

# CHRONIC CONDITIONS RISING IN LOW- AND MIDDLE-INCOME COUNTRIES: THE CASE OF CANCER CONTROL

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Non-communicable diseases (NCDs) are increasing, especially in low- and middle-income countries. The number of new cancer cases is predicted to rise to over 20 million worldwide by 2025. These trends represent major challenges for sustainable development and are now being tackled by the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) through the Global Action Plan against NCDs. Reductions in smoking, alcohol drinking, obesity and physical inactivity are key prevention strategies for NCDs but some cancer-specific preventive tools, e.g., vaccination against HBV and HPV and screening, can also be extremely effective.

## Assembling the evidence for NCD action

The burden from non-communicable diseases (NCDs), also called chronic conditions, mainly including cancer, cardiovascular diseases, stroke, diabetes and chronic obstructive pulmonary disease, is rapidly increasing globally. The World Health Organization (WHO) has estimated that, of the total 57 million deaths worldwide in 2008, two-thirds (36 million) were caused by NCDs, with a further 15% rise to 44 million NCD deaths projected by 2020.<sup>1</sup> The largest proportional increases are predicted in Africa, South-East Asia and the Eastern Mediterranean region.

With the scale of the burden and its rapid spread globally, WHO has been raising awareness on the need to place a higher priority on NCDs. This culminated in the World Health Assembly on 27 May 2013 during which the Ministers of Health of 194 countries adopted the Global Action Plan for Prevention and Control of NCDs.<sup>2</sup> WHO has, therefore, the mandate to coordinate Member States, United Nations (UN) agencies (including the International Agency for Research on Cancer [IARC]) and other relevant public and private stakeholders to address the prevention of NCDs. WHO has engaged in establishing a set of voluntary global targets, including a 25% relative reduction of premature mortality from NCDs by 2025 (Figure 1). The target of a 25% reduction was chosen because many high-income countries achieved

improvements of that size in premature NCD mortality in the last decade or two. A Global Monitoring Framework including 25 indicators (Figure 2) has been established to assess progress in the implementation of national strategies and plans on NCDs.

## The causes of the rising NCD burden

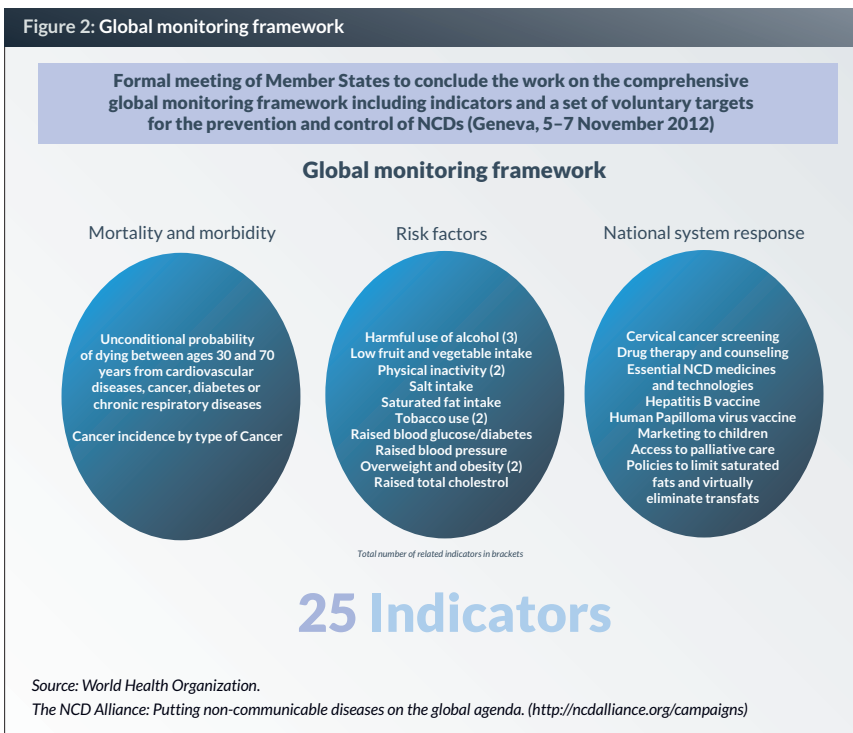
The second part of the twentieth century witnessed enormous progress in improving health and survival around the world. Average life expectancy at birth rose from 48 years in 1950–1955 to 68 years in 2005–2010.<sup>3</sup> Increasing longevity and slow declines in fertility has led to a rapid growth and ageing of the world's populations, particularly in low- and middle-income countries. The transformation in the scale of the NCD burden arises from such demographic, as well as epidemiologic transitions.<sup>4,5</sup> The control of malnutrition and pandemics of infection (such as TB and malaria) has brought about a reduction in deaths from communicable diseases. That NCDs have displaced communicable diseases as the major cause of death is also linked to higher average life expectancy and an increasing adoption of behaviours often associated with “western” lifestyles, most notably in countries transiting towards higher levels of human development. They include a rising prevalence of smoking, overweight and obesity, and physical

Figure 1: Voluntary global NCD targets for 2025



Japan and the Republic of Korea), life expectancy at birth now exceeds 80 years. Perhaps contrary to common perception, the more highly developed regions of the world do not exhibit the highest age-standardized death rates of NCDs (Group II in Figure 3).<sup>3</sup> If the underlying population age structure was equal – as seen by comparing the age-standardized and non-standardized (crude) death rates in Figure 3, Africa would have the highest NCD mortality worldwide, in relative terms. It is therefore essential to bear in mind that low- and middle-income countries often experience a “double burden” of disease: still rather high death rates of infectious diseases alongside a high and ever-increasing burden from the major NCDs (Figure 3).

Figure 2: Global monitoring framework



There are different ways to establish priorities and achievable targets in the prevention of NCDs and the focus of WHO has been on common, modifiable risk factors shared across the spectrum of key diseases (Figures 1 and 2). In addition, high-priority medical interventions had to be feasible and potentially cost-effective in primary care settings in any country, i.e., so-called best-buys.<sup>6</sup> Obviously, best-buys vary markedly from one country to another according to the variable impact of different NCDs and, in particular, individual cancer sites.

**Cancer: A multifaceted disease and a major cause of death**

Cancer is a complex disease with its own epidemiological transition: as countries move towards high levels of

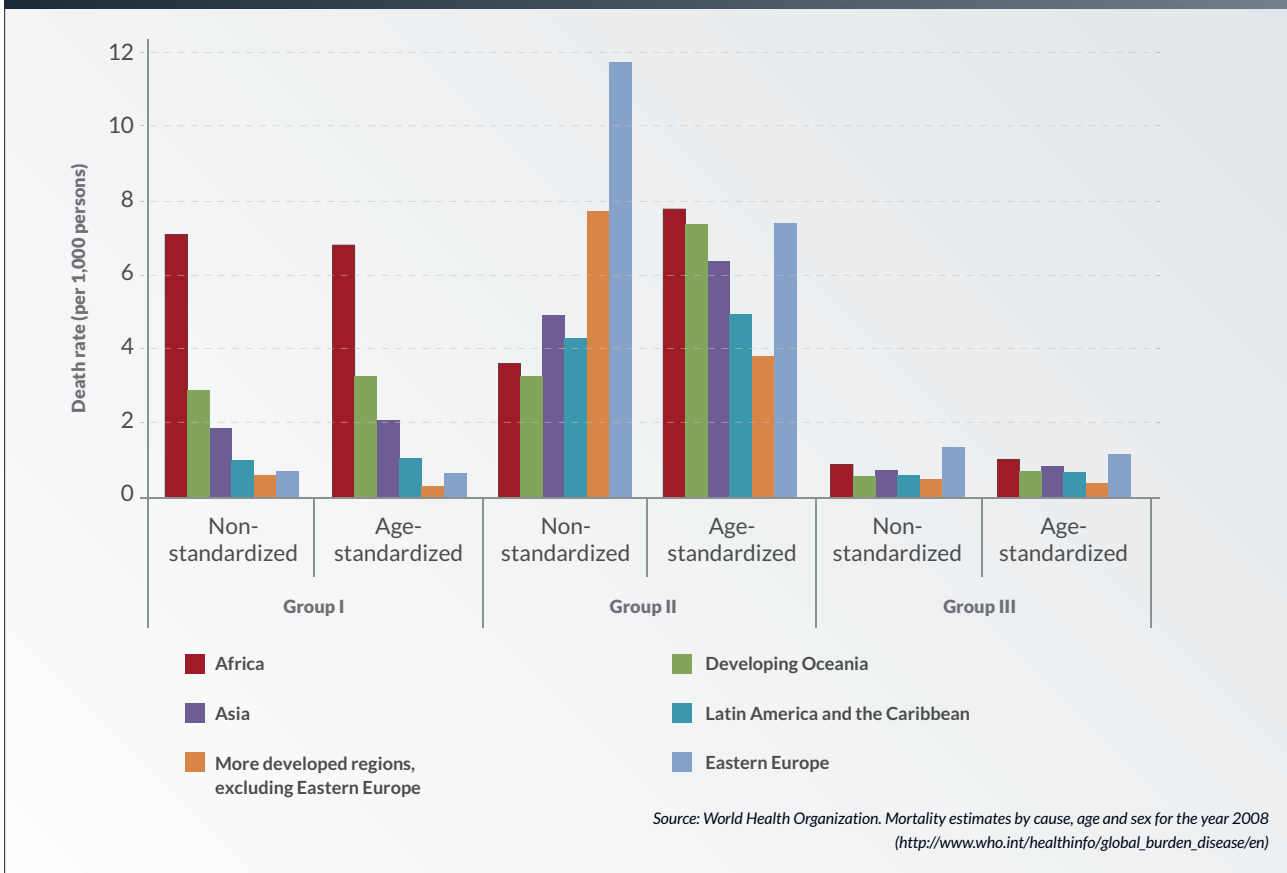
inactivity; the major risk factors for the most common NCD types: cancer, cardiovascular diseases, stroke, diabetes and chronic obstructive pulmonary diseases.

**Comparing the NCD burden and priorities**

In a number of high-income countries (e.g., Australia, Canada, France, Italy, Spain, Norway, Sweden, Switzerland, Israel,

human development, cancers associated with infection and poverty (e.g. cancers of the stomach, liver and cervix) are surpassed in their magnitude by those more associated with affluence (e.g. cancers of female breast, prostate and colon). In high-income countries, the control of infectious disease and the lowering of death rates of cerebrovascular disease and stroke, have led to cancer becoming increasingly one of

Figure 3: Non-standardized and age-standardized death rates (World population) by cause and regions, 2008<sup>3</sup>; Group I = Communicable diseases; Group II = Non-communicable diseases; Group III = Injuries

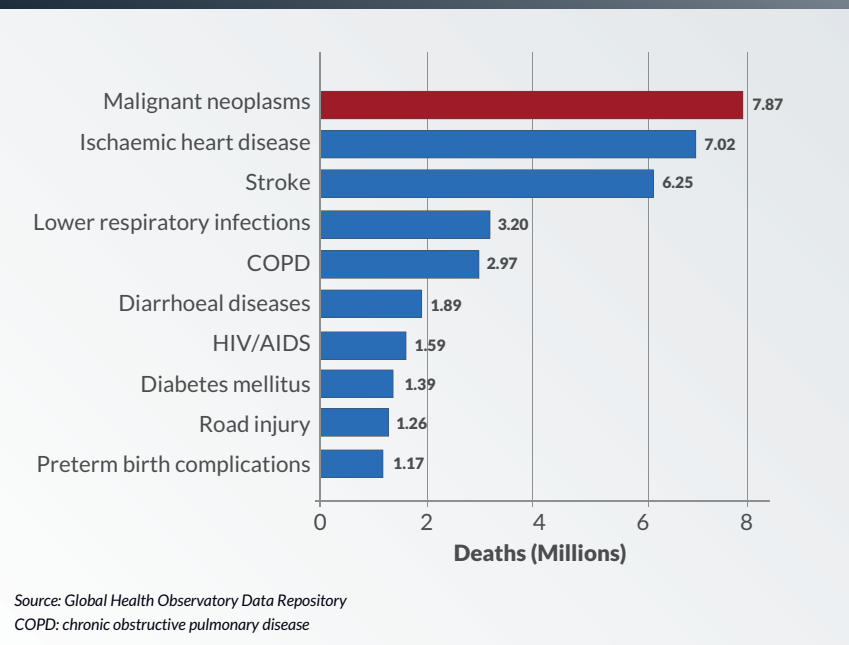


the main obstacles to continued improvement in life expectancy. The flipside, as for NCDs overall, is, however, the double burden of infection-related cancers and increasing rates of cancers associated with Western lifestyles, as observed in low-income settings, for example, in Uganda<sup>7</sup> and Zimbabwe.<sup>8</sup>

Cancer is a very important cause of death in human populations. We will examine it in terms of “burden”: as numbers of new events (cancer cases, cancer deaths), an indicator of the scale and thus potential human and economic cost of the disease, as well as age-standardized incidence rates that allow comparisons across populations independently from the age structures.

In examining the cancer profiles worldwide, we mainly used four quartiles of the UNDP Human Development Index (HDI)<sup>9</sup> as markers of socioeconomic development, given the HDI takes into account levels of national education and life

Figure 4: The 10 leading causes of death worldwide<sup>9</sup>



expectancy as well as income.

According to WHO estimates for 2011 (<http://who.int/mediacentre/factsheets/fs310/en/>), the 7.9 million cancer deaths outrank deaths from every other major cause

Figure 5: The five most common causes of cancer incidence and mortality by sex categorising countries according to four levels of human development index<sup>9</sup>



of death worldwide (Figure 4). Further, an estimated 4.2 million people died between the ages 30 and 69 from cancer in the same year, representing the most common form of premature death globally and almost one-third of the total premature NCD mortality burden (of 13.8 million). Figure 5 illustrates the complexity of cancer by portraying the five most common causes of cancer incidence and mortality by sex, as estimated in GLOBOCAN in 2012,<sup>10</sup> categorizing countries according to four levels of HDI<sup>9</sup> and separating the vastly-populated countries of China and India. There are then 16 different types of cancer that can be considered major forms of cancer in terms of frequency of occurrence or death in one or more of these regions or countries, 10 in men and 12 in women.

Cancer thus differs from the other NCDs by including a wide range of important cancer sites and types that vary substantially with respect to their geographic distribution, aetiology and treatment options.<sup>11</sup> The IARC Monograph series has recently provided up-to-date information on cancer sites associated with more than 100 carcinogenic

agents.<sup>12</sup> Although some risk factors, notably smoking, can affect a large number of cancer types<sup>13-18</sup> there is no universal risk factor for cancer. In addition, different risk factors, including those affecting early stages and late stages of carcinogenesis, are typically involved in the causation of cancer in any given site.<sup>19</sup> As is apparent in Figure 5, distinct patterns of cancer types at a regional and national level exist but prevention strategies should ideally be implemented even in regions where those cancers are at present relatively uncommon, given the full extent of cancers related to those risk factors will appear only in the future. Predictions of the future cancer burden derived from the recent trends observed in the major cancers alongside UN demographic projections, suggest the number of new cases of cancer will surpass 20 million as early as 2025, a 41% increase from 2012.<sup>20</sup>

### Confronting the rise of cancer: The role of prevention

What can be done to tackle the impending cancer epidemic?

Table 1: Number of new cancer cases<sup>a</sup> in 2008 attributable to infectious agents, by geographic region<sup>25</sup>

	Number of new cases in 2008	Number attributable to infection	PAF (%)
<b>Africa</b>			
Sub-Saharan Africa	550,000	180,000	32.7%
North Africa and west Asia	390,000	49,000	12.7%
<b>Asia</b>			
India	950,000	200,000	20.8%
Other central Asia	470,000	81,000	17.0%
China	2,800,000	740,000	26.1%
Japan	620,000	120,000	19.2%
Other east Asia	1,000,000	230,000	22.5%
<b>America</b>			
South America <sup>b</sup>	910,000	150,000	17.0%
North America	1,600,000	63,000	4.0%
<b>Europe</b>	3,200,000	220,000	7.0%
<b>Oceania</b>			
Australia and New Zealand	130,000	4,200	3.3%
Other Oceania	8,800	1,600	18.2%
<b>More developed regions<sup>c</sup></b>	5,600,000	410,000	7.4%
<b>Less developed regions<sup>d</sup></b>	7,100,000	1,600,000	22.9%
<b>World</b>	12,700,000	2,000,000	16.1%

PAF=population attributable fraction. <sup>a</sup>Numbers are rounded to two significant digits. <sup>b</sup>Includes Mexico.

<sup>c</sup>Total for Japan, North America, Europe, and Australia and New Zealand. <sup>d</sup>Total for all other regions.

Many of the NCD risk factors mentioned in Figure 1 are highly relevant to the prevention of cancer of the lung (smoking), and fairly relevant to the one or other of cancers of the breast and colon (overweight and lack of physical activity, and alcohol). These three cancer sites have lower incidence and mortality in the lowest-income countries but they are increasing because of less favourable trends in smoking than in high-income countries;<sup>21</sup> and rapid changes in lifestyle e.g., increase in obesity and sedentary life, and reproductive habits, i.e., decrease and postponement of childbearing that are associated with breast cancer increases. Some caution is needed in interpreting these global estimates given the variable quality and coverage of sources of cancer registration (see <http://globocan.iarc.fr>), vital registration,<sup>22</sup> and assumptions in predicting the future cancer burden.<sup>23</sup>

However, some preventive tools target individual cancer sites, but not necessarily other NCDs, can be extremely effective and potentially cost-effective. For instance, among the four cancer sites that show much more elevated incidence and mortality in low- than high-income countries (cervix, liver, stomach and oesophagus),<sup>24</sup> all except cancer of the oesophagus are predominantly caused by chronic infections, although tobacco and/or alcohol consumption also play a role.

Conservative estimates showed that about two million cancer cases per year (16% of the global cancer burden) are attributable to a few chronic infections.<sup>25</sup> Huge variations are

seen by continent and country. The fraction of cancer attributable to infections is largest in sub-Saharan Africa (32.7%) and China (26.1%) and smallest in Australia and New Zealand and in North America ( $\leq 4\%$ ) (Table 1). In addition, at a country-level, the fraction of cancer attributable to infections also tends to be larger in the poor than in the rich making the prevention or eradication of these infections a powerful tool to overcome health inequalities in cancer incidence within and between countries. It is therefore highly appropriate that vaccination against two of the principal cancer-causing infectious agents, i.e., human papillomavirus (HPV) (100% of cancer of the cervix, the majority of cancers of the ano-genital tract, and some in the oro-pharynx); and hepatitis B virus (HBV) (the most important cause of hepatocellular carcinoma worldwide) are included in the Global Monitoring Framework (Figure 2); these are however not among the priority targets (Figure 1).

### Confronting the rise of cancer: The role of early detection and screening

Another feature of the majority of cancers is that they have a long latent phase and are preceded by pre-neoplastic lesions. Early detection and treatment of cancer or precancerous lesions allowed substantial declines in cancer mortality in high-income countries and would greatly improve survival in less developed countries in which access to expensive cancer treatment is limited.<sup>26</sup> Firm evidence of the efficacy of

screening programmes in the reduction of cancer mortality exists for three cancer sites: the cervix uteri, breast and colon-rectum.<sup>27-29</sup>

Cervical cancer screening stands out compared to other cancer screenings as it allows the recognition and treatment of precancerous lesions using relatively inexpensive and minimally invasive tests (Pap smear, visual inspection techniques and HPV-testing) that can be chosen according to different country settings. The superiority of HPV-testing compared to cytology in terms of sensitivity, duration of negative predictive value and reproducibility of test results across different diagnostic laboratories has been demonstrated by a number of randomized clinical trials and prospective data in high- and low-income countries.<sup>30</sup> The superiority of HPV-testing has been recently recognized in the new WHO Guidelines for cervical cancer screening<sup>31</sup> and a simple and cheap HPV test, careHPV™ (Qiagen), has proved to be very accurate. Unfortunately, HPV vaccination and HPV-testing had been evaluated in the Global Action Plan against NCDs before the cost of the HPV vaccines and HPV test started to decrease. They have both been recently reclassified as best-buys in a re-evaluation of the basic cancer package<sup>32</sup> to which WHO participated.

There remains an important gap between the feasibility of the secondary prevention of cardiovascular diseases and cancer. Screening approaches in cancer (early detection of neoplastic or pre-neoplastic lesions that require surgical ablation) are more complicated, expensive and potentially more harmful than those in cardiovascular diseases (detection and medical treatment of predisposing conditions such as hypertension and hypercholesterolemia).

### **Rearticulating cancer control: Therapy and palliation in low-income settings**

Finally, cancer patients require specialized centres in which accurate diagnoses and multi-therapeutic approaches can be made available. The Global Action Plan against NCDs endorsed, however, only essential medicines and technologies that can be used in primary care settings. The only clinical intervention for cancer explicitly included was, therefore, palliative care using oral morphine, a cheap and simple intervention that is, however, rarely available in low-income countries because of fears of inappropriate drug use.<sup>33</sup>

In an expanded cancer care package not restricted to best-buys in low-income countries, WHO also included mammography, breast cancer treatment, screening for cancer of the colon and oral cavity, and treatment of paediatric cancers.<sup>32</sup> Obviously, screening programmes need

to be tailored to the needs and resources of different countries. In high-income countries, for instance, the randomized evidence indicates that around one breast cancer death would be prevented in the long term for every 400 women aged 50–70 years who would regularly have mammography over a 10-year period.<sup>34</sup> In low- and middle-income countries breast cancer rates are still lower than in high-income countries and resources might be better used to raise awareness and encourage more women with palpable breast lumps to seek and receive treatment in a timely manner.<sup>35</sup>

Treatment of cancer patients is, however, a strong aspiration in every country. In middle-income countries it is increasingly common that families are impoverished and health expenses overcharged by the purchase of sometimes inappropriate and unnecessarily expensive cancer treatments. It would be, therefore, essential that WHO and other UN agencies (including IARC and the International Atomic Energy Agency) fully articulate the term of “cancer control” and re-assess which essential medicines and technologies should be recommended for cancer in the low- and middle-income countries (see Mendis et al,<sup>33</sup> for a similar exercise on the management of cardiovascular diseases and diabetes).

In conclusion, the mobilization against cancer still requires much more global and regional coordination of resource-linked policy and strategy. At present, individual countries must often determine their own course of action with varying degree of success. ●

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*Dr Silvia Franceschi was trained as an MD and gynaecologist and obtained a Masters degree in Epidemiology at Oxford under the supervision of Sir Richard Doll. After having led the Epidemiology Unit of the Aviano Cancer Center, she became Head of the Infections and Cancer Epidemiology Group at the International Agency for Research on Cancer (IARC), Lyon, France in 2000. She led international studies on the relationship between infectious agents and cancer, most notably human papillomavirus and HIV. She is the author of over 1,000 publications in peer-reviewed journals. She is Special Advisor to the IARC Director for the collaboration with the World Health Organization and other United Nations agencies.*

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2005–2010. He has a PhD in epidemiology from the London School of Hygiene and Tropical Medicine, and degrees in statistics from the University of Aberdeen and the University of Leicester. His areas of research are in the descriptive epidemiology of cancer, including the estimation of the global cancer burden, the analysis and interpretation of time trends of cancer and future predictions, and their linkages with human development transitions. There is an ever-pressing need for a

sustainable expansion of the coverage and quality of cancer registries in less developed countries to improve cancer surveillance and planning. A major interest and remit of the Section is therefore in support of the implementation and development of population-based cancer registries in these settings through the Global Initiative for Cancer Registration in LMIC (GICR, <http://www.gicr.fr>).

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