A strategy for cancer prevention and control research*

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Cancer is an important cause of morbidity and mortality in industrial countries. Recently changes in life-style and the environment in developing countries have coincided with increases in the incidence of certain cancers which might be related to these factors. A strategy for the prevention of all such cancers is presented, which involves research in a sequence of five phases to identify suitable interventions and to confirm their effectiveness in population studies, prior to their application on a nationwide scale.

In 1982, the US National Cancer Institute (NCI) engaged in a major exercise to review, reformulate, and reorganize the priorities in its national cancer prevention programme. The result was a strategy for systematically coordinating the most promising research leads and channelling them into applied research studies on the effectiveness of various interventions. In the prevention of cancer, priority should be given to those that cause the greatest morbidity and mortality, those for which a substantial risk is associated with certain exposures, and those for which apparently effective actions are available.

The strategy follows a stepwise approach, covering five phases which ensure the scientific validity of the research and the efficacy of the preventive intervention. As developed at the NCI, the strategy encompasses an area broader than primary prevention and is applicable to the entire spectrum of cancer control, that is, both prevention (primary prevention and screening) and management of cancer (diagnosis, treatment, rehabilitation, and continuing care). This article describes the five phases of cancer control and their application in terms of only primary prevention.

This strategy is adaptable to suit most countries, both developed and developing. However, the development and implementation of a national programme for cancer prevention require qualified personnel—particularly those with training and experience in the disciplines of epidemiology, biostatistics, behavioural science, health promotion and disease control administration—and the placement of these individuals in responsible positions.

The term “cancer prevention” is defined here to mean applied research to test a specific intervention aimed at having a measurable impact on a cancer problem in a population. The purpose of the intervention is to reduce a particular cancer's incidence, morbidity, and mortality rates in the population. Every intervention for cancer prevention must be based on scientific evidence from laboratory and/or clinical research of a cause-and-effect association between a biological, clinical, or behavioural factor and the cancer in question. The aim of this type of prevention research is to develop methods, plans or policies for interventions that will benefit the population, as well as to develop systems for evaluating and monitoring large-scale applications of these interventions. Thus, cancer prevention research begins by bringing together all the facts pertaining to a given cancer, such as cause-and-effect associations, so that a potential intervention can be planned; it then proceeds to test the efficacy of this intervention and its impact when applied to large populations.

**PHASES IN THE STRATEGY**

The new strategy is derived in part from a report of the President's Biomedical Research Panel submitted to the President and the Congress of the United States in 1976 and modified in 1981 by the NCI's Board of Scientific Counselors. The statement of the Board emphasizes that cancer prevention efforts must follow an ordered sequence: from basic research—through applied research, clinical trials and demonstration projects for testing the efficacy and safety of the proposed action or intervention, and education of professional and lay persons about these developments—to application of the intervention and its evaluation in large populations.

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The five phases of the new strategy (Fig. 1) are described below.

**Phase I: hypothesis development**

Hypothesis development here refers to the process of bringing together (a) the available scientific evidence about a cancer problem and (b) the possible interventions that could be applied to that problem. From this information, a hypothesis is formulated to test the effectiveness of the intervention when applied. Subsequent research trials and evaluations should determine whether or not the intervention has influenced the problem by reducing this cancer's incidence, morbidity, and/or mortality rates in the population.

Although the formulation of the hypothesis in this phase must be supported by evidence from the scientific literature or the results of previous research (e.g., descriptive or analytical studies and other basic laboratory, clinical, or behavioural research), these are not considered part of cancer prevention research because they are not linked to the intervention component. They are prerequisites to prevention research.

Phase I develops the hypothesis; the subsequent phases will test the hypothesis in comparative or controlled studies.

**Phase II: methods development**

Methodological research in this phase will identify and characterize the parameters and variables which must be controlled or monitored in subsequent intervention studies, and will ensure that reliable procedures are available before the intervention is begun. This phase might therefore include pilot tests to investigate the feasibility or acceptability of using a proposed intervention in a specific population group; 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 approaches to carry out 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 risks to the human subject. The methods that have been tested and proven in phase II will be incorporated in the studies in the next phase. Thus, many phase II studies will have to determine whether the available knowledge and technology can be applied successfully in interventions in the proposed quantitative phase III and IV studies.

**Phase III: controlled intervention trials**

The aim of the controlled studies in phase III is to test the hypothesis developed in phase I, using the methodology validated in phase II. These studies will test the efficacy of the intervention on a group of individuals who may be selected to give an optimal interpretation of the efficacy. The test group may be more homogeneous than the actual target population, and may be a less representative sample if this should facilitate the research management. In controlled intervention trials, the study group is compared to a group where no intervention was applied, or different interventions may be compared with one another and with the control group.

Case-control analyses or studies may be used to determine the benefits from an intervention; cases are defined as individuals who received the intervention, and the controls would be appropriately matched. Other studies may compare the impact of the intervention in a community or town with a comparable town that did not have the intervention. Thus, the populations studied need not be representative of a larger population. Nevertheless, the cancer prevention hypothesis must be given a careful, scientific assessment in this phase. Certain cohort or cross-
sectional studies (1) (though technically not case-control) might be conducted in phase III if they do not meet the criteria for a defined population (phase IV) study.

**Phase IV: defined population studies**

The purpose of these studies is to quantify the impact of the intervention when it is applied to a defined population. These carefully controlled studies must be conducted in a large, well-characterized population or in a selected sample that is representative of the target population; methods are required for identifying the population denominators and the occurrence of cancer within the population. If the study is well designed, inferences that are applicable to the entire target population can be drawn from the results. The quantitative data on the study population should permit calculations of the incidence, morbidity and/or mortality rates both before and after the introduction of the intervention. These rates may be considered to reflect the situation in larger defined populations that could benefit from the intervention. In some instances, the study may focus on institutions responsible for prevention activities or on providers of care, etc., rather than on individuals in the population.

A defined population is characterized by the number of individuals as well as demographic features such as age, sex, ethnic group; social and economic factors such as occupation, education, socioeconomic status; vital statistics such as incidence, morbidity, and mortality; personal or lifestyle factors such as diet or smoking; genetic and biological characteristics; and other factors associated with disease. The population may often include persons having certain common demographic characteristics who live within a specified geographical area.

Thus, phase IV studies provide further validation of the methodology developed in phases II and III and resolve new issues which arise during the process of applying the intervention to population groups that are larger than those required for phase III studies. Defined population studies require various amounts of community involvement depending on how common the chosen cancer is, the predicted size of the effect, and the size of the population sample needed to show a significant intervention effect. In many such studies, the unit for analysis is the population group rather than the individual.

**Phase V: demonstration and implementation**

The purpose of phase V studies is to apply in a large community the intervention that was proved effective in phase IV and to measure its public health impact, for which a system of evaluation and quality control procedures are needed. In many cases, these studies may be part of other programme efforts to make the intervention more cost-effective for public health programmes. Thus, phase V studies are conducted only after careful research in each of the preceding phases has provided results that justify implementation of the intervention. At the completion of this phase, therefore, a proven intervention with demonstrated public health effectiveness in reducing cancer incidence, morbidity, or mortality would have been introduced in a population, and a process for monitoring the impact of the programme would be in place.

At the National Cancer Institute, all cancer prevention research studies are classified into these phases. As new studies are planned, the background or rationale for each one would have identified the results from earlier studies that justify investigation through the phases of the new strategy. This orderly approach to cancer prevention research will ensure that adequate research precedes large-scale implementation of the intervention. Research and implementation programmes must be mutually reinforcing. Only by coordinated planning and execution of this research strategy can there be maximum benefits from the resources invested, the highest standards in the activities supported, and the best chances for the research effort to continue to provide advances suitable for future applications.

**EXAMPLES OF THE NEED FOR A NEW STRATEGY**

Smoking, diet, and occupation are three leading types of exposure that may contribute substantially to cancer risk. The following summaries of each of these areas illustrate how the new strategy of research in five phases could be a constructive step towards prevention of certain cancers in large populations.

Research on smoking cessation has been reviewed in the latest Surgeon General's report (2) on "The health consequences of smoking". It is clear from this series of reports that thousands of studies have demonstrated that cigarette smoking is the main cause of lung cancer. This exhaustive research on the causes of lung cancer is a prerequisite to research for the prevention effort, e.g., concerning actions or interventions to prevent smoking, especially on a population basis. Very little of this latter type of prevention research has been done. Most of the research on self-help approaches, minimal interventions, predictors of outcome, and methods of maintaining cessation would be classified in phase II or III in our model, these studies being focused on small selected groups even when they are carefully controlled. A great gap in our knowledge exists about
what type of programme will have the greatest impact in large, defined populations and about what type will be most cost-effective. This classification of the strategy into the proposed phases points to a great need for defined population studies to provide a sound scientific basis for national anti-smoking efforts, as well as broad international efforts at smoking prevention and cessation based on what is already known.

The state of knowledge and information pertinent to diet, nutrition, and cancer incidence was reviewed in a recent report by a committee of the Assembly of Life Sciences of the United States National Research Council (3). The report presents a series of recommendations on dietary components (nutrients and toxic contaminants) and nutritional factors for communication to the public. It appears from this report that we are in phases I and II with regard to diet and cancer control. In recent years, several excellent hypotheses have been developed on how diet can affect cancer risk. These were derived from cross-cultural and case-control epidemiological research and related laboratory investigations (3). Although many scientists believe that it is reasonable to make public recommendations based on the existing evidence, from a research standpoint more work on methods is needed to modify, confirm or refute these hypotheses. Better methods are needed to achieve standardization and quality control of dietary and intake information for international studies. It is also necessary to begin phase III prospective intervention trials to see whether dietary changes can lower cancer incidence. Thus, the present major need in this area relates to phases II and III, both basic and clinical research being linked to these trials.

Estimates of cancer deaths attributable to occupational factors and quantitative estimates of avoidable risks of cancer in the USA have been made by Doll & Peto (4). Many case-control and cohort epidemiological studies have identified specific industrial chemicals or specific occupational groups and the associated risks (3). Based on these data, improvements in industry have been made. Some phase III research has been carried out on occupational cancers but the extent of the problem is not known and the attributable risks have not been well studied. The greatest research need may well be phase IV studies to demonstrate to what extent and by what actions the occupational factors and the incidence of occupational cancers may be reduced.

A final example relates to screening for breast cancer. It is included here because early detection programmes are sometimes placed under the general heading of prevention, even though the aim is not to lower the incidence. Convincing evidence that early detection benefits the patient is seen in the Health Insurance Plan (HIP) study (3) of the efficacy of mammography and clinical screening for breast cancer. In this study, a random sample of 31,000 women aged 40-60 years were offered screening examinations. Fifteen years of follow-up provided evidence that screening-linked diagnoses and treatment could lessen the number of breast cancer deaths (3, 7). This would also be an excellent phase III study but we do not know whether this is the best intervention for the population on a national scale. What cannot be determined from the study, for example, are the potential population benefits and the value of mammography as compared to breast self-examination. Perhaps more phase III and certainly phase IV studies are needed to determine the potential population benefits of breast cancer screening. Information on costs and on practical means of achieving wide adoption of this intervention should be collected as part of phase IV studies.

CONCLUSIONS

The United States' National Cancer Institute has proposed and is following a strategy which provides a scientific basis for classifying research on interventions aimed at reducing cancer incidence, morbidity, and mortality. The key to this strategy is the analysis of research in terms of an orderly sequence of five phases.

Countries without large research capabilities like those in the USA may nevertheless use this strategy and the research phases to determine appropriate research and programme activities. As the knowledge base grows and more cancer prevention interventions have been tested for implementation (phase V), their adaptability to new geographical settings will be most efficiently determined by appropriate methodological (phase II) studies. With the combined evidence from these phase V studies, supplemented by geographically adapted phase II studies, a country with limited resources may well be able to move directly into phase V (demonstration and programme implementation) without having to perform controlled trials (phase III) or defined population (phase IV) studies. The result should be more efficient use of resources and an improved chance of benefiting the population through reduced cancer incidence, morbidity, and mortality.
CANCER PREVENTION AND CONTROL

RÉSUMÉ

STRATÉGIE DE RECHERCHE: PRÉVENTION DU CANCER ET LUTTE ANTICANCÉREUSE

En 1982, le US National Cancer Institute a entamé une importante opération de révision, de reformulation et de réorganisation des priorités de son programme national de prévention du cancer, qui a débouché sur une stratégie visant à coordonner de façon systématique les voies de recherche les plus prometteuses et à les convertir en recherches appliquées sur l'efficacité de diverses interventions.

Cette stratégie suit une approche échelonnée comportant cinq phases qui assurent la validité scientifique de la recherche et l'efficacité de l'opération de prévention. Etant adaptable, elle peut être utilisée par la majorité des pays, tant développés qu'en développement.

Phase 1: l'élaboration d'une hypothèse consiste en premier lieu à réunir a) les preuves scientifiques existantes au sujet de tel ou tel problème relatif au cancer et b) les interventions applicables à ce problème. Sur la base de cette information, on formule une hypothèse pour vérifier l'efficacité de l'intervention. On procédera ultérieurement à d'autres essais et évaluations pour déterminer si l'intervention a, ou non, agi sur le problème en réduisant les taux d'incidence, de morbidité et de mortalité de ce cancer dans la population.

Si la formulation de l'hypothèse à ce stade doit s'appuyer sur des preuves fournies par la littérature scientifique ou les résultats de recherches antérieures (par exemple études descriptive ou analytiques et autres recherches fondamentales de laboratoire, cliniques ou comportementales), ces travaux, n'étant pas liés à l'intervention proprement dite, ne sont pas considérés comme faisant partie de la recherche sur la prévention du cancer.

Phase 2: la mise au point de la méthodologie consiste à déterminer et définir les paramètres et les variables qui seront à contrôler ou surveiller dans les études suivantes. On s'assure ainsi, avant d'entamer l'intervention, que l'on dispose de méthodes fiables. Cette phase peut comporter: des essais pilotes servant à vérifier la faisabilité ou l'acceptabilité de l'intervention proposée dans un groupe particulier; des études visant à évaluer le potentiel de participation aux futures activités de l'intervention; l'expérimentation pilote de l'exécution; et la validation des formules, instruments ou questionnaires de collecte des données. Les méthodes dont la valeur a été confirmée à la phase 2 sont incorpores dans les études de phase suivante.

Phase 3: le but des essais contrôlés est de vérifier l'hypothèse de la phase 1 au moyen de la méthodologie validée à la phase 2. On testera l'efficacité de l'intervention sur un groupe de personnes, qui pourra être choisi de façon à permettre une interprétation optimale de l'efficacité. Dans les essais contrôlés, on peut comparer le groupe testé avec un groupe témoin, ou comparer différentes interventions l'une par rapport à l'autre ou avec le groupe témoin.

Phase 4: l'objet des études sur une population définie est de quantifier les effets de l'intervention sur un groupe particulier. Ces études soigneusement contrôlées doivent être faites sur une population nombreuse, bien caractérisée, ou sur un échantillon choisi, représentatif de la population visée. Des méthodes sont requises pour déterminer les caractéristiques de la population et la présence du cancer dans cette population. Si l'étude est bien conçue, on pourra déduire de ses résultats des inferences applicables à l'ensemble de la population visée.

Une population définie sera caractérisée par divers éléments: nombre d'individus et facteurs démographiques tels que l'âge, le sexe et le groupe ethnique; facteurs sociaux et économiques tels que la profession, les études et le statut socio-économique; statistiques concernant la maladie (incidence, morbidité et mortalité); facteurs personnels ou mode de vie (type d'alimentation, usage du tabac, etc.); facteurs génétiques et biologiques; et autres facteurs associés à la maladie.

Phase 5: les études de démonstration et de mise en œuvre ont pour objet d'appliquer à une large collectivité l'intervention qui a fait ses preuves à la phase 4 et d'en mesurer les effets sur la santé publique, à cette fin, un système d'évaluation et des procédures de contrôle de la qualité sont nécessaires. Ces études sont très souvent incorporées dans d'autres activités du programme visant à améliorer le rapport coût/efficacité de l'intervention en vue de l'action de santé publique. On ne les entreprend qu'après avoir examiné si aucun des phases précédentes a donné des résultats qui justifient l'exécution de l'intervention. À l'issue de cette phase, on aura donc mis en œuvre dans une population une intervention dont l'efficacité sur la santé publique, c'est-à-dire la capacité de réduire l'incidence, la morbidité ou la mortalité associées au cancer, aura été démontrée, et l'on aura également mis en place un système de surveillance des effets du programme.

L'article présente des exemples de l'utilité de la nouvelle stratégie en se référant au tabagisme, à l'alimentation et à la profession. C'est-à-dire à trois grands domaines d'exposition pouvant contribuer de façon importante au risque de cancer.

REFERENCES


