

Comments and Critique

SEARCH Programme of the International Agency for Research on Cancer

INTRODUCTION

DIFFERENT populations have contrasting levels of different cancers [1] and levels within one country can change considerably over time [2]. However, migrants generally acquire the cancer patterns of their new home, sometimes within a generation. For example, migrants to Australia from countries with low levels of breast cancer had the higher levels found among Australian-born people within two decades of arrival; migrants from Japan to the United States took two generations to acquire the same higher rates found in people born in the United States [3]. Furthermore, groups such as Seventh Day Adventists or Mormons, residents of urban and rural portions of the same region and blacks and whites in the United States, whose lifestyles differentiate them from other members of the same community, have distinctive cancer patterns.

From such evidence and from complementary information from experimental studies, the environmental theory of carcinogenesis has evolved. A substantial majority of the estimated 6 million new cases of human cancer, excluding non-melanoma skin cancer, that are diagnosed every year worldwide [4] may be caused by an environmental component, defining environment to include a wide range of ill-defined items of lifestyle such as dietary, social and cultural practices [5].

Although the present belief that most forms of human cancer are avoidable is widely held, preventable causes for most have yet to be identified with any certainty. While we know, for example, of a variety of factors thought to be associated with breast cancer risk, we do not know which factors to alter to reduce the incidence (over half a million new cases worldwide each year). In contrast, most cases of lung cancer, perhaps over 85%, could be avoided simply by the elimination of cigarette smoking.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

The IARC was established nearly 25 years ago with an orientation towards cancer aetiology and the generation, collection and dissemination of information about the prevention of cancer. Cancer prevention remains the focus of the agency's activities. The IARC has sixteen member states (Australia, Belgium, Canada, Finland, France, West Germany, Italy, Japan, Norway, Netherlands, Sweden, U.S.S.R., U.K. and U.S.A.), and Denmark and Switzerland have joined this year (1990). Each member state participates actively in the scientific programme and activities.

The agency has helped to integrate epidemiology with laboratory investigations in studies of cancer aetiology and runs programmes in laboratory science as well as in epidemiology. From its earlier days some of the most important projects of the agency have been examples of this close integration, such as the sero-epidemiological studies of Burkitt's lymphoma and the work that sought the cause of the high incidence of oesophageal cancer in the Caspian littoral of Iran. The series *Cancer Incidence in Five Continents* (the fifth volume has been published [1]) and the monograph programme (e.g. Ref. [6]) are examples of the unique international role of the IARC since its inception.

The research activities of the IARC [7] are concentrated on epidemiological and laboratory science with statistical, computing and administrative support. Within epidemiology, there are four main areas of activity: descriptive epidemiology, field and intervention studies, biostatistics and analytical epidemiology. The Unit of Analytical Epidemiology has been active for many years in occupational cancer (for example, exposure to silica [8]) and more recently has become active in nutrition and cancer,

and in a programme of multicentre case-control studies, which has the acronym SEARCH.

SURVEILLANCE OF ENVIRONMENTAL ASPECTS RELATED TO CANCER IN HUMANS (SEARCH)

The SEARCH programme was initiated at the IARC to generate, formulate and test by epidemiological methods, and on an international basis, hypotheses about putative risk factors for various forms of cancer. SEARCH studies have attracted considerable scientific interest and have been funded in centres throughout the world. For each form of cancer studied, identifiable experts have been brought together to advise on hypotheses requiring investigation and to help develop study protocols to be implemented in participating centres. Cancer epidemiologists and basic scientists from many parts of the world have come together and protocols have been developed to replicate research in dispersed and dissimilar populations. SEARCH aims to include centres with very high and very low disease frequencies and also some centres with contrasting levels of exposure to the factor(s) being investigated. Thus findings can be subjected to the crucial epidemiological test of reproducibility at an early stage. The goal of the SEARCH programme is to identify causes of cancer and thereby help to increase prospects for prevention.

Cancers to be studied are chosen in collaboration with participants and are discussed and approved by the SEARCH Advisory Group and subsequently the Scientific Council of the IARC. Potential participants take the documentation prepared by the IARC staff and the *ad hoc* committee of experts and seek funds to conduct the study locally. Some centres use core funding available within their institute while many centres have to compete for research funds. The IARC organizes meetings of participants before the study starts and regularly throughout the study. IARC staff prepare a core questionnaire in consultation with the participants which is translated into the local language by the local investigator. An interviewer's manual is circulated to participants with a coding manual, which is continually upgraded as new situations are encountered. A recent innovation has been the writing of a computer program that checks range and consistency in the data and corresponds to the core questionnaire; this program is written at the IARC and distributed to each participant. The purpose is to facilitate data transfer to the IARC and to minimize the time for correcting data. Data are cleaned and analysed centrally at the IARC with the input of the participants.

SEARCH studies cover a wide range of cancers. A collaborative study of cancers of the pancreas, gallbladder and bile ducts has just finished successfully in five centres. There are studies at an advanced stage of data collection on childhood and adult brain tumours (nine and ten centres, respectively). Data collection is starting in a large study of breast and colorectal cancer (approximately 10–20 centres should eventually participate) and collaborators in a study of childhood leukaemia meet in 1990; risk factors for this malignancy are virtually unknown. An international committee is finalizing protocols for the study of malignant melanoma: a case-control study and a collaborative cohort study of patients with acquired dysplastic naevus.

Cancer of the pancreas, gallbladder and bile duct

This study, which was the first SEARCH study conceived in 1983, was designed to evaluate the role of habits such as cigarette smoking and alcohol and coffee consumption, of occupational exposure to certain chemicals, of various dietary factors

(especially fat and vegetable intake), and of conditions such as diabetes and atopia on the risk of pancreas cancer, a cancer which is difficult to study easily in any single centre. The first results will be published later this year and findings for gallbladder cancer and bile duct cancer will follow.

Brain tumours

Brain tumours in children are sufficiently uncommon to make their study in a single centre difficult, as reflected by the limited information available about the cause of these tumours. A major hypothesis being tested in this study relates to the role of exposure to nitrosamines, nitrosatable substances and inhibitors of nitrosation in the aetiology of this form of cancer. Data on possible exposure to nitrosamines or their precursors as a result of passive smoking, from certain dietary sources and through intake of nitrate and nitrite from food and water are being collected with data on vitamin C intake, which can inhibit nitrosamine formation from amino substrates in man.

The study hypotheses for the study in adults are similar to those for childhood cancer but also include certain occupations and exposure to chemicals, (from hobbies as well as from work) and cigarette smoking.

Breast and colorectal cancer

Breast cancer and colorectal cancer may have several common risk factors, in particular nutritional. This study has been designed to investigate the role of alcohol consumption in the aetiology of breast cancer in women, the possible protective role of coffee consumption in colorectal cancer and the role of dietary intake (especially fat, cholesterol and vitamin A) in the aetiology of both cancers. Study centres are situated in Western and Central Europe, in North and Central America and in Asia, where there are contrasts in the incidence of both diseases and the pattern of intake of fat, vegetables and alcohol. Several nested biological studies are optional for participating centres.

Childhood leukaemia and related haematological malignancies

Little is known about the aetiology of these forms of cancer, especially because of the rarity of this group of diseases. In collaboration with the European Organization for the Research and Treatment of Cancer a multicentre protocol has been prepared, principally to test Greaves' hypothesis [9] about the aetiological role of parental exposure to chemicals and ionizing radiation, postnatal domestic exposure to solvents, pesticides and in some centres electromagnetic fields, and radon, and parental smoking. Data collection should begin before the end of 1990 in some centres.

Malignant melanoma

Many populations are experiencing a rapid increase in the incidence of malignant melanoma. Two studies are at an advanced stage of planning. The first is a multicentre case-control study of malignant melanoma, including non-cutaneous melanoma, designed to examine the relation between malignant melanoma risk and a wide variety of factors: eye, skin and hair colour; history, number, type and distribution of naevi on the body; sun exposure and sunburn; exposure to artificial and fluorescent light; substances used to promote suntan; and family history of melanoma and naevi. At the same time a multicentre cohort follow-up of patients with a newly removed naevus, whether dysplastic by histological examination or by clinical suspicion, will examine the role of behavioural characteristics and pathological characteristics of the naevus on melanoma risk.

CONCLUSIONS

Epidemiological methods have improved greatly in the past 10 years in study design and analysis. Several flaws in earlier studies have been identified, and many recently completed studies and current studies will hopefully clarify issues in epidemiology that are vague at present. Furthermore, the development of epidemiology as a specialty in many parts of the world means that good studies will now be possible at the extremes of disease incidence and exposure. The SEARCH network, bringing together experienced researchers internationally and incorporating a training component, is an interesting innovation by the IARC with the potential to make an important contribution to knowledge of cancer causes.

Peter Boyle
SEARCH Programme
Unit of Analytical Epidemiology
International Agency for Research on Cancer
150 cours Albert-Thomas
69372 Lyon cedex 08
France

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Europe against Cancer

It is too early to evaluate whether the 'Europe against Cancer' programme will reach its objective, i.e. to reduce by 15%, compared with the presently increasing trend, the number of deaths by cancer in the year 2000 in the European community. Nevertheless, the report* on the first 1987-89 action plan of the programme shows that good results have been achieved.

In the fight against tobacco, the highest priority of the programme, four Community laws have been adopted: one resolution to ban smoking in public places, and three directives about the labelling of tobacco products, the prohibition of high-tar cigarettes and the banning of direct and indirect advertisement on television. These legal actions have also contributed, with the anti-tobacco campaigns partly financed by this European programme, to the general decline in the number of smokers observed in most European Community countries over the past three years.

This success is also due to the involvement of a series of partners of the programme. Indeed, more than one hundred governmental and non-governmental institutions have been mobilized and coordinated by the European Commission. This joint effort has been rewarded by a noticeable improvement

in public awareness of the European Code against Cancer, particularly during the European year against cancer, in most European countries, and most spectacularly in Portugal where the proportion of people who had heard about this code jumped from 29 to 56%.

Many results have been achieved in the other areas covered by the programme, including medical research and especially in radiotherapy. Two techniques have been evaluated. The first is boron neutron capture radiotherapy and a pilot clinical facility is being built in Petten (The Netherlands) to test this treatment which has given promising results in Japan. The second technique, successfully tested in the U.S.A., uses light ions. On the basis of the present feasibility study, Europe will probably have to consider supporting the building of one or two such facilities in the European community.

Altogether, the first 1987-89 action plan of the Europe against Cancer programme has shown that the European Community can contribute specifically and usefully to the fight against cancer. This is indeed why the Council of health ministers has adopted, on May 17, a second 1990-94 action plan with an increased budget.

Michel Richonniere
Coordinator
European Commission

*Report on the Europe against Cancer 1987-89 action plan.
Brussels: European Commission COM(90) 185, May 1990.