort and cross-sectional prevalence surveys which are scheduled for springtime of 1993.

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, and interim analyses of the data have been performed. 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.

Accrual also continues on a third randomized trial, BTCG 89-01, that 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 (Edatrexate).

Followup has continued for previous BTCG studies. During the past year, a final analysis was undertaken for BTCG 83-01, demonstrating lack of efficacy for intra-arterial BCNU. The Group continues to plan studies to investigate improvements to the multimodality therapy of brain tumors.

Design Issues in Large-scale Intervention Trials Relating to Women's Health

The Section has been involved in consultations on two large-scale projects involving issues in Women's Health. One of these is the NCI sponsored randomized trial of tamoxifen for preventing breast cancer. Issues here have included projecting the probabilities of developing breast cancer for specific categories of women at high risk. The second is the new NIH Women's Health Initiative, where consultations have involved issues in the design of both a large-scale trial where individuals are randomized to various combinations of interventions to prevent cancer, cardiovascular disease, and osteoporosis, and a community trial comparing different behavioral intervention strategies applied at a community level.

Characterizing the American Diet

Work has been completed on a summary of national survey data on fruit and vegetable consumption. The data indicated strongly that during the 1970's through the mid 1980's, the time

period for which such data are available, consumption fell far short of the 5 or more daily servings of vegetables and fruit recommended by the DHHS and the USDA. For example, on any given day, large numbers of U.S. adults did not include any fruits or vegetables in their diet. This project generated considerable media interest, and interviews were given to help disseminate this information to the public.

A comparison of eating patterns of Whites, Blacks, and Hispanics using food frequency data from the 1987 Cancer Control Supplement to the 1987 National Health Interview Survey is being undertaken in collaboration with the Applied Research Branch. Very large and consistent differences in mean numbers of servings between Hispanics and other Americans were investigated using stratification methods and comparisons with other results in the literature. A new approach was developed in which the proportion of non-consumers and median intakes among consumers is estimated. This approach provides results more comparable to those of others. Dietary patterns of Cuban, Mexican, and Puerto Rican Americans are also being examined.

These data are also being used to characterize the nutrient content and numbers of servings of various foods for diets that are high in fat and diets that are low in fat, in collaboration with the Applied Research Branch and the Division of Cancer Etiology. Several methods of estimating the correlation between intake of fat and a variety of nutrients, which adjust differences due to age, sex, and caloric intake are being compared.

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.

Evaluation of the Primary Care Nutrition Guide

The Section has provided statistical consultation to the Public Health Applications Research Branch on the design of an evaluation of the NCI's Primary Care Nutrition Guide among internal medicine primary care physicians. A three arm randomized design, in which physician practices will be randomly assigned, will be used to evaluate the guide. The physicians assigned to the first arm will be given the guide and training on how to apply the guide to their practice. In the second arm, physicians will be given the Primary Care Nutrition Guide with training withheld. Physicians in the third arm will receive a different guide on smoking cessation and no training. About four months after training or after the mailing of the guides, the physicians in the study 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.

Design and Analysis of Pharmacokinetic Studies of Selenium (Z01 CN 00107-09 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. 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. These models suggest that there are important kinetic differences between selenite and selenomethionine. Selenium from selenomethionine was better absorbed and retained than selenium from selenite, and the whole-body turnover was greater. In contrast to selenite, which is excreted after turnover in the peripheral tissues, selenomethionine is reutilization. If recycled material is incorporated into metabolically active species, this reutilization could be advantageous and may have implications for cancer control.

An analysis of variations in total selenium levels in the plasma, urine, and feces, both within and between individuals consuming a special diet providing a constant intake of selenium, indicates high levels of within subject variability, especially fecal samples and 24-hour urine collections. This information suggests that plasma levels are preferable for measuring selenium status, but that multiple measures are desirable to enhance the precision with which status is measured.

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 how the natural history and risk characteristics of populations apply 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 database 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, supplemented with recent information, and compiled into a proceedings volume which will be published by Hogrefe and Huber Publishers. 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 database questionnaire has been developed and definition of terminology has been refined. Initial collection of data and conditions for participation in the international database were discussed at a meeting in London, England in July, 1991.

Studies in Cancer Screening (Z01 CN 00106-09 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 databases also provide an opportunity for the development and testing of new techniques for data analysis.

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 database 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.

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 continued 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. A collaborative effort was also initiated with investigators at Boston University who are involved in screening for skin cancer in the U.S. Study designs were considered for evaluation of such screening and work was begun on a publication to survey screening and prevention activities for skin cancer.

Screening Trial for Prostate, Lung, Colorectal, and Ovarian Cancer – the PLCO Trial

During the past year the staff of the Screening Section 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 PLCO Trial, namely the Study Coordinating and Data Management Center (CC), the Screening Centers (SCs), and the Laboratory to perform blood testing (Lab). This is a major trial of cancer screening in males and females for four cancers that comprise more than 50% of the incidence and mortality of cancer—lung, prostate, colorectal, and ovarian cancers. The trial design calls for a total sample size of 74,000 males and 74,000 females 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 among males and lung, colorectal, and ovarian cancers among females, 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, annual digital rectal examination and three-yearly flexible sigmoidoscopy for colorectal cancer, and annual pelvic examination, CA-125 marker and transvaginal ultrasound for ovarian cancer. The concept for this trial was approved at the January 31, 1991 meeting of the DCPC Board of Scientific Counselors. The RFP for the CC was issued on March 28, 1991 and the RFP for the SCs was issued on April 25, 1991. The RFP for the Lab is in preparation. Initiation of the pilot phase of the trial is planned for early 1992.

Research in Cancer Screening and Statistical Methodology (Z01 CN 00105-09 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.

Mortality Analysis of Screening Randomized Trials

The analysis of a cancer screening randomized controlled trial in which there is appreciable followup after the trial's screening intervention has stopped is difficult because the effect is diluted after screening ceases. This project considers the Overall Analysis involving all the individuals randomized and a Limited Analysis based on subgroups of individuals with cancer diagnosed during defined periods from entry into the study. A simple model has been developed to demonstrate and estimate the dilution that can occur depending upon the analysis done. Statistical testing procedures are presented and illustrated for the two analysis approaches.

The determination of comparable case groups is critical to the validity of the Limited Analysis. Procedures to assess comparability of subgroups of cancers are investigated. The cancer incidence and covariates that reflect the natural history of the cancers are considered. First, the cancers in the subgroups being considered as possible comparable groups to be used in the Limited Analysis are examined. Second, the cancers that arise after these candidate groups are defined are investigated for their comparability. If these are not comparable, the candidate cases cannot be. This consideration of the late cancer groups has not been explicitly suggested previously.

Case-Control Studies

This project focuses on the ability of the case-control study to provide estimates of the efficacy of screening, 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 has been demonstrated that this, in general, results in 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.

Work is currently underway to assess available cancer screening models for use in simulating case-control screening studies. One promising candidate is the MISCAN model developed by investigators in the Netherlands. The chosen model will be used to simulate both screened and unscreened populations under various conditions involving alternative levels of compliance, self-selection bias, screening benefit and other variables. Case-control studies will be conducted in the simulated populations, where the truth is known, to determine the magnitude and direction of bias in the case-control design in various settings.

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 I and that the older age group had a beneficial shift of usual stage II cancers to stage I.

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. Simple methods have also been developed for finding the observed information matrix when using the EM algorithm with missing categorical data. A symbolic method has been developed for determining identifiable models in experimental designs involving 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

To analyze grouped survival data subject to informative censoring, the following two-part model has been proposed: a logistic regression model for the hazard for failure, given covariates, and a logistic regression model for the hazard for informative censoring, given time of failure and covariates. The model can be applied to survival data arising from a double sampling design: in a full followup (FF) sample, subjects are followed after censoring, and in a partial followup (PF) sample, subjects are not followed after censoring. The methodology has wide applications in clinical trials where censoring is due to leaving the study because of difficulties in compliance with the protocol, occupational epidemiology studies where censoring results from leaving the workplace, and hospital mortality studies where censoring is due to hospital discharge. Under some circumstances, the

model can also be applied to data arising from only a PF sample. Design considerations for double sampling have been investigated and a score test for informative censoring has been developed.

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.

Estimation of Lead Time and Benefit in Randomized Screening Studies

To evaluate the effectiveness of screening for disease, randomized clinical trials offer the most objective comparison between survival of screen-detected cases versus clinically-detected cases, particularly because an estimate of the benefit of screening in nonrandomized studies may be confounded by the bias due to lead time in detection of disease by screening. It is important to have an estimate from randomized trials of the average lead time due to a screening method, particularly in relation to the true benefit, in order to prepare for the psychological consequences of the advanced knowledge and costs of treatment for the disease. Methods are developed to estimate not only the benefit of screening unaffected by lead time bias but also the average lead time. Measurements on covariates are considered in assessing the existence of a possible dependence of lead time on the benefit or on other variables. Application of the methodology to data from previous randomized screening trials is being pursued.

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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:

- Conducting epidemiologic studies relating dietary, genetic, and lifestyle factors to the etiology of cancer;
- 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 to test the effect of nutritional and chemopreventive agents and diet modification in reducing cancer risk;
- Conducting studies to evaluate potential methods of early cancer detection; 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 FY91.

Etiologic Studies:

NHANES I Epidemiologic Followup Survey: Chemoprevention/Nutrition Aspects
(Z01 CN 00104-09 CPSB)

The purpose of the NHANES (National Health and Nutrition Examination Survey) Epidemiologic Followup 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 followup 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 targetted 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 followup 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 followup 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.

Followup of this cohort has continued. The 1986 followup of the elderly focused on the 3,850 subjects from NHANES I who were over 75 at the time of the 1981-84 followup. The 1987 followup 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. Future followups are also proposed which will extend the period of observation of this cohort to an average of over 20 years. A concept was recently approved for CPSB to contribute $400,000 toward additional followup, which will include an interview in 1992 as well as collection of hospital and death records.

Preliminary estimates indicate that the yield of cancer cases has increased by approximately 40% through the end of the 1987 followup, relative to the number of cases identified through 1984. Since the 1981-84 followup 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. Other analyses in progress include the relation of vasectomy to prostate cancer and the modifying effects of physical activity (as a proxy for underlying disease) on the cholesterol-cancer association.

This epidemiologic followup 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 Followup of the Breast Cancer Detection and Demonstration Project (BCDDP)
(Z01 CN 00143-07 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 followup (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 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 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 followup of the LTF subcohorts was completed in 1990, and further followup is being planned.

Our analysis of data from the first 5 years of followup 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 00146-03 CPSB)

The objective of this project was to develop a cancer database 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 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 (central adiposity ratio, defined as the ratio of the sum of central/peripheral skinfold thicknesses) and breast cancer in women. There was no association between degree of adiposity, as measured by the sum of the five skinfolds or by body mass index (weight in kg divided by height in m^2) and subsequent breast cancer.

We also studied the relation between self-reported physical activity and large bowel cancer. Inactivity was associated with an increased risk of large bowel cancer in men but not women. The narrow range of physical activity and the minimal heavy activity reported by women in this cohort may have limited our ability to detect an inverse association in women.

We have recently completed an analysis of serum lipoproteins and large bowel cancer. This 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. We are also investigating the relation of physical activity and breast cancer in women.

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

Nutritional Factors and Cancer in the Framingham Offspring Study (Z01 CN 00147-03 CPSB)

The objective of this project was to develop a cancer database 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 in Boston, MA and the National Heart, Lung, and Blood Institute.

Finland Studies of Nutrition and Cancer (Z01 CN 00148-03 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, including breast and lung, are being assessed. Analyses to date have revealed an 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 00149-03 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 diet in the incident case-control study found that even after controlling for other risk factors (i.e., radon, arsenic, tobacco), a protective effect was observed among men with the highest (as compared with the lowest) intakes of yellow/light green vegetables and tomatoes.

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.

Esophageal Cancer Genetics Studies (Z01 CN 00150-03 CPSB)

The overall goal of this project is to develop an understanding of the genetic as well as environmental influences involved in the etiology of esophageal cancer. The study is being conducted in North Central China where rates of this cancer are the highest in the world and where genetic factors are suspected of playing an important role. Specific objectives of the studies are 1) to determine if esophageal cancer aggregates in families, 2) to study the genetic transmission or segregation of esophageal cancer within families, 3) to distinguish genetic versus environmental influences in the etiology of esophageal cancer, and 4) to assess family history of esophageal cancer as a risk factor for the disease. To accomplish these objectives, data from several sources have been drawn together, including multi-generation family pedigrees collected in 1979 from an entire county in Shanxi Province, supplemented with information from a subset of families in selected villages who were reinterviewed in 1989 to update pedigrees and vital status data; multi-generation family pedigrees from 24 high-risk families in Hunan Province; and a small case-control study conducted in Shanxi Province.

Results thus far indicate that subjects with a positive family history had nearly an 8-fold risk of esophageal cancer compared to subjects with a negative family history. Segregation analysis using data from Hunan Province were most compatible with genetic transmission by an autosomal recessive gene.

This study is being conducted collaboratively with scientists at the Chinese Academy of Medical Sciences.

Fels Early Nutrition and Growth Study (Z01 CN 00154-02 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 available from the Fels Study and the Division of Human Biology of the Wright State School of Medicine have been linked to calorie, macro- and micronutrient data for 106 girls. Adult height and weight are also available. 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).

A validation substudy of remote dietary recall is also being conducted. Retrospective food frequency questionnaires asking about food habits during adolescence are being sent to some of the now adult women. These will be compared to dietary records for these girls as teenagers.

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

Clinical Nutrition Studies:

Human Studies of Diet and Nutrition (Z01 CN 00101-09 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 non-smokers 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-tetra-norprostaten-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. Calcium, magnesium, manganese, iron, zinc and copper intake, and fecal excretion 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 that purified beta-carotene produced a substantially greater plasma response than similar quantities of carotenoids from food sources. However, some foods, such as carrots and broccoli, did increase plasma levels of certain carotenoids. 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 conducted a clinical metabolic study to examine the effect of alcohol ingestion on hormonal status as one potential mechanism of action. Preliminary results from the controlled feeding component of the study indicate that consumption of the equivalent of two drinks per day in premenopausal women results in significant elevations in several hormones. Plasma DHEA sulfate increased in both the follicular and luteal phases, and plasma estrone and estradiol increased in the peri-ovulatory phase while urinary estrone and estriol increased in the luteal phase. While further evaluation of the cross-sectional component of the study is in progress, these results suggest that alcohol consumption may lead to greater exposure of the breast to estrogens.

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 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, immune function, and prooxidant stress. Forty healthy male volunteers 24-57 years of age consumed a controlled basal diet providing 40% of energy from fat (P:S ratio about 0.8:1), 130 mg/1000 kcal cholesterol, and a minimum of 23 mg/day of alpha-tocopherol for three experimental periods lasting a total of 28 weeks. During period 1 (10 weeks) the diet was supplemented with placebo capsules (15 x 1 g/day) consisting of a blend of fats approaching the fatty acid profile of the basal diet. This was followed by a second 10-week period during which the subjects received 15 x 1 g/day capsules of fish oil concentrate. During period 3 (8 weeks) they continued the 15 g/day intake of fish oil concentrate but received an additional 200 mg/day of alpha-tocopherol. Results to date showed a 14% reduction of prostaglandin M, the excretory metabolite of prostaglandin E after 10 weeks of fish oil concentrate supplementation compared to the placebo supplementation period. Fish oil supplementation suppressed blastogenesis (as measured by the mitogenic response of peripheral blood mononuclear cells), but this effect was reversed by concurrent supplementation with alpha-tocopherol.

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 the 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 00153-02 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.

All six DISC clinical centers have agreed to participate in the NCI sponsored ancillary study on hormones. A total of 663 children were randomized into the intervention and control groups. Children enrolled in the trial were girls 7.8-10.1 years old or boys 8.6-10.8 years old who had LDL-cholesterol levels between the 80^{th} and 98^{th} percentile but who were 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 75 mg/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 followup. Additional followup 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; University of Pittsburgh in Pittsburgh, PA; and the University of Iowa in Iowa City, IA.

Prevention Studies:

Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (Z01 CN 00100-09 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 followup 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.

An additional study ancillary to the ATBC Study was initiated which will determine the effect of the intervention agents on the development and progression of chronic atrophic gastritis, gastric dysplasia, and gastric adenocarcinoma, conditions with high prevalence in Finland. This ancillary study is being conducted collaboratively with 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 00103-09 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 have been completed and a manuscript reporting the results of the 3-year intervention phase has been submitted for publication.

This study is being conducted collaboratively with the Surveillance Program of the Division of Cancer Prevention and Control; the Walter Reed Army Medical Center in Washington, DC; the Fitzsimmons Army Medical Center in Aurora, CO; the Brooke Army Medical Center in San Antonio, TX; the Eisenhower Army Medical Center in Augusta, GA; the Portsmouth Naval Medical Center in Portsmouth, VA; Northwestern University in Chicago, IL; the University of Arkansas in Little Rock, AK; and the Roswell Park Memorial Institute in Buffalo, NY.

Nutrition Intervention Studies of Esophageal Cancer in Linxian, China
(Z01 CN 00112-08 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 6-year active intervention phase of the Dysplasia Trial concluded in the spring of 1991. The General Population Trial will continue until the fall of 1991. Additional cytologic and histologic surveys were conducted among participants from both trials in the spring of 1991. Post-intervention followup is planned for participants from both trials.

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 00151-03 CPSB)

The primary objective of this study is to determine whether a low fat, high fiber, and high fruit and vegetable dietary pattern will decrease the recurrence rate of adenomatous polyps of the large

bowel. A secondary objective of this study is to determine how this dietary pattern affects markers of large bowel epithelial cell proliferation, whether the proliferation markers predict neoplasia (polyp recurrence), and to what extent changes in proliferation indexes account for the observed intervention effect.

Large bowel cancer is the second leading cause of death from malignant disease in the United States. It is estimated that over 150,000 persons in this country will be diagnosed with large bowel cancer this year and over 60,000 people will die from the disease.

The evidence that diet plays a key role in large bowel carcinogenesis is strong and growing. A large body of ecologic, analytic epidemiologic, human metabolic, and animal experimental data suggests that three dietary factors increase the risk of large bowel cancer: high dietary fat, low dietary fiber, and low fruit and vegetable intake. The intervention diet is targeted toward achieving a dietary pattern consisting of 20% of calories from fat, 18 g of total dietary fiber per 1000 kcal, and 5-8 daily servings of fruits and vegetables. The usual diet for the control group, based on data from the NHIS, is expected to comprise 36-38% of calories from fat, 10-15 g per day of dietary fiber, and 3.5 servings of vegetables and fruits daily. By embracing three promising dietary hypotheses simultaneously, the low fat, high fiber, vegetable and fruit-enriched intervention diet is intended to maximize the possibility of reducing polyp recurrence. We emphasize that the demonstration of any effect of diet on the neoplastic process would be a major advance that would spur further research in this area.

Fat, fiber, and vegetables and fruits do not represent the only dietary hypotheses for large bowel cancer. However, a dietary pattern comprising low fat, high fiber, and enhanced vegetable and fruit consumption is likely to be accompanied by reductions in the consumption of, for example, meat, food mutagens, and total calories, each of which has been implicated in large bowel carcinogenesis.

Large bowel adenomas (polyps) present a unique opportunity to conduct an intervention trial because of the high prevalence of these lesions in the general population (over 30% in adults over 50 years of age), the high polyp recurrence rate (over 10% annually) in those who have undergone polypectomy, and the strong link between polyps and cancer. It is generally accepted that large bowel adenomas are an obligate precursor lesion for most large bowel cancers. An intervention, therefore, that reduces the recurrence of large bowel polyps would have a strong likelihood of reducing the incidence of large bowel cancer.

Micro-level mechanisms in large bowel carcinogenesis (or events tightly linked to such mechanisms) may serve as intermediate endpoints if an exposure-induced change in the endpoint would necessarily imply a similar exposure-induced change in the occurrence of neoplasia. Studies that utilize cell proliferation markers as endpoints are extremely interesting and suggestive, but it remains to be resolved whether inferences about cancer (or neoplasia in general) from these studies are valid. In a prospective study like the Polyp Prevention Trial, it is possible to relate diet to the intermediate endpoint, the intermediate endpoint to adenoma formation, and finally to determine the extent to which any diet-adenoma relation is mediated by changes in the intermediate endpoint.

A positive diet-adenoma finding from this trial, taken in conjunction with the emerging findings on diet and large bowel cancer from existing and planned large cohort studies, will bring us very close to proving a causal link between diet and large bowel cancer, thereby providing a scientific foundation for a practical biologically sound strategy for preventing this disease.

This will be a multi-center, randomized, controlled trial involving 2,000 men and women. The projected sample size of 2,000 (1,000 in each of the intervention and control groups) will permit the detection with 90% power of a reduction of 24% in the polyp recurrence rate. Potential participants who have an adenoma removed within three months, meet the eligibility criteria, successfully fill out a series of dietary assessment instruments (a form of "run-in"), and complete the informed consent

will be randomized into the study. Randomization at each Clinical Center is expected to take up to 2 years. Participants will undergo colonoscopy again at one and four years into the study. Although the recurrence of one or more adenomas is the primary endpoint of the study, it will also be possible to relate the dietary intervention to number, size, and histotype of polyps.

One of the critical (and expensive) components of this trial is intensive nutrition counselling of participants in the intervention group. The general nutrition intervention strategy will integrate the teaching of nutrition skills, self-monitoring techniques, behavior modification techniques, and social support systems. The major strategy for the nutrition counselling will be a step-by-step approach to dietary change based on the needs and abilities of the individual participant. Group counselling will be implemented in the second year of followup. The control group subjects will be provided, if needed, with counselling and education materials on basic nutrition principles for maintaining nutritionally adequate diets, with no emphasis being placed on modification of fat, fiber, or vegetable and fruit intake. The nutrition intervention materials have been developed by the Project Officers in conjunction with other CPSB and DCPC staff.

For dietary assessment, food frequency questionnaires and 4-day diet records will be administered prior to randomization and annually after randomization. In addition, unannounced 24-hour dietary recalls will be administered by telephone to a 10% sample of participants on a yearly basis. Blood specimens will be also be collected for analysis of serum lipids, carotenoids, and other parameters; blood will also be stored for possible DNA analysis.

In order to perform the intermediate endpoint studies, rectal (and possibly other) biopsy specimens will be obtained at baseline and at or shortly before each of the colonoscopic procedures. Both bromdeoxyuridine and proliferating cell nuclear antigen assays will be performed on the biopsy specimens.

Awards for the Data and Nutrition Coordinating Center and the 10 Clinical Centers were made in September, 1990. Three of the Centers are serving as Vanguard Centers and began randomization in June, 1991. The other Centers will begin randomization in October, 1991.

This study is being conducted collaboratively with scientists from the Biometry Branch and the Diet and Cancer Branch of the Division of Cancer Prevention and Control; the University of Pittsburgh in Pittsburgh, PA; the Kaiser Foundation Research Institute in Oakland, CA; the Memorial Sloan Kettering Cancer Center in New York, NY; the University of Illinois in Chicago, IL; the Kaiser Foundation in Portland, OR; the State University of New York at Buffalo, NY; the Walter Reed Army Medical Center in Washington, DC; the University of Utah in Salt Lake City, UT; and the Edward Hines Jr. Veterans Administration Hospital in Chicago, IL.

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.

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.

A database with specific carotenoid values of foods has recently been completed as a joint effort of the USDA and the NCI. This database will be used to determine the carotenoid content of fruits and vegetables which have been inversely associated with cancer incidence from available epidemiologic databases. Another focus of this effort will be on the comparison of estimates of the diet-cancer relation with earlier analyses as well as the exploration of the carotenoid-cancer relation for foods rich in specific carotenoids and for different cancer sites. In addition, the diet-plasma carotenoid relation will be examined among high-risk groups for cancer. Different dietary methods to assess carotenoid status in the same individual and among individuals have been used in epidemiologic studies and differences in carotenoid status by method will be compared as well as the diet-plasma correlations. Moreover an effort will be undertaken to develop a core set of questions that reflect carotenoid intake across various demographic sub-groups in the United States.

A large number of studies have shown that increased body size is associated with an increased risk for cancer, especially cancers of the breast and colon. The direct relation of height to cancer suggests a role for remote nutrition, particularly total caloric intake during growth, in carcinogenesis. Physical inactivity has also been linked to colon cancer. We plan to further explore the hypotheses that body size and physical activity are 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 and breast cancer risk factors among children. Methodologic questions about the assessment of dietary intake in youth via questionnaires administered to adults will also be addressed.

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.

Plans are being developed to prospectively examine lung cancer risk factors—including diet, radon, arsenic, and tobacco exposures—as well as genetic factors and micronutrients in greater detail among the tin miners in Yunnan Province, China.

Plans have been initiated to determine the feasibility of developing a sputum bank which could be used to test for early markers of lung cancer among these tin miners.

Initial evaluations indicate that there is substantial value for balloon cytology in predicting subsequent esophageal cancer among subjects living in high-risk areas for esophageal cancer in Henan Province, China. Plans are underway to further evaluate the usefulness of balloon cytology in identifying precancerous and early cancerous lesions of the esophagus. In addition, we are planning to compare a number of new non-invasive methods of treating early esophageal lesions through the endoscope. If these strategies prove to be as promising as they appear, we will consider conducting a screening trial using these techniques.

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.

We are considering conducting a carefully controlled dietary study in postmenopausal women to evaluate changes in hormone levels, percent body fat, and body fat distribution as potential mechanisms to explain the observed association between weight loss and breast cancer in postmenopausal women.

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 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.

It has been reported that men, smokers, drinkers of alcohol, and women taking oral contraceptives have significantly lower plasma alpha- and beta-carotene levels. It is unknown whether this is due to differences in dietary intake or metabolism. Using a series of approaches, including analyses of existing samples from previous studies, new controlled feeding studies, and new studies using C-13 labelled isotopes, we plan to examine these observations and study the metabolism and distribution of specific carotenoids among individuals with constitutional and lifestyle factors that can influence plasma carotenoid levels.

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 scheduled to complete active intervention by 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 followup of this cohort through the Finnish cancer registry after the intervention phase has been completed. Some form of active followup is also under consideration at this time.

The ISO-BCC Study concluded active intervention in June 1990 and an average of 18 months of 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—work is in progress 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, and the natural history and evolution of skeletal hyperostosis in the control population; we also plan to further elucidate the risk factors (including diet) for basal and squamous cell skin cancers.

The Linxian nutrition intervention studies will conclude active intervention in 1991 and a 5-year post-intervention followup 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 has just started to randomize participants and is planned to run through 1997.

There have been very few clinical trials conducted which determine the effect of chemopreventive agents on biological markers or surrogate endpoints in high-risk populations. One such trial currently being planned will involve determining the success of promising new chemopreventive agents in reducing bronchial metaplasia among a small group of tin miners in China, an occupational group with exposure to tobacco, radon, and arsenic, who have lung cancer rates among the highest in the world. Two particularly promising groups of compounds in various stages of testing being considered for use here are the retinoids (synthetic analogues of vitamin A) and the dithiolthiones (purified substances found in a number of the cruciferous vegetables).

Nutritional assessment of the Yunnan, China tin miners suggests that intake of several micronutrients, most notably selenium and beta-carotene, is low. We are considering the possibility of conducting a nutritional intervention study using nutrients such as these among several thousand of these high-risk miners to try to prevent lung cancer.

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Laboratory of Nutritional and Molecular Regulation

OBJECTIVES

The overall objectives of the Laboratory of Nutritional and Molecular Regulation can be summarized as follows:

- 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.

OVERVIEW

During the past year, the LNMR has actively recruited a scientific staff representing various disciplines to carry out its objectives to elucidate mechanisms relevant to diet, nutrients, and cancer prevention. This multi-disciplinary approach using the methods and strategies of nutritional science, biochemistry, molecular biology, and cell biology will focus on epidemiologic relationships between diet and cancer.

ACCOMPLISHMENTS AND PLANS

A New Mechanism for Carcinogen Resistance: Regulation by Diet and Nutrients
(Z01 CN 00155-01 LNMR)

Chemical carcinogenesis has been the subject of intense study, and these studies have emphasized primarily activation and detoxification mechanisms. However, the concept of cellular resistance to carcinogens based on cellular efflux mechanisms has not been previously invoked. We proposed that the efflux pump, mediated by a plasma membrane glycoprotein (P-gp) and coded for by MDR1, not only confers resistance to pleotropic cytotoxic drugs but also to chemical carcinogens. Using a series of human breast cancer cells (MCF-7) with different stages of adriamycin resistance which correlated with expression of P-gp, we showed that resistance to benzo(a)pyrene is correlated to its cellular efflux mediated by P-gp. Findings supporting this hypothesis included 1) increased IC_{50} for benzo(a)pyrene corresponding to increased P-gp levels; 2) increased rates of benzo(a)pyrene efflux corresponding to increased P-gp levels; 3) inhibition of benzo(a)pyrene efflux with verapamil, a known inhibitor of the P-gp mediated efflux pump for cytotoxic drugs; and 4) benzo(a)pyrene inhibition of azidopine binding to P-gp.

Having established that cellular resistance to benzo(a)-pyrene can be mediated by P-gp, we will undertake additional studies to elucidate mechanisms by which nutrients regulate P-gp expression or modulate its function. Application to both cell culture and animal models of carcinogenesis will be necessary to establish the relevance of this new mechanism for carcinogen resistance. Characterization of the expression of the genes MDR1 and MDR3 will be undertaken to better understand the molecular mechanisms by which dietary constituents regulate the efflux pump.

Protection Mechanisms Against Endogenous Carcinogens and Nutritional Regulation in Placenta-Related Cells (Z01 CN 00156-01 LNMR)

We have proposed that plasma membrane glycoprotein 170 (P-gp), responsible for multidrug resistance (MDR), also may function as a chemical carcinogen efflux pump that can be regulated by diet and nutrients. The placenta is known to express high levels of P-gp but its function in this tissue has not been elucidated. We considered placenta-related cell lines a useful model for studying nutrient-dependent regulation of P-gp. Of special interest is the exposure of placenta to high levels of sex hormones which are known to interact with P-gp. We will examine the expression of the genes MDR1 and MDR3 in transformed SV40-mutant amnion epithelial cells, in transformed placental trophoblast cells, in placental fibroblast cells, and in choriocarcinoma cells. Regulatory agents including the MDR competitor progesterone, the MDR enhancer estradiol, and nutrients such as retinoic acid, dexamethasone, and dibutyryl cyclic AMP will be examined for their regulatory roles in the expression of MDR and the prevention of carcinogenesis.

The Effect of Proteins, Peptides and Amino Acids on Carcinogenesis
(Z01 CN 00157-01 LNMR)

Renewed interest in protein intake and cancer incidence has focused on qualitative differences in proteins from various sources as well as on the contribution of proteins to total caloric intake. We proposed a novel mechanism mediating the effect of proteins on mitogenesis and carcinogenesis. Our hypothesis is based on the known modulatory effects of proline and its oxidized intermediate, pyrroline 5-carboxylate, on metabolic events in post-receptor signaling. Additionally, iminodipeptides—dipeptides with proline or hydroxyproline at the carboxyl terminus—are delivered to tissues and hydrolyzed by a specific enzyme, prolidase. We showed that these iminodipeptides can serve as an important source of proline for cells. A cultured cell line auxotrophic for proline attained maximal growth rates on GLY-PRO in the absence of added free proline. This finding showed that dietary sources of protein supplying different levels of iminodipeptides could differentially deliver proline to tissues. Another interesting feature of pyrroline 5-carboxylate is its function as an intercellular communicator. We showed that the cellular release of pyrroline 5-carboxylate is augmented by insulin and IGF-1. Feeding studies in rats under a variety of dietary conditions will provide a better understanding of the regulation of pyrroline 5-carboxylate levels in plasma.

These regulatory mechanisms involving proline and pyrroline 5-carboxylate may be especially relevant to prostate tissues. Since prostate epithelial cells are known to exhibit special metabolic features, e.g. the secretion of large amounts of citrate derived presumably from aspartate, the metabolism of amino acids, and the regulation of the redox and energy states are critically important. Additionally, the conversion of testosterone to dihydrotestosterone, a redox-dependent enzymatic step, is considered critical for progression of prostatic cancer. The linkage of proline and pyrroline 5-carboxylate to these metabolic and redox features may be specially important for prostatic cancer. We will investigate the importance of the proline cycle and pyrroline 5-carboxylate-mediated events in both rat prostate tissues and in normal and malignant cultured human prostate cells.

Finally, the gene for human pyrroline 5-carboxylate reductase has been cloned. This enzyme is critical in the regulatory effects of pyrroline 5-carboxylate. We are raising polyclonal antibodies to

peptides based on the deduced sequence. These antibodies will allow studies on enzyme localization and on mechanisms linking pyrroline 5-carboxylate to its modulation of post-receptor signaling.

Dietary Lipids and Signal Transduction in Breast Cells (Z01 CN 00158-01 LNMR)

Although associations between dietary fat and increased risk of cancer have been known for some time, a clear understanding of the mechanistic relationship between fat and carcinogenesis has remained elusive. The influence of dietary fat on the production of lipid mediators and the regulation of membrane phospholipases are emphasized in this project. A cell culture model using tumorigenic and nontumorigenic human breast epithelial cells is used to study the effects of membrane lipids on cell signaling mechanisms. These cells respond to a number of agonists which stimulate phospholipase D to release phosphatidic acid and diacylglycerol from membrane phospholipids. Using newly developed methodologies, we have produce marked changes in the fatty acid composition of membrane lipids. The consequences of these membrane changes on membrane signaling, mitogenesis, and on the function of carcinogen efflux mechanisms are being investigated.

Regulation of Tumor Supressor Protein p53 (Z01 CN 00159-01 LNMR)

The involvement of the tumor supressor protein p53 in tumorigenesis is well-established but the regulation of p53 function at the molecular level is not understood. Phosphorylation and dephosphorylation of p53 are attractive possibilities in this regulation. Using a molecular biological approach, we have substituted serine residue 315 with alanine in p53. Serine 315 is known to be phosphorylated by cell cycle-dependent kinases. A cell culture system is being developed to assess the functional consequence of this change in p53. Another site for phosphorylation-dependent regulation is serine 298. This residue may be phosphorylated by casein kinase II. We plan to identify and characterize nutritional and/or hormonal factors which may modulate the phosphorylation state of p53 thereby regulating its function.

Nutritional Regulation of Ras Proto-oncogene Activity (Z01 CN 00160-01 LNMR)

The important role of mutant ras gene products in a variety of human cancers has been well established. In addition, elevated levels of unmutated ras proteins are found in many colon and breast cancers. Ras-mediated escape from normal regulation appears to be a frequent event in the multi-step genesis of cancer. Of special interest to us are these questions: "Do changes in nutritional status affect ras activity?" and "How do these nutritional manipulations interact with regulation of proliferation by growth factors and hormones?" Several observations suggest that nutritional status may affect ras activity: a yeast equivalent of a key regulatory protein acts as a sensor for nutritional status; certain lipids have been shown to have both direct and indirect effects on ras activity. We have set up a cell culture system using cells Y-1 and MCF-7 which have high levels of ras expression. These cells, respectively, express 20 to 50 and 5 to 10-fold the level of normal ras protein seen in other cell lines. They will enable us to investigate the effects of a wide variety of lipids, growth factors, and other modulators on ras activity. We will assess this modulation by ras membrane localization, post-translational modifications, bound guanine nucleotide ratios, and mRNA levels.

An *in vitro* Model to Assess Biochemical and Molecular Biological Effects of Dietary Fiber on Colonic Cell Lines (Z01 CN 00161-01 LNMR)

Although dietary fiber intake has been associated with decreased rates of colon cancer, the mechanisms for this protective effect are not well understood. Investigators have emphasized the effects of fiber on intestinal transit time and on the possible binding of potential carcinogens by

fiber. We propose that fiber may play a more active role. Many fibers can be degraded by colonic microflora to yield complex carbohydrates; these complex carbohydrates may play an important metabolic role in the growth and regulation of colonic mucosa cells. We will incubate various fibers with human fecal inoculum under anaerobic conditions and then will isolate and characterize the resultant complex carbohydrates. The characterized molecules will be added to cultures of two colonic cell lines, LS 174 and CCD 841, and their effects on these cells will be assessed by measurements of mucin production, PGE_2 synthesis, induction of ornithine decarboxylase, and expression of C-myc.

Effects of Vitamin A Nutriture on Retinoid Metabolism (Z01 CN 00162-01 LNMR)

There is a large body of evidence suggesting that important relationships exist between retinoids and cancer. Both a therapeutic and preventive role for retinoids have been indicated. Relevant to the role of retinoids in carcinogenesis, we are investigating the effects of supplementation of diets either low or normal in vitamin A content with synthetic retinoids on retinoid turnover. As expected, plasma retinol declined in animals supplemented with synthetic retinoids. We are now performing *in vivo* tracer kinetics of retinol metabolism. Following IV injection of radiolabelled retinol associated with its normal plasma transport protein, retinol-binding protein, we are collecting samples of plasma, tissue, urine, and feces over a 40 day period. Labelled and unlabelled vitamin A compounds will be characterized and quantitated. Using physiologically based computer modelling and multicompartmental analysis techniques, we will develop mathematical models of vitamin A metabolism. These models will provide both quantitative and descriptive information concerning the movement of retinoids among tissues, uptake and utilization of retinoids by tissues, and how synthetic retinoids affect vitamin A metabolism. In addition, we are establishing methodologic approaches to test physiologic control mechanisms deduced from the mathematical model. These approaches include the cellular uptake and processing of vitamin A in isolated tissues and cultured cells.

LABORATORY OF NUTRITIONAL AND MOLECULAR REGULATION STAFF

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LABORATORY OF NUTRITIONAL AND MOLECULAR REGULATION BIBLIOGRAPHY

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BIOMARKERS AND PREVENTION RESEARCH BRANCH

OVERALL OBJECTIVES

The Biomarkers and Prevention Research Branch, composed of the Office of the Chief and the Experimental Biochemistry Section, was administratively approved in early 1991. An off-campus facility is being acquired to house the administrative and laboratory activities of this group. The objectives of the Branch which is projected to occupy its space in late 1991 are summarized in its functional statement:

- "Plans, develops and conducts intramural research to identify new tools for the early detection of epithelial cancers.
- Establishes tissue banks which permit validation of new early detection and intermediate end point markers.
- Validates the utility of intermediate end point markers which could be used in carefully designed cancer intervention trials.
- Trains clinical and basic science professionals who are interested in rational prevention development.
- Facilitates the development of technologies which enable large scale screening and prevention trials.
- Coordinates activities with other divisional elements to facilitate clinical trial development and to achieve interaction with relevant groups.
- Plans, develops and conducts intramural clinical in the biochemical pathways of neuroendocrine and epithelial cancers.
- Identifies *in vitro* and *in vivo* tumor model systems which allow systematic evaluation of pathways that are amenable to specific biochemical inhibition.
- Evaluates specific tumor inhibitors from *in vivo* and *in vitro* studies which would lead to FDA approval for clinical trials.
- Interacts with other Branch elements to conduct multidisciplinary clinical and basic science projects."

AREAS OF RESEARCH EMPHASIS AND SPECIFIC OBJECTIVES

Pilot study of peptide growth factor antagonist for the prevention therapy of lung cancer.

Investigators of the Biomarkers and Prevention Research Branch have been central to the identification of gastrin releasing peptide (GRP) as a potential tumor promoter in lung cancer. A specific monoclonal antibody to GRP has been used in a clinical trial to determine if neutralizing the growth factor is of clinical benefit. Due to progress in the field of protein chemistry a peptide antagonist, which we have shown to block growth of small cell lung cancer cells in nude mice, is now available

for testing in humans. This will provide an opportunity to evaluate the relative benefits of a peptide antagonist versus monoclonal antibodies to determine which is more suitable for application as a rational intervention agent. To facilitate pharmacologic analysis, this study would also involve the use of tracer radionuclide doses to permit precise analysis. Radionuclide imaging work would be done in collaboration with the NIH Nuclear Medicine Department as they participated in the previous chemical trials analysis of radiolabeled GRP monoclonal antibodies.

Studies of early activation events in patients with "epithelium at risk."

To obtain relevant clinical materials, a protocol will be developed to systematically study the remaining organ at risk in (or normal tissues removed from) individuals who have undergone curative treatment for lung, colon, breast, or ovarian cancer.

Individuals who have experienced a cancer at any of these sites still have an increased risk of developing subsequent primary cancers in the same or a related site. We propose to accrue and serially follow a cohort of these patients to obtain relevant followup material (for example, with sputum specimens, breast aspirates, endoscopic, or bronchoscopic biopsies) so that genetic and biologic marker expression can be catalogued. When possible their results will be compared to the biologic characteristics and molecular phenotype of the patient's original tumor. Research and development for new early detection tools requires ongoing access to such material. In addition, an understanding of the early genetic events in the development of epithelial cancers may suggest preventative intervention strategies. As part of the monitoring protocol, prompt referral of protocol subjects to appropriate oncologic specialists when new cancers are detected by the laboratory analysis will be a required aspect of the study.

Use of photodynamic laser therapy to control early lung cancer.

If an early detection tool (sputum immunocytochemical analysis) is shown to be effective in screening for individuals with early stages of lung cancer, individuals with cancer confined only to the epithelium of the lung airways would be identified much more frequently. Currently, no approach is available for treating the disease at this early phase. However, one can administer porphyrin compounds, which are taken up in rapidly dividing tissues, and couple that with exposure to laser light to destroy areas of cancerous cells in lung airways. The laser light excites the porphyrin in the tissue and preferentially kills the malignant cells. This may be beneficial, since this approach could destroy foci of early cancer, particularly those that can arise in areas of chronic injury. Conceptually, this would be similar to removing colon polyps in an individual being routinely screened due to a high risk for colon cancer.

Scientists at the Los Almos National Laboratories have developed a new class of porphyrin, which is copper-based rather than iron-based. In collaboration with this group and other NIH groups, we propose to do a preliminary clinical evaluation of this compound to determine its utility in photodynamic laser therapy of the airway.

We are developing this compound because of the advantage it affords in that the copper in the porphyrin ring can be replaced with radioactive copper. This radiolabeled compound allows localization of the porphyrin within the airways. Investigators from the Biomarkers Branch and NIH Nuclear Medicine Department have collaborated before to do this type of analysis (to define the localization of monoclonal antibodies in lung tissue). If successful, this analysis may provide another effective therapeutic approach to early lung cancer. Through the use of Nuclear Medicine techniques, direct airway delivery of this copper porphyrin carrying a very high energy radionuclide could be used to directly destroy the potentially cancerous sites within the lung airway. The accuracy of this approach could be further refined by coupling the copper porphyrin to monoclonal antibodies which then specifically bind areas of carcinogenic injury.

This challenging research project requires research strength in several diverse areas from several different groups. Fortunately these groups already exist at the NIH and Los Almos and have a track record of effective collaboration.

Pharmacology of established chemopreventional agents.

Studies have recently suggested a role for tamoxifen and 13 cis retinoic acid as chemoprevention agents for breast cancer and upper aerodigestive cancers (head and neck, esophageal, and lung cancer), respectively. To date, the critical information regarding the lowest possible effective dose as well as the heterogeneity of drug metabolism in the general population have not been established. In collaboration with pharmacologists from the Food and Drug Administration, investigators for the Biomarkers and Prevention Research Branch will intensively study a small number of subjects to establish the optimal biologic dose to permit interference with estrogen stimulation of breast carcinogenesis. In addition, a practical approach to ensuring adequate dosing will be developed by monitoring drug metabolites in blood or urine. Finally, a similar analysis will be done of 13 cis retinoic acid and its effects on squamous epithelium.

The chemoprevention and evaluation approach to cancer will require long periods of therapy. The need to give enough drug to have the desired biologic effect but not excessive amounts of drugs such that a subject experiences side effects imposes a very challenging requirement of this field. The basis for success arises from a rational dosing schedule validated by direct clinical observation. The initial efforts for such rational pharmacologic dosing would be tamoxifen for breast cancer prevention and 13 cis retinoic acid for upper aerodigestive cancers.

PROGRESS IN THE ESTABLISHMENT OF THE BRANCH AND RECRUITMENT OF SCIENTIFIC STAFF

Elements of the Branch are temporarily occupying space at the National Cancer Institute—Navy Medical Oncology Branch where they were previously assigned. The BPRB has recruited a number of talented investigators and support staff and is proceeding with the space acquisition process. Leased laboratory space on the I-270 corridor in Gaithersburg is expected in December, 1991. Layout design and equipment ordering is largely completed so meaningful Branch laboratory activities should start in early 1992. A phased start up of clinical activities will be ongoing over the next year following occupancy.

BIOMARKERS AND PREVENTION RESEARCH BRANCH STAFF

Branch Chief	James L. Mulshine, M.D.
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Research Associates	Dennis Sanders, M.D., Ph.D. Eva Szabo, M.D. Anita Sabichi, M.D.
Staff Fellow	John Jones, Ph.D.
Guest Researchers	Frank Scott, Ph.D. Kathyrn Quinn, Ph.D.
Visiting Fellow	Noamichi Iwai, M.D.
Data Systems Analyst	Ruby Phelps, B.A.
Research Nurse	Cynthia Boland, R.N.
Technicians	Ingalill Avis, R.N. Sandra Jensen, M.S. Mae Jean Miller, M.D. Lisa Preiss, B.A.

Intramural Project Summaries

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, 1990 to September 30, 1991

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
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	D. L. Weed	Senior Staff Fellow	BMCCES, BB, DCPC, NCI
	K. C. Chu	Health Science Administrator	CDB, CCO, DCPC, NCI
	D. Friedman	Epidemiology & Biostatics Fellow	REB, DCE, NCI

COOPERATING UNITS *(if any)*
Early Detection Branch, DCPC, NCI; Radiation Epidemiology Branch, DCE, NCI

LAB/BRANCH
Biometry Branch, DCPC

SECTION
Screening Section

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

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	1.8	0.4

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews
Analysis of data originally obtained from Human Subjects/Human Tissue

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

The focus of this project is development and refinement of statistical procedures for the design and analysis of cancer screening and related studies. Problems under investigation include derivation and comparison of data analysis methods, assessment of case-control studies for screening evaluation, development of models of cancer screening, and approaches to the analysis of categorical data. Properties of case-control studies in the context of screening evaluation are being considered. 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. A simple model was developed to estimate dilution in a screening trial where followup continues after screening has ended. This was applied to both the Overall Analysis of all randomized individuals and a Limited Analysis of restricted subgroups of cases defined at certain intervals from study entry. Criteria were developed for comparability of the restricted case subgroups used in the Limited Analysis. Data from diagnostic testing and screening can often be analyzed using techniques for missing categorical data. Simple techniques have been developed for obtaining closed-form maximum likelihood estimates and their asymptotic variances and for finding the observed information matrix when using the EM algorithm with missing categorical data. A symbolic method has been developed for determining identifiable models in experimental designs involving missing categorical data. Methods have also been developed for analyzing data from randomized screening trials to estimate the benefit of screening unaffected by lead time bias and also the average lead time. Measurements on covariates are considered in assessing the existence of a possible dependence of lead time on the benefit or other variables.

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, 1990 to September 30, 1991

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
	J. K. Gohagen	Expert	EDB, DCPC, NCI

COOPERATING UNITS *(if any)*
Early Detection Branch, DCPC, NCI; University of Minnesota (W. Woods); Boston University (H. Koh).

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.

Screening Section investigators collaborated with the Early Detection Branch and the Research Contracts Branch in developing the Project Plans and RFP's for the major components of the PLCO Trial. This is a major trial of cancer screening in males and females for four cancers that comprise more than 50% of the incidence and mortality of cancer--lung, prostate, colorectal, and ovarian cancers. The trial design calls for a total sample size of 74,000 males and 74,000 females between the ages of 60 and 74 who are to be divided at random into a screened group and a control group. The screening techniques to be used are annual digital rectal examination and prostate specific antigen for prostate cancer, annual chest film for lung cancer, annual digital rectal examination and three-year flexible sigmoidoscopy for colorectal cancer, and annual pelvic examination, CA-125 marker and transvaginal ultrasound for ovarian cancer. Initiation of the pilot phase of the trial is planned for early 1992.

The database 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.

Evaluation of screening for neuroblastoma in infants is also being addressed in conjunction with investigators at the University of Minnesota. Staff are consulting in a controlled study to assess the measurement of urinary catecholamine metabolites VMA and HVA as screening tests for this tumor. Staff are also involved in examining the status and evaluation of skin cancer screening in the US in conjunction with investigators at Boston University.

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

PROJECT NUMBER
Z01 CN 00107-09 BB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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 00101-09 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. 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. The models indicate important kinetic differences between selenite and selenomethionine, with selenium from selenomethionine better absorbed and retained, and reutilized.

An analysis of variations in total selenium levels in the plasma, urine and feces indicates high levels of within-subject variability, especially in urine and fecal samples, suggesting plasma levels are preferable, with multiple measures to enhance precision when determining selenium status.

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

PROJECT NUMBER
Z01 CN 00113-08BB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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:
1.2	1.0	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 and Black cancer cases compared to Whites has been underway, revealing major differences, possibly useful in etiologic studies. While completion of the Asian-American component awaits 1990 population census data, the analysis of Black cases nears completion.

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 has been completed, and is being prepared for publication.

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. Study of these measurements with cardiovascular diseases has been completed and is being submitted for publication.

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

PROJECT NUMBER
Z01 CN 00115-08 BB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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. Byrne)

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.

Data on kidney cancer diagnosed among white residents of Iowa during 1973-88 were available from the SEER program. Data for 1973-77 were used to compute baseline rates for the major site/type subgroups of kidney cancer within each of the 99 counties in the state. Data for 1978-88 were monitored for increasing incidence over the baseline rates using the sets technique. Alarms signaling an increase in incidence were triggered in 39 counties for renal parenchyma cancer and in 34 counties for renal pelvis cancer.

In collaboration with researchers in the Environmental Epidemiology Branch, HHV-6 antibody titers in chronic fatigue syndrome patients were investigated and found to be higher than for controls, but the difference was not statistically significant. In another study for healthy blood donors from Africa and Asia, HHV-6 reactivity was significantly higher for Ghanaians than for Malaysians or Americans.

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 occurrence of early menopause among female members of this cohort was determined using survival analysis methodology and compared to the risk among sisters of the survivors. Survivors were found to be at an increased rate for early menopause. The rate 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 1,289 survivors who were nonsmokers when their cancer was diagnosed was compared to that among 1,930 sibling controls. Using conditional maximum likelihood methods, the smoking rate at last followup among survivors was found to be 92% of the rate among controls.

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

PROJECT NUMBER
Z01 CN 00116-08 BB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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. These programs are now operational on the NIH Convex Computer system.

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

PROJECT NUMBER
Z01 CN 00119-08 BB

PERIOD COVERED
October 1, 1990 to September 30,1991

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; Prevention and Control Extramural Research Branch, DCPC; Public Health Applications Research Branch, DCPC; Division of Cancer Treatment, NCI; Division of Cancer Etiology, 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); 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 second survey of the Evaluation Cohort; further analysis of baseline data, a random sample of ninth-grade students to measure smoking knowledge, attitudes, and behavior; and designing the final cohort and cross-sectional surveys to be completed in 1993. 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 consulting on design issues in large-scale randomized intervention trials relating to women's health; characterizing the American diet using data from large national surveys and analyzing the relation of dietary patterns to demographic variables; collaborating on analysis of a study of food purchasing behavior and consumer nutrition education, involving a supermarket-based intervention; and designing an evaluation, using a three-arm randomized design, of the NCI's Primary Care Nutrition Guide.

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

PROJECT NUMBER
Z01 CN 00121-07 BB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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	Hebrew University

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 ☐ (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 the development of biostatistical methods appropriate for epidemiologic and experimental studies related to cancer prevention and control.

Poisson regression methods are often used to analyze the relationship of a county's cancer mortality to its demographic, economic, and ecologic characteristics. Because of variability of cancer risk among members of the county's population, the Poisson assumption is theoretically invalid. This research will evaluate the actual degree of intra-county temporal heterogeneity for the major cancer sites.

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. Only the scale parameter in parametric models and the proportionality parameter in semi-parametric models are assumed to vary among patients through their prognostic variables. Because extraneous hazard rate heterogeneity can produce substantial deviations from this assumption, this research will compare the fits of a Weibull model with a Gamma-mixture of Weibull models to estimate the degree of heterogeneity and its biasing effect on estimated parameters and on the hazard ratio.

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 used to project cancer figures for a forty year period. 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 DECsystem-10 to the Convex computer (DCRT's replacement for the DECsystem-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.

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

PROJECT NUMBER
Z01 CN 00100-09 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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	Medical Officer	CPSB, DCPC, NCI
Others:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
	B. K. Edwards	Associate Director	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 followup 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.

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

PROJECT NUMBER
Z01 CN 00101-09 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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)*

PI:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
Others:	A. Schatzkin	Medical Officer	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
	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 00103-09 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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	Associate Director	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 00104-09 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
NHANES I Epidemiologic Followup 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	Medical Officer	CPSB, DCPC, NCI
	G. Block	Epidemiologist	ARB, DCPC, NCI
	A. Schatzkin	Medical Officer	CPSB, DCPC, NCI
	M. Reichman	Staff 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 followup 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 followup survey was completed in 1984. A continued followup 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. Further followup in 1992 is planned.

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.

This study is being conducted by several of the National Institutes of Health and the National Center for Health Statistics.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 CN 00112-08 CPSB

PERIOD COVERED

October 1, 1990 to September 30, 1991

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
	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 00143-07 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Continued Followup 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:	A. Schatzkin	Medical Officer	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 followup (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 further continued followup is in process.

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 00146-03 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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:	J. Dorgan	Prevention Fellow	CPSB, 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 00147-03 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 00147-03 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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:	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 followup 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 00146-03 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 00148-03 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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	Medical Officer	CPSB, DCPC, NCI
Others:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
	B. K. Edwards	Associate Director	SP, DCPC, NCI
	A. M. Hartman	Health Statistician	ARB, DCPC, NCI
	M. Rautalahti	Visiting Fellow	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 00149-03 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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, and the Division of Cancer Etiology at NCI.

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

PROJECT NUMBER
Z01 CN 00150-03 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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:	P. R. Taylor	Branch Chief	CPSB, DCPC, NCI
Others:	S. Dawsey	Staff Fellow	CPSB, DCPC, NCI
	N. Hu	Visiting Associate	CPSB, DCPC, NCI

COOPERATING UNITS *(if any)*
Chinese Academy of Medical Sciences

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

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.

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

PROJECT NUMBER
Z01 CN 00151-03 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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	Medical Officer	CPSB, DCPC, NCI
	E. Lanza	Nutritionist	CPSB, DCPC, NCI
Others:	L. Freedman	Visiting Scientist	BB, DCPC, NCI
	C. Clifford	Health Scientist Administrator	DCB, 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 and Diet & Cancer Branch, DCPC; U of Pittsburg (Pittsburg, PA); Kaiser Found Res Inst (Oakland, CA); Memorial Sloan Kettering Cancer Ctr (New York, NY); U of Illinois (Chicago, IL); Kaiser Found (Portland, OR); U of New York (Buffalo, NY); Walter Reed Army Med Ctr (Washington, DC); U of Utah (Salt Lake City, UT); and Edward Hines Jr. VA Hospital (Chicago, IL)

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 a low fat, high fiber, high fruit and vegetable dietary pattern will decrease the recurrence rate of large bowel adenomatous polyps. This is a multi-center randomized controlled trial involving 2,000 men and women. Study participants are being randomized into either the experimental diet group or a control group (usual diet). Recruitment will take up to two years, and the followup time from randomization is four years.

The study has three secondary objectives: 1) to investigate the relation between the dietary intervention and several putative intermediate endpoints in large bowel carcinogenesis, particularly markers of colonic epithelial cell proliferation; 2) to evaluate whether these intermediate endpoints correlate with subsequent neoplasia (adenoma formation); and 3) to determine the extent to which changes in the intermediate endpoints account for the observed effect.

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

PROJECT NUMBER
Z01 CN 00153-02 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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:	A. Schatzkin	Medical Officer	CPSB, DCPC, NCI
Others:	J. Dorgan	Staff Fellow	CPSB, DCPC, NCI
	M. Reichman	Staff Fellow	CPSB, DCPC, NCI
	P. R. Taylor	Branch Chief	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); U of Iowa (Iowa City, IA)

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

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; University of Pittsburgh in Pittsburgh, PA; and the University of Iowa in Iowa City, IA.

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

PROJECT NUMBER
Z01 CN 00154-02 CPSB

PERIOD COVERED
October 1, 1990 to September 30, 1991

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 Medical Officer 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 00155-01 LNMR

PERIOD COVERED
October 1, 1990 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
A New Mechanism for Carcinogen Resistance: Regulation by Diet and Nutrients

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

PI:	G.C. Yeh	Senior Investigator	LNMR, CPRP, DCPC, NCI
Others:	J.M. Phang	Lab Chief	LNMR, CPRP, DCPC, NCI
	J. Lopaczynska	Visiting Fellow	LNMR, CPRP, DCPC, NCI
	J. Critchfield	IRTA Fellow	LNMR, CPRP, DCPC, NCI
	M. Poore	Biolab Technician	LNMR, CPRP, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Nutritional and Molecular Regulation

SECTION

INSTITUTE AND LOCATION
NCI, Frederick, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.75	2.75	1.0

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 mechanism by which oncogenes are activated by environmental and dietary carcinogens in human cancers remains unclear. For chemical carcinogens, the emphasis has been on activation and detoxification mechanism. We propose another cellular protection mechanism against chemical carcinogens: carcinogen resistance through increased efflux. An attractive possibility is that the pleotropic drug efflux pump mediated by a plasma membrane glycoprotein serves to protect normal tissues against carcinogenic insult.

The multidrug resistant gene (MDR) codes for a 170 KDa plasma membrane glycoprotein (p-gp), originally described by Ling et al., which functions as an energy-dependent chemotherapeutic drug efflux pump in cancer cells. We propose that it may also work as an efflux pump for chemical carcinogens. Using human breast cancer MCF-7 cells with different stages of adriamycin resistance and corresponding p-gp levels to test our hypothesis, we found that chemical carcinogen, benzo(a)pyrene, may share the mechanism for drug efflux in these cells derived by continuous exposure to adriamycin. We are studying the role of the p-gp as an efflux pump for other dietary carcinogens. Its regulation by nutrients may be the first step in cancer prevention.

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

PROJECT NUMBER
Z01 CN 00156-01 LNMR

PERIOD COVERED
April 7, 1991 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Nutritional Regulation of Carcinogens in Placenta-Related Cells

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

PI:	C.A. Plouzek	Senior Staff Fellow	LNMR, CPRP, DCPC, NCI
Others:	G.C. Yeh	Senior Investigator	LNMR, CPRP, DCPC, NCI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Nutritional and Molecular Regulation

SECTION

INSTITUTE AND LOCATION
NCI, Frederick, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	0.0

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 plasma membrane glycoprotein 170 (P-gp) that is responsible for multidrug resistance, MDR, also may function as a chemical carcinogen efflux pump that can be regulated by diet and nutrients. P-gp is found predominantly in the cells lining the luminal space of a variety of tissues, including the placenta and the endometrium of the gravid uterus of the mouse, but the functional role of P-gp in normal tissues has not been determined. The regulation of expression of MDR by nutrients in placenta-related cell lines will be studied. We will examine the expression of MDR1 and MDR3 in in-vitro models, such as a newly transformed origin-defective SV40-mutant amnion epithelial cell line, HAA58OD-8C; a transformed placental trophoblast cell line; a placental fibroblast cell line; and a choriocarcinoma cell line, JEG-3. Hybridization experiments with newly developed MDR probes which are specific for MDR1 and MDR3 will soon be conducted to determine the feasibility of these cell lines as models of MDR expression. Regulatory agents such as the known MDR competitor, progesterone, the MDR enhancer, estradiol, and nutrients such as retinoic acid, dexamethasone, and dibutyryl cAMP will be examined for their regulatory roles in the expression of MDR and the prevention of carcinogenesis.

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

PROJECT NUMBER
Z01 CN 00157-01 LNMR

PERIOD COVERED
October 1, 1990 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Effect of Proteins, Peptides and Amino Acids on Carcinogenesis

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

PI:	J.M. Phang	Lab Chief	LNMR, CPRP, DCPC, NCI
Others:	G.C. Yeh	Senior Investigator	LNMR, CPRP, DCPC, NCI
	B.A. Semon	Staff Fellow	LNMR, CPRP, DCPC, NCI
	K. Emmerson	IRTA Fellow	LNMR, CPRP, DCPC, NCI
	J.P. Henry	IRTA Fellow	LNMR, CPRP, DCPC, NCI
	S.J. Downing	Chemist	LNMR, CPRP, DCPC, NCI

COOPERATING UNITS *(if any)*
David Valle, M.D., Johns Hopkins School of Medicine, Baltimore, MD

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Laboratory of Nutritional and Molecular Regulation

SECTION

INSTITUTE AND LOCATION
NCI, Frederick, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.4	2.4	1.0

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.)*

Modulation of cellular signaling mechanisms by qualitative differences in dietary proteins and their metabolites were studied at the level of:

A. Iminopeptides
B. Release of pyrroline 5-carboxylate (P5C), and
C. Effect of pyrroline 5-carboxylate on mitogenesis.

A. Iminodipeptides. Dipeptides containing proline or hydroxyproline circulate in plasma and are delivered to tissues where they are hydrolyzed by prolidase. Using a proline-auxotrophic cell line, we showed that a variety of iminodipeptides could satisfy the proline requirements for growth. This is the first demonstration that iminodipeptides can serve as the sole source of proline.

B. Release of pyrroline 5-carboxylate. Previous work showed that P5C circulates in human plasma. In cultured human fibroblasts, P5C is released into the medium. The rate of accumulation is markedly increased by serum insulin and insulin-like growth factor-1 but not by platelet-derived growth factor. Thus, the production and/or release of P5C is under hormone control.

C. Effect of pyrroline 5-carboxylate on mitogenesis. P5C stimulates PRPP and purine ribonucleotide synthesis synergistically with platelet-derived growth factor. It also increases the incorporation of thymidine in serum-activated cells. Inhibitor studies suggest that the effect is due to the production of inositol phosphates.

The significance of the project is to elucidate the mechanisms by which qualitative differences in dietary proteins relate to cancer cause and prevention either as an independent mechanism or as a mechanism adjunctive to dietary fat and/or total caloric intake.

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

PROJECT NUMBER
Z01 CN 00158-01 LNMR

PERIOD COVERED
October 1, 1991 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Dietary Lipids and Signal Transduction in Breast Cells

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

PI:	C.J. Welsh	Senior Staff Fellow	LNMR, CPRP, DCPC, NCI
Others:	J.M. Phang	Lab Chief	LNMR, CPRP, DCPC, NCI

COOPERATING UNITS *(if any)*

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INSTITUTE AND LOCATION
NCI, Frederick, Maryland

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0.75	0.75	0.0

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- ☐ (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.)*

Cellular membrane lipids serve as a source of lipid mediators which regulate the signaling mechanisms that govern mitogenesis. Since dietary fats provide lipids used for cellular membranes, fat intake could affect the quantity and quality of lipid mediators that are available for regulating mitogenic activity. Growth factors and hormones stimulate the production of lipid mediators by activating phospholipase D. This phospholipase hydrolyzes membrane phospholipids to provide the lipid mediators phosphatidic acid and diacylglycerol. The influence of dietary fat on the production of these lipid mediators and the regulation of phospholipase D is the focus of this work.

A cell culture model using tumorigenic and nontumorigenic human breast epithelial cells has been established to study the effects of membrane lipids on cell signaling mechanisms. The cells respond with increased phospholipase D activity when exposed to a variety of physiologically relevant agonists including epidermal growth factor, transforming growth factor alpha and phorbol esters. The phospholipase D is differentially regulated in tumorigenic breast cells which are resistant to drugs commonly used for chemotherapy. The fatty acids of these cells can also be modified in a manner that simulates dietary changes. The characteristics of the phospholipase D and the ability to modify the membrane lipids are valuable assets of the model that will be used to study the effects of dietary fat on cell signaling mechanisms that regulate mitogenesis.

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

PROJECT NUMBER
Z01 CN 00159-01 LNMR

PERIOD COVERED
October 1, 1990 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Regulation of Tumor Suppressor Protein p53

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

PI:	T. Wang	Senior Staff Fellow	LNMR, CPRP, DCPC, NCI
Others:	J.M. Phang	Lab Chief	LNMR, CPRP, DCPC, NCI

COOPERATING UNITS *(if any)*

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INSTITUTE AND LOCATION
NCI, Frederick, Maryland

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 involvement of the tumor suppressor protein p53 in the process of tumorgenesis is well established. However, little is known about the function and regulation of p53 at the molecular level. It is known that p53 can be phosphorylated in-vitro by cell cycle dependent kinases and casein kinase II, but the function and the regulation of such processes is still not clear. The goals of our project are to examine the roles of phosphorylation on p53's function as a tumor suppressor protein, to elucidate possible regulatory mechanisms of p53 phosphorylation, and to examine the involvement of nutritional and/or hormonal factors that may serve as effectors of this process. We have taken a molecular biological approach, which utilized manipulation of cDNA coding for the p53 by site-directed mutagenesis, to alter specific amino acid residues that are suspected phosphorylation sites. This approach will allow us to examine effects of specific changes in the protein. At present, we are in the process of developing a cell culture system which will allow us to assess the effects of the changes.

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

PROJECT NUMBER
Z01 CN 00160-01 LNMR

PERIOD COVERED
October 1, 1990 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Nutritional Regulation of Ras Proto-oncogene Activity

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

PI:	S.N. Perkins	Senior Staff Fellow	LNMR, CPRP, DCPC, NCI
Others:	J.M. Phang	Lab Chief	LNMR, CPRP, DCPC, NCI

COOPERATING UNITS *(if any)*

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INSTITUTE AND LOCATION
NCI, Frederick, Maryland

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 primary goal of this project is to investigate the links between nutritional factors and the activity of ras proteins in a cell culture system. The important role of mutated ras gene products in a variety of human cancers is well established. In addition, many (but not all) studies suggest that elevated levels of unmutated ras proteins are found in many colon and breast cancers. Although the function of ras in the cell remains to be determined, escape by ras from normal regulation can result in morphological transformation and appears to be a frequent event in the multi-step genesis of cancer. Several observations suggest that nutritional status may affect ras activity. First, the equivalent of a key regulatory protein of ras activity appears to act as a sensor for nutritional status in yeast; similar functions may have been conserved in higher eucaryotes. Second, specific lipids have been shown to have direct and indirect effects on ras activity in-vitro. Third, nutritional parameters may modulate ras activity by influencing the post-translational lipid modifications of the proteins that are required for activity. Conceivably, such lipid effects could be involved in the epidemiologic correlations between dietary fat and colon and breast cancers. Our first goal has been to set up a cell culture system. In most cells ras expression is low and difficult to detect. We have confirmed that Y-1 cells and MCF-7 cells, respectively, express 20-50 and 5-10 fold the level of normal ras protein seen in other cell lines. These cells will enable us to investigate the effects of a variety of lipids, growth factors and other modulators on ras activity, as assessed by ras membrane localization, post-translational modifications, bound guanine nucleotide ratios, and messenger RNA levels.

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

PROJECT NUMBER
Z01 CN 00161-01 LNMR

PERIOD COVERED
March 10, 1991 to September 30, 1991

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

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

PI:	N. Sathyamoorthy	Senior Staff Fellow	LNMR, CPRP, DCPC, NCI
Others:	J.M. Phang	Lab Chief	LNMR, CPRP, DCPC, NCI

COOPERATING UNITS *(If any)*

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INSTITUTE AND LOCATION
NCI, Frederick, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.6	0.0

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.)*

An in-vitro model is being established to assess biochemical and molecular biological effects of dietary fiber on two colonic cell lines, LS174 and CCD841.

Although fiber is defined as a non-starch polysaccharide that cannot be digested by man, there is a considerable amount of degradation of fiber that occurs in the gut as a result of bacterial action. The complex carbohydrates that may be released as a result of bacterial action may elicit a significant biological response in colonic mucosal cells. In order to study this aspect various fibers will be incubated with human fecal inoculum under anaerobic conditions. Complex carbohydrates produced by this fermentation will be isolated and characterized. The effect of these complex carbohydrates on the colonic cell lines will be monitored by assaying for 1) mucin production, 2) PGE2 synthesis, 3) Ornithine decarboxylase activity, and 4) expression of C-myc.

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

PROJECT NUMBER
Z01 CN 00162-01 LNMR

PERIOD COVERED
October 1, 1990 to September 30, 1991

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effects of Vitamin A Nutriture on Retinoid Metabolism

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

PI:	K.C. Lewis	Staff Fellow	LNMR, CPRP, DCPC, NCI
Others:	J.M. Phang	Lab Chief	LNMR, CPRP, DCPC, NCI
	L.A. Zech	Senior Scientist	LMMB, DCBDC, NCI

COOPERATING UNITS *(if any)*
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INSTITUTE AND LOCATION
NCI, Frederick, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	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.)*

There is a large body of evidence suggesting that important relationships exist between retinoids and cancer. Both a therapeutic and preventive role for retinoids have been indicated by a variety of research. To investigate the role of retinoids in various carcinogenic processes we have begun a series of retinoid turnover studies using rats, to investigate the effects of supplementation of diets either low or normal in vitamin A content with synthetic retinoids (either 4-HPR or all-trans retinoic acid). As expected, based on work from other laboratories, there was a decline in plasma retinol in rats fed these synthetic retinoids. We are now in the process of carrying out in-vivo tracer kinetics studies of retinol metabolism to examine how these changes in plasma retinol affect plasma and tissue retinol kinetics. Following IV injection of radiolabelled retinol associated with its normal plasma transport protein, retinol-binding protein, samples of plasma, a variety of tissues, urine, and feces are collected over time periods ranging from 15 minutes to 40 days. Labelled and unlabelled vitamin A compounds will be characterized and quantitated. Using physiologically based computer modelling and multi compartmental analysis techniques, we will develop mathematical models of vitamin A metabolism. These models will provide both quantitative and descriptive information concerning the movement of retinoids of interest among the various tissues, the uptake and utilization of retinoids by these tissues, and the effects of synthetic retinoids on vitamin A metabolism in individual tissues as well as in the whole body.


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