POLICY AND PRACTICE

# Coordinated Research and the Question of an 'IARC' for the Asian-Pacific?

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## Abstract

**The stated goal of the APOCP/APJCP is to promote an increased awareness in all areas of cancer prevention and stimulate practical intervention approaches. Whether this should be targeted solely through the publication of the APJCP or also through activities in institutions independently capable of research has yet to be decided by the membership. This will in fact be debated at the forthcoming First General Assembly Conference but we have already argued earlier for an APOCP Training Centre/Practical Prevention Program Pilot Centre and indeed made a practical start. Since the International Agency for Research on Cancer (IARC) and the Union International Contra Cancrum (UICC) are already active in the Asian Pacific the question arises as to what relationship the APOCP should aim for with these international bodies. If they had local offices sited conveniently for efforts specific to this region of the world, coordination and the search for financial support would be greatly facilitated. In particular, one could then envisage an expanded Asian country base for the IARC which would allow greatly enhanced promotion of collaborative projects in our region, with a balanced mix of primary and secondary prevention activities appropriate to the prevailing socioeconomic environments. Possibly under the auspices of the Asian Pacific Federation of Organizations for Cancer Control and Research (APFOCC) through the UICC, the APOCP could act as a local partner to an 'IARC' institute for the Asian Pacific. If this idea is ever to be realised we must promote debate and establish concensus so that our voices can be heard. The question we ask now is whether it should indeed be official policy of the APOCP?**

**Key Words:** APOCP - IARC - UICC - international cooperation - research coordination

This article was originally conceived and written as an Editorial with the primary focus on chemoprevention, since four of the articles in the present issue of the APJCP address aspects of this area of cancer research, providing strong evidence of interest in Asia (Ichihara et al., 2002; Jiwajinda et al., 2002; Saha and Das, 2002; Tepsuwan et al., 2002). As eloquently argued by Sporn and Suh in their review (2000), cure rates for major malignancies unfortunately remain very low, despite many advances in chemotherapy, and great expectations from molecular gene therapy may be unduly naive. Thus the obvious conclusion is that primary and secondary preventive efforts continue to be of major importance. However, with an eye on the forthcoming APOCP First General Assembly Conference and the need to stimulate debate on future directions a decision was made to also play a devils advocate role with reference to setting up a coordinating center for research and information dissemination in Asia. For this purpose a critical posture was adopted regarding how the International Agency for Cancer Research (IARC) might take the lead, which elicited pertinent comments from Drs Parkin and Vainio of IARC itself, and Dr Stewart, Head of the South East Health Cancer Control Program in NSW, Australia. Their kind help is gratefully acknowledged with regard to the present amended version. We should stress that the opinions expressed are our own and not necessarily a reflection of the official policy of the APOCP.

To return to chemoprevention for a moment, great care is clearly necessary in selection of which agents should be introduced into clinical trials, given the unfortunate results of beta-carotene application (The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group,1994; Omenn, 1998). The fact that this antioxidant might under certain circumstances act as a pro-oxidant (Truscott, 1996; Paolini et al., 2001), and therefore exert a detrimental effect, might have been predicted if preliminary experiments had been performed in animal

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models. Indeed, beta-carotene has now been shown to promote lung cancer development in mice after carcinogen exposure (Takasuka et al., 2002). While the results of a multitude of epidemiological studies have pointed to general protective effects of a vegetable consumption (as comprehensively reviewed in 'Food, Nutrition and the Prevention of Cancer: a Global Perspective'1997, jointly produced by The World Cancer Research Fund/American Institute for Cancer Research), the obvious inference is that conclusions can not be simply drawn about individual compounds considered as active components. Comprehensive research is required to ensure that all possible precautions are made to avoid any recurrence of such dramatic failure (Vainio, 2000). The range of general issues that need to be taken into account is listed in Table 1.There are in fact a multitude of possible influences of individual compounds and as an example of complexity, in terms of mechanisms that could be operating, only a selection of the published activities of the chemopreventive agent resveratrol are here given in Table 2. It is beyond the ability of a single laboratory to encompass all aspects in a research program, so that coordination of efforts is a high priority for efficient development of chemopreventive agents.

**Table 1. Issues in Chemoprevention Research**

| |
|---|
| Pointers from epidemiological studies |
| Efficacy in experimental animals |
| Mechanisms of action, lack of toxicity |
| Likelihood of efficacy in the human situation |
| Use of surrogate markers to assess efficacy |
| Choice of natural or synthetic |
| Educational concerns |

**Table 2. Activities of the Chemopreventive Agent Resveratrol (after Gusman et al., 2001)**

| |
|---|
| Antibacterial and antifungal actions |
| Antioxidant and free radical scavenging actions |
| Inhibition of lipid peroxidation and inflammation |
| Inhibition of eicosanoid synthesis |
| Vasorelaxing and antiplatelet aggregation potential |
| Oestrogenic/antioestrogenic activity |
| Inhibition of kinase activity |

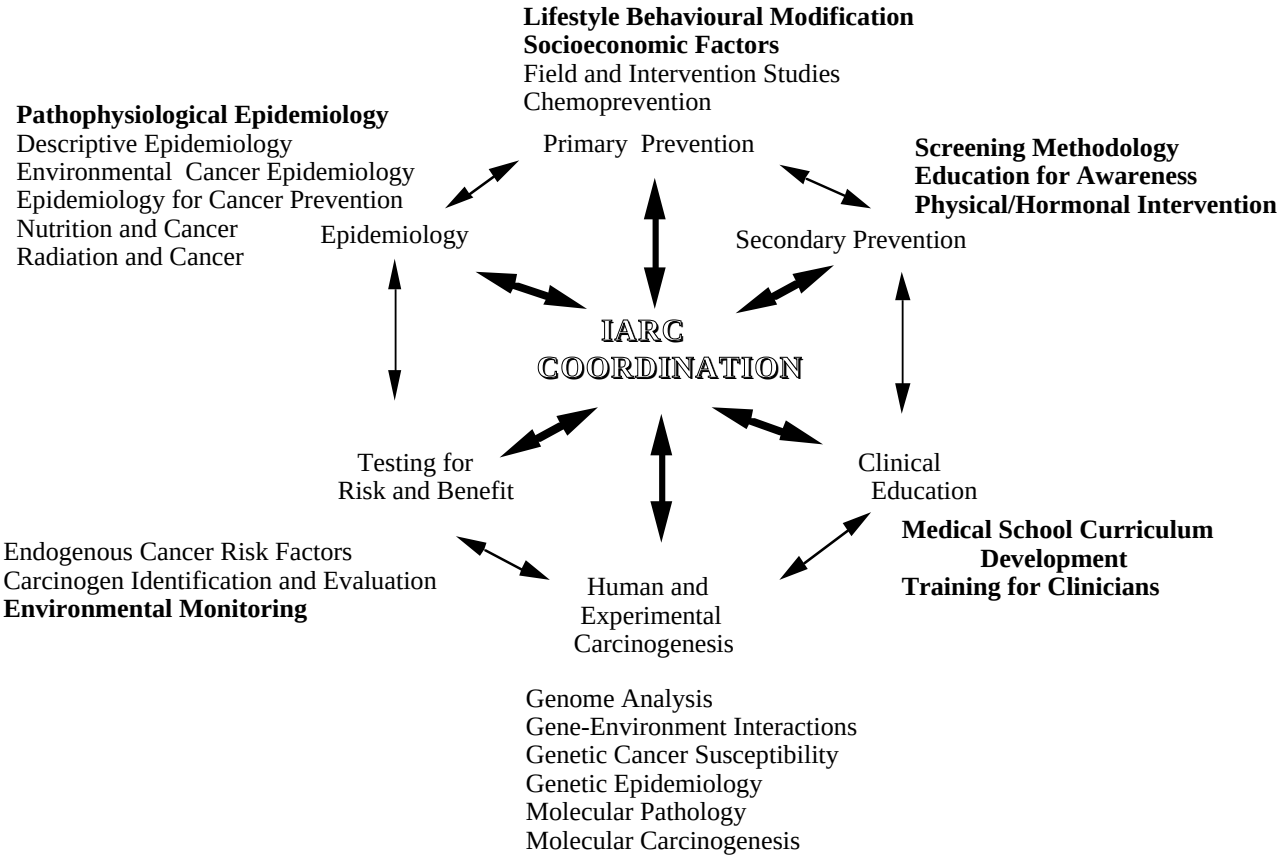
The natural coordinator of chemoprevention research in the various countries of the world is the International Agency for Research on Cancer (IARC). Despite only a very small staff and limited budget for the Unit for Chemoprevention, the Agency has in fact been very active in producing books on general principles and specific agents (for examples see Hakama et al., 1996; Stewart et al., 1996; IARC Working Group on the Evaluation of Cancer Preventive Agents, 1997; 1998a; 1998b; 1999; Miller et al., 2001; Vainio and Bianchini, 2001). Unfortunately, the involvement of Asian scientists in the working groups responsible has been very limited, as can be seen from data for the participation rates for different areas of the world given in Table 3. Only a single voice from the continent with over half of the population in the world, from Japan, was available at individual meetings, and then only at six of the total of eight which were held. It is perhaps not surprising in view of the geographical considerations that there were sixteen times as many participants from European countries, but the same can not explain the twelve times as many scientists invited to attend from North America. While observers were also present at some of the meetings, they were all from European countries.

As researchers active in cancer prevention in Asia, the present authors feel, in line with the aims of the APOCP, that they have an obligation to stress the achievements of this part of the world and contribute to improving its research potential. In an earlier editorial, we pointed out the role that the APJCP is playing as a journal accessible to Asian authors (Tajima et al., 2002).

**Table 3. Participation in IARC Working Groups Relevant to Chemoprevention by Area of the World**

| | Europe | North America | Australasia | Asia |
|---|---|---|---|---|
| Scientific Publications | | | | |
| Chemoprevention in Cancer Control (1996) | 19* | 6 | 2 | 1 |
| Principles of Chemoprevention (1996) | 17 | 10 | 1 | 1 |
| Biomarkers in Cancer Chemoprevention (2001) | 19 | 8 | 0 | 0 |
| Handbooks of Cancer Prevention | | | | |
| 1 NSAID's (1997) | 8 (1**) | 11 | 1 | 1 |
| 2 Carotenoids (1998) | 10 (3) | 8 | 0 | 1 |
| 3 Vitamin A (1998) | 9 (1) | 9 | 1 | 1 |
| 4 Retinoids (1999) | 6 | 15 | 1 | 0 |
| 5 Sunscreens (2001) | 11 (1) | 6 | 5 | 1 |
| Total | 99 (6) | 73 | 11 | 6 |

* No of participants-participations ** Present as observers




**Text Figure. IARC Research Units Aligned with Reference to an Ecological Model for Fields of Major Focus in Cancer Prevention (normal face, presently existing; boldface, newly envisaged).**

The question that we wish to address here is how the only international body set up to promote collaboration cancer research might take the lead in future. This is not in any way to denigrate the massive contribution to efforts in Asia that the IARC has made in the past, especially with regard to setting up of Cancer Registries. The Unit of Descriptive Epidemiology in particular, has been essential to this endeavour and has also been very active in the area of cancer screening, most recently with the assistance of a major grant from the Bill and Belinda Gates Foundation. Since a new Director of the IARC will be recruited next year to take office in 2004, its future research emphasis is now open to a certain extent. It therefore behoves responsible scientists across the Asian Pacific to express opinions about what they would wish for from the Agency, since setting up a separate new institution to perform the roles for which it is admirably suited in our region would only be a very poor alternative to leadership from Lyon.

**Table 4. The Four Main Objectives of the IARC**

| |
|---|
| Monitoring global cancer occurrence |
| Identifying the causes of cancer |
| Elucidation of mechanisms of carcinogenesis |
| Developing scientific strategies for cancer control |

There are a large number of areas, especially regarding development of active strategies for cancer control, which are as important as the genetic and molecular aspects now given most attention and funding at the Agency. It has been argued that an ecological approach to coordination is necessary for prevention of non-infectious chronic disease (Egger and Swinburn, 1997; Moore and Tsuda, 1998b) and to promote discussion, we have made a very subjective attempt to describe the Unit composition of IARC in this context (see the Text Figure). Possible new Units for specific topics well within the original charter to promote international collaboration in cancer research (see Table 4 for objectives stated in the IARC website), have similarly been aligned with the main areas of focus, in our again admittedly very subjective view of what would constitute an even balance. Once more we would like to stress that the APJCP is a forum for debate and that all views are welcome - not only those of the Chief Editors of the journal. We are therefore particularly pleased to welcome an article from Dr Vainio in the present issue, focused on the IARC as a 'Global Science Force' for cancer prevention (Vainio, 2002).

The areas that we personally feel deserve more stress include, for example, the largely unchartered territory of behavioural modification, associated socioeconomic factors, and screening (Tsuda and Moore, 2002), an essential aspect of secondary prevention for which there is at present no responsible unit as such at IARC headquarters in Lyon. Research into means to raise awareness of the efficacy of early detection and treatment might also warrant specialist attention. Given the problems in differential diagnosis of screening-detected lesions most likely to progress to malignancy (Tsuda and Moore, 2002), the field of non-invasive intervention for many of those testing positive also deserves more emphasis. Clearly, the success of many efforts at primary and secondary prevention will depend to a large extent on the cooperation of clinicians. Therefore, research into how they are best to be motivated and trained is warranted. The lack of any standard medical school undergraduate curriculum is the reason for the original production of our Introductory Volume: Cancer Prevention in Tables and Figures (APOCP Core Group, 1999) and research into student knowledge and attitudes very largely remains to be explored (Moore and Tokudome, 2000). The same could be said for motivation and continued training of clinicians (Chamberlain et al., 1995).

Finally, we have a large number of people working in Lyon on essential aspects of epidemiology. However, the pathophysiology underlying tumour development is not receiving major attention to our knowledge (Moore et al., 1998a). Analyses at the molecular or genetic level are clearly of great interest, and in the context of pathophysiology we can cite the work of Tsuchiya's group on p53 mutations pointing to differences in aetiological factors for subtypes of lung adenocarcinomas (Hashimoto et al., 2000). Comparisons of ostensibly identical tumours in different countries, which IARC is uniquely positioned to perform, might allow major advances in this area (Moore et al., 1999a; 1999b). While we are arguing in particular from an Asian viewpoint, the type of research to which we have drawn attention is just as important to European countries, currently shouldering most of the financial burden of the Agency, as emphasized in a recent WHO publication (2002).

The reader should hopefully be asking how increasing the research contribution of IARC by expansion of its activities might be achieved (see also Vainio, 2002). The task of its promotion of world wide efforts is hampered by the facts of geography and financial constraints, both of which might be approached by increments not only to the country membership but also the facilities at which activities could take place. The prevailing economic situation is very unfortunate, but, as the toll from cancer is rapidly rising in Asia and other areas of the world, we hope that, despite the setback suffered with the withdrawal of Argentina and Brazil from the list of member states, efforts to increase the country participation might well meet with success under the right conditions. Additional revenue from new members could then be utilized to expand the role of the Agency in promoting collaborative research into chemoprevention and of course all of the the other areas that we have highlighted. As an incentive, and also for ergonomic efficiency, setting up satellite centers could be envisaged, directed from Lyon, to specifically instigate and coordinate regional research projects. Thus, programs mimicking the massive European

**Table 5. Data for GDP and Population of Selected Countries of the World (after Fishburn, 2001)**

| *Region*/Country | GDP(bn$) | Population (m) |
|---|---|---|
| *Asia Pacific* | | |
| Australia* | 398 | 19.6 |
| Japan* | 4,055 | 127.0 |
| South Korea | 458 | 48.1 |
| China | 1,309 | 1,300.0 |
| India | 520 | 1,000.0 |
| Thailand | 113 | 63.5 |
| Malaysia | 95 | 24.2 |
| Singapore | 88 | 4.2 |
| Indonesia | 189 | 219.5 |
| New Zealand | 54 | 3.9 |
| *Europe/Africa* | | |
| Denmark* | 185 | 5.4 |
| Finland* | 142 | 5.2 |
| France* | 1,472 | 59.9 |
| Germany* | 2,128 | 82.0 |
| Italy* | 1,234 | 58.0 |
| Norway* | 175 | 4.5 |
| Sweden* | 255 | 8.9 |
| Switzerland* | 265 | 7.3 |
| United Kingdom* | 1,525 | 59.8 |
| Spain | 659 | 39.6 |
| Portugal | 123 | 10.1 |
| Austria | 214 | 8.2 |
| Greece | 133 | 10.6 |
| Poland | 202 | 38.7 |
| Hungary | 63 | 10.0 |
| Czech Republic | 67 | 10.2 |
| Russian Federation | 345 | 144.4 |
| Turkey | 146 | 67.2 |
| South Africa | 117 | 45.5 |
| *The Americas* | | |
| Canada* | 778 | 31.2 |
| USA* | 10,708 | 286.9 |
| Mexico | 625 | 102.3 |
| Venezuela | 142 | 25.1 |
| Brazil | 514 | 169.6 |
| Argentina | 286 | 37.9 |

* Presently member countries of IARC

collaboration for nutrition and cancer might become possible, taking advantages of the variation evident across the Asian Pacific, for example. This in fact not a new idea since at the birth of the IARC there were three so-called Regional Centres, in Jamaica, Singapore and Kenya (and subsequently another in Iran). A glance at data for GDP and populations for selected countries of the world provides interesting food for thought in the context of who might be persuaded to join (see Table 5). With participation of only a total of 15 countries at present, the designation of International could be considered a misnomer. After all, only approximately one quarter of the population of the world are currently directly represented.

The Lyon headquarters of IARC is centrally located in Europe, facilitating efforts at coordination in the region with the greatest country membership at present. We are naturally ourselves posing the establishment of a modest institution which would be conveniently placed to promote cooperation within Asia and the Pacific, hopefully with participation by the giants China and India, but also other countries with a developed research capacity and economies of the same size order as many of the present members of IARC. Clearly, other smaller states might also wish to join if the financial costs were not too onerous and the benefits were tangible. A sister satellite institute could also be envisaged for the Americas, to provide equitable balance across the globe and devote attention to the specific problems faced by the Central, South and North America. Geography and history would suggest that Euro-Africa is the third natural entity.

While subjective, the areas of research that we have briefly highlighted are of obvious importance for all our communities, independent of which area of the world, and the strategy of the IARC impacts on all of us working in cancer prevention research. Similarly, the activities of the International Union Against Cancer (UICC), also now rethinking its strategy (Tajima and Moore, 2002), are directly of interest to the APOCP. It must be stressed that the views espoused here are our own and are not presently official policy of the organization. However, we will be discussing their validity at the forthcoming APOCP General Assembly Conference (see the Scientific Meetings section of the present issue). The necessity for collaboration and an appropriate infrastructure is real, but decisions as to the future role of our organization and its relationship to IARC and UICC must be made by all the membership. Like the proposals made regarding APFOCC in an earlier issue of the journal (Moore, 2002), the questions that will be tabled in Nagoya in October concern you. Your attendance if possible and your opinions, especially your critical comments, are therefore requested - in the interest of democratic debate. To this end, we will be conducting a simple questionnaire by email, the results of which will be aired at the meeting. Please take the opportunity to participate, one way or another.

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