Pediatric Oncology

Archie Bleyer
Ronald Barr
Lynn Ries
Jeremy Whelan
Andrea Ferrari *Editors*

Cancer in Adolescents and Young Adults

Second Edition

Springer

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Editors
Archie Bleyer
Bend
OR
USA

Ronald Barr
McMaster University
Hamilton,
Ontario
Canada

Lynn Ries
RiesSearch LLC
Rockville
MD
USA

Jeremy Whelan
University College Hospital
London
UK

Andrea Ferrari
Pediatric Oncology Unit
National Tumor Institute
Milano
Italy

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Foreword

If anything, a 2nd edition of Cancer in Adolescents and Young Adults (AYA) is overdue. An inordinate number of events, organizations, and happenings have occurred since the 1st edition was published in 2007.

In 2000, I launched Planet Cancer, the first online community for young adults with cancer. I had one goal: to keep others from experiencing the same crushing isolation I had felt as a 26-year-old with cancer. There were no support groups, resources, or websites just for AYAs. We were an anomaly in the waiting rooms, and no one quite knew what to do with us when we turned up. On the research side, the extent to which the AYA population was invisible was highlighted by the unexpected challenge of a simple literature review in preparation for the 2005 National Cancer Institute/LIVESTRONG Foundation Progress Review Group (PRG): because the age range was undefined and there were no key AYA search terms. Searches delivered hundreds of thousands of mostly irrelevant results or nothing at all.

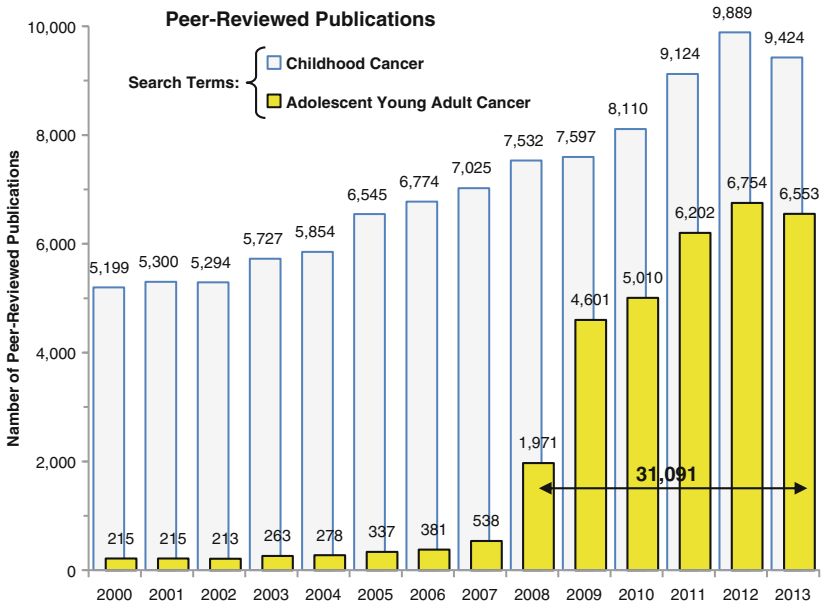
The world has changed dramatically in the years since I was a patient—computers are in everyone's pockets, monthly Facebook users outnumber the population of China, and the human genome has been sequenced. Targeted molecular therapies now save people's lives every day, and there are findings that indicate specific biological distinctions in AYAs with certain cancers compared to their older and younger counterparts facing the same diagnoses. And AYA oncology is, if not completely institutionalized, much more visible. Google delivers nearly 17 million hits to a search request for "young adult oncology." The term "AYA" is solidly ensconced in the cancer literature and lexicon, no longer requiring a follow-up explanation after every use of the acronym. And the number of peer-reviewed publications on AYA has skyrocketed (Figure) although there are still fewer than those reporting results in children with cancer. (The irony here is that, in 2011, there were almost eight times more diagnoses of cancer in AYAs than in children under 15.)

The Progress Review Group established an age range of 15–39 for AYAs, based on Dr. Archie Bleyer's startling "gap," the graphed abyss showing the relative lack of survival rate improvement in this population. However, the age range in the 1st edition was limited to 15–29, resulting in an omission of nearly two-thirds of the AYA patient population. This edition expands the age range according to the broader definition of 15–39, allowing a more thorough exploration of the variety of diagnoses and challenges that occur across the entire AYA spectrum.

But while recognition has increased, the evidence base to support beneficial changes in practice is still growing and will require strong and cohesive calls for change to ensure that such changes are implemented. Thus the new chapter on advocacy in this edition, exploring key components of driving change, the critical participants of successful efforts, and the different paths that progress has been taken internationally.

Thanks to the passion and dedication of many AYA champions around the world, we have come far. And while we still have a long way to go before AYA patients have their own clearly defined, evidence-based care path, I look forward to seeing the progress that will be achieved by the time a 3rd edition hits the press.

Heidi Adams
President and CEO, Critical Mass: The Young Adult Cancer Alliance,
Austin, Texas, USA



Foreword

Despite the remarkable progress made in the treatment of cancer in the pediatric population, cancer remains the leading cause of death from disease in children in the United States. Five-year event free survival exceeds 80 % for many but not all childhood cancers, and late effects are an ongoing challenge for a large number of survivors. Moreover, this progress has not been shared equally across the pediatric-young adult realm, with progress in improving the outcome for adolescents and young adults with cancer too frequently lagging behind advances in other age groups. A number of factors contribute to this, including the lower participation of older adolescents and young adults in clinical trials.

The 1st edition of this textbook highlighted efforts aimed at addressing the scope of the problem of adolescent and young adult under-representation in clinical trials and offered evidence that such a discrepancy may partially explain outcome differences. Chapters presented information about biologic differences between specific cancer subtypes most common in younger children and those exhibited by the same cancers in adolescents and young adults and offered insight into leading factors that contribute to outcome differences as well as potential treatment strategies.

This 2nd edition updates and expands on the work of the original text. Notably, the focus now spans the 15–39 year range, an age group specified by the 2005 Progress Review Group of Adolescent and Young (AYA) Oncology. In these updated chapters, new concepts are presented and data summarized to help bridge our gaps in knowledge. The presenting symptoms and signs, diagnosis, staging, treatment, and late effects are reviewed for each of the common malignancies, together with the epidemiology and risk factors. Principles and practices of care for adolescent and young adult patients with cancer are then discussed, with separate chapters covering specialized units, adherence/compliance, psychological support and related issues, quality of life outcomes, rehabilitation and exercise, late effects, ethical issues, access to care after therapy, future health, resources for survivors, and financial considerations. There are also chapters on access to care before and during therapy, clinical trials, future challenges and opportunities, and international perspectives.

The epidemiology portions use both the International Classification of Childhood Cancer (ICCC) and the International Classification of Diseases-Oncology (ICD-O) because cancers occurring in this age group span the pediatric-to-adult spectrum of diseases. This book will help educate medical

providers and the public about cancer incidence and survival in this age group and provide impetus for further research to improve the survival and the quality of life of these young people.

The Children's Oncology Group (COG), a National Cancer Institute (NCI)-supported clinical trial group, is the world's largest organization devoted exclusively to childhood and adolescent cancer research. The COG unites more than 9,000 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centers around the world. With the advent of the NCI's new National Clinical Trials Network (NCTN), of which COG is the single pediatric focused group alongside four network groups focused on cancers of the adult population, our hope is that, by increasing research studies designed specifically for the AYA population, the current gap in outcome will begin to close. To this end, we look forward to increased enrollment of AYA patients with cancer onto clinical trials, an overarching goal of the current edition of this book.

Peter C. Adamson, MD
Chair, Children's Oncology Group,
Philadelphia, Pennsylvania, USA

Foreword

Adolescents and young adults 15–39 years of age are making the transition from childhood to adulthood, not only physically and psychologically but also financially and educationally. When the burden of cancer is added, it becomes part of this extraordinary and challenging time in their growth and development. They are also unique in the types of cancers that they develop and present problems that neither pediatric nor adult-treating oncologists are fully comfortable in managing. It is no surprise therefore that 15- to 39-year-olds are often lost in a health-care system that concentrates on pediatric and adult cancers, with the resultant limited participation of the intermediate age group in clinical trials.

Until recently, little attention and few resources were devoted to studying the incidence, biology, and treatment outcomes in this age group. With the ability to gather data specific to this age group, the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program allows us to estimate that, in the year 2015, there will be between 86,840 and 87,470 new cases of cancer among 15- to 39-year-olds in the United States, including between 71,030 and 71,540 cases of invasive cancer. Compared to the estimated 11,900 cases of all cancer diagnosed in children younger than 15 years of age, the cancer incidence rate in 15- to 39-year-olds is 7.5-fold greater.

With the establishment of the Adolescent and Young Adult Committee of the NCI-funded Children's Oncology Group (COG) in 2000 and with support from the Aflac Foundation, an organized program in research and education for and about young people with cancer has been initiated. I first heard of this initiative in 1996 when I was Chair of the Cooperative Group Chairs.

In 2005, the NCI conducted an evaluation of the issues facing older adolescents and young adults with cancer. Known as a Progress Review Group, this effort was co-sponsored by the NCI and the LIVESTRONG Foundation, and its impact continues to be implemented by the COG, the Critical Mass Young Adult Cancer Alliance, and other national and international organizations. The mission is to identify and prioritize the scientific, medical, and psychosocial barriers facing adolescent and young adult cancer patients and to develop strategies to improve their outcomes. I have had the privilege to co-Chair, along with Drs. Barry Anderson and Archie Bleyer, the Clinical Trials/Research Subcommittee of the Program Review Group that has partially achieved its goal to increase the participation of young adults and older adolescents in clinical trials.

In 2013, the cooperative groups established the "Intergroup AYA Oncology-NCTN Task Force" and invited representatives from each of the NCTN cooperative groups. This Intergroup effort has now had two face-to-face meetings and will assume responsibility for advancing a collaborative program of research for Adolescents and Young Adults across the NCI NCTN (National Clinical Trials Network).

This comprehensive treatise on cancer in adolescents and young adults, edited by Bleyer, Barr and Colleagues, has helped enable the mission of the Program Review Group. It reviews the presenting symptoms and signs, diagnosis, staging, treatment, and late effects for each of the common malignancies in the age group. It would not have been possible without the support of the cooperative group enterprise in the United States or without the extensive data collection efforts of the NCI's SEER program.

I congratulate the editors and authors on the second edition and look forward to continued successful impact of the book and national initiative.

Robert Comis, MD
Co-chair, ECOG-ACRIN Cancer Research Group, and President and Chairman, Coalition of Cancer Cooperative Groups (CCCG), Philadelphia, Pennsylvania, USA

Foreword

For the past 25 years, the Teenage Cancer Trust has shown the spotlight on the additional disadvantages experienced by teenage and young adult cancer patients.

As a Founder of the Charity, I have been proud to work both within the United Kingdom and worldwide to redress the dearth of focus experienced by young cancer patients in regard to clinical trials and other research, resources, specialist psychological services, rehabilitation, and particular cancers among other issues. Within the United Kingdom, this formerly neglected cohort of cancer patients has now been recognized not only at the clinical level but also by government. We now see this recognition repeated elsewhere in the world, and the publication of the second edition of Cancer in Adolescents and Young Adults is an example of the enhanced awareness of the problems of the co-incidence of youth and cancer.

Many of those contributing to the first edition and also to this edition have been the flag bearers to put young people with cancer on the map—not the least of which are Archie Bleyer and Ronnie Barr who have proved to be motivating voices in the field and originated the 1st edition.

This edition not only updates the original but extends the scope, bringing in new and respected voices from those dedicated practitioners in many fields who have embraced the message promoted by Teenage Cancer Trust many years ago. It will make a valuable contribution to the pool of knowledge and experience put forward by Teenage Cancer Trust's International Conferences and prove to be an essential tool in the fight to improve outcomes in this very sensitive and complex group of cancer patients.

The issues addressed are wide ranging and will be of great assistance to those working in the field seeking to increase clinical trial involvement and improvement in outcomes currently experienced by other cancer groups but not correspondingly by young people. This edition embraces a wider field, in regard to age, topics, authors, and editors, and so offers increased expertise to its readers.

The contributors, their work, and their research lend respect to the quality and usefulness of "Cancer in Adolescents and Young Adults," and I commend them and the editors and co-editors for this informative, inspirational, and valuable book.

Myrna Whiteson, MBE
Life President—Teenage Cancer Trust,
London, UK

Preface

The Evolution of Adolescent Oncology in the United States

Background

Although the history of adolescent and young adult (AYA) oncology is relatively recent, there is evidence that cancer in AYAs precedes and transcends written human history [1–3]. One of the earliest cases of cancer in an AYA was found by Louis Leakey in 1932 in the remains of either a *Homo erectus* or an *Australopithecus* and was suggestive of a Burkitt lymphoma. Osteosarcoma, which has its peak occurrence in the second decade of life, has been found in Egyptian mummies estimated to be AYAs. A case of possible osteosarcoma was also discovered in the mummified skeletal remains of a Peruvian Inca. Centuries, if not millennia later, and late in the history of modern medicine, AYA oncology was born. This review of the recent history, after decades to millennia of omission, describes the major events and rationale that led to the AYA oncology discipline beginning with adolescent oncology.

From time immemorial, adolescents have been criticized for their behavior. Socrates complained that "children today are tyrants; they contradict their parents, gobble their food, and tyrannize their teachers." Homer declared "thou knowst the over-eager vehemence of youth, how quick in temper, and in judgment weak." Shakespeare suggested that teenagers be put into suspended animation until of age [4]. Ambivalence, rebellion, desire for freedom from family, conflicts with parents, reaction with intensity, identification with their peers, and sexual activities are archetypal of this age group. An imbalanced rate of demands for privileges and acceptance of responsibility, coupled with the desire to be autonomous and different, has led to antipathy and dislike of adolescent behaviors. Yet these characteristics may be appropriate for this age group and likely constitute one of the pillars of human advancements over the ages.

For adolescents, the transition from childhood to adult status is both difficult and stressful. As such, many experience ambivalence and physical and emotional turmoil, which threaten their ability to become healthy and productive adults. Cancer, a catastrophic, life-threatening disease, has major physical, functional, psychological, and social implications, which are amplified in the AYA age group. While cancer in AYAs is not rare, it poses a

sufficiently distinctive challenge to require specialized services [5]. In the 1970s, when cancer was becoming a more "chronic" disease and promising reports of successful treatment in several types of cancer, which heretofore were deemed incurable, appeared in the literature, physicians began treating their patients with curative rather than palliative intent [6]. At that point, it became apparent that a catastrophic disease with uncertain outcome requiring intensive therapy is difficult to face without a major social support system [7]. It had been recognized for some time that care for AYA patients demands an understanding of the process of physical, mental, psychological, and social growth and development [8]. Adolescent services had been in existence in the United States since 1951, when Dr. J. Roswell Gallagher established a unit for adolescent medicine at Boston Children's Hospital [9].

A Decade of Experience: 1978–1989

Against this background, the first adolescent oncology unit, where one of the authors (CKT) was the director, was established in 1978. This was enabled by a grant from the National Cancer Institute (NCI). The unit was founded through the efforts and support of Dr. James Wallace, the then director of the Division of Cancer Control and Rehabilitation, and the endorsement of Dr. Gerald Murphy, the then Institute Director at Roswell Park Memorial Institute. While adolescent medicine as an entity was not new, the idea of a separate unit for adolescent cancer patients was unique. Establishment of a unit dedicated specifically to cancer was received enthusiastically by patients and their families alike. The reception by medical and surgical subspecialists was far less enthusiastic. There was considerable opposition, expressed and implied, by various medical and surgical services. The ten-bed unit, which was located in a separate building and connected to the main hospital, was resented by most departments on several principles. Most medical and surgical staff physicians preferred their patients to be hospitalized on their own floors. Some were unwilling to lose the adolescent population from their services. Our much more modern facility for adolescents and young adults than the then older hospital floors was also resented. Only with the strong support of Dr. Gerald Murphy, the devotion and resilience of the unit staff, and the demand of patients and their families did the unit survive and flourish. Dr. Murphy had personal experience with adolescence in his own biological and adopted children and had considerable knowledge of adolescents' desires and behavior.

The physical structure of the unit, which was designed with the patients' input, proved to be a major draw [10]. The unit was painted with bright colors and geometric designs appealing to AYA patients. It included a sizable patient lounge with bright furniture, a large aquarium, and decorations. An arcade-like recreation room with the latest in electronic games then available, football, air hockey, bumper pool table, jukebox, stereo system, large TV, and musical instruments, drew the patients' friends to visit them in the hospital. An extensive exercise and arts and crafts room, a classroom, and a library with books and magazines appealing to the age group were provided.

A well-stocked and equipped kitchen with dining room allowed patients and their parents to cook and dine together. There was no dress code. A laundry room was available to patients so that they could wear their own, not the hospital's, clothes. A room designated as a quiet room was furnished for patients and their families who wanted to take some time off and not be disturbed by anyone, including medical personnel. A separate parents' lounge and room to stay when their child was critically ill allowed parents to be involved, but not intrusively. Selection of the staff for the unit was based largely on their desire and ability to work with AYA patients. Primary nursing care proved to be essential for the operation of the unit. Various programs were designed to promote communication and support emotional stability in crisis situations. A teacher visited patients on a daily basis and, through an agreement with a local college, post-secondary education was available. In retrospect, the educational opportunities offered, especially for those less engaged in school prior to the diagnosis of cancer, were an important function of the unit [10]. Among other programs offered were music therapy, group sessions, and career planning. The unit, in those early days, offered a computer for patients' use, which was then unique. With a grant from Poets and Writers Inc., a creative writing program was established. The unit's monthly newsletter, entitled "Now and Then News," often contained excellent articles or poems expressing patients' and staff's feelings and experiences.

Offices of the staff, including the medical director, patient care coordinator, family counselor, and occupational therapist, were in the unit and open to patients and their families and friends. Patients' records were computerized, allowing access, using a series of codes, to the patients' prior admissions and discharge notes. This was probably one of the earliest attempts at computerized medical record keeping. The unit shared a research laboratory and accepted pre- and postdoctoral trainees.

The rules governing the unit, including visiting hours and visitors' age limit and number, were liberal [4]. A monthly family night was hosted for the patients and their families to attend. In-patient field trips decreased the monotony of staying in the hospital. A home and terminal-care program was designed for patients who opted to stay at home at the end of life. An evaluation program periodically examined satisfaction with the various aspects of the unit's operation by the patients, their families, and staff [10, 11].

Shortly after the establishment of the unit, it became apparent that information regarding care of the adolescent cancer patients was scanty, if not nonexistent. In a series of investigations, the medical and psychological effects of the diagnosis and treatment of cancer in adolescents were probed. Since nowhere are these effects more exaggerated than with loss of a limb and its effect on body image, physical, psychological, and social functioning of the patient, a major effort was placed on these areas of study. These studies described various aspects of the bone tumors [12–14] and the short- and long-term effects of the amputation on the patients' lives [15–17]. The research found that, in general, despite all adversities, in the long-term most amputee patients had adjusted to their circumstances and were leading full and productive lives [15, 17]. Other investigations probed the role of social support systems [7, 18]. Evaluation of the pattern of religiosity and locus of control

revealed that adolescent cancer patients were not significantly more religious than established norms [19]. However, among younger adolescents, the diagnosis and treatment of cancer may have accelerated the development of internality, which is expected to be associated with increased age [19].

Early during the experience of the unit, significant noncompliance with self-administered cancer therapy was noted. This led to a series of studies of patients and parents and a means to improve compliance [20–25]. Since the psychological aspects of the disease play an important role in the care of patients, great emphasis was placed on this aspect of care [11, 26, 27]. Depression had been observed and studied extensively in adult cancer patients, but no systematic evaluation was available for adolescent cancer patients. In a series of studies, the rate of self-reported depression in cancer patients was examined [28]. Issues pertaining to long-term survivors were other venues for early research. With improved survival, the short- and long-term sequelae of cancer and its treatment, the effects on the vocational achievements of the patients, and their function in the workplace were investigated [29, 30]. This disclosed a greater degree of functional deficits in unemployed than in employed cancer survivors and in health, life, and disability insurance issues [29]. Nevertheless, there was no significant relationship between health status and employment. As a whole, former cancer patients had a higher average income compared to a control group and were competitive members in the workplace [29]. The experiences in establishment of a specialized unit, together with the care and nutrition of these patients, were published [8, 30]. Along with annual adolescent oncology conferences, these reports attracted a large number of interested individuals to work and train in the unit. Publication of the first book solely devoted to adolescent oncology [31] increased the awareness of cancer in adolescents and young adults, albeit to a limited extent.

In 1989, when Dr. Gerald Murphy left Roswell Park, the unit, which was then by far the most modern and progressive floor of the hospital, was viewed as an “extravagance” by the new administration. For cost-cutting purposes, it was decided that its resources should be shared with pediatrics. Consequently, in October of 1989, despite the pleas of dedicated staff and patients, the unit was merged with pediatrics and the AYA cancer program was effectively closed.

Scaling Up: 1992—The Present

A new chapter in AYA oncology commenced when, in October 1992, the American Cancer Society (ACS) sponsored a workshop on Adolescents and Young Adults with Cancer [32]. The conference served as a watershed for recognition of the special needs of this group of patients. It was attended by, and had the support of, Dr. Gerald P. Murphy who, after leaving Roswell Park Cancer Institute and State University of New York, had accepted a position as the chief medical officer of the ACS. To organize this conference was a departure from prior attitudes toward the importance of specialized care for AYA cancer patients. Before the leadership of Dr. Murphy, when an earlier confer-

ence, entitled "Advances in Care of the Child with Cancer," was being planned by the ACS in 1985, the first author (CKT) suggested that the subject of adolescent oncology be included in the agenda. The organizer of that conference indicated that nothing was new or important enough in adolescent oncology to merit a session, and the subject was declined. The 1992 "Adolescent and Young Adult Conference" was attended by many leaders in pediatrics, adolescent medicine, and medical and surgical oncology, including the chairs of the major pediatric cancer groups. The workshops included sessions on long-term care and lifetime follow-up [33], insurance and employability [34], psychological and emotional issues, specialized support groups and compliance [35], and clinical research implications [36]. The published proceedings of the conference had an important conclusion, which recognized cancer as a significant health problem in the AYA population [32]. It observed that the incidence rate of cancer in patients 15–19 years of age is equal to that of 0–4-year-olds and 1.6 times that in patients between 5 and 14 years of age [37, 38]. The report also brought attention to the relatively infrequent participation of AYAs in clinical trials and ignited initiatives to include AYAs in these endeavors [38–41]. The 1992 conference also emphasized the necessity for long-term follow-up and psychosocial support and called attention to discrimination in insurance and employment [37]. The concluding remarks included recommendations to remedy these concerns [37].

In 1996, the first report on the relative lack of progress in improving survival in adolescents with cancer was published [42]. In 1997, the relative lack of adolescents with cancer on clinical trials compared with children was reported [43]. These observations led the then Chair of the Children's Cancer Group (author AB) to form a task force within the group to research the problem, which led to the appointment, in 1998, of the first AYA Committee in the national cooperative group program of the US NCI. The concept was included for the first time in an NCI Cooperative Group Chair's Competitive Renewal Application, presented at a Site Visit in 1998, and funded with an *Outstanding to Excellent* score rating.

In 1999, the first NCI Workshop was convened by Malcolm Smith, MD, PhD, and author AB to assess how to increase clinical trial participation by AYA cancer patients. Twenty-eight attendees included chairs and other leaders of the NCI cooperative groups, surgeons, radiation oncologists, medical oncologists, and other specialists in the common cancers in AYAs, as well as ten NCI leaders and a health insurance industry representative.

The genesis of the Children's Cancer Group AYA Committee and the NCI Workshop were harbingers of the fact that there are currently approximately 37 million individuals between the ages of 10 and 19 years living in the United States and, based on SEER and other data, the incidence of cancer in 15- to 19-year-olds was on the rise [39, 43–47]. In the United States, this increased an average of 0.7 % per year from 1975 to 1997 [40], yet no age-defined health-care system or providers were generally available to the majority of adolescents [48]. On the other hand, in the United States, the mortality from cancer in the age group decreased at the rate of 3.3 % per year for the period 1965–1974 and 2.6 % per year for the period 1975–1984. Thus, the health care of this group of patients was considered fragmented, in the United

States and elsewhere, between medical, pediatric, and general practitioners and others [49].

In 2000, the four major national pediatric cancer cooperative group organizations (Children's Cancer Group, Pediatric Oncology Group, National Wilms' Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group) merged into a single national group called the Children's Oncology Group (COG). With this coalescence, an expanded AYA Committee was established to intensify AYA oncology research.

In 2004, the first national philanthropic contribution to AYA oncology research occurred with a grant from the Aflac Foundation to the COG for research by its AYA Committee. The total contribution since then by the Aflac Foundation exceeds US$1.5M. In 2005–2006, the NCI and Livestrong Foundation sponsored the Progress Review Group (PRG) on AYA Oncology [50] that was attended by 97 representatives of the scientific, health care, advocacy, and health insurance organizations. A strategic plan based on the PRG was developed by the Livestrong Young Adult Alliance [51].

The PRG was a sentinel event in the evolution of AYA oncology, subsequent to which much of what has occurred nationally and internationally has been derived. It has been described as the most (albeit the last) productive of the series of PRGs held by the NCI.

The COG AYA Committee took steps to organize a comprehensive program including subcommittees for all major categories of oncological disorders common among AYA patients. The committee now consists of more than 120 members who represent nearly 20 disciplines and is sustained by funding from the NCI and the health insurance industry. It is organized into five Strategy Groups (disease-specific clinical trials, behavioral oncology, health services research, epidemiology, and awareness) and a sentinel task force on survivorship transition. In addition, the committee has established task forces on access to clinical trials and care, cancer control and community oncology programs, adolescent treatment adherence, exercise and adventure therapy, and development of an informative website.

Unfortunately, years after the demonstration of the benefits of treatment of adolescent patients in a unit of their own [10, 52], only a handful of specialized adolescent oncology services in the United States are operational. In the United Kingdom, the Teenage Cancer Trust (TCT) is an advocate of these units [53]. There are currently 27 operational units, and there are plans for the establishment of a TCT unit in every regional cancer center. Adolescent oncology units can provide an environment where the age-appropriate atmosphere and facilities, coupled with medical, technological, and psychosocial expertise, can provide specialized care while reducing dropouts from the treatment as well as short- and long-term side effects of cancer and its therapy. In an inquiry sent to 238 COG institutions in the United States, of the 196 that responded, only one hospital had a formal designated adolescent oncology unit (unpublished observation, CKT 2004). In the same inquiry, ten admitted their patients to a general adolescent unit, and only seven had staff who identified specifically with the care of these patients. While adolescents are generally resilient [54, 55], in adult units these patients are frightened by

the generation gap, adults disfigured by cancer, and rigid rules imposed upon them while they are hospitalized. Medical oncologists tend to regard 16- to 21-year-olds as adults and do not make a distinction between them and older patients [56]. Furthermore, diagnoses common in older adults are rare in adolescents and young adults [56]. While disputed, at least for some oncological diseases, the treatment of adolescents according to a pediatric protocol has yielded better results than medical oncology protocols [5, 57–59]. In a pediatric setting, however, AYAs are often demeaned by an atmosphere created for very young children and the childlike manner with which they are often dealt, not considering their age and accomplishments. The patients are often bypassed by the pediatric staff, who habitually communicate with their parents rather than interact directly with the patient.

The history of the development of adolescent oncology would be incomplete if one were remiss in failing to mention the developments in psychosocial and long-term care of the patients [60]. With increased survival, the problems concerning quality of life have gained prominence. Subjects such as "psychological aspects of cancer survivors," "late effects," "long-term survivors clinics," "second cancer," and "transition to adult care," which did not exist before, found their way into the lexicon of oncologists in the United States and elsewhere [61–66]. Likewise, with significant societal changes in the 1970s and 1980s, the subject of death and dying, which once was "taboo," is discussed openly and has become a new area for research and open discussion. Hospice care, introduced initially by physician Dame Cicely Saunders in the United Kingdom in the early 1960s and culminating with the opening of the first hospice in 1967, has found its way to the United States and has become a part of end- of-life patient care. The American Academy of Hospice and Palliative Medicine, originally chartered as the Academy of Hospice Physicians, was established in 1988 [67]. Publication of 500 interviews with dying patients entitled "On Death and Dying" and analysis by Dr. Elisabeth Kubler-Ross [68] catalyzed a more open discussion with dying individuals, including AYA patients. The trend continues with most major adult and pediatric cancer study groups having established committees on end-of-life care.

Important recent developments in the United States include the publication of guidelines on AYA oncology by the National Comprehensive Cancer Network [69] and the formation of an AYA working group within the National Clinical Trials Network. Corresponding initiatives have been undertaken elsewhere in the world, as in the United Kingdom [70].

The evolution of AYA oncology in the United States and other parts of the world formed the stimulus to prepare a second edition of Cancer in Adolescents and Young Adults. Assembling a large group of authors from many disciplines has enabled the editors to take advantage of international expertise and experience and address a comprehensive compendium of topics across the spectrum of AYA oncology.

Tampa, FL, USA — Cameron K. Tebbi
Portland, OR, USA — Archie Bleyer

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Contents

1 Adolescent and Young Adult Oncology: Historical and Global Perspectives

Ronald Barr, Lynn Ries, Andrea Ferrari, Jeremy Whelan, and Archie Bleyer

Since the first edition of *Cancer in Adolescents and Young Adults* was published in 2007, there have been numerous milestones in the journey of adolescent and young adult (AYA) oncology. These include an expansion of the age range from 15–29 to 15–39 years and a commensurate increase in the number and scope of the constituent chapters.

The evidence that AYA oncology (AYAO) has "arrived" includes the establishment of a society [1] and journals [2, 3] devoted to the subject. The first topic addressed in the first issue of the *Journal of Adolescent and Young Adult Oncology* was "what should the age range be for AYA oncology." A case was made for flexibility and context specificity [4]. From a health-care delivery perspective, most countries have adopted a mid-teens to mid-20s range. Formerly, the USA [5] and Canada [6] have taken 15–29 years for epidemiologic reasons. In the context of clinical trial accrual, the Children's Oncology Group (COG) has extended its upper age limit to 50 in some instances [7], while no limit has been suggested for long-term follow-up; some participants in the Childhood Cancer Survivor Study have now passed 50 years of age [8]. For this second edition, we have taken a middle ground by adhering to the 15- to 39-year age range proposed by the US National Cancer Institute (NCI) Progress Review Group on AYA Oncology in 2006 [9].

The wider age range has major implications, beginning with a dramatic effect on disease distribution, now influenced markedly by the epithelial tumors so prevalent among older adults. Consequently, attention has to be paid to carcinomas of the bladder, lung, head and neck, and even prostate, among others. But it means

R. Barr (✉)
Departments of Pediatrics, Pathology and Medicine, McMaster University,
Hamilton, ON, Canada
e-mail: rbarr@mcmaster.ca

L. Ries
Division of Cancer Control and Population Sciences (DCCPS), National Cancer Institute,
Surveillance Research Program (SRP), Surveillance, Epidemiology and End Results (SEER) Program,
9609 Medical Center Drive,
Room 4E326, MSC 9765,
Bethesda, MD 20892-9765, USA
e-mail: lynn_ries@nih.gov

A. Ferrari
Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori,
via Giacomo Venezian, 1, Milano 20133, Italy
e-mail: andrea.ferrari@istitutotumori.mi.it

J. Whelan
Professor of Cancer Medicine and Consultant Medical Oncologist, The London Sarcoma Service,
University College Hospital, London, UK
e-mail: jeremy.whelan@uclh.nhs.uk

A. Bleyer
Department of Radiation Medicine, Oregon Health and Sciences University, Portland, OR, USA
e-mail: ableyer@gmail.com

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also that the disease-specific chapters that deal with disorders more common in those under 30 now have to incorporate consideration of patients approaching middle age. Meanwhile, greater focus has fallen on sexuality and oncofertility, as well as palliative and end-of-life care, reflecting the inclusion of more AYAs in the reproductive age group and a lower survival rate from cancer overall in the fourth decade of life [10] than in younger AYAs.

But this second edition is only one of the accomplishments of the expanding AYA cancer discipline and community. There are many others to celebrate as illustrated by a review of historical events in North America, the United Kingdom, and Australia (Figs. 1.1, 1.2, and 1.3).

In retrospect, the first publication that identified an AYA cancer gap per se appeared in 1996 [11], following which a series of national programs emanated in North America (Fig. 1.1). The Children's Cancer Group (CCG) created a committee devoted to AYAO research that in 1998 was supported via a Cooperative Group grant from the NCI. In 2000, the first NCI workshop on AYAO was held that stimulated other cooperative groups to include AYAO in their research plans.

Formed in 2005 by a unique partnership between the NCI and the LIVESTRONG Foundation, the *Progress Review Group on Adolescent and Young Adult Oncology* remains active and in September 2013 hosted a workshop on *Next Steps in Adolescent and Young Adult Oncology*: *An Update on Progress and Recommendations for the Future* [12]. Various products of that meeting are under development and being published. The NCI also restructured its cooperative group program with the formation of the National Clinical Trials Network in 2014 [13]. In 2013, COG joined ranks with the NCI adult cooperative group AYA committees to

Fig. 1.1 Landmark events in the development of AYA oncology in North America. *CCG* Children's Cancer Group, *NCI* National Cancer Institute, *PRG* Progress Review Group, *JAYAO* Journal of Adolescent and Young Adult Oncology, *IOM* Institute of Medicine, *NCCN* National Comprehensive Cancer Network, *Aflac* Aflac Foundation, *LSYAA* LIVESTRONG Young Adult Alliance, *CMYACA* Critical Mass Young Adult Cancer Alliance

coordinate intergroup efforts to conduct AYAO research, both at the translational and clinical trial levels.

A parallel development in North America was the formation of a *Critical Mass Young Adult Cancer Alliance* [14], an entity that began life as the LIVESTRONG Young Adult Alliance (LSYAA) under the auspices of the LIVESTRONG Foundation in 2006 [15]. *Critical Mass* and LSYAA aggregated AYAO-focused nonprofit organizations, medical institutions, patient advocacy groups, government agencies, clinicians, researchers, and dedicated individuals. One of their outcomes was a position statement on the preferred training of health-care professionals for AYAO [16]. That same year, the National Comprehensive Cancer Network issued its supportive care guidelines in AYAO [17], and in 2013 the Institute of Medicine in the USA convened a workshop devoted to this subject [18].

North of the border momentum in AYAO received a major boost in 2008 when funds from the federal government were provided, through the agency of the Canadian Partnership Against Cancer, to establish and operate a national Task Force on Adolescent and Young Adult Cancer. The Task Force has held two international workshops, in 2010 [19] and 2012, that have led to a series of recommendations [20], akin to those of the Progress Review Group, and a Framework for Action [21] to advance the discipline. A parallel activity has resulted in the approval of a 1-year, postgraduate diploma program in AYAO (a designated "Area of Focused Competence") by the Royal College of Physicians and Surgeons of Canada.

Across "the pond," there has been a continuing surge of activity (Fig. 1.2) building on the foundation of the Teenage Cancer Trust that has built more than 20 centers for teenagers and

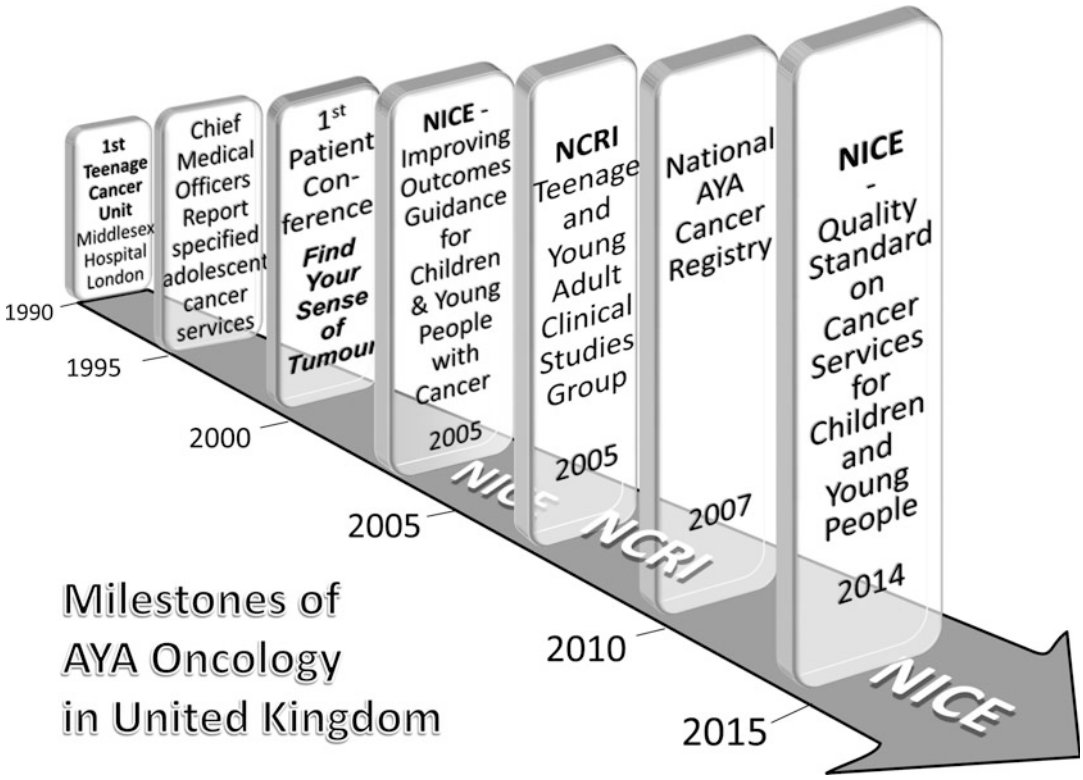

Fig. 1.2 Landmark events in the development of AYA oncology in the United Kingdom. *NICE* National Institute for Health and Care Excellence, *NCRI* National Cancer Research Institute

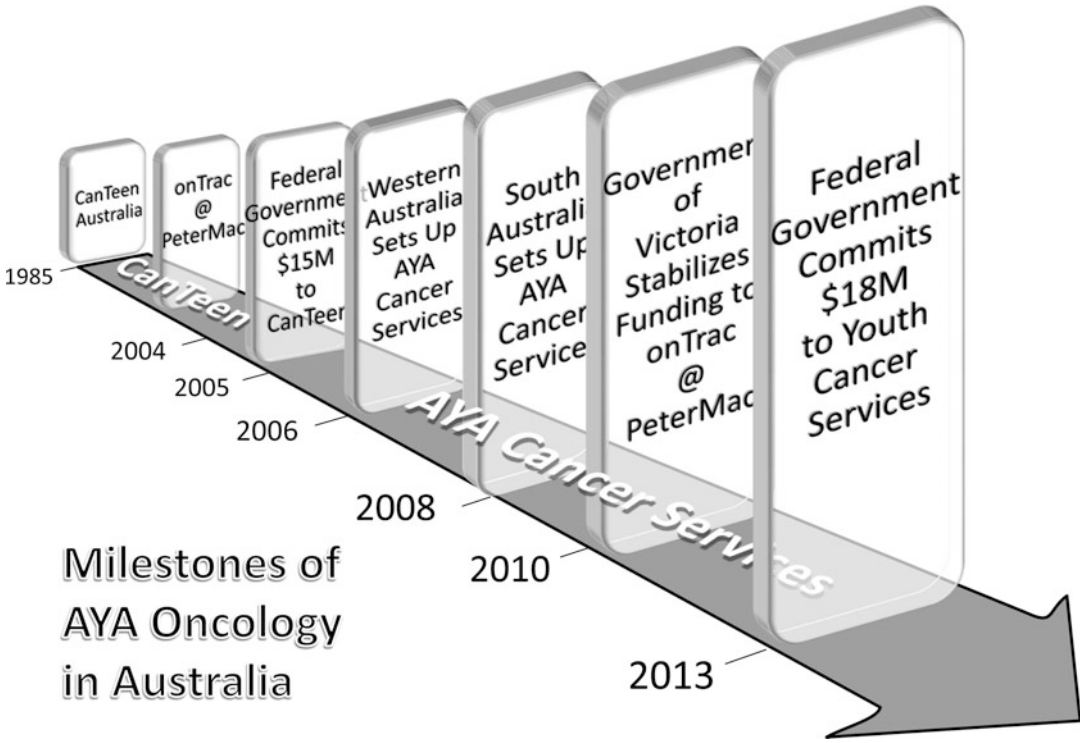

Fig. 1.3 Landmark events in the development of AYA oncology in Australia. *PeterMac* Peter MacCallum Cancer Centre

young adults, ages 13–24, in the United Kingdom since 1990 and continues to host a biennial international symposium. In 2005 the National Institute for Health and Care Excellence (NICE) in the United Kingdom issued a document entitled "Improving outcomes: Guidance in children and young people with cancer" that recommended, in particular, appropriate referral paths in England [22]. At about the same time, the National Cancer Research Institute formed a Teenage and Young Adult Clinical Studies Group (CSG), and the National Cancer Research Network (NCRN) was established. The NCRN set out to double the accrual to cancer clinical trials within 3 years for patients of all ages, from 3.5 % in 2001. This goal was surpassed easily, with a rate of 14 % achieved, and the United Kingdom was labeled "the cancer clinical trials recruitment capital of the world" [23].

The CSG reported in 2008 that accrual to cancer trials of young adults, ages 20–24 years, had declined and that no AYAs with brain tumors who were older than 16 years had been recruited to available trials [24]. In a report 6 years later [25], the CSG noted that accrual rates 15–19-year-olds had improved considerably. The work of the CSG will be a useful guide for the AYA intergroup of the NCTN.

In continental Europe there was limited activity in AYAO at the national level until 2010. An important boost was the provision of funding for 4 years (2011–2015) from the European Commission to build the European Network for Cancer Research in Children and Adolescents (ENCCA) [26]. This organization spans 11 countries and has 34 partners – health-care institutions, advocacy groups, pharmaceutical companies, regulatory bodies involved in drug development, and the health policy community. Although it will sunset in 2015, ENCCA will continue its work in AYAO as the European Network for Teenagers and Young Adults with Cancer. The success of ENCCA reflects its broad composition of stakeholders, especially the productive interaction

between pediatric and medical oncologists, a pattern that has been mirrored in some national projects, as exemplified in Italy where the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) that coordinates the care of children with cancer in all 49 children's hospitals in the country formed a committee on adolescents in 2010. A particular challenge encountered was the considerable variability in the upper age limit for admission to children's hospitals, some as low as 14 years. The AIEOP committee expanded to form SIAMO (Società Italiana Adolescenti con Malattie Oncoematologiche) that includes oncologists who provide care to adults, among other partners [27].

Meanwhile, across the other (bigger) "pond" from North America, Youth Cancer Services (YCS) in Australia received a further commitment of funding from the federal government in 2013, after an initial funding flow in 2007. There are five YCS centers in Australia that cover the entire country which has a large land mass and widely dispersed population. YCS was the product of the AYA Cancer Reference Group formed by Cancer Australia in 2007 and operates in partnership with *CanTeen*, a highly experienced and long-standing consumer support organization through which the federal funds flow (Fig. 1.3). CanTeen has also negotiated successfully with state governments and a large corporate charity, the Sony Foundation, for additional support. The need to develop different models of care, to accommodate the highly varied demography, has been well described [28]. It is exemplified by the functional partnership between the YCS in Adelaide, South Australia, and the Royal Darwin Hospital in Northern Territory – 3,000 km distant! Many of the lessons learned in tackling such challenges should prove to be of value in other parts of the world.

A parallel development over the years since the late 1990s has been the proliferation of AYA cancer websites and awareness generation via social media, starting with Teens Living with Cancer and Planet Cancer in 1999–2000 [29, 30], and rapidly expanded by *I'm Too Young For This* [31] and other progenitors. Today there are innumerable supportive care and informational websites.

So much for the advancement of AYAO in high-income countries (HICs), the great majority of young people live in less privileged societies where they constitute a higher proportion of the population [32]. It has been estimated that there are more than one million incident cases of cancer in AYAs and nearly 400,000 deaths globally each year [33, 34]. Who will provide appropriate care to them? As has been the pattern in HICs, the practitioners of pediatric oncology took up the gauntlet; a symposium on AYAO was held during the meeting of the International Society of Paediatric Oncology (SIOP) in Geneva [35]. But that was almost a decade ago (2006) and there had been no repetition on the SIOP agenda until 2014. Perhaps the leadership will come from our partners in the advocacy community who have been so successful to date. The LIVESTRONG, Teenage Cancer Trust, and CanTeen have all made their mark. Together with CanTeen New Zealand, and Seventy K, these organizations drafted the *International Charter of Rights for Young People with Cancer* in 2010 [36]. Could they form the basis of a truly global initiative, similar to Childhood Cancer International? If so we should all put our collective shoulders to that wheel.

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Cancer Incidence, Survival, and Mortality Among Adolescents and Young Adults

2

Lynn Ries, Annalisa Trama, Kayo Nakata, Gemma Gatta, Laura Botta, and Archie Bleyer

Abstract

While the epidemiology of cancer has been studied in children and older adults for more than a half century, little attention had been paid to the cancers in between those that occur in the older adolescents and young adult (AYA) between 15 and 40 years of age. Yet as recently ascertained, more than a million new cases of invasive cancer are diagnosed in AYAs annually worldwide. Not only are the array of cancers that are diagnosed in AYAs unique, accumulating evidence suggests that many are biologically distinct from what appears to be the same neoplasm in younger and older persons. AYA cancers may thereby have different etiologies and require different therapeutic strategies. Many cancers peak in incidence in AYAs, and there is an intermediate peak between the well-known childhood cancer peak and the predominant one that occurs in the elderly. If the cancers that account for the childhood peak are embryonal/fetal cancers and those that account for the peak late in life as the

L. Ries (✉)
Division of Cancer Control and Population Sciences (DCCPS), National Cancer Institute (Contractor), Surveillance Research Program (SRP), Surveillance, Epidemiology and End Results (SEER) Program, 9609 Medical Center Drive, Room 4E326, MSC 9765, Bethesda, MD 20892-9765, USA
e-mail: lynn_ries@nih.gov

A. Trama • G. Gatta • L. Botta
Evaluative Epidemiology Unit, Department of Preventive and Predictive Medicine, Fondazione IRCCS Istituto Nazionale Tumori, via Giacomo Venezian 1, Milano 20133, Italy
e-mail: annalisa.trama@istitutotumori.mi.it; gemma.gatta@istitutotumori.mi.it; laura.botta@istitutotumori.mi.it

K. Nakata
Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
e-mail: nakata-ka@mc.pref.osaka.jp

A. Bleyer
Department of Radiation Medicine, Oregon Health and Sciences University, Portland, OR, USA
e-mail: ableyer@gmail.com

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cancers of aging, the AYA peak may be considered as due to cancers of intermediate growth and maturation. For most of the past quarter century, the incidence of the AYA cancers has been increasing for reasons that have not been ascertained. In Europe, the United States, and Japan, the 5-year survival rates of the vast majority of cancers in AYA have been remarkably similar. In the United States, the overall rate of survival improvement had been less in AYAs than in either younger or older patients. The trends and patterns of incidence do offer certain clues as to cancer causation in AYAs and potential methods of prevention. Detailed analyses of incidence patterns by geographic region and demographic factors together with determination of variations in incidence in time and space should provide additional insights into etiology and separate lines of investigation and therapeutic opportunities.

2.1 Introduction

Since the first edition of this textbook was published, we have learned that more than one million new cases of invasive cancers have been diagnosed annually worldwide in adolescent and young adult (AYA) persons (Table 2.1). In most socioeconomically advantaged countries, cancer is a leading cause of death due to disease among AYAs. In the United States, cancer is the second most common cause of death due to disease, after suicide, and the most common cause of death in AYA females.

This chapter expands the age range used in the first edition of 15–29 years of age to a higher upper age limit, 39 years, as defined by the National Cancer Institute Progress Review Group of 2004–2005 [1] and explained in the introductory chapter. Thus, most of the data in this chapter are new, and previously unreported observations are identified as such. The overview in this chapter emphasizes general epidemiologic and survival comparisons of the different cancers by sites and organ systems and how they vary over age, sex, and time. To the extent possible, global, continental, and national data, including those of regional areas in Europe, of Japan, and of the United States, are included. Detailed results for specific sites can be found in the site-specific chapters.

2.2 Sources of Information and Modes of Analysis: Incidence, Survival, and Mortality

2.2.1 Age

The age range for AYAs in this edition of the textbook is 15–39 years, inclusively. It had been 15–29 years in an initial United States (US) National Cancer Institute (NCI) treatise [2], but during the second NCI Workshop on AYA oncology, the upper age limit was raised to 39 years [1]. The Progress Review Group (PRG) on AYA Oncology in 2004–2005 affirmed this age range with full cognizance of the increased heterogeneity and diversity that the additional years encompassed [3].

2.3 Data Sources and Analyses

The data from Europe were obtained from EUROCARE-5 for survival analyses (Fig. 2.1). The data from Japan are taken from six prefectures (J-CANSIS) (Fig. 2.1) representing 14 % of the country's population and in more detail from the Osaka Cancer Registry. Data from the United States were obtained from the NCI Surveillance, Epidemiology, and End Results (SEER) Program

Table 2.1 Worldwide cancer incidence and death: frequencies and rates for ages 15–39 in 2012 based on GLOBOCAN, 2012

Age 15–39	**Estimated cases**[a]	**Incidence rate**	**Estimated deaths**	**Death rate**
All cancers	1,048,821	37.5	390,579	14.0
Males	383,209	26.8	183,116	12.8
Females	665,612	48.7	207,463	15.2
LDR[b]	807,768	33.8	349,529	14.6
MDR[c]	241,053	58.4	41,050	9.9
Age group	**Estimated cases**	**Incidence rate**	**Estimated deaths**	**Death rate**
All ages[d]	14,067,894	182.0	8,201,575	102.4
0–14	163,284	8.8	79,956	4.3
15–39	1,048,821	37.5	390,579	14.0
40–44	655,050	138.8	264,542	56.1
45–49	933,844	220.9	409,105	96.8
50–54	1,239,316	338.2	577,123	157.5
55–59	1,577,831	489.1	784,558	243.2
60–64	1,765,236	683.9	929,790	360.2
65–69	1,671,710	895.8	939,692	503.6
70–74	1,609,588	1114.4	1,023,544	708.7
75+	3,403,214	1544.0	2,802,686	1271.6

Source: GLOBOCAN 2012, IARC – 14.9.2015: http://globocan.iarc.fr, IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France

[a]All invasive cancers except basal and squamous skin cancer

[b]*LDR* less developed regions, all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia

[c]*MDR* more developed regions, all regions of Europe plus Northern America, Australia/New Zealand, and Japan

[d]All ages, rates are ASR. Other rates are crude

(Fig. 2.1). GLOBOCAN data were used to assess incidence by continent and in Europe by region.

2.3.1 Incidence

GLOBOCAN estimates for 2012 were used for the worldwide projections of cancer incidence counts and rates by sex and cancer site [4]. For the presentation of the incidence data by population, we identified first two large geographic regions: a more developed region (MDR) including all regions of Europe plus Northern America, Australia/New Zealand, and Japan versus less developed regions (LDR), including all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia, and Polynesia. Furthermore, for a more detailed description, we also identified six geographic regions: North America (N America) (United States and Canada) and Northern, Western, and Southern Europe (N, W, S Europe), Central and Eastern Europe (C & E Europe), South America (S America), Asia, and Africa. A listing of the countries in each group can be found in the reference for GLOBOCAN [5].

The SEER Program collected cancer incidence and survival data on approximately 10 % of the US population between 1973 and 1992 (SEER9), 14 % of the US population between 1992 and 2000 (SEER13), and 26 % thereafter (SEER18) (Fig. 2.1), the last of which has 28–29 % of the country's 15- to 39-year-olds. The SEER Program, described in detail elsewhere [6], collects information on primary site and detailed histology according to the International Classification of Diseases for Oncology third edition (ICD-O-3) [7] since 2001. Prior to 2001, site and histology were collected based on International Classification of Diseases

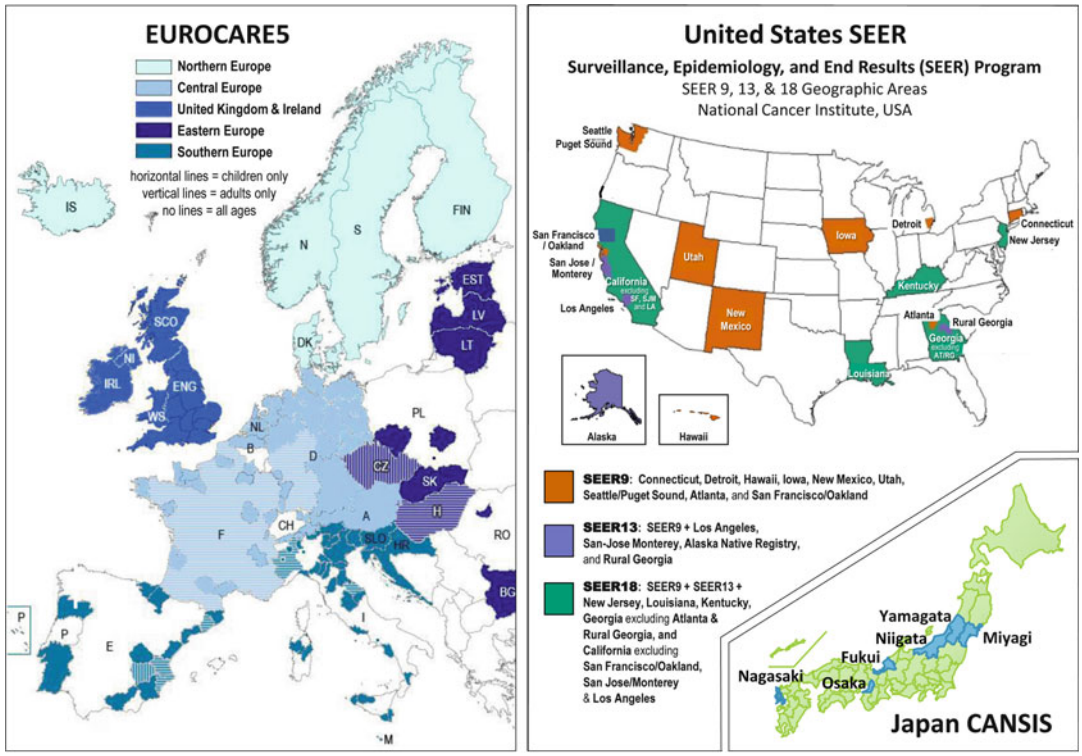

Fig. 2.1 Cancer registries included in EUROCARE-5, US SEER, and J-CANSIS

for Oncology 1976 (ICD-O-1) up to 1992 and International Classification of Diseases for Oncology second edition (ICD-O-2) [8] from 1992 to 2000. The ICD-O-3 hematopoietic codes were updated based on WHO classification of tumours of haematopoietic and lymphoid tissues (2008) [9]. Long-term trends were based on 9 SEER geographic areas (SEER9) [10] and more recent information since 2000 on 18 SEER geographic areas (SEER18) [5]. SEER*Stat (version 8.1.5), Excel 2007, and STATA 13 were used for analysis of SEER data.

In order to analyze site and histology, the SEER data were recoded into meaningful groups. For some chapters, the AYA recode based on Barr et al. [11] was used because it was designed to group site and histology with an emphasis on histology for the AYA age group. The AYA recode was adapted slightly to account for the new hematopoietic codes implemented in 2010 [12]. Since the upper age limit of the AYA age group was raised to 39 years of age [1], some of the chapters used the SEER site recode [13] to emphasize primary site, i.e., all histologies except lymphoma are included for each of the solid tumors. In the AYA recode, the histologies are usually limited to carcinomas for the solid tumors and excluded in situ tumors. In situ cancers of the bladder were combined with the invasive tumors, and pilocytic astrocytomas were excluded.

2.3.2 Survival

European survival data were obtained from EUROCARE (EUROpean CAncer REgistry-based study on survival and care of cancer patients) fifth edition [14]. EUROCARE is the widest collaborative research project on cancer survival in Europe. It started in 1989 to provide an updated description of cancer survival time trends and survival differences across European countries, measure cancer prevalence, and study patterns of care of cancer patients. The fifth edition, EUROCARE-5, included data on more than

21 million cancer diagnoses provided by 116 cancer registries (including 10 specialized childhood cancer registry) in 30 European countries from Jan 1, 1978, to Dec 31, 2007, with the date of death updated to at least December 31, 2008 (except for France cancer registries; December 31, 2007) (Fig. 2.1) [15].

Survival was analyzed for 56,505 cancer cases in European children (age <15 years), 312,483 cancer cases in AYAs (age 15–39 years), and 3,567,383 cancer cases in adults (40–69) diagnosed during the period 2000–2007. Only malignant cancers were included (pilocytic astrocytoma was excluded). Patients who had more than one type of cancer were included in the survival analyses; thus, if two or more cancers were diagnosed in a single patient, all were included in the analyses. More information on the database and the quality can be found in Trama et al. [16].

Individual types of AYA cancers were grouped into 19 diagnostic categories affecting AYAs and children and 20 carcinoma categories affecting AYAs and adults (Table 2.4) defined by the International Classification of Childhood Cancers (ICCC) third edition [17] with the addition of "all cancers combined." We estimated relative survival, the ratio of observed survival to the expected survival in the general population of the same age and sex, to correct for deaths from causes other than the cancer under investigation. We used the cohort approach, Ederer II method [18], to estimate survival for patients diagnosed in 2000–2007 and followed up until at least the end of 2008, enabling estimation of 5-year relative survival. We used a complete analysis which is a modification of traditional cohort analysis, in which more recently diagnosed patients are also included, even if they could not possibly have completed the entire follow-up interval of interest [19].

The differences in survival by age groups (0–14 vs 15–39 and 15–39 vs 40–69) were tested with a z test with a significance level $\alpha = 0.05$ [20]. The survival for the comparison of adults and AYAs was truncated at 69 years of age. To compare children and AYAs, survival in Europe as a whole was obtained by directly weighting the regional grouping survival estimates with weightings proportional to the population of 0–39 years in each regional grouping in 2000–2007. To provide the overall EU survival for adults, the weighting used to estimate survival in Europe was proportional to the adult population (15–99 years) [21].

Japanese survival data were obtained from J-CANSIS (Japanese CANcer Survival Information for Society), representing 14 % of the country's population. J-CANSIS data were provided by the population-based cancer registries of six prefectures (Yamagata, Miyagi, Fukui, Niigata, Osaka, and Nagasaki). These prefectural cancer registries have cancer records with high data quality (death certificate only = 3.9–17.7 %) and have been used to estimate national statistics for cancer survival in Japan for a long time. Survival was analyzed for 1852 Japanese children (aged 0–14 years) and 13, 190 AYAs (age 15–39 years) diagnosed with cancer during the period 2000–2006. The same site/histology groupings as in the European and SEER data were used (pilocytic astrocytoma was excluded). The maximum likelihood method was applied to estimate relative survival using the strel command in the publicly available STATA program. More information on the database and its quality can be found elsewhere [22].

To assess changes in survival over time from 1999 to 2007, 5-year relative survival was estimated by the period approach [19] for patients under observation/follow-up in 1999–2001 (diagnosed 1995–2001), 2002–2004 (diagnosed 1998–2004), and 2005–2007 (diagnosed 2001–2007). To assess the statistical significance of survival changes over time, the relative survival was modeled with a generalized linear model, which implies a Poisson distribution of the number of observed deaths in each interval. The Poisson regression model, with the year of diagnosis included as a continuous variable, was used to obtain the average yearly reduction in mortality for the period of diagnosis 1999–2007 expressed as the relative excess risk of death. The relative excess risk of death was estimated for each diagnostic group for Europe as a whole adjusted by country, age class, sex, and year of diagnosis.

The US survival data from 18 SEER geographic areas from 2000 to 2007 were used for the comparison of survival data from Europe and Japan. The same site/histology groupings were used as in the European data: in situ bladder cancers were included, and pilocytic astrocytomas were excluded. For urinary bladder, benign, in situ, and invasive tumors were included for Europe and in situ and invasive tumors for SEER. In addition, carcinoids (ICD-O-3 8240–8244) were excluded from the colon and appendix in both the European and SEER analyses.

Five-year survival trends in the United States were assessed from 1975 to 2012 by excluding Kaposi sarcoma and non-Hodgkin lymphoma in males and thyroid cancer in females. The former was necessary since the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic during the 1980s and early 1990s markedly increased the incidence of Kaposi sarcoma and non-Hodgkin lymphoma (NHL) in AYA males, cancers with such a poor prognosis that the overall survival rate substantively declined. The latter was necessary because of the overdiagnosis of thyroid cancer, predominantly in females, that began in the 1990s and has escalated since, progressively inflating the overall survival in AYA females.

2.3.3 Mortality

GLOBOCAN estimates for 2012 were used for the worldwide projections of cancer mortality counts and rates by sex and cancer site [10]. The US mortality data were from the National Center for Health Statistics (NCHS) as analyzed by the SEER Program which obtained files containing all deaths occurring in the United States by calendar year since 1969. Further details can be found elsewhere [6]. Only the underlying cause of death was used in the calculation of death rates. Cause of death was coded according to ICD-9 (1979–1988) and ICD-10 (1999+). Mortality groupings were used that correspond to the SEER site recode [17].

2.4 Global, Regional, and National Perspectives

2.4.1 Incidence

2.4.1.1 Cancer Incidence Worldwide

Worldwide over one million AYAs aged 15–39 years were diagnosed with malignant cancer in 2012 based on GLOBOCAN [4] (Table 2.1), which is 7 % of the 14.1 million new cancer cases of all ages worldwide estimated by GLOBOCAN for the same year [23].

The mix of malignant tumors in AYAs differs from that for all ages combined and from that in both younger and older persons. For all ages and both sexes, the top five cancers worldwide in 2012, in order of incidence, were cancer of the lung (13 %), breast (12 %), colorectum (10 %), prostate (8 %), and stomach (7 %) [23]. For AYAs, the order for the same year was breast cancer (18 %), cervix uteri cancer (11 %), thyroid cancer (8 %), leukemia (6 %), and central nervous system (CNS) tumors (4 %) (Table 2.2). In the United States, the predominant cancers in AYA males and females differ from the worldwide sequence in that, for the year 2012, the order was thyroid carcinoma (16 %), breast carcinoma (15 %), melanoma (9 %), cervix uteri carcinoma (7 %), and colorectal carcinoma (6 %).

Figures 2.2 and 2.3 illustrate with the United States data how the cancer mix in AYAs is highly age dependent within the AYA age span, as the cancers of childhood transit to those in adulthood (Fig. 2.2). From the youngest AYAs to the oldest, the incidence of breast cancer increases from extremely rare to the most frequent cancer. Cancer of the female genital tract (cervix, uterus, vagina, vulva) undergoes a similar increase. Leukemia on the other hand decreases from the most frequent type in children to a few percent in the oldest AYAs. When considered as a proportion of all cancer (Fig. 2.3), at least seven cancers have their highest percentage within the AYA age range: thyroid cancer, Hodgkin lymphoma, testis cancer, osteosarcoma, Ewing tumor, and Kaposi sarcoma. More than half of the cancers in AYAs are accounted for by those

Table 2.2 Worldwide estimated cancer incidence and mortality frequencies for ages 15–39 in 2012 based on GLOBOCAN

	Incidence					Mortality				
Cancer	Males and females	Males	Females	Overall rank	Male to female ratio	Males and females	Males	Females	Overall rank	Male to female ratio
All cancers[a]	1,048,821	383,209	665,612		0.6	390,579	183,116	207,463		0.9
Bladder	7401	4856	2545	21	1.9	1639	1149	490	22	2.3
Brain, nervous system	46,915	26,670	20,245	5	1.3	23,661	13,814	9847	5	1.4
Breast (female only)	191,844		191,844	1		48,961		48,961	1	
Cervix uteri	111,503		111,503	2		28,201		28,201	4	
Colorectum	42,647	21,947	20,700	7	1.1	21,474	10,979	10,495	6	1.0
Corpus uteri	15,535		15,535	18		1608		1608	23	
Gallbladder	3879	1401	2478	24	0.6	2411	958	1453	21	0.7
Hodgkin lymphoma	28,330	15,396	12,934	11	1.2	6199	3727	2472	14	1.5
Kaposi sarcoma	22,975	14,437	8538	16	1.7	8795	5032	3763	12	1.3
Kidney	13,660	7798	5862	19	1.3	3722	1912	1810	19	1.1
Larynx	3506	2575	931	25	2.8	1388	1002	386	24	2.6
Leukemia	61,432	35,313	26,119	4	1.4	45,169	26,322	18,847	2	1.4
Lip, oral cavity	24,251	15,267	8984	14	1.7	10,327	7836	2491	10	3.1
Liver	42,372	32,871	9501	8	3.5	37,528	29,765	7763	3	3.8
Lung	23,182	13,465	9717	15	1.4	15,977	9636	6341	9	1.5
Melanoma of the skin	26,600	10,055	16,545	12	0.6	3200	1642	1558	20	1.1
Multiple myeloma	2277	1444	833	26	1.7	743	497	246	27	2.0
Nasopharynx	15,949	10,340	5609	17	1.8	5547	3505	2042	15	1.7
Non-Hodgkin lymphoma	45,824	27,229	18,595	6	1.5	20,214	12,118	8096	7	1.5
Esophagus	8737	5362	3375	20	1.6	6986	3927	3059	13	1.3
Other pharynx	5727	3726	2001	22	1.9	3935	2680	1255	17	2.1
Ovary	31,492		31,492	10		9498		9498	11	
Pancreas	5310	2800	2510	23	1.1	3888	2243	1645	18	1.4
Prostate	1087	1087		27		978	978		26	
Stomach	26,313	13,598	12,715	13	1.1	18,697	9689	9008	8	1.1
Testis	33,871	33,871		9		4233	4233		16	
Thyroid	83,980	16,734	67,246	3	0.2	1116	251	865	25	0.3

Source: GLOBOCAN 2012 (19.3.2015v): http://globocan.iarc.fr, IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France

[a]All invasive cancers except basal and squamous skin cancer

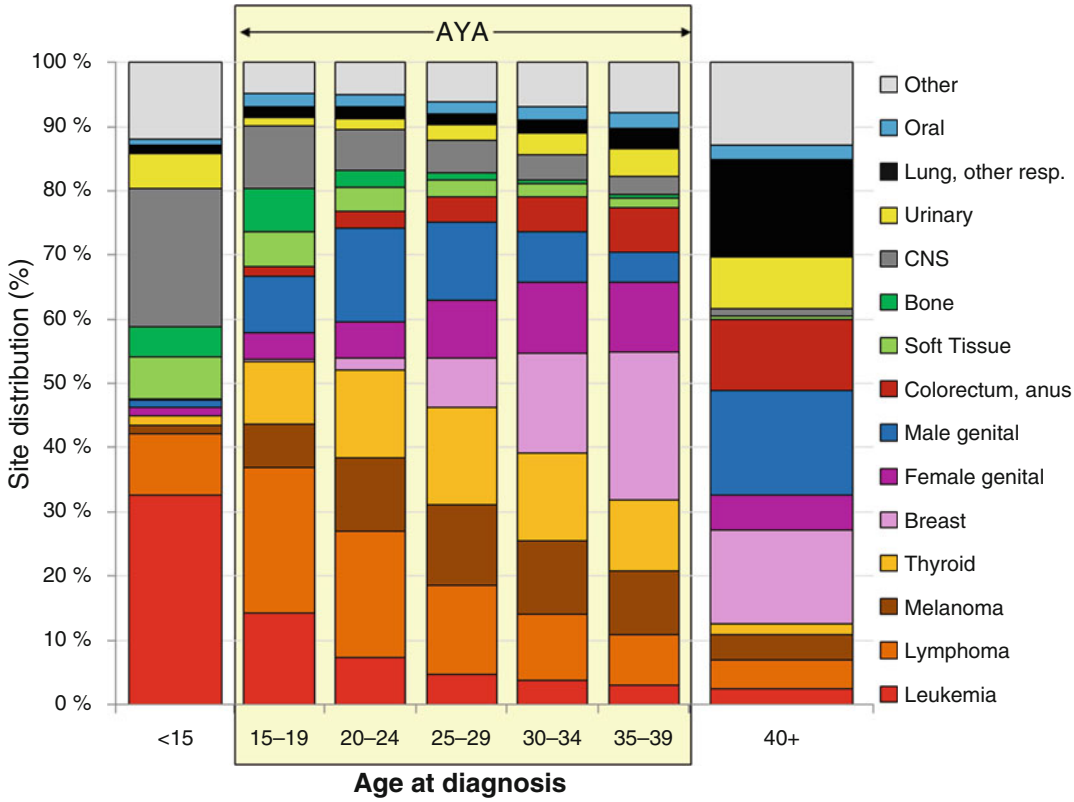

Fig. 2.2 Cancer site distribution, US SEER18, 2000–2011, by age

that peak in proportion during the AYAs years, further rendering the array of cancer types unique to the age group.

Nearly two-thirds of the incident cases were in females because the most common cancers in this age group are female-specific tumors (cervix uteri and other female gynecologic malignancies) or sites where the rates among females are much higher than for males (breast and thyroid) (Table 2.2). The most common cancer site for ages 15–39 years was female breast cancer with nearly 192,000 cases worldwide in 2012. The second most common was cancer of the cervix uteri and third was cancer of the thyroid, with 112,000 and 84,000 cases, respectively (Table 2.2). In AYA males, the most common was the leukemia, with 35,000 cases worldwide in 2012, followed by testis cancer and liver cancer with 34,000 and 33,000 cases, respectively (Table 2.2).

2.4.1.2 Worldwide Geographic Variation

A broad grouping was used as a first cut of MDR. Since the populations of the LDR are so much greater than the MDR, it is expected based on GLOBOCAN estimates that more than two-thirds of the cases among 15–39-year-olds will reside in LDR, while the incidence rate is lower in LDR than MDR (Table 2.1).

Worldwide, the cancer incidence rates for AYAs vary from country to country and continent to continent. Figures 2.4 and 2.5 show, for males and females, respectively, the higher rates of total invasive cancers for North America (N America) (United States and Canada) and Northern, Western, and Southern Europe (N, W, S Europe) compared to the overall world rate of Central and Eastern Europe (C and E Europe), South America (S America), Asia, and Africa. While the overall cancer rates for N America and N, W, S Europe

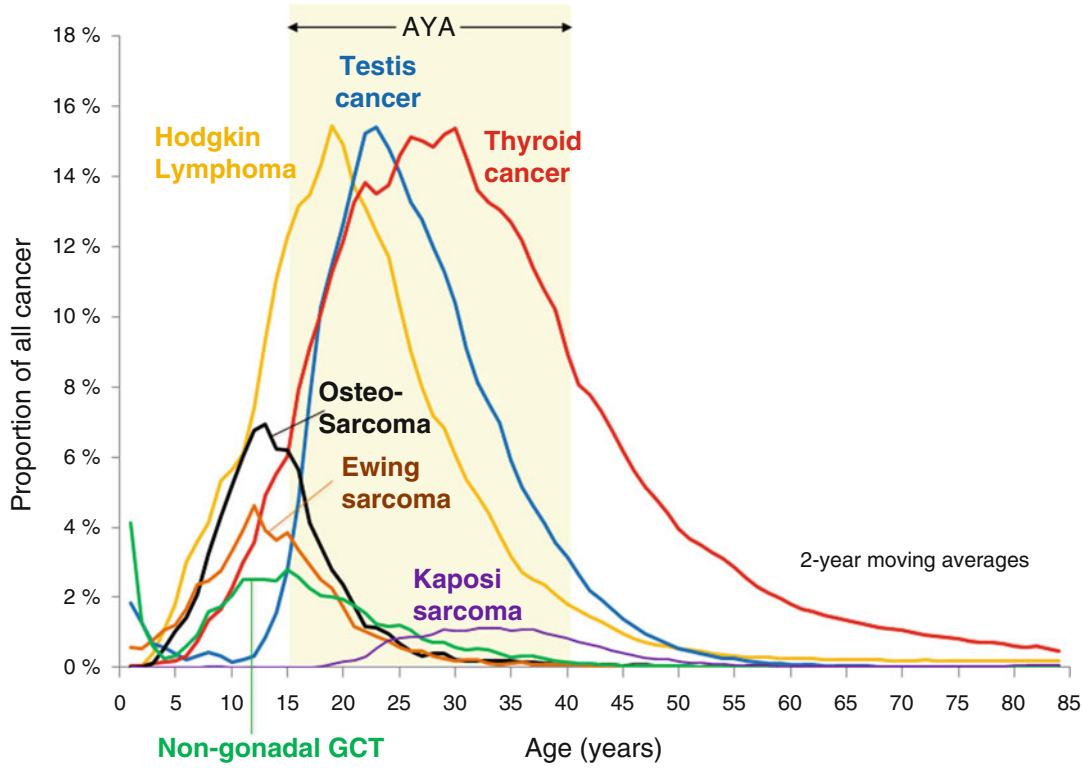

Fig. 2.3 Invasive cancers that have the highest proportion in AYAs, US SEER13, by single year of age

are similar, there are differences by site. In males, colorectal and renal cancer and leukemia and thyroid cancers are higher in N America, and melanoma and testicular cancer are higher in N, W, S Europe. The high rate in males of Kaposi sarcoma (KS) in Africa is in sharp contrast to the almost nonexistent KS rate in Asia and C and E Europe. Liver cancer is higher in Africa and Asia than in Europe (N, W, S and C and E Europe) and N America. In contrast, leukemia incidence rates in males are much lower in Africa than the other countries. Testicular cancer is much higher in N America and N, W, S Europe than in other regions. The incidence of nasopharyngeal cancer is higher in Asia than in any other regions.

For females (Fig. 2.5), the AYA breast cancer rates are similar between N, W, S Europe and N America, but nearly double those for the other regions. The rates for cancer of the cervix uteri range from a low of 6.7 in N America to a high of 14 per 100,000 females in S America and C and E Europe where it is the number one cancer among AYA females. The cervical cancer rates for N, W, S Europe are lower than for C and E Europe. However, in North Europe, cervix cancer incidence is also high in the Baltic countries which are included in the N, W, S Europe (data not shown). Thyroid cancer among AYA females in N America has more than double the rate of any other group of countries, and the thyroid cancer rate in Africa is one-twentieth that of N America. For females, N America has the highest rates for cancers of the colorectum, corpus uteri, and kidney and leukemia and NHL. S America has the highest rate for cancers of the ovary and the second highest rate for corpus uteri. While the KS rate among African females is lower than that for African males, the rate for African females is much higher than in the other country groups. Melanoma is higher in N, W, S Europe and N America and very low in Asia and Africa. For AYA females, nearly half of the

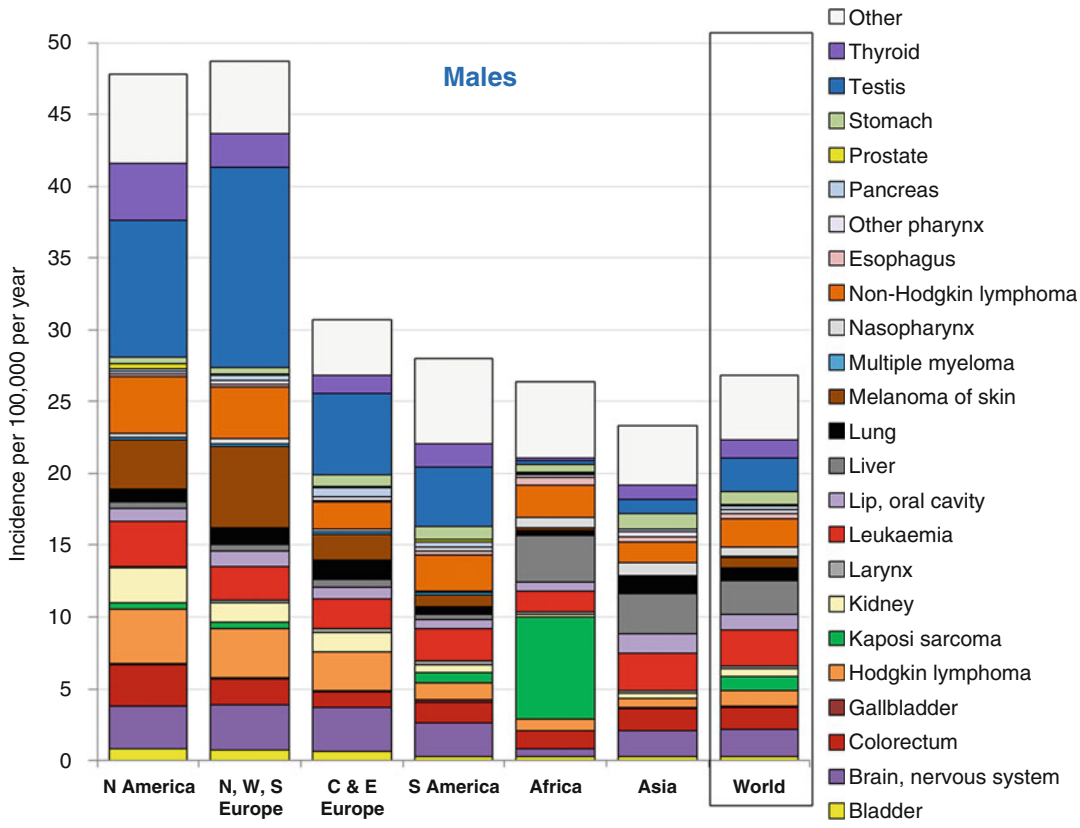

Fig. 2.4 World cancer crude incidence rates, age 15–39, 2012, by geographic area and site, males. GLOBOCAN, *N* North/Northern, *S* South/Southern, *W* Western, *C* Central, *E* Eastern

cancers are breast or thyroid in N America and breast or cervix in C and E Europe, S America, Africa, and Asia. While Asia has the lowest breast cancer rate, breast cancer comprises nearly 30 % of the cancer burden among AYA females.

2.4.1.3 Overall Incidence by Single Years of Age (US SEER)

Since GLOBOCAN data are not available in finer age breakdowns than 15–39 years of age, SEER data were used to show how the cancer sites can vary across the age groups comprising the AYA group. Figure 2.6 shows the incidence rates for males and females by single years of age. After the childhood cancer peak between 2 and 4 years of age, the incidence decreases until age 8 in girls and 10 in boys and then increases exponentially until age 60 after which the increase slows until it plateaus after age 80. In females, the incidence is a smoothly exponential phase from age 10 to 50, whereas in males it is triphasic with separate exponential phases from age 10 to 25, 25 to 40, and 40 to 60. Males have a higher incidence from infancy to age 20 and after age 55, whereas females have a distinctly higher rate in between and particularly during the older AYA years.

2.4.1.4 Individual Cancer Incidence by 5-Year Age Intervals (US SEER)

For ages 15–39 years, the overall cancer incidence rate increases with each 5-year age group from around 20 (ages 15–19) to 130 (ages 35–39) per 100,000 (Fig. 2.7). The rates for the 35–39-year-olds are much higher than the rates for other age groups for males and

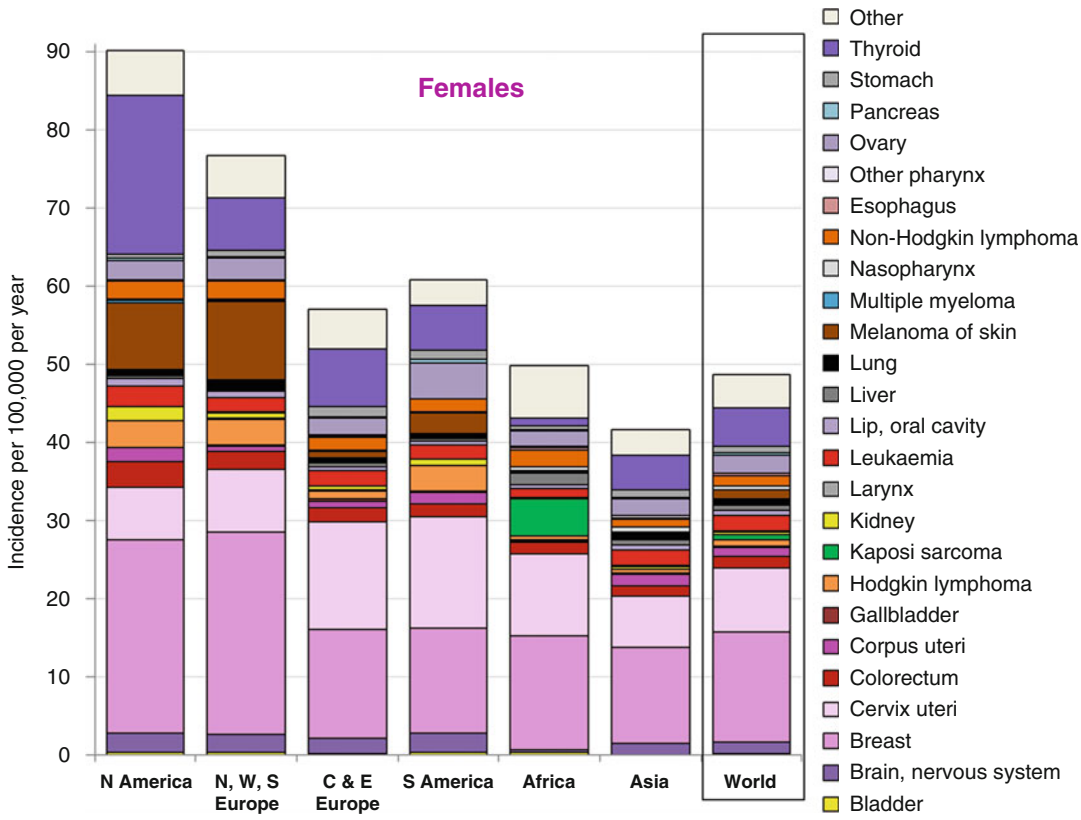

Fig. 2.5 World cancer crude incidence rates, age 15–39, 2012, by geographic area and site, females. GLOBOCAN, *N* North/Northern, *S* South/Southern, *W* Western, *C* Central, *E* Eastern

females. The rates for children under 15 years of age are less than the 15–19 age group and for those 40 and over are much greater (notice the scale break) than the 35–39 age group. For males (Fig. 2.8), the incidence rates range from less than 25–90 per 100,000 compared to a range of less than 25 to over 170 per 100,000 for females. For the older AYA age groups especially 35–39 years, the overall rates for males (Fig. 2.8) are lower than that for females (Fig. 2.9). Even though breast cancer is predominately a cancer for females, it remains the cancer with the highest rate for both males and females combined and females alone for the 35–39-year age group. The increase in the breast cancer rate across the female age groups is dramatic, and it ranges from 0.2 for ages 15–19 to 60.1 per 100,000 for females aged 35–39 (Fig. 2.9).

2.4.1.5 Individual Cancer Incidence by Age Group, Site, and Sex (US SEER)

In order to portray the incidence rates and trends more graphically, broader groups of sites were used in Figs. 2.7, 2.8, and 2.9. For males, genital (mostly testicular) cancer predominates for most age groups (from 20 years onward) except age group 35–39 in which three sites (lymphoma, male genital, and melanoma) dominate the picture.

For males aged 15–19 years, more than half of the cancers are leukemia, lymphoma, or genital tumors with corresponding rates of 3.6, 5.2, and 3.7 per 100,000. For males, the colorectal cancer rates increase from less than 1 per 100,000 for ages 15–19 to nearly 10 per 100,000 in 35–39-year-olds. Similarly, there is a large increase in cancer risk for melanoma between

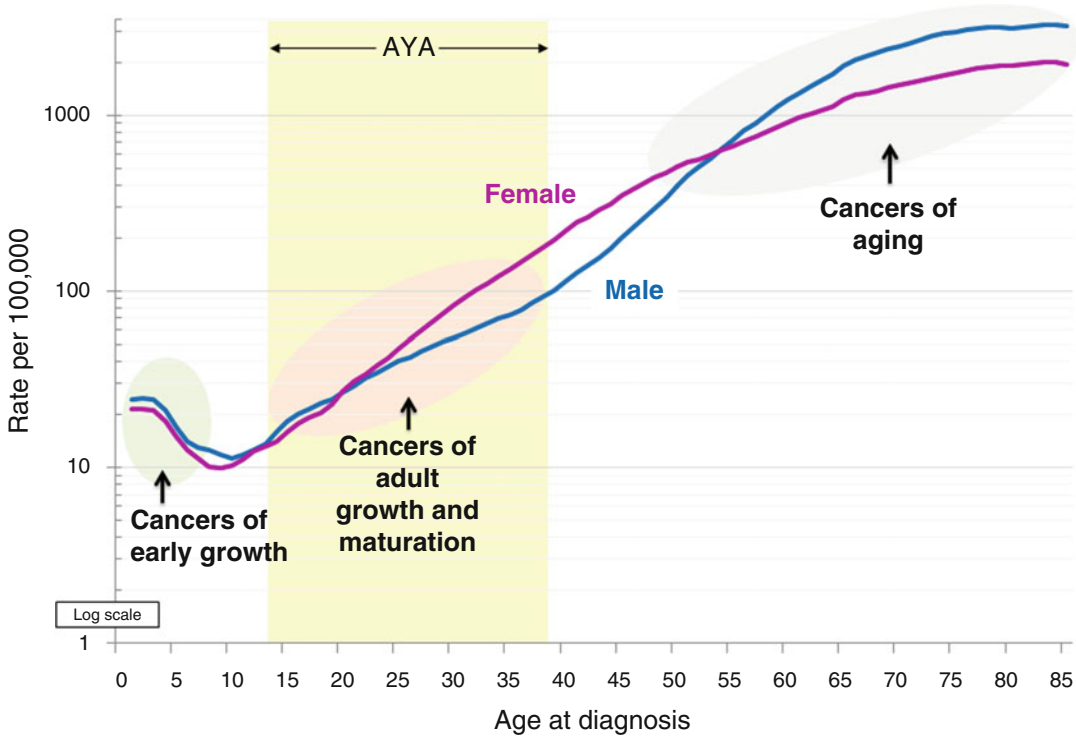

Fig. 2.6 Incidence of invasive cancer, 2000–2011, US SEER18, by single year of age and sex

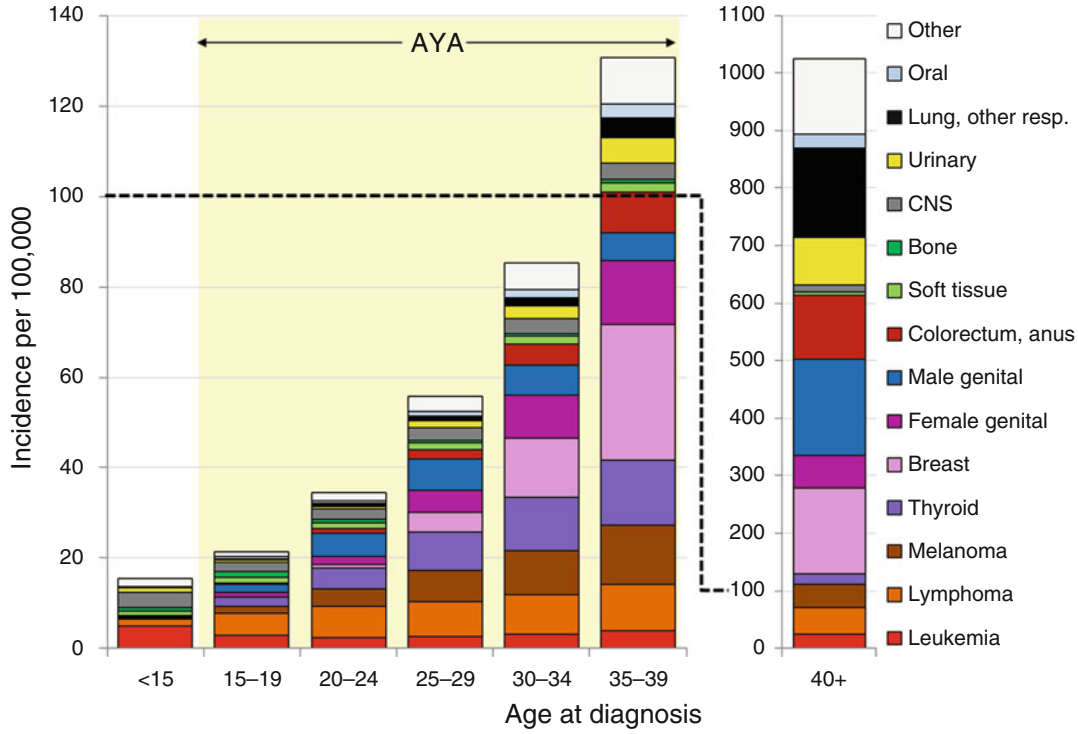

Fig. 2.7 Cancer incidence rates, 2000–2011, US SEER18, males and females, by site and age

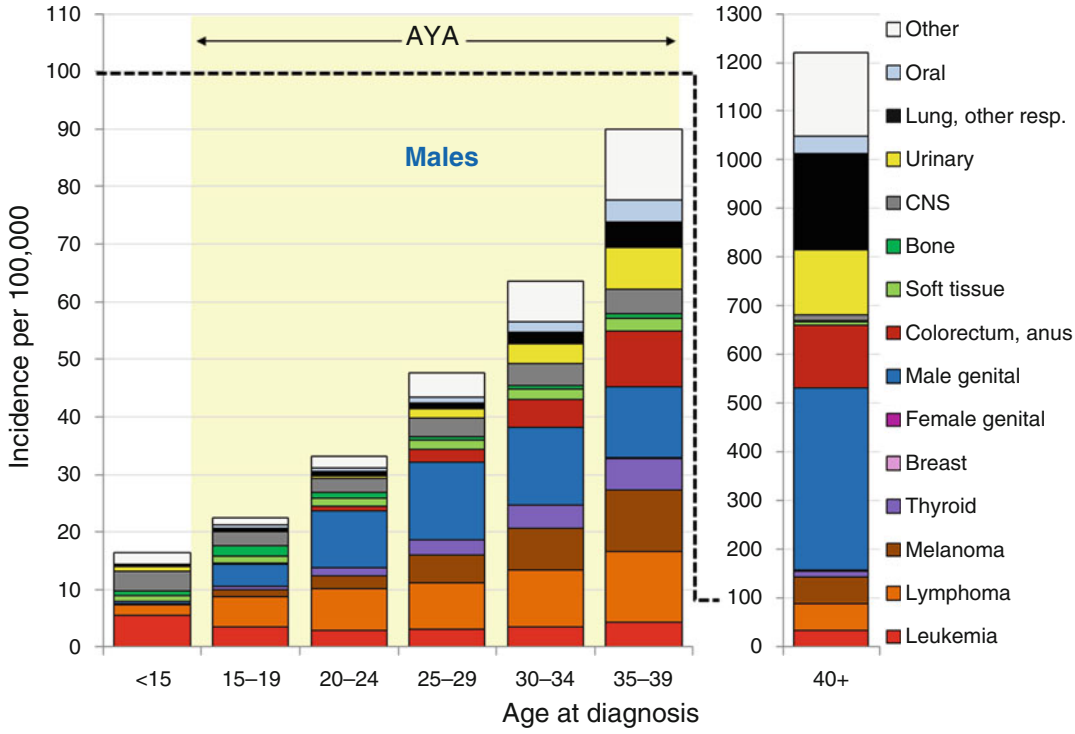

Fig. 2.8 Cancer incidence rates, 2000–2011, US SEER18, males, by site and age (Note that the ordinate scale is different here from that used in Fig. 2.9)

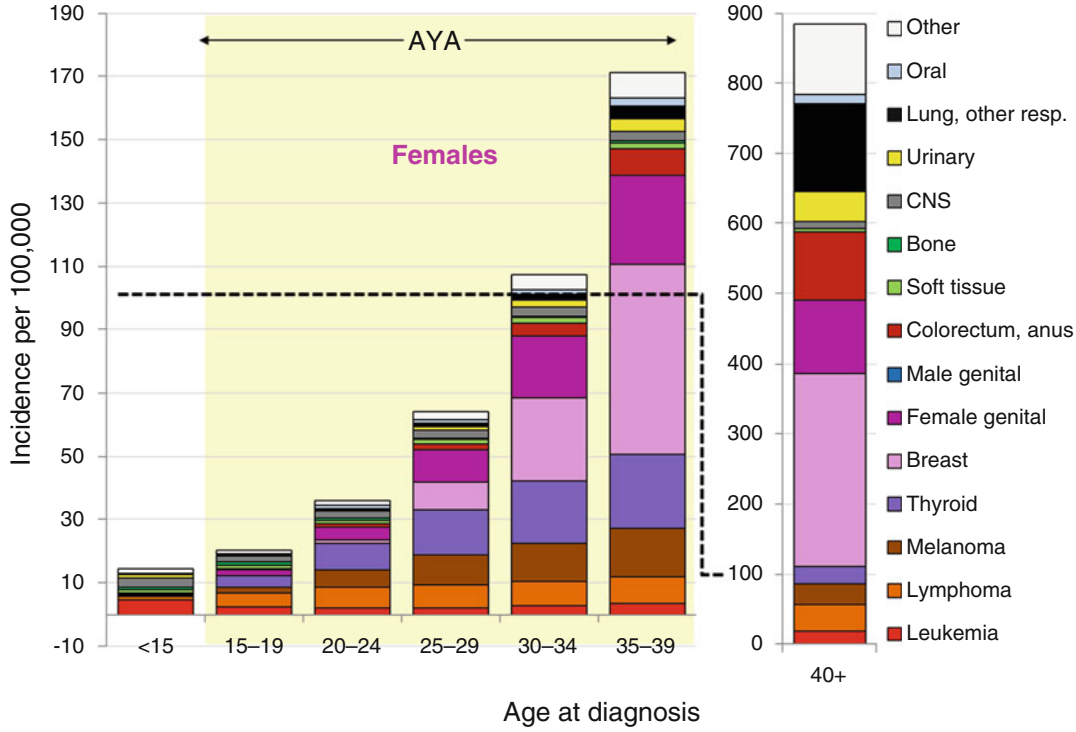

Fig. 2.9 Cancer incidence rates by site and age, 2000–2011, US SEER18, females (Note that the ordinate scale is different here from that used in Fig. 2.8)

ages 15–19 and 35–39. Invasive CNS tumor rates and leukemia rates varied between 2 and 4 per 100,000 across all AYA age groups.

In proportional terms, breast cancer alone comprises 35% of all female cancers in the 35–39-year age group and together with thyroid and genital cancers comprise over half of the cancers in this age group. Breast cancer is very rare for 15–19 (0.2) in comparison to 60 per 100,000 for ages 35–39. Large increases in rates across the age groups were seen for melanoma and cancers of the thyroid, genital tract, and colorectum.

Figure 2.10 shows the incidence rates for ages 15–39 combined by sex for a detailed list of over 25 cancer sites. Based on US SEER data, breast cancer is the number one cancer among AYA females with a rate of nearly 21 per 100,000, which is more than double the highest rate among males, cancer of the testis (10.17 per 100,000) (Fig. 2.10). For females, thyroid and melanoma complete the top three and for males, melanoma and NHL complete the top three. Cancer among AYAs is relatively rare with only female breast cancer, female thyroid cancer, and cancer of the testis with rates over 10 per 100,000 females/males.

2.4.1.6 Incidence Trends by Site (US SEER)

Figure 2.11 depicts for American AYAs the average annual percent change (APC) during 2000-2011 of the incidence rate of cancer and of 28 individual types of cancer for females and for males. The average was 1% per year in females and 0.25% per year in males. For females, about half of the cancers show decreasing incidence trends and half show increasing trends. For males, more cancers decreased than increased in incidence. Lung and cervix uteri showed the largest decreases for females, whereas Kaposi sarcoma, anus, eye, and urinary bladder had decreases of more than 2% per year for males. Two cancers, those of the kidney and thyroid, have had disproportionately greater increases in both females and males. For kidney cancer, the increases were 6.1% and 5.8% per year in males and females,

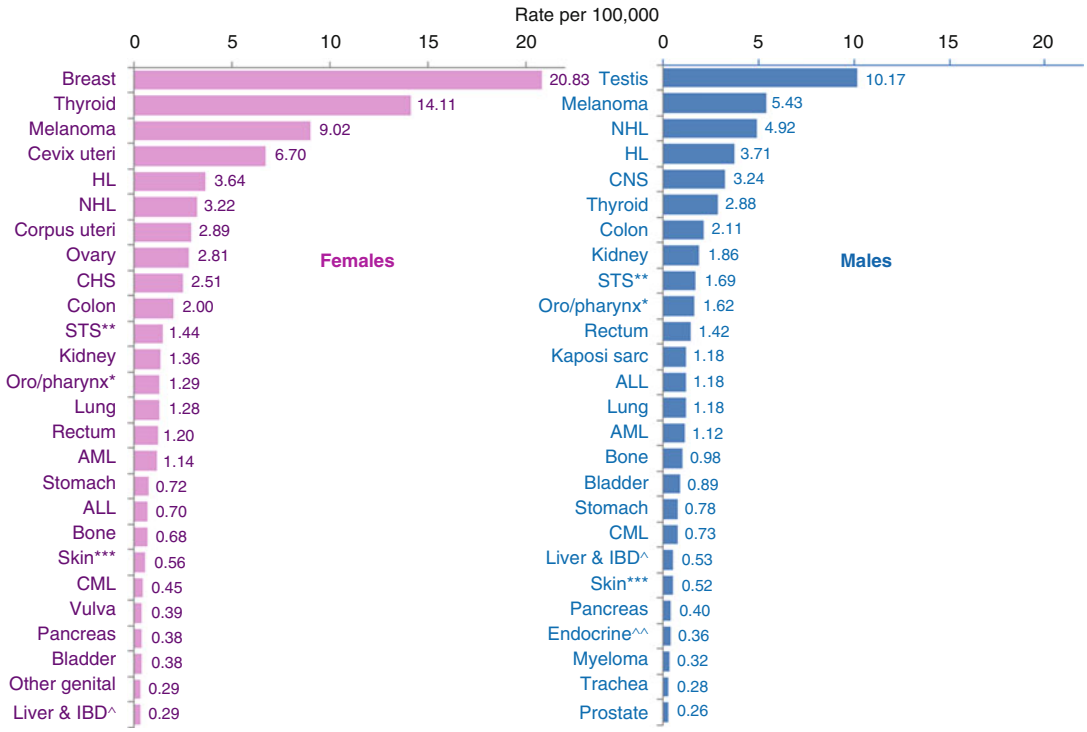

Fig. 2.10 Cancer incidence rates, 2000–2011, ages 15–39, US SEER18, by site and sex. *oral cavity and oropharynx **soft-tissue sarcoma ***nonmelanoma skin cancer ^intrahepatic bile duct ^^non-thyroid endocrine