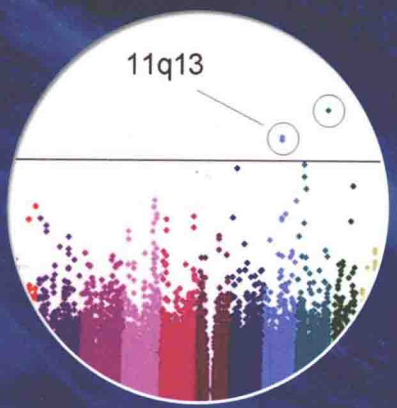

World Cancer Report 2014

Edited by BERNARD W. STEWART and CHRISTOPHER P. WILD

International Agency for Research on Cancer

World Health Organization

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Cover images, from top to bottom: A woman in The Gambia prepares cereal, using scales to measure portions (Credit: C.P. Wild/IARC). Next-generation gene sequencing equipment in use at the Joint Genome Institute in Walnut Creek, California, USA (Credit: Joint Genome Institute, U.S. Department of Energy Genomic Science Program). Manhattan plot of pooled genome-wide association study (GWAS) results (Credit: P. Brennan/IARC). A group of researchers from the Epigenetics Group in the Section of Mechanisms of Carcinogenesis at IARC (Credit: R. Dray/IARC). Representative example of high-grade serous carcinoma, one of the main types of ovarian carcinoma (Credit: J. Prat, Autonomous University of Barcelona). Background image: The Blue Marble: Next Generation is a mosaic of satellite data taken mostly from a NASA sensor called the Moderate Resolution Imaging Spectroradiometer (MODIS) that flies aboard NASA's Terra and Aqua satellites (Credit: NASA/Goddard Space Flight Center/Reto Stöckli).

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Contents

Foreword

The world has opened its eyes to the threat posed by cancer and other noncommunicable diseases (NCDs). Realization is growing, in global political circles and in civil society, that these diseases constitute a major obstacle to human development and well-being.

The United Nations General Assembly High-Level Meeting on the Prevention and Control of Noncommunicable Diseases, held in September 2011, marked a turning point in the awareness of political leaders and the international community of the need for urgent action to avert a worldwide crisis.

The new figures and projections of the global cancer burden presented in this edition of *World Cancer Report* starkly highlight the problem: the incidence of cancer has increased from 12.7 million in 2008 to 14.1 million in 2012, and this trend is projected to continue, with the number of new cases expected to rise a further 75%. This will bring the number of cancer cases close to 25 million over the next two decades. The greatest impact will unquestionably be in low- and middle-income countries, many of which are ill-equipped to cope with this escalation in the number of people with cancer.

Many developing countries find themselves in the grip of cancers from two vastly different worlds. Those associated with the world of poverty, including infection-related cancers, are still common, while those associated with the world of plenty are increasingly prevalent, owing to the adoption of industrialized lifestyles, with increasing use of tobacco, consumption of alcohol and highly processed foods, and lack of physical activity.

This rising burden of cancer and other NCDs places enormous strains on the health-care systems of developing countries. Coupled with ageing populations and the spiralling costs of cancer treatment, increasing demands are placed on the health-care budgets of even the wealthiest nations. As a result, prevention is central to reducing or reversing the rise in cancer burden. The central role of prevention was acknowledged in the Political Declaration adopted at the United Nations meeting, which described it as the cornerstone of the global response.

The United Nations Political Declaration gave WHO a clear mandate to coordinate the global response to this threat along with some important time-bound responsibilities captured within the Global Action Plan for the Prevention and Control of NCDs 2013–2020. IARC's contribution has been and will continue to be instrumental in this process. Independent, robust scientific evidence is the foundation of the formulation of sound public health policies. The high-quality research produced by IARC is essential for the development of evidence-based guidelines and policy by WHO, and for the adoption of regulatory decisions by national institutions to protect the health of their populations.

This new edition of *World Cancer Report* represents a timely update on the state of knowledge on cancer statistics, causes, and mechanisms, and on how this knowledge can be applied for the implementation of effective, resource-appropriate strategies for cancer prevention and early detection. I am confident that *World Cancer Report 2014*, like the previous editions, will constitute a key reference tool that will find extensive use among scientists, public health workers, and governments in supporting the implementation of national and regional plans for cancer prevention and control.

Dr Margaret Chan

Director-General
World Health Organization

Preface

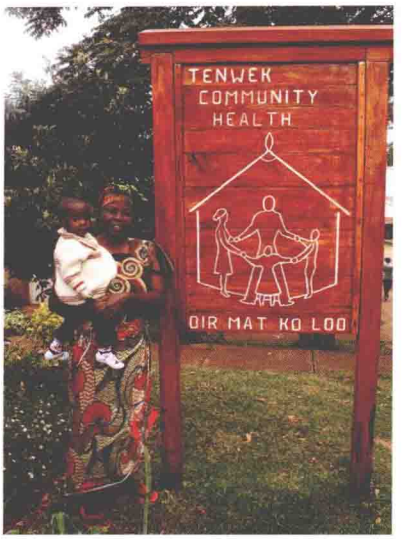
Cancer is costly. First and foremost there is the human cost, comprising the uncertainty and suffering that a diagnosis of cancer brings in its wake. Behind each statistic of a new cancer case is an individual face, accompanied by the faces of family and friends drawn into this singular event. The harrowing experience of a cancer diagnosis is a truly universal one, played out in every community worldwide, every day.

In contrast, as a cancer patient moves beyond diagnosis, individual experiences diversify across the world. In fact, the future of a cancer patient depends in large part on where the person lives. In less economically developed countries, cancer is typically diagnosed at more advanced stages of disease, while access to effective treatment is limited or unavailable, as is palliative care. Even within more economically developed countries, there are disparities in access to care among different communities. The experiences of individual cancer patients all too frequently reflect the worst of global inequalities.

Cancer also has a societal cost; enormous human potential is lost, and treating and caring for an increasing number of cancer patients has an escalating economic impact. This too is a universal experience, but again the details differ greatly between countries. *World Cancer Report 2014* reveals a cancer burden that is projected to increase by about 70% worldwide in just two decades, but it is in the lowest-income countries with the least-developed cancer services that the impact will be greatest. Already, the early onset of some common cancers (e.g. cervix, liver) and generally poorer survival in low- and middle-income countries mean that the burden of years of life lost to cancer in these countries is similar to that in higher-income countries. Given population growth, ageing, and the spread of risk factors, such as tobacco use, the situation will worsen in the next decades, posing a major challenge to health systems in low- and middle-income countries, so that this divide between the experiences of individual cancer patients will only broaden. Taken in isolation, this is a dark prediction.

It is time to take up the challenges posed by the markedly increasing number of cancer cases globally. The particularly heavy burden projected to fall on low- and middle-income countries makes it implausible to treat our way out of cancer; even the highest-income countries will struggle to cope with the spiralling costs of treatment and care. Therefore, elucidating the causes and devising effective prevention strategies are essential components of cancer control, as is the gathering of accurate data on cancer occurrence from population-based cancer registries. These approaches will complement the benefits in improved access to affordable and effective cancer treatment.

In parallel to work carried out on causes and prevention, remarkable progress has been made in understanding the molecular and cellular events that transform a normal functioning cell into part of a malignant growth that can kill its host. These exciting advances in basic science have ramifications that are evident throughout this edition of *World Cancer Report*, notably in classifying cancers, in providing new avenues for clues about their causes, in highlighting opportunities for early detection and prevention, and in laying a foundation for the development of new, targeted treatments in the clinic. As never before, there is an opportunity to bring together interdisciplinary cancer expertise so that the advances of basic science are translated into both improved treatment and more widespread prevention and early detection. This integrated and complementary approach reflects not only the duty of care to today's cancer patients but also the duty of care to the next generation, to free as many people as possible from the threat of this disease.



In the highlands of Kenya among the Kalenji people, who incidentally have provided some of the greatest middle- and long-distance runners in the world, there is a saying: "We should put out the fire while it is still small." It is this saying that greets patients arriving at the Tenwek Mission Hospital in the Western Highlands (see photo). We might adopt it as an idiom for cancer prevention. Since the middle of the last century, enormous progress has been made in identifying the causes of cancer, so that more than 50% of cases could be prevented based on current knowledge. These successes in identifying cancer causes must be complemented by an evaluation of the most effective interventions and an understanding of how best to support their implementation into specific health-care settings. Collectively, this knowledge provides huge potential for reducing the cancer burden; one can only imagine the interest that would follow an announcement of the availability of new cancer treatments able to cure 50% of all patients. Therefore, prevention must be writ large in cancer control plans if we are to defy the dark prediction of the statistics.

The International Agency for Research on Cancer (IARC) will play its part as it works for cancer prevention and control, with a particular commitment to low- and middle-income countries. IARC has a primary role in promoting international collaboration, and this role, acting as a catalyst for research, is increasingly proving to be vital because national questions can only be answered by international studies. Furthermore, the interdisciplinary approach taken by IARC is bearing fruit as knowledge about mechanisms of carcinogenesis casts new light on the causes and prevention of the disease.

The personal impact of cancer should never be far from the minds of all whose careers lead them to join in efforts to reduce the burden of suffering due to cancer. At the same time, cancer professionals from all disciplines need reliable knowledge on which to act, and the general public has the same need in order to make informed decisions. It is in this context that *World Cancer Report 2014* provides its up-to-date description of the occurrence, causes, underlying mechanisms, and prevention of cancer. My hope is that it will be a catalyst for collectively meeting the challenges of cancer in a way that benefits people in an inclusive way worldwide.

Dr Christopher P. Wild

Director
International Agency for Research on Cancer

Introduction

Research underpins the development and implementation of all measures calculated to reduce the cancer burden. In addressing cancer research developed over the five-year period since the previous edition of *World Cancer Report* was published, all the contributors to this volume faced the challenge of identifying the most pertinent developments. At the same time, an interval of five years represents a suitable time frame to reappraise the descriptive epidemiology of cancer occurrence worldwide – with this edition of *World Cancer Report* incorporating GLOBOCAN 2012 data as they became available in the weeks immediately before publication – and to assess cancer occurrence in relation to the broad and rapidly expanding knowledge available for cancer control.

Cancer etiology and biology

Specification of cancer incidence and mortality data with varying degrees of confidence for virtually all countries is fundamental to cancer control. These data – particularly as they relate to specific tumour types – not only establish the burden of disease as it may impinge upon public health and clinical services planning; they also indicate, in many instances, causative relationships, the impact of socioeconomic differences, and priorities that may be accorded to particular cancer control options.

In many cases, differences in cancer incidence between countries reflect the decades-old perception that cancer is a disease of affluence. But this perception is inadequate, having been displaced initially by the level of tobacco-induced lung cancer in China and some other Asian countries, and more recently as cancer rates are expected to grow due to the impact of rapid increases in the prevalence of obesity, which is not confined to high-income countries. Cancers associated with chronic infections remain a particularly important challenge in low- and middle-income countries. These differing and evolving profiles of risk factors are occurring against the background of marked demographic changes, characterized in many countries by an ageing and growing population, which will see the greatest proportional increases in cancer burden falling on some of the economically poorest regions of the world. *World Cancer Report* illustrates that cancer is truly a global problem.

The impacts of tobacco, obesity, and infections are just part of a broad spectrum of other agents and risk factors that contribute to cancer development and that, together, influence the striking geographical heterogeneity in incidence rates. Certain of these risk factors are non-modifiable, for example race, familial genetic background, and reproductive and hormonal history. Exposure to carcinogens may result from what are often characterized as lifestyle choices, which include alcohol consumption and behaviour in relation to avoidable sun exposure. Finally, people may be exposed to carcinogens in circumstances over which they have little or no control, which is the case in relation to occupational exposures, the effects of pollution (e.g. of ambient air or water), and exposures resulting from the use of particular foods, drugs, or consumer products. Priorities accorded to avoiding the impact of various causative agents may be influenced by attributable risk: the proportion of total cancers for which a particular agent or circumstance played a causal role in the development. Such quantitative determinations may vary markedly depending on which community or country is under consideration. The overarching principle, however, is that people should not be knowingly exposed to circumstances likely to increase their risk of developing cancer.

Analytical epidemiological studies, often incorporating molecular and biological measurements made possible through the availability of, for example, archived blood and/or tissue samples, increasingly identify key biological processes whose relevance is initially indicated through experimental studies. The past five years has witnessed the identity of many cancer pathways being derived from whole-genome sequencing for multiple cases of each major tumour type, and from analogous comprehensive data of the "–omics" sciences, which encompass genomics, transcriptomics, proteomics, metabolomics, and the like. These data have been generated through international collaboration. Genomic and similar data provide singular insight into the nature of cancer cell development within the context of normal tissue. These data offer, for example, the prospect of improved detection of early-stage disease, but also more refined molecular classification of malignancy with relevance to descriptive and etiological epidemiology. They also reveal perturbed signalling and other alterations in cancer cells, which,

by definition, establish at least a basis for what is termed targeted therapy. Such opportunities are already being translated into clinical practice. The elucidation of biological changes that characterize cancer cells has been paralleled by observations at the cellular level to the effect that malignant tumours are inadequately understood as simply a mass of cancer cells: malignant tumours are also made up of fibrous, inflammatory, vascular, and immunological cell populations. Any one or more of these populations may be, at particular times, critical to tumour development and hence may offer an approach to prevention or therapy.

Reducing cancer incidence and mortality

Community awareness of the burden of cancer is inevitably focused on the development of improved therapies to the benefit of cancer patients, and media reports of "breakthroughs" are often the vehicle for reporting novel developments. The challenge posed by agent-specific resistance largely accounts for the reality of persistent disease despite incremental progress. This challenge highlights the certain benefits accruing from the adoption of measures to prevent cancer – benefits that accrue, however, in the longer term. For example, the impact of reduced cigarette consumption at the population level on lung cancer incidence came with a lag of some two to three decades. While smoking cessation is the most effective cancer preventive measure involving reduced exposure to proven carcinogens, cancer prevention involves a broad spectrum of initiatives, extending from vaccination – to ameliorate or prevent entirely the impact of relevant infections – through to screening tests aimed at detection, and consequently treatment, of early-stage disease.

National planning and international collaboration have emerged as critical to effective cancer control. Along with GLOBOCAN 2012 and the availability of genomic and related data, this edition of *World Cancer Report* highlights the WHO Framework Convention on Tobacco Control, the first international treaty negotiated under the auspices of WHO. As a response to the major recognized cause of cancer, tobacco control measures are almost universally applicable: what is effective in one country has been established as likely to be effective in most, if not all, countries. Although priorities must be accorded on a national basis, options for cancer control are increasingly available to countries and communities based on what has succeeded elsewhere. The inherent worth and benefit of collaboration across national boundaries is established for cancer control. Without doubt, national governments are seeking this internationally established evidence base, developed free from vested interests, for implementation at the local level.

The scope and design of *World Cancer Report*

Comprehensive texts on clinical oncology, often including sections on epidemiology, cancer biology, and public health matters, are published regularly and typically extend to thousands of pages. Likewise, annual reviews provide both researchers and clinicians with comprehensive coverage of recent publications in particular disciplines or concerning specified types of cancer or advances in therapies. *World Cancer Report* is readily distinguished from both these types of publication with reference to its scope and design. Concerning scope, emphasis on the global burden of cancer, and the environmental, lifestyle, and biological factors that might account for that burden, elevates the means of cancer prevention and their implementation to singular prominence. *World Cancer Report* does not address clinical care and the determination of optimal therapies, notwithstanding the exciting promise of these areas. Concerning design, *World Cancer Report* seeks to provide authoritative assessments through several different presentational approaches, while maintaining a publication of manageable length.

We, as editors, are grateful to the contributors to *World Cancer Report*, who, without exception, are aware of literally hundreds of publications that could be reasonably cited in the respective chapters were it not for length constraints that the present publication imposes. Because of these limitations, and the possibility that inevitable generalizations may preclude an appreciation of complexity, *World Cancer Report* features "boxes" in which a further group of investigators outline how certain precise issues are being elucidated with relevance to particular chapters.

The structure of *World Cancer Report 2014* is essentially in line with that adopted for earlier editions. However, *World Cancer Report 2014* is distinguished from its predecessors by the inclusion of a series of "Perspectives". Several prominent investigators have been invited to provide a personal viewpoint without the boundaries implicit in the headings of particular chapters. The perspectives offered are both distinctive and challenging, and serve to indicate the variety of issues immediately relevant to cancer control that either remain as challenges for further research or have yet to achieve their full potential by comprehensive implementation.

Cancer continues as a scourge of humankind. Increasingly, cancer is a particular burden on the populations of low- and middle-income countries. Cancer control may be achieved in large part through the insight gained from research, through detailed knowledge of how individuals and communities are affected, and through implementation of policies whose efficacy is often proven by the experience of other countries or groups of countries. The inclusion in this volume of several examples of national cancer control planning further demonstrates both the specific and general experiences from which lessons can be drawn in translating research-derived evidence into practice. *World Cancer Report 2014* therefore captures the dynamic state of both cancer research and cancer control worldwide with respect to what has been achieved, and what remains to be accomplished, to the benefit of the global community.

Bernard W. Stewart and Christopher P. Wild (Editors)
Lyon, December 2013

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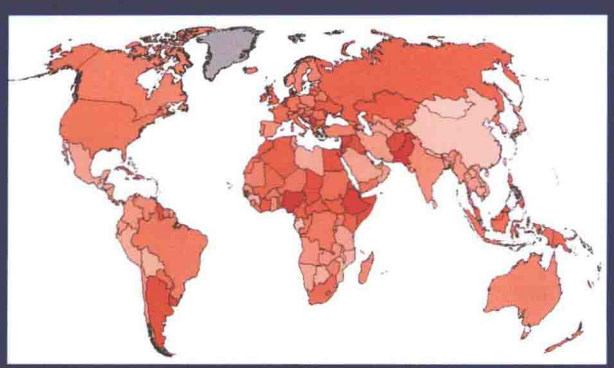
Cancer worldwide

Cancer affects all of humankind, but there are marked differences across local, national, and regional boundaries, particularly when considering specific tumour types rather than cancer as a whole. Epidemiological data on incidence of cancer and deaths caused by cancer vary enormously in coverage and quality between countries and regions worldwide, ranging from complete coverage by national cancer registries to population-based registries covering a part of the country, hospital-based registries, or no available data at all on cancer occurrence. In the absence of data, inferences must be drawn from surrounding countries to provide the best estimate possible. This edition of *World Cancer Report* provides data from GLOBOCAN 2012, the most current appraisal of the distribution of cancer worldwide. The findings show that high-resource countries have the highest incidence of cancer and also provide the best services for detection, diagnosis, and treatment, as may be inferred from mortality and survival data. The highest prevalence proportions of cancer also occur in these populations. The most common cancers include lung, breast, prostate, and colorectal cancers. In countries in epidemiological transition, these cancers are increasingly common but incidence of stomach, oesophageal, and liver cancers remains high. Data from low-resource countries show that cervical cancer is still often the most common cancer among women. In low- and middle-resource countries, incidence of particular tumours may be relatively low, but corresponding mortality data often reflect late-stage diagnosis as the norm and consequently poor clinical outcomes. Worldwide, differences in cancer incidence have been recognized for more than half a century as indicating different causes and, by inference, different opportunities for prevention. These lines of investigation have been greatly refined in recent years. Accordingly, cancer epidemiological data as now presented not only establish the burden of cancer but also underpin and very often confirm determinations of causation and opportunities for prevention, as elaborated in subsequent sections of this Report.



1.1 The global and regional burden of cancer

1 WORLDWIDE

David Forman
Jacques Ferlay

Bernard W. Stewart (reviewer)
Christopher P. Wild (reviewer)

Summary

- Cancer is a major cause of morbidity and mortality, with approximately 14 million new cases and 8 million cancer-related deaths in 2012, affecting populations in all countries and all regions. These estimates correspond to age-standardized incidence and mortality rates of 182 and 102 per 100 000, respectively.
- Among men, the five most common sites of cancer diagnosed in 2012 were the lung (16.7% of the total), prostate (15.0%), colorectum (10.0%), stomach (8.5%), and liver (7.5%). Among women, the five most common incident sites of cancer were the breast (25.2% of the total), colorectum (9.2%), lung (8.7%), cervix (7.9%), and stomach (4.8%).
- Among men, lung cancer had the highest incidence (34.2 per 100 000) and prostate cancer had the second highest incidence (31.1 per 100 000). Among women, breast cancer had a substantially higher incidence (43.3 per 100 000) than any other cancer; the next highest incidence was of colorectal cancer (14.3 per 100 000).
- Prevalence estimates for 2012 indicate that there were 8.7 million people (older than 15 years) alive who had had a cancer diagnosed in the previous year, 22.0 million with a diagnosis in the previous 3 years, and 32.6 million with a diagnosis in the previous 5 years.
- The worldwide estimate for the number of cancers diagnosed in childhood (ages 0–14 years) in 2012 is 165 000 (95 000 in boys and 70 000 in girls).
- For all cancers combined (excluding non-melanoma skin cancer) the highest incidence rates are associated with the high-income countries of North America and western Europe (together with Japan, the Republic of Korea, Australia, and New Zealand).
- More than 60% of the world's cancer cases occur in Africa, Asia, and Central and South America, and these regions account for about 70% of the cancer deaths.
- The distribution of cancer in world regions indicates marked, and sometimes extreme, differences with respect to particular tumour types. Such data are key to any understanding of causation, and hence the development of preventive measures.

Robust statistics on cancer occurrence and outcome are an essential prerequisite for national and regional programmes of cancer control and for informing the cancer research agenda. Since 1984, IARC has regularly published estimates of the global and regional burden of cancer in terms of both incidence and mortality [1]. Since 2001, such estimates have also been made available for all major countries of the world through the GLOBOCAN project [2,3]. These estimates are based on all sources of information available for any given country

Fig. 1.1.1. Fishermen in Bahia de Kino, Mexico. On a world scale, intermediate cancer incidence rates occur in Central and South America.