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Cancer Prevention II

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Preface

More than 180 participants and experts from 31 countries met for the fifth time in 10 years in St. Gallen, Switzerland for a 3-day conference to discuss important current issues of clinical cancer prevention. The meeting was again organized and co-sponsored by St. Gallen Oncology Conferences (SONK).

While SONK has been extremely successful in organizing large international congresses on "Primary Therapy of Early Breast Cancer" as well as "Supportive Care in Cancer" for more than 20 years, the idea of promoting interdisciplinary, clinically oriented meetings on cancer prevention is a more recent and not yet generally accepted and welcomed concept in modern oncology. Since today's medical expenses are soaring and medical research budgets are stagnating or even being cut, neither politicians nor industry is willing to risk an additional unpredictable channel of expenses, such as that demanded by clinical cancer prevention efforts!

In Switzerland—and we fear in many other parts of the globe—some 97%–98% or even a greater percentage of health budgets is spent for curative and palliative/rehabilitative medicine. Since a meager 2%–3% of national health budgets is for preventive medicine, even less than that proportion is specifically allocated for cancer prevention. When the money for "curing and caring" for the diseased populace runs short, there is likely not much left for partly controversial disease prevention in the (still) healthy part of the population. Although this might be an extremely short-sighted view, it is noticeably prevalent with health politicians and even with large parts of the medical profession, at least in Continental Europe, today.

Despite this ironic situation, we have decided to keep trying to promote the promising field of clinical cancer prevention by organizing biannual international conferences in view of the accumulating interactions between molecular genetics and biology, epidemiology and clinical cancer prevention. Together with a growing number of scientific and professional partners, we intend to periodically set the stage for a comprehensive scientific discussion forum critically analyzing the development of more efficient and more acceptable primary and secondary cancer prevention approaches for the future. It is rather unfortunate that the oncology-oriented pharmaceutical industry—especially in Europe—is not yet willing or prepared to support this fascinating field, especially chemoprevention, by more appropriate research involvement and educational funding.

It was our privilege to co-organize this meeting again on behalf of the International Society of Cancer Prevention (ISCaP, New York, NY, USA) together with the European School of Oncology (ESO, Milan, Italy) and the European Society of Medical Oncology (ESMO, Lugano). For this fifth prevention conference in March 2008 we were able to generate some new and greatly welcomed additional and "neutral" supporters or sponsors: Cancer Research UK (CRUK, London, UK), the Union Internationale Contre le Cancer (UICC, Geneva, Switzerland), the European Association of Cancer Research (EACR, Nottingham, UK), the American Cancer Society (ACS, Atlanta, GA, USA), and the Swiss Cancer League (Bern, Switzerland). Very little financial support was provided by industry. The local organizers were Prof. Hans-Jörg Senn, MD, Prof. Ursula Kapp, MD, and Prof. Florian Otto, all from the prevention-oriented Tumor Center ZeTuP in St. Gallen, Switzerland.

This 2008 St. Gallen International Cancer Prevention Conference—in contrast to the previous meetings in 2004 and 2006—was primarily targeted to primary prevention, and even more specifically at the chemoprevention of major cancer types such as breast, colorectal, cervical, and lung. Besides the traditional sessions on health politics and organ-site-oriented cancer prevention efforts, we tried for the first time to upgrade this 2008 conference with a well-prepared consensus session on the present state of the art of chemoprevention of colorectal cancer by aspirin and nonsteroidal antiinflammatory drugs (NSAIDs), chaired by Prof. Jack Cuzick, president of ISCaP and director of the Wolfson Institute of Preventive Medicine in London, UK, and by Dr. Peter Greenwald, the director of the prevention branch of the NCI in Bethesda, MD, USA.

This consensus of the use of aspirin and NSAIDs in chemoprevention of colorectal cancers will be published separately in a major oncology journal. As is the tradition, the majority of the invited expert contributions to the conference are published in this internationally well-known series, *Recent Results in Cancer Research*, by Springer. We hope you enjoy its multifaceted content.

Already the organizers invite dedicated scientists, epidemiologists, and clinicians interested in primary and secondary (clinical) cancer prevention to the next international cancer prevention conference, which will be held in St. Gallen, 18–20 March 2010.

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Part I

Cancer Prevention and Health Politics

Do We Make Optimal Use of the Potential of Cancer Prevention?

1

Peter Greenwald and Barbara K. Dunn

Abstract Three decades of intensive experimental and clinical research on cancer prevention have yielded an impressive body of scientific knowledge about cancer epidemiology, causation, and preventative measures. Despite our increased understanding in these critical areas, this knowledge is not being translated adequately into initiatives that will impact public health. The recent release of the World Cancer Research Fund/American Institute for Cancer Research report on diet and lifestyle strategies for cancer prevention—grounded in an evidence-based, systematic review of the published literature—is a strong acknowledgment of the benefits of a lifestyle approach to reduce cancer risk. The report also emphasizes the need to increase basic nutritional science research to make optimal use of the knowledge gained in the past three decades. Medical approaches—represented by chemoprevention clinical trials—also have become more focused based on results from basic science leads. The expansion of preclinical chemoprevention studies and greater attention to "first-in-human" prevention trials that safely shorten the timeline for new drug development are needed. The development of a prevention focus for what the U.S. Food and Drug Administration calls "exploratory investigational new drug studies" and what investigators at the National Cancer Institute are calling "phase 0" clinical trials will contribute to the decision-making involved in designing larger cancer prevention clinical trials. Past achievements in phase III prevention clinical trials—such as the Prostate Cancer Prevention Trial, the Breast Cancer Prevention Trial, and the Study of Tamoxifen and Raloxifene—have provided early successes as evidence of the potential for public benefit to be derived from this research. Nevertheless, the application of these findings to clinical practice and the design of future prevention trials remains a challenge. Current strategies include the refinement of risk assessment models for several major cancers. Additional initiatives, based on emerging basic and clinical research, involve the development of potential biomarkers for cancer risk and early detection by the National Cancer Institute's Early Detection Research Network. Although a recent progress report indicates that biomarkers of cancer susceptibility and exposure have been identified, continued work is needed to validate such markers for clinical use. Using this information optimally for prevention through lifestyle changes or medical interventions will

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demand commitments from public and private research institutions. Another area of emerging research is the development of a systems biology approach to cancer prevention. This will demand the creation of multidisciplinary teams of researchers from biological sciences, informatics and engineering scientists, and researchers from many fields not generally focused on disease prevention. To facilitate this and other new approaches, and to make effective use of information and strategies for cancer prevention, intensive training efforts must be implemented to develop the next generation of basic and clinical scientists—and physician researchers—capable of working in a cross- and multidisciplinary research environment. Training current researchers in new approaches will add efficiency to their combined research experiences.

1.1 Introduction

For most of the past 35 years, trends in the incidence and mortality rates of all major cancers in the United States showed steady increases. This pattern changed in the 1990s when decreases started to emerge (National Cancer Institute 2007), with mortality rates declining at approximately half that of incidence rates (Ries et al. 2007). While for some of the most common types of cancer in the United States—breast, prostate, colorectal, and lung—considerable progress has been made regarding mortality and incidence, in specific cancer types in some population groups (e.g., lung cancer in women and prostate cancer among African Americans) such progress is not evident.

The role of cancer prevention underlies much of this observed decrease in cancer incidence and mortality. For three decades, an impressive body of research has accumulated indicating that lifestyle and medical prevention strategies can have a major impact on cancer incidence and mortality. Nevertheless, doubt exists as to whether clinicians and other health professionals are making optimal use of existing knowledge regarding cancer prevention strategies. Cancer prevention offers a key opportunity to reduce the disease burden both on individuals and on the healthcare system. To achieve the maximum benefit from cancer reduction, major initiatives in prevention must include both lifestyle and chemoprevention approaches.

The following sections discuss current research on lifestyle and medical intervention studies—as well as selected molecular and genetic studies—in cancer prevention. In addition, a review is presented of progress in several areas: the translation of research findings into public benefit; new approaches for designing and developing clinical trials to target individuals most likely to benefit from trial findings; and suggestions for increased and novel approaches to training with a goal of producing the multidisciplinary researchers needed for working with emerging high-throughput and "-omic" (e.g., genomic, proteomic, transcriptomic, and metabolomic) technologies.

1.2 Lifestyle Interventions

Preventing cancer through lifestyle modifications and other interventions has received increased attention in the past decade as more is understood about the role of nutrition, weight gain/loss, and the level of physical activity and cancer risk. Since the Doll and Peto quantitative analysis of estimates of avoidable cancer risks in 1981 (Doll and Peto 1981), accumulating evidence suggests that lifestyle may contribute to as much as 70% of cancer cases; nutrition alone is a factor in at least 30%–40% of cancers. Adopting lifestyle modifications—in areas involving diet,

physical activity, use of tobacco, and weight control—offers a major approach to cancer prevention for most individuals. In the past, however, apart from the avoidance of tobacco, limited convincing evidence had been available to make recommendations regarding these lifestyle areas. This situation changed rapidly as findings from basic, epidemiological, and clinical research began to fill in gaps in our knowledge. For example, the recent release of *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective* (World Cancer Research Fund 2007)—the 2007 expert report developed and published by the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR)—highlighted the role of lifestyle on cancer prevention. The report is evidence-based and draws from a substantial body of cancer prevention literature published in the past decade.

What distinguishes this recent report from past documents is the utilization of increasingly available data from controlled clinical trials and large prospective studies on nutrition and cancer. Table 1.1 highlights the recommendations from the report, which incorporates government recommendations (U.S. Department of Health and Human Services 2005). Table 1.2 highlights the report's findings on lifestyle factors and decreased or increased risk of cancer by cancer site. The inclusion of a factor in Table 1.2 indicates that the authors of the report found the evidence to be either "probable" or "convincing" for its use in assessing the level of cancer risk. "Convincing" is the highest level of evidence for a recommendation, based on the judgment that the evidence will be unlikely to change over time and is based on congruent results from at least two independent cohorts. The underlying evidence has favorable attributes including: (1) no substantial heterogeneity in the data; (2) plausible dose responses; (3) consistent evidence from laboratory studies; and (4) accountability for error. Taken in totality, the evidence suggests that specific lifestyle changes could have a major impact on cancer prevention if optimal use of the information became part of physician practice and public policy recommendations.

Table 1.1 WCRF/AICR (2007) recommendations adapted from *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*, incorporating 2005 U.S. dietary guidelines

General recommendations for cancer prevention
1. Be as lean as possible without becoming underweight (goal: BMI 21–23)
2. Be physically active for at least 30 min every day
3. Avoid sugary drinks. Limit consumption of energy-dense foods (particularly processed foods high in added sugar, or low in fiber, or high in fat)
4. Eat more of a variety of vegetables, fruits, whole grains and legumes such as beans
5. Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats
6. If consumed at all, limit alcoholic drinks to 2 for men and 1 for women a day
7. Limit consumption of salty foods and foods processed with salt (sodium). Avoid moldy cereals (grains) or legumes
8. Aim to meet nutritional needs through diet alone. Do not use supplements to protect against cancer
Special population recommendations
9. New mothers ideally should breastfeed exclusively for up to 6 months and then add other liquids and foods
10. Cancer survivors after treatment should follow the recommendations for cancer prevention

Table 1.2 Convincing evidence of decreased or increased risk of cancer by cancer site and lifestyle factor (*Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*; WCRF/AICR 2007)

Lifestyle factors with probable and/or convincing decreased risk of cancer[a]	
Colorectum	Foods containing dietary fiber, garlic, milk, calcium supplements, increased physical activity (probable evidence)
Mouth, pharynx, larynx	Non-starchy vegetables, fruits, foods containing carotenoids (probable evidence)
Esophagus	Non-starchy vegetables, fruits, foods containing beta-carotene (probable evidence)
Stomach	Non-starchy vegetables, *Allium* vegetables, fruits (probable evidence)
Lung	Fruits, foods containing carotenoids (probable evidence)
Pancreas	Foods containing folate (probable evidence)
Prostate	Foods containing lycopene, foods containing selenium, selenium supplements (probable evidence)
Breast	Lactation
Lifestyle factors with probable and convincing increased risk of cancer[a]	
Liver	Aflatoxins
Colorectum	Red meat, processed meat, alcoholic drinks (men only), body fatness, abdominal fatness, adult-attained height
Lung	Arsenic in drinking water, beta-carotene supplements
Mouth, pharynx, larynx	Alcoholic drinks
Esophagus	Alcoholic drinks, body fatness
Breast, premenopausal	Alcoholic drinks (probable evidence)
Breast, post-menopausal	Alcoholic drinks, body fatness, adult-attained height
Pancreas	Body fatness
Endometrial	Body fatness
Kidney	Body fatness

[a] Evidence is convincing unless otherwise noted as probable

The potential for research opportunities geared toward improving the science of nutrition and cancer emerged directly from this report. These opportunities include integrating the recommendations on chronic diseases, and on promoting positive health and well-being. The relationship between causation and prevention should be elucidated and a revived look at descriptive studies, such as those on migrant populations, is needed.

Other important research gaps include studies on determinants of rapid growth and early puberty; dietary energy restriction in humans; food systems and dietary patterns; foods common in traditional diets; populations in parts of the world for which cancer is uncommon; and follow-up studies of exclusively breastfed children. There also is a need to develop standard definitions of physical activity and processed meat, and to determine when in the course of life specific preventative interventions are most effective. WCRF and AICR have committed to regularly updating the report as new evidence is published. (A summary and complete report can be found at http://www.wcrf.org/research/fnatpoc.lasso.)

Other important findings of the past decade relating lifestyle interventions to cancer prevention include the emerging recognition of obesity as a major factor in cancer etiology. Calle and

colleagues suggested that being overweight or obese contributes to 15%–20% of cancer deaths; given the increasing numbers of obese Americans, the promotion of weight control has potential as a broadly effective lifestyle approach to cancer prevention (Calle et al. 2003). Regular, moderate physical activity also has been associated with reduced risk of various cancers, including colon cancer (Samad et al. 2005).

A preventative approach of lifestyle modifications that targets diet, physical activity, and weight control is likely to impact morbidity and mortality due to cancer.

1.3 Medical Interventions

Unlike lifestyle interventions, which are generally designed to target cancer risk broadly in populations, medical interventions are more specific in that they focus on limited cancer types in individuals or subpopulation groups that are at increased risk of developing those cancers. Both types of intervention, however, are important for overall reductions in cancer morbidity and mortality. The field of study involving the medical intervention approach to cancer prevention is maturing as it incorporates knowledge generated from basic, epidemiological, and clinical research. In particular, the increased understanding of the molecular, genetic, and epigenetic processes that contribute to or prevent carcinogenesis feeds directly into the formulation of medical preventative interventions. New approaches for designing and implementing cancer prevention clinical trials will also directly affect investigators' ability to provide evidence of benefits (or lack of benefit) for medical interventions. The use of emerging technologies and the collaborative efforts of multidisciplinary research teams are expected to accelerate the pace of new discoveries.

1.4 The Changing Landscape of Clinical Studies

The use of lifestyle or medical interventions ideally depends on their evaluation in clinical trials—preferably testing each intervention in relation to a control group in a randomized controlled trial (RCT). Before cancer prevention agents—nutrient- and non-nutrient-based—can be tested in RCTs, however, they must undergo testing in a phased clinical trial regimen to guarantee the safety and efficacy of the agent. For cancer prevention clinical research, the U.S. National Cancer Institute (NCI) traditionally has used a three-phase approach for testing chemoprevention agents. These potential chemoprevention agents are tested for safety and pharmacokinetic profiles in a small number of individuals (phase I trial); intermediate-endpoint biomarkers that are modulated by the agent and have potential to serve as surrogates for clinical disease endpoints are identified and tracked in trials with as many as several hundred individuals (phase II trial or a combination of phase I and phase II trials); and a large-scale, randomized, controlled trial is conducted to determine if the agent reduces cancer risk, the critical clinical endpoint in cancer prevention research (phase III trial). NCI encourages extensive follow-up to further evaluate the long-term safety and efficacy of an intervention. More than 150 potential chemopreventative agents have been identified in preclinical studies sponsored by the NCI's Division of Cancer Prevention (DCP), and development continues on the more than 40 agents that have shown evidence of safety and chemopreventative efficacy. Figure 1.1 depicts the approach of chemoprevention research and the stages in the carcinogenic process that may be targeted by chemopreventative agents.

An effort is being made at NCI to shorten the time an agent spends in the phased system, and