POLICY AND PRACTICE

Social Responsibility in Cancer Prevention Research: IARC as a 'Global Science Force'

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Abstract

Ten million new cancer patients are diagnosed each year worldwide. Many specific causes of cancer are known, ranging from factors related to lifestyle, diet and chronic infections to occupational exposures. Primary and secondary prevention continue to be of major importance in cancer control globally. The global burden of cancer, especially the part attributable to infectious diseases, disproportionally affects populations in developing countries. Inadequate access to treatment (pharmaceuticals and other modern technology) plays a role in perpetuating this disparity. Drugs and vaccines may not be accessible because of excessive cost or because development of the required products has been neglected. The remarkable advances in molecular understanding of the carcinogenesis process over the past 25 years have transformed the approaches to cancer control. Promising new tools in preventive oncology, such as immunization (vaccines) and chemoprevention, have emerged. Vaccines are currently being tested in trials e.g., against hepatitis B virus and human papillomaviruses. Chemoprevention has been successfully achieved in animal experiments, and has been validated in several clinical trials. The current agents and strategies should not be regarded as a panacea; more effective and safer vaccines and chemopreventive agents are needed. Future enhanced efforts on an international basis are needed to coordinate the prevention and intervention research efforts in a cost-efficient and affordable manner. Cancer prevention deserves continuing high priority in terms of both research and application, also in the developing countries. New ventures may be built on possible expansion of IARC's role in prevention and intervention research into a "Global Science Force" by following the examples of e.g., the Gambia Hepatitis Intervention Study and the cervix cancer screening trials in India. WHO's support with its regional offices would be beneficial, together with further national funding and support, and research collaboration and funding from more wealthy countries.

Key Words: Global cancer burden - cancer prevention - preventive oncology - genomics - chemoprevention - early diagnosis - screening - vaccinations - hepatitis B virus - smoking - sunlight and skin cancer - asbestos and mesothelioma - cervix cancer - papillomaviruses

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Health and Disease Burden in a Global Context

In his opening lecture to the XVI IEA World Congress of Epidemiology (in Montreal, August 18-22, 2002), Mr Stephen Lewis, a newly appointed UN Secretary General's Special Envoy for HIV/AIDS, drew attention to the spread of HIV/AIDS in Africa and the near-total lack of medication, with only 2% of the HIV-infected people who need medication actually receiving it. Mr Lewis also paid attention to the contrast between the enormous resources devoted to anti-terrorist actions (including the war in Afghanistan) after the World Trade Center disaster one year ago in which nearly 3000 people died and the near-total lack of resources for AIDS treatments to delay the over one million deaths each year in sub-Saharan Africa alone. His talk thus emphasized the social responsibility of scientists to promote the public health implications of their work, and this applies particularly clearly also in the field of cancer prevention.

Health and disease are increasingly seen in a global context. The distribution of disease between different populations and over time helps to define causal hypotheses, and to quantify the potential for prevention. Estimation of the burden of cancer in terms of incidence, mortality and prevalence is a first step to setting up appropriate control measures in the global context. The latest results of such an exercise, based on the most recent available international data from the IARC, show that there were 10 million new cancer cases, 6 million deaths, and 22 million people living with cancer in 2000 (Parkin, 2001, Table 1). The profile varies greatly in different populations, and the evidence suggests that this variation is mainly a consequence of different lifestyles and environmental factors, which should be amenable to preventive interventions. In 2000 there were slightly more new cancer cases (53%) and deaths (57%) occurring in developing than in developed countries. Since the biggest changes in the demography of the world will

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take place in less developed areas, more and more of the future world cancer burden will occur in these regions. World population growth and ageing imply a progressive increase in the cancer burden – 15 million new cases and 10 million deaths are expected in 2020, even if current incidence rates remain unchanged. Nearly three quarters of these predicted new cancer cases will live in countries with less than 5% of the world's resources for cancer control and treatment. If one considers quality healthcare is a basic human right, this situation is nothing less than alarming.

Cancer control comprises five components: prevention, early detection and screening, treatment, rehabilitation and palliative care. The World Health Organization (WHO) has developed the concept of national cancer programmes with the goals of preventing future cancers, diagnosing cancers early, providing curative therapy when available, ensuring freedom from suffering and reaching all members of the population (WHO, 2002). The mission statement of the International Agency for Research on Cancer (IARC), a research arm of the WHO, is to conduct and promote international collaboration in cancer research with the objective of improving health through a reduction in the incidence of and mortality from cancer throughout the world (IARC, 2002).

Population attributable risks help in establishing priorities for cancer control. Table 2 shows the estimated percentages of cancer deaths attributable to various causes in people aged under 65 years in the USA. Similar estimates probably apply to most developed countries. The population attributable risk for tobacco-induced cancers is of the order of 30% in Western populations, but over the world as a whole it is closer to 20%. For dietary–associated cancers it is perhaps 30%, and for cancers associated with infection, 15% (Pisani et al., 1997; WHO, 2002). For occupational and environmental carcinogens, the population attributable risk may be around 3-9%, depending on the prevalence and intensity of exposure in the particular population. It seems probable that the proportion of cancer resulting from occupational factors is decreasing in many developed countries, due to the introduction of appropriate control measures in the later part of the 20th century. The challenge for many developing countries, as they undertake the process of industrialization, is to ensure that they do not import the carcinogenic hazards related to various occupations. Overall,

it appears that if we could apply all the knowledge we have now, we could prevent over half the cancers in the world.

Cancer Prevention: Important to Act in Time

That we have notoriously been late in cancer prevention in many areas is now clear (European Environment Agency, 2001). Over the next 50 years we will see thousands of extra skin cancers as today's children grow up exposed to the higher levels of ultraviolet radiation penetrating the normally protective ozone layer through the 'hole' created by chlorofluorocarbons and other synthetic halogenated chemicals. Over the same period thousands of Europeans, Americans, Africans and Asians will die from the most painful terminal cancer, mesothelioma, caused by the inhalation of asbestos dust. In addition to mesothelioma, asbestos exposure is causing many more cases of lung cancer. In both of the above cases we were late: the hazards of these beneficial technologies were not taken seriously until it was too late to stop their irreversible impacts. A further example of delayed action is tobacco smoking, where the smoking epidemic continued globally at the same time as the deadly consequences of smoking have increasingly reflected in cancer statistics. Worldwide, the two major causes of death whose effects are now increasing rapidly are HIV and tobacco (Peto and Lopez, 2001). All of these phenomena have such long latent periods (decades) between the first exposure and late effects that the 'pipelines' of unstoppable consequences were already set in motion before actions could be taken to stop exposures. Misplaced 'certainty' about the absence of harm has played a key role in delaying some preventive actions. As late as 2000, Canada (one of the asbestos producing countries) objected at the WTO to the asbestos ban of France (introduced in 1997) but the WTO ruled in favour of the ban; this demonstrates the strong economic and political interests which are still related to asbestos use.

Some undeniable successes in controlling cancer have occurred. Tobacco-associated cancers are in decline – but only in a few countries. Stomach and cervical cancers are decreasing in several countries. Apart from cervical cancer, this success comes from prevention, which deserves continuing high priority in terms of both research and application.

Table 1. Numbers of Cancer Deaths and New Cases in the World as Estimated for 2000 and Predicted for 2020[1]

Year	Region	New cases (millions)	Deaths (millions)
2000	More developed countries	4.7	2.6
	Less developed countries	5.4	3.6
	All countries	10.1	6.2
2020	More developed countries	6.0	3.5
	Less developed countries	9.3	6.3
	All countries	15.3	9.8

[1]Ferlay et al (2001)

Table 2. Causes of Cancer Deaths in the United States of America (under the age of 65)

Cause of cancer (or contributory factor)	Best estimate	Range of acceptable estimates
Tobacco	30	25-40
Alcohol	3	2-4
Diet	35	10-70
Reproductive and sexual behaviour	7	1-13
Occupation	4	2-8
Pollution	2	1-5
Industrial by-products	1	1-2
Medicines and medical procedures	1	0.5-3
Geophysical factors	3	2-4
Infection	10	1-?

Source: Doll and Peto (1981)

The 'war' on cancer, declared by President Richard Nixon some 30 years ago, has thus had only limited success. After a quarter of century of rapid advances, cancer research has undoubtedly developed into a logical science, where complexities of the disease, described in the laboratory, clinic, as well as in populations, have become understandable in terms of a certain number of underlying principles. We are beginning to understand the intricate workings of the human genome – ultimately responsible for controlling all biological processes in health and disease. The announcement of the sequencing of the human genome in 2001 represents an unprecedented milestone in the advancement of our knowledge on the molecular basis of life itself. This information generated by genomics will, over time, provide major benefits for the prevention, diagnosis and management of diseases such as cancer. Gene chips and microarrays are already available that detect minute changes in the genetic code of considerable relevance. Novel screening technologies have the potential to detect just a few cancer cells in a patient. An example of this was recently described in Cancer Research, where a protein-biochip surface-enhanced laser desorption/ionization (SELDI) mass spectrometer approach was used to detect proteins that were affinity-bound to a protein-chip array (Adam et al., 2002). The advantage of this screening technique includes earlier detection of prostate cancer – the authors' experience suggests that prostate cancer might be detected five or more years earlier with this technique than with the conventional screening for prostate-specific antigen (PSA).

But has the knowledge gained been utilized in practical cancer prevention? It was argued some 20 years ago by Richard Peto that mechanistic evidence may not be needed before launching public health actions (Peto, 1984). The demand to know more about the mechanisms may sometimes be used as an argument for inaction. Evidence supporting the importance of socio-environmental factors in cancer prevention has been sufficient to initiate action for control even when molecular mechanistic evidence was lacking (e.g., smoking, asbestos, hepatitis B virus). In the 1960s, almost 250 men in every 100000 per year in the UK died before the age of 70 years from smoking-related diseases (including cancers) – today, the figure has more than halved to about 100 per 100,000 per year. A spectacular success achieved mainly through persuading people to quit smoking even in the absence of knowledge on the exact mechanisms of smoking- induced cancer. Molecular and other biomarker data may, however, help to make sense of some of the observations in population-based studies in the future, especially in subgroup analyses.

The New Discipline of Chemoprevention

Clinical cancer is the end of a chaotic process, termed carcinogenesis, which in humans often requires two or three decades. Based on the detailed knowledge we have developed of this process and the role of various etiological and protective factors, it is now a widely accepted concept that cancer is largely a preventable disease (WHO, 2002). In addition to cancer therapy and primary prevention of cancer, a new paradigm of cancer chemoprevention has emerged. The possibilities for curing many major malignancies unfortunately remain very limited, despite many advances in therapy, and the great expectations from molecular gene therapy may be unduly optimistic (Sporn and Suh, 2002). Thus primary and secondary preventive efforts continue to be of major importance and many authors have stressed the potential use of chemical compounds, which can suppress processes responsible for tumorigenesis. Chemoprevention aims to stop the progression of the carcinogenesis process at a preclinical stage, and even reverse the process, by modulating DNA damage and repair mechanisms, DNA methylation pathways influencing gene expression and cellular phenotypes, causing antioxidant defense and oxidative stress modulation, targeting receptors and signalling pathways, cell-cycle controls and check-points, and application of antiangiogenic properties. There have already been some successful clinical trials, for example with the estrogen analogues tamoxifen and raloxifene against breast cancer in high risk women. At the same time, tamoxifen seems less then ideal for 'healthy' women, because it has adverse consequences which, even through they are infrequent, manifest themselves in the large numbers of women who are destined never to develop breast cancer (Love, 2001; IBIS Investigators, 2002). In addition,

compounds such as aspirin and aspirin type drugs offer great promise (IARC, 1997; Wakabayashi, 2000; Vainio et al., 2002). This knowledge can provide a framework for cancer prevention research that includes biomarkers of early responses, research on biological mechanisms underlying putative cancer relationships, and identification of the molecular targets of cancer prevention.

Widening the Gap between the Global 'Rich' and 'Poor'

The field of cancer prevention will benefit from technological advances in molecular biology and genetics. But as technology becomes more complex, the gap between the global rich and poor will widen. The "10/90 gap" has been used to refer to the wide disparity in global spending on health research between developed and developing countries (Global Forum for Health Research, 2000). In economically more advanced countries the production of pharmaceuticals and vaccines is being developed with modern genomics technology – but vaccines are still needed, especially for impoverished countries, for such important diseases as HIV/AIDS, malaria and tuberculosis. The export of unhealthy lifestyles – cigarette smoking, 'fast food' with high energy content and high glycaemic index, sedentary occupations, promiscuous sexual habits – will disproportionately increase the incidence of cancer and other chronic diseases such as cardiovascular diseases and diabetes in many developing countries, which can least afford the treatment costs.

The lack of biotechnology and information technology in developing countries is also of concern. Genomics research involves large-scale creation and utilization of databases with a high level of automation, and therefore requires heavy capital investment. As such, it has been carried out primarily in developed countries, in both the public and private sectors. Although much of the genomics research was initially undertaken in the public sector, private company spending has recently moved ahead and is now substantially higher than government and not-for-profit expenditure. The private sector does not invest in research aimed at diagnosis, therapeutics, or prevention for diseases that are predominant in developing countries because the populations that are afflicted and most likely to need them do not have the purchasing power. In order to ensure high return on their investments, companies tend to focus their research and development efforts on products aimed at diseases and health problems that are most prevalent among populations of the developed countries. In 1997, for example, it was estimated that low- and medium-income countries accounted for only 20% of the global pharmaceutical market, even though they made up over 80% of the world's population (Widdus, 2001). The lack of market incentives for the global pharmaceutical industry to pursue genomics–based research and development related to diseases of the world's poor countries means that, unless mechanisms can be fostered to expand investment by public and private institutions in both developed and developing countries, the potential of genomics to combat these diseases will not be realized and existing inequalities in health will be exacerbated.

What seems increasingly likely is that genetic polymorphisms of various sorts will be identified that allow consideration of an individual's susceptibility to various cancers. Whether that will then result in an improved ability to control cancer generally is unclear. If a particular subgroup that is at increased risk of a specific cancer can be identified, it may be worthwhile for these individuals to use appropriate chemopreventive agents to prevent that cancer or to concentrate screening efforts on them. This could make certain types of cancer control actions more cost-effective, but might not necessarily result in a greater impact in the population as a whole.

A key factor to ensure success in cancer prevention is careful targeting and adequate use of limited resources. In developed countries, cancer prevention programmes may lead towards individualized prevention by combining genetic, environmental and lifestyle data to construct very specific personalized messages. Interventions to reduce environmental exposures could be targeted to those with particular polymorphisms – although the utility of such an approach has yet to be demonstrated. For many cancers, the number of genes that contribute to susceptibility is likely to be large, and the effects of each gene or allele will be weak. For example, suppose there are a dozen or more genes that contribute to lung cancer. Attempting to identify susceptible subgroups for public health interventions would be too complex to be of practical value. However, it was recently suggested that the gene-expression risk profiles, based on association of particular profiles with patient survival, can identify stage I lung adenocarcinoma, and distinguish between patients at high risk and low risk of recurrent or metastatic disease within this subgroup (Beer et al., 2002).

Thus, for most chronic diseases, it is likely that more persons will benefit from modification of lifestyle or environmental factors than from knowledge of their genotypes. If scientists direct their efforts towards a comprehensive search for the genetic underpinnings of every discrete health outcome, and ignore environmental exposures and attributable risk, we are likely to miss many opportunities to prevent disease (Millikan, 2002). Undoubtedly, over-optimistic expectations on the ability of genomics research to solve cancer problems emerged in the period of excitement following the sequencing of the human genome (Burn et al., 2001). This stemmed in part from a lack of appreciation of complexity of the cancer causation, and in part from the tendency of some scientists to overemphasize the immediate medical importance of their work to the media and to granting agencies.

Globalization of Unhealthy Lifestyles

Unhealthy consumption patterns and lifestyles are driving the emerging cancer epidemic in developing

countries, which currently have more new cancer cases annually than the developed countries. Globalization of unhealthy lifestyles (tobacco use, unhealthy diet, and physical inactivity) is a key factor in this process. Control of tobacco use is the most urgent need. With simple but forceful 'anti-smoking' programmes, to stop people from taking up the habit, and to help smokers to quit smoking, we could have a major effect on future disease trends (cancer, cardiovascular disease, chronic obstructive pulmonary disease). The struggle is a difficult one, especially since the tobacco industry is using enormous amounts of money to market its products in the countries where smoking is not yet widely established.

Infections are another important cause of cancer especially in the developing world, where an estimated 22% of cancer has an infectious cause (Pisani et al., 1997). Many infectious diseases are affected by rapid urbanization and spread as a result of unsanitary conditions, crowding, and changes in human behaviour and sexual activities in developing countries. Poor inner-city and periurban populations are less likely than other sections of the population to be immunized against infectious diseases.

Immunization for cancer prevention

Hepatitis B vaccination can be expected to prevent liver cancer in high-risk countries with a high prevalence of infection. However, infants need to be vaccinated, and a major impact on liver cancer incidence cannot be expected for about 40 years, although there are other, more immediate non-cancer benefits from vaccination. Hepatitis B immunization in children has already reduced the incidence of infection in China, Korea and West Africa. IARC, in collaboration with the Government of the Republic of the Gambia and the laboratories of the United Kingdom Medical Research Council (MRC), and with financial support from the Italian Government, has conducted a large scale hepatitis intervention study in the Gambia. The first phase of the study involved the introduction over a five-year period of vaccine against hepatitis B virus (HBV) into the expanded programme of vaccination of the Gambia, so that about one half of the children born in the years 1986-1990 received the vaccine, while an equal number did not. The vaccine proved to have 95% efficiency in protecting against chronic HBV infection. The cancer incidence among vaccinated and control individuals is now been followed (IARC, 2001).

Cancer of the cervix, the commonest women's cancer in parts of India and Latin-America, is clearly associated with certain subtypes of human papillomavirus (HPV). Prophylactic vaccines may soon become available against oncogenic papillomaviruses. However, even if a vaccine for HPV becomes available soon, it will take at least 30 years from vaccination before there is a clear effect on invasive cancer of the cervix. In contrast, screening and or treatment, if effective, can have a rapid impact. For some time, the incidence and mortality associated with cancer of the cervix has been falling in developed countries. In Sweden, for example, much of the decline is attributable to screening, but some of decline is due to early detection and treatment (Ponten et al., 1995).

Several methods for early detection of cervix cancer, such as visual inspection with acetic acid (VIA) and with magnification (VIAM), visual inspection with Lugol's iodine (VILI), conventional cytology and HPV testing are being evaluated in cluster-randomized intervention trials and cross-sectional studies for their accuracy in detecting high-grade cervical precursor lesions and in preventing invasive cervical cancer (IARC, 2001). These studies are coordinated by IARC (Dr Sankaranaranayan), and funded largely by external sources (Bill and Melinda Gates Foundation). The trials are currently under way in several districts in India and elsewhere, and the first results are expected in 2004.

Helicobacter pylori is associated with stomach cancer. Vaccines are also being developed for *H. pylori*. Even without any 'planned' intervention, there has been a remarkable downward trend in stomach cancer incidence worldwide. Dissecting out the complex factors responsible for this trend, including food storage, contamination, preparation and content is a considerable challenge.

Other cancer-causing infections are schistosomiasis, liver fluke, and HIV. Vaccine development is under way for each of them. Unfortunately, market economy restrictions may slow down the development of vaccines by the pharmaceutical industry, vaccines which are critically needed to bring the infections and related cancers under control. Particularly in relation to HIV and AIDS, attempts are being made to combine skills and resources of public sector programmes with participation from the pharmaceutical industry. Clearly, the effectiveness of any infection control or immunization programme in reducing the cancer burden will depend on many factors and require careful research and field evaluation.

"Global Science Force": a Role for the IARC?

When Harold Varmus (2001) summarized the various sessions of the Nobel Prize Centennial 1901-2001 in Stockholm last year, he emphasized the importance of global perspectives in science. Dr Varmus suggested that a 'Global Science Force' should be established in order to develop the necessary infrastructure for international research. The cancer problems of the developing world are global concerns, and consequently, there is a critical (and moral) need for greater investment at global level in research directed at the cancer problems of the developing countries. While the developing countries' participation in international efforts may be hampered by financial constraints, as exemplified by the quick withdrawal of Argentina and Brazil from the IARC's membership in the late 1990's, the future role of the IARC, as the WHO's specialized cancer research institute with independent financing and management, may well fulfill many of the requirements for the 'Global Science Force' suggested by Dr Varmus. The IARC's mission and research aims are of obvious importance to all parts of the

world (IARC, 2002). The Agency, located in Lyon, France, is currently financed and governed by the 15 participating countries, from Europe, North America, Australia and Japan. Its location has allowed and facilitated the coordination of large studies such as the unprecedented EPIC study (European Prospective Investigation on Nutrition and Cancer) involving almost half a million people from 11 European countries. The activities of the IARC have, however, in no way been limited to Europe: large-scale intervention studies have been or are being carried out during the last two decades in for example, India (cervix cancer screening), China (chemoprevention of oesophageal precursor lesions), the Gambia (hepatitis B vaccination trial), and Venezuela (chemoprevention of stomach cancer). However, efforts to increase developing country participation in the IARC's activities are well worth pursuing. As an incentive, and also for geopolitical and economic efficiency, it has been suggested that setting up satellite (regional) centres could increase the interest of the developing countries to join the IARC (Moore and Tajima, 2002). The Gambia Hepatitis Intervention Study and the cervix cancer early detection trials in India may serve as examples for future intervention activities in developing countries. The more participatory 'field-study' structure may facilitate the receipt of local and regional support, and allow better coordination and management of the multicentric activities. It may also be taken as an argument to obtain greater support from WHO as a whole.

Strategies and future action plans are necessary, but money is essential. Poverty causes ill health. While rich nations have failed to steer a course towards devoting 0.7% of their GNP for official development assistance, many countries (such as Sweden and Denmark) are already using considerable amounts to support and develop health activities in developing countries. At the September 2000 UN Millenium Summit, chaired by the ex-prime minister of Finland, Mr Harri Holkeri, the world's political leaders committed themselves to halving the number of people living in poverty by the year 2015. Development goals and targets were set, including several in health. The support necessary for the different regional cancer prevention research programmes might be obtained from rich countries through this channel of development assistance.

Acknowledgement

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