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BREAST CANCER RISK FACTORS AMONG SCREENING PROGRAM PARTICIPANTS

L. A. Brinton, R. R. Williams, R. N. Hoover, J. F. Fraumeni, Jr.

To examine whether the usual risk factors for breast cancer apply to individuals participating in screening programs, information from the Breast Cancer Detection Demonstration Project (BCDDP) was utilized for a case-control study. Analysis of 405 cancer cases and 1156 normal screenees indicated that all except one of the recognized risk factors applied to this group of women. Risk was not increased by a prior breast biopsy, possibly because of the selective nature of biopsies in this group of women. The data also provided an opportunity to evaluate the influence of the use of a number of drugs on breast cancer risk; these included estrogens, oral contraceptives, thyroid medications, diabetic preparations, and anti-hypertensives.

BREAST SELF-EXAMINATION IN WOMEN AT HIGH RISK FOR BREAST CANCER

Patricia T. Kelly, Ph.D., Virginia L. Ernster, Ph.D.

The use of breast self-examination in the detection of early breast cancer has long been advocated. Yet no previous study has considered the meaning of this procedure to women in general, and especially to women at high risk of developing the disease. In the present study, forty-two women with a maternal history of breast cancer were interviewed in depth about their current health practices and concerns relating to their breasts. Subjects were drawn from two programs which encouraged breast self-examination. Although 69 percent of the subjects examined their breasts at least once every three months, most had little confidence in their own ability to detect malignant lumps and experienced great anxiety associated with breast self-examination. The rich qualitative information collected greatly enhanced the meaning of the quantitative data: the women studied articulated a range of feelings about breast self-examination, and had coped with their concerns in a variety of ways. Many expressed the need for medical services to help them with their special relationship to breast cancer. If the attitudes and practices elicited in this study also characterize other groups at high risk for the disease, it appears that current efforts to encourage breast self-examination can only go so far. We propose the establishment of a pilot clinic that would provide prompt and regular breast examinations by health professionals, and counseling for women regarding their risk of breast cancer. It is important that screening techniques advocated for various cancers not deter those at greatest risk.

PROGRESS REPORT ON SCREENING PROGRAM FOR THE DETECTION OF EARLY COLON CANCER
AND COLON ADENOMAS USING FECAL OCCULT BLOOD TESTING

Sidney J. Winawer, M.D., Mary Gingher, B. A., Daniel G. Miller, M.D.,
David Schottenfeld, M.D.

We have embarked on a mass screening program for the early detection of colorectal cancer and for the identification of patients with premalignant adenomas based on screening asymptomatic men and women age 40 and older with fecal occult blood testing and sigmoidoscopy. Approximately 20,000 patient examinations have been performed. The rate of positive slides has been 1%, and the yield of neoplastic lesions in these patients has been 50%, including adenomas and cancers. Pathological staging of the cancers in the screened group has been favorable as compared to the control group. We are now in the third examination cycle of our patient population. Data from the first examination cycle, representing the first screening of the population, has now been analyzed providing our first firm report of prevalence of neoplastic lesions in the various subgroups. A change in screening material and methods was made during the past year based on a manufacturer's product change and laboratory observations. This included use of the new Hemoccult II slide^R, and rehydration of the slides to restore reactivity lost on standing and desiccation. The rate of positive slides increased from the previous 1% to 4-5%. True and false-positives are now being analyzed in patients completely investigated in this group. Our results demonstrate a higher prevalence of neoplastic lesions in patients screened with fecal occult blood testing as compared to control patients. Increased detection of cancers with favorable pathological staging is expected to improve survival. Identification and removal of premalignant adenomas may have a favorable effect on future risk for colon cancer in the screened group. Material and method changes will have to be carefully assessed before reconsidering incorporation into this screening approach. Final analysis of first examination cycle data and identification of costs will provide a basis for cost-analysis within the framework of a prospective ongoing screening program. Cost-analysis and patient compliance factors will be major thrusts of the program in the current year.

COMMUNITY SCREENING OF HIGH-RISK CANCER GROUPS

Nathaniel Ching, M.D., Carlo Grossi, M.D., Thomas F. Nealon, Jr., M.D.

A program to identify subjects of high-risk of developing cancer of the lung, breast, gastrointestinal tract and female genital tract was initiated in a well defined community served by our hospital center. Once so identified these high-risk individuals are to be educated as to their high-risk and need for regular screening evaluations and/or actions to reduce the risks. A self-administered comprehensive health, occupational and smoking history questionnaire was designed and distributed first to all employees in the medical center. The returned questionnaires were analyzed and the subjects classified as to having: 1) no assignable risk area, 2) symptoms that require immediate examination by a physician, or 3) a greater risk of developing specific cancers. All are polled yearly by mail as to the status of their health. English and Spanish questionnaires were distributed to 3,500 employees and 516 (14.8%) were returned. High-risk subjects were identified and contacted as outlined in the following table:

	<u>Letters</u>	<u>Response</u>
High-risk G.I.	57	11 (19.2%)
High-risk breast	65	14 (21.5%)
High-risk lung	76	14 (19.7%)
Immediate examinations	94	6 (6.3%)

Although the response was small the concentration on high-risk subjects may increase the yield and improve the cost/benefit ratio of expensive screening activities. Two of eleven who responded for examination by sigmoidoscopy were found to have polyps. The specifics of criteria selection will be detailed in the presentation.

RESULTS OF COLLABORATIVE STUDIES BY PARTICIPATING CANSCREEN CLINICS

B. Samson, M.D., P. Grover, Ph.D., D. Winchester, M.D., E. Day, M.D.,
D. Miller, M.D.

CANSSCREEN is a cancer prevention and detection program which follows disease-specific clinical algorithms for selective testing and health education for fourteen forms of cancer, and hypertension. The clinics are operated by nurse clinicians and health counselors. The goal of the program is the detection of high-risk indicators for cancer which are amenable to intervention by primary prevention or diagnosis and treatment.

Three clinics are currently operating with local autonomy and collaborating with regard to uniformity of practices and pooling of medical data. From July 1975 to August 1977, 3,560 patients were seen at the collaborating clinics; 493 referrals were made for suspicious findings (13.8%); 30 cancers were diagnosed (.84%). This rate of 8.4 per thousand compares favorably with the findings of cancer detection programs carried out by physicians. Additional recommendations for testing, frequency of examination, and personal behavior are made on the basis of historical risk factors and clinical findings.

Results of risk factor recommendations for mammography and proctoscopy will be presented, as well as a summary of the programs for primary prevention. Cost analyses indicate the importance of adequate patient-flow for cost-effectiveness. Preliminary data indicate that the CANSCREEN PROGRAM is potentially cost-effective. Problems of outreach, follow-up, and end-result evaluation will be discussed.

COMPUTER SIMULATION OF A SCREENING PROGRAM FOR THE EARLY DETECTION OF CANCER

B. J. Flehinger, J. S. Smart

A computer-based simulator has been developed to analyze the effects of screening strategies on the development and cure of cancer in a population. It is assumed that cancer of a specific organ occurs during an individual's life at an age governed by a given probability distribution. After that, it progresses through a sequence of stages in which the probability of detection by screening procedures increases with stage and the probability of cure decreases. The simulator produces a probabilistic characterization of the progression and cure of the disease in the population under a schedule of periodic screening. Various assumptions about the rates of incidence and progress of the cancer can be checked against experimental data and the possible effects of proposed screening strategies can be evaluated.

AN ANALYSIS OF SPUTUM CYTOLOGY DATA ON URANIUM MINERS CONTROLLING FOR
RADIATION EXPOSURE AND CIGARETTE SMOKING

Thomas J. Mason, Ph.D., Philip C. Prorok, Ph.D.

Utilizing information on uranium miners provided by Dr. Victor Archer of NIOSH, we have identified 739 persons whose sputum samples were identified by Dr. Geno Saccomanno as having metaplastic cells with moderate atypia. For these individuals, data were available with regard to working level months (WLM's) of radiation exposure as well as their history of cigarette smoking. Subdividing this group of individuals into 4 WLM categories and 5 smoking categories (which include those who never smoked, those who quit smoking, light, moderate and heavy smokers), we have investigated changes in sputum cytology categories. These categories include normal cells only, metaplastic cells with mild, moderate and marked atypia, cells suggestive of malignancy but equivocal, and those strongly suggestive of malignancy. Average duration times in cytologic states as a function of the prior cytologic state were calculated for each of the 20 combinations of radiation exposure and cigarette smoking categories which we identified. Emphasis is given in the analysis to differences between these time periods in an attempt to evaluate the utility of sputum cytology in detecting early lung cancer.

USES OF A MATHEMATICAL MODEL OF BREAST CANCER TO AID IN CONSIDERING CERTAIN ISSUES ASSOCIATED WITH SCREENING FOR BREAST CANCER

Michael Shwartz

A mathematical model of breast cancer has been developed and shown to be consistent with both clinical data and data from breast cancer screening programs. This model has been used for an analysis of the benefits of alternative screening strategies for breast cancer, the results of which have been reported elsewhere. In addition, there are a variety of ways in which the model can be used in considering issues involved in designing and interpreting data from breast cancer screening programs:

- (1) To aid in interpreting and extrapolating data from demonstration projects. For example, by use of the model we show that detection rates reported by the Breast Cancer Detection Demonstration Projects are not inconsistent with incidence rates reported by the Third National Cancer Survey. Also, we demonstrate how improvement in mortality can be estimated from the fact that about 50% of all tumors detected at screening are detected by mammography alone.
- (2) To adjust data collected in a controlled (or non-controlled) trial to account for lead time and length biases. We use the model to calculate the magnitude of lead time and length biases in a prototype screening program.
- (3) To suggest hypotheses about the disease process. We show that a plausible model of the natural history of breast cancer (plausible in the sense that model predictions using this natural history are in accord with data) is one in which the probability of metastasis to the axillary lymph nodes is more a function of time of exposure to the primary tumor than to factors that determine the growth rate of the tumor. We also show that to the extent this model is not true, the benefits of screening will be less.
- (4) To suggest and help design research problems and priorities. For example, we show that the underlying distribution of tumor growth rates is the prime determinant of the extent to which intensive screening with mammography will detect tumors that would not otherwise come to treatment in a woman's lifetime. Further, we determine the effect of different assumptions about the distribution of growth rates on the predicted age-specific prevalence of breast cancer at autopsy. Hence, we provide the basis for designing an analysis of the age-specific prevalence of breast cancer at autopsy and suggest that this would be an important study in order to interpret data from screening programs. Also, we show the potentially large role of self-examinations in reducing the mortality threat from breast cancer and hence provide theoretical justification for assigning a high priority to actual experiments to investigate the benefits of this modality.
- (5) To help structure policy debate. We show the sensitivity of benefits of different screening policies to the measure of benefit considered. Thus, we emphasize the importance of considering explicitly in the decision-making process the priorities that should be assigned to different measures of the benefits of screening.

THE ECONOMICS OF SECONDARY PREVENTION. SCREENING FOR DISEASE

Marvin M. Kristein

This study aims at analyzing the economic efficiency of screening principles and applying these to currently established screening (of asymptomatic populations) approaches for major areas of cancer. This particular application will be emphasizing screening for colon cancer.

The basic theory of the economics of screening involves the following components: what is currently known of the natural history of a particular disease, clinical practice standards, epidemiology, economic analysis of (and costs and benefit values assigned to) the epidemiological evidence and the clinical standards, an organized system in which to arrange these factors, and a final summary formula which allows us to compare the costs and the benefits and display a result that policy makers can consider. Each of these components is extensively discussed.

SOCIAL AND ECONOMIC IMPLICATIONS OF CANCER IN THE UNITED STATES

Thomas A. Hodgson and Dorothy P. Rice

The economic cost of cancer in 1975 in the United States is estimated at about \$22 billion, assuming a 6 percent discount rate for indirect costs. About \$4 billion was spent for hospital care, and \$1.2 billion for physicians' services, while indirect costs due to morbidity and mortality amounted to \$17 billion.

This paper discusses recent estimates of economic costs, including methodological aspects and economic principles employed, and provides new information by cancer site on expenditures for hospital care, physicians' services, and costs due to mortality. For hospital care and mortality, costs are estimated for the following cancer sites by age and sex:

- All neoplasms
- Malignant neoplasms
 - Buccal cavity and pharynx
 - Stomach
 - Intestine and rectum
 - Other digestive organs
 - Trachea, lung and bronchus
 - Other respiratory organs
 - Bone, connective and other soft tissue
 - Skin
 - Breast
 - Cervix uteri
 - Other parts of uterus
 - Other female genital organs
 - Male genital organs
 - Urinary organs
 - Other and unspecified sites
- Leukemia
- Other lymphatic and hematopoietic tissues
- Benign neoplasms and neoplasms of unspecified nature

Expenditures for physicians' services are estimated by place of visit for:

- All neoplasms
- Digestive organs
- Respiratory organs
- Skin
- Breast
- Female genital organs
- Male genital organs
- Leukemia
- Benign neoplasms and neoplasms of unspecified sites
- All other neoplasms

Costs of neoplasms are compared with total costs for all diseases to indicate the relative burden of cancer. Although economic costs are not a complete measure of the burden of disease, they represent potential benefits of reduced cancer morbidity and mortality. By means of the methodology employed, a large part of the burden of disease can be estimated and these estimates are consistent across the spectrum of disease categories.

HEALTH EDUCATION RESEARCH IN PREVENTIVE ONCOLOGY: A STUDY OF FACTORS
INFLUENCING THE PRACTICE OF BREAST SELF-EXAMINATION

Katherine E. Crosson, M.P.H., Anita E. Nessel, M.S., Paul F. Engstrom, M.D.,
Prakash L. Grover, Ph.D.

In the absence of definitive etiologic data, preventive oncology programs often rely on health education strategies directed at secondary prevention. Breast cancer education programs illustrate this approach with their emphasis on the practice of breast self-examination (BSE) for the early detection of breast cancer.

At the Fox Chance Cancer Center in Philadelphia, Pennsylvania, Health Education has been integrated into a Breast Cancer Network Demonstration Project. Briefly, this demonstration project utilizes a multi-disciplinary team approach to assure that advanced and reliable methods of detection and treatment of breast cancer are available in a network of community hospitals. A hospital-based Community Health Educator is an important member of this multi-disciplinary team. In the first two years of the project, the Network Health Educators implemented standardized breast cancer education programs for approximately six thousand hospital employees, patients and community women.

This paper describes a one year evaluation study designed to determine the effectiveness of the education program, as well as the role that specific attitudinal and demographic factors play in the adoption of a regular breast self-examination. The study sample was comprised of a thousand women, 517 of whom had participated in the initial education program and a control group of 483. The women in the study completed a questionnaire, and sub-samples of both the experimental and control groups demonstrated the BSE technique on a breast model.

Study results indicate that women in the experimental group report more frequent practice of BSE than those in the control group. Several variables with assumed importance to the practice of BSE were also examined. The data suggest that the Health Belief Model may not provide a useful structure for designing breast self-examination public education programs; however, in both the control and the experimental group, physician reinforcement of BSE was associated with routine practice. Further results and implications of the study will be discussed.

INVOLVEMENT OF PHYSICIANS IN PREVENTIVE CANCER EDUCATION

Amiram Oleinik, M.A.

In the context of an ongoing patient education project given in clinics of the Kupat-Holim Health Insurance Institution, a Cancer Education program has been introduced.

With the financial aid of the Israel Cancer Association, a teaching unit called "Cancer Can be Beaten" has been developed. The unit consists of a set of slides and accompanying text material organized to attain pre-stated informative attitudinal and behavioral goals which can be adjusted to the specific needs of different target groups.

A pilot study to test the effectiveness of the teaching program was carried out in the Kupat-Holim Community Clinics. The slides and text were presented to groups of patients attending the clinic by the family physician.

A multiple choice self-administered questionnaire was prepared covering questions pertaining to knowledge, attitude and stated behavior. Socio-demographic aspects of the respondents were also included. The same questionnaire was filled out before and after the lecture.

Analysis of the questionnaires showed interesting shifts in the responses following the use of the teaching unit.

It was interesting also to note the response of the physicians, as many of them approached the subject with considerable reluctance (some refused to participate). The audience received the talks and slide presentation with much interest and in fact encouraged the physicians. As a result the latter felt much more secure after this initial experience. The response and feedback received from physicians who delivered these talks showed in fact the extent of their fears and the relief they experienced as they realized that it is possible to talk with the public openly about cancer.

We have learned that by having the physician communicate in a teaching situation with his patients, in both patient and physician changes were induced.

Concerning the subject of cancer, the ability to induce such changes have important bearings on factors concerning prevention, such as changes of life style, help in early diagnosis and cooperation in therapeutic intervention if needed.

A STRATEGY FOR BEHAVIORAL CHANGE AT A MULTI-SITE CANCER SCREENING CLINIC -
SOME COMPLIANCE FINDINGS

Marilyn Snyder, MPH, Glenys Burton, BA

The objective of the CANSCREEN PROGRAM is to reduce morbidity and mortality resulting from early detectable cancer. Its health education strategy - a personalized, risk factor approach, with patients playing a major role in forming their own health plans is discussed. The program is a screening clinic which uses a team approach to find early detectable cancer as well as to encourage self-monitoring and improved health behavior.

Health counselors, as part of a larger team, are used to plan behavior change with the patient at the time of the visit. The specific behaviors that the counselor effects are follow-through with recommended medical referrals, smoking cessation, breast self-examination, reduction of alcohol consumption, and protection from sun exposure. Primary prevention is stressed with smokers. A continuing relationship with the patient is fostered by the use of telephone counseling calls which are made in accordance with specially designed protocols.

Compliance rates for the first 1,200 patients screened are reported. Health counseling protocols and compliance results for the following behavioral problems are discussed: smoking (362, or 30% of the population smoked), alcohol consumption in combination with smoking (41, or 11% of the smokers were also heavy or daily drinkers), and breast self-examination (300, or 67% of the population were counseled in breast self-examination).

Results are presented with suggestions for improving compliance and altering present strategies.

THE RELATIONSHIP OF HEPATITIS B VIRUS TO PRIMARY HEPATOCELLULAR CARCINOMA

W. Thomas London, Bernard Larouze, Hie-Won Hann, Robert L. Yarrish,
Baruch S. Blumberg

Many retrospective studies have shown that primary hepatocellular carcinoma (HPC) is closely associated with chronic infection with hepatitis B virus (HBV). Recent prospective studies in Japan suggest that HBV infection is an essential element in the etiology of PHC. Among Japanese railway workers, 5% of chronic carriers of HBV, without previously known liver disease, but with serum α -aspartate aminotransferase (SGOT) levels > 40 KU, developed PHC within 2 years. No cases of PHC occurred in $> 18,000$ non-carrier controls during this interval (Sakumi, personal communication). Obada reported (Clinician 24:63-66, 1977) that among Japanese patients with cirrhosis followed for 3 1/2 years 6 of 25 chronic carriers developed PHC compared with 0 of 17 with antibodies to the surface antigen of HBV (anti-HBs) and 1 of 43 uninfected patients.

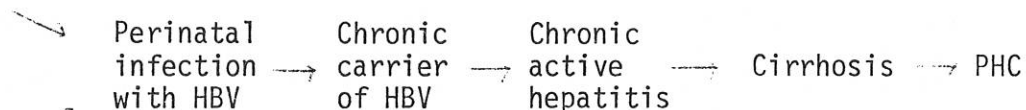
We have proposed that PHC is the end result of the following sequence:

Mother

Chronic carrier
of HBV

Father

anti-HBs (-)



Studies in Korea and Senegal support this scheme. In Senegal 70% of 28 mothers of PHC cases were HBsAg(+) (control mothers 6%) and 0 of 27 fathers had anti-HBs antibodies (control fathers 48%). In Korea all 14 cases of chronic active hepatitis and all 6 cases of post necrotic cirrhosis were chronic carriers of HBV (hepatitis B surface antigen, HBsAg, was detected in their blood). Ten of 12 cases of PHC were chronic carriers and the remaining cases had antibodies to the core antigen of HBV (anti-HBc). Three percent of 224 controls were carriers. Preliminary data suggest that mothers of cases of chronic liver disease without PHC are not carriers (0 positive of 9 tested), but mothers of PHC cases may be carriers (1 positive of 1 tested). Fathers of patients with PHC or chronic liver disease lack anti-HBs (0 positive of 9 tested).

HBV may also be involved in the etiology and/or pathogenesis of PHC in the U. S. Among 30 PHC patients in Philadelphia 62% had anti-HBc antibodies compared with a prevalence of 21-34% in three age and sex matched control groups (patients with lung cancer, colon cancer, blood donors).

The relation of chronic HBV infection to PHC appears to be as close as the relationship between cigarette smoking and lung cancer. The ultimate test of the hypothesis that HBV is the etiologic agent of most cases of PHC is whether prevention of infection with HBV significantly reduces the risk of PHC.

VARIATIONS IN BREAST CANCER MORTALITY AMONG AMERICAN INDIAN TRIBES

Nicholas L. Petrakis, M.D.

American Indian women are reported to have low mortality rates from breast cancer, however comparisons of rates between tribal groups have not been reported. Since the nonIndian contribution to the Amerindian gene pool varies considerably among different tribes, it was hypothesized that reported differences in cancer rates might provide information on genetic and environmental contribution to breast cancer susceptibility.

These studies were based on the Mason-McKay compilation of "U.S. Cancer Mortality by County 1950-1969" where counties were selected from states which contained major Indian reservations which occupied the entire or large portions of a county and which had virtually no black or Oriental populations. This made it likely that recorded nonwhite cancer rates referred to Indians. Indian/white mortality ratios were calculated for these reservations.

Considerable variation was found in mortality rates and mortality ratios for breast cancer among Indians from the Southwest as compared to upper Midwestern and Northern Rocky Mountain areas. Lowest rates occurred in the Navaho and Hopi and the highest among the Sioux. No major differences were found among the reservations with respect to socioeconomic status, parity, proportion of women with early pregnancies or in nutritional status.

The findings suggest that the higher rates among Northern Indians may be related to the historically known greater nonIndian genetic admixture.

EPIDEMIOLOGY OF STOMACH CANCER IN CHILE

Rolando Armijo, M.D., Anne Coulson

Chile ranks second in the world in mortality from stomach cancer which is the most important site for both sexes and accounts for 30% of deaths from malignant neoplasms. Analysis of deaths from its 25 provinces for a 15-year period (1957-1971) shows a peculiar geographic pattern of high and low risk areas. Three agricultural provinces south of Santiago show a median rate of 50.1 per 100,000. Both extremes of the country (3,000 miles apart) carry less than one-half the risk. In spite of a small decline nationally, the trends are maintained in both low and high risk areas. The national decline affects age groups under 60. The proportion of males in the high risk area is 52% in contrast to 66.3% in the low risk areas.

Data on use of nitrates were collected for the period 1945-1972. A high correlation was found between death rates and cumulative per capita exposure to nitrogen fertilizers. Controlling for confounding socioeconomic variables the correlation holds at a significant level. This epidemiological evidence agrees with biochemical findings on the carcinogenic role of N-nitroso compounds in experimental animals.

A case-control and a nitrate ecology study are in progress, aiming at elucidation of the carcinogenic effect of N-nitroso compounds in man in a natural setting.

DNA TARGETS FOR CARCINOGENS WITHIN LIVING HUMAN CELLS

John H. Frenster, Sharon R. Landrum, Marilyn A. Masek, Shirley L. Nakatsu

Carcinogenic chemicals, oncogenic viruses, and steroid hormones all prefer to bind to single-stranded portions of the host cell genome (Cancer Res. 36, 3394, 1976). Localized DNA helix openings provide short stretches of such single-stranded DNA, and are necessary to permit the induction of gene de-repression characteristic of human neoplasms (Nature 269, 752, 1977). We have developed a high-resolution electron microscopic technique for directly analyzing DNA helix openings within living cells (J. Natl. Cancer Inst. 59, 839, 1977), and have quantitated this technique for use within individual cells undergoing cell differentiation within human bone marrow. 431 normal differentiating cells were analyzed. DNA helix openings were found only within the extended 10 millimicron microfibrils of the active euchromatin portion of the cell nucleus, and ranged in length from 25-700 millimicrons, corresponding to 70-2000 base pairs in DNA helix length. During such bone marrow cell differentiation, these DNA helix openings were observed to decrease in both size and number per cell, correlating with the decreased rate of neoplastic transformation occurring in cells undergoing cell differentiation and maturation.

CARCINOGENESIS BY IONIZING RADIATION

Helen Q. Woodard, Ph.D.

The first radiation induced human tumors to be recognized as such were skin cancers due to X-rays and osteogenic sarcomas due to ingestion of radium-226. Many other types are known now. Probabilities of induction vary with the dose, dose rate and quality of the radiation, the age at exposure, and, most importantly, with the tissue at risk. Estimates of risk are complicated by lack of knowledge of the shape of the dose-response curve and uncertainties as to the existence of a threshold value. For these and other reasons the validity of extrapolation from high doses in experimental animals to low doses in humans is often doubtful. Certain retrospective studies in humans do, however, permit the estimate of the relative risks of leukemia and various solid tumors. Data from atomic bomb casualties, uranium miners, spondylitis and thorotrast patients and some other medically exposed cases recently analyzed by the author will be discussed. Owing to its short mean induction period, leukemia poses the greatest immediate threat to populations exposed over the whole or a substantial fraction of the body, but it now appears that, for persons of long life expectancy, the risk of developing solid tumors may be equally great. The risk of osteogenic sarcoma is negligible after most diagnostic procedures but becomes significant in bones which have been included in radiation therapy fields.

PROTECTING THE CANCER PATIENT AGAINST DRUG-INDUCED SECOND TUMORS:
POTENTIAL FOR CHEMOPREVENTION

Richard H. Adamson, Susan M. Sieber, Vincent T. DeVita, Jr.

Although studies on the prevention or reversal of chemical carcinogenesis in experimental animals have been reported, such studies in humans have only recently been initiated. In view of the rapidly growing list of known human carcinogens, it is now important to institute a search for chemicals able to prevent human cancer. Prerequisites for carrying out clinical trials of potential chemoprotective agents are: (1) an adequate knowledge of the nature of the carcinogen and the extent of human exposure, (2) the possibility of administering the chemoprotective agent prior to each exposure to carcinogen, and (3) the availability of a control population, e.g., a group receiving the carcinogen but not the chemoprotective agent. Specific groups of cancer patients, such as long-term survivors of Hodgkin's disease and patients on adjuvant therapy, may be at high risk for developing a second primary tumor as a consequence of chemotherapy; the agents most frequently associated with these second tumors are alkylating agents such as melphalan, and combination regimens such as MOPP. Moreover, sufficient numbers of these patients have developed second primaries that estimates of the dose of drug required for tumor development can be made. It is proposed therefore that these patients represent an ideal study group for evaluating potential chemoprotective agents. Any agents found active in preventing induction of second tumors by antitumor drugs might also find wider application in preventing carcinogenesis by other chemicals. It is obvious that chemoprotective agents must be non-toxic and must not reduce the therapeutic effects of anti-tumor drugs. Two nucleophiles, cysteamine and N-acetylcysteine, are currently being evaluated in animal models for their ability to prevent carcinogenesis by procarbazine, antitumor antibiotics and alkylating agents (melphalan in particular). Thus far it has been demonstrated that the antitumor effects of these agents are not diminished by prior administration of either nucleophile.

IS METRONIDAZOLE (FLAGYL) CARCINOGENIC IN HUMANS?

C. M. Beard, M.P.H., K. L. Noller, M.D., W. O'Fallon, Ph.D., L. T. Kurland, M.D.

The drug Metronidazole was shown to be an effective systemic trichomonocidal agent for humans in 1960. However, animal studies have shown the drug to be both carcinogenic and mutagenic. The drug caused an increased incidence of lung tumors and lymphomas in mice and an increased incidence of benign mammary fibroadenomas and adenocarcinomas in rats.

The first long-term follow-up study of humans exposed to the drug will be reported. Using the diagnostic index of the Mayo Clinic, all women in the community with a diagnosis of trichomonas vaginitis from 1960-1969 were identified through their medical records. Medical records were reviewed and detailed abstracts of selected items of information prepared on 767 women who received Metronidazole as treatment during the 1960's for the trichomonas infection. Information abstracted concerning the trichomonas infection included age at first diagnosis, age at first treatment with Metronidazole and other treatment for the infection. Information about subsequent diagnosis of cancer and evidence that Metronidazole had been given during pregnancy was also obtained.

Median ages at first diagnosis and first treatment of trichomonas were 26 years and 28 years respectively. The median period of clinical follow-up since first treatment is 9 years. As recently as 1977, 292 of the subjects had been reexamined. Follow-up on those not seen in 1977 will be performed by letter and telephone.

To date, 36 women have developed cancer since the treatment with Metronidazole. Of these, 15 had cancer in situ of the uterine cervix. Using person-years of follow-up, the observed incidence of cancer of the various sites will be compared to expected incidence rates based on studies in the Rochester population and/or data from the cancer registries of Connecticut, Upper New York State, and the Third National Cancer Survey.

OVARIAN CANCER: A CASE-CONTROL STUDY OF RISK FACTORS

J. F. Annegers, D. G. Decker, W. M. O'Fallon, L. T. Kurland

Ovarian cancer accounts for 12,000 deaths per year in the United States. To date, there has been little success in establishing major risk factors.

The incidence rates for ovarian cancer over the 40-year period 1935-1974 were determined for the population of Rochester, Minnesota. Trends in incidence rates, corrected for the population at risk (i.e., those with ovaries), will be presented.

Risk factors for epithelial ovarian cancers occurring in Rochester from 1945-1974 were examined in 116 patients and 464 controls. Among the characteristics studied, only nulliparity was found to be a significant risk factor -- relative risk 1.8 (95% confidence interval 1.2-2.8). Other suspected risk factors including hypertension, obesity, age at menopause, prior therapeutic pelvic radiation, and prior exogenous estrogen exposure were not found to differ significantly between cases and controls. One finding of interest was that the ovarian cancer patients had a significantly lower frequency of prior hysterectomy and/or unilateral oophorectomy than the control group. Thus, our data show that hysterectomy, even when one or both ovaries are preserved, is associated with a lower risk of subsequent ovarian cancer.

PROGRESS WITH A STUDY OF CAUSES OF DEATH IN A WESTERN PENNSYLVANIA

ISOLATE OF OLD ORDER AMISH

A.R. Taylor Denues, Ph.D., M.P.H., Florence S. Denues, L.P.N., John Denues, Lyn Proehle

The classical, special epidemiologic interest of 'peculiar peoples' is heightened in our era of rapid change. In Western Pennsylvania we are pursuing comprehensive planning for improving cancer works, especially in non-metropolitan regions. These studies include efforts to discern special groups of persons who might either particularly suffer from or contribute to etiologic understanding of cancers. Examples of the former include regional occupational exposures (as in coal, steel, petrochemical, ceramic or hardwood industries); the Old Order Amish with their dominantly agrarian life rooted in Switzerland in the 1790's and retained in 20th Century America, exemplify the latter. A particular isolate here, in Western Pennsylvania, of these followers of Jakob Amman who are religiously conservative of their nonconformity to the world dates from the 1840's. In this group, the way of life includes as key elements a garden-dominated diet of non-commercial, non-processed food; traditional dress; much physical labor; rural habitation; and pervasive religious faith. The possibility seemed evident that study might reveal unique patterns of morbidity and mortality among such folk, for whom environmental influences are both different from 'mainstream' America and reinforced by the genetic founder effect in this close lineage. Even the difficult discrimination between effects of heredity and of environment on health might be helped by such study. From gentle inquiry and much listening we are developing carefully-documented causes of death for all decedents in this community from 1903 to date. The major statistical problems of deriving rates and of discerning significant differences will be discussed, together with preliminary results.

THE NEW TREND IN STATEWIDE CANCER INCIDENCE REGISTERS

Anita K. Bahn, et al.

Interest in the environmental causes of cancer has resulted in a renewed effort by State Health Departments in the Northeastern part of the United States (Maryland, New Jersey, Pennsylvania) to establish statewide cancer incidence registers. The incidence population-based register is discussed from the standpoint of current need for this type of information, its objectives, alternative sources and types of data, estimated cost, quality and timeliness of information. Potential uses of the register for epidemiology and cancer control will be illustrated. The advantages and disadvantages of this type of register are compared with other types of cancer data bases. Plans for patient information exchange among registers of neighboring states will be described.

