

# ADOLESCENT AND YOUNG ADULT (AYA) CANCERS: DISTINCT BIOLOGY, DIFFERENT THERAPY?

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## Abstract

That cancer may have a different biology in young adults and older adolescents than in younger or older persons is becoming more evident. This review summarises recent reports that contain such data in five of the common types of cancer in adolescents and young adults: sarcomas, acute lymphoblastic and myelogenous leukaemia, colorectal and breast cancer. The findings, along with those in other cancers and with the unique array of cancer types in adolescents and young adults and their age-dependent incidence patterns, suggest that cancer biology in the age group may be different more often than not. Regardless, there is now sufficient evidence to merit methodical research of the underlying biology of cancer in young adults and older adolescents, with the implication that cancer therapy in the age group cannot be optimised until differences and similarities are established. Initiatives underway to address this need include implementation of the US National Cancer Institute Adolescent and Young Adult Oncology Program Review Group by the LiveStrong Young Adult Alliance, the Aflac/CureSearch Adolescent and Young Adult Cancer Research Program, the Children's Oncology Group Adolescent and Young Adult Committee and a combined effort of the US National Adult Cancer Cooperative Groups.

Whereas the diagnosis of cancer in adolescents and young adults (AYAs) used to have, as a group, a better prognosis than children with malignant disease, survival trends suggest that the prognosis of 15 to 39 year-olds is now worse than in younger patients and may be worse than in older patients, especially those diagnosed between 25 and 35 years, as shown in figure 1. In this chart, Kaposi sarcoma is both included and excluded because of the HIV/AIDS epidemic during the late 1980s and early 1990s that skew the survival progress in young adults. In 2006, AYA oncology became a national agenda in the US with the release of an official report from the AYA Oncology Program Review Group (PRG) that evaluated the problem as part of a joint venture between the US National Cancer Institute and the Lance Armstrong Foundation.<sup>1,2</sup> To implement the recommendations, a LiveStrong Young Adult Alliance was formed and now has 110 organisations in the US, Canada and Australia, with a responsibility to promote and apply the PRG recommendations.<sup>2</sup>

The recommendations covered awareness, prevention/cancer control/epidemiology/risk, biology, access, health insurance, clinical care models, clinical trials/research, special populations, psychosocial/behavioural factors, health-related quality of life and long-term effects. The science task force of the LiveStrong Young Adult Alliance is charged with implementing sub-recommendations of the PRG that address clinical and translational research needs. This commentary reviews the two primary executive recommendations (numbered 1 and 3 in the report) of the PRG report with respect to biology and translational research, and provides evidence published since the report that suggests the biology of cancer is often different when it occurs during the AYA years than at other ages. More detail regarding biologic differences between cancer in AYAs versus other-age patients is provided in a review by the author and colleagues.<sup>3</sup>

## AYA Oncology PRG executive

**recommendation 1:** *Identify the characteristics that distinguish the unique cancer burden in the older adolescent and young adult cancer patient.*

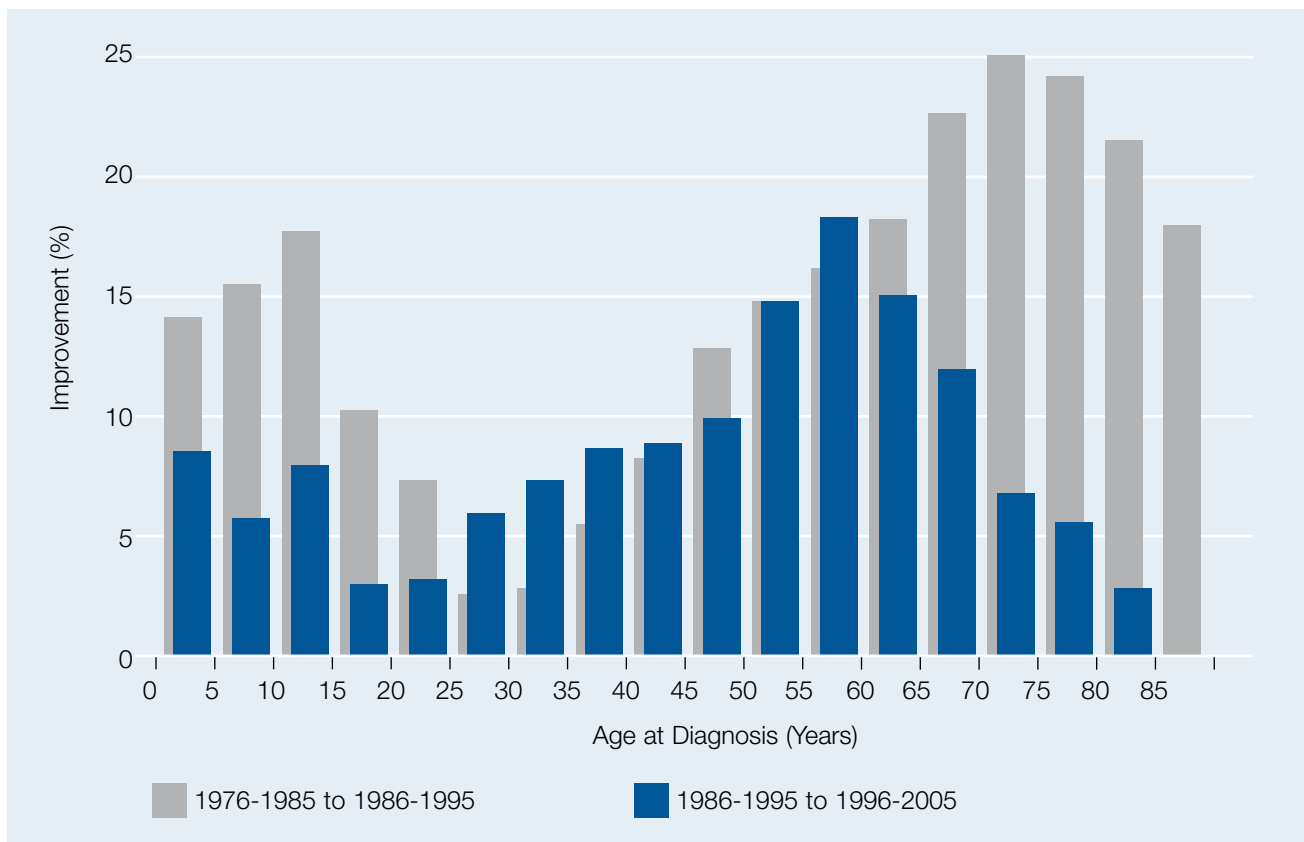
### **Morphobiologic subtypes of cancer in AYAs**

At no other time in life is the array of cancer types similar to those affecting AYAs (figure 2). Nearly 90% of all invasive cancers during this age span is accounted for by 10 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.<sup>3</sup> Breast and colorectal carcinomas begin to occur with measurable proportionality in 20 to 29 year-olds.<sup>3</sup> 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.<sup>3</sup>

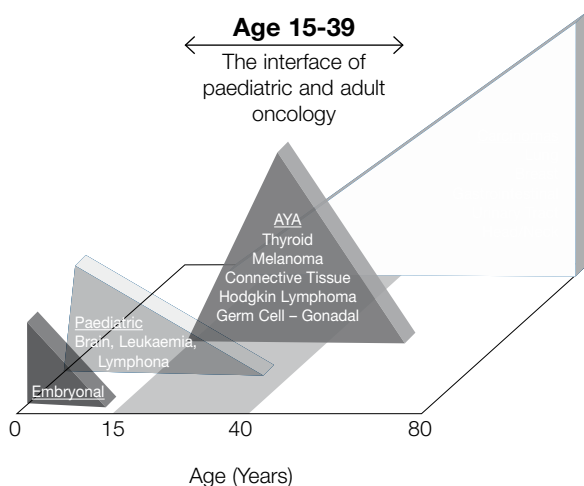
### **Different outcomes with the same therapy**

In addition to the mounting data for a distinct biology of cancer during the AYA years, additional evidence is suggested by the majority of the common cancers in AYAs that have a different outcome with the same therapy used in younger and older patients. Those with a worse survival rate in AYAs than that in both younger and older patients include breast cancer, colorectal cancer, soft tissue sarcomas, non-Hodgkin lymphomas considered as a group, and the leukaemias in aggregate.<sup>3</sup> Those that have a lower survival in AYAs than in younger patients include acute lymphoblastic leukaemia, Ewing sarcoma, kidney cancer (including Wilms' tumour), neuroblastoma, Hodgkin lymphoma, uterine cervix carcinoma, ovarian cancer (including stromal tumours), brain tumours and liver cancer.<sup>3</sup>

**Figure 1:** Improvement in 5-year relative survival of patients diagnosed with any invasive cancer except Kaposi sarcoma from 1976-1985 to 1986-1995 and from 1986-1995 to 1996-2005, US Surveillance, Epidemiology and End-Results (SEER) Program. Kaposi sarcoma is excluded because the HIV era during the late 1980s and early 1990s and the associated transient Kaposi sarcoma epidemic skews the overall results in 20 to 49 year-olds.



**Figure 2**  
Cancer in 15 to 39 year-olds represents the interface between paediatric and adult oncology.



### Examples of different biology

Recent reports on the two most common leukaemias in AYAs provide more evidence that the biology of cancer in AYAs is different than it is in younger and older persons. The distinctness is also apparent in sarcomas and in breast and colorectal carcinomas, solid tumours with biologic knowledge that is among the most well developed.

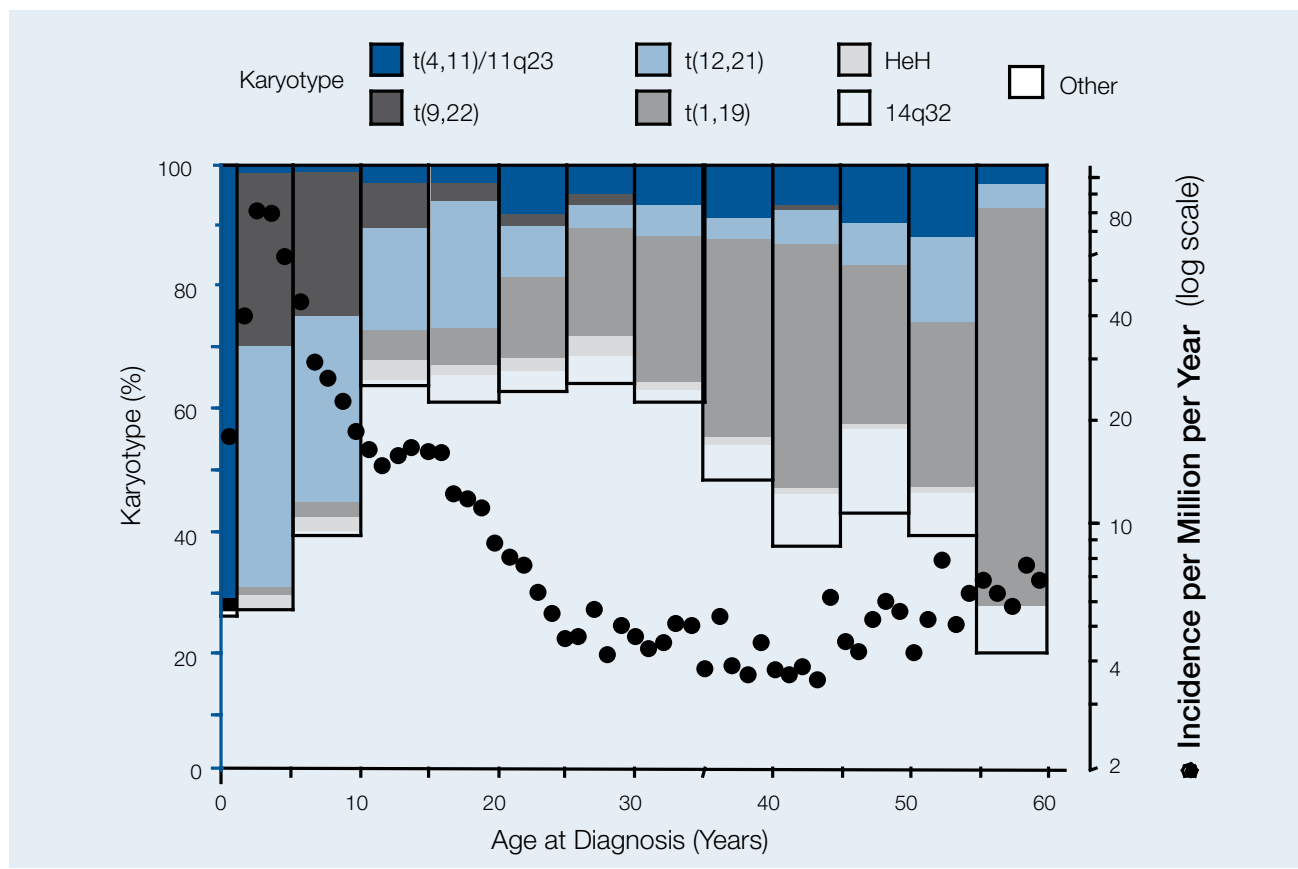
### Acute Lymphoblastic Leukaemia (ALL)

Harrison at Newcastle University in England published data from Moorman on the age dependence of malignant karyotypes of acute lymphoblastic leukaemia (ALL).<sup>4</sup> Although their report was focused on the frequency of known cytogenetic abnormalities in ALL, their data do show that the majority of patients who are between 10 and 35 years of age have not been demonstrated to have any of the frequent karyotypes and have either normal cytogenetics, yet-to-be-characterised (unknown) abnormalities, or other karyotypes that are rare in younger and older persons. In figure 3, their data are shown in columns that are turned upside down from their published graph, with the white area below the coloured bars representing other, normal or unknown karyotypes. Approximately two thirds of the patients 10 to 34 years of age have ALL with other or normal karyotypes. At all other ages the corresponding proportion is substantively lower, 20 to 45%.

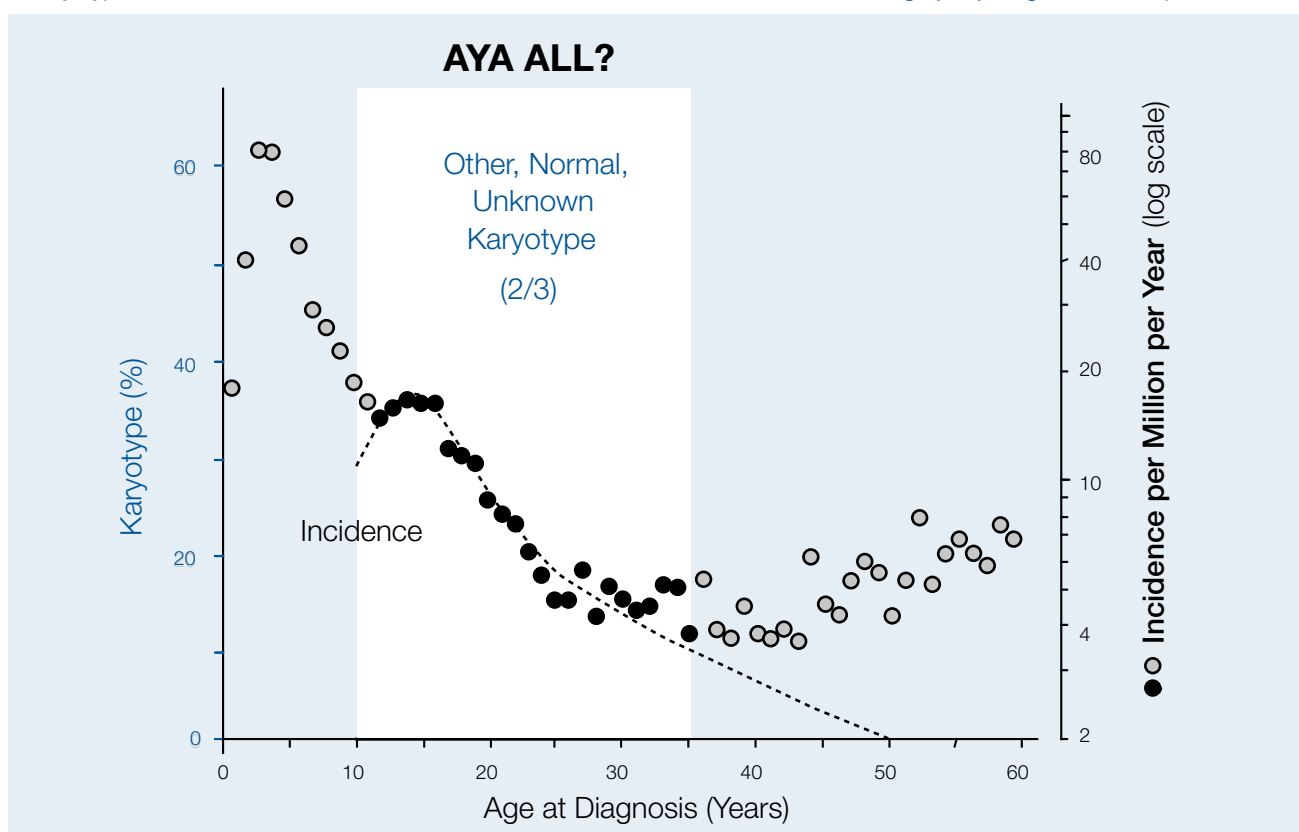
Superimposed on the karyotype bars are the incidence rates of ALL in the US by year of age at diagnosis (circles). Bleyer et al have previously demonstrated that there is an intermediate age peak in the incidence v age pattern that in figure 3 is demonstrated by the solid (black) circles on semi-log coordinates.

These patterns demonstrate an age correlation between incidence and karyotype (figure 4) that together provide new evidence for a type or types of ALL that predominate

**Figure 3:** ALL incidence versus karyotype by age. Karyotype data were derived from Moorman as published by Harrison.<sup>4</sup> The incidence data as a function of individual year of age at diagnosis were obtained from the 1973-2003 database of the US SEER program and shown on semi-log coordinates.



**Figure 4:** Adolescent and young adult (AYA) Acute Lymphoblastic Leukaemia (ALL)? The age at which karyotypes other (normal, unknown and other rare) than that show in Figure 3 are indicated by the gray zone. The 2/3 (two thirds) refers to the proportion of all karyotypes that are normal, unknown or rare, in contrast to the less than half in this category in younger and older patients.



in AYA patients, suggesting an AYA ALL that should be distinguished from childhood ALL and the types that occur in older adults. If so, the best therapy may be neither a paediatric or adult-derived regimen, but a unique treatment that would best be determined by knowing the underlying molecular mechanism(s) of leukemogenesis and developing therapy accordingly (molecular targeting).

### Acute Myelogenous Leukaemia (AML)

In a special issue of *Blood* celebrating the 50th anniversary of the American Society of Hematology, Rowley's review of the cytogenetics of acute myelogenous leukaemia (AML) includes new data of the age dependence of AML translocations v age.<sup>5</sup> The age-dependent pattern discloses that t(15;17), characteristic of acute promyelocytic leukaemia, peaks in incidence between 20 and 39 years of age (figure 5), and that t(11q23), a particularly difficult-to-treat type of AML, has its lowest frequency in the age group (figure 5).

Of potentially greater significance, and almost identical to the age-dependent pattern in ALL (see above and figure 4), the incidence of the biologic subtype of AML that has a normal karyotype peaks in 20 to 39 year-olds (figure 6). As in ALL described above, these new data implicate a AYA type of AML that either has no (known) cytogenetic abnormality or one that has yet to be discovered. Either way, these data too suggest that AML in AYAs may need a different type of therapy than that currently used in younger and older patients. That t(15;17) AML is predominantly an AYA leukaemia that is best treated with agents that are specific for the translocation (all-trans retinoic acid, arsenic trioxide) is exemplary of this potential.

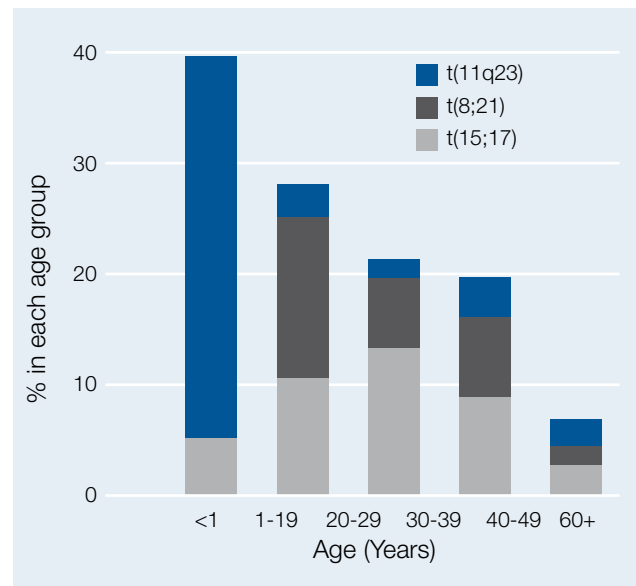
### Sarcomas

Several soft-tissue sarcomas predominate during the AYA years (figure 7). Those with specific cytogenetic abnormalities that imply an AYA-restricted phenomenon are synovial cell sarcoma (t(X;18)(p11.2;q11.2)), alveolar soft part sarcoma (der(17)t(X;17)(p11.2;q25)) and desmoplastic small round cell tumour (t(11;22)(p13;q12)). Two of the three major bone sarcomas, osteosarcoma and Ewing sarcoma, are distinctly AYA cancers (chondrosarcoma is not). Ewing sarcoma is nearly always a t(11;22)(q24;q12) cell. Gain of 1q or loss of 16q in Ewing sarcoma have both been associated with statistically significant poorer outcomes and were more common in patients  $\geq 15$  years of age compared to children.<sup>6</sup> The 1q gain and 16q loss may render the sarcoma cells resistant to ifosfamide and etoposide and thereby explain the lack of benefit in AYAs of these drugs in contradistinction to their demonstrated efficacy in children.<sup>7</sup>

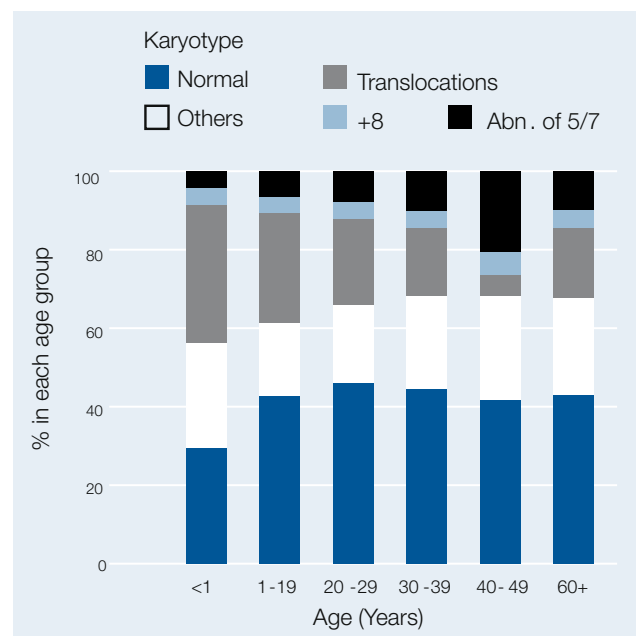
### Colorectal carcinoma

Colorectal cancers in AYAs have at least three distinguishing biologic features: the highest incidence of microsatellite instability; the highest incidence of the heritable forms – familial adenomatous polyposis, characterised by mutations in the APC gene, and hereditary non-polyposis colon cancer, characterised mutations in mismatch repair genes MSH2, MLH1, and PMS2; and a predominance of mucinous adenocarcinoma.<sup>8</sup> Secondary characteristics that are more prevalent in AYAs are more advanced state

**Figure 5:** Translocations in AML versus patient age at diagnosis, as modified from Rowley JD.<sup>5</sup>



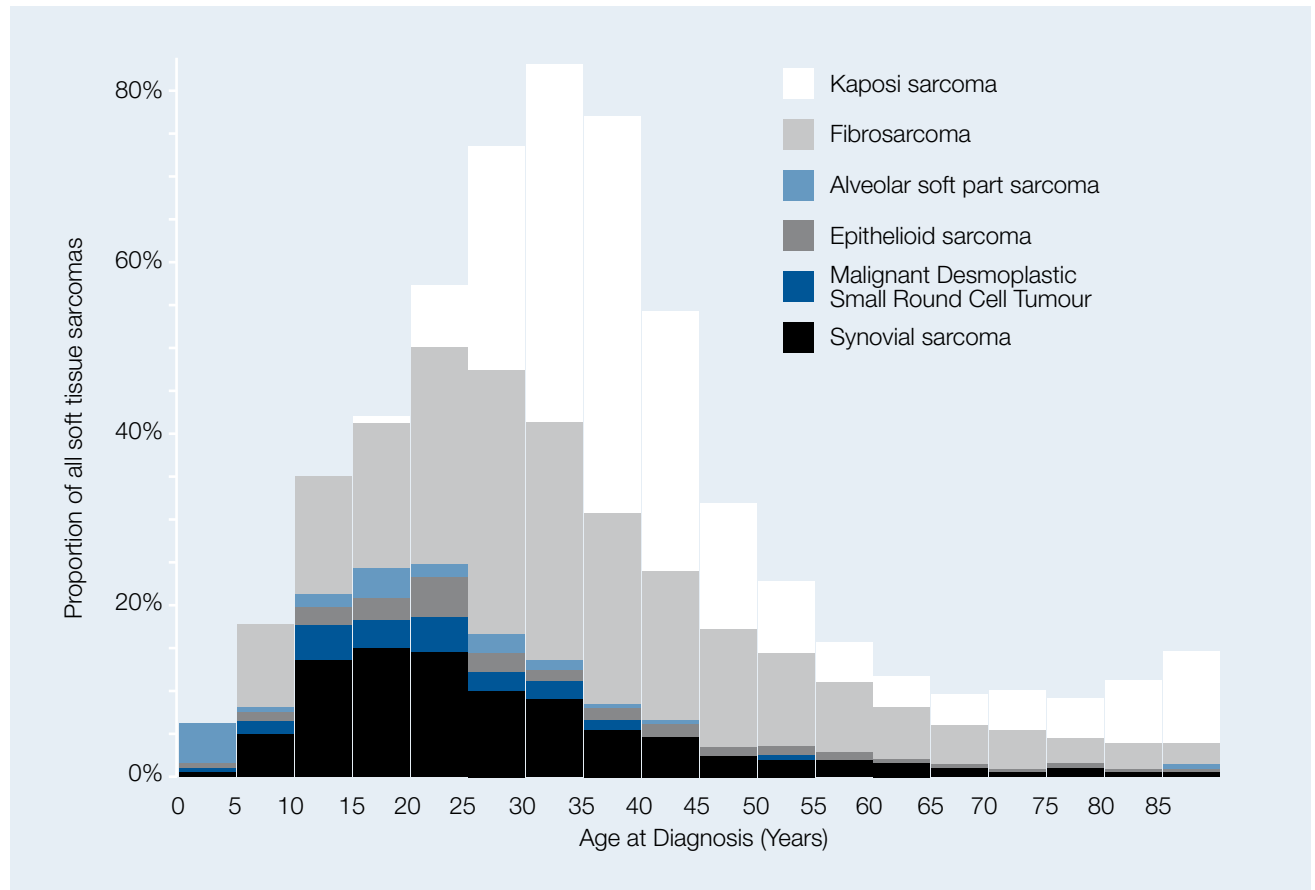
**Figure 6:** Karyotypes in AML versus patient age at diagnosis, as modified from Rowley JD.<sup>5</sup>



tumours, poorly differentiated and signet-ring histologies, a primary tumour that arises in the rectum and proximal colon, and a 40% higher incidence ratio of rectal cancer in females than males between age 25 and 50, in contrast to no sex difference for colon cancer.<sup>3,8-11</sup>

Microsatellite instability characterises both the sporadic non-inherited cancers of AYA colorectal cancer and hereditary non-polyposis colon cancer, but not familial adenomatous polyposis. Mucinous adenocarcinoma occurs in nearly 50% of AYA colorectal cancers compared to 2-4% in older adults. Despite the peak of inherited forms in AYAs, non-inherited, sporadic forms of colorectal cancer predominate the age group.<sup>11</sup> In contrast to older patients, the sporadic cancers usually do not have the K-RAS mutations, loss

**Figure 7:** Sarcomas with peak incidence in AYAs as a proportion of all soft-tissue sarcomas. Data from NCI Surveillance, Epidemiology, and End Results (SEER) Program SEER 17 Registries, 2000-2005, [www.seer.cancer.gov/seerstat](http://www.seer.cancer.gov/seerstat). [www.seer.gov](http://www.seer.gov) (accessed December 21, 2008). Fibrosarcoma includes periosteal fibrosarcoma, fibromyxosarcoma, pigmented dermatofibrosarcoma protuberans, dermatofibrosarcoma, and fibrosarcoma NOS. The era (2000-2005) avoids the HIV/AIDS-related Kaposi sarcoma epidemic that occurred in the 1980s and early 1990s.



of heterozygosity at chromosome 17p or 18q, and other mutations in tumour suppressor genes and oncogenes.<sup>12,13</sup> 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,<sup>14</sup> and it is likely to be increasingly problematic with molecularly targeted agents.

### **Breast cancer**

Below age 45, the younger a woman when diagnosed with breast cancer, the worse the expected outcome, a pattern that is independent of stage and extent of disease at diagnosis, and of histologic type.<sup>3,15</sup> Young women with breast cancer are more likely to have larger tumours with more frequent nodal spread and a greater number of involved lymph nodes than older women.<sup>16</sup> Young women have the highest incidence of tumours that are devoid of both the estrogen receptor (ER) and progesterone receptor (PR) (including lower quantitative progesterone and ER mRNA expression<sup>17</sup>) and also the growth factor receptor ERBB2 known as HER2. These 'triple negative' tumours are associated with a worse prognosis than those cancers that express at least one of the receptors, and has obvious therapeutic implications in that most of the treatments for older patients directed at ER, PR, and HER2 targets (tamoxifen and congeners, aromatase

inhibitors, trastuzumab and analogues) are ineffective in most young breast cancer patients. Genomic expression analysis has revealed 367 biologically relevant gene sets significantly distinguishing breast tumours arising in young women, as well as higher epidermal growth factor receptor expression.<sup>16</sup> The difference between young and older women may be more in transcriptome changes such as mRNA rather than in genomic differences. Among women with ER positive RNA tumours, younger cases have been found to express more cell cycle genes and the growth factor amphiregulin, whereas tumours in older women expressed higher levels of four different homeobox genes in addition to ER (ESR1).<sup>17</sup>

Breast cancer in young women has also been reported to have greater de-regulation of the transcription factor phosphatidylinositol 3-kinase (P13K) and pathways involving the MYC oncogene.<sup>17</sup> Among younger women, de-regulation of the P13K and beta-catenin pathways is associated with a worse outcome than those with de-regulation of the oncogenes MYC and SRC. This pattern contrasts with that in older women, in whom a worse outcome is associated with de-regulation of the E2F transcription factors and a concurrent low de-regulation of P13K and MYC.<sup>18</sup>

## AYA Oncology PRG Executive

**Recommendation 3:** *Create the tools to study the older adolescent and young adult cancer problem.*

### **AYA cancer clinical trials and trial participation**

With the possible exception of elderly adults over 75 years of age, young adults have the lowest rate of cancer clinical trial participation. Only one in 50 25 to 29 year-olds diagnosed with cancer in the US during the decade ending 2005 were entered on to a national treatment trial,<sup>19</sup> in contrast to one in every two to three children less than age 10 and one in 20 to 25 older adults.<sup>20</sup> Prior analyses have shown that the progress in survival prolongation as a function of age is correlated with age pattern of both the number and proportion of patients entered on to a clinical trial.<sup>21,22</sup> The implication of course, is that improved clinical trial participation and specimen acquisition for translational research is key to acceleration of progress in the treatment of cancer in AYAs. Reasons for the poor clinical trial participation in adolescents probably differs from those in older patients, such as undescribed differences in biology, delays in diagnosis, poor compliance or intolerance of therapy, and treatment by physicians less familiar with their diseases and psychosocial needs.

A large prospective database of AYA cancer patients and specific assessment tools will facilitate research in the age group, including specific recommendations for institutional review boards. Standardisation of search terms and grant coding would enable evaluation of research efforts and progress so that the research that is applicable to the cancers in AYAs can be identified and collated. An improved nosologic classification system could overcome the limitations of the system used for adults (International Classification of Disease) on one hand and that for children (International Childhood Cancer Classification) on the other.<sup>6,23</sup>

### **AYA biorepositories and translational research**

Age-dependent patterns reinforce the need to study the molecular biology of cancer in the AYAs and not just in children or older adults. Until the biology is demonstrated to be the same, cancer in AYAs should not be assumed to be so. Also, there is a need to collect tumour (and normal tissue) specimens in AYA patients for translational research and tissue biorepositories, a deficiency in tumour banks in general that has been previously noted.<sup>24,25</sup>

### **AYA oncology, clinical trials and treatment optimisation**

The US NCI-sponsored paediatric and adult cooperative groups have launched a national initiative to improve the accrual of AYAs on to cancer clinical trials. In North America, Australia and New Zealand, the Children's Oncology Group (COG) established an AYA committee with goals to: improve access to care through understanding barriers to participation; develop a cancer resource network that provides information about clinical trials to patients, families, providers and the public; enhance adolescent treatment adherence with protocol-prescribed therapy; and increase accrual of adolescents with cancer

to trials specifically designed for patients in this age group and disease. In conjunction with the US adult cooperative groups, the COG increased the number of national clinical trials provided to AYA cancer patients by raising the upper age limit to 30, 40 and 50 years of age, depending on the cancer. A measure of success was achieved in 2005-2006, with increased accruals to cancer treatment trials in comparison with the two previous years among AYA patients in comparison to both younger and older patients.<sup>25</sup> A measure of success may be apparent in the categories of cancer with the greatest increase in accrual, leukaemia and lymphoma. These appear to have had an acceleration in the rate of decline in national mortality within the 15 to 29 year age group, in contrast to patients less than 15 years of age who have had an attenuation in their national death rate (Friedman S, Finnigan S, Montello M, Budd T, Anderson B, Trimble EL, personal communication). In 2008, the three major adult cooperative groups in the US adopted a COG regimen for a combined group trial for patients with newly-diagnosed ALL who are less than 31 years of age.

To what extent cancer in AYAs is truly biologically different from what otherwise appears to be the same cancer in other age groups remains to be determined. Meanwhile, there is now enough evidence that merits methodical study of the underlying biology of cancer as a function of patient age, with the full implication that cancer treatment in AYAs cannot be optimised until whatever differences that exist are discovered and enable more effective therapeutic strategies.

### **Acknowledgement**

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