The distinctive biology of cancer in adolescents and young adults

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Abstract | One explanation for the relative lack of progress in treating cancer in adolescents and young adults is that the biology of malignant diseases in this age group is different than in younger and older persons, not only in the spectrum of cancers but also within individual cancer types and within the patient (host). Molecular, epidemiological and therapeutic outcome comparisons offer clues to this distinctiveness in most of the common cancers of adolescents and young adults. Translational and clinical research should not assume that the biology of cancers and patients is the same as in other age groups, and treatment strategies should be tailored to the differences.

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After a half century of oncology focusing on cancer in children and in older adults, attention has turned to adolescents and young adults (AYAs)[1–3], in part because of a lack of progress in this age group relative to younger and older patients[4]. After conducting a Progress Review Group (PRG) on AYA oncology[2], the US National Cancer Institute (NCI) released recommendations that included "improving the understanding of host/patient biology of ageing and cancers, including sarcomas, leukaemias, lymphomas, and breast and colorectal carcinomas" and "investigating a potential biologic basis of age-related differences in outcome for AYA cancers." The responsibility for implementing these recommendations has been assumed by the LIVESTRONG Young Adult Alliance (see URL in Further information), a coalition of organizations dedicated to addressing the care of and research in young adults with cancer[5].

A priority of the Science Task Force of the Alliance is to summarize what is known about the differences between AYAs and other age groups in the biology and therapeutic outcomes of cancer. This Review will summarize available evidence upon which further strategies for improving the survival of AYAs with cancer can be based. As the PRG selected the age range of 15–39 years for the definition of AYAs, this Review will compare that age span with younger and older ages.

Unique composition of cancer types in AYAs

An obvious difference between malignant diseases in AYAs and those affecting both younger and older persons is the distinctive array of cancer types that occur in AYAs (FIG. 1). At no other time in life is this array similar. Nearly 90% of all invasive cancers during this age span is accounted for by ten groups: in rank order, breast cancer, lymphomas, melanoma, female genital tract tumours (ovary and uterine cervix), thyroid carcinoma, sarcomas, testicular cancer, colorectal carcinoma, leukaemias and brain tumours (FIG. 1a). Among 15–19-year-olds, the most frequent group is lymphomas, followed by leukaemias, sarcomas and brain tumours, whereas in 20–29-year-olds the order is lymphomas, melanoma, thyroid cancer and testicular cancer[4]. Breast and colorectal carcinomas begin to occur with measurable proportionality in 20–29-year-olds[4]. Most of the specific cancers that are common in AYAs are proportionately more common than in other age groups, including Hodgkin lymphoma, melanoma, testicular cancer, cancer of the ovary and uterine cervix, thyroid cancer, soft-tissue and bone sarcomas (FIG. 1c).

This distribution contrasts with that in young children in whom embryonal, small round-cell tumours such as neuroblastoma, Wilms tumour, retinoblastoma, rhabdomyosarcoma and teratomas are common, and with middle-aged and older persons in whom epithelial malignancies (carcinomas) account for more than

At a glance

- The relative lack of progress in treating cancer in adolescents and young adults (AYAs) is in part due to a lack of appreciation of differences in the biology of malignant diseases in this age group relative to younger and older persons.
- Molecular, epidemiological and therapeutic outcome comparisons offer clues to this distinctiveness in most of the common cancers of AYAs, including leukaemias, lymphomas, sarcomas, melanoma, and carcinomas of the breast, colon, rectum and nasopharynx.
- Translational and clinical research should not assume that the biology of cancers and AYA hosts is the same as in other age groups, even if the diseases seem the same clinically and histopathologically.
- A systematic review of previously reported biological and therapeutic outcomes, that combines older adolescent and young adult patients with younger and older persons, should be made of biological differences if the numbers of subjects or samples permit an adequate assessment.
- In addition, prospective studies evaluating potential biological differences should be incorporated into investigations that include patients across the age spectrum.
- Therapeutic strategies tailored to the AYA age group, based on the distinct biology of the cancer and the host, might improve outcomes and prognosis.

85% of cancers. Among this older age group, the top ten invasive cancers in rank order are carcinomas of the prostate, breast, colorectum and urinary bladder, lymphomas, malignant melanoma, and carcinomas of the ovary, kidney and pancreas[4].

Furthermore, several cancers peak in incidence during the AYA years. Distinctive among these are Hodgkin lymphoma, testicular cancer, bone sarcomas and Kaposi sarcoma (FIG. 1b). Acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML), ovarian tumours and non-Kaposi, soft-tissue sarcomas have an AYA peak before increasing to a higher incidence rate during later adult life (FIG. 1b). This pattern may indicate different biological types of cancer with the same histology, one that arises in AYAs and another that occurs at an older age.

Acute lymphoblastic leukaemia (ALL) appears to have an incidence peak among males in the AYA age range in addition to the well-known peaks during childhood and late adult life (FIG. 2a). This incidence pattern, not previously appreciated, suggests a biologically different kind of ALL within the AYA age group, at least within males. In addition, the distinct male versus female pattern in ALL incidence suggests a biological difference in AYAs from that in both younger and older patients (FIG. 2b). The higher incidence in males that begins during their adolescent growth spurt and continues throughout their young adult years also suggests that androgens or other male hormones might contribute to the development of ALL, rather than there having to be a biologically distinct ALL in this age group.

Progress Review Group (PRG). Panel of experts assembled by the US National Cancer Institute to assess the state of the science of a cancer or cancer group and make recommendations for future research.

Differences in therapeutic outcomes

AYAs with malignant diseases have not enjoyed the same degree of survival prolongation and mortality reduction as either younger or older patients[4]. A plausible biological basis for this deficit is that nearly all therapies administered to AYAs are derived from either younger or older patients[1,3]. Also, there has been a relative lack of clinical trial activity (with less appreciation for potential biological differences) and of tumour specimens for translational research from patients in this age group (and thereby less opportunity for study and discovery of differences). If the biology of these cancers differs then optimal treatment may also. This is particularly true for the recently developed molecularly targeted agents.

A variety of cancers prevalent in AYAs have a worse survival than the same cancers in younger or older patients. Those with a worse survival rate than that in both younger and older patients include breast cancer, colorectal cancer, soft-tissue sarcomas, non-Hodgkin lymphomas considered as a group, and leukaemia in aggregate[4] (FIG. 3a). Those that have a lower survival in AYAs than in younger patients include ALL, Ewing sarcoma, kidney cancer (including Wilms tumour), Hodgkin lymphoma, uterine cervix carcinoma, ovarian cancer (including stromal tumours), brain tumours and liver cancer (FIG. 3b). Neuroblastoma also follows the pattern of decreasing survival with increasing age.

As a group, non-Kaposi sarcomas have a survival–age relationship that is complex and includes a nadir in survival in the early AYA range (FIG. 4a), probably due to the large variety of sarcomas within the group. The early AYA nadir is attributable to the predominance of embryonal rhabdomyosarcoma in younger patients. In older patients, the survival curve is a composite of many types of sarcomas (fibrosarcoma, liposarcoma, leiomyosarcoma, undifferentiated sarcoma and gastrointestinal stromal tumour (GIST), among others) in which AYA may differ from older patients. On the other hand, Kaposi sarcoma has a much worse prognosis in younger than in older adults, probably because most of the cases in younger adults occur in persons with AIDS (which also suggests a basic biological difference).

The cancers with a similar prognosis across the age range are thyroid and testicular cancer, both of which have an excellent survival except in the most elderly (FIG. 4b). Melanoma may be the only type of cancer that has, in general, a better overall survival in AYAs than in younger patients and the most elderly (FIG. 4b).

ALL. The prognosis of ALL declines dramatically with age across the AYA range. Between 10 and 30 years of age, the 5-year survival rate plummets from 85% to <35% (FIG. 3b). Some of the decline is due to an increase in unfavourable biological subgroups that occur with increasing age (summarized below in Clues from cancer biology), but the magnitude of decline is much greater and more rapid than can be explained on this basis[6]. A major factor in the decline is the use of treatment regimens that have been subsequently found to be inferior to paediatric protocols used in the same age group[3,4]. Another factor may be the existence of a biologically distinct kind of ALL in AYAs, as suggested by the incidence pattern (FIGS 2,3) and by a sharp decrease in survival between 10 and 20 years of age among patients treated with the same or similar 'paediatric' regimens.

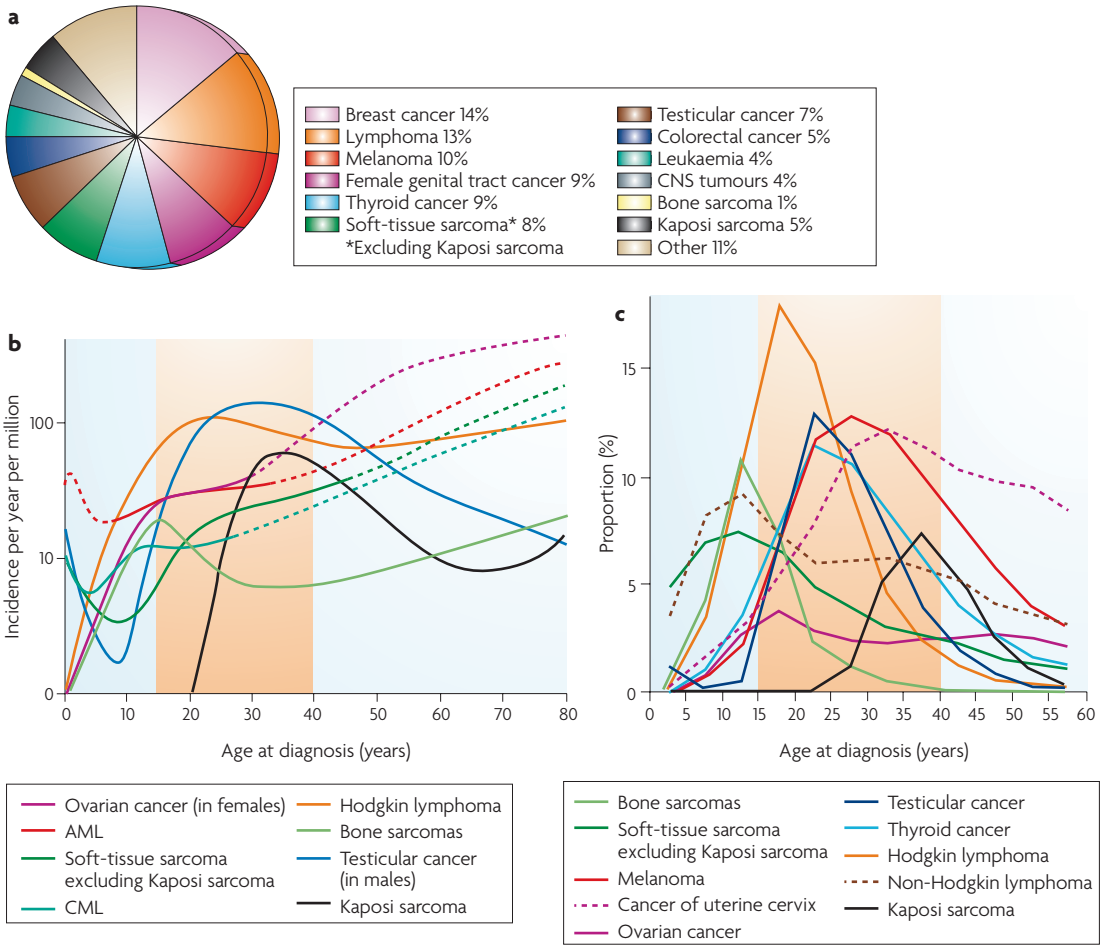

Figure 1 | **Relative occurrence of the most common types of cancer in 15–39-year-olds. a** | Relative frequency of the common types of cancer in 15–39-year-olds, 1992–2002. **b** | Cancers with an incidence peak between 15 and 39 years, 1975–2002. Ovary and testis cancer are evaluated relative to their gender. Segments of broken line represent incident patterns before or after the adolescent and young adult peak. The curves were created from data from individual years of age and were smoothed. **c** | Incident cancers as a proportion of all invasive cancer in the age group by age at diagnosis, 1975–2002. Each cancer is in proportion to cancer in males and females, including testis, ovary and uterine cervix cancers. The yellow background zone indicates the 15–39-year age range. Data from 5-year age intervals up to age 60. Data from US Surveillance Epidemiology and End Results (see URL in Further information), accessed 7 January, 2006. AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; CNS, central nervous system.

Breast cancer. Below age 45, the younger a woman is when diagnosed with breast cancer, the worse the expected outcome (FIG. 5a). This pattern is independent of stage and extent of disease at diagnosis, and of histological type (FIG. 5b,c).

Colorectal cancer. For both males and females with colon and rectal cancers, the younger the patient below 40 years of age, the worse the survival, overall and for stages I, II and III (FIG. 6). In stage IV, the survival is so much worse that age dependence is not apparent. Young patients also generally present with advanced disease[7].

Ewing sarcoma. In one of the first multivariate analyses of prognostic factors in Ewing sarcoma, survival was found to be inversely proportional to age[8]. Subsequent studies indicated that the worse outcome was due, at least in part, to more advanced disease in adults at the time of diagnosis, including the volume of the primary tumour and its predisposition to arise in the pelvis in older patients[9]. However, in a retrospective study of <100 patients with Ewing sarcoma, from age 16 to 48 years, all of whom were treated identically with an intensive regimen, age was not found to be an independent determinant of survival, whereas the volume of tumour was predictive[10]. This was corroborated in a subsequent study that intensified treatment for those with large volume tumours and did not find any effect of age on survival[11].

On the other hand, in a larger randomized trial of 518 patients with Ewing sarcoma, conducted by the Children's Oncology Group (COG), older patients were again noted to have a worse outcome[12]. The 5-year event-free survival was 60–70% for patients <18 years of age and 44% for those ≥18 years (P <0.01)[12]. The benefit of the addition of ifosfamide and etoposide

observed in younger patients was not observed in patients over age 17. In a subsequent COG study with 568 eligible patients, similar findings were noted (4-year event-free survival of 50% and 70% for patients older or younger than 17 years of age, respectively, and benefit from interval compression chemotherapy that occurred in the younger patients but not in the older group)[13]. These observations in the two largest studies conducted to date suggest that the biology of Ewing sarcoma in AYA patients might be different from that in younger patients.

Wilms tumour. A review of 51 adults aged 16–55 with Wilms tumour has shown similar survival rates for early-stage disease, but clearly worse outcomes for advanced disease (stage III and IV) in AYA and older adult patients versus children[14]. In Europe, stage-specific survivals of about half that achieved in children have been observed, along with longer lag times (time from first tumour-specific symptom or sign to diagnosis) in adults than in children (P. Grundy, personal communication).

Neuroblastoma. AYAs with neuroblastoma are much more likely to present with advanced disease than are children. In a series of 30 AYAs with a median age of 19 years, 27 presented with stage IV disease, two had stage III, one had stage IIB and none had stage I or IIA[15]. This contrasts with children in whom >30% have stage I or IIA disease. Twelve of the 30 AYA patients had major responses with surgery and multi-agent chemotherapy[15]. This contrasts with the experience in children with advanced disease in whom response rates of 60–80% are achieved.

Rhabdomyosarcoma. A distinctly lower survival rate has been observed in AYAs with rhabdomyosarcoma than in younger patients[16], a difference that is only partially explained by the use of adult rather than paediatric treatment regimens. The alveolar variant of rhabdomyosarcoma, which carries an unfavourable prognosis and is typified by translocations involving chromosome 13, is more common in the AYA age group than in children. The increasing alveolar/embryonal ratio with age may help explain the worse outcome in older patients.

Clues from cancer biology

Breast cancer. Young women with breast cancer are more likely to have larger, less hormone-sensitive tumours of higher grade, with more frequent spread to lymph nodes and a greater number of involved lymph nodes than older women[17]. Young women have the highest incidence of the so-called 'triple-negative' tumours, which are devoid of the both the oestrogen and progesterone hormone receptors and also the growth factor receptor ERBB2 (also known as HER2). Triple-negative tumours are associated with a worse prognosis than those cancers that express at least one of these receptors[18]. This differential effect may be partly due to fewer therapeutic options for these patients than for those who have these receptors (for example, tamoxifen and trastuzumab).

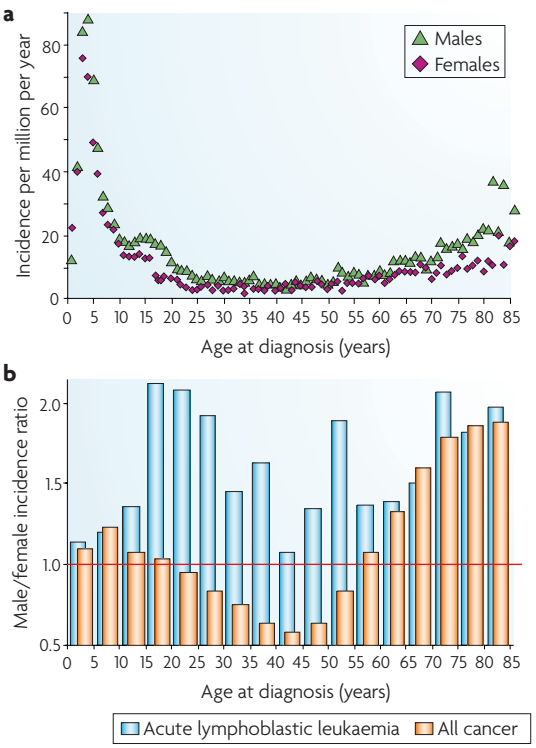

Figure 2 | **Incidence of acute lymphoblastic leukaemia (ALL) as a function of age at diagnosis and gender.** **a** | Incidence in males and females as a function of individual year of age, 1973–2004. Data from US Surveillance Epidemiology and End Results (see URL in Further information), accessed 28 August 2007. **b** | Male/female incidence ratio in patients with ALL in comparison with the male/female incidence ratio of all invasive cancer, as a function of 5-year age intervals, 1973–1999. The ordinate is expressed as a log function. Data from US Surveillance Epidemiology and End Results (see URL in Further information), accessed 1 June 2005.

Breast cancer at an early age is more likely to be associated with an increased familial risk, especially in women born with *BRCA1* mutations[19], although proportionately few breast cancers in 15–39-year-olds are attributable to inherited forms. In one study of women with breast cancer diagnosed before age 30, *BRCA1*, *BRCA2* and *TP53* mutations were found in about half of women with strong family histories of breast cancer and in less than 10% of women with non-familial breast cancer[20] .

In a comparison of breast cancer in 200 pre-menopausal women with that in 211 post-menopausal women who did not differ in oestrogen or progesterone receptor status by immunohistochemistry, the following differences were found in the younger group, half of whom were younger than 40: larger tumour size ($P \leq 0.0005$), higher tumour grade ($P < 0.0001$), greater lymph node positivity ($P < 0.05$), higher expression of ERBB2 ($P < 0.05$), lower quantitative oestrogen receptor expression (mRNA), and greater deregulation of phosphatidylinositol 3-kinase (PI3K) and pathways involving the *MYC* oncogene[21]. Among the young women, deregulation of the PI3K and β-catenin (encoded by *CTNNB1*) pathways

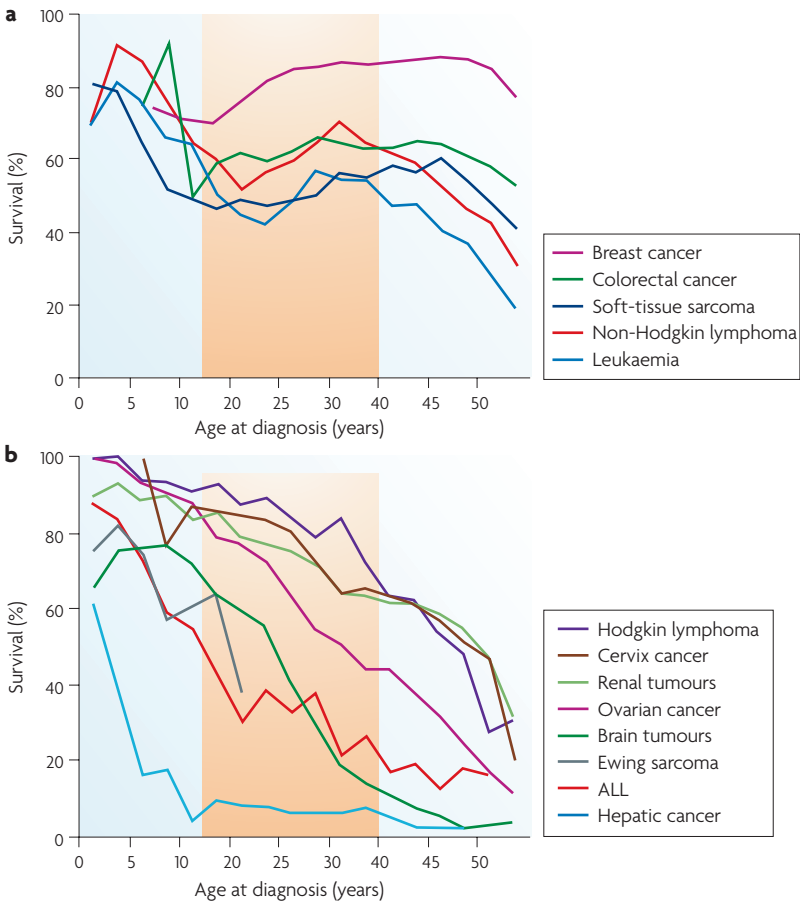

Figure 3 | **Cancers with 5-year relative survival rates that are lower in adolescents and young adults (AYAs) than in younger or older patients.** Data from US Surveillance Epidemiology and End Results (see URL in Further information) 1993–1997. The yellow background zone indicates the 15–39-year age range. **a** | Cancers that have a lower survival in AYAs than in both younger or older patients. **b** | Cancers that have a lower survival in AYAs than in younger patients. Adapted, with permission, from REF. 3 © American Cancer Society (2007).

were associated with a worse outcome than those with deregulation of the oncogenes *MYC* and *SRC* (P <0.01), in contrast to a pattern in older women in whom a worse outcome was associated with deregulation of the E2F transcription factors and a concurrent low deregulation of PI3K and MYC (P <0.01). The investigators concluded that there is a different biological type of breast cancer in women younger than 45, with different oncogenic pathway deregulation and chemosensitivities that potentially could be exploited therapeutically[21].

Colorectal cancer. Colorectal cancers in AYAs have at least two distinguishing biological features: the highest incidence of microsatellite instability (MSI) and the highest incidence of the heritable forms of colorectal cancer (familial adenomatous polyposis (FAP), characterized by mutations in the adenomatous polyposis coli (*APC*) gene, and hereditary non-polyposis colon cancer (HNPCC), characterized mutations in mismatch repair genes mutS homologue 2 (*MSH2*), mutL homologue 1 (*MLH1*) and postmeiotic segregation increased 2 (*PMS2*)). In HNPCC, the two features are related, in that MSI is a hallmark of HNPCC. However, they are not related in FAP. Non-inherited, sporadic forms of colorectal cancer in AYAs often do not have the *KRAS* mutations, loss of heterozygosity (LOH) at chromosome 17p or 18q, and other mutations in tumour suppressor genes and oncogenes that are typical of colon cancer in older patients[22,23]. In that the underlying abnormality in the cancer cell determines its susceptibility to anti-neoplastic agents, colorectal cancers in AYAs are likely to require different therapies for optimal benefit to the patient. This difference may explain why adjuvant chemotherapy has to date been of little to no benefit in young adults with carcinoma of the colon in comparison with older adults[24], and it is likely to be an increasing problem with molecularly targeted agents.

The pattern of histopathological types of colorectal cancer also differs in AYAs compared with older patients. Mucinous adenocarcinoma, generally associated with a worse prognosis, occurs in nearly 50% of AYA colorectal cancers compared with 2–4% in older adults. In the largest study of AYAs with colorectal cancer from a single institution, 368 patients ≤40 years of age were evaluated. The proportion of poorly differentiated tumours, mucin-producing tumours and advanced-stage tumours (Duke stages C and D) were each inversely proportional to age (P <0.01, P <0.001 and P <0.001, respectively), each characteristic of which is associated with a worse prognosis[25]. Other studies have shown that AYA patients have a higher incidence of signet-ring histology and of a primary tumour that arose in the rectum and proximal colon[26,27]. According to US Surveillance Epidemiology and End Results (SEER; see URL in Further information) data, more females than males develop rectal cancer between age 25 and 50 (ratio ~1.4), whereas there appears to be no sex difference for colon cancer.

Between 1964 and 2003, 77 patients referred to St Jude Children's Research Hospital with colorectal carcinoma were 7–19 years of age, 59% of whom were age 15–19 years. None had a preceding diagnosis of polyposis syndrome; colonic polyps were found in 22% and 10% had multiple polyps[28]. Overall outcome was poor, with 80% of the patients dying within 5 years. The most striking biological difference discerned in this study was mucinous adenocarcinoma, which was found in 62% of the patients, leading the authors to conclude that "the biology of colorectal carcinoma differs in paediatric and adult patients and may contribute to the poor outcome." A more recent report of 27 patients <30 years of age treated at the Istituto Nazionale Tumori, Milan, Italy between 1985 and 2005 supports the poor outcome of the youngest patients. Among 20 19–29-year-olds, the 5-year overall survival was 73%. Among seven younger patients (age 9–18, median 12 years), five had unfavourable histotypes (poorly differentiated or mucinous adenocarcinoma) and all but one had advanced disease at diagnosis. Their overall survival was 23% at 5 years despite surgical resection that was complete in five cases and post-operative chemotherapy in all[29].

Microsatellite instability
A condition manifested by damaged DNA due to defects in the normal DNA repair process and characterized by unstable sequences of repeating units of 1–4 base pairs in length.

Familial adenomatous polyposis
An inherited mutation in the *APC* or *MUTYH* gene results in numerous polyps in the large intestine that usually undergo malignant transformation into colon cancer when not treated.

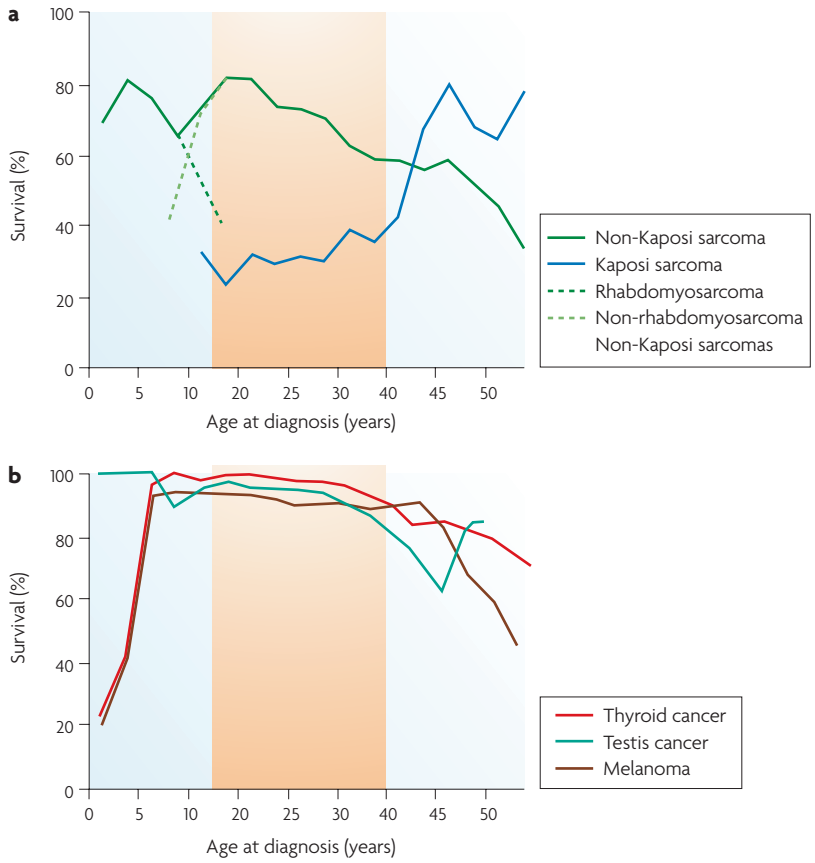

Figure 4 | **Other cancers with 5-year relative survival rates that have different patterns in adolescents and young adults (AYAs) from those in younger or older patients.** Data from US Surveillance Epidemiology and End Results (see URL in Further information) 1993–1997. The yellow background zone indicates the 15–39-year age range. **a** | Sarcomas. **b** | Cancers that have an equivalent or better survival in AYAs than in younger or older patients. Adapted, with permission, from REF. 3 © American Cancer Society (2007).

ALL. Compared with children, AYAs with ALL are more likely to have adverse biological characteristics, such as L2 morphology[30], pro-T cell immunophenotype and the t(9,22) *BCR–ABL* (Philadelphia chromosome) translocation[31]. The *BCR–ABL* genotype occurs in <3% of children and in 3–26% of AYAs with ALL[32]. Nearly half of all children but only 10% of adolescents have blast cells with a favourable genotype, such as the *TEL–AML1* translocation[31]. Although the proportion of T-cell ALL does not change much during childhood and adolescence[31], the Hox$^+$ subtype is more common in AYAs than in younger and older patients and is associated with a worse prognosis[33]. The p57 (encoded by *CDKN1C*) and p15 (encoded by *CDKN2B*) growth-regulating kinase genes and the *TP73* tumour suppressor gene have been observed to be more methylated in ALL among adults than in children[34]. As several anti-neoplastic agents are now available that target hypermethylation sites on DNA, this difference might have therapeutic significance in AYA ALL.

Recently, several reports have implicated a treatment effect rather than differences in underlying biology for differences between ALL outcomes in AYAs versus adults. This is based on observations that, in AYAs, paediatric treatment regimens have been superior to those used by haematologists and medical oncologists who treat adult patients[35–41]. However, even paediatric treatment regimens are not as effective in older adolescents with ALL as in younger adolescents and children, suggesting that a biological influence accounts for some of the difference.

Non-Hodgkin lymphoma. Children and adolescents with diffuse large B-cell lymphoma (DLBCL) have been observed to have event-free survival rates superior to those in adults. Whereas 15% of the cases of DLBCL in adults have a translocation t(14;18), involving the *BCL2* gene, an adverse prognostic factor, none of 63 cases of paediatric DLBCL were found to have this translocation by either immunohistochemistry or fluorescence *in situ* hybridization[42]. During what age range the translocation appears in DLBCL is not known, but it is likely to be during early- to mid-adulthood and, if so, DLBCL has a biologically different profile in AYAs than in older adults.

Ewing sarcoma. Different chromosomal abnormalities in Ewing sarcoma have been found to explain some of the age-dependent clinical correlations described above. In one study of tumour samples from 134 patients, gain of 1q or loss of 16q were both associated with statistically significant poorer outcome and were more common in patients ≥15 years of age than in children[43]. It might be that 1q gain and 16q loss render the sarcoma cells resistant to ifosfamide and etoposide, thereby explaining the outcome of the aforementioned study.

GIST. In patients with GIST diagnosed before age 40, *KIT* and platelet-derived growth factor receptor β (*PDGFRB*) mutations are usually not present in the neoplastic cells, in contradistinction to their usual presence in older patients[44]. This difference probably accounts for the relative lack of benefit of imatinib therapy in young patients with GIST, in contrast to its consistent efficacy in older patients[45]. AYAs with GIST are more likely than older patients to be female and to have multiple primary tumours.

Liver cancer. Malignant hepatocellular tumours in AYAs have different clinical presentation, histopathological findings, immunohistochemistry and treatment response than younger children[46]. 'Transitional' liver cell tumours are a novel group of aggressive neoplasms that occur predominantly in AYAs and overexpress β-catenin, in contrast to liver cancers in both younger and older patients[47].

Melanoma. AYAs are more likely to have malignant melanoma that is not related to solar exposure, in contrast to older persons. As described above and shown in FIG. 4b, melanoma appears to be the only type of cancer that has a better overall survival in AYAs than either in younger patients or older patients. Relative to children, the reason for the better outcome in AYAs

Hereditary non-polyposis colon cancer
(HNPCC). Colon cancer emanating from inherited mutations known as Lynch syndrome that prevent self-repair capability of DNA and also increase risk of stomach, small intestine, liver, uterus, ovary, brain and skin cancer.

L2 morphology
A French–American–British (FAB) system histological type of leukaemic lymphoblast characterized by larger and more variable size, more cytoplasm and a worse prognosis than the L1 type.

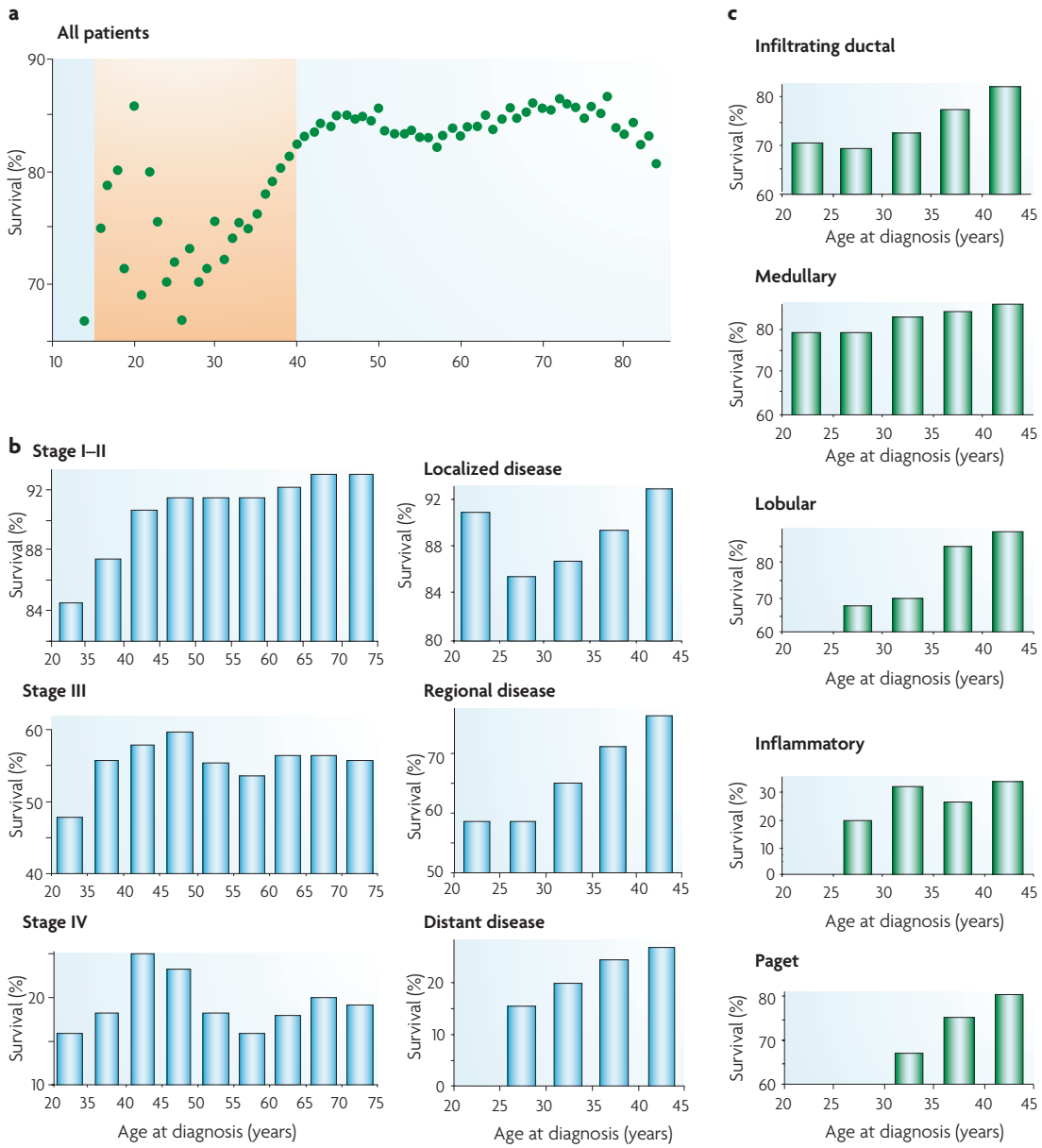

Figure 5 | **Breast cancer survival rates in US women, by age at diagnosis. a** | Data for all patients, by individual year of age at diagnosis. The yellow background zone indicates the 15–39-year age range. **b** | By stage and extent of disease at diagnosis, as a function of 5-year age intervals. **c** | By type of histology, as a function of 5-year age intervals. Data from US Surveillance Epidemiology and End Results (see URL in Further information) 1975-1998, accessed 28 August 2007.

is primarily related to more favourable biological presentations. In separate studies of 9,185 and 2,816 patients <25 years of age, the AYA patients had thinner lesions, more favourable histologies and more localized disease (P <0.001 for each characteristic)[48,49]. Whereas boys had a twofold greater predilection than girls, a reverse ratio of twofold greater incidence in females occurs during adolescense[4]. Relative to older adults, patients under 50 years of age were found to have 2.5 times the incidence of *BRAF* mutations[50], which are found in 40–50% of primary melanomas and are correlated with lower mitotic rate and thinner tumours.

Other cancers. Several other cancer types with low frequency in AYAs have biological differences in this age group compared with adults or children. Translocations involving chromosomes 2, 16 and 22 appear to be more likely among AYAs with liposarcoma than in patients of other ages. AYA females with ovarian cancer are more likely to have 'borderline' tumours than are older and younger patients. Nasopharyngeal carcinomas are more commonly of the undifferentiated type than in older patients. In AYA patients, carcinoma of the tongue is more often devoid of the *TP53* mutations that are characteristic of this cancer in older patients, and is less likely to be related to carcinogenic exposures such as tobacco.

Borderline tumour
Tumours of the ovary with epithelial (carcinoma) and stromal (non-epithelial) elements that are histologically of an intermediate grade between benign and malignant and of uncertain malignant potential.

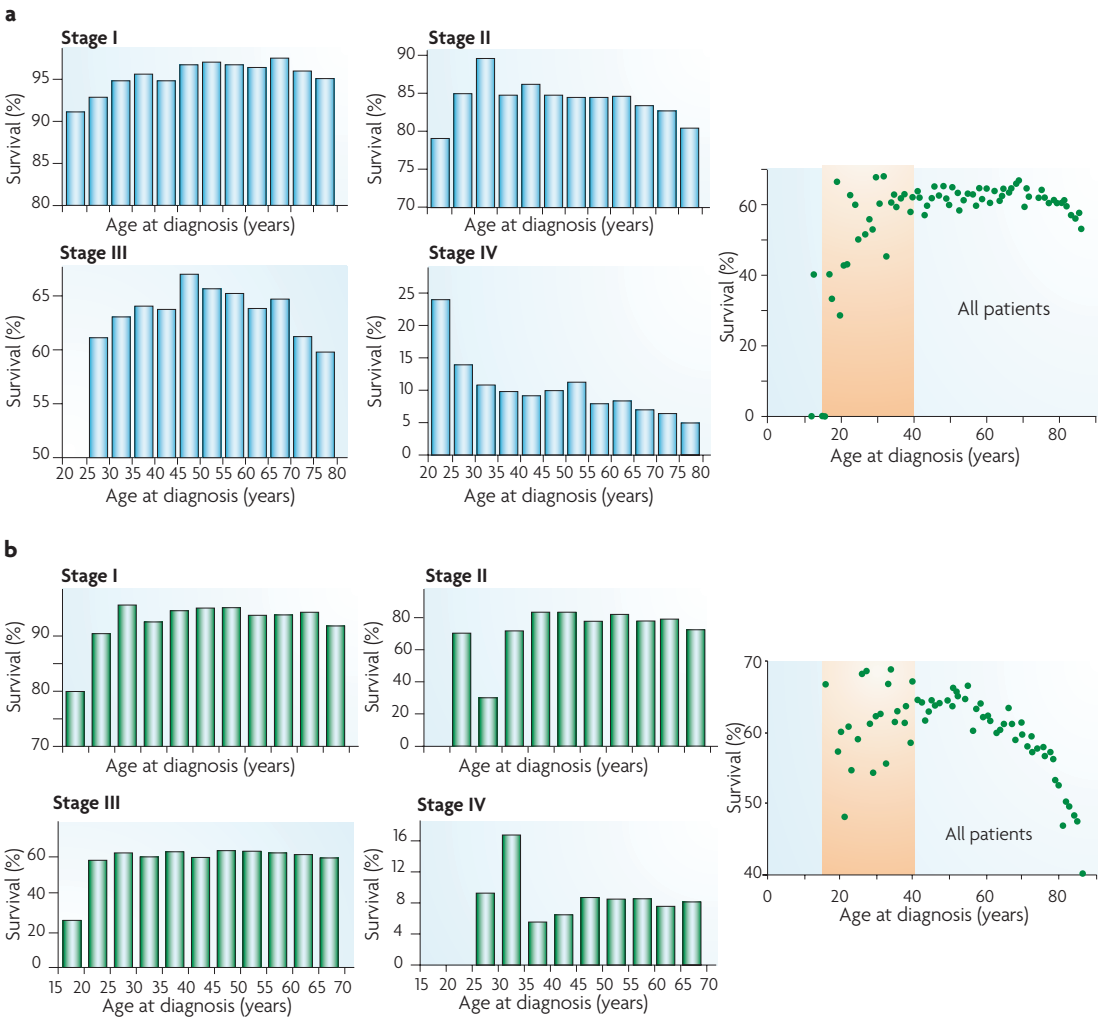

Figure 6 | **Survival by age of diagnosis 1993–1998. a** | Colon. **b** | Rectum. The yellow background zone indicates the 15–39-year age range. Data are from US Surveillance Epidemiology and End Results (see URL in Further information), accessed 10 September 2007.

Potential differences in host biology

AYAs may have a physiology (for example, hormonal), pharmacology (for example, drug clearance), polymorphisms or genomic properties that differ from younger and older persons with respect to cancer susceptibility and treatment.

Family cancer syndromes. An obvious example is the increased occurrence of cancer during the AYA years in individuals with familial cancer syndromes. Nonetheless, because the syndromes are relatively rare, few account for more than a small percentage of the cancers that occur in AYAs. As mentioned above, *BRCA1*, *BRCA2* and *TP53* mutations have been found in <5% of women with breast cancers before age 30 in women without family histories of breast cancer[19]. In 100 women with endometrial cancer before age 50 who were rigorously evaluated for HNPCC by full sequencing, large deletion analysis and immunocytochemistry of the *MLH1*, *MSH2* and *MSH6* genes, MSI analysis and *MLH1* promoter hypermethylation status, nine were found to have the syndrome[50]. All nine were between 39 and 49 years of age and none of 45 women aged 24–43 had HNPCC.

Pharmacological and physiological factors. Age-related changes in the pharmacology of drugs may affect treatment efficacy and toxicities. These changes may be due to epigenetic effects, such as hormonal changes during the pubescence–menopause trajectory, or to physiological changes that affect volumes of distribution (for example, adiposity versus lean body mass), protein binding, hepatic and renal function, or to drug–drug interactions that may be different as result of different drug exposures among AYAs. The increased incidence of obesity in AYA patients compared with younger patients has been associated with poorer outcomes in both ALL[51] and AML[52]. In ALL therapy, AYA patients experience more peripheral neuropathy[53], glucose intolerance[54], pancreatitis and osteonecrosis[55,56], the latter toxicity requiring modification of the dexamethasone dosage schedule in adolescents.

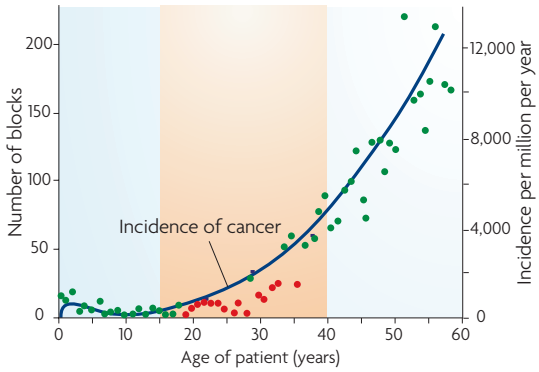

Figure 7 | **Tumour bank specimens versus incidence of cancer as a function of patient age.** The paediatric specimen data were derived from 4,451 tumours collected in 2003–2004 by the Cooperative Human Tissue Network (data kindly provided by J. Smith). The adult specimen data of 3,215 tumours were obtained from the Southern Cooperative Human Tissue Network collected from hospitals in Birmingham, Alabama, USA from 1 January 2000 to 3 May 2005 (data kindly provided by K. Sexton). Data for the cancer incidence curve were derived from US Surveillance Epidemiology and End Results for 1975–2000 (see URL in Further information). Tumour bank specimens are represented by the dots and cancer incidence is shown by the curve. The yellow background zone indicates the 15–39-year age range. The age group of 18–36 years (red symbols) had 57% (301) of 527 specimens expected, as projected from polynomial regression of 10–18- and 37–59-year-old patients.

The period of greatest physical change occurs in AYAs, and includes gender-specific changes in body composition. Gender-related differences in incidence and outcome have been observed in patients with melanoma, Hodgkin lymphoma, Ewing sarcoma and osteosarcoma. In patients with Ewing sarcoma, both age and gender were associated with side effects of chemotherapy, suggesting that growth and pubertal changes may affect drug metabolism[57].

In general, AYAs have greater renal, hepatic and haematopoeitic capacity than do older people. Also, coexisting morbidities complicate therapy more commonly in older adults than patients in the AYA age range. Yet medical oncologists have used the same dosage regimens and dose modification guidelines in AYAs that they derived from their older, larger patient population. As result, AYA patients on adult treatment regimens may be under-treated relative to their biopharmacological tolerance.

Future plans

As summarized in the NCI PRG report[2] and elsewhere[3], the lack of improvement in survival outcomes for AYAs over the past few decades contrasts sharply with dramatic improvements in childhood cancer cure rates and the recent, steady improvement in overall cancer survival rates among older adults. Most of the advances in cancer diagnosis and treatment in children and older adults have been achieved through an integrated understanding of tumour biology and the normal biology of the patient, which has outpaced the state of this knowledge about the AYA population. Attributing this lack of progress to a lack of knowledge about the biology of tumours in AYAs and of host/patient differences as a function of age, the PRG recommended five categories of priorities:

Analyse AYA data in published trials and databases. The PRG recommended that AYA data be mined retrospectively from sources that have sufficient data but did not report results of the AYA subset separately. A retrospective analysis should include an effort to obtain and analyse such data from information held in databases by clinical trials groups and centres, health-care networks, the US Food and Drug Administration and the pharmaceutical industry. The results of retrospective data analyses could then be used in conjunction with known disease impact factors to clarify features of diseases, ascertain treatment pharmacology, evaluate outcome disparities and uncover other effects that are unique to AYA cancer patients. This information could then be combined with the information about the cancers that have the most impact to prioritize the development of new clinical trials targeting the AYA population.

Increase specimens available for translational research. AYA tumour specimens are under-represented in the US national tissue banks (FIG. 7), placing a constraint on translational research in AYA oncology. The national tumour repositories should be funded appropriately to solicit specifically for both tumour and normal tissue specimens from AYA cancer patients.

Increase clinical trial activity in AYA patients. AYA patients have the lowest participation rate in clinical trials of all age groups[58]. Most of what has been learned about treating cancer has come from clinical trials, and hence the paucity of AYA patients in clinical trials might be the single most important factor in the lack of progress in this age group. Also, increasing the clinical trial enterprise for AYA cancer patients will improve tumour and normal tissue specimen acquisition, as biological specimens are often procured in this context.

Focus on the cancers with most impact. From an analysis of the most prevalent cancers, those in which there has been the least amount of progress and is the greatest potential affect on overall progress, sarcomas, leukaemias, lymphomas, breast cancer and colorectal carcinomas, were identified by the PRG to be of the highest priority for investigation[1,5]. The three major adult cooperative groups in North America have agreed to conduct the same clinical trial that is based on a current COG regimen in their newly diagnosed 15–30-year-old patients with ALL. The adult cooperative groups will be comparing their results with those in COG patients of the same age who will be given the same regimen. A cross-study questionnaire will attempt to assess demographic,

financial, psychosocial and practice-related factors to explain differences in results that may occur. Relevant technical and scientific breakthroughs are being made in fields such as genomics, stem cell research and ageing. In particular, sequencing of the human genome and new technologies for global molecular analysis were recommended to study molecular differences among AYA, childhood and adult cancers.

Improve understanding of host/patient biology. The biology of ageing in this population has been understudied, yet might be relevant to many AYA cancers. This population might have unique genetic and epigenetic differences compared with either younger or older age groups, as well as important physiological (including hormonal) and pharmacological differences (for example, effects of sexual maturation, pregnancy, obesity and drug interactions). These factors should be evaluated for how they affect the absorption, distribution, protein binding, metabolism and excretion of drugs, and the response to treatment.

Finally, a better classification system for the unique range of cancers that occur in AYAs is needed[59]. The use of a hybrid system based on paediatric (International Classification of Childhood Cancer) and adult (International Classification of Disease) approaches to characterize the cancers in AYAs is artefactual and suboptimal in utility. As was successfully and rewardingly accomplished for childhood cancer, AYA oncology would benefit from the creation of its own classification system.

Conclusions

There are sufficient clues of distinctiveness in the biology, epidemiology and outcomes of the cancers affecting AYAs to indicate that these diseases are frequently different than at other ages. Translational and clinical research should not assume that the biology is the same as in younger or older patients, even if the cancer seems the same clinically and histopathologically. Previously reported biological and therapeutic outcomes that combined AYAs with younger or older patients should be reviewed systematically for biological differences if the numbers of subjects (or samples) permit an adequate assessment. In addition, prospective studies evaluating potential biological differences should be incorporated into investigations that include patients across the age spectrum. Therapeutic strategies tailored to this age group, based on the biology of the cancer and the host, may improve outcomes and prognosis, a pressing opportunity given the relative lack of progress in AYAs with cancer and their psychosocial and societal challenges.

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DATABASES

Entrez Gene: http://www.ncbi.nlm.nlm.nih.gov/entrez/query.fcgi?db=gene
APC | *BRAF* | *BRCA1* | *BRCA2* | *CDKN1C* | *CDKN2B* | *CTNNB1* | ERBB2 | *KIT* | *KRAS* | *MLH1* | *MSH2* | *MSH6* | *MYC* | *PDGFRB* | *PMS2* | *SRC* | *TP53* | *TP73*

National Cancer Institute: http://www.cancer.gov/
acute lymphoblastic leukaemia | acute myeloid leukaemia | bladder cancer | brain tumour | breast cancer | cervical cancer | chronic myeloid leukaemia | colorectal cancer | endometrial cancer | Ewing sarcoma | gastrointestinal stromal tumour | Hodgkin lymphoma | Kaposi sarcoma | kidney cancer | leukaemia | liver cancer | lymphoma | melanoma | neuroblastoma | ovarian cancer | pancreatic cancer | prostate cancer | retinoblastoma | rhabdomyosarcoma | sarcomas | teratoma | testicular cancer | thyroid carcinoma | Wilms tumour

National Cancer Institute Drug Dictionary:
http://www.cancer.gov/drugdictionary/
dexamethasone | etoposide | ifosfamide | imatinib | tamoxifen | trastuzumab

FURTHER INFORMATION

A. Bleyer's homepage: http://www.defeatcancer.info
LIVESTRONG Young Adult Alliance:
http://www.livestrong.org/yaa
US Surveillance Epidemiology and End Results:
http://seer.cancer.gov/

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