Cancer Treatment and Research
Series Editor: Steven T. Rosen

Vincenzo Zappia · Salvatore Panico
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Advances in Nutrition and Cancer

Indexed in PubMed/Medline

Springer

Cancer Treatment and Research

Volume 159

Series Editor

Steven T. Rosen, Chicago, IL, USA

For further volumes:
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Advances in Nutrition and Cancer

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ISSN 0927-3042
ISBN 978-3-642-38006-8 ISBN 978-3-642-38007-5 (eBook)
DOI 10.1007/978-3-642-38007-5
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013947358

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

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

The Third International Conference on *Advances in Nutrition and Cancer*, held in May 2012, was sponsored by the National Institute for Cancer Research "Fondazione G. Pascale," Naples, the non-profit Association Arfacid onlus, Naples, the Oncology Research Center of Mercogliano, the Departments of Biochemistry and of General Pathology of the Second University of Naples, the Departments of Clinical Medicine and Molecular Oncology of the University of Naples "Federico II," the Institute of Food Science of the National Research Council, Avellino, and the Italian Institute for Philosophical Studies of Naples.

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.

The editorial coordination between the editors, authors, and Springer Verlag was handled by Janet Gates and the organizing secretariat by Paola Colonna and Pina Carfora.

The editors acknowledge Dr. Giuseppe Iacomino for his valuable assistance in the Conference organization. They also express their gratitude to the authors of the articles and to Springer Verlag for having made possible the publication of this volume.

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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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V. Zappia et al. (eds.), *Advances in Nutrition and Cancer*,
Cancer Treatment and Research 159, DOI: 10.1007/978-3-642-38007-5_1,

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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.

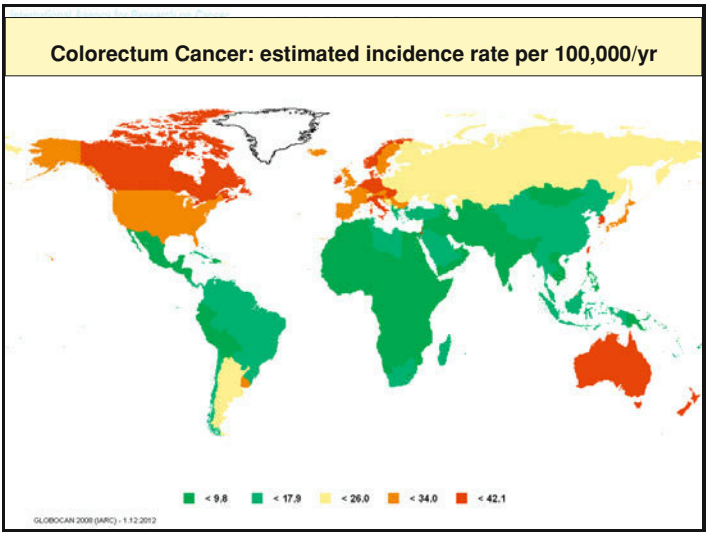
Evidence from experimental animal models to demonstrate that alcohol can cause cancer also took much longer to accrue than for chemicals in cigarette smoke. The main mechanisms that have been identified to date for the influence of alcohol on cancer risk [19] include DNA damage by acetaldehyde that may 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)



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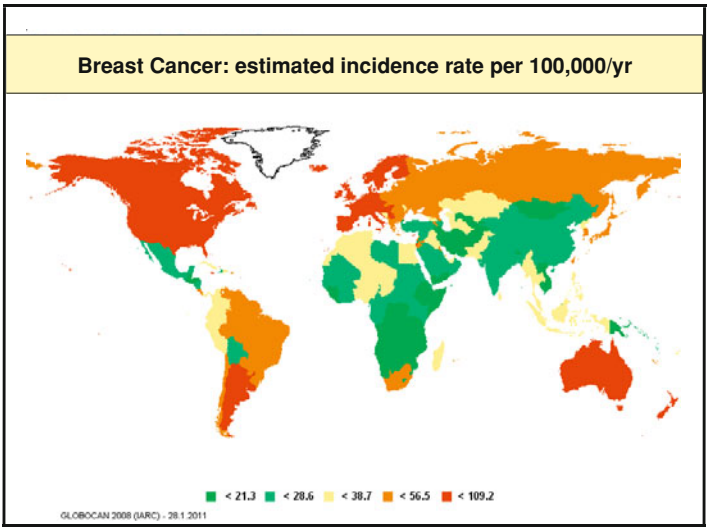

Fig. 1 GLOBOCAN 2008 estimated cancer incidence rate worldwide per 100,000/yr for (**a**) colorectum and (**b**) breast cancer. Reproduced from [14]

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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• Anne Tjønneland, Danish Cancer Society, Copenha

France
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• Paolo Vineis, University of Turin and HuGeF Foundation.

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United Kingdom
• Nicholas E Day, Kay-Tee Khaw, Sheila Bingham†, Nicolas Wareham, John Danesh, University of Cambridge.
• 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;

this was used to calibrate results from each centre to correct for possible systematic between-centre over/underestimations in the baseline dietary assessments.

Since the initial baseline collection, cohort participants have been followed up to obtain information on changes in major dietary and lifestyle factors including a series of questions on whether the subjects had suffered from a number of common diseases and medical conditions.

Follow-up aimed at identifying cancer cases occurring among the EPIC cohort is mostly based on record linkage with population cancer registries data. In some EPIC centres (i.e. in France, Germany and Greece) where the area of residence of the participants does not coincide with that of comprehensive cancer registries, cancer incidence data are gathered via a combination of other methods including active follow-up of study subjects and their next-of-kin, health insurance records and clinical and pathology registries.

Data have since been stored in a central secured database located at IARC-WHO and are made available to EPIC collaborators for specific studies. So far, over 60,000 newly incident cancer cases have been reported, including around 14,000 breast, 3,600 lung, 5,200 colorectal, 1,180 pancreatic and 1,400 endometrial cancer cases, giving scope for well-powered studies on cancer causation.

3 Research Highlights on Nutrition and Metabolic Factors and Cancer

EPIC represents a large and mature resource for epidemiological studies of cancer aetiology. Data can be integrated from studies on diet, physical activity, anthropometry and biomarker measurements to build a broad picture of the role of nutrition and metabolic factors in cancer causation. Here, some highlights of this research within EPIC are summarised.

3.1 Foods and Nutrients

Specific research projects conducted within EPIC on the relationship between consumption of specific foods and nutrients and cancer risk have either identified or clarified a number of associations with the risk of developing specific cancers; these are briefly outlined below.

Fibre and particularly cereal fibre has been consistently found to be strongly associated with reduced risk of developing colorectal cancer [2, 3]. Red meat and processed meat were associated with increased risk of digestive tract cancers, including stomach, colon and rectum [17, 32].

The blood levels of a number of nutrients were found to be significantly associated with reduced cancer risk. Notable associations suggesting a protective effect include B vitamins and cancers of the colorectum [12] and lung [23], ascorbic acid and some carotenoids and cancer of the stomach [20], Vitamin D and cancer of the colorectum [22].

However, the focus of this paper is on the major findings concerning the association of anthropometric and metabolic factors with cancer risk.

3.2 Obesity

The relationship between body mass index (BMI) or other anthropometric measures and cancer risk has been investigated for a number of cancer types in the EPIC population. Body weight and BMI were found to be positively associated with risk of colon cancer in men, whereas weak or no associations exist in women. However, when waist circumference and waist–hip ratio (WHR), indicators of abdominal obesity, were analysed in the EPIC study, they were found to be predictive of subsequent risk of developing colon cancer in both men and women, with relative risk for the highest versus the lowest quintile of WHR of 1.51 for men (95 % CI = 1.06–2.15); and 1.52 for women (95 % CI = 1.12–2.05) [33].

The association of abdominal obesity with colon cancer risk may also vary depending on hormone replacement therapy (HRT) use in postmenopausal women as it appears more strongly in women who never took HRT; further studies will be needed to investigate this [33].

The relative risk for endometrial cancer for women with a waist circumference of $\geq$88 cm versus <80 cm was 1.76 (95 % CI = 1.42–2.19); weight, waist and hip circumferences and WHR were also strongly associated with increased risk of endometrial cancer [16].

In EPIC, overweight (expressed as BMI) was a significant predictor of breast cancer risk in postmenopausal women not using HRT. When restricting the analyses to women who were taking HRT at baseline or had taken HRT in the few years preceding baseline, an apparent weakening of the association of BMI with breast cancer risk was observed [27]. Similar results were reported by other cohort studies (for example [18]). However, this interpretation of the results does not take into account the real-time sequence of the two risk factors. In fact, these women first gained weight during their life and subsequently started taking (or not taking) HRT. Therefore, the interpretation should be that HRT increased breast cancer risk more markedly in lean women and progressively less markedly in overweight and obese women (Fig. 3).

Among premenopausal women, weight and BMI were slightly inversely associated with breast cancer. Although this effect was non-significant in EPIC, it was in agreement with a number of other studies, thus stimulating an unexpected research question. There are no known mechanisms that would satisfactorily explain why overweight and obese women would be at slightly reduced breast cancer risk before age 45–50.

This unexpected association was corroborated by the EPIC finding that increasing C-peptide levels as a marker of insulin resistance are associated in an opposite direction with breast cancer risk, predicting an increase in risk after menopause but a slight decrease in risk before menopause [49].

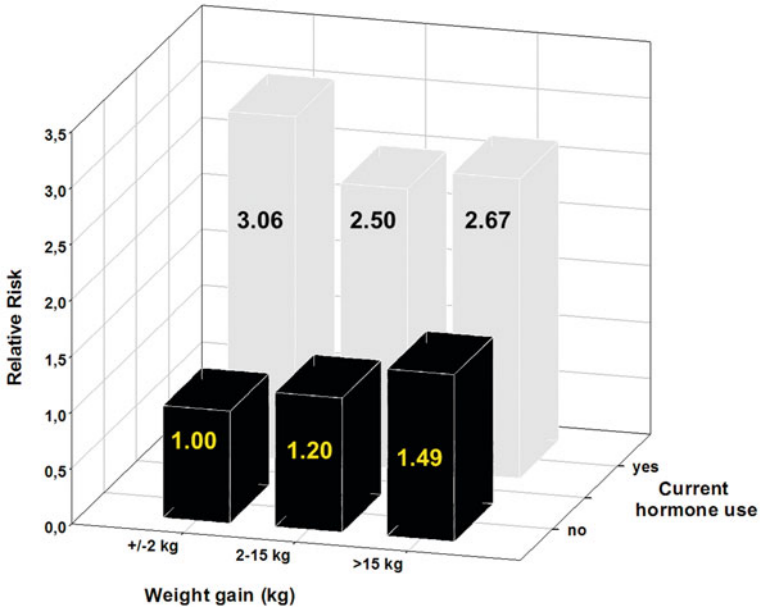

Fig. 3 Multivariate-adjusted relative risk of breast cancer by weight gain category and current hormone use among postmenopausal women in the EPIC study

Given the range of effects observed in different segments of the population, it will be important to understand the mechanisms by which obesity affects cancer risk. There is substantial evidence supporting the theory that hormonal mechanisms play a central role in breast cancer aetiology.

Moderate and high levels of physical activity, combining recreational and household activities, were associated with a reduced risk of breast cancer, independently of the level of overweight. Heterogeneous associations were observed by breast cancer hormone receptor status indicating hormone-related mechanisms [28, 40].

Similarly, a reduced colorectal cancer risk was observed in relation to increased physical activity. The risk was halved in subjects who were physically active and slim compared to those being overweight and sedentary [15].

No association with physical activity has been found for a number of other cancer types including lymphoid neoplasms [48].

3.3 Height

Consistent with the theory that early, rapid growth could predispose to increased cancer risk later in life, height was also shown to be associated with increased risk of a number of cancers and with overall cancer incidence and mortality [50].

The association is particularly evident for colorectal and breast cancer risk in EPIC. For colorectal cancer, tall men (≥180.5 cm) and women (≥167.5 cm) have a RR of 1.40 (95 % CI = 0.99–1.98) and 1.79 (95 % CI = 1.30–2.46), respectively, compared to short men (<168 cm) and short women (<156 cm) with a linear relationship over the full scale of height [33].

The risk of breast cancer for being tall compared to being short among pre- and postmenopausal women was 1.33 (95 % CI 0.96–1.84) and 1.40 (95 % CI 1.16–1.69), also with a linear relationship predicting an increased risk for each additional 5 cm of height of 1.05 (95 % CI 1.00–1.16) in premenopausal and 1.10 (95 % CI 1.05–1.16) in postmenopausal women [27].

The mechanism by which height affects cancer risk is unclear but is likely to be due to a combination of genetic, environmental, hormonal and nutritional factors. What is intriguing is that metabolic factors must operate in early age before full height is attained, to leave an "imprint" for risk of disease in later life. Understanding the factors that influence both growth and subsequent risk of different non-communicable diseases, including cancer and cardiovascular and respiratory diseases, should be an important subject for future research as it may pave the way to yet unknown disease mechanisms.

3.4 Insulin Resistance

Insulin resistance is a complex metabolic condition in which the uptake of glucose at the cellular level requires higher than normal levels of insulin. When the condition is mild, the pancreas is able to increase insulin synthesis and compensate for the higher demand. When the condition becomes more serious, the pancreas may not be able to produce enough insulin and therefore high levels of insulin coexist with high glycemia. This condition may precede the clinical appearance of type 2 diabetes for years or may persist at a mild level without ever leading to overt diabetes during a person's life.

The two most widely used serum markers of insulin resistance are C-peptide and glycated haemoglobin (HbA1c). Elevated C-peptide level is an earlier marker of insulin resistance than HbA1c. Glycated haemoglobin reaches above normal levels when high insulin secretion is not sufficient to compensate peripheral insulin resistance and control glycaemia while C-peptide, being a marker of insulin secretion, may start being elevated when glycaemia and HbA1c are still within the normal range. For this reason, we used C-peptide in a number of investigations in EPIC into the association of insulin resistance with subsequent cancer risk.

We first reported a strongly positive association between serum C-peptide levels and relative risk of colon and rectal cancer in the New York University Women's Health Study, with an odds ratio of 2.92 (95 % CI 1.26–6.75) for the highest versus lowest quintiles [24]. This was replicated for colon and rectum cancer within EPIC, with a much larger number of cancer cases, though the association was less strong [21].

A positive association has also been observed for cancer of the endometrium at all ages [4]. For cancer of the breast, an opposite effect was found in premenopausal versus postmenopausal women (as described above, [49]). Breast cancer risk was significantly reduced in subjects who were less than 50 years of age at cancer diagnosis and had elevated C-peptide levels at baseline [49].

3.5 Sex Steroid Hormones

An underlying hormonal mechanism is indicated for many of the associations of anthropometric traits with cancer as described above. This has led to detailed studies on individual hormonal factors and cancer risk, as exemplified by work on breast cancer in EPIC.

In postmenopausal women (where BMI is positively associated with breast cancer risk), BMI was positively correlated with serum levels of estrone, free estradiol and free testosterone [25]. Sex hormone–binding globulin (SHBG) levels showed an inverse relationship with BMI; this glycoprotein sequesters androgens and estrogens such that the bound form is unavailable to bind its cellular receptor. In addition to these observations, elevated levels of a panel of hormones was found to be a strong predictor of increased breast cancer risk, with SHBG the only factor to be associated with reduced breast cancer risk (Fig. 4) [25].

In contrast, in premenopausal women (where there is an inverse association of BMI and breast cancer risk), these associations were not apparent for estrogens or SHBG. However, elevated androgens were associated with increased risk of breast cancer [26].

4 Conclusions

It is clear that a number of chemical, physical and biological carcinogens have a major role in cancer causation and in some cases account for most of the variations in cancer incidence across the world. However, they cannot explain the global variations for a large number of cancers that represent a significant proportion of the world's total cancer burden.

Research conducted during past decades, and particularly those based on large prospective studies including EPIC, has found that diet, nutrition, physical activity and anthropometry have major influences on population risk of cancer.

From a scientific point of view, the unravelling of the mechanistic effects underlying the increased cancer risk associated with some components of current Western diet and lifestyle is challenging. The effect may be due to fine modulation or modest dysregulation of normal physiological processes rather than gross disruption, as may be the case for some strong exogenous carcinogens.

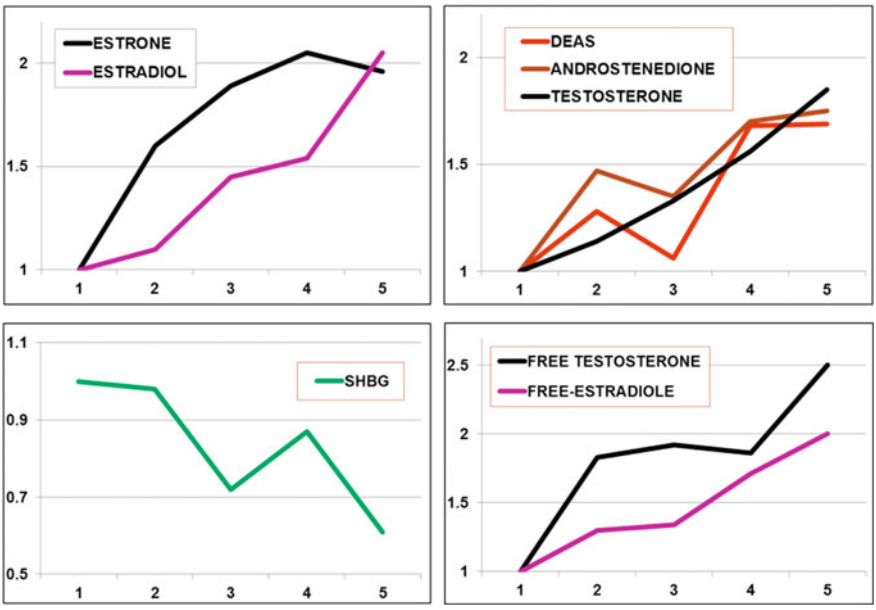

Fig. 4 Relative risk of breast cancer by quintiles of serum sex steroid levels among 300,000 postmenopausal women in the EPIC study with average follow-up of 8 years. Odds ratio estimated by conditional logistic regression with study centre, age at blood donation, time of day of blood donation and fasting status at blood donation as matching factors for breast cancer cases and control subjects. x axis: quintiles of hormone concentration from low [45] to high [10]; y axis: relative risk

From a public health point of view, these metabolic lifestyle factors are of great interest as they largely overlap with the major known risk factors of cardiovascular diseases and diabetes, therefore offering the opportunity of targeting the prevention of a number of non-communicable diseases with the same panel of public health interventions [13].

Acknowledgments The author would like to acknowledge Claire Westwood for assistance with preparation of the manuscript, and the following for financial support of the EPIC study: European Commission (DG-SANCO); International Agency for Research on Cancer; Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); Ministry of Health and Social Solidarity, Stavros Niarchos Foundation and Hellenic Health Foundation (Greece); Italian Association for Research on Cancer (AIRC) and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); ERC-2009-AdG 232997 and Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health. (Norway); Health Research Fund (FIS), Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020) (Spain); Swedish Cancer Society, Swedish Scientific Council and Regional

Government of Skåne and Västerbotten (Sweden); Cancer Research UK, Medical Research Council, Stroke Association, British Heart Foundation, Department of Health, Food Standards Agency, and Wellcome Trust (United Kingdom).

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