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Gian Luigi Russo · Alfredo Budillon
Fulvio Della Ragione *Editors*

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Advances in Nutrition and Cancer

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Preface

This volume includes 26 contributions presented at the Third International Conference on *Advances in Nutrition and Cancer* held in Naples, Italy, in May 2012 at the National Institute for Cancer Research.

The major aim of the meeting was to illustrate the most recent and innovative projects in this area and to propose novel strategies for chemoprevention as well as molecular epidemiology and dietary intervention programs. During the conference a group of experts from different areas discussed pivotal and current topics on the key issues related to the interactions between human nutrition and malignancies.

Comparing the themes reported here with those discussed in the two previous meetings (1992, 1998), the major scientific advancements certainly derive from the extensive use of molecular biology, molecular epidemiology, and a variety of epigenetic approaches in nutrition research.

Today, cancer affects about 24 million people worldwide and is responsible for over six million deaths each year. Although early diagnosis has made some progress, in most cases tumors are still treated at advanced stages, with limited therapeutic success. Prevention is therefore a fundamental approach for fighting this severe pandemic. In this context the fundamental conclusion of Doll and Peto (1981), suggesting that at least 30 % of all cancers might be prevented by dietary regimens, is still relevant and has been confirmed by a large variety of results: the association among diet, nutrition, and cancer risk is not in question.

The first part of the volume focuses on general aspects relating life style, diet, and cancer. The molecular mechanisms underlying the connections among obesity, energy balance, physical activity, and cancer risk/progression are extensively covered as well as the presumptive association of salt intake and alcoholic and carbonated soft drinks with digestive tract cancers.

A large variety of phytochemicals and natural antioxidants have been characterized and proposed as potential chemopreventive/chemotherapeutic agents. The effects and mechanisms of the action of resveratrol, quercetin, and sulforaphane, as well as the conflicting results on selenium and selenoproteins, are reported in the second part.

It is well known that, in several tissues, diet can modulate the methylation status of the cells and epigenetic factors influenced by diet are receiving major attention in cancer prevention and as therapeutic targets. The third part is devoted to these

fundamental and most promising issues. An interesting new area deals with the adverse intrauterine environments induced by maternal diet, which influence DNA methylation and predispose to diseases in adulthood.

The fourth part deals with the beneficial effects of a functional food, olive oil, in cancer prevention. The evidence of the chemopreventive effects of extra-virgin olive oil, the major source of fat in the Mediterranean diet, associated with low incidence of cardiovascular diseases and of several tumors, such as breast cancer, is analyzed. Special emphasis has been placed on the effects of antioxidants on human hepatoma cells and on their chemical interactions with other food ingredients affecting nutritional and sensory quality.

The last two parts deal with fundamental results such as the epidemiologic evidence that lifestyle (including diet regimen) effectively prevents cancer recurrence.

Space has also been given to anti-angiogenesis: numerous preclinical, chemical, and epidemiological data have demonstrated that angiogenesis inhibition can be applied in cancer prevention and that several diet-derived chemopreventive components have angiogenesis as a common target. The relationship of the human gut microbiome with gastrointestinal malignancies has also been discussed; the understanding of the dynamic interplay between the gut microbiome, the immune system, and dietary exposure may contribute to future cancer prevention strategies.

As demonstrated in this volume, the inter-disciplinary approach has already yielded a rich harvest of basic knowledge concerning cancer development and will provide the seeds for future breakthroughs in clinical progress. The text is intended to furnish the reader with a general view of the state of the art in this very central and solid area of research. We will be satisfied if the multidisciplinary nature of these proceedings informs and stimulates the readers as much as it did the participants in the conference. It is our hope that the volume will encourage further research and understanding of all aspects of this intriguing and complex field.

Vincenzo Zappia

Acknowledgments

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The meeting received the authoritative patronage of the Accademia Nazionale dei Lincei, Consiglio Nazionale delle Ricerche, Regione Campania, Comune di Napoli, Provincia di Napoli, Seconda Università degli Studi di Napoli, Università degli Studi di Napoli "Federico II," Lega Italiana per la Lotta contro i Tumori—Sezione di Napoli, Associazione Italiana di Oncologia Medica, Società Italiana di Biochimica, Società Italiana di Cancerologia, and the Ordine dei Medici di Napoli.

Contributors to the conference included: Banca di Credito Popolare, Roche, Acen, Biorad, DBA Italia, Delchimica, Diasorin, Euroclone, Farmacia Morrica, Istituto Varelli, Life Technologies, Microtech, Strategies Consulting, Vinci Biochem, and Carl Zeiss.

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Part I
Life Style, Diet and Cancer

The Role of Metabolic Carcinogenesis in Cancer Causation and Prevention: Evidence from the European Prospective Investigation into Cancer and Nutrition

Elio Riboli

Abstract

The theory that nutrition might be involved in the causation and prevention of cancer arose over 100 years ago from laboratory studies of the effect of diet on tumour growth. During the mid-20th century, the major focus of cancer epidemiology was on the role of tobacco and alcohol. It was not until the early 1980s, following a seminal report from Doll and Peto on cancer causes, that major research programmes on nutrition and cancer were instigated. The European Prospective Investigation into Cancer and Nutrition (EPIC) was established at IARC-WHO as a large prospective cohort study designed specifically to investigate the relationship of diet, nutritional factors, anthropometry and physical activity with cancer risk. Since the early 1990s, EPIC has made a major contribution to understanding the effect of these factors on population risk of cancer. This chapter summarises the development of the field of nutritional cancer epidemiology, and describes how the EPIC study was designed to investigate cancer and nutrition. Key findings from EPIC in the role of nutrition and metabolic factors and cancer are highlighted.

Keywords

Nutrition · Diet · Metabolic factors · Anthropometry · Steroid hormones · Cancer · Epidemiology · Large prospective cohort studies · European Prospective Investigation into Cancer and Nutrition

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1 Historical Background

The theory that nutrition might be involved in the causation or prevention of cancer developed at the beginning of the 1900s with the first laboratory studies on the effect of different diets on the development and growth of tumours. This early research found that tumours, either spontaneous or transplanted, would grow in well-nourished rodents while calorie-restricted diets inhibited tumour growth. The calorie restriction required to inhibit tumour growth was substantial compared to ad libitum. Further studies showed that calorie restriction also prevented recurrence of spontaneous tumours transplanted after excision [30, 36, 42].

In the 1930s, Albert Tannenbaum and his collaborators, [44, 46, 47] commenced three decades of laboratory research on the effect of hypercaloric, hyperlipidic or hyperproteic diets on cancer causation using rodent models. They found that some tumours were particularly influenced by either a hypercaloric or hyperlipidic diet, or both, particularly tumours of the mammary gland, liver and lung. This was complemented by the work of Baumann who demonstrated that at least part of the tumour-promoting effect of increased dietary fat was due to corresponding increased caloric intake [29].

The first known epidemiological study on diet and cancer in humans was published in 1933. This study of 462 cancer patients and 435 controls found that people who consumed more vegetables had a reduced risk of cancer, and those who drank more beer had a higher risk of developing cancers of the upper digestive tract [41].

Tannenbaum led what was probably the first retrospective cohort study to investigate the effect of obesity on mortality from cancer and other diseases. The study used data from North American life insurance companies and found that there was a 30–50 % increase in mortality from cancer among people who were obese at the time they had first subscribed to the health insurance policy [45].

These results did not substantially modify mainstream approaches to cancer research; the prevailing hypothesis at the time was that cancer was caused by chemical or physical compounds that could be found in the living environment

including the air, drinking water, food (as contaminants or chemical additives) or in occupational settings. Therefore, the majority of studies on cancer were essentially designed to identify new carcinogens and understand the mechanism of chemical and physical carcinogenesis.

The two major factors being investigated as potential lifestyle-related carcinogens at the time were tobacco and alcohol. The role of tobacco was clearly identified in the 1950s by the studies led in England by Richard Doll and Bradford Hill [5–8], and in the US by Ernst Wynder [51]. These studies demonstrated that the carcinogenic effect of being a lifelong smoker was exceptionally strong. For example, starting smoking at around age 18–20 and smoking 20–30 cigarettes per day multiplied the risk of developing lung cancer by 30- to 40-fold. The identification of a number of chemical compounds present in cigarette smoke and their testing in laboratory carcinogenesis models rapidly provided strong mechanistic support to the epidemiological studies.

The paradigm for the accrual of scientific evidence linking alcohol to cancer was much less straightforward for a number of reasons, one being the strength of the association between alcohol consumption and cancer risk. In fact, the relative increase in cancer risk due to alcohol consumption is substantial but not as strong as with cigarettes and lung cancer. Typically, elevated alcohol consumption—for example in the order of 70–80 g of alcohol per day (equivalent to one bottle of wine or four pints of beer)—is associated with up to 5- or 6-fold increase in risk of developing cancers of the upper aerodigestive tract (mouth, pharynx, larynx and oesophagus) with a multiplicative effect for drinkers who also smoke. However, the relative risk increase for most other cancers (e.g. cancer of the colorectum, liver and breast) is much more modest, in the order of 1.5-fold.

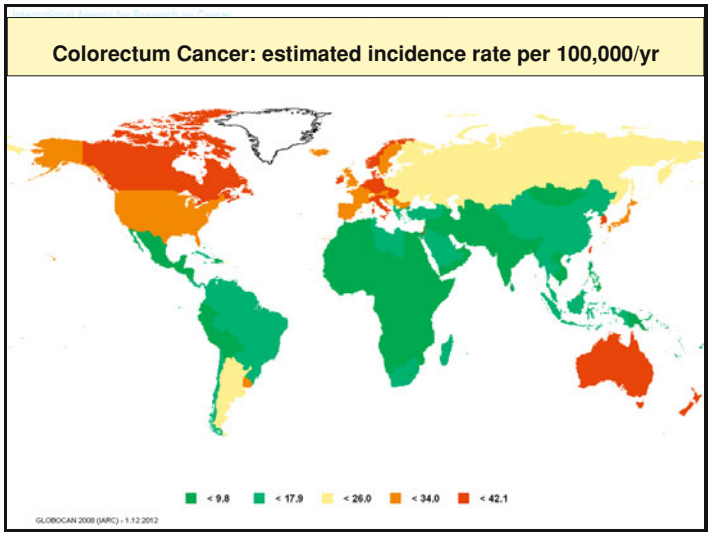
Evidence from experimental animal models to demonstrate that alcohol can cause cancer also took much longer to accrue than for chemicals in cigarette smoke. The main mechanisms that have been identified to date for the influence of alcohol on cancer risk [19] include DNA damage by acetaldehyde that may be particularly relevant for upper GI tract, liver; increased secretion and bioavailability of oestrogens, in relation to mammary tumours; production of reactive oxygen and nitrogen species and changes in folate metabolism.

As for diet, it was not until the 1960s and 1970s that the first case–control studies emerged that were designed with modern epidemiological methods to investigate the possible role of diet in the risk of developing cancer. The first studies investigated mainly cancers of the digestive tract (oesophagus, stomach, colon, rectum), respiratory tract (larynx, lung) and breast [31]. This renewed interest in nutrition was stimulated by the publication of data on cancer incidence in different global populations [9, 10].

Population-based cancer registry data indicated that the global incidence of many cancers varied enormously, with up to 15–20-fold differences in the incidence of some cancers between different populations around the world (Fig. 1).

For some cancers, such as lung or liver, the most likely explanation for these variations was found in the different history and prevalence of tobacco smoking or, as lately demonstrated, the incidence and prevalence of hepatitis B and C, exposure

(a)



(b)

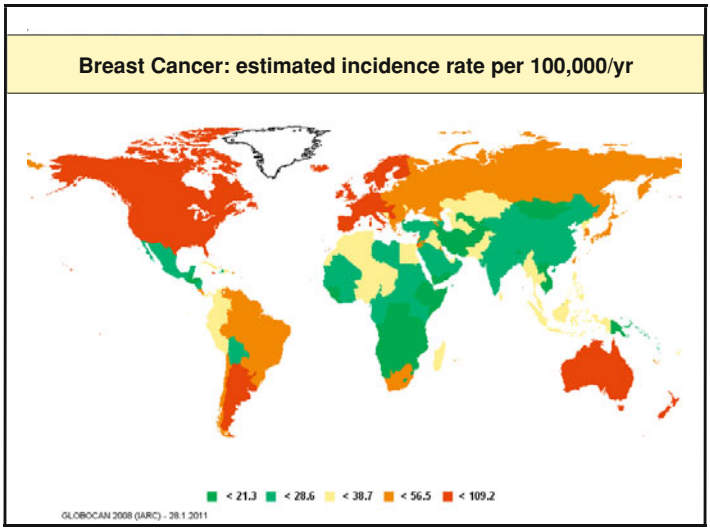


Fig. 1 GLOBOCAN 2008 estimated cancer incidence rate worldwide per 100,000/yr for (**a**) colorectum and (**b**) breast cancer. Reproduced from [14]

to aflatoxins from mould-contaminated food and alcoholic beverage consumption. For many other cancers, such as breast, colon and rectum, prostate and stomach, the explanations of the causes underlying these huge variations were unknown, but stimulated the hypothesis that diet could have a role in their aetiology.

Early dietary epidemiological studies investigated the association between cancer risk and particular foods. Gradually, some evidence emerged that consumption of certain foods might be associated with reduced cancer risk, particularly fruits, vegetables and fibre-rich cereals. Conversely, it was found that consumption of salt-preserved food (including pickled vegetables and salt-preserved meat), red meat and animal fat (as opposed to vegetable fat) could increase cancer risk.

Although this work enhanced the concept of a link between diet and cancer risk, the research focussed on the type of food, not on precise measurement of the total amount of food consumed, the corresponding nutrient intake or the total energy from food. There was also no notion of the potential importance of investigating the effects of weight and physical activity on cancer risk. At the time, it was considered that fat intake was most likely to increase cancer risk only via its chemical and nutritional characteristics, rather than by contributing to excessive total energy intake; obesity was not then considered a major risk factor and none of the studies had clearly separated the effect of caloric intake from the effects of fat intake.

In 1981, Richard Doll and Richard Peto published a milestone report on cancer causes in the US in which they estimated that 35 % of cancer could be due to nutrition, but with a very wide confidence interval of 10 or 70 % [11]. The publication of this report in combination with a report on Diet and Cancer from the US National Academy of Science (National Academy of Science 1982) provided significant impetus for IARC-WHO to initiate a new research programme on nutrition and cancer within the Unit of Analytical Epidemiology directed by Dr Rodolfo Saracci.

The establishment of large-scale prospective cohort studies specifically designed to investigate the relationship of diet, nutritional factors, anthropometry and physical activity to cancer risk contributed to a new era in cancer epidemiology. The first such studies were started in North America. Particularly, Walter Willett at Harvard University did seminal work in developing new diet questionnaires specifically tailored for use in very large cohort studies and in formalising the importance and the methods to account and adjust for the intake of macronutrients and the energy they provide.

On the European side, at IARC collaboration with the University of Lund, Sweden, commenced to design a prospective cohort study in Malmö, while in parallel the Danish Cancer Society started planning a similar project in Copenhagen and Aarhus.

Other researchers had started considering the design of prospective studies on nutrition in the Netherlands, the United Kingdom (Cambridge), Italy (Milan) and France (Paris).

At IARC, this new interest was built on through the development of a research programme on nutrition and cancer which formed the basis for initiating the planning of a multicentre European prospective cohort study that eventually became the European Prospective Investigation into Cancer and Nutrition (EPIC).

2 The Design and Establishment of the EPIC Project

The EPIC project was initiated in 1989 with a series of methodological studies aimed at testing the relative validity and reproducibility of diet measurement methods specifically designed to be used in large, multicentre and multilanguage cohort studies.

The basic design of these methodological studies consisted of two repeat measurements obtained with the newly designed diet assessment questionnaires, at the start and end of a one-year period. Diet questionnaire results were compared to a reference method consisting of the average diet intake estimated with 12 repeat 24-h dietary recalls (24 HDR) administered monthly throughout the study period.

Biomarkers measured in four repeat blood samples and in four repeat 24-h urine collections were used to compare with estimated diet intake of specific nutrients and foods [43].

These studies also pilot-tested the feasibility of collecting detailed lifestyle and medical history data and biological samples from a large number of study participants in a cost-effective manner. Successful completion of this methodological and pilot phase paved the way to the funding, by the Europe against Cancer programme of the European Commission and by a number of national institutions, of the full-scale project.

Enrolment for EPIC began in 1992 in 17 research centres in 7 core EPIC countries (France, Germany, Greece, Italy, The Netherlands, Spain and the UK). Over the next 2–3 years, additional research centres that were conducting similar prospective studies in Denmark, Norway and Sweden also joined the EPIC consortium.

Recruitment took place mostly from 1993–1999 and largely invited study participants from the general population in certain geographical areas with an age range of 35–70 years. Some exceptions existed, for example, the Utrecht cohort, which was based on women who underwent breast screening, the Oxford cohort that targeted both the general population and vegetarians and vegans and the French cohort composed of members of the national health insurance of school employees.

By the end of the study participant recruitment phase in 1999, EPIC became the largest prospective cohort study with a baseline biobank specifically designed to investigate the relationship between nutrition and cancer, with 521,330 participants from 23 study centres across 10 European countries (Fig. 2).

The prospective cohort approach included the collection of baseline questionnaires on diet and lifestyle factors, as well as the measurement according to standardised protocols of anthropometric characteristics (weight, height, sitting height, waist and hip circumferences), blood pressure and pulse rate. EPIC was also the first study to collect and store blood from a very large number of participants: 388,467 blood samples of 30 ml volume were collected and aliquoted into 28 plastic straws of citrated plasma and serum, stored in liquid nitrogen, with aliquots divided for security reasons between the central biorepository at IARC and in each national centre.

European Prospective Investigation into Cancer and Nutrition (EPIC): Key Investigators and Collaborating Centres

Imperial College London (ICL)
• Elio Riboli (EPIC Coordinator), Gwyneth Davey†, Marc Gunter, Teresa Norat.

International Agency for Research on Cancer/ World Health Organization (IARC, Lyon)
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France
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• Pagona Lagiou, University of Athens Medical School.

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• Paolo Vineis, University of Turin and HuGeF Foundation.

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• Aurelio Barricarte, Navarre Public Health Institute, Pamplona.
• Miren Dorronsoro, Public Health Office of Guipuzcoa, San Sebastian.
• Carmen Navarro, Murcia Regional Health Council, Murcia.
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United Kingdom
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• Timothy J Key, Ruth C Travis, University of Oxford.

Fig. 2 European centres participating in the EPIC consortium with key collaborators

A key feature of EPIC is its wide geographical coverage, which means that the study comprises populations with varying dietary and lifestyle habits and different underlying cancer incidence rates. This study design including heterogeneity in both the exposure of interest, and the disease outcome was conceived to increase the overall statistical power of identifying diet–diseases relationships.

On the other hand, this diversity in diet and language might introduce systematic over or underestimation of the intake of specific foods and nutrients across study centres. To address these methodological challenges, we developed a research programme aimed at improving diet measurement via the introduction of an in-built calibration sub-study. A detailed 24-h dietary recall assessment was made in 7 % of the cohort (38,000 individuals) across each of the EPIC countries;