

科技资料

Causation and Prevention of Human Cancer

ECP Symposium No. 8

CAUSATION AND PREVENTION OF HUMAN CANCER

**Proceedings of the 8th Annual Symposium of the
European Organization for Cooperation in Cancer
Prevention Studies (ECP),
Heidelberg, Germany, April 2–3, 1990.**

Editors:

Michael J Hill, DSc, FRCPath.

Chairman ECP Scientific Committee, Brussels, Belgium;
PHLS Centre for Applied Microbiology and Research,
Bacterial Metabolism Research Laboratory,
Salisbury, UK

and **Attilio Giacosa**, MD

Scientific Coordinator, ECP, Belgium, Brussels;
National Institute for Cancer Prevention, Genoa, Italy



KLUWER ACADEMIC PUBLISHERS
DORDRECHT / BOSTON / LONDON

Distributors

for the United States and Canada: Kluwer Academic Publishers, PO Box 358, Accord Station, Hingham, MA 02018-0358, USA

for all other countries: Kluwer Academic Publishers Group, Distribution Center, PO Box 322, 3300 AH Dordrecht, The Netherlands

British Library Cataloguing in Publication Data

European Organization for Cooperation in Cancer Prevention Studies *Symposium (8th: 1990: Heidelberg, Germany)*

Causation and prevention of human cancer.

1. Man. Cancer

I. Title II. Hill, M.J. (Michael James) 1939 – III. Giacosa, A.

616.994

ISBN 0-7923-1084-5

Copyright

© 1991 by Kluwer Academic Publishers

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior permission from the publishers, Kluwer Academic Publishers BV, PO Box 17, 3300 AA Dordrecht, The Netherlands.

Published in the United Kingdom by Kluwer Academic Publishers, PO Box 55, Lancaster, UK.

Kluwer Academic Publishers BV incorporates the publishing programmes of D. Reidel, Martinus Nijhoff, Dr W. Junk and MTP Press.

Printed in Great Britain by Butler and Tanner Ltd., Frome and London.

CAUSATION AND PREVENTION OF HUMAN CANCER

DEVELOPMENTS IN ONCOLOGY

Recent volumes

46. F.M. Muggia and M. Rozenzweig (eds.): *Clinical Evaluation of Antitumor Therapy*. 1987 ISBN 0-89838-803-1
47. F.A. Valeriote and L. Baker (eds.): *Biochemical Modulation of Anticancer Agents*. Experimental and Clinical Approaches. 1986 ISBN 0-89838-827-9
48. B.A. Stoll (ed.): *Pointers to Cancer Prognosis*. 1987 ISBN 0-89838-841-4; Pb. 0-89838-8767
49. K.H. Hollmann and J.M. Verley (eds.): *New Frontiers in Mammary Pathology*. 1986 ISBN 0-89838-852-X
50. D.J. Ruiter, G.J. Fleuren and S.O. Warnaar (eds.): *Application of Monoclonal Antibodies in Tumor Pathology*. 1987 ISBN 0-89838-853-8
51. A.H.G. Paterson and A.W. Lees (eds.): *Fundamental Problems in Breast Cancer*. 1987 ISBN 0-89838-863-5
52. M. Chatel, F. Darcel and J. Pecker (eds.): *Brain Oncology*. 1987 ISBN 0-89838-954-2
53. M.P. Hacker, Y.S. Lazo and T.R. Tritton (eds.): *Organ Directed Toxicities of Anticancer Drugs*. 1988 ISBN 0-89838-356-0
54. M. Nicolini, (ed.): *Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy*. 1988 ISBN 0-89838-358-7
55. J.R. Ryan and L.O. Baker (eds.): *Recent Concepts in Sarcoma Treatment*. 1988 ISBN 0-89838-376-5
56. M.A. Rich, J.C. Hager and D.M. Lopez (eds.): *Breast Cancer: Scientific and Clinical Aspects*. 1988 ISBN 0-89838-387-0
57. B.A. Stoll (ed.): *Women at High Risk to Breast Cancer*. 1989 ISBN 0-89838-416-8
58. M.A. Rich, J.C. Hager and I. Keydar (eds.): *Breast Cancer: Progress in Biology, Clinical Management and Prevention*. 1989 ISBN 0-7923-0507-8
59. P.I. Reed, M. Carboni, B.J. Johnston and S. Guadagni (eds.): *New Trends in Gastric Cancer*. Background and Videosurgery. 1990 ISBN 0-7923-8917-4
60. H.K. Awwad: *Radiation Oncology: Radiobiological and Physiological Perspectives*. The Boundary-Zone between Clinical Radiotherapy and Fundamental Radiobiology and Physiology. 1990 ISBN 0-7923-0783-6
61. J.L. Evelhoch, W. Negendank, F.A. Valeriote and L.H. Baker (eds.): *Magnetic Resonance in Experimental and Clinical Oncology*. 1990 ISBN 0-7923-0935-9
62. B.A. Stoll (ed.): *Approaches to Breast Cancer Prevention*. (forthcoming) ISBN 0-7923-0995-2
63. M.J. Hill and A. Giacosa (eds.): *Causation and Prevention of Human Cancer*. 1990 ISBN 0-7923-1084-5
64. J.R.W. Masters (ed.): *Human Cancer in Primary Culture*. A Handbook. (forthcoming) ISBN 0-7923-1088-8

FOREWORD

The European Organization for Cooperation in Cancer Prevention Studies (ECP) was established in 1981 to promote collaboration between scientists working in the various European countries on cancer causation and prevention.

In order to achieve this aim, various working groups - to deal with specific cancers or aspects of cancer aetiology, and to explore the opportunities for advances on a cooperative European basis - were established. It was also decided to hold annual symposia to draw general attention to fields in which there seemed to be many opportunities for progress in matters of prevention.

These symposia have been devoted to themes of high priority to cancer prevention: "Tobacco and Cancer" (1983), "Hormones and Sexual Factors in Human Cancer Aetiology" (1984), "Diet and Human Carcinogenesis" (1985), "Concepts and Theories in Carcinogenesis" (1986), "Preventive Strategies for Cancer related to Immune Deficiencies" (1987), "Gastric Carcinogenesis" (1988), and "Breast, Ovarian and Endometrial Cancer: Aetiological and Epidemiological Relationships" (1989).

This volume contains the proceedings of the 1990 ECP symposium held in Heidelberg, FRG, at the Deutsches Krebsforschungszentrum (DKFZ), on April 2-3 on "Causation and Prevention of Human Cancer".

We are indebted to the speakers for their contribution during the symposium and for their prompt submission of manuscripts. We are grateful to the sponsors, SmithKline Diagnostics and Röhm Pharma.

Our special thanks go to Dr M.C. Stanei-Gueur for preparing and typing the camera forms of all manuscripts.

Michael J. HILL

CONTENTS

	Foreword	vii
1.	Introduction and overview of ECP M J Hill	1
2.	Non-invasive markers of carcinogen exposure in humans D E G Shuker	9
3.	Mediterranean diet and cancer A Trichopoulou, E Mossialos, J Skalkides	17
4.	Europe against cancer: 1987-1989 results and 1990-1994 perspectives A Vanvossel	27
5.	Precancerous lesions of the colorectum. Descriptive epidemiology and diet-related aetiological factors J Faivre, M C Boutron	33
6.	Diet and precancerous lesions of the stomach P I Reed	49
7.	Reproductive factors, oral contraceptives and breast cancer: the importance of unifying hypotheses C La Vecchia	69
8.	Female hormones: for which cancers do they matter? S Franceschi	89
9.	Tobacco-specific nitrosamines : underestimated carcinogens in tobacco and tobacco smoke S Fischer, B Spiegelhalder, R Preussman	107
10.	Malignant melanoma: an epidemiological phenomenon F Lejeune, D Lienard, J André, M Joarlette, R Sacre, M Dramaix, D Roseeuw, A Verhest, G Achten	125

11.	Healthy eating and public education J V Wheelock	139
12.	Cancer primary prevention : a gap between knowledge and intervention A Giacosa	157
	Index of Authors	159
	Subject Index	161

1

INTRODUCTION AND OVERVIEW OF ECP

Michael J Hill

ECP Headquarters, 5 av. R. Vandendriessche, 1150 Brussels, Belgium

WHAT IS ECP ?

ECP is the European organisation for cooperation in Cancer Prevention studies and was set up to achieve in the field of cancer prevention what EORTC attempts to do in the field of cancer treatment.

WHY SET UP ECP ?

Within the European Community cancer causes more than 700000 deaths per annum, and a good proportion of these must be preventable. The first step in cancer prevention must be the determination of cancer causation and, although in the case of lung cancer this has been known for many years, the causes of the other major cancers in western populations have still to be determined. Thus there is a need for large scale epidemiological studies. Within Europe there is a wide range in the incidence of most human cancers (Table 1). This range is far wider than that to be seen within any single European country; it is also very much wider than that seen within the United States. Thus, for the planning of multi-centre cooperative studies of cancer causation Europe should provide an almost perfect location.

It has been estimated that 30-40% of human cancers are caused by dietary factors, principally cancers of the digestive tract and the hormone-dependent cancers. This number should be reduced by appropriate changes in the diet but the optimum diet for prevention of these cancers has still to be identified. There is a need, therefore, for large scale multi-centre studies of the relation between diet and the risk of cancer at the various sites, and to determine the nature of the mechanisms of dietary carcinogenesis that need to be countered.

TABLE 1: Range in mortality within the European Community from cancer at various sites (data from Levi et al. 1989)

	Males		Females			
	Max	Min	Max	Min		
Mouth/pharynx	France	15.6 Greece	1.7	Scotland 1.5 Greece	0.6	
Oesophagus	France	13.3 Greece	1.9	Scotland	4.0 Greece	0.6
Stomach	Portugal	29.7 Denmark	12.2	Portugal	14.5 France	5.4
Colon/rectum	Denmark	24.3 Greece	7.7	Ireland	18.7 Greece	6.9
Liver	Spain	9.1 Ireland	0.9	Spain	6.3 Portugal	0.4
Pancreas	Netherlands	9.3 Spain	4.3	Denmark	7.1 Spain	2.4
Lung	Scotland	83.5 Portugal	20.1	Scotland	23.2 Portugal	3.6
Ovary				Denmark	10.8 Spain	2.3
Breast				England	28.2 Spain	13.5
Prostate	Belgium	17.5 Greece	7.3			

There is concern about the possible risk of cancer associated with use of the contraceptive pill or of hormone-replacement therapy. Both of these treatments have been in common usage for less than 20 years and so it is too soon to be able to estimate the magnitude of the risk of those cancers diagnosed late in life. Premenopausal cancers are relatively uncommon and so there is need for large scale epidemiological studies to obtain sufficient numbers of cases to give clues to the magnitude of the cancer risk (if any) as soon as possible.

The risks from tobacco usage, other than those directly associated with the smoking of cigarettes, have received relatively little attention. This is understandable but there is now a perceived risk of lung cancer associated with "passive smoking" and a suspected risk associated with tobacco chewing. This latter is now becoming a source of great concern because of the growing popularity of chewing tobacco amongst children in some European countries. Again, it will be necessary to organise studies of large cohorts of, for example, tobacco-chewing children, in order to obtain clear evidence in the minimum time.

Not only does Europe offer a wide range in incidence of all of the most common cancers, it also has a similarly wide range in dietary patterns, environmental exposures (such as, for example, UV light exposure in the UK or Denmark in comparison with Italy or Spain), and of social attitudes to, for example, contraception or sexual freedom. Europe offers an ideal "laboratory" within which to test or to formulate hypotheses on the causation of human cancers, and it would be more sensible to conduct studies of, for example, the role of diet in human cancer within the European context rather than, as at present, within national borders.

A number of cancers are of importance not because they necessarily have a high prevalence but because of the impact of each individual case. One example is cancer of the ovary in young women. Although the actual number of such cases in any individual country each year is small this is the second commonest site of cancer in premenopausal women. Each case usually results in the death of a young mother and the consequence effect on the rest of family, particularly the young children, left behind can be devastating. Since these cancers are not common studies carried out within national boundaries tend to be small and to give statistically insignificant results. It would clearly be better to carry out studies of such cancers at the European, continent-wide, level rather than within national boundaries.

Intervention anywhere in Europe to prevent, or to reduce the incidence of, cancer at the major sites needs to take account of the realities of the Common Agricultural Policy. For example we need to recognize that the amount of money spent on the whole Europe Against Cancer programme is

less than 1% of the subsidy given by the CAP to, farmers to Produce tobacco ! For political reasons the CAP also goes against the advice of most health experts in Europe in promoting butter at the expense of margarine and in generally promoting the consumption of meat and dairy products. This very real conflict between the health lobby and the CAP can only be fought at the European level; national campaigns are likely to have much less impact than they warrant.

For all these reasons a group of European scientists and clinicians decided to set up ECP, to try to take advantage of the unique advantages offered by the European "laboratory" to study the causation and then the prevention of the cancers of importance in Europe and to try to operate in parallel with the work of EORTC in the field of cancer treatment.

ORGANISATION OF ECP

The scientific work is divided into 7 broad areas covered by the Working Groups; three of these are site-specific, namely the colon, the stomach and the breast. Three are directed to causes, namely tobacco, virus and AIDS, and hormones and sexual factors. The final one is devoted to public education, since experience with smoking and lung cancer suggests that finding the cause of a cancer may be much simpler than persuading the general public to take the steps necessary to avoid that cause. Each of the working groups has major research projects and also organises the annual symposia and workshops. The Groups and Group Heads are listed in Table 2. Some of the major projects being carried out by the Groups are discussed in detail elsewhere in this symposium in the presentations by the Heads of Groups and so will not be discussed here.

The overall scientific programme of ECP is monitored by the Scientific Committee. This body includes all of the Heads of Working Groups and a number of distinguished

scientists chosen for their expertise in the various aspects of cancer prevention and to include representatives of all countries of the European Community. The current members are listed in Table 3. The Scientific Committee has a Chairman (me) and also has a Scientific coordinator (Dr A. Giacosa) who coordinates and ensures the smooth running of the work of the groups.

The administrative work of ECP is carried out by the Secretariat, based in Brussels. The whole organisation is ultimately controlled by the ECP Administrative Council, which has six members including the Chairman and the Scientific Coordinator. The overall structure of ECP is illustrated in Table 4.

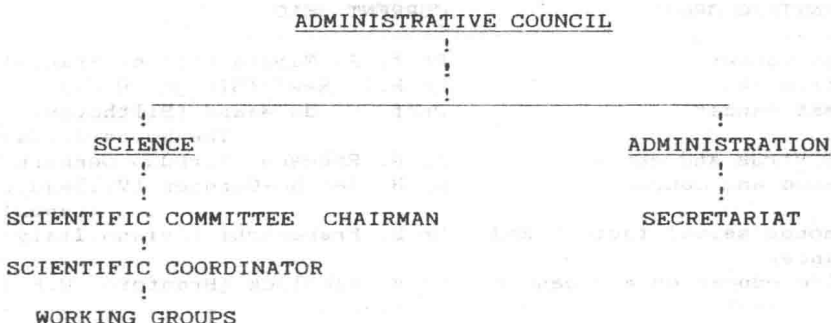
TABLE 2: The scientific groups in ECP and their current heads.

SCIENTIFIC GROUP	CURRENT HEAD
Colon cancer	Prof. J. Faivre (Dijon, France)
Gastric cancer	Dr P.I. Reed (Slough, U.K.)
Breast cancer	Prof. F. de Waard (Bilthoven, The Netherlands)
AIDS/Virus and cancer	Dr P. Ebbesen (Aarhus, Denmark)
Tobacco and cancer	Dr H. Sancho-Garnier (Villejuif, France)
Hormones/sexual factors and cancer	Dr S. Franceschi (Aviano, Italy)
Public education and cancer	Dr V. Wheelock (Bradford, U.K.)

TABLE 3: The ECP Scientific Committee (as at April, 1990)

Name	Country	Main area of expertise
F de Waard	The Netherlands	Head of breast cancer group
J Faivre	France	Head of colon cancer group
P I Reed	U.K.	Head of gastric cancer group
P Ebbesen	Denmark	Head of AIDS/virus group
S Franceschi	Italy	Head of Hormones/sexual factors group
H Sancho-Garnier	France	Head of tobacco group
V Wheelock	U.K.	Head of public education group
R Preussmann	F.R.G.	Chemical carcinogenesis
J Wahrendorf	F.R.G.	Cancer epidemiology
E Benito	Spain	Colorectal cancer
T Salvador-Llivina	Spain	Public education and cancer
A Trichopoulou	Greece	Nutrition and cancer
L Santi	Italy	All aspects of cancer research
C O'Morain	Ireland	Colorectal cancer
C L West	The Netherlands	Nutrition and cancer
L Cayolla da Motta	Portugal	All aspects
A Burny	Belgium	Viruses and cancer
A Maskens	Belgium	Tobacco/Public education
L Dobrossy	W.H.O.	All aspects
J Esteve	I.A.R.C.	Cancer epidemiology/ statistics
A Giacosa	Italy	Scientific coordinator
M Hill	U.K.	Chairman

TABLE 4: The administrative structure of ECP



ACTIVITIES OF ECP

In addition to the concerted action research projects carried out by the ECP Working Groups, ECP also organises an annual symposium series and workshops.

TABLE 5: The annual symposia organised by ECP.

YEAR	SUBJECT	LOCATION
1983	Tobacco and human cancer	Brussels
1984*	Hormones and sexual factors in human cancer eatiology	Bruges
1985*	Diet and human cancer	Aarhus
1986*	Concepts and theories in carcinogenesis	Bruges
1987	Preventive strategies for cancers related to immune deficiencies	Brussels
1988*	Gastric carcinogenesis	London
1989	Breast, ovarian and endometrial cancer: epidemiological and aetiological relationships	Bilthoven
1990*	Causation and prevention of human cancer	Heidelberg

* symposium published in the ECP Symposium series.

In the Annual Symposium series the Working Group take turns to choose the topic and to organize the meeting. The symposia are listed in Table 5; the main aim of these symposia has been to present the state-of-the-art in the knowledge of cancer causation and hence prevention of cancer in the field under discussion. One of the annual symposia is going to be organized by the colon group in the near future; this is one of the most active groups in ECP but is

the only group that has not yet had one of the symposia.

Each of the working groups has at least one major project in progress, and these go through an evolutionary process outlined in Table 6. All of the projects are reviewed by the Scientific Committee at an early stage and must be approved by that body. Since the Scientific Coordinator is responsible for the coordination of the scientific work of all of the groups, that person is involved in the genesis and development of the projects. The formulation of a project can be simplified by the early organisation of a workshop. This can be used to examine closely a well-defined area of potential research and to prepare for the start of a new project.

TABLE 6: Steps taken in the formulation of an ECP project.

-
1. FORMULATION OF PROJECT <---> SCIENTIFIC COMMITTEE
 2. ASSEMBLY OF POTENTIAL COLLABORATORS
 3. WORKING PARTY FORMULATES PROTOCOL
 4. COLLABORATORS SEEK LOCAL FUNDING
 5. ECP SEEKS CENTRAL FUNDING FROM EC
-

Table 7 lists a number of examples of such workshops organised by the ECP Working Groups. For example, the workshop on "Tobacco and Cancer" in Brussels in 1989 led directly to the formulation of at least three good projects for that Working Group.

One of the major problems with organising multinational concerted-action studies within Europe has been to find funding for the central analyses and coordination of the work. National funding bodies are only willing to fund the analyses of samples from their own country within their own country and have been unwilling to fund analyses from other countries. This, of course, makes nonsense of the concept of multinational collaboration and prevents the clear advantages of central analysis from being realized.

Fortunately, the EC "Europe Against Cancer" programme has been able to fill this gap and to fund the central analyses in a number of ECP projects. The second major problem has been to fund the work in the countries with a low incidence of the cancer of interest, or in those countries where cancer research takes a low priority in comparison with other diseases that are more widespread or more acute. This problem has still to be resolved.

TABLE 7: Some of the workshops organised by ECP (other than "progress" workshops)

GROUP	SUBJECT	PLACE	YEAR
Diet	Advice on a healthy diet (with IUNS)	Aarhus	1985
Hormones	Optimisation of influence of ovarian steroid consumption on cancer risk	Munich	1986
Colon	Causation and prevention of colon cancer	Dijon	1987
Tobacco	Tobacco and cancer	Brussels	1988
Public Education	Update or recommendations for healthy eating in relation to cancer	Genova	1990

CONCLUSIONS

ECP has been formed for less than 10 years but has already made a great impression on the cancer research scene, mainly because the need for such a body is so self-evident. In the near future ECP will be ready to publish the results of its first major projects, and will also begin to publish its own journal, the European Journal of Cancer Prevention, in collaboration with Churchill-Livingstone.

2

NON-INVASIVE MARKERS OF CARCINOGEN EXPOSURE IN HUMANS

David E G Shuker

International Agency for Research on Cancer, 150 Cours Albert Thomas,
69372 Lyon Cedex 08, France

INTRODUCTION

Human exposure to chemical carcinogens will almost always result in the formation of characteristic adducts with proteins and nucleic acids. This is a consequence of the electrophilic nature of the active metabolites of most carcinogens and the nucleophilic properties of nitrogen atoms present in nucleic acids and sulphur, nitrogen and oxygen atoms in amino acid residues (1,2). Studies in experimental animals have demonstrated that DNA in target tissue(s) is modified following treatment with many different chemical carcinogens (3). In consequence, there has been much interest in recent years in developing methods to determine the levels of DNA adducts and related damage as an alternative and more relevant measure of human exposure to carcinogens (4). However, in contrast to the situation in experimental animals, only in relatively exceptional cases can DNA from target tissues be obtained from humans and there is, therefore, a need for less invasive methodology which allows access to the same information.

Protein adducts have been investigated as surrogate markers of DNA alkylation. In the case of ethylene oxide, studies have shown that a definite relationship exists between haemoglobin adducts such as N-2-hydroxyethyl-histidine and S-2-hydroxyethylcysteine and DNA adducts such as N-7-(2-hydroxyethyl)guanine (5). 4-Aminobiphenyl, a potent human bladder carcinogen, is present in tobacco smoke and forms an adduct with haemoglobin (6). Aflatoxin B₁ forms adducts with albumin, as well as with liver DNA, and the protein adduct has been used for human biomonitoring (7). From a methodological point of view, the analysis of protein adducts requires only a small sample of blood and quantitation is carried out immunochemically or by gas chromatography-mass spectrometry (GC-MS). It would appear to be the case that the relationship between DNA and protein