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Epidemiology: A Step Forward in the Scientific Approach to Preventing Cancer Through Chemoprevention

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Synopsis

Until quite recently, the rigor and systematic approach applied to clinical research had never been applied to cancer prevention research. During 1982–83, however, the National Cancer Institute (NCI) carefully reviewed the needs and potentials in cancer prevention and control and developed a new policy for prevention research, requiring that development of cancer intervention follow an orderly sequence of research phases. These phases provide systematic assessment of interventions so that only those proven to be effective are brought to widespread implementation.

The author presents an overview of the new cancer prevention research policy; explains the manner in which epidemiologic studies contribute to development of policy and research; and describes NCI's research plan for chemoprevention, providing highlights of research studies that have contributed to its development and that will be implemented under the plan.

At the National Cancer Institute (NCI) in the Division of Cancer Prevention and Control, we have recently taken a long, hard look at the concepts of prevention and control as they have been historically understood and applied. We found an important lesson for future cancer research in two examples, one negative and one positive.

The negative example is our short progress on the route to preventing lung cancer caused by cigarette smoking. Although research has established for at least two decades that the most effective means of preventing lung cancer is to eliminate cigarette smoking, only recently has a concentrated effort been made to develop policies to achieve that goal. We still lack knowledge about how to influence smoking behavior, especially among youths. Had we developed a strategy 20 years ago for ascertaining when a research base is adequate to support policymaking and information dissemination, and acted more forcefully on that strategy, we might have fewer deaths from lung cancer today.

The positive example is the clinical progress made in cancer therapy since the 1950s. A research strategy evolved, based on clinical trials as a means of evaluating the efficacy of treatments. Then, in 1955, the National Cooperative Chemotherapy Program was organized, ensuring participation of the best researchers in the nation, high standards, and compatibility of studies. As results became available, they were quickly communicated and

adopted. New leads for further advances were systematically brought into the process. Advanced tests led into well-defined phases of human clinical trials.

Until quite recently, the rigor and systematic approach applied to clinical research had never been applied to cancer prevention research. During 1982–83, however, the NCI carefully reviewed the needs and potentials in cancer prevention and control and developed a new policy for prevention research, guided by three basic assumptions:

- that the scientific method of inquiry is an essential part of cancer control;
- that the pursuit of excellence in science and the potential for reducing incidence, morbidity, and mortality in numerically important ways are prime considerations in setting priorities for action;
- that the planning and conduct of activities are built on existing strengths of the National Cancer Program.

The policy is also based on a clear, consistent definition of cancer prevention. Cancer prevention has as a major foundation etiologic research. Cancer prevention is defined as *applied research* to *systematically* test or introduce a specific *intervention* aimed at having a *measurable impact* on an important cancer problem. The purpose of the intervention is to reduce cancer incidence (and, thus, also morbidity and mortality) rates in populations.

Prevention Research: Strategy

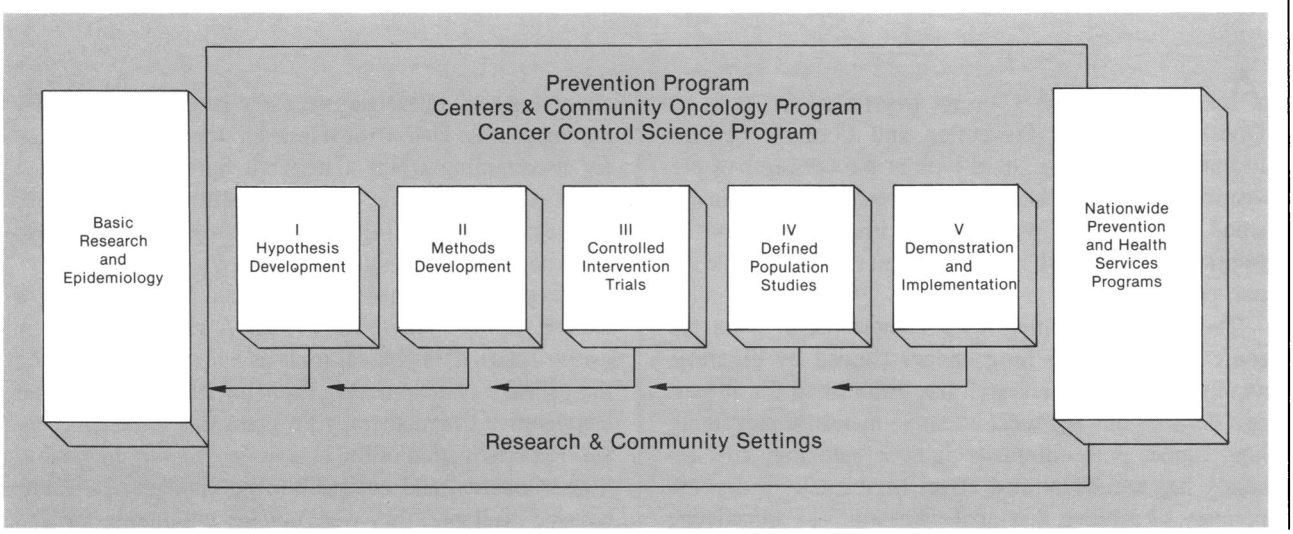
The outcome of this planning effort was a major strategy for prevention research. The Division of Cancer Prevention and Control (DCPC) now requires that development of cancer interventions follow an orderly sequence of research phases (fig. 1). The phases are designed to enable DCPC to assess the rigor of proposed interventions in a systematic manner. Each phase carefully, incrementally advances the research concept, thus allowing only those interventions evaluated and proven to be effective to be brought to widespread implementation.

In Phase I, *Hypothesis Development*, research leads are derived from a synthesis of available scientific evidence, from basic laboratory, epidemiologic, and clinical studies, about a cancer problem and possible interventions. A testable hypothesis is formulated about the effectiveness of the intervention in reducing incidence, morbidity, or mortality rates in populations. Phase I develops the hypothesis; Phases II–V test the hypothesis in comparative or controlled studies.

In Phase II, *Methods Development*, the accuracy and validity of procedures are ensured before the study is begun, to test the hypothesis. Phase II might include the following types of studies: pilot tests to investigate the feasibility or acceptance of using a proposed intervention in a specific population subgroup; studies to assess potential participation (compliance) in future intervention studies; development, pilot testing, and validation of data-collection forms, instruments, or questionnaires; testing of translations of materials from other languages; comparative pilot tests of alternative forms or approaches to performing the intervention; and tests of the applicability of methods used with other diseases or disciplines. Often an intervention must be assessed in terms of sensitivity and specificity, cost-effectiveness, and minimal subject risks.

In Phase III, *Controlled Intervention Trials*, the hypothesis developed in Phase I is tested, using the methods validated in Phase II. A Phase III study tests the

Figure 1. Cancer control phases



efficacy of the preventive intervention in a group of individuals. Rather than being a representative sample, the group may be more homogeneous than the actual target population, and may be chosen in a setting that facilitates research management. In controlled intervention trials, the study group is compared with a group that does not receive an intervention, or different interventions are compared with one another, and/or with a control group.

In Phase IV, *Defined Population Studies*, an intervention proven to be efficacious in Phase III is applied in a carefully controlled study of a defined population. The study population is a large, distinct, and well-characterized population or is a representative sample of such a population. Results from a well-designed population study can be generalized to the entire target population. For example, estimates can be derived for rates of exposure, incidence, morbidity, mortality, and survival, and for predicting changes in these as a result of the intervention under study. Thus, the studies provide the evidence of potential benefit that warrants proceeding to demonstration and implementation studies on a broader scale.

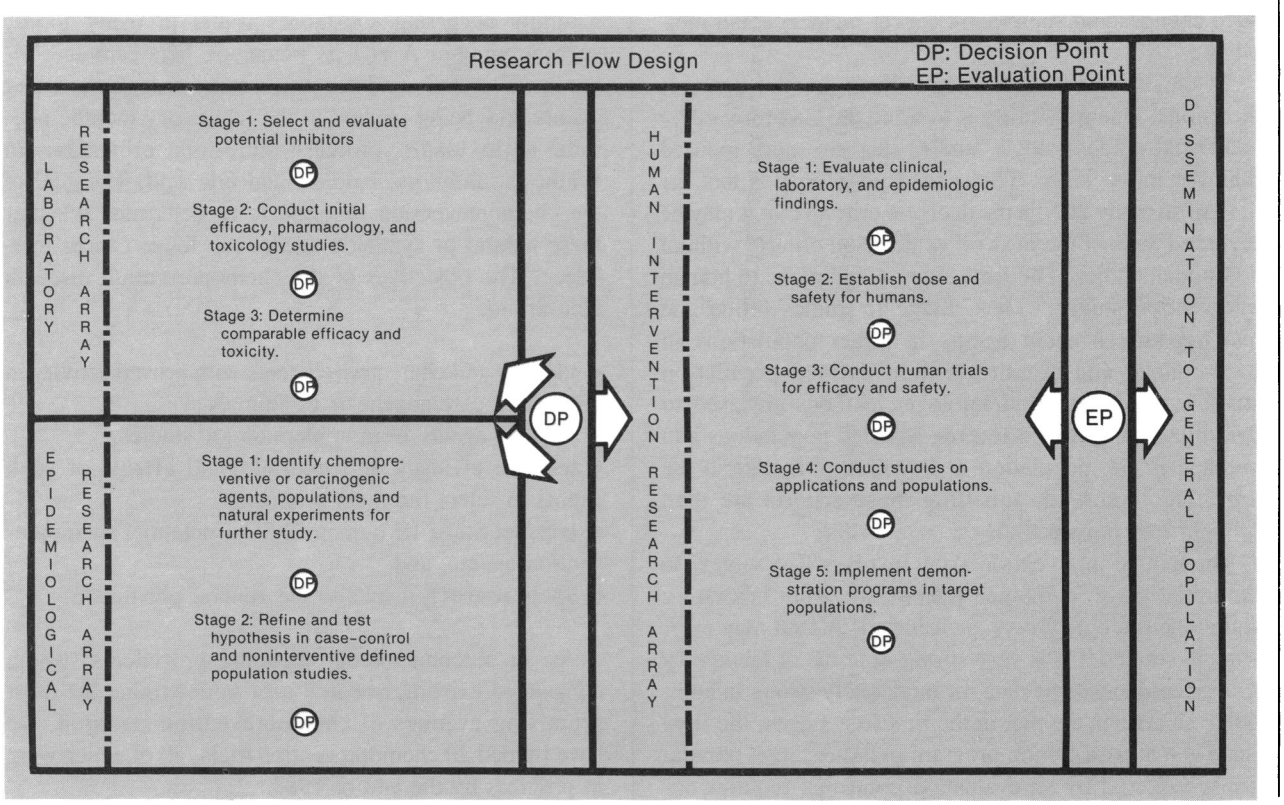
In Phase V, *Demonstration and Implementation*, the research process culminates in studies that apply a proven intervention to a community at large. An evaluation component is built into Phase V studies to provide the final assessment of costs and benefits of implementing the cancer prevention intervention on a nationwide scale. Thus, at the end of Phase V, a proven intervention with public health effectiveness in reducing cancer incidence, morbidity, or mortality would have been introduced in a population with known characteristics, and a process for monitoring the impact of the program would be in place.

Role of Epidemiology in Research Plans

The DCPC's prevention program was reorganized and expanded in 1983; it now has five content priorities: smoking, tobacco, and cancer; chemoprevention; diet and cancer; occupational cancer; and cancer detection. For all these prevention areas, we use a research flow design that includes epidemiologic research.

All prevention research and methods development derive from three research categories: laboratory research, epidemiologic research, and human intervention studies. The flow of this research logic is shown in figure 2 in terms of the chemoprevention program. We envision an array of stages in laboratory research, an array of stages in epidemiologic research, and leads from either of these to be brought into human intervention studies that may lead to broad preventive application. A decision point ("DP" in the figure) is established at the end of each

Figure 2. NCI Chemoprevention Program



'Thus, at the end of Phase V, a proven intervention with public health effectiveness in reducing cancer incidence, morbidity, or mortality would have been introduced in a population with known characteristics, and a process for monitoring the impact of the program would be in place.'

array and also at the end of each stage. The decision points require establishment of criteria for evaluating the leads at that array or stage.

The epidemiologic research array (fig. 2) begins with a review of available literature and current research. In addition to identifying potential agents for further study, the objective is to identify populations for epidemiologic studies and for human intervention studies. The third activity in this initial stage is a monitoring function: identifying and evaluating naturally occurring experiments. For example, populations may unexpectedly change an aspect of their lifestyles, such as diet. We must be prepared to monitor the relationships between such changes and subsequent cancer incidence and mortality.

At the Stage I decision point, there are two possible directions. One possibility is to bring the lead forward by additional epidemiologic studies that are more focused than the initial leads. The second possibility is that the lead so strongly fulfills the decision criteria that it may be reviewed against the next set of decision criteria without additional studies. The lead, then, could move to human intervention studies. Thus, Stage II studies refine and test hypotheses about agents in target populations in case-control and nonintervention defined population studies. Analytical epidemiologic methods are used to determine preventive effects in selected populations and perhaps in the population at large. Again, criteria are specified, and leads fulfilling these criteria are then brought into human trials.

The human intervention array involves five stages. In the initial stage, combined information from laboratory and epidemiologic arrays is evaluated. A lead may enter clinical studies if it is very strong in terms of laboratory data or epidemiologic data, or moderately strong in both. After all criteria are met in the first four stages, the final stage is a demonstration program in larger target populations, followed by an evaluation point that requires ongoing monitoring of the population to document the anticipated effect of the intervention.

The Chemoprevention Research Plan

Chemoprevention is the introduction into the diet of specific chemicals, such as vitamins, synthetic analogs, or other substances, for the purpose of reducing cancer incidence. The agents to be used are chemically defined and can be admininstered in precisely specified dosages. An advantage of the chemoprevention approach is that it may be easier to add a constituent to the diet for preventive purposes than to achieve acceptance of a major modification of dietary patterns.

In contrast to the chemoprevention research program, which deals with micronutrients, the related diet and cancer research program focuses on macronutrients that may be either added to or subtracted from the diet. Rather than examining precise dosages of one or a few defined agents, the dietary studies will examine the effects of dietary changes in classes of foods or nutrient content in roughly estimated percentages. For both programs, the ultimate aim is to develop effective and acceptable ways to lower cancer incidence by means of dietary modifications.

The growing and converging bodies of basic and epidemiologic evidence on the inhibition of cancer suggest that chemoprevention merits an aggressive research effort. Potential chemopreventive agents include several naturally occurring substances found in many foods, such as vitamin A and its precursor, beta-carotene; vitamins C and E; and the trace metal selenium. Other agents now being studied in the laboratory include phenolic antioxidants, protease inhibitors, prostaglandin synthesis inhibitors, indoles, and uric acid. The goal of the chemoprevention program is to determine whether these natural or synthetic agents can lower cancer incidence. The objectives of the chemoprevention research plan are to:

- identify and characterize agents with proven activity in preventing carcinogenesis in animals,
- identify agents from epidemiologic studies,
- test the efficacy and toxicological effects of such agents to select the most promising,
- conduct Stage III human trials of potential chemoprevention agents, and
- apply research results to the general population.

As an outcome of our planning procedures, which considered existing research data to determine the most promising avenues of chemoprevention research, we have funded 20 chemoprevention trials, all of which were in progress by the end of 1983.

Research on vitamin A and cancer. Many of the chemoprevention trials we have funded are testing the relationship between cancer and dietary vitamin A, beta-carotene, and synthetic retinoids (analogs of vitamin A). Beta-carotene is present in leafy green and yellow vegetables; it is converted to vitamin A in the digestive tract. Laboratory and human studies have led to the hypothesis that ingestion of these agents is inversely related to cancer. A historically important study in chemoprevention was done by Lasnitzki (*1*), who developed a method for growing mouse prostate cells on a watch glass, for transforming these cells into cancer cells by adding a carcinogen, and for inhibiting the transformation by adding vitamin A. She also inhibited a later stage of cancer cell development by adding vitamin A. Subsequently, other researchers showed that retinoic acid inhibits and reduces cancer (*2,3*).

Epidemiologic data also support the vitamin A hypothesis. About 20 studies in various parts of the world suggest an inverse association between eating foods containing vitamin A or beta-carotene and various types of human cancer; risk is thereby reduced by 30–50 percent. For example, several case-control epidemiologic studies show lower vegetable consumption or lower estimates of vitamin A intake among cancer patients than among controls. This relationship is supported by three cohort studies in which a negative association between lung cancer and an index of vitamin A was observed. The first of these studies, by Bjelke (*4*), involved 8,278 Norwegian men. Hirayama (*5*) made a similar observation in a study of 265,118 Japanese adults and suggested that ex-smokers might particularly benefit from daily vegetable consumption. Shekelle and associates (*6*) found dietary carotene to be inversely related to lung cancer in 2,107 American men. Three studies of serum or plasma vitamin A in lung cancer patients, as compared with controls, showed mixed results, but two prospective studies were consistent in demonstrating an inverse relationship between retinol in stored sera and subsequent occurrence of lung cancer (*7,8*).

In the only intervention trial reported to date, Gouveia and associates (*9*) examined the effect of the synthetic retinoid Etretinate on 34 heavy smokers with bronchial metaplasia. The index of metaplasia scores dropped significantly in the 12 study subjects who completed 6 months of treatment. This preliminary study will need confirmation because the number of cases is small and the precision of the metaplasia score is uncertain.

The combined strength of these and other research leads is being tested in a number of the 20 human trials supported by the National Cancer Institute in its chemoprevention program. These trials comprise studies of prevention in general populations and high-risk groups, studies aimed at preventing precancerous lesions from becoming malignant, and studies of ways to prevent new primary cancers. Examples of NCI-funded research in each of these four categories follow.

General population study. In a general population intervention study, researchers are currently testing whether cancer can be reduced in study subjects as compared with matched controls. The subjects of this study, being conducted by Dr. Charles Hennekens and colleagues at Harvard University, are about 22,000 physicians in the United States. The 5-year, randomized human trial will examine whether or not beta-carotene contributes to a decrease in total cancer incidence in this population and whether aspirin reduces cardiovascular mortality.

High-risk groups. In another human trial, Dr. Gilbert Omenn and his associates at the University of Washington are investigating the relationship between lung cancers and mesotheliomas in asbestos workers and these workers' intake of vitamin A and retinoids. The study population consists of 2,500 men, 45 years of age or older, who are at risk for bronchogenic carcinoma or malignant mesothelioma, as defined by diagnostic signs of asbestosis. The specific aims of the trial are (*a*) to determine the efficacy of chemoprevention of these malignancies with daily, oral administration of 13-cis retinol, and (*b*) to assess toxicity and safety of such a chemoprevention regimen. This is one of the first studies aimed at seeing if cancer risk can be reduced *after* exposure to carcinogens has occurred.

Another study, by Dr. Gary Goodman at the same institution, is testing the efficacy of vitamin A and a synthetic retinoid in reducing lung cancer risk among a population of smokers. This may be especially useful for ex-smokers.

Precancerous lesions. Other human trials are studying the potential of chemopreventive measures for preventing conditions that may be precancerous from developing into cancer. One of these conditions is cervical dysplasia, an abnormal cell formation in the cervix of the uterus. NCI has funded two Stage I trials of a retinoid to study the prevention of cervical dysplasia and to determine if any topical or systemic toxicity occurs with increased dosages of the retinoid.

Dr. Frank Meyskens, at the University of Arizona, is using retinyl acetate in gel form. It is embedded in a collagen sponge, within a cervical cap, and is applied by a physician. In Dr. Seymour Romney's study at the Albert Einstein School of Medicine in New York, the patient applies the retinyl acetate gel to her cervix with a vaginal applicator. These Stage I trials will be followed

by double-blind studies to compare the preventive effects of the retinoid with those of a placebo.

Prevention of new primary cancers. Nearly 400,000 new cases of basal cell carcinoma, one type of skin cancer, are diagnosed each year. Although surgery yields a cure rate of at least 95 percent, the development of new tumors in these patients ranges from 20 percent in patients with one or more previous basal cell carcinomas to nearly 100 percent in patients with eight or more.

The subject of four chemoprevention trials is the prevention of new primary skin cancers in patients previously treated for basal cell carcinoma. Two studies use beta-carotene and two use the synthetic retinoid 13-cis retinoic acid (isotretinoin). For example, Drs. Joseph Tangrea and Earl Gross of the National Cancer Institute are conducting a 5-year study of 1,800 white men and women, ages 45–70 years, who have had two or more basal cell carcinomas. This study will evaluate the effectiveness of low-dosage levels of 13-cis retinoic acid in reducing new incidence of basal cell carcinomas and will examine possible side effects associated with long-term administration of this agent. The knowledge from these trials will also provide insights useful in the design of studies aimed at preventing more aggressive types of cancer.

The relationship between diet and cancer has not yet been precisely defined. Published estimates of the percentage of cancer deaths attributable to diet range as high as 60–70 percent (*10,11*), but 30 percent seems a reasonable, conservative estimate. Although we hope chemoprevention initiatives will be useful against many types of cancer, including lung cancer, the best thing we can all do about lung cancer is to encourage people not to smoke. Chemoprevention and diet-and-cancer research are promising areas that will receive increasing emphasis.

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The Task of Epidemiology in Designing Strategies for the Use of Hepatitis B Virus Vaccine

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THE RECENT DEVELOPMENT OF SAFE, immunogenic, and effective vaccines to prevent hepatitis B virus (HBV) infection has been rightly hailed as a major advance in medical science. It has been estimated that more than 200 million persons worldwide are chronically infected with this virus, which takes an unmeasured toll of lives from cirrhosis and primary hepatocellular carcinoma (PHC) (*1*). This is one of the most common causes of deaths from cancer in the world, and it may now be considered a vaccine-preventable disease. The development of strategies to utilize these vaccines effectively poses an exciting challenge to epidemiologists, since patterns of HBV transmission and the risk of acquiring infection vary from continent to continent, from the