



Published in final edited form as:

J Adolesc Young Adult Oncol. 2025 February ; 14(1): 33–42. doi:10.1089/jayao.2024.0095.

Abatement of the Survival Cliff in Older Adolescents and Young Adults with Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma in the United States

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Abstract

Purpose: In 2018, a “survival cliff” in the United States was identified among older adolescent and young adult (AYA) patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL). This study reassessed the cliff and associated putative causes.

Methods: Survival data were obtained using the U.S. Surveillance Research Program, National Cancer Institute (NCI) SEER 22 Registries. Accrual data on cancer treatment trials conducted by the NCI cooperative groups and NCI-designated cancer centers were obtained from the NCI Cancer Therapy Evaluation Program. Trend and average percent changes and statistical significances were identified with the NCI Joinpoint Regression Program.

Results: A previous cliff-like decrement in the survival of 17- to 20-year-olds is no longer apparent, overall and in all racial and ethnic groups. The “survival cliff” age range was coincident with a clinical trial accrual cliff, and both diminished when more clinical trials were available

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Authors' Contributions

A.B., E.T., and S.S. authored the original report.1 For this report, A.B. performed the analyses and wrote the first draft. Each of the coauthors reviewed and edited the article, and several recommended additional analyses and refinements.

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Author Disclosure Statement

The authors are not aware of any competing financial interests.

to, and participated in by, young adult patients. Older AYA patients of ages 30–39 had minimal improvement in clinical trial accrual and least survival gain among the AYA age group.

Conclusion: The survival cliff has abated, resulting in thousands of fewer premature deaths and tens of thousands of years of life saved—a remarkable achievement. The survival improvement may be attributed to improved clinical trial availability for and recruitment and participation of AYAs on treatment trials, application of pediatric-inspired ALL treatment regimens to AYAs, expanded national health insurance for —18 to 25 year olds, improved AYA cancer services, and a national focus on AYA oncology.

Keywords

adolescents and young adults; survival progress; clinical trials

Introduction

In 2018, several of us reported a “survival cliff” in the United States among older adolescent and young adult (AYA) patients with acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) diagnosed during 2000–2004.¹ As shown in Figure 1, the *cliff* was an abrupt decrement between ages 16 and 19 in the 5-year survival rate of ALL and LBL patients diagnosed during 2000–2004. In just 3 years, the survival rate decreased from 73% to 52%, an absolute 21% and at an average percent change (APC) of –10.6.¹ In older patients, the survival rate declined at an APC of 1.7. Based on survival trends in ≤15 and 20- to 85-year-olds, AYAs 16 to 35 years of age during 2000–2004 had an estimated excess of total of 26,600 years of life lost (Fig. 1; red shading).

The survival cliff occurred simultaneously with lower accrual to clinical treatment trials registered with the U.S. National Cancer Institute (NCI) Cancer Therapy and Evaluation Program (CTEP) (Fig. 1). Joinpoint regression identifies an absolute 33% decrease accruals during similar years of the survival cliff, from 38% of 17-year-olds to 5% of 22-year-olds, an absolute percent decrease of 33% and APC of –32.6 (Fig. 1).¹ We concluded that the survival cliff was due in part to a sharp decline in clinical trial availability for, and participation by, AYAs. Others have since evaluated the problem, with the most recent publications emphasizing continued urgent need to solve it.^{2,3} Six years after our report, we hoped that the cliff would be less steep and that AYAs with ALL and LBL in the United States would have a better survival. Herein, we report evidence for not only a favorable trend but also disappearance of the cliff and offer evidence suggesting why such has occurred.

Methods and Materials

Survival data up to the age of 84 for patients diagnosed annually during 2000–2019 were obtained with Surveillance Research Program, NCI SEER*Stat software version 5.0.1,⁴ from SEER 22 Registries that represent 48%–50% of the U.S. population. When Illinois and Massachusetts are excluded from SEER22 (designated SEER22[–]) in the Research Plus database, this represents 42%–44% of the U.S. population. The prior study¹ was based on SEER8 registries that represented 29% of the U.S. population. Joinpoint Regression Program v.5.0.1⁵ was used to identify trend changes and APC values, using weighted

least squares, logarithmic transformation, and when standard errors were not available, constant variance. Average annual percent change (AAPC) was designated by the Joinpoint regression program. The Site and Morphology code definitions for ALL and LBL were AYA site recode 2020 Revision classifications 1.1 and 2.1.1., respectively.⁴

Accrual data up to the age of 84 for patients enrolled during 2000–2015 on NCI-sponsored Phase I, II, and III cancer treatment trials conducted by the NCI cooperative groups and NCI-designated cancer centers were provided by CTEP were provided in 2016 by CTEP, NCI.¹ The numerator of the accrual proportion was the number of patients entered onto the clinical trials selected for evaluation from the CTEP-provided data. The denominator was based on the SEER22 incidence of patients in the cancer and age category and population census data obtained from the U.S. government census website.⁶ No individual patients or individual clinical trials were identified, contacted, or reviewed. Institutional Review Board review was not required.

Results

ALL and LBL survival rates in AYAs since 2000

With a range of 1937–6164 patients in 5 eras evaluated during 2002–2017, joinpoint analysis of 3-calendar-year intervals shows the AYA ALL+LBL “survival cliff” in 16 to 22 year olds to have progressively shortened since 2002 (Fig. 2). For those diagnosed during 2002–2003, 2007–2011, and 2012–2015, the cliff APCs were –16.3, –12.2, and –7.8, respectively, and the absolute % decreases were 30%, 25%, and 17%, respectively (Fig. 2 diagram and table). By 2015–2017, the cliff disappeared, during which the survival rate APC of –1.6 for all 5- to 40-year-olds applied to the 16- to 22-year-olds (Fig. 2 table). According to the joinpoint regressions, AYAs older than those in the survival cliff age range, 22 to 39 years of age, had 5-year survival rates increase from 42%–45% during 2002–2003 to 55%–75% during 2015–2017; the latter inversely proportional to age (Fig. 2).

The survival cliff was present for all race/ethnicities in the U.S. before 2010 (Fig. 3). In non-Hispanic White, non-Hispanic Black and Hispanic people, it did not abate until 2015–2019 (Fig. 3; upper panels and lower left panel) and in non-Hispanic Asian/Pacific Islander people it abated during 2010–2014 (Fig. 3; lower right panel). Over the AYA age range, non-Hispanic Black and non-Hispanic Asians/Pacific Islander people at the bottom of the cliff, ages 21–26, had a worse survival than older AYAs (Fig. 3; bottom panels).

ALL and LBL Treatment Trial Accruals 2002–2015

Since 2002, entry onto ALL and LBL treatment trials sponsored by CTEP increased in 15- to 30-year-olds, with the difference inversely proportional to age, from an estimated 25% to 56% of all U.S. 16-year-old patients and from 3% to 14% in 22-year-olds (Fig. 4). During 2002–2005, the accrual cliff occurred in 17 to 22 year olds at an APC of –30.5 and $p = 0.004$ (Fig. 4; red data). By 2012–2015 it was half as precipitous, at an APC of –15.8 and spread out over a 15- to 31-year age span (Fig. 4; green data). Also, the significance of the declines during 2002–2005 increased from $p = 0.01$ before age 16 to $p = 0.004$ after age 16 (Fig. 4 red data), and from nonsignificant before age 15 to significant ($p < 0.001$) after age

15 during 2012–2015 (Fig. 4; green data). Among 30- to 40-year-olds, however, the accrual proportion was <10% and there was no increase from 2002 to 2015 (Fig. 4).

The accrual and estimated accrual proportion in 15- to 19-year-olds on ALL and LBL trials increased through 2003–2015 at statistically significant rates (APC 8.2 and 7.8, respectively, both $p = 0.02$) (Fig. 5; green data). Accruals also increased in 20- to 29-year-olds, (APC 13.3, $p = 0.005$) (Fig. 5; upper panel orange data), but the oldest AYA group (age 30–39) did not have an accrual increase (Fig. 5; upper panel red data). Accrual proportion, however, did not increase in either 20–29 or 30- to 39-year-olds (Fig. 5; lower panel).

Correlation of Survival Rate and Treatment Trial Accrual Trends

In 17- to 20-year-old patients diagnosed with ALL or LBL during 2003–2017 and in whom the survival cliff occurred, the decrement in cancer-specific survival rate during the survival cliff declined in proportion to the increase in the treatment trial accrual rate in the age group (Fig. 6). The correlation was statistically significant for both the survival rate in patients diagnosed during the 3-year accrual intervals ($p = 0.006$) (Fig. 6; lower regression) and those diagnosed during the subsequent 3 calendar years ($p = 0.006$) (Fig. 6; steeper regression).

Discussion

Among all ages in the United States, AYAs diagnosed with cancer have been reported to have had the least clinical trial participation and resultant least survival prolongation and mortality reduction.^{1,7–9} During the last two decades, the survival “cliff” in young American AYAs with ALL and LBL has decreased, overall and in all major races/ethnicities. Based on survival trends in younger and older patients, American AYAs diagnosed during 2000–2004 with ALL or LBL when 16–35 years of age can be estimated to have had an excess of 26,600 years of life lost (Fig. 1 red shading). Overall, in terms of the total U.S. benefit, the survival profiles in Figure 2 can be interpreted to indicate that approximately 26,600 lives of AYAs, 15 to 39 years of age with ALL or LBL were spared during 2003–2017 by the improved survival.

The superimposed “cliff” patterns (Fig. 1) strongly suggest that the survival cliff was due in large part to the accrual cliff, and the correlation of survival decrement associated with the cliffs with accrual (Fig. 2) support a causal relationship, as previously implicated.¹ This progress is particularly noteworthy since the greatest effort to increase clinical trial accruals in AYAs was directed at ALL, the most common pediatric cancer. New clinical trials in ALL specifically designed for AYAs were launched,^{10–12} particularly those that applied pediatric type of chemotherapy regimens had outstanding success in improving survival and cure rates in the 85%–95% range for children under 10 years of age (Fig. 1). Exemplary are those conducted by the Cancer and Acute Leukemia Group B and The Alliance,^{13–15} Children’s Oncology Group (COG),^{14,16,17,18} Dana–Farber Cancer Institute,^{19,20} Nordic Pediatric Hematology Oncology and Baltic Centers,²¹ and Berlin–Frankfurt–Münster and Gruppo Italiano Malattie EMatologiche dell’Adulto.²² Another explanation for the improvement in younger AYAs is the cooperation between COG and the adult cooperative groups that study the overlapping AYA age range. Several of the adult cooperative groups created their own AYA committees focused on studying cancers prevalent in the AYAs. Also, the National

Comprehensive Cancer Network released practice guidelines for ALL,²³ and an increasing number of presentations and publications on the topic occurred at national meetings and appeared in the peer-reviewed medical literature.¹ An effort in Ontario, Canada, which is to specifically study the 15- to 21-year age interval for determinants of outcome, including access to clinical trials, has also helped²⁴. The extra effort that had been expended successfully on increasing the clinical trial participation of adolescents with cancer^{25–32} has apparently been successful in extending the trend to older AYAs. In 2014, the NCI organized the National Clinical Trial Network (NCTN) and National Community Oncology Research Program (NCORP) that include missives representing the AYA interests of AYAs and the pediatric and adult cooperative groups.³³ The timing of NCTN does not, however, explain the cliff erosion during 2002–2014 but has to some extent at least since. As of January 2024, the NCTN and NCORP had 18 cross-network treatment trials, 12 led by the COG and 6 by the adult NCTN.³⁴

Another possible contributing factor in the United States is the Patient Protection and Affordable Care Act (ACA) that was enacted nationally in 2010 and required insurance companies to allow 18 to 25 year olds to continue to be covered through their parents' insurance plans, the Dependent Coverage Expansion (DCE). This should have allowed more patients of this age to be better able financially to participate in available clinical trials at major centers and further enabled survival improvement and cure. An early suggestion that the ACA would benefit young AYAs is the observation that uninsured AYAs were less likely to enroll in clinical trials, in 2006, before the ACA, but not in 2012/2013 after the ACA was implemented.³⁵ Also a prior report suggested that the survival of AYAs in the DCE age group improved after the ACA was enacted.³⁶ Current evidence suggests that survival has improved after a diagnosis of invasive cancer since the ACA DCE was implemented. For all invasive cancer, the AAPC in 5-year relative survival rate during the first 6 years of the ACA, 2010–2015, was greater in the ACA-DCE-impacted age range of 18 to 25 years than in any other age group between 9 and 54 years of age (Fig. 7 lower panel). It also contrasts with the age-dependent trends in younger and older patients and was also statistically significant, whereas it was not in any of the younger age groups above age 6 or in the next oldest age group (Fig. 7 lower panel). For ALL and LBL, a benefit is suggested by the switch in the negative trend change as a function of age in younger patients to a positive trend that started in the ACA age group (Fig. 7 upper panel). That ALL and LBL represent only 3% of all invasive cancers in 18 to 25 year olds may compromise the capability of their survival rate to detect an ACA impact. Also, the ALL-LBL survival cliff was shrinking before the ACA was enacted in 2010 (Fig. 2).

Another barrier to clinical trials accrual in the AYA years is the referral of patients to centers with, or access to clinical trials. In Utah, with one children's hospital and one National Comprehensive Cancer Network center, the referral of cancer patients to either center dropped with each year of age from 14 at 92% to 17 at 44%.²⁸ By age 20, 2 of every 3 patients stayed in or were referred to private practices and by age 25 less than 30% of the patients were ever seen at an academic medical center.²⁸ Thus, a "referral cliff" also exists in AYA oncology.

Many other factors contribute to lack of participation in clinical trials. In addition to economic and insurance-based factors, these can be classified as issues of continuity of care and philosophy, provider bias, patient/family preferences, and cooperative group and cancer center limitations.³⁸ Psychosocial factors that are particularly challenging for AYAs with cancer include identity³⁹, relationships³⁹, mental health³⁹, autonomy³⁹, occupation,³⁹ sexuality,^{40,41} and fertility.^{42,43} Another factor is race/ethnicity, particularly in view of evidence that participation of Hispanic, Black, and Asian AYAs with cancer worsened from 2006 to 2013.^{35,44,45} For ALL specifically, the focus of the next stage for AYAs should not only involve novel treatment approaches but also standardization and optimization of supportive care measures, psychosocial support, adherence interventions, oncofertility treatment, and survivorship care. All these efforts should simultaneously work to address health disparities to ensure that a future of improved outcomes is experienced equitably for all AYA patients.⁴⁶

Participation in clinical trials also provides biospecimens for AYAs that are under-represented in biobank repositories and have thereby restricted translational research.¹ Also as mentioned above, the array of cancers in AYAs is distinctly different from that at any other age, and those that appear to be the same as in other age groups are often of a different biology. The need for translational research is greater and more challenging in AYAs than in any other age group.⁴⁷ Increased availability of treatment trials with laboratory correlates and accrual to them are essential to improving the outcome of cancer in AYAs.

Recent studies have suggested that effective evidence-based treatment strategies generated in AYA treatment trials may not be rapidly adopted by oncologists.⁴⁸ ALL, where the evidence is most abundant, only 31% of AYA patients in the greater San Francisco Bay area received a demonstrably superior pediatric type of regimen during 2008–2012, and the rate declined thereafter to 21%.⁴⁸ That the pediatric-inspired regimens for ALL therapy have been demonstrated to be more effective than most regimens originally developed in adult patients is well established.⁴⁹ Adult facilities treating ≥ 2 AYA ALL patients per year captured in the region were statistically significantly more likely to administer a pediatric regimen than lower volume centers, further indicating the importance of referral patterns.⁴⁸ The need for continued improvement of AYAs to clinical trial accrual remains a significant challenge, not only in community settings and low AYA volume centers but also among minorities.⁵⁰ Fortunately, NCI-designated cancer centers are evaluating their own AYA referral patterns and clinical trial determinants,⁵¹ and intergroup efforts are under way within the current organizational structure of the federal clinical trials enterprise, including the NCTN, to create novel opportunities for collaborative AYA oncology research among the pediatric and adult NCTN groups.^{52,53}

Limitations of the results presented herein include the lack comparing survival rates of AYAs who participated in clinical trials with those of AYAs who did not participate. Also, the clinical trial accrual data analyzed include phase I, II, and III trials combined, and since phase III trials are most meaningful in comparing new versus older therapies, the accuracy of the results may be limited. Also, the clinical trial data do not include trials sponsored by the pharmaceutical industry that can predominate at certain age levels. Among AYAs however, these trials are less common since AYAs have different cancers than do older adults

and, since they represent a much smaller population than those of older age, fewer drugs are developed for them by the industry. Also, the extent to which elimination of the survival cliff by itself helped increase the survival rate in older AYAs is uncertain. Nonetheless, the causes of its abatement undoubtedly contributed to the overall AYA benefit.

Conclusions and Recommendations

A previous decrement in survival of older adolescents and young adults with ALL and LBL in the United States is no longer apparent, resulting in 1 thousands of fewer premature deaths and tens of thousands of years of life saved, and impacting all major races in the country. Primary reasons include increased clinical trials available to, and participation by, 15- to 29-year-old patients, the application of pediatric-inspired treatment regimens to AYAs, recently available expanded national health insurance coverage for 18- to 25-year-old people improved AYA cancer services, and a national focus on AYA oncology. Older AYAs with ALL or LBL have not had a similar increase in clinical trial accrual, however, and their survival improvement is largely due to the elimination of the survival gap in younger AYAs. They need more of what younger AYAs have benefitted from, including health insurance for all AYAs and not just for those less than 25 years of age who are able to continue on the parents' insurance plan. Altogether, the recently established National Cancer Treatment Network, National Community Oncology Research Program, and the FDA may help eliminate the clinical trial accrual gap.

Acknowledgment

The authors thank Nita Seibel and Shanda Finnegan for compiling and providing the data on the CTEP-sponsored treatment trials and the NCI SEER program for its publicly available databases, without either of which little of this report would have been feasible.

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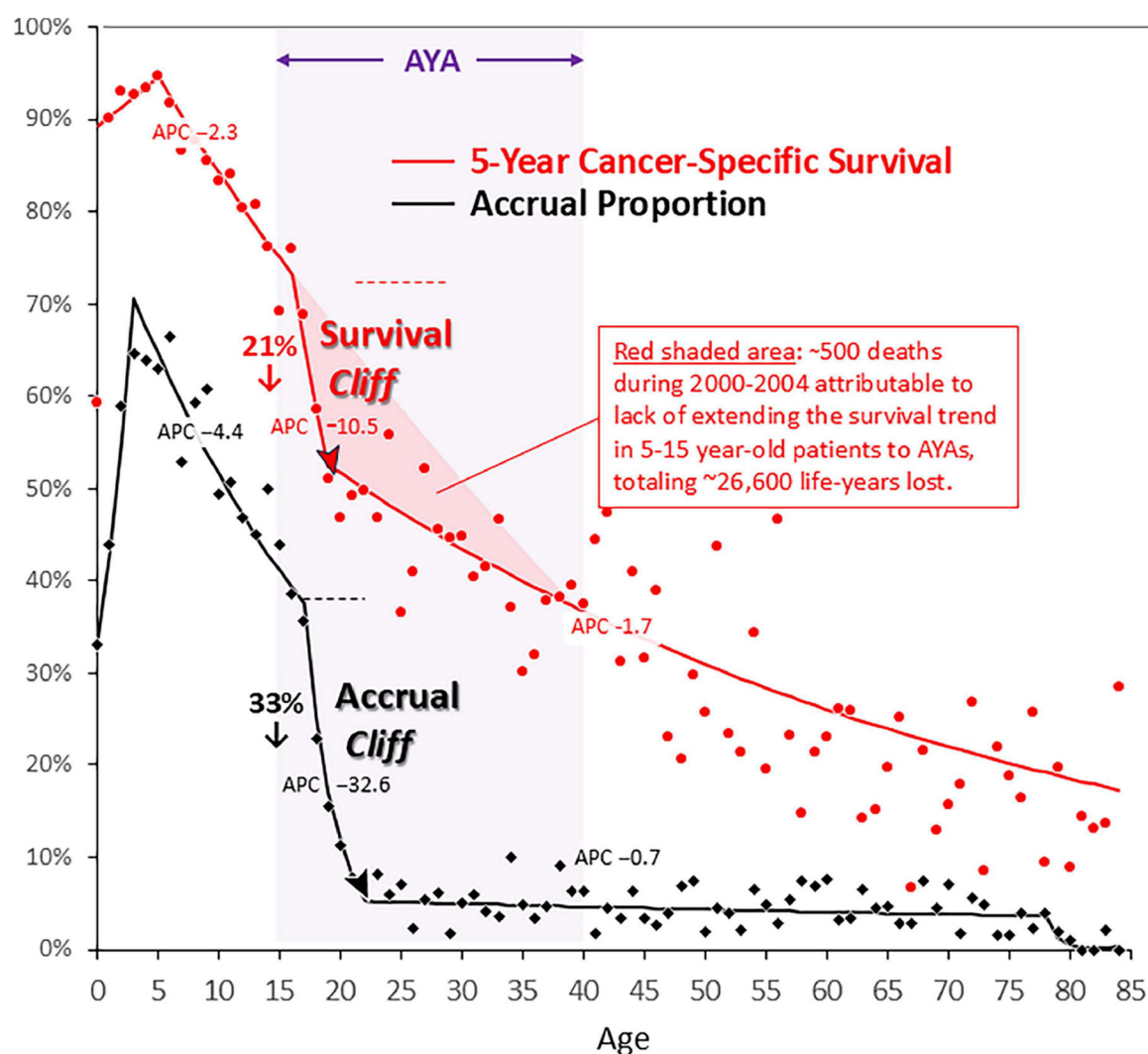


FIG. 1.

Joinpoint/average percent change (APC) analysis of 5-year cancer-specific survival of patients with ALL or LBL (red data), and estimated clinical trial accrual proportion of all U.S. patients with ALL or LBL (black data), 2000–2004, by single year of age. ALL, acute lymphoblastic leukemia; LBL, lymphoblastic lymphoma. Regression is joinpoint. Percentage (%) values refer to the “cliffs.” Sources: Updated from Bleyer et al.,¹ with survival data from SEER*Stat from SEER22² via SEER*Stat⁴ and APC analysis per Joinpoint regressions.⁵ Treatment trial accruals from CTEP provided in 2016 courtesy of Nita Seibel and Shanda Finnegan, CTEP, NCI.¹

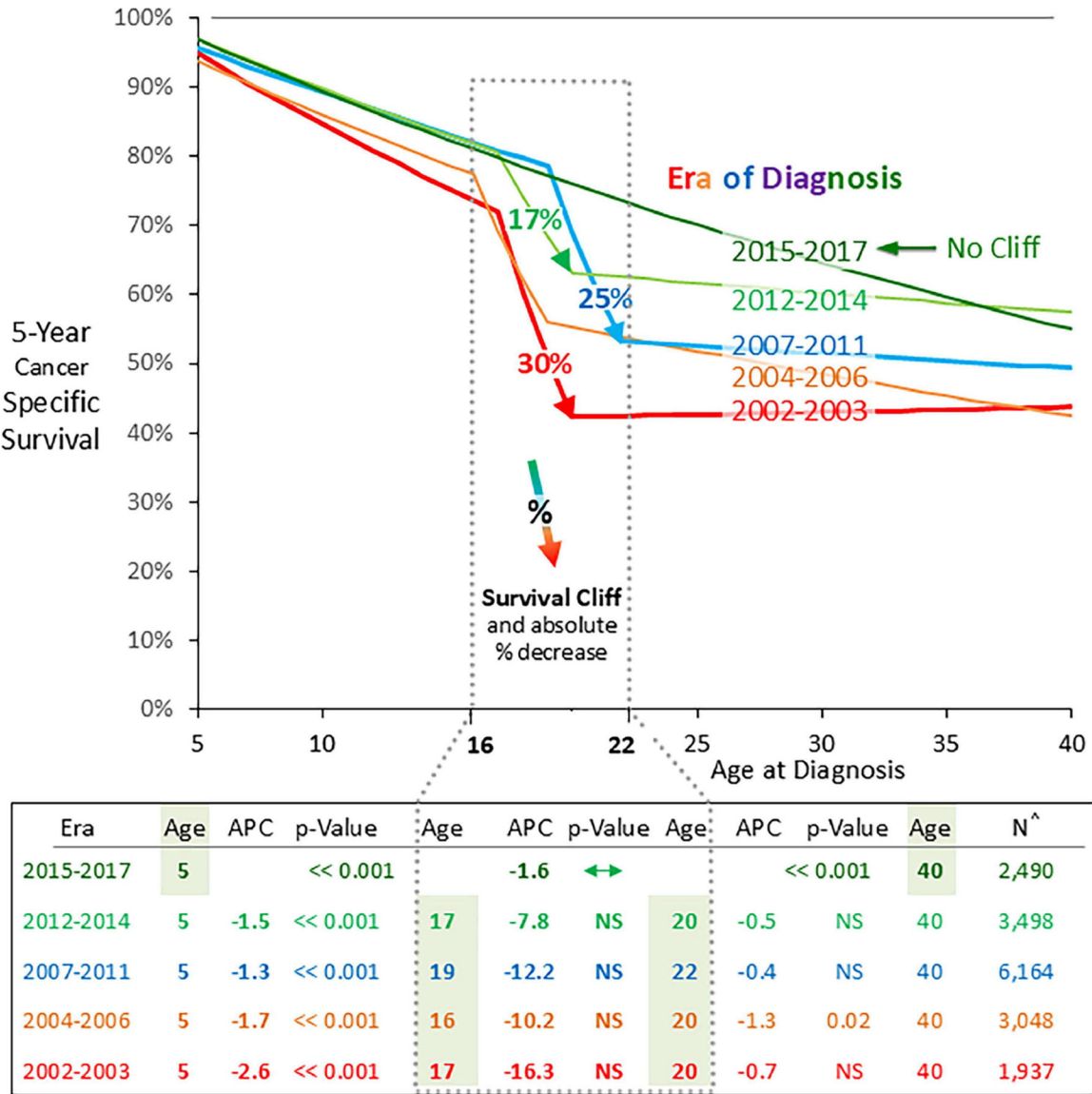


FIG. 2. Joinpoint/average percent change (APC) analysis of 5-year cancer-specific survival of patients with ALL or LBL, age 5–40, by single year of age and era of diagnosis during 2003–2017; U.S. SEER22⁺. [^]N—Total number of patients in era group. Data Source: SEER22⁺ via SEER*Stat.⁴

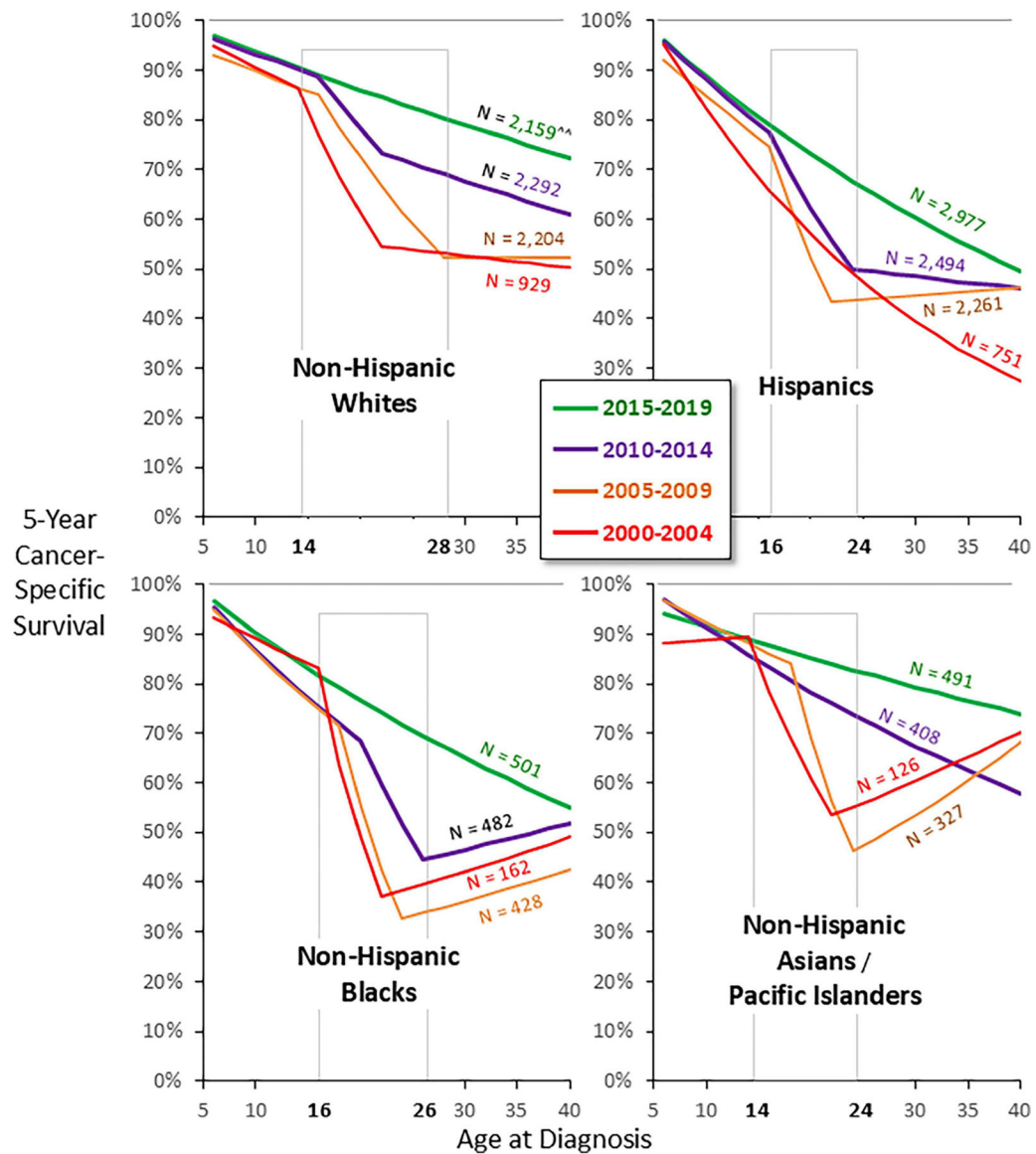


FIG. 3.

Joinpoint/average percent change (APC) analysis of 5-year cancer-specific survival of patients with ALL or LBL, U.S. SEER22⁻, Age 5–40, by single year of age, [^] race^{^^}, and 2000–2019 by 5-calendar-year intervals. [^] Joinpoint analysis applied to 2-age-years running average. ^{^^} Ethnicity not available for single years of age. ^{^^^} N—Total number of patients in era. Data Source: SEER22⁻ via SEER*Stat.⁴

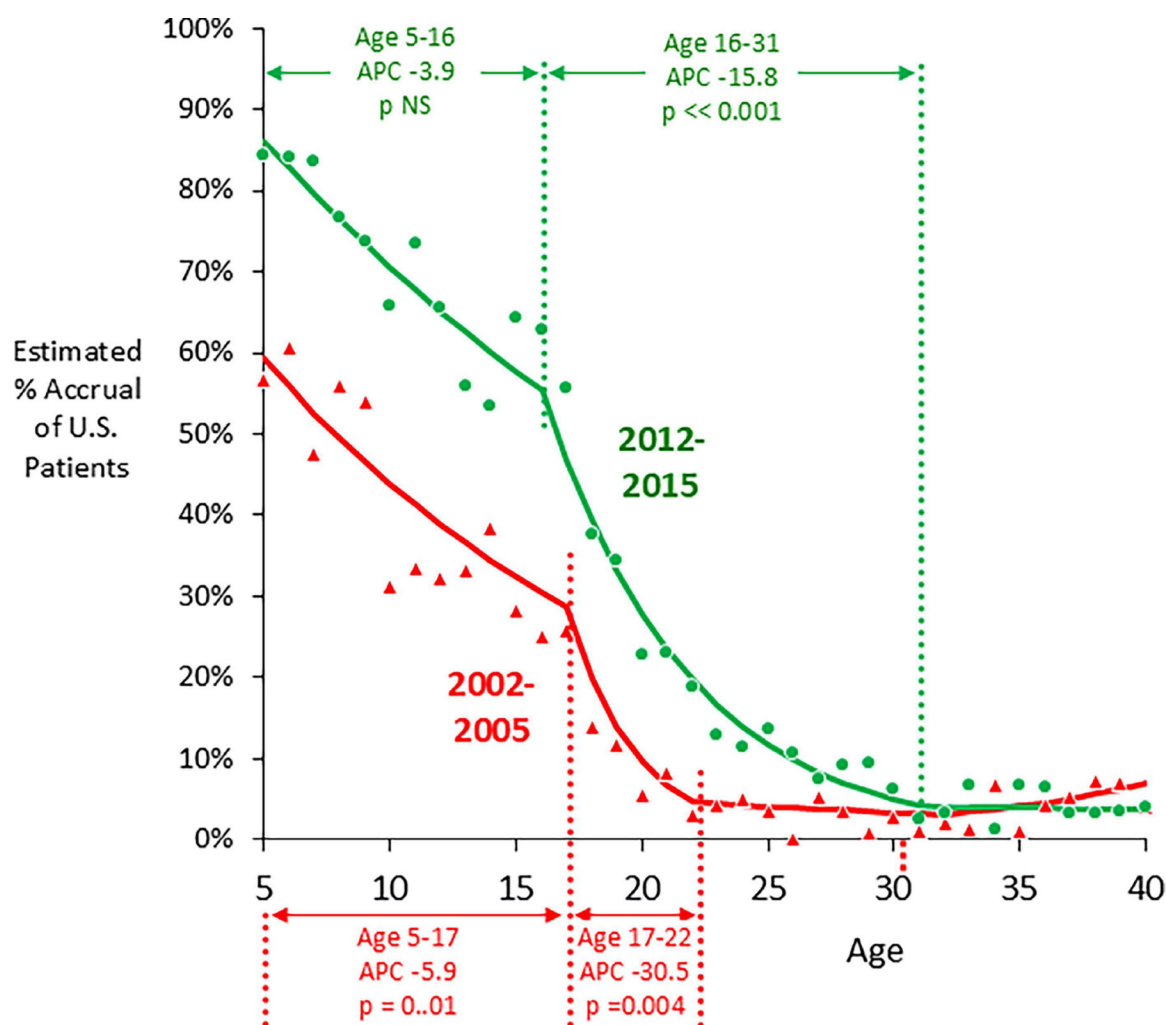
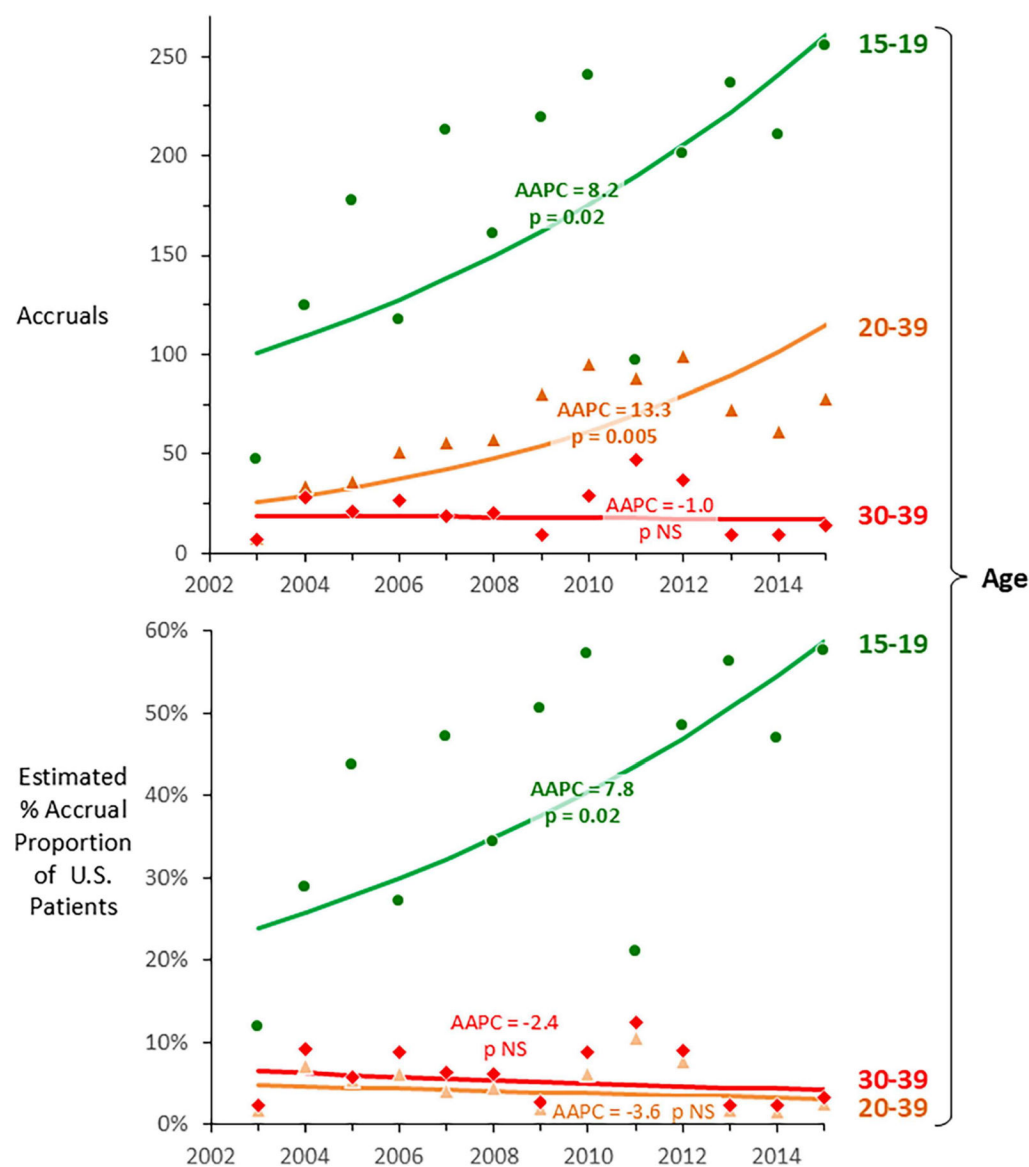
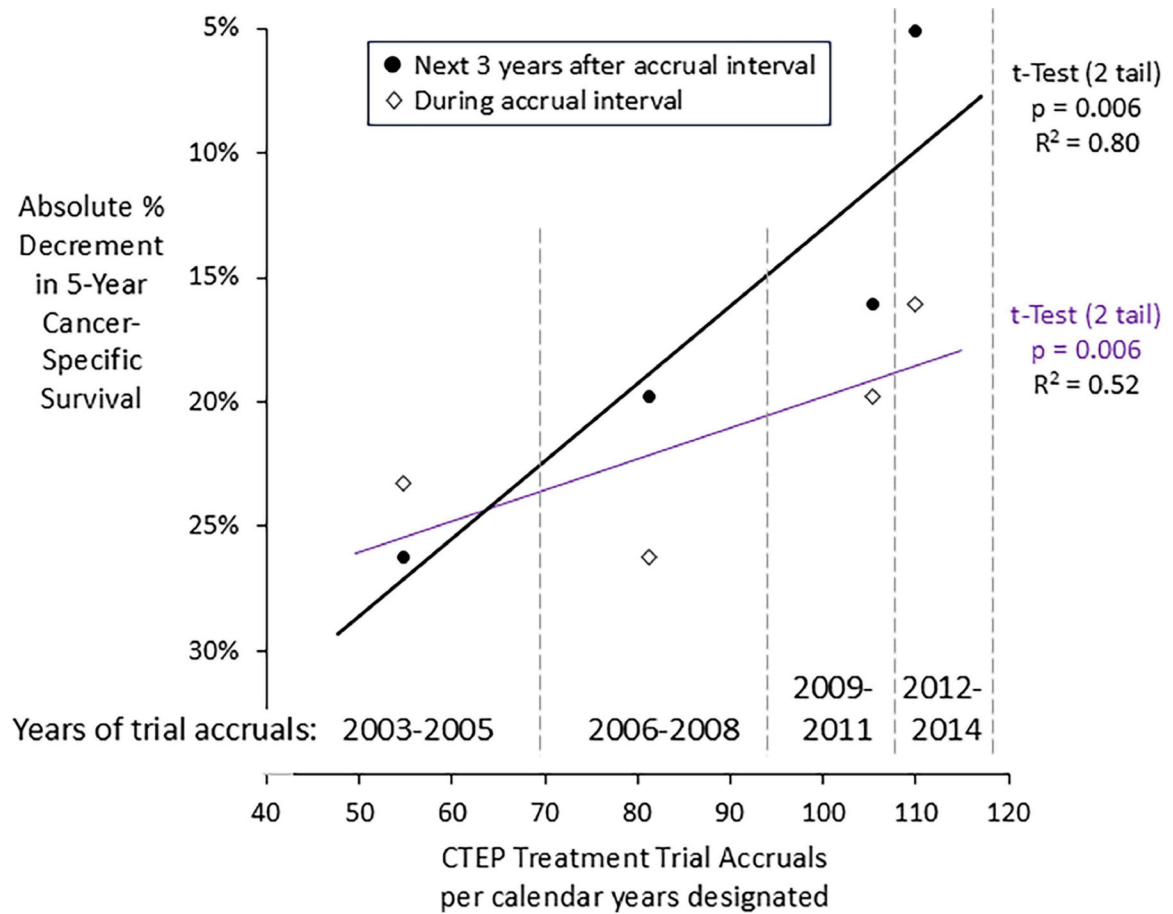


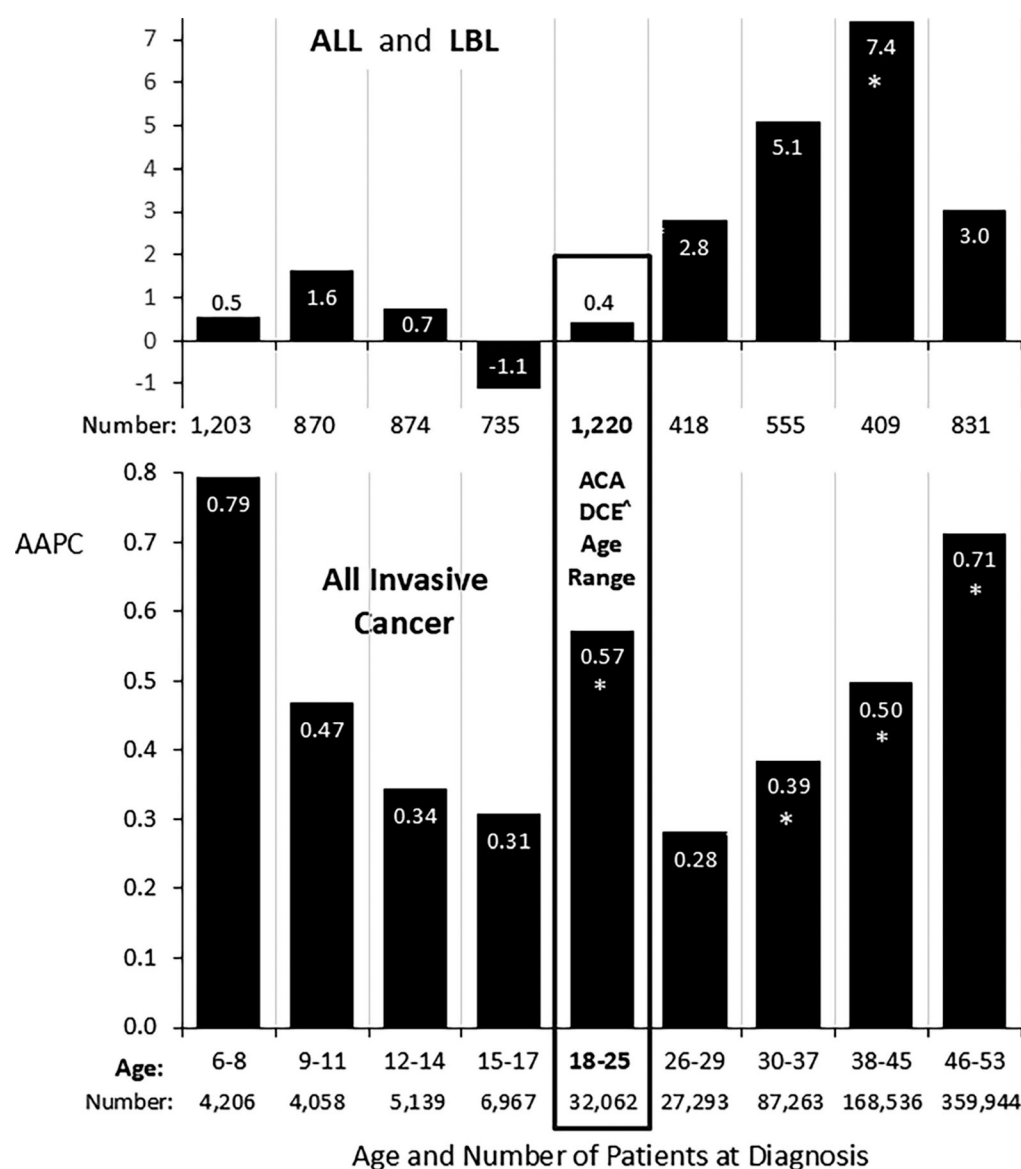
FIG. 4. Joinpoint/average percent change (APC) analysis of estimated clinical trial accrual percentage of U.S. patients ages 5–40 onto CTEP-sponsored ALL and LBL treatment trials, by single year of age and diagnosed in either 2002–2004 or 2012–2014. Data Source: Accrual data provided in 2016 courtesy of Nita Seibel and Shanda Finnegan, CTEP, NCI.¹

**FIG. 5.**

Joinpoint/average annual percent change (AAPC) analysis of annual clinical trial accruals onto CTEP-sponsored ALL and LBL treatment trials and estimated clinical trial accrual proportion of U.S., 2003–2015, ages 15–39, by age. Data Sources: Accrual data provided in 2016 courtesy of Nita Seibel and Shanda Finnegan, CTEP, NCI;¹ Accrual proportion based on SEER22² via SEER*Stat⁴ and U.S. Census Bureau data.⁶

**FIG. 6.**

Correlation of U.S. AYA survival decrement (Cliff) with CTEP-sponsored clinical trial accruals in 17- to 20-year-olds with ALL or LBL, by 3-calendar-year intervals. Data Sources: Survival data for SEER22- via SEER*Stat;⁴ Accrual data provided in 2016 by CTEP, NCI;¹ Accrual proportion based on SEER22⁻⁴ and U.S. Census Bureau data.⁶

**FIG. 7.**

Average annual percent change (AAPC) in 5-year relative survival of Americans with invasive cancer during 2010–2015, the 5 years after implementation of the Affordable Care Act in the United States, Ages 6–53, by 3- or 8-year age intervals. ^ACA DCE—Affordable Care Act’s Dependent Coverage Expansion. * $p < 0.05$ Data Source: SEER22[–] via SEER*Stat.⁴