Cancer is a global and growing, but not uniform, problem. An increasing proportion of the burden is falling on low-income and middle-income countries because of not only demographic change but also a transition in risk factors, whereby the consequences of the globalisation of economies and behaviours are adding to an existing burden of cancers of infectious origin. We argue that primary prevention is a particularly effective way to fight cancer, with between a third and a half of cancers being preventable on the basis of present knowledge of risk factors. Primary prevention has several advantages: the effectiveness could have benefits for people other than those directly targeted, avoidance of exposure to carcinogenic agents is likely to prevent other non-communicable diseases, and the cause could be removed or reduced in the long term—eg, through regulatory measures against occupational or environmental exposures (ie, the preventive effort does not need to be renewed with every generation, which is especially important when resources are in short supply). Primary prevention must therefore be prioritised as an integral part of global cancer control.

Introduction

We have three main goals in this Series paper: to show that cancer is a global problem, although not a uniform one, with an increasing proportion of the burden falling on low-income and middle-income countries; to describe some of the successes and failures in addressing of cancer prevention at a population level; and to argue that primary prevention is a particularly effective approach to tackle the impending increases in cancer on a global scale. We limit our focus to primary prevention, and only tangentially discuss early detection and screening, albeit recognising that primary prevention should be a complement to secondary prevention and treatment in overall cancer-control strategies. We make these points in view of the political focus on the control of non-communicable diseases (NCDs) after the high-level meeting of the UN General Assembly in September, 2011.1

One strong argument in favour of primary prevention is that the cause could be removed or greatly reduced in the long term. This potential is especially important when resources are scarce, and represents a marked distinction from early detection, screening, and therapies. Primary prevention might also have an effect for people other than those who are directly targeted by it. A typical instance is herd immunity, in which vaccination can prevent the disease in many more individuals than only those vaccinated. Similarly, banning of smoking in public places has a positive effect not only on the target population—those potentially exposed to second-hand smoke—but also on smokers, who will tend to smoke less, or quit.2 This situation is less evident with therapies or screening, when inclusion of many individuals is generally necessary for preventive success,3 although wider benefits of screening could result from increased awareness in a population, and the potential for such collateral benefits merits assessment. Additionally, primary cancer prevention can have benefits in addition to those for cancer, in view of the shared risk-factors with several other NCDs.

Globalisation of cancer

The Human Development Index (HDI) is a useful classifier for the globalisation of cancer,1 because it takes into account education and life expectancy as well as national income, with countries categorised into one of four levels of development: low, medium, high, and very high. Although communicable diseases and nutrition-related disorders are still the most common causes of death in low-HDI countries, they are projected to be overtaken by NCDs, including cancer, by 2030.5 The projected increase in global cancer burden—from 12.7 million new cases in 2008, to 22.2 million by 2030—indicates population growth and an evolving age distribution together with other important changes in underlying incidence, allied to the prevalence and distribution of risk factors. For example, the spread of tobacco use in low-income and middle-income countries will exert a major effect on cancer burden in the coming decades.5 In relation to obesity, for the first time more people are overweight than are underweight worldwide. By 2015, NCDs associated with over-nutrition are estimated to surpass under-nutrition as the leading causes of death in low-income countries.7

Key messages

• Primary prevention is the most effective way to fight cancer
• Prevention needs to be integrated with early diagnosis and therapies
• A considerable increase in the absolute numbers of cancer cases and deaths is foreseen in low-income countries in the next decades; therefore urgent action is needed
• Cancer is a heterogeneous group of diseases with causes spanning from infectious agents to behavioural and environmental exposures—a one-size-fits-all strategy for cancer control will not succeed
• Primary prevention has the advantage of preventing other (communicable and non-communicable) diseases that have risk factors in common with cancer; by contrast with therapies, prevention (in some cases) does not need to be renewed at each generation, which is an advantage in low-resource settings

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Global patterns and mortality

In 2008, 28.8 million people globally were estimated to be within 5 years of being diagnosed with cancer, with close to half of these living in very high HDI countries, which comprise only a sixth of the world's population. By contrast, the 3.4 billion people living in low-HDI and medium-HDI countries have only slightly more than a third of the global cancer prevalence (10.8 million cases). This disparity is due to two components: higher rates of newly diagnosed cancers in the high-HDI and very-high-HDI countries, and lower survival rates in medium-HDI and low-HDI countries.
Incidence for a given cancer can vary by one to two orders of magnitude by geographical region—eg, breast cancer (figure 1A). According to GLOBOCAN,7 breast cancer incidence in 2008 was almost five times greater in western Europe than in eastern Africa, taking into account the different age structures (figure 1B).7 An inverse association is noted with cervical cancer, the second most common cancer in women worldwide.9

Mortality figures also differ by geographical region, but the differences are often less pronounced across countries and regions than they are for incidence—eg, breast cancer mortality varies only three-fold by region (figure 1B). Figure 2 shows a similar tendency for prostate cancer, with smaller differences in mortality across regions (a nine-fold difference) than in incidence (>25-fold difference).

These patterns mean that many more new cancer cases are diagnosed for each person dying from cancer in high-HDI countries than in low-HDI countries. As with prevalence, this is due both to higher incidence in high-HDI countries and to lower survival proportions in many low-HDI countries.10,11 Africa especially lags far behind in terms of capacity for cancer treatment and care; many African nations have no pathology or radiotherapy services,12,13 which gives one measure of the gap between low-HDI and high-HDI countries. Cancers are also frequently diagnosed at a much more advanced stage in low-HDI countries. Few comparative population-based studies of survival are available in Africa, but 5 year survival from breast cancer in The Gambia and Uganda was substantially worse than in China, Singapore, South Korea, and Turkey.10 However, the difference in the ratio of incidence to mortality cannot be attributed solely to lower survival in less-developed countries and is probably due also to earlier detection of the disease, including through screening, in high-HDI countries. Early detection, diagnosis, and screening offer major opportunities to reduce mortality from breast and cervical cancer in low-income and middle-income countries.14,15 Screening, however, can bring its own risks of over-diagnosis and overtreatment16—a topic of intense debate.17–19

Cancer transition: time trends

Time trends in cancer incidence and mortality vary substantially for different cancers and countries. The cancer transition in low-HDI countries combined with growing and ageing populations means that many countries are facing a double burden of cancer—ie, the burden associated with infectious agents combined with that associated with an increasingly westernised lifestyle.

The situation in high-income countries is more nuanced. On the one hand, some countries have encouraging trends for mortality—eg, in the USA, cancer mortality decreased by 23% in men and 15% in women between 1990 and 2008.20 This pattern, also apparent in other high-income countries, is largely due to changing smoking habits, especially in men, but it also affects cancers not directly associated with smoking (eg, prostate and breast cancer) or weakly associated with it (eg, colon cancer). On the other hand, incidence for some cancer types is increasing in several medium-HDI and high-HDI countries. The work by Bray and colleagues,4 based on longitudinal data from high-quality cancer registries,21 shows that in medium-HDI and high-HDI settings decreases in cervical and stomach cancer incidence seem to be more than offset by increases in the incidence of cancers of the female breast, prostate, and colorectum. Increases in breast cancer in low-HDI countries will be largely due to changes in reproductive practices, with women choosing to have fewer children, have their first pregnancy later in life, and breastfeed for a shorter period.

Some specific areas of concern exist in higher-HDI countries in relation to cancer trends, such as rising rates and marked geographical differences (figure 3) for testicular cancer,22 colorectal cancer in young people in the USA,23 and liver cancer (the rise in liver cancer possibly due to increased incidence of infection with hepatitis C virus, rising obesity rates, and misuse of alcohol).24,25

What are the major risk factors for cancer?

The WHO Global Status Report on NCDs addresses several risk factors for cancer, including tobacco use, alcohol consumption, little physical activity, and unhealthy diet.26 However, cancer is far more heterogeneous than are...
other NCDs, and needs a nuanced and geographically-specific policy, rather than a generalised one focusing on a narrow set of shared personal and behavioural risk factors. A prime example is chronic oncogenic infections, which cause an estimated 16% of cancers globally but have an order of magnitude difference in regional contribution. Application of an understanding of the relative importance of risk factors and appropriate prevention strategies to a regional or national level globally would contribute greatly to prioritisation of cancer-control planning in low-HDI and medium-HDI countries.

**Tobacco**

Reduction of tobacco consumption through primary prevention could contribute the largest number of cancer deaths avoided globally. The benefits of not starting to smoke and of stopping smoking have been clearly shown. Anti-tobacco activities in very-high-HDI and high-HDI countries have probably prevented millions of cancers overall in recent decades, although preventive measures are far from sufficient in most countries. Full implementation of the WHO Framework Convention on Tobacco Control by signatories to this binding international treaty is therefore vital. Priority must be given to international multisector cooperation to prevent the spread of tobacco use in low-income and middle-income countries.

The evidence base for the success of public-health interventions against tobacco is strong. The near 40% reduction in lung cancer deaths in men between 1991 and 2003 in the USA can be attributed to smoking decreases in the past half century. However, although adult smoking prevalence has decreased overall, socioeconomic gradients in smoking still persist and require consideration in further implementation of tobacco control measures.

**Occupational carcinogens**

Considerable progress has been made in occupational cancer prevention in high-HDI countries, starting as far back as 1921, when the first International Labour Organization report on aromatic amines was published. Elimination or substantial reduction of exposure to asbestos, aromatic amines, benzidine, benzene, and other carcinogens in high-HDI countries has prevented many thousands of cancer cases. Good evidence exists of the decline in bladder cancer due to reduced exposure to aromatic amines in the UK and USA, and less compelling evidence is available for leukaemias due to benzene. The effects of asbestos exposure persist for decades after exposure cessation, and the peak of mesotheliomas and lung cancers attributable to asbestos has not yet been observed in many countries. Nonetheless, a decrease in mesothelioma risk has already been recorded in the USA and Sweden, where strict measures to control asbestos exposure at work were introduced first, in the early 1970s, and among workers of former asbestos industries more than 30 years since cessation of exposure. Despite progress, occupational carcinogens remain a priority because of the unequal distribution of exposures in society. Emerging problems include the unacceptable export of high-risk occupational exposures to low-HDI countries and the inadequate protection of workers in many such industrial settings.

**Diet, obesity, and physical inactivity**

Obesity is a risk factor for breast (post-menopausal), colorectal, endometrium, kidney, oesophageal, and pancreatic cancers. Alcohol is associated with liver, upper aerodigestive tract, breast, and colorectal cancers. The consumption of red and processed meats and a diet low in fibre have been associated with colorectal cancer. The consumption of red and processed meats and a diet low in fibre have been associated with colorectal cancer. The consumption of red and processed meats and a diet low in fibre have been associated with colorectal cancer. The consumption of red and processed meats and a diet low in fibre have been associated with colorectal cancer. The consumption of red and processed meats and a diet low in fibre have been associated with colorectal cancer.

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In women, cervical cancer accounted for about half of the infection-related burden of cancer; in men, liver and gastric cancers accounted for more than 80%. Notably, around 30% of infection-attributable cancers occur in people younger than 50 years.

One of the most important advances in cancer prevention in the past decade was the development and implementation of HPV vaccination to prevent cervical cancer. A priority should be to ensure that the vaccine reaches the populations with the highest prevalences of HPV infection and cervical cancer. This target is demanding in terms of sustainability in low-HDI and medium-HDI countries, and in attainment of the targeted coverage, which is set at greater than 70%. Successful delivery of HPV vaccine in such settings will need multiple barriers to be addressed, including sociocultural issues. Challenges are substantially greater than in high-HDI countries—eg, the difficulty to reach girls for three doses in settings where school attendance is low. In this respect, the observations of strong immune responses with two or even one dose of HPV vaccine have major implications for compliance. Careful assessment of how mass vaccination will interact with screening activities for cervical cancer is needed, as is the degree of benefit of vaccination of men.

Another effective vaccine for cancer prevention is the one against hepatitis B virus. Again, implementation is particularly relevant to lower-HDI countries in view of the higher prevalence of the infection. Reductions in hepatocellular carcinoma incidence are already being observed, where the vaccine was introduced in the 1980s. Despite these successes, challenges remain—eg, the most common route of infection in Asian countries is vertical transmission from mother to child, but screening of pregnant women and passive immunisation with human hepatitis B immunoglobulin are not affordable for many low-income and middle-income countries. The unsolved problem for the poorest countries is the cost of the vaccine.

Environmental carcinogens

The extent of exposure to environmental carcinogens is unknown, particularly in low-HDI countries, although the burden can add up to several hundred thousands, even if estimates are limited to the main known carcinogenic exposures—arsenic, air pollution, aflatoxin, polychlorinated biphenyls, radon, and asbestos. The effects of additional exposures such as metals (chromium, cadmium, nickel, beryllium) and other known human carcinogens are difficult to quantify because almost no information is available for the number of exposed people. Economic growth leading to urbanisation and industrialisation in Africa, for example, is resulting in increasing exposures to modern environmental health hazards. As a report from the UN Environment Programme has stressed, the estimated costs of poisoning from pesticides alone in sub-Saharan Africa exceeds the total annual amount of overseas health-related...
development aid, although the contribution of chemical exposures to cancer burden is unknown.

Exposure to diesel exhaust—emissions classified as human carcinogens (group 1) by an International Agency for Research on Cancer (IARC) Working Group—is almost universal. Exposure through the use of diesel generators in residential settings is a largely overlooked hazard in many low-HDI countries. An issue that is still contentious is the effect of electromagnetic fields—this is an area of potential public health importance, but for which scientific evidence is not definitive. Other uncertain but important areas include non-occupational exposure to pesticides, to disinfection by-products, and to several solvents. Residential exposure to radon is a relevant problem in several areas of the world, and causes an increased risk of lung cancer.

Another environmental and preventable risk factor for skin cancer is excessive exposure to sunlight, including to sunbeds. Uniform increases in melanoma incidence across all ages have been noted in many European countries. Strategies aimed at reduction of sun exposure across different age groups provide important evidence for primary prevention as shown, for example, in the community-wide SunSmart programme in Australia.

Causes of causes

Tackling of the worldwide NCDs epidemic will be impossible if prevention is limited to promotion of health behaviours at the individual level. Low physical activity, for example, is closely associated with changes in living conditions that promote or facilitate a sedentary behaviour—the so-called built environment. Additionally, the quality of food consumed is associated with income and education and is being driven by availability and industry marketing. Economic growth in low-HDI countries is likely, in the absence of government regulation, to translate to further consumption of unhealthy commodities. Therefore, prevention is hardly feasible in the absence of structural changes that also include taxation, regulation, or bans (such as the successful ban of trans-fat acids in New York, USA in the context of a more general strategy to promote health). Effective introduction of such societal changes will affect vested interests and meet opposition, both direct (including lobbying and bribing) and indirect (through creation of doubt and delay in achievement of change).

A clear example of a cause of causes is socioeconomic status. In high-HDI countries, cancer still shows higher incidence and mortality in low socioeconomic groups than in high socio-economic groups, which is not completely explained by known risk factors, suggesting that the existence of other unknown determinants is associated with low socioeconomic status. Thus, tackling of poverty could also affect risk-factor distribution and the effectiveness of primary prevention of cancer.

Primary prevention

An overall estimate of preventable cancers

Genetic variants are unlikely to account for a major proportion of cancer cases; 5–10% are attributable to highly penetrant mutations such as in BRCA1 or mismatch repair genes, and an unknown proportion to the interaction between low-penetrant variants and external risk factors. For a long time, since the publication of Doll and Peto’s The causes of cancer containing estimates for the USA, the proportion of cancers in a population that is attributable to known risk factors has been a controversial issue. The most recent estimates have been provided by Parkin and colleagues for the UK. Parkin and colleagues’ report has several merits: past exposures are considered in relation to present cancers (to take latency into account); risks are estimated with attainable levels of exposure as reference categories; and 14 risk factors and 18 cancer sites are considered. The conclusion is that 45% of cancers in men and 40% in women could have been prevented had risk factors been reduced to the optimum levels or eliminated (e.g., tobacco).

Estimates of the proportion of cancers that can be prevented will differ substantially geographically, showing the prevalence of different risk factors, hence the need to set prevention priorities at a local and regional level. This need is best characterised within the categories of the low-HDI and medium-HDI countries, where the estimates from the USA and the UK cannot be directly applied. In simplification of messages for political effect, it is important to avoid a failure to adapt and support solutions that will bring the most benefits for public health to particular settings.

Threats to primary prevention and integration with care

There are reasons to believe that an exclusively individualised approach to prevention is unlikely to have a strong effect on cancer incidence, whereas societal actions are likely to be more effective. For example, Elbrahim and Davey Smith reviewed the evidence on health promotion in high-income countries and concluded that there is little evidence that large and expensive health-promotion programmes aimed at individuals have been successful. They also argue that there is even less reason to believe that such interventions focused on individual lifestyle will be successful in low-income and middle-income countries, and findings consistent with this view have been reported from a randomised trial in India. Industries associated with unhealthy commodities (such as tobacco, alcohol, and foods high in sugar, fat, and salt) support initiatives aimed at individual behavioural change rather than regulatory controls, but only regulatory controls might deliver the necessary effects. An analogy between personalised medicine and personalised prevention would be unhelpful. Individualised therapy based on the molecular genetics of a specific tumour is not necessarily a valid model for an analogous strategy of personalised prevention.
needed is a greater investment in implementation research to understand how to translate effectively from evidence that a particular prevention strategy can work to one which does work in a specific health-care setting.

There are also reasons unrelated to science that are a cause for concern in the implementation of cancer prevention. The tendency to reduce public expenditure and to privatise parts of the health-care systems will affect preventive activities such as health promotion, which are not appealing for investment from the private sector.88 This tendency is especially evident in a period of economic crisis, as the case of Greece shows.89 The reduction in the budgets available for primary care will probably affect the ability of general practitioners to promote educational messages. In the USA, Europe, and Canada less than 4% of the public budget is spent on cancer prevention (including all types).89 Additionally, because cancer usually takes several decades to develop, investment in prevention takes time to show results. Politically and in wider society, therefore, a commitment to cancer prevention needs vision, leadership, and a commitment to the next generations (panel). Fineberg81 has described the reasons why prevention is not implemented in practice, including that the success of prevention is invisible, that statistical lives have little emotional effect, that prevention is expected to produce a net financial return (whereas treatment is expected only to be worth its cost), and that commercial interests as well as personal, religious, or cultural beliefs could conflict with disease prevention.81

Patterns of change are now global—ie, the free market approach has permeated the world and has made western patterns of consumption and behaviour widespread. A culture based on alcohol consumption, ultra-processed food, low physical activity, and long periods spent in front of a computer is now widespread (including in urban areas of low-income and middle-income countries), albeit with strong socioeconomic differentials.32,90 These global patterns, which spread rapidly, are not matched by similarly globalised and effective health prevention messages. Primary prevention tends to be local, and so far is mostly promoted with old technologies.89

Although our focus has been primary prevention, this approach is clearly not sufficient to fight cancer, especially in low-income and middle income countries. Late diagnosis and insufficient effective treatment are a major problem in low-income and middle-income countries, and more integrated strategies that combine access to care and prevention are needed.89 Atun and colleagues93 reviewed the issues involved in improvement of evidence that a particular prevention strategy can work to one which does work in a specific health-care setting.

Cancer is a global and growing, but not uniform, problem. We have argued that primary prevention is an especially effective—and probably also cost-effective—way to fight cancer, with between a third and a half of cancers being preventable, on the basis of present knowledge. If complemented by earlier detection and more effective treatment, cancer control would progress markedly. However, present social and economic trends do not promote prevention. The benefits of prevention take time to manifest, and prevention needs leadership and vision from policy makers. Global styles of consumption, fostered by changes in the economy (eg, in the quality and availability of food) and behaviours (eg, the low levels of physical activity associated with the built environment) are not counteracted by global preventive initiatives. The effect of the economic crisis on social services is likely to hamper primary prevention and increase social disparities; however, the evidence-base exists to reverse such trends. The spread of the cancer epidemic to poorer countries should, and could, be stopped now.

Conclusions
Cancer is a global and growing, but not uniform, problem. We have argued that primary prevention is an especially effective—and probably also cost-effective—way to fight cancer, with between a third and a half of cancers being preventable, on the basis of present knowledge. If complemented by earlier detection and more effective treatment, cancer control would progress markedly. However, present social and economic trends do not promote prevention. The benefits of prevention take time to manifest, and prevention needs leadership and vision from policy makers. Global styles of consumption, fostered by changes in the economy (eg, in the quality and availability of food) and behaviours (eg, the low levels of physical activity associated with the built environment) are not counteracted by global preventive initiatives. The effect of the economic crisis on social services is likely to hamper primary prevention and increase social disparities; however, the evidence-base exists to reverse such trends. The spread of the cancer epidemic to poorer countries should, and could, be stopped now.

Contributors
PV and CPW contributed equally to the writing of this paper.

Conflicts of interest
We declare that we have no conflicts of interest.

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