Curr Oncol Rep (2013) 15:332–346
DOI 10.1007/s11912-013-0327-3

PEDIATRIC ONCOLOGY (S EPELMAN, SECTION EDITOR)

Cancer in Adolescents and Young Adults in Countries with Limited Resources

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Published online: 7 July 2013

Abstract Cancer in adolescents and young adults (AYA) represents a higher fraction of all cancer in countries that are still undergoing a demographic transition. Such countries tend to have much younger populations, and therefore unless they have a particularly low incidence of cancer in this age group, will have a higher burden of cancer (absolute number of cases with cancer) in AYA. Cancers in AYA are comprised of the tail end of the incidence curve of cancers that have their peak incidence, or occur almost exclusively in childhood, the beginning of the incidence curve of cancers that primarily affect the elderly, and a third set of cancers that have their peak incidence (or are at least common) in the AYA age group (e.g., testicular cancer, sarcomas, melanoma, thyroid cancer). Many, but not all, of these cancers require radiation or cancer surgery, but the poorest countries do not have a sufficient number of radiation therapy units and surgical oncologists, or indeed medical and pediatric oncologists, to deal with the burden of cancer they face. The AYA age group is particularly important, both with regard to their contribution to the economy now and in the future (the majority are in the "working" age-group defined as 15–64 years), as well as their important role in caring for their families. Moreover, some of these cancers are eminently curable with chemotherapy alone, and more could be cured by simply improving the efficiency of existing health services and providing education and training to both the public as well as oncologists and other specialists required for the care of AYA (although such individuals will not necessarily be exclusively concerned with this age group). Of particular importance is the detection and diagnosis of cancer patients at the earliest possible time in the course of their disease. Avoiding delays in initiating therapy, which are partly due to the poverty and lack of education of the public as well as to a failure on the part of primary health care providers to recognize the possibility of cancer, would lead not only to improved survival and less toxicity, but is likely to reduce the need for radiation as well as the cost of treatment. There are few good quality clinical trials that take place in the LMIC (in relationship to the extent of the existing cancer burden), and research training should be an integral component of capacity building. Research on the efficacy and toxicity of standardized treatment approaches that are either based on principles established in the HIC, or adapted from treatment protocols used in the HIC, would be a good place to begin, but health policy and multisectoral collaboration are essential if improved survival rates are to be achieved. Decisions will also need to be made regarding the treatment of diseases in which radiation or cancer surgery are important elements, when one or both of the latter are unavailable. Late effects are important in this young population in HIC, and protocol adaptations or design in LMIC should take into consideration the significant fraction of cured patients with late effects who were treated in HIC in an era where improving response and survival rates was the paramount consideration—the situation that applies today in less developed countries. Special adolescent units which better deal with psychological issues of young cancer patients are rare in LMIC and the psychosocial issues faced by adolescents are much less studied. Although survival is the first consideration, attention to psychosocial and financial issues may reduce existing delays in initiating therapy and also the fraction of patients that abandon therapy.

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Keywords cancer · adolescents · young adult · countries with limited resources

Introduction

Adolescents and young adults (AYA) account for a significant proportion of the populations of the majority of the world's countries, which are still undergoing demographic transitions from the agriculture-based economies that existed prior to the industrial revolution, to technology-driven economies [1]. The scale and duration of the transitions varies greatly as a result of numerous geographical, environmental, political and even religious factors, which results in equally variable levels of socio-economic development (Table 1) and also both qualitative and quantitative differences in the burden of disease. There are various approaches to classifying countries according to their level of development. The World Bank's classification is based solely on Gross National Income per capita (Table 2) [2], while the United Nations Development Program's Human Development Index, combines indicators for life expectancy at birth (which in large part is a measure of overall health), education and income into a single index of human development (HDI) [3]. While approximately a billion people live in countries that have completed the transition and have stable or even declining populations (high-income countries, or HIC, in the World Bank's classification (Table 2)), the remaining 6 billion live in countries in which only some of the benefits of the modern era have reached some of the people, such that the mortality rate remains high, and the birth rate, although falling, is higher than the mortality rate. This results in continued growth of the populations of such countries. In the World Bank's classification, countries are classified into low- and middle-income countries, the latter being further divided into lower-middle and upper-middle income countries. Although GNI per capita alone does not do justice to the overall level of development and is an average for the entire country, in which there may be large variations in different regions, or between urban and rural populations, GNI per capita will be used in the present article as a convenient means of classifying countries according to their available resources. Even in high-income countries there are marked disparities in access to health care, a situation that is complicated by immigrant populations seeking an improved standard of living, a variable fraction of whom may have entered the country illegally.

While more food, cleaner water, improved hygiene and medical progress, particularly the prevention (by vaccines) and treatment of common infections have decreased the mortality rate and prolonged the lifespan of the world's population, this has also resulted in an increase in non-communicable diseases (NCDs), including cancer, which are more common in older people. In addition, the industrial revolution has led to exposure to new risk factors for NCDs. Cancer, in particular, requires a broad range of health professionals as well as expensive drugs and equipment to treat, and while prevention may be preferable to therapy, only a few cancers can be effectively prevented. Most patients in LMIC have limited access to care because of the paucity of resources, including human, physical and financial, which results in fewer centers, fewer specialists, poor availability of medicines and equipment needed for treatment and a high average cost of traveling to one of the few treatment centers in the country, and the necessity of paying for both diagnosis and treatment out-of-pocket because of the lack of health insurance [4]. The ongoing increase in noncommunicable diseases, which in 2008 accounted for 36 million of the 56 million deaths, is a global phenomenon, but has a more detrimental effect on the LMIC (which account for 80 % of the mortality from NCDs) because of their already high disease burdens. On average, 29 % of deaths from NCDs occur before the age of 60 in these countries, and over 60 % in the poorest, for example, many African countries [5]. Although the age structure of the population and limitations in health services has much to do with the higher mortality rates overall, and the higher fraction of NCDs in people less than 60 years old in lower income countries, these figures emphasize the fact that many NCDs occur in people still in the most productive period of their lives such that the impact on the economy is large. HIC, however, must grapple with the socioeconomic problems brought about by the increased number of retired persons who consume most of the health care resources of these countries, but no longer contribute to the economy.

The age-structure of populations is not only of considerable importance with respect to the most afflicted age groups in terms of NCDs, but also influences the economy of a country, which in turn has a major impact on the access of the population to education and health. For example, in Uganda, the median age is 15 years (i.e., half the population is less than the age of 15 years), so that the fraction of people at "working age" (15-64) is correspondingly much smaller than in HIC countries with older populations. So is the proportion of persons educated sufficiently to undertake higher education, or to pay for it. Because of the slow rate of economic progress, transportation is poorly developed, and there are fewer and less well equipped and staffed hospitals, often to the point of absence of particular technologies (30 countries, for example, completely lack radiation therapy units and 80 % of Africans have no access to radiotherapy [6]) or specialists, including pathologists, oncologists, nurses, pharmacists and a broad variety of health workers). This causes a vicious cycle; the more limited the health services, including both public health and clinical medicine, the more ill health there will be, and the more ill health there is, the poorer will be the education and organization of the workforce. It is essential to address the multiple problems

Table 1 Developmental Indicators for selected countries and regions in the fraction of the population aged 15–39 years. Source, World Bank and Globocan

	Population (millions)	GNI per capita	GDP (trillions)	Labor Force (millions)	% living on < $1.25 per day	% living on < $2 per day	Median age of population	Proportion aged 15-39	Percentage of Labor force with tertiary education	Total Health Expenditure per capita (Current US dollars)	Government Health Expenditure (% of total)	Life Expectancy at birth	Total Cancer Incidence rate (ASR)	Total Cancer Mortality rate (ASR)	Cancer incidence rate in AYA age group (ASR)	Cancer Mortality rate in AYA age group (ASR)
Tanzania	46.2	1,500	23.9	22.1	68	88	18.7	37.81	-	31	14	58	87.2	70.2	26.0	15.3
Bangladesh	150.5	1,940	111.9	72.3	43	77	23.6	43.92	-	23.3	7.4	69	124.8	95.7	28.9	15.6
Philippines	94.8	4,140	224.7	38.7	18.42	41.53	23.1	40.89	28.0	77.3	7.5	69	116.1	75.9	29.9	14.0
Mexico	114.8	15,390	1,153.3	49.6	1.1	5.2	26.7	41.07	17.3	603.7	12.1	77	128.4	77.6	39.4	14.4
Saudi Arabia	28.0	24,700	576.8	9.5	-	-	25.7	45.68	-	679.6	7.0	74	87.6	63.1	21.4	10.0
Belgium	11.0	39,190	513.6	4.9	-	-	42.6	30.53	38.9	4,618	15.1	80	306.8	116.2	68.3	9.8
HIC	1,335.0	38,524	46,606.1	551.2	-	-	-	31.30[a]	39.6[a]	4,877	18	80	255.8[a]	111.1[a]	54.2[a]	10.9[a]
UMIC	2,489.0	10,699	18,235.0	1,322.0	9	20	-	40.18[b]	-	379.7	9.9	73	146.8[b]	100.6[b]	33.4[b]	16.5[b]
LMIC	2,532.8	3,811	4,767.9	519.2	30.2	59.5	-		-	70.9	5.9	68				
LIC	816.8	1,370	472.7	364.6	48.4	74.3	-		-	26.9	-	59				

Latest available figures, predominantly from 2011. Population data for % AYA calculation from 2010 estimates made by the UN Population Division

Agencies which provide data on the proportion aged 15–39 years and cancer incidence and mortality classify countries differently, i.e., more developed—Europe, Northern America (i.e., excluding Mexico), Australia, New Zealand and Japan (this corresponds approximately to the World Bank's High Income Countries)—and less developed countries, which include all regions of Africa, Asia, excluding Japan, Latin America and the Caribbean, as well as Micronesia, Melanesia and Polynesia. Dashes indicate no available data

[a] More developed countries

[b] Less developed countries

Table 2 The world bank classification of economies in 2011

- Low-income countries had GNI per capita of US$1,026 or less.
- Lower middle income countries had GNI per capita between US$1,026 and US$4,036.
- Upper middle income countries had GNI per capita between US$4,036 and US$12,476.
- High-income countries had GNI above US$12,476.

that exist simultaneously, since the solution of one without corresponding improvement in others will have at best a limited effect.

Particular problems in LMIC are delay in diagnosis and the abandonment of care, in part caused by the relatively high cost of care compared to average income (the WHO reports that 100 million people each year cross the line into poverty as a result of health care payments). Both of these problems would be greatly reduced if stable health financing systems were available to all [6], but the limitations in diagnostic accuracy and the poorer outcomes of interventions are also due to the inadequate numbers of well-educated health workers furnished with adequate facilities and the therapeutic modalities to deal with the existing cancer burden. Unfortunately, even gaining access to the health system by no means guarantees an outcome similar to that achieved in HIC with the exception, perhaps, of the few major institutions in some of the more developmentally advanced upper middle income countries (UMIC). In general, there is limited ability to assess the needs of the country because of the lack of cancer registries. Similarly, the limited infrastructure for the conduct of clinical trials designed to determine what works best in the local context essentially eliminates the ability to improve treatment outcome, at least in countries at the lower end of the developmental scale.

While these deficiencies apply to a varying degree to all LMIC and to all cancer patients, there are additional problems for adolescents and young adults (AYA) that result from the broad spectrum of tumors that are encountered, some of which have their peak occurrence in this age group (although the upper age of “young adults” is variably defined) and also their special psychosocial needs, resulting from their need for greater autonomy and consequent rejection, to variable degrees, of authority figures. There is limited information regarding the extent to which the psychosocial issues of adolescence differ in different populations. Yet adolescents and young adults represent a numerically important part of the populations of less developed countries (Table 1), whose populations are very young compared to those of the majority of high income countries. They have the major part of their lives to live and do much to assure the vitality of the country, and its energy, motivation and enthusiasm. It is only in recent years that the HIC have recognized the need for health specialists who focus on adolescents and young adults. In general, treatment approaches for adults and children have developed separately, because, for the most part, the diseases they develop are very different, but there is no sharp age cut-off between children and adults and, the diseases that occur more frequently in adults do also occur in children, albeit at a much lower frequency and vice versa. It is in the AYA age group that the patterns of disease most obviously meet. Because of their younger populations, LMIC would be expected to see proportionately more cancers in this age group, but the difference is lessened by the lower incidence rates of cancer in the LMIC (Fig. 1), although mortality in the AYA age group is quite similar to that of HIC, indicating a worse treatment outcome. Table 3 shows the actual number of cancer cases and cancer deaths in children (aged 0–14 years) and 15–39 year olds in comparison to the number of cancer cases at all ages in less and more developed regions.

Because of their young age, late effects arising from the treatment of cancers in AYAs are particularly important [7, 8]. In addition to infertility, the possibility of cardiac problems in patients who receive anthracyclines or radiation to the heart and neurological deficits from irradiation of the brain, second malignancies are a particular problem. Indeed, some of the malignancies encountered in AYAs are second malignancies that have developed as a consequence of treatment given for a cancer that occurred many years before (e.g., breast cancer in young adult females whose treatment for Hodgkin lymphoma included radiation to the chest) and

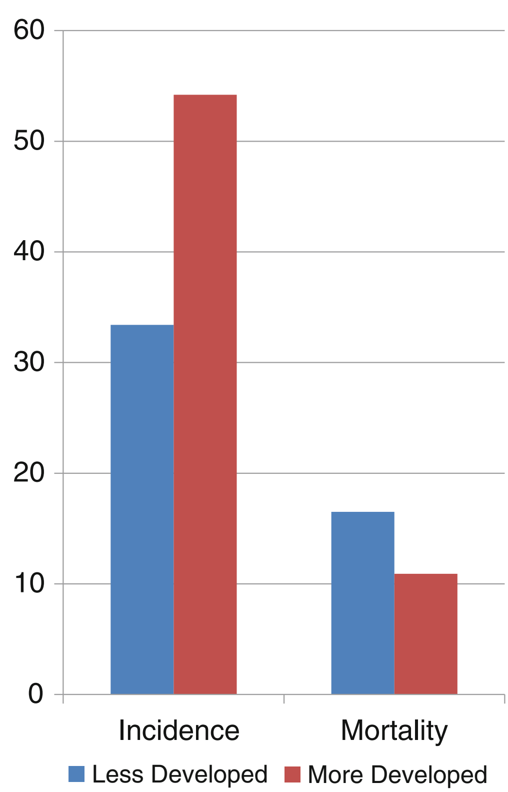

Fig. 1 Age standardized incidence rates (number of incident cases per 100,000 per year) and mortality rates of all cancers, both sexes, between the ages of 15–39 years. Data from Globocan 2008, ref. 4

Table 3 Actual numbers of cases of cancer and deaths in males and females in two different age groups and all ages in more and less developed regions (data from Globocan, 2008, ref. 4)

Incident cases	0–14 years	15–39 years	All ages
More developed regions	27,910	228,744	5,555,281
Less developed regions	147,148	772,297	7,107,273
Deaths			
More developed regions	5,607	45,954	2,744,840
Less developed regions	90,832	380,561	4,819,962

also to the particularly high predisposition to second malignancies seen in some tumors, such as retinoblastoma. Although retinoblastoma itself is very rare in AYAs, the second malignancies associated with it often occur in adolescents or young adults. Radiation, depending upon tissue tolerance and the volume irradiated, is a particular problem in this regard and in adolescents, who have not completed their growth, has the added problem of the cessation of musculoskeletal growth in the radiated area. While at present, there are no known alternatives to radiation therapy in many tumors, there has been a reluctance to study the possibility of reducing the dose, field size or eliminating radiation therapy completely when chemotherapy is a highly effective modality (e.g., in Hodgkin lymphoma)—often because the more senior oncologists remember a period when results were very poor, and do not wish to risk higher failure rates. Nonetheless, the use of radiation therapy in childhood cancers, for example, has declined markedly since the 1970s [9].

Similar considerations apply to extensive surgery, which may sometimes be markedly reduced or avoided altogether by giving chemotherapy initially to reduce the size of the tumor. In Wilms' tumor in children, for example, this approach has led to much simpler surgery with no detrimental effect on survival. Although Wilms' tumor is very rare in AYAs, being primarily a tumor of infants, a few, often atypical cases have been reported in adolescence [10]. In LMIC, tumors tend to be considerably larger than in the HIC because of the many factors that lead to late presentation, such that radiation fields or the extent of surgery required, is on average higher than in the HIC. Neoadjuvant therapy (chemotherapy first), if successful would reduce need for highly trained cancer surgeons and radiation therapists as well as late effects, although to determine the value of this approach would require many clinical trials. Late effects, of course, were not a major consideration prior to the era when significant numbers of patients survived long enough for the late toxicities to become manifest. In many countries, this is still the case today, but as capacity for cancer care increases, it should be possible to avoid or minimize therapy components known to be associated with significant late effects, at least in some tumors.

Age and Cancer – the Spectrum of Tumors in AYAs

Cancer is generally thought of as a disease of the elderly, but while the incidence rate is much greater in the elderly, accounting for two-thirds of all cancer, at least in HIC with a high proportion of elderly people, cancer is the commonest cause of disease-related mortality in the USA and UK in persons between the ages of 15 and 24. Although the incidence rate of cancer in this age group is much lower than the incidence rate in persons above the age of 65, it is higher than in children 0–14 years old. The incidence rate is also higher in more developed regions than in less developed regions, but mortality is almost the same, indicating a worse outcome of therapy or access to therapy in the latter (Fig. 1) (Table 1). The relative proportions of different cancers vary considerably depending in part upon the definition of AYA (with respect to the age at which children are considered adolescents at the lower end of the age-range, and the age at which adults are no longer considered "young" at the upper end) because of true differences in incidence of various cancers in different age groups. This is well illustrated in Fig. 2, although this figure is based on data from the USA. When the incidence rates of less and more developed countries are compared, it is notable that some cancers have a similar incidence rate (lung and cervix, for example), while others vary markedly (testicular cancer and melanoma, for example) (Fig. 3).

At the young end of the age range of AYAs, many of the cancers are those that predominate in childhood. Some childhood cancers occur almost exclusively in infants, presumably because they are derived from fetal cells that have persisted after birth, and which may have been exposed to carcinogens during gestation (e.g., the "blastomas" such as retinoblastoma, hepatoblastoma and nephroblastoma). Alternatively, they may be associated with inherited conditions such as Beckwith–Wiedemann syndrome, which predisposes to Wilms' and hepatoblastoma (although these are generally tumors of early childhood), and the variants of neurofibromatosis. In type I neurofibromatosis, malignant transformation occurs in 3–5 % of cases—usually in AYAs. Type 2 neurofibromatosis is associated with acoustic neuromas and can be associated with ependymomas, gliomas, meningiomas and schwannomas that also often occur in AYAs. Other inherited disorders give rise to different tumor types. For example the diseases associated with the Li–Fraumeni syndrome, an inherited disease usually caused by mutations in the p53 gene or its regulatory regions, include adrenocortical carcinoma, sarcomas (soft tissue and bone), breast cancer, brain tumors and leukemia. When breast cancer occurs in a young woman, an inherited predisposition should be suspected; the peak age of breast cancer in the Li–Fraumeni syndrome is 45 years and 50 % of individuals with Li–Fraumeni syndrome have developed

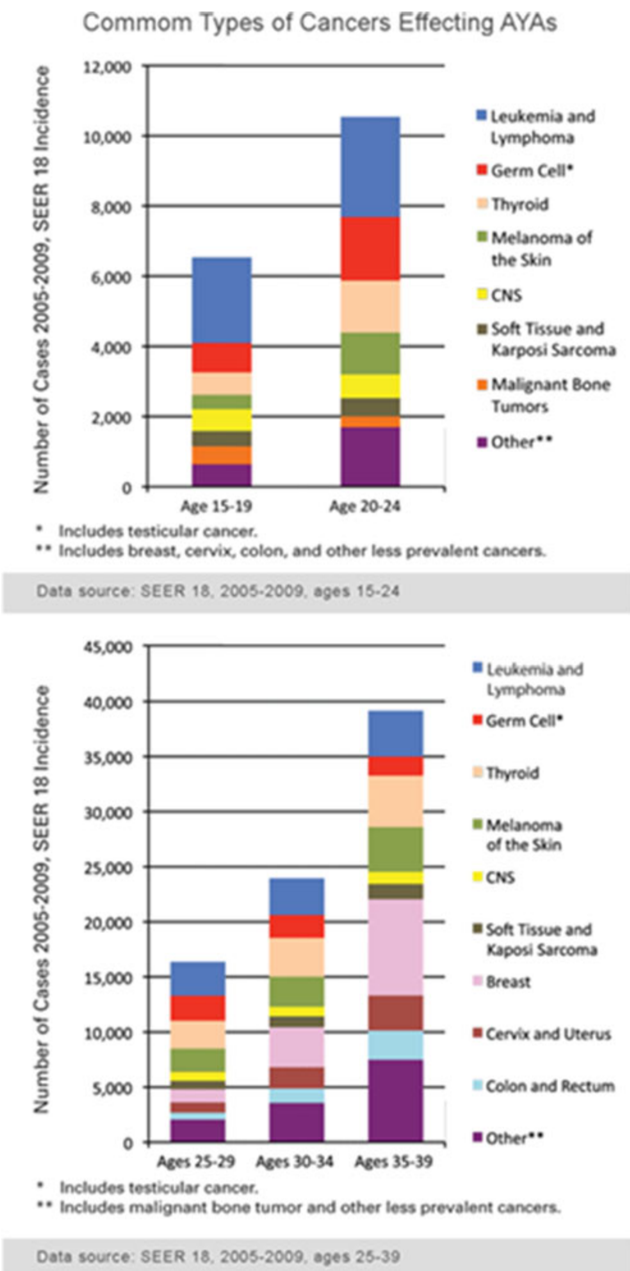

Fig. 2 Main types of cancers (actual numbers) in AYAs, both sexes, in 5-year age groups. From National Cancer Institute

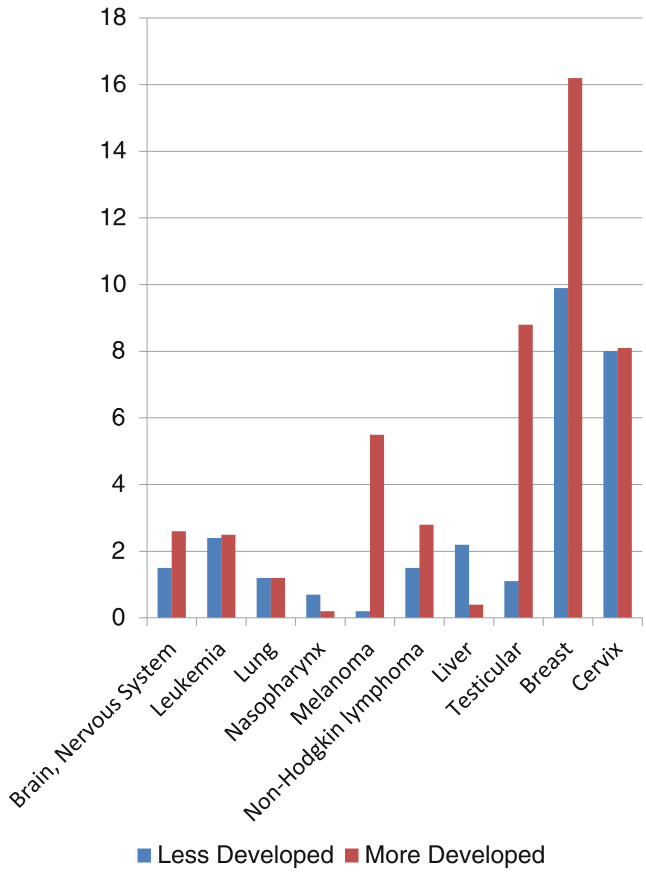

Fig. 3 Age standardized incidence rates of selected cancers in more and less developed regions. Data from Globocan 2008, ref. 4

a cancer by age 50 years. The broad range of tumors and the presence of genetic lesions in p53 strongly suggest that the biological basis for tumors in the Li–Fraumeni syndrome is failure of the p53 pathway to eradicate cells which have developed genetic aberrations.

At the higher end of the AYA age group, cancers which are rarely or never seen in children begin to appear. Many of these continue to increase in incidence throughout life, probably because the degree of exposure to a carcinogen (e.g., tobacco) is an important determinant of occurrence. Very poor people, for example, cannot afford to smoke large numbers of manufactured cigarettes, and tend to have less tobacco-related lung cancer. Conversely, high exposure rates to carcinogens (or less exposure to highly potent carcinogens) is likely to result in cancers developing at a younger age. Skin (scrotal) cancers in young boys, for example, were first observed by Sir Percival Pott in 1775 due to the massive exposure of young chimney sweeps to soot, while cleaning the large numbers of factory chimneys built in the early phases of the industrial revolution by physically climbing up the narrow chimneys—best accomplished by agile boys [11]. These children never bathed, and even slept on the bags of soot they had swept from the chimneys.

Some of the cancers common in older adults that begin to appear in AYAs continue to increase in incidence throughout life, suggesting that the cumulative exposure to carcinogens is one of the main determinants of whether or not cancer develops (in concert, of course, with many host factors). This is the case for all cancers combined and applies to both more and less developed countries (Fig. 4). Not all cancers, however, increase in incidence throughout life. Breast cancer, for example, increases in incidence to the

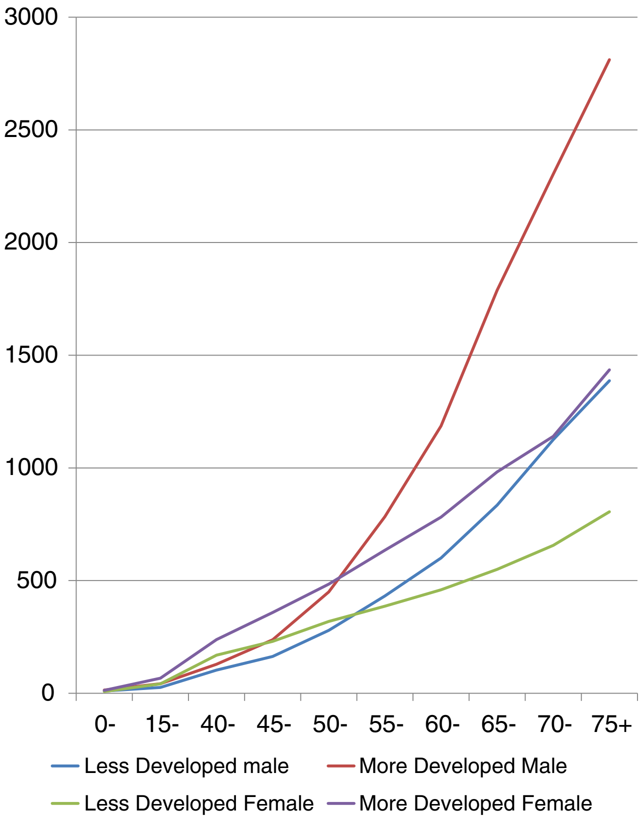

Fig. 4 Age-specific incidence rates per 100,000 per year in all cancers combined (*x*-axis = age) in more and less developed countries. Data from Globocan 2008, ref. 4

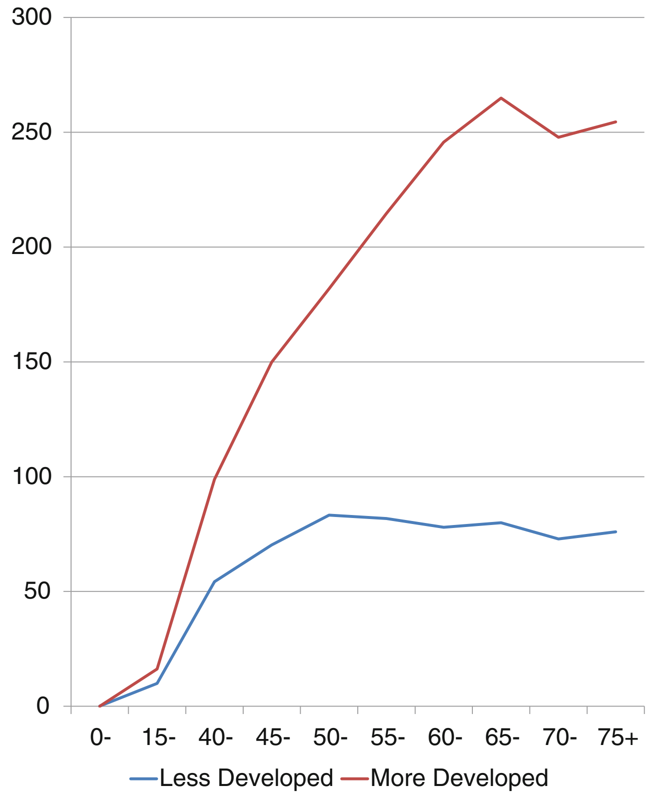

Fig. 5 Breast Cancer: Age-specific incidence rates per 100,000 per year in more and less developed countries. Data from Globocan 2008, ref. 4

age of approximately 45 years in the LMIC and Japan, but unlike breast cancer in most HIC (such as Europe and the USA), the age-specific incidence rate does not increase as women continue to age in LMIC and Japan. A possible explanation for this is the importance of diet in post-menopausal breast cancer. The much lower exposure to trans- and saturated fats in the less developed countries (and Japan) may well be the reason for the much lower incidence of breast cancer later in life, compared to populations in Europe and the USA (Fig. 5). It would seem probable from this observation that postmenopausal breast cancer is comprised primarily of subtypes associated with being overweight and the consumption of greater quantities of trans or saturated fats, although more research will be necessary to confirm or refute this hypothesis.

Some cancers peak in incidence at particular ages or even have multiphasic age peaks. For example, acute lymphoblastic leukemia has its peak incidences in young children and the elderly, and Hodgkin lymphoma classically has a bimodal age-incidence curve. Cancers which have a peak occurrence at a much younger age do so usually because the cell type from which the cancer develops is itself only present at a particular age, although it is also possible that the microenvironment able to support the growth of the specific cancer cells is peculiar to a certain age. This is easy to understand in the case of gestational choriocarcinoma, for example, since this is a placental tumor and the trophoblastic cells from which choriocarcinomas arise is present only in women who become pregnant (the ovum must be fertilized for trophoblastic tissues to develop). Less obvious examples are BL, which, although it occurs at all ages, has a peak incidence at approximately 7 years of age in Africa [12]. Involvement of the jaw in African BL, however, occurs predominantly in young children aged 2 to 4 years, while involvement of the breast occurs almost always in pubertal girls or lactating women. Since BL in general, can occur at other sites in children or adults at any age (although the incidence of BL varies with age), the age-specificity of tumor in the jaw or in the breast suggests that microenvironments suitable for the growth of BL cells occur in the jaw only in young children, although at other sites throughout life. Although the reason for this one possible explanation is that it relates to the creation of a suitable microenvironment in the jaws during the development of the permanent teeth (e.g., an environment that contains several growth factors relevant to both the development of teeth and to BL cells). Such microenvironments could be unique to the developing permanent teeth (the tumor cells, in fact, grow into the pulp within the teeth), or could occur in other parts of the body at other ages. However, outside equatorial Africa, the classical African BL jaw tumors are rare indeed (there is some evidence that in an earlier era they were more common in some countries, e.g., Turkey [13]). In contrast, BL in the USA and almost all other countries, lacks the florid jaw tumors seen in young African children with BL. This suggests that the microenvironment suitable for the proliferation of tumors in the jaw is a consequence of an environmental agent that occurs essentially exclusively in Africa (interestingly, malaria causes xerostomia which leads to gum and tooth infection and shedding). In contrast, breast involvement occurs in both Africans and non-Africans, and presumably reflects physiological changes in the breast tissue at the time of puberty and lactation. BL in the USA has three age peaks at approximately 10, 40 and 75 years, each of approximately similar height, the reason for which is unknown. The middle age peak, however, has been shown to include the majority of HIV-associated BLs. Prior to the HIV epidemic this peak was barely visible [14]. The reasons for the higher age range for patients with HIV+ BL remain unknown.

The spectrum of cancers seen in AYAs, then, is comprised of some tumors that typically arise in childhood, and may be very rare in AYAs, and some that typically occur in older adults, most of which continue to increase in incidence throughout life. The proportion of such tumors will depend on the upper age that is used to define AYAs. However, there is a third group of tumors—those that have an age peak, or at least are more common than carcinomas in the AYA range, such as testicular tumors, bone sarcomas (Ewing's tumor and osteosarcoma) and soft-tissue sarcomas [15, 16] (Fig. 2). Subsets of these tumors may more often occur in other age groups. Alveolar rhabdomyosarcoma, for example, occurs more often in teenagers or young adults, while embryonal rhabdomyosarcoma occurs more often in infants and young children. They also vary quite markedly in incidence in different world regions, and with socioeconomic level. For example, testicular tumors are the most common cancers in young men aged 15–24 years in most HIC. However, this is not so for less developed regions, where this early age peak in testicular cancer is not seen (Fig. 6). Hematological malignancies and brain tumors occur throughout life, although different subtypes often have different peak ages or increase progressively throughout life. In AYAs, leukemias and lymphomas, which account for approximately 50 % of childhood cancers throughout the world, continue to predominate in young AYAs, but the relative proportions of different cancers changes with increasing age, e.g., in successive each 5-year age groups. Although the incidence of some cancers decreases as age increases, the largest numerical change is due to carcinomas, whose incidence rapidly increases with age. Carcinomas also vary in incidence in different world regions, the most common being lung, breast, prostate and colon at a global level. This is presumably a consequence of cumulative exposure to relevant risk factors.

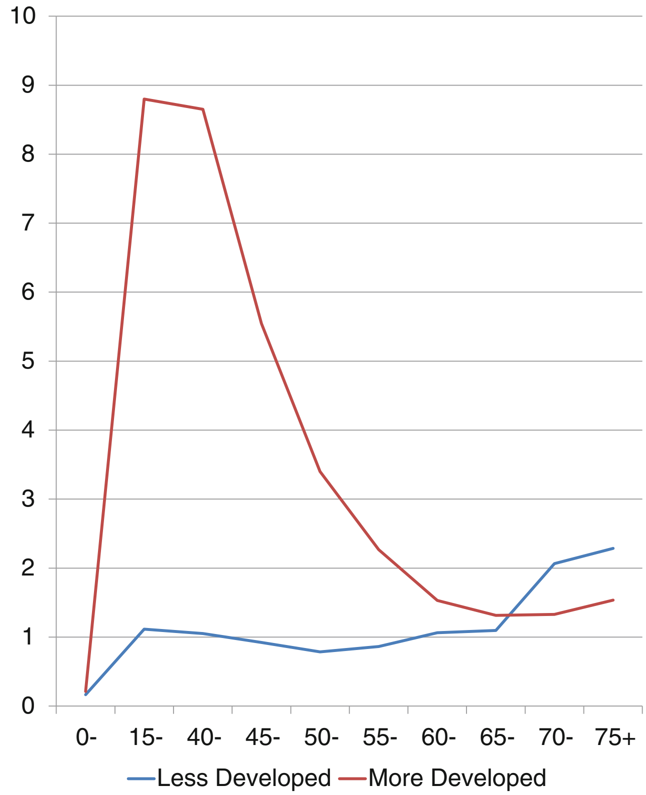

Fig. 6 Testicular Cancer: Age-specific incidence rates per 100,000 per year in more and less developed countries. Data from Globocan 2008, ref. 4

Cancers Predisposed to by Chronic Infections

Cancer in LMIC is more likely to be associated with infection than is the case in HIC. Hepatocellular carcinoma, for example, is strongly associated with hepatitis B or C infection in Asia and Africa, where the high incidence is believed to result from mother to child transmission of one of these viruses. Social factors (lifestyle) greatly influence the incidence of many diseases associated with environmental risk factors [17], some of which are often (but not always) grouped together; e.g., high alcohol consumption is often coupled to hepatitis B or C (or both) infection and low social class in HIC. Non-alcoholic fatty liver disease, related to obesity, is likely to be an increasingly important risk factor in hepatoma, whose incidence, particularly in intrahepatic bile duct cancer, which has increased 16-fold within a few decades, is rising in AYAs at a global level, and is expected to continue to do so [18, 19]. A number of investigators have also suggested that an infectious agent is in some way associated with the "early age peak" of ALL which occurs between 2–5 years and is largely caused by ALL associated with the Tel/AML1 translocations. The early age peak emerged in different populations at different times throughout the 20th century, seemingly in step with the technological revolution that was ongoing, although the reason for this remains unknown [20]. Human papilloma virus is almost certainly a causal element in cervical cancer, which has a higher incidence than breast cancer in the lower income countries and subpopulations within countries. Its lower incidence in most HIC is a result of effective screening.

Differences in Age-Specific Incidence Rates in More and Less Developed Regions

Thus, while the incidence of some cancers is similar in 15–24 year olds in more and less developed countries, in other cancers there are major differences (Figs. 3, 5, 6, 7, 8, 9 and 10). This is well shown by a recent report from Shanghai in which the trends in cancer incidence among men and women aged between 15 and 49 years of age were studied in urban Shanghai in the period 1973 to 2005 [••21]. The investigators found that the overall incidence of cancer in males decreased by 0.5 % per year, whereas cancer in females increased slightly by 0.8 % per year. In this age-group as a whole, the rank order of the top 5 cancers in males was liver, stomach, lung, colorectal and nasopharyngeal cancer, and that in females, breast, stomach, colorectal, thyroid and ovarian cancers. Oesophageal, stomach and liver decreased in incidence in both sexes, while renal cancer, non-Hodgkin lymphoma and brain and nervous system cancers increased in both sexes, and both breast and ovarian cancers increased in females. During the period under study, cancer of the stomach was the most commonly diagnosed cancer, accounting for approximately 12 % of all cancers. Liver cancer had the highest incidence in males, although the incidence decreased over time in both sexes (Fig. 11a). In contrast, breast cancer was the most commonly diagnosed cancer in females, and its incidence increased over time (Fig. 11b). Breast cancer accounted for 29 % of cancers diagnosed in females and increased in incidence from 13.3 per 100,000 in 1973–1975 to 29.9 per 100,000 in 2003–2005. Ovarian cancer also increased by 64 % during the study period.

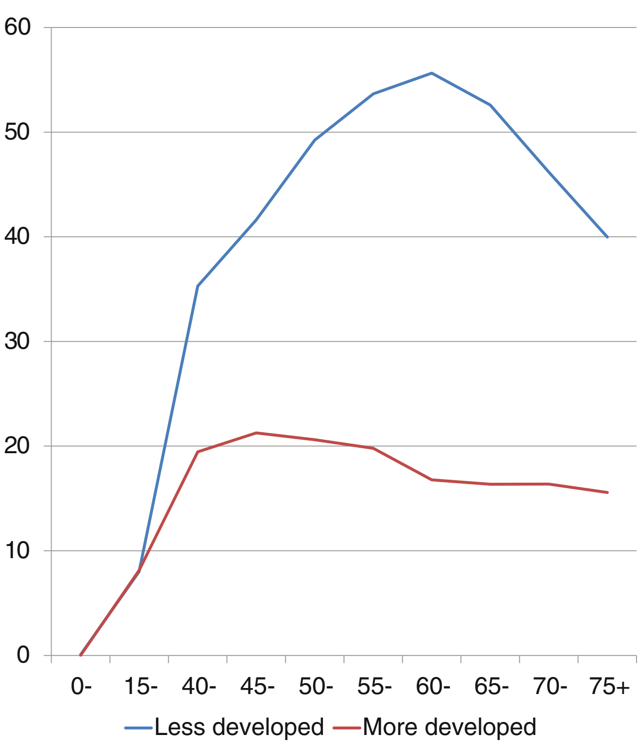

Fig. 7 Cervical Cancer: Age-specific incidence rates per 100,000 per year in more and less developed countries. Data from Globocan 2008, ref. 4

Ensuring Early Diagnosis and Prompt Treatment

In the less developed countries in particular, cure is much more likely to be achieved when the two main components of the health system (public health and clinical medicine) are used to maximal benefit. Thus, if parents or family are unaware that cancer can occur in adolescents, they may not perceive the potential serious nature of the early symptoms and fail to seek help until the cancer has become advanced. Perhaps the single most important "warning sign" is the presence of a mass anywhere, but there is a very long list of symptoms which may prove to be caused by cancer, of which persistent swelling of lymph nodes for 2–3 weeks, changes in shape, color or ulceration of a mole or naevus, abnormal vaginal bleeding, neurological symptoms, including recurrent or persistent headache, abnormal behavior, posture or gait, unilateral weakness, difficulty with balance, unusual clumsiness, or systemic symptoms such as fatigue, weight loss, malaise, night sweats, persistent unexplained fevers or cough, although by no means exhaustive, are among the most common, although the majority of patients with these symptoms will not have cancer. Nevertheless, symptoms of this kind should be investigated, and biopsy performed, if persistent (the definition of "persistent" being a matter of clinical judgement). Only in a few circumstances is treatment for cancer appropriately initiated prior to biopsy e.g., brain stem tumors, Wilms tumor, when neoadjuvant surgery is to be performed and suspected testicular cancer, when an orchiectomy should be performed immediately rather than an incisional biopsy. Chronic infection is the major alternative diagnosis to cancer in this age group, particularly tuberculosis and infestation by a variety of parasites. In some cases a therapeutic trial of antibiotics or anti-parasitic drugs may be indicated, but there is clearly a need for the development of simple, noninvasive tests (e.g., for tuberculosis) at the point of

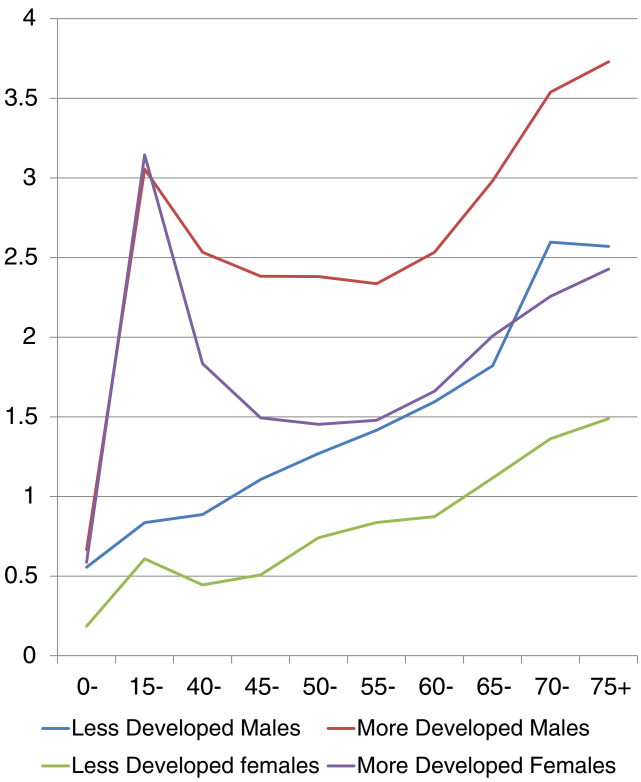

Fig. 8 Hodgkin lymphoma: Age-specific incidence rates per 100,000 per year in more and less developed countries. Data from Globocan 2008, ref. 4

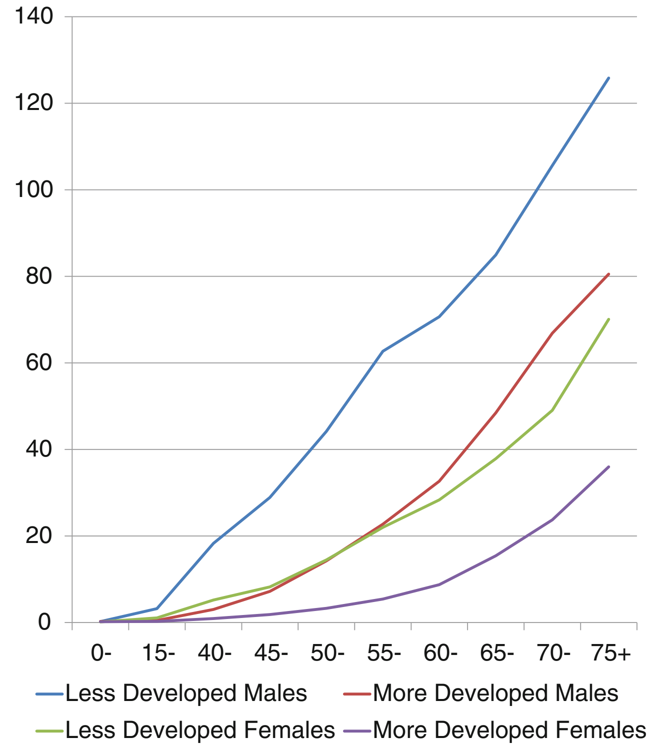

Fig. 10 Liver Cancer: Age-specific incidence rates per 100,000 per year in more and less developed countries. Data from Globocan 2008, ref. 4

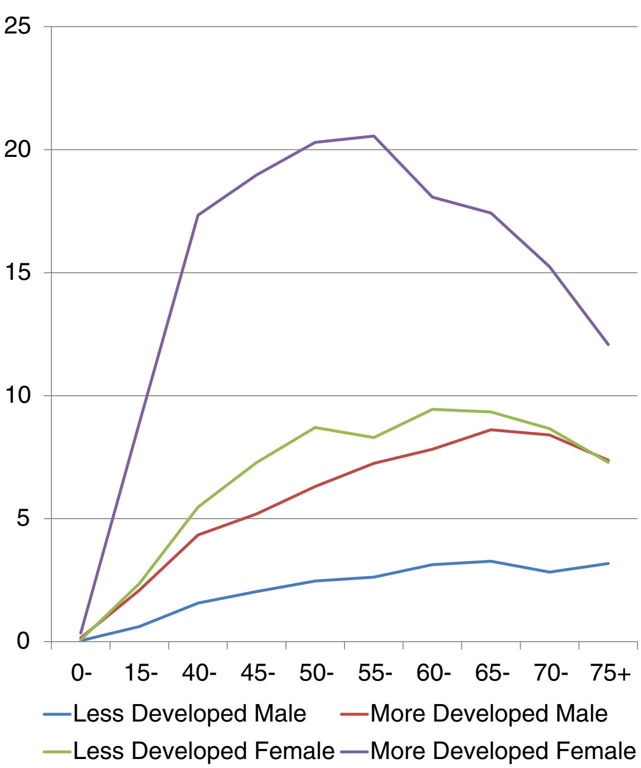

Fig. 9 Thyroid Cancer: Age-specific incidence rates per 100,000 per year in more and less developed countries. Data from Globocan 2008, ref. 4

service. In the absence of inexpensive diagnostic devices, the judgment required by the primary care-giver can be supplemented by regionally relevant lists of the likeliest cause of a given symptom or sign (easily made available on a computer or smart phone), or simple algorithms that can be performed before referral to a distant center at considerable cost (e.g., ultrasound examination, a full blood count, serological testing or search for ova or parasites in urine or stool). The broad range of cancers that occur in AYAs makes diagnosis particularly difficult, although classical syndromes, such as jaw tumors in BL, a lump in the breast after the age of 30 years, vaginal bleeding or dysparunia, a testicular mass, changes in a skin naevus, persistent lymphadenopathy or unexplained weight loss should immediately raise the possibility of cancer. Better collaboration among primary, secondary and tertiary care givers would allow for educational programs dealing with referral guidelines, and prior consultation by telephone or video link in specific cases about the need for referral.

In HIC it has become clear that smoking and overeating, especially when the diet is high in trans and saturated fat, a sedentary lifestyle with minimal or no exercise and excessive alcohol consumption are risk factors for cancer. Although in LMIC the proportion of the population exposed to these risk factors remains quite low, it is rising, and there is no reason to

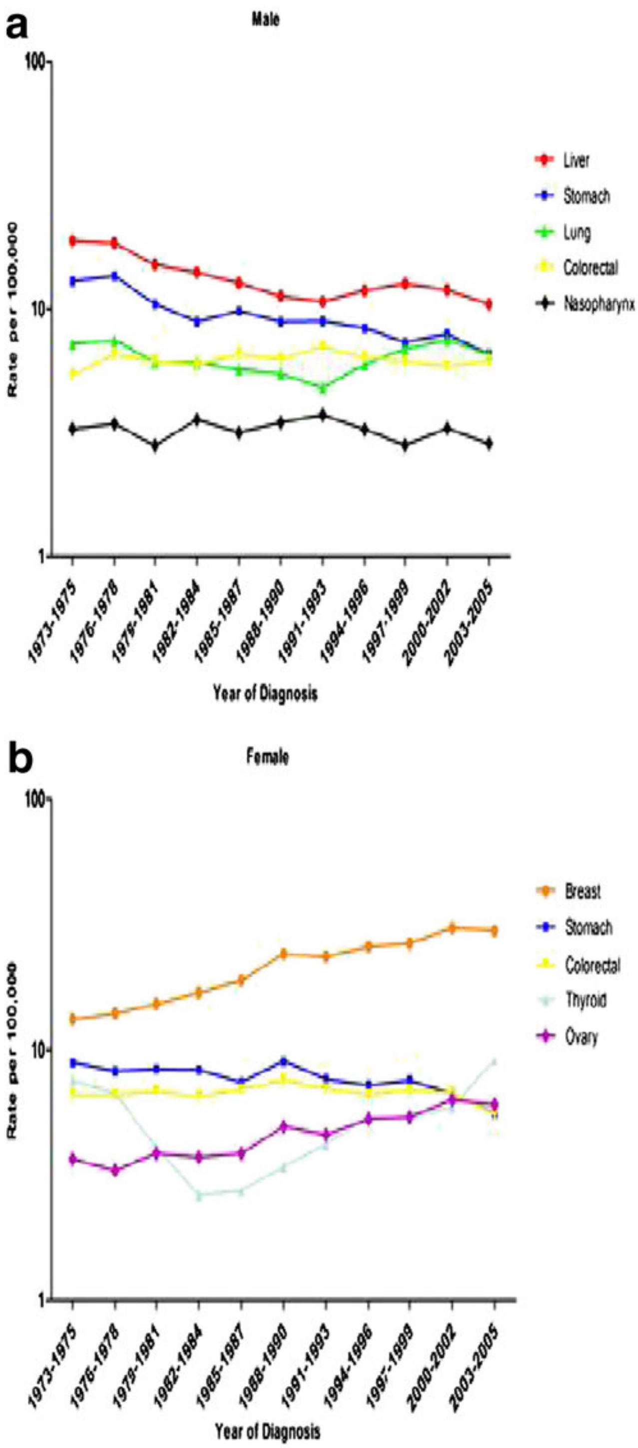

Fig. 11 Age standardized Incidence rates per 100,000 per year of the commonest cancers in AYAs in Shanghai between 1973 and 2004 (see reference 12). (**a**) Males, (**b**) Females

doubt that these risk factors will increase in frequency as countries undergo socioeconomic development. Programs to educate the public—starting no later than adolescence, about the importance of a healthy lifestyle should be initiated immediately, and supported by policies designed to alter behavior patterns. In this respect, the LMIC have the possibility of initiating measures to ensure a healthy lifestyle before these risk factors have had a major impact on the incidence of cancer.

Improving Access to Care

Yet while there is a paucity of resources in less developed countries resulting in limited access to specialized care, these deficiencies can, to an increasing degree, be compensated for by modern technology, a significant proportion of which is sufficiently inexpensive to have already reached or is soon to reach the less-developed countries (e.g., computers, mobile devices and a broad range of medical devices and machines). Unfortunately, such equipment is poorly distributed and maintained, and there is often limited expertise in its use in LMIC. Nonetheless, technological advances show promise of greatly improving the situation; new miniaturized devices for diagnosis should soon become widely available at an affordable price. Being highly portable and robust [22] and requiring minimal energy to operate, they will be increasingly used for point-of-service measurements such that accurate diagnoses could be available in minutes to hours, potentially avoiding the expense to the patient of a visit to a tertiary hospital, already greatly overcrowded and likely to be very far away. The ability to rapidly diagnose or exclude the diagnosis of tuberculosis, for example, in swollen lymph nodes, or to assess a blood film or bone marrow smear using a simple digitally based telemedicine system, such as iPath used by INCTR, could be used within or between countries for rapid consultation and education leading to major time and cost savings for both patient and health system.

The physician has other problems in countries with limited resources. He or she has little access to information and has little opportunity for continuing education – even the cost of attending an international meeting may be prohibitive. This needs to be changed, but while external assistance may be critical, it is essential that LMIC countries themselves initiate programs and develop tools and systems relevant to their own needs, and that outside agencies or consultants understand the need to build sustainable infrastructure that is not simply a replication of what works or what is accepted in their own country, but where possible, utilizes new approaches made possible by technical advances that reduce the need for trained pathologists while simultaneously speeding up diagnosis.

The value of collaboration and the organization of health services and continuing education in a geographical fashion cannot be overemphasized—at the present time there is little communication between hospitals or attempts to develop national standards for diagnosis or treatment. The first consideration are to increase survival as much as possible while at the same time, reducing the risks associated with cancer therapy. Both goals are served by ensuring early, accurate diagnosis and prompt initiation of therapy by persons familiar with the complications of the disease and its treatment.

Treatment

The AYA age-group contains such a wide range of tumor types that only a few general remarks regarding treatment can be made here. In the USA, concern was expressed a decade or so ago that adolescents with cancer had a worse outcome than children with cancer. It was recognized that far fewer adolescents than children entered clinical trials and that many were treated by medical oncologists unfamiliar with many of the diseases that occur in AYAs. Many pediatric oncologists suggested that this group of patients deserved its own set of specialists. Whether there are enough specialists, even in the HIC for this to be possible in all cases is highly questionable, but specialists in a small set of diseases are more likely to obtain good results, and this means that to the extent possible, experts in specific diseases should be involved in the care of AYA patients. This is more important than the specialist being familiar with a specific age -group. For example, either pediatric oncologists or medical oncologists are competent to treat the tumors in AYAs that they more often see in children or older adults respectively. Radiotherapists and surgeons should be discouraged from implementing treatment without additional consultations unless the patient is appropriately treated with one of these modalities alone; multidisciplinary conferences are likely to be particularly valuable in AYAs. Some may choose to specialize in cancers in AYAs or to conduct research on cancers occurring in these age groups (which may well, in some cases, be biologically different), or the consequences, in terms of late effects and psychosocial issues, of cancer treatment. However, in LMIC, there are often no pediatric or even medical, surgical or radiation oncologists in the country or in a large region of the country, such that AYA specialists may be an unaffordable luxury.

The conduct of clinical trials is another way in which experts can have major input into treatment in a large network of hospitals, for research protocols are written by few and carried out by many. Because of the fact that rather few clinical trials have been undertaken specifically in AYAs there is a strong need in HIC as well as LMIC to expand clinical research in this patient group, and wherever possible, to merge clinical research with standard treatment. This would, of course, require additional infrastructure for data collection, and appropriate ethical review, but is likely to improve the results of treatment by increasing discipline with respect to protocol adherence, increasing the number of patients enrolled into research studies and ensuring that experts are involved in the design of treatment protocols.

Another challenge that needs to be addressed is the shortage of radiation therapy units in LMIC. In many tumors, particularly carcinomas and many sarcomas and brain tumors, radiation is an important component of therapy, but is simply not available [23]. As mentioned, using neoadjuvant therapy to try to shrink the tumor until it is surgically resectable may be an approach worthy of clinical research in at least some tumors (e.g., cervical cancer), but most patients with extensive tumors in low-income countries are ineligible for radiation, which is almost always a local or regional form of therapy, so that in most patients, radiation is primarily used at present for palliation. The question can be posed, however, for a number of diseases, whether the dose or volume of radiation therapy can be reduced, even if only for a fraction of patients (e.g., with specific disease sites or stage) since the simpler the radiation therapy, the more patients can be treated per machine in a given time period. This will vary with disease and stage as well as the effectiveness of chemotherapy and the availability of surgeons able to perform any necessary additional surgery. An answer could only be obtained through carefully conducted clinical trials in centers with the necessary research infrastructure. Improving research capability is likely to be cost-beneficial compared to building many more radiotherapy unit and training the necessary staff, and would have the additional advantage that many other types of clinical studies relevant to LMIC could be conducted. Good supportive care and well trained oncologists would also be necessary, and such studies are more likely to be conducted in major institutions in UMIC than in LMIC or LIC. In many diseases, or disease stages, the role of radiation in the era of combination chemotherapy has not been adequately addressed. The use of radiation in Hodgkin lymphoma, for example, was for decades after the development of effective chemotherapy regimens, strongly recommended by oncologists since it was the first therapy shown to be capable of producing long-term survival, but today, many patients are treated without radiation, and the roll of radiation in some patients, e.g. with bulky mediastinal disease is still controversial—in large part because the need for radiation depends upon the effectiveness of the chemotherapy regimen used. In Uganda it was shown many years ago that a high fraction of patients with Hodgkin lymphoma can be treated effectively without radiation, with survival rates being in excess of 70 % at 5 years [24]. Earlier diagnosis in a number of diseases would increase the fraction of patients who may be adequately treated with chemotherapy, or rarely, surgery alone. Examining the role of radiation in selected tumors or tumor stages is a much more important issue for the LMIC than the HIC, where sophisticated radiotherapy equipment is readily available. Even in HIC, however, some cancers (particularly hematological neoplasms and testicular tumors) radiation is no longer a standard component of therapy. Where no known alternative to radiation is known, and clinical trials are not underway, there may be no choice other than to treat patients with chemotherapy and, potentially, surgery, accepting a lower survival rate as the best possible outcome achievable under the circumstances [••25]. In patients with very extensive disease, palliative care, with or without radiation therapy now used to control symptoms, may be the only realistic alternative.

Without knowing the outcome of specific treatment protocols (even if adapted from protocols in use in HIC) in the setting of countries with limited resources, progress in improving survival rates will not be possible. There are no standard approaches to adapting protocols for low resource settings, although as a general rule, their anticipated bone marrow toxicity is reduced by modifying dosage and dose rate. This does not necessarily reduce the efficacy of the therapy, which may have been more intensive than necessary [26] although the likelihood that it will is high. Treatment elements that require close monitoring (e.g., high-dose methotrexate infusions), and therefore more well trained nurses and sometimes additional equipment such as infusion pumps, or protocols that use very high doses of drugs with a resulting high incidence of fever and neutropenia (which, apart from being life-threatening, carry additional cost in terms of hospital and staff time and the required antibiotics), and protocols using drugs given by continuous infusion (over many hours or days) may not be suitable for use in LMIC, or in some regions of such countries.

Survivorship

The late toxic effects of chemotherapy are well known in HIC, but very few studies have been done in the LMIC. Because survivors in this set of patients still have most of their lives to lead, the establishment of rehabilitation programs is particularly important and likely to be cost effective. Counseling patients on late effects in general and the risks of second malignancies is important, since many of these patients may be treated again and achieve long-term survival after treatment of the second tumor. This is a good reason to follow patients for as long as feasible, although if good collaborative networks are established, they may not need to return to the tertiary hospital for standard follow up studies (if any). There is no reason why they could not be seen by a primary or secondary care physician who has been given an indication of what to look for and provides reports to the tertiary care hospital at intervals, so that long-term survival and late effects can be assessed in as many patients as possible, and modifications made to treatment with a high risk of late effects.

Research

At the present time, only a few percent of research articles published in the world come from less-developed and, not surprisingly, with the exception of some of the more advanced centers in UMICs, a standard of care has yet to be established in these countries. Using unodified treatment protocols obtained from HIC is often not appropriate in the absence of toxicity data in the population in the LIMC. Treatment protocols for the less developed countries should be carefully thought out, with cost and toxicity very much in mind, and tested in the resource setting in which they will be used before being considered “standard care” in limited resource settings. While there is much discussion about the conduct of research in less developed countries, the simple collection of data regarding response and toxicity provides important information and thus constitutes research—in effect, allowing an evidence-based approach which would otherwise not be possible. Some studies may be undertaken with the cost–benefit ratio in mind, although since prices can change rapidly, the findings may be undermined by post-trial changes in price. In this regard, international regulations may be needed to avoid manufacturers or distributors of chemotherapy drugs from increasing the price as the market expands. Since the chemotherapy used in academic centers in LMIC, even for research studies, will almost always be generic (pharmaceutical companies tend to undertake their own drug development studies, usually through contract research organizations) there should be a sufficient number of manufacturers, including those in the developing countries themselves, to keep drug prices low. This is an area where policy decisions at a national level relevant to the financing of cancer care are critical to ensuring access of patients to the treatment they need [••25].

Cancer and Culture

In more-developed countries, interest in the cancers of AYAs developed because of their overall differences from other age groups and their failure to fit in with the simpler idea of cancers of children or cancers of adults. Moreover, the psychosocial needs of AYERs differ from those of either of the other groups. Their peers, even at the expense of family, become critically important to them, and collaboration, for good or ill, is stronger at this age than in any other. AYAs strive for new experiences, and new thrills in all aspects of life and as such are the driving force for cultural change in society. This means too, that AYAs are the age group in which good or bad habits tend to develop—the age at which many take up smoking or the harmful use of alcohol and risk taking behaviour peaks (hence the high incidence of trauma and increasing incidence of cancer later in life). But young people also undergo higher education and with mind and body at their peak, AYAs are often the age-group responsible for the development of new scientific discoveries and new behaviours in every walk of life—seen, of couse, by older generations, fixed in their ways, as rebelliousness, and altogether negative—and indeed, these energies can be channeled into negative directions if harshly suppressed. Perhaps the time has come to take a much greater interest in the psychosocial aspects of AYAs, not just in terms of their patterns of cancer and anti-authoritarian behaviour, but in their psychology and energy, and ensure that appropriate outlets for their risk-taking behavior exist which lead to positive outcomes rather than negative—and in the field of cancer and medicine, a new perspective on the social determinants of disease. For it is in this age group, that the seeds of the future patterns of disease are sown.

Conclusions

In addition to essential national research with respect to care, there is much research relating to risk factors in diseases rare, but not unknown in HIC, that would be of value to all. Assisting less-developed countries to develop research programs of their own may be one of the most important elements of knowledge transfer, since the ability to conduct research leads to independence, a mind-set conducive to developing novel preventive and therapeutic programs and the collection of accurate data —for without this, cancer care in the less-developed countries, whether in the AYA age group, children or in elderly adults, will take a very long time to improve.

Compliance with Ethics Guidelines

Conflict of Interest Ian Magrath declares no potential conflict of interest.
Sidnei Epelman declares no potential conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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