Relative Lack of Conditional Survival Improvement in Young Adults With Cancer

Archie Bleyer,[a,b] Mehee Choi,[b] C. David Fuller,[c,d] Charles R. Thomas Jr,[b] and Samuel J. Wang[b,e]

Cancer prognosis is usually reported in terms of survival from time of diagnosis. For patients surviving a period of time after diagnosis, conditional survival (CS) accounts for changing risk over time. This report provides information on how CS in cancer patients changes as a function of age at diagnosis. Using data from the US Surveillance, Epidemiology and End Results database, we examined survival for patients diagnosed between 1973 and 2002. The average annual percent change (AAPC) in CS during the first 5 years after diagnosis was evaluated for the 14 most common cancers occurring in young adults, defined as 15- to 39-year-olds, and how they compared with cancers that are more common in older and younger patients. For all cancers, young adult patients had less CS improvement over time than younger or older patients, and this difference was most pronounced in those aged 20 to 29 years (45% below the mean). Eleven of the 14 most common cancers in 15- to 39-year-olds either had a lower CS improvement after diagnosis than either younger or older patients, or than just the older patients. Young adults with leukemia had the greatest improvement in CS over time. In conclusion, young adults with cancer have not enjoyed the same improvement in CS over time compared with other age groups. Explanations for this deficit include the biologic nature of the type of cancers in young adults and less effective therapies for patients in the age group. Regardless of the reasons, the deficit is yet another challenge faced by young adult patients that merits further study.
Semin Oncol 36:460-467. © 2009 Published by Elsevier Inc.

Although survival rates are usually determined from the time of diagnosis, a patient's prognosis changes over time because of changing risk. After a patient has lived for a period of time after diagnosis and treatment, prognosis almost always improves if the cancer has not recurred and other complications have not occurred. Rather than assessing initial risk, conditional survival (CS) gives patients and their treatment team a more realistic view of life expectancy as a function of time after a cancer diagnosis.[1] CS, which is based on the concept of conditional probability, accounts for the fact that hazard rates can change over time. CS can be of important practical value to both patients and their healthcare providers.[2] Patients and their families may want to know how their prognosis is changing over time, as they survive for longer periods of time following diagnosis and treatment. Providers can make use of CS information to determine more objectively the appropriate frequency of follow-up visits and surveillance testing.

We and others have previously reported CS analyses for various sites,[3,4] including breast,[5-8] lung,[9-11] colon,[12,13] rectum,[14] anus,[15] gallbladder,[16,17] gastric,[18] prostate,[19] ovarian cancer,[20] head and neck,[21] and brain tumors.[22-24] We also have reported that the rate of CS improvement after diagnosis varies with age at diagnosis, with 15- to 44-year-olds having had less improvement in CS after a diagnosis of invasive cancer than either younger or older patients.[25] Despite starting with a more favorable prognosis than patients <15 years of age, the 15- to 20-year age group suffers a worse prognosis within 5 years after diagnosis (Figure 1A). Patients 30 to 44 years of age start with an overall prognosis

[a]St. Charles Medical Center, Bend, OR.
[b]Department of Radiation Medicine, Oregon Health and Science University, Portland, OR.
[c]Department of Radiation Oncology, University of Texas Health Science Center at San Antonio, San Antonio, TX.
[d]Graduate Division of Radiological Sciences, University of Texas Health Science Center at San Antonio, San Antonio, TX.
[e]Department of Medical Informatics and Clinical Epidemiology, Oregon Health and Science University, Portland, OR.
A preliminary report of this work was published as an abstract in the 2006 Proceedings of the 48th Annual Meeting of the American Society for Therapeutic Radiology and Oncology.
Supported in part by the Aflac Foundation.
Address correspondence to Archie Bleyer, MD, St. Charles Medical Center, 2500 NE Neff Rd, Bend, OR 97701. E-mail: ableyer@gmail.com
0270-9295/09/$ - see front matter

doi:10.1053/j.seminoncol.2009.07.004

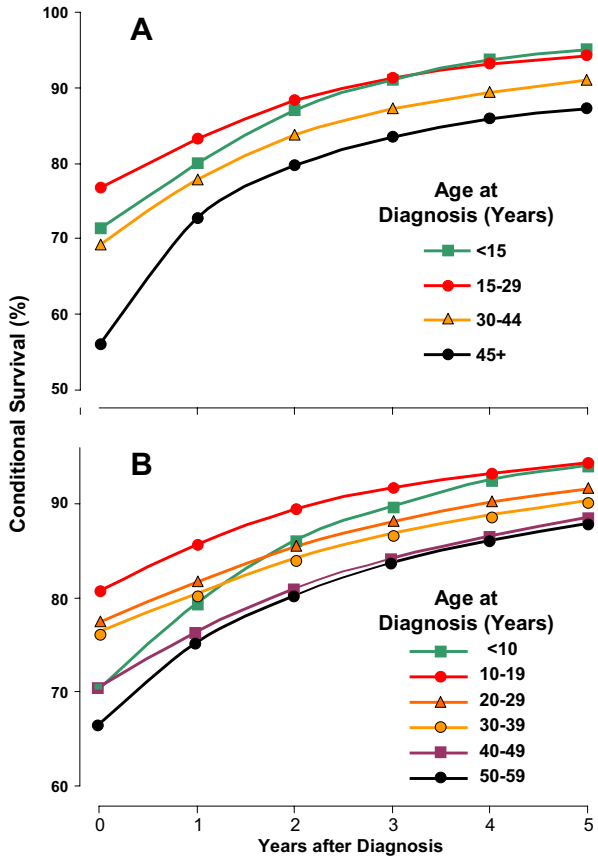

Figure 1. Five-year conditional relative survival curves by age at diagnosis, as a function of elapsed time since diagnosis. Each point represents the probability of surviving an additional 5 years, after having already survived the given number of years since diagnosis (CS), SEER9, 1975–2002. (A) All invasive cancers. (B) Young adult cancers: 14 most common cancers in 15- to 39-year-olds.

similar to those <15 years of age but diverge to a worse prognosis within 2–3 years (Figure 1A).

There is increasing awareness that young adults and older adolescents have not enjoyed the same degree of improvement in prognosis over the past several decades as have younger and older patients.[26–29] Historically, less attention and fewer resources have been devoted to studying treatment and outcomes for this age group,[30–32] In 2006, the National Cancer Institute (NCI) Adolescent and Young Adult Oncology Progress Review Group addressed this deficit and issued a formal report with wide-ranging recommendations.[33]

Because of our prior observation of a worse improvement in CS for young adult cancer patients,[34] we undertook a more detailed analysis of CS in the this population, including individual types of cancer. We hypothesized that patients in the young adult age range experience a different pattern of CS change over time, either because of the unique characteristics of the mix of cancers in this age group or because young adults have not had the advantages in early cancer detection and treatment that have occurred in older or younger patients.

METHODS

Using the NCI's Surveillance, Epidemiology and End Results (SEER) database,[35] we examined survival curves for patients with all invasive cancers to determine how CS changes as a function of time. We analyzed survival data on 2,346,184 patients in the SEER database in their original nine registries (SEER9) for whom 5-year relative survival rates are available up to 25 years after diagnosis in patients diagnosed between 1975 and 2002 (accessed May 30, 2009).[35] Using SEER*Stat,[36] the 14 most commonly occurring cancers in the young adult age range, defined as 15 to 39 years inclusive, were analyzed individually and collectively over all age groups, and the results were compared with all invasive cancers and with the remaining cancers in the young adult age group. Kaposi sarcoma was not included and was excluded from the soft tissue sarcoma group because it was largely confined to the middle range of the analysis interval (1975–2002) with a peak incidence in 1989 in association with the HIV/AIDS epidemic.[37]

The primary comparator was the average annual percent change (AAPC) in the 5-year relative CS. The AAPC is a method commonly used by SEER and other epidemiologists to express and compare rate changes. The calculation involves fitting a straight line to the natural logarithm of the annual percent change.[38] Although change in CS as a function of survival time after diagnosis is not exponential (Figure 1), we applied AAPC analysis to 1-, 2-, 3-, 4-, and 5-year CS rates and compared it with the absolute increments after 1 and 2 years of survival. For AAPC we used the percent change in CS from one year of survival to the next. We also applied AAPC analyses to both the absolute CS rates and their logarithm values. The latter is customarily used by SEER since the rate changes measured are more logarithmic than linear, as is true in CS rate changes (Figure 1) and, indeed, the logarithmic method does demonstrate a greater correlation with the incremental increases in the first 2 years (Table 1). For the analyses conducted in this study, comparable if not identical results were obtained with either relative and observed survivals and with AAPCs derived from either linear and logarithmic values of CS rates, such that only the relative survival results and AAPCs derived from log values are reported here.

RESULTS

The types of cancer and the number of patients who were 15 to 39 years of age and their 14 most frequent cancers, accounting for 82% of all cancers in the age range, are shown in Table 2. In order of decreasing

Table 1. Comparison of AAPC Method Versus Survival Increments During the First 2 Years After Diagnosis in 15- to 39-Year-Olds With Invasive Cancer, Using Their 14 Most Frequent Types of Cancer* and the Remaining Group of Cancers (15 observations) for SEER9 Relative Survival Data of 1975–2002

	5-Year AAPC Method (relative survival) versus:			
	1-Year Increment		2-Year Increment	
	Log	Linear	Log	Linear
R^2	0.81	0.53	0.93	0.82
F value	56.5	14.8	179.8	60.2
P value	.000004	.002	.00000001	.000003

*Excluding Kaposi sarcoma.

incidence, the cancers are breast cancer, malignant melanoma, thyroid cancer, testis cancer, Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), cancer of uterine cervix, brain and spinal cord tumors (CNS tumors), colorectal cancer, cancer of ovary, soft tissue sarcomas (excluding Kaposi sarcoma), acute myelogenous leukemia (AML), bone sarcomas, and acute lymphoblastic leukemia (ALL). Many of these cancers have their peak incidence between 15 and 40 years of age.[39] Most other cancers peak in incidence in either younger or older patients.

Table 2 also lists the absolute improvement in CS rates after 1 and 2 years survival and the average improvement after 1, 2, 3, 4, and 5 years survival, the

Table 2. Number of Patients and Increases in the 5-Year CS 1 Year, 2 Years, and 5 Years (latter measured by AAPC) After Diagnosis in 15- to 39-Years-Olds, by Type of Cancer and in Rank Order of 5-Year AAPC in CS, SEER9, 1975–2002

				Conditional Survival: Age 15–39		
				Increase After 1 Year Survival*	Increase After 2 Years Survival*	Increase After 1, 2, 3, 4, and 5 Years Survival
Method	All Ages No.	Age 15–39 No.	% of Age 15–39 Total	Absolute Increase	Absolute Increase	Average† 5-Year AAPC
Total	2,333,562	153,075	100%			
Young adult cancers: 14 most common cancers in 15- to 39-year-olds						
Thyroid cancer	32,914	13,251	8%	0.2%	0.2%	0.0
Melanoma	72,086	17,252	11%	1.1%	2.4%	1.2
Hodgkin lymphoma	18,281	10,643	7%	1.1%	2.9%	1.2
Testis cancer	16,052	11,832	7%	2.4%	4.7%	1.3
Cancer of uterine cervix	30,773	9,476	6%	3.9%	9.7%	2.7
Breast cancer	346,790	23,954	15%	−2.0%	1.7%	3.4
Ovary cancer	42,789	3,923	2%	6.7%	12.5%	3.6
CNS tumors	36,956	7,222	5%	9.7%	19.6%	5.7
Soft tissue sarcoma‡	13,880	3,174	2%	10.0%	20.7%	5.9
Bone sarcoma	5,082	2,013	1%	5.0%	16.3%	6.1
NHL	86,390	9,773	6%	34.1%	47.4%	8.2
Colorectal cancer	290,261	6,287	4%	16.1%	32.1%	9.7
ALL	8,233	1,635	1%	32.3%	79.7%	21.4
AML	17,276	2,473	2%	56.0%	118.4%	22.5
Total young adult cancers‡	1,030,618	125,180	82%	6.0%	11.1%	3.5
Other cancers‡	1,302,944	27,895	18%	21.7%	34.8%	7.0
Ratio of CS in young adult cancers *v* other cancers‡				.28	.32	.50

*Relative survival rates.
†Average of AAPCs of 5-year age intervals from age at diagnosis of 15 to 39 years.
‡Excluding Kaposi sarcoma.

latter using the AAPC method, for each of the 14 most frequent cancer types in the 15- to 39-year-olds, for these cancers considered together, and for all invasive cancer (excluding Kaposi sarcoma). As a group, 15- to 39-year-olds with the prevalent cancers in their age group had one fourth to one third the rate of CS improvement during the first year and first 2 years after diagnosis, and one half the rate over the first 5 years after diagnosis, in comparison to the average for those with cancers more common in younger or older persons (Table 2, bottom row).

When compared to other age groups, 15- to 39-year-olds had the lowest CS improvement of all age groups for all cancers (Figure 2 upper panel) and particularly for the types of cancer that characterize their age group (Figure 1B and Figure 2 middle panel). Those 20 to 29 years of age had the least improvement, approximately 45% less than the mean of all age groups (Figure 2 upper and middle panels). For the other types of cancer, their age group had a more favorable CS improvement (Figure 2 lower panel).

When considered individually, five of the 14 most frequent types of cancer had a lower CS improvement as a function of time after diagnosis in young adults than in either younger or older persons: melanoma, testicular carcinoma, CNS tumors, bone sarcomas, and soft tissue sarcomas excluding Kaposi sarcoma (Figure 3 upper panel). Six have had a CS improvement that was less than in older patients: ALL, AML, thyroid cancer, Hodgkin lymphoma, cancer of the ovary, and cancer of the uterine cervix (Figure 3 middle panel). Overall, 11 of the 14 cancers have had less CS improvement in 15- to 39-year-olds than in older patients. The remaining three evaluated cancers have had a CS improvement that was higher in 15-to 39-year-olds than in older patients, two of which rarely in occur in patients <15 years of age: breast cancer and colorectal cancer (Figure 3 lower panel).

When the absolute values of the average percent improvement in the 5-year conditional relative survival rates are compared among the common cancers in 15- to 39-year-olds (Figure 4), a correlation is apparent between the type of cancer and the CS improvement during the first 5 years after diagnosis. The most aggressive cancers with the fastest recurrence rates—ALL and AML—show the greatest CS improvement over time. Those with the least improvement are among the slowest growing tumors: thyroid cancer, Hodgkin lymphoma, and NHL, the last of which in the older adult population is predominated by follicular and other low-grade types of lymphoma.

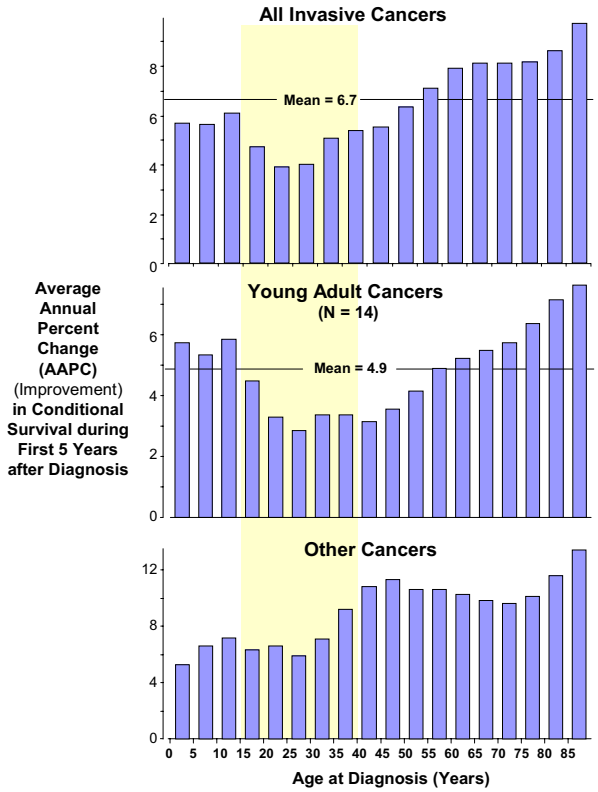

Figure 2. AAPC in 5-year relative CS during first 5 years after diagnosis, by age at diagnosis, for all invasive cancers (upper panel), the 14 most frequent cancers in 15- to 39-year-olds (young adult cancers, middle panel), and for the remaining cancers (lower panel), SEER9, 1975–2002.

DISCUSSION

In this study, we found that young adults have not enjoyed the same increase in survival expectation as a function of time after diagnosis either overall or for most of their common cancers compared with younger and older age groups. The overall deficit does not appear to be due to the different nature of cancers in young adults since individual cancers show the pattern, including several that are considered to be the same cancer across their entire age range of incidence from the youngest to the oldest patient. To what, then, is the deficit due?

The rate of increase in CS may be due to several factors. (1) The prognosis at diagnosis, the initial survival projection, determines the slope of the rise, with the worst initial survival having the greatest opportunity for increase (and slope). The greater the initial death rate, the more likely surviving patients who have passed the initial period of risk of death will continue to survive. (2) The pace of cancer growth—the rapidity of disease progression and recurrence—affects the rate of increase, with fast-growing tumors tending to have steeper slopes and an earlier plateau in ultimate survival. (3) Similarly, the effectiveness of initial therapy affects the rate of increase in CS, with therapy that is more effective in controlling the cancer leading to a more rapid increase while inadequate therapy that slows disease progression, but is not curative, delaying the ultimate outcome and decreasing CS. (4) Delayed fatal toxicities and second cancers that cause deaths

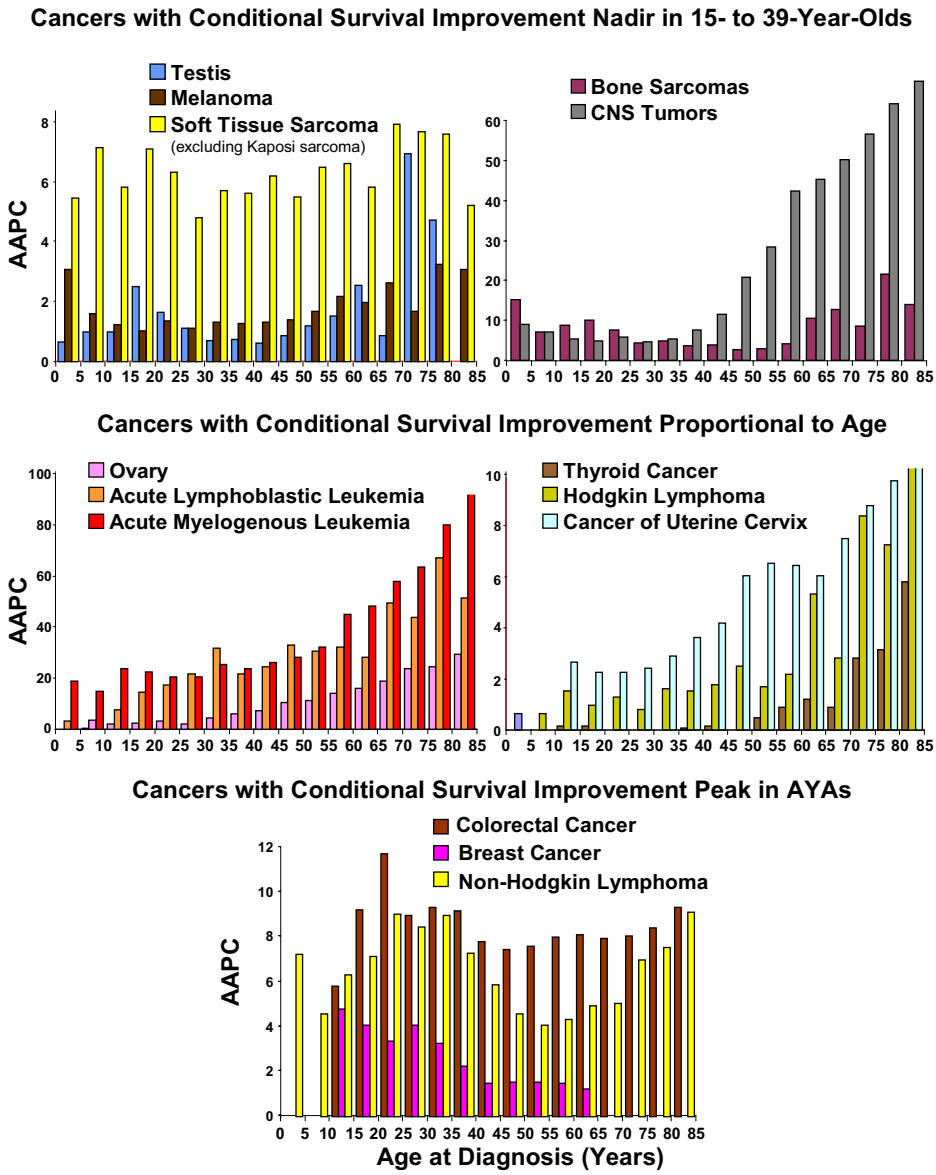

Figure 3. AAPC in 5-year relative CS during the first 5 years of the 14 most frequent types of cancer in 15- to 39-year-olds, according to whether the AAPC was less in their age range than in either younger or older patients (upper panel), the AAPC was lower in them than in older patients (middle panel), or the AAPC was greatest in their age range (lower panel), SEER9, 1975–2002. The yellow zone depicts the 15- to 39-year age range.

slow CS improvement. This factor is particularly dependent on the effectiveness and safety of the initial therapy, as well as its carcinogenic potential.

For young adults, each explanation appears to be important. (1) The initial survival projection factor is apparent from the better initial prognosis (survival expectation at diagnosis) among young adult patients (Figure 1, red and orange curves), overall, than younger or older patients (Figure 1, green and black curves). (2) The pace of disease determines how rapidly survival is affected. Young adults have a better short-term prognosis in that more of their cancers have a slower pace of disease than the common cancers in younger and older patients. Examples are thyroid cancer, melanoma, brain tumors, sarcomas, breast cancer and cervical carcinoma, each of which is characterized by a longer time to diagnosis or a longer interval to recurrence and survival time. (3) Less effective treatment in young adult patients may also be a contributor, as principally evidenced by their lower CS improvement in individual types of cancer: 11 of 14 cancers evaluated each had lower CS rates of improvement than either younger or older patients, five of which had lower rates than in both younger and older patients. (4) Finally, young adults may be diagnosed at more advanced stages of cancer compared to younger and older persons, as appears to be the case for breast and colorectal cancers.[40] If so, a greater difficulty ultimately

in overcoming their cancers and less adequate therapy may contribute to the young adult deficit in CS. In this study, delayed fatal toxicities and deaths from second malignant neoplasms are not likely to be major factors since these occurrences usually occur later than the first 5 years after diagnosis, the period of CS assessment evaluated in this study.

That treatment effect may be a major factor is ominous, especially given the trend in CS rates during the past quarter century (Figure 5). The rate of CS improvement in young adults has demonstrated little improvement over the 28 years from 1975 to 1998 in contrast to younger and older patients in whom the AAPC declined dramatically (Figure 5). As previously shown,[26,32] young adults and older adolescents with cancer have had less progress in survival improvement and mortality reduction than children and older adults with cancer. This relative lack of effect on CS in this age group is additional evidence for a treatment effect. It also may be evidence for an excess of fatal adverse late effects in young adults, either because of inadequate, noncurative initial therapy delaying cancer recurrence or due to increased second malignant neoplasms. The latter also may be related to the initial therapy if, as is possible in many cases, the carcinogenicity of the therapy in susceptible hosts leads to a significant rate of second malignant neoplasms.

This apparent relationship between the CS improvement as a function of time from diagnosis (Figure 4) suggests that colorectal cancer is a relatively rapidly progressive cancer in young adults and older adolescents, which is consistent with the known greater aggressiveness of this tumor in young adults.[41] The data also suggest that bone sarcomas may be more indolent in young adults and older adolescents, which is consistent with the heterogeneity of non-osseous sarcomas in young adults and the predominance of low-grade sarcomas among them. However, the pattern is not consistent for breast cancer, which is known to present, in general, at a more advanced stage and to have a more virulent course in young adults and older adolescents than in older persons.[41]

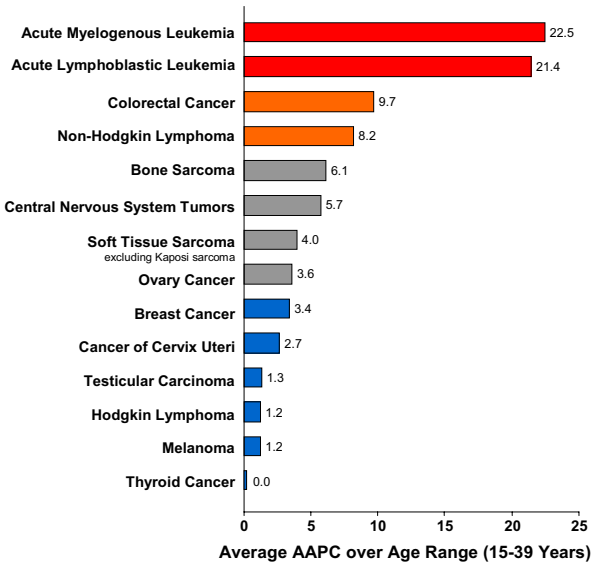

Figure 4. Correlation of 14 most common types of cancer in 15- to 39-year-olds with AAPC in 5-year relative CS during the first 5 years after diagnosis in 15- to 39-year-olds, SEER9, 1975–2002. The AAPC is the average of the AAPCs of 5-year age intervals from age 15 to 39. Slowest growing/recurring cancers (blue) have lower AAPCs than rapidly growing/recurring cancers (orange/red). Acute leukemias have the greatest AAPC; thyroid cancer, melanoma, and Hodgkin lymphoma have the lowest AAPC.

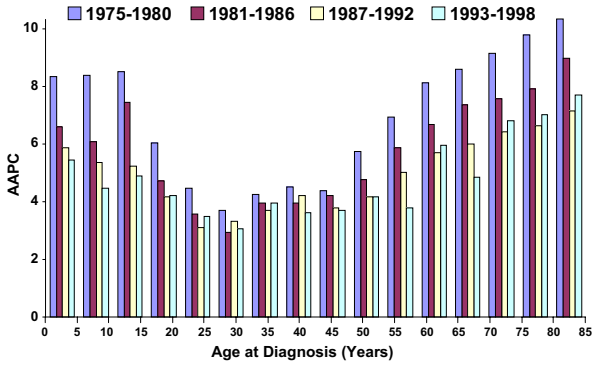

Figure 5. AAPC in 5-year relative conditional survival by era (6 calendar-year intervals) in 15- to 39-year-old patients with their 14 most common types of cancer, SEER9, 1975–2002.

The opposite, complementary nature of the rate of CS increase among the cancers that characterize the young adult age group versus other cancers (Figure 2) deserves further interpretation. One explanation is that cancers that have a peak incidence in younger and older persons are biologically more rapidly curable or have had better treatment developed for them. Another explanation is that the cancers that characterize the young adult age group have, in aggregate, a better prognosis to start with and thereby have less capacity for survival improvement.

In any event, young adults and older adolescents, as well as their families, do not have as much survival benefit to look forward to as time passes from diagnosis of cancer. This is yet another deficit faced by this age group that, along with multiple other challenges, merits additional attention.[26,31,40–42]

REFERENCES

1. Henson DE, Ries LA. On the estimation of survival. Semin Surg Oncol. 1994;10:2–6.
2. Gloeckler Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the Surveillance, Epidemiology, and End Results (SEER) program. Oncologist. 2003;8:541–52.
3. Janssen-Heijnen ML, Houterman S, Lemmens VE, Bren-

ner H, Steyerberg EW, Coebergh JW. Prognosis for long-term survivors of cancer. Ann Oncol. 2007;18:1408–13.
4. Kato I, Severson RK, Schwartz AG. Conditional median survival of patients with advanced carcinoma: Surveillance, Epidemiology, and End Results Data. Cancer. 2001; 92:2211–9.
5. Henson DE, Ries LA, Carriaga MT. Conditional survival of 56,268 patients with breast cancer. Cancer. 1995;76:237–42.
6. Meng L, Maskarinec G, Lee J. Ethnicity and conditional breast cancer survival in Hawaii. J Clin Epidemiol. 1997; 50:1289–96.
7. Wang SJ, Luh JY, Fuller CD, Thomas CR. Impact of ethnicity on conditional survival of breast cancer patients: analysis from the SEER database. 28th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8, 2005.
8. Wang SJ, Luh JY, Fuller CD, Thomas CR. Geographic variation in conditional survival for breast cancer patients: a SEER database analysis. 29th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8, 2006.
9. Merrill RM, Henson DE, Barnes M. Conditional survival among patients with carcinoma of the lung. Chest. 1999; 116:697–703.
10. Skuladottir H, Olsen JH. Conditional survival of patients with the four major histologic subgroups of lung cancer in Denmark. J Clin Oncol. 2003;21:3035–40.
11. Wang SJ, Fuller CD, Thomas CR. Ethnic disparities in conditional survival of patients with non-small cell lung cancer. J Thorac Oncol. 2007;2:180–90.
12. Merrill RM, Henson DE, Ries LA. Conditional survival estimates in 34,963 patients with invasive carcinoma of the colon. Dis Colon Rectum. 1998;41:1097–106.
13. Wang S, Zamboni B, Wieand H, Wieand HS, Yothers G, Dignam JJ, et al. Conditional survival for patients with colon cancer: an analysis of National Surgical Adjuvant Breast and Bowel Project (NSABP) trials C-03 through C-06 [abstract 6005]. J Clin Oncol, ASCO Annual Meeting Proceedings. 2006;24:6005.
14. Wang SJ, Fuller CD, Emery R, Thomas CR. Conditional survival in rectal cancer: a SEER database analysis. Gastrointestinal Cancer Res. 2007;1:84–9.
15. Klish DS, Wang SJ, Kimler BF, Thomas CR. Improved prognosis with time after diagnosis for patients with anal cancer. American Radium Society, 88th Annual Meeting, Wailea, HI, May 6, 2006.
16. Fuller CD, Wang SJ, Thomas CR. Conditional survival of gallbladder adenocarcinoma treated with radiotherapy: Analysis from the SEER database [abstract]. Proc 47th Annual ASTRO Meeting (Amer Soc Therap Radio Oncol). 2005;63:S274.
17. Thomas CR, Fuller CD, Starling G, Wang SJ. Conditional survival in gallbladder carcinoma: results from the SEER 11 dataset [abstract 4130]. J Clin Oncol, ASCO Annual Meeting Proceedings. 2006;24:4130.
18. Wang SJ, Emery R, Fuller CD, Kim JS, Sittig DF, Thomas CR. Conditional survival in gastric cancer: a SEER database analysis. Gastric Cancer. 2007;10:153–8.
19. Luh JY, Wang SJ, Fuller CD, Thomas CR. A SEER database analysis of conditional survival for prostate cancer patients [abstract 14506]. J Clin Oncol, 2006 ASCO Annual Meeting Proceedings. 2006;24:14506.
20. Choi M, Fuller CD, Thomas CR Jr, Wang SJ. Conditional survival in ovarian cancer: results from the SEER dataset 1988–2001. Gynecol Oncol. 2008;109:203–9.
21. Fuller CD, Wang SJ, Thomas CR Jr, Hoffman HT, Goldwein JW, Weber RS, et al. Conditional survival in head and neck squamous cell carcinoma: results from the SEER dataset 1973–1998. Cancer. 2007;109:1331–43.
22. Davis FG, McCarthy BJ, Freels S, Kupelian V, Bondy ML. The conditional probability of survival of patients with primary malignant brain tumors: Surveillance, Epidemiology, and End Results (SEER) data. Cancer. 1999;85: 485–91.
23. Hwang SL, Yang YH, Lieu AS, Chuang MC, Chang SJ, Chang YY, et al. The conditional survival statistics for survivors with primary supratentorial astrocytic tumors. J Neurooncol. 2000;50:257–64.
24. Lin CL, Lieu AS, Lee KS, et al. The conditional probabilities of survival in patients with anaplastic astrocytoma or glioblastoma multiforme. Surg Neurol. 2003;60: 402–6.
25. Wang SJ, Fuller CD, Luh JL, Thomas CR, Bleyer A. Older adolescents and young adults with cancer: conditional survival deficit. Proc 48th Annual ASTRO Meeting (Amer Soc Therap Radio Oncol). 2006;S135–6.
26. Bleyer A, O'Leary M, Barr R, Ries LAG, editors. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975–2000. NIH Pub No. 06–5767. Bethesda, MD: National Cancer Institute; 2006.
27. Zebrack B, Bleyer A, Albritton K, Madearis S, Tang J. Assessing the health care needs of adolescent and young adult cancer patients and survivors. Cancer. 2006;107: 2915–23.
28. Gibbon DG, Schaar D, Kamen B. A call to action: cancer in adolescents and young adults: an unrecognized healthcare disparity. J Pediatr Hematol Oncol. 2006;28:549–51.
29. Bleyer A, Barr R, editors. Cancer in adolescents and young adults. New York: Springer, 2007.
30. Pentheroudakis G, Pavlidis N. Juvenile cancer: improving care for adolescents and young adults within the frame of medical oncology. Ann.Oncol. 2005;16:181–8.
31. Bleyer WA. Cancer in older adolescents and young adults: epidemiology, diagnosis, treatment, survival, and importance of clinical trials. Med Pediatr Oncol. 2002;38:1–10.
32. Bleyer A. The adolescent and young adult gap in cancer care and outcome. Curr Probl Pediatr Adolesc Health Care. 2005;35:182–217.
33. Closing the gap: research and care imperatives for adolescents and young adults with cancer, Adolescent and Young Adult Oncology Progress Review Group. Bethesda, MD: National Cancer Institute; 2007.
34. Albritton K, Bleyer WA. The management of cancer in the older adolescent. Eur J Cancer. 2003;39:2584–99.
35. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 13 Regs Public-Use, Nov 2004 Sub (1973–2002), in: National Cancer Institute D, Surveillance Research Program, Cancer Statistics Branch. Released April 2006, based on the November 2005 submission, 2004.

36. National Cancer Institute SEER*Stat software (www.seer.cancer.gov/seerstat) version 6.5.1, April 14, 2009 [accessed June 7, 2009].
37. http://seer.cancer.gov/csr/1975_2006/browse_csr.php?section=10&page=sect_10_zfig.01.html [accessed June 7, 2009].
38. http://seer.cancer.gov/seerstat/ WebHelp/seerstat.htm#Trend_Algorithms.htm [accessed June 7, 2009].
39. Bleyer A, Barr R. Cancer in young adults 20- to 39-years of age: overview. Semin Oncol. 2009;36:193–205.
40. Martin S, Ulrich C, Munsell M, Taylor S, Lange G, Bleyer A. Delays in cancer diagnosis in underinsured young adults and older adolescents. Oncologist. 2007;12:816–24.
41. Bleyer A, Barr R, Hayes-Lattin B, Thomas D, Ellis C, Anderson B. The distinctive biology of cancer in adolescents and young adults. Nat Rev Cancer. 2008;8:288–98.
42. Bleyer A, Budd T, Montello M. Adolescents and young adults with cancer: the scope of the problem and criticality of clinical trials. Cancer. 2006;107:1645–55.