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Report by the Director of the International Agency for Research on Cancer (IARC)

1. The **International Agency for Research on Cancer (IARC)** was created in 1965 as an integral part of the World Health Organization and is located in Lyons (France). The IARC Governing Council is composed of delegates from the 16 Member States (Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, The Netherlands, Norway, Russian Federation, Sweden, Switzerland, United Kingdom, United States of America) and the Director-General of WHO. The Scientific Council, consisting of international cancer research experts, critically reviews the work of the Agency, gives advice on future research strategies and reports to the Governing Council. During the past year, approximately 240 people from more than 35 countries worked at the Agency. The annual regular budget for the biennium 1998-1999 will be approximately US$ 18 million. Of the total budget, 20%-25% is provided by extrabudgetary sources, usually through competitive research grants.

2. **Scientific strategy.** The Agency pursues three main objectives: the identification of the causes of human cancer, the elucidation of the mechanisms of carcinogenesis and the development of scientific strategies for cancer prevention. Within this framework, priority is given to projects that can be more efficiently realized by international cooperation than on a national or regional level.

3. **Geographic variations in cancer occurrence.** In many parts of the world a dramatic shift in cancer occurrence is observed. In several newly industrialized regions cancer has become, unexpectedly fast, one of the leading causes of death. These changes have been predicted by cancer epidemiologists for many years, but even they are surprised by the speed at which these changes are occurring, e.g., the emergence of cancer of the breast, colon and prostate in several countries in which these neoplasms were hardly known only 20 to 30 years ago. This is reported in Volume VII (1997) of IARC's epidemiological flagship publication, *Cancer incidence in five continents*, which covers the years 1988-1992 and contains data from 182 population groups in 50 countries. For the first time, we were able to include data from registries in Argentina, Republic of Korea, Uruguay and Viet Nam.

4. **Survival of cancer patients.** Survival data allow the calculation of the prevalence of organ-specific neoplasms in a given country and provide a basis for national cancer control strategies to be pursued in collaboration with the WHO programme on cancer control. The Agency's first comprehensive, population-based study, *Survival of cancer patients in Europe (EUROCARE)*, evoked a strong reaction in the public health community since it revealed surprisingly large differences, even among highly developed countries. Significant differences in survival were revealed when comparison was made with developing countries, for people with cancers that can be successfully treated by chemotherapy (malignant lymphomas, leukaemia, testicular tumours) and modest differences for neoplasms that can be cured by early detection and surgical intervention.

No significant differences were found in the survival from tumours largely refractive to therapy, e.g., carcinomas of the pancreas, lung and liver.

5. **Environmental carcinogens.** The IARC *Monographs* on the evaluation of carcinogenic risks to humans published in 1997 conclude that PCDD ("dioxin") and crystalline silica inhaled in the form of quartz or cristobalite from occupational sources are carcinogenic to humans. IARC scientists coordinated several studies on the adverse health effect of exposure to styrene, man-made vitreous fibres, organic mercury compounds and substances affecting workers in the paper, wood, leather and asphalt industry and in biological research laboratories. A major epidemiological study on environmental tobacco smoke has been completed and revealed a significant dose-response relationship between passive smoking (at home or at the workplace) and lung cancer.

6. **Cancers associated with chronic infections.** IARC epidemiologists have estimated that in developing countries up to 20% of all human neoplasms develop in association with chronic infectious conditions. In the past biennium, working groups have concluded that there is sufficient evidence to classify infection with human immunodeficiency virus (HIV-1), human T-cell lymphotropic virus (HTLV-1), Epstein-Barr virus (EBV) and the Kaposi sarcoma-associated herpesvirus 8 as carcinogenic to humans (IARC *Monographs*, Vol. 67 and 70). The risk of developing cervical cancer is closely related to sexual behaviour of both the woman and her male partner. Multicentre case-control studies clearly demonstrated a cervical cancer risk associated with infection with a variety of human papillomaviruses (HPV) other than types 16 and 18. There is circumstantial evidence that HPV18 is closely associated with adenocarcinoma, while HPV16 and its variants are more frequently related to squamous cell carcinoma of the cervix.

7. **Nutrition and cancer.** In western European countries and North America more than 30% of tumours are associated with dietary habits, but the nutritional components responsible and their biological role in the evolution of cancer of the breast, colon and prostate are still ill-defined. An international prospective epidemiological study on nutrition and cancer ("EPIC") combines investigation of dietary habits, nutritional and anthropomorphic status, lifestyle and environmental factors with laboratory investigations. By the end of 1997, more than 440 000 individuals had been recruited, and more than 340 000 blood samples deposited at the Agency for long-term storage in liquid nitrogen. Biochemical analyses of serum samples have begun and it is anticipated that collection and evaluation of data on the most frequent cancer sites will begin in 1998.

8. **Cancer genetics.** Mutations in the breast-cancer susceptibility genes BRCA1 and BRCA2 show regional and ethnic preferences. IARC is coordinating an international study of the frequency and type of breast-cancer gene mutations in various parts of the world. Information on the occurrence of such mutations is potentially important for the estimation of genetic cancer risks and for early detection of breast cancer. The Agency has made considerable progress towards the identification of the gene underlying X-linked lymphoproliferative disease (XLP) associated with very high sensitivity to Epstein-Barr virus infection. The XLP gene has been mapped and the candidate XLP genomic region at Xq25 sequenced, but so far disease-associated mutations have not been found.

9. **Gene-environment interactions.** IARC is currently concentrating on the biological role of the gene responsible for ADP-ribosylation (PARP). Mutations and genetic polymorphisms can significantly influence the process of malignant transformation but environmental and lifestyle factors still play an important role by either accelerating or delaying the clinical manifestation of neoplasms.

10. **Organ-specific carcinogenesis.** The understanding of organ-specific carcinogenesis can provide a molecular basis for possible intervention strategies, including gene therapy. Squamous cell carcinomas of the oesophagus associated with tobacco and alcohol use frequently contain GC→TA transversion mutations while in adenocarcinomas that develop in connection with chronic oesophagitis and Barret's oesophagus, GC→AT transitions prevail. Glioblastomas, the most common malignant brain tumours, develop through different genetic pathways. Primary (*de novo*) glioblastomas typically show overexpression of the EGF receptor and, less frequently, PTEN mutations, p16 deletions and MDM2 overexpression. In contrast, secondary glioblastomas

that develop from low-grade astrocytomas, carry p53 mutations as a genetic hallmark. In many regions, the incidence of head and neck cancer has increased dramatically as a result of alcohol and tobacco use. In addition, infection with human papillomaviruses is found in up to 40% of cases of carcinomas of the oral cavity. IARC studies on skin cancer indicate that UV-induced CC→TT tandem mutations are predictors of basal cell carcinoma but do not reflect total UV exposure.

11. **Tumour biology.** Several studies have focused on the role of DNA repair enzymes in carcinogenesis and response to radiotherapy. Heterozygous carriers of a mutation in the ataxia teleangiectasia (ATM) gene have an increased risk of breast cancer. Such patients may also have an acute or late over-reaction to radiotherapy and this can be predicted from the response of lymphoblastoid cell lines derived from these patients. Functional loss of DNA mismatch repair mechanisms, manifesting as genomic microsatellite instability, plays a role in some human neoplasms and enhances susceptibility to mutation by environmental carcinogens. Connexins mediating gap-junction intercellular communication (GJIC) are capable of tumour suppression. Screening of human neoplasms revealed several polymorphisms in connexin genes but mutations appear to be rare. The IARC database on p53 mutations is extensively used by scientists worldwide and now includes germline mutations.

12. **Prevention and early detection.** The most important project of the Agency in the domain of primary cancer prevention is the Gambia hepatitis intervention study, launched in 1986. A total of 122 577 children were vaccinated against hepatitis B virus (HBV) and at the age of nine years, 83% are still free of infection and 94% are not chronic carriers. The children will be followed up for a further 25 years to assess the net effect of vaccination in disease prevention in comparison with other causative factors, e.g., aflatoxin B1 exposure.

13. **Cancer chemoprevention.** Natural products, micronutrients and drugs may prevent the formation of tumours or delay their clinical manifestation. Although observational studies suggest that acetylsalicylic acid (aspirin) reduces the risk of colon cancer in humans, an IARC working group judged the evidence as limited, mainly because of the lack of reliable information on dose and length of treatment, and it recommended conducting controlled or randomized trials. The results concerning acetylsalicylic acid and related nonsteroidal, anti-inflammatory drugs were published as Volume 1 of a new series, *IARC Handbooks of cancer prevention*. A second meeting on chemoprophylaxis using carotenoids was held in December 1997.

14. **Publications.** During 1997, IARC staff authored a total of 279 articles and reports, of which 60% were published in peer-reviewed journals, contributed 40 book chapters and edited 20 books. During the same period, the Agency published three volumes of the IARC *Monographs* on the evaluation of carcinogenic risks to humans, six volumes of the series *IARC Scientific Publications*, and a book on human pathology, *Pathology and genetics of tumours of the nervous system*. The first two volumes in the new series, *IARC CancerBase*, were produced in-house, one on *Cancer in the European Union*, the other as an electronic version of Volume VII of *Cancer incidence in five continents*.

15. **Fellowships and training courses.** The IARC cancer research fellowship programme continued to award approximately 12 postdoctoral fellowships per year for the training of promising young scientists in an outstanding research institution abroad. During the past year, the Agency conducted four training courses, mainly on cancer epidemiology. A new course on cancer genetics in Sestri Levante (Italy) may become a regular annual event, similar to the IARC summer school on cancer registration and epidemiology in Lyons.

16. **WHO programme on cancer control.** The programme is now located in IARC. Its aim is to further develop and promote global strategies to reduce the incidence, morbidity and mortality of cancer. The programme seeks to encourage and advise on the development of national cancer plans. Such strategies will include prevention, early detection, optimal organization of treatment facilities, and palliative care.

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