

Health insurance status and outcomes in children, adolescents, and young adults: a systematic review and meta-analysis

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ABSTRACT

Background. The impacts of health insurance status on survival outcomes in children, adolescents, and young adults (aged 0-39 years) with malignant tumors have not been addressed in depth. The present study aimed to identify significant relationships of health insurance condition with overall survival or all-cause mortality among children (age 0-14 years) and adolescents and young adults (AYAs, age 15-39 years) with malignant tumors.

Methods. PubMed, Wiley Cochrane Central Register of Controlled Trials, Econlit, CINAHL, Web of Knowledge, PsychInfo, Business Source Premier, ProQuest Dissertation & Theses Database, and SCOPUS were systematically searched from inception to February 29, 2020 with no language restriction. All related articles comparing the effect of health insurance status on the risk of overall survival and the risk of all-cause mortality in malignant conditions affecting children and AYAs were identified. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were computed using a random- or fixed-effect model as per the heterogeneity evaluated using Cochran's Q and I² statistics.

Results. Fourteen studies including 149,680 individuals were selected for this meta-analysis. The pooled RR for all-cause mortality with insurance versus without insurance was 0.78 (95%CI, 0.71-0.86; I²=33.7%). Among the insurance types, patients with private insurance presented with a lower all-cause mortality (RR 0.70, 95% CI 0.60-0.82), with considerable heterogeneity (I²=83.3%).

Conclusions. The findings of this review suggest that a lack of or insufficient insurance is related to all-cause mortality of AYAs with malignant cancers. Strategies aimed at identifying causality and reducing disparities are warranted.

Key words: children, adolescents and young adults, malignancy, health insurance, survival analysis.

The survival of malignancy-affected children¹ and adolescents and young adults (AYAs, aged 15-39 years)² has largely improved in the past 50 decades due to the remarkable progress in medicine, including diagnostics, pharmacology, combined treatments and techniques. Leading causes of death among

all mortality reasons in this age group vary as a function of age, sex, and Socio-demographic Index (SDI) status, a composite indicator of development status generated for the Global Burden of Diseases, Injuries, and Risk Factors (GBD).³ A data from the 2004 GBD⁴ found that traffic accidents were the largest cause in both sexes, and maternal conditions were a leading cause of female deaths. Nevertheless, in data from the 2013 GBD with age range from 1 to 24 years, it was found that neoplasms had become the major cause of death in 1-9 year olds of both sexes, and in 10- to 24-year-old females in

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Malaysia⁵, although the major cause of death in 10- to 24-year-old males remained road traffic injuries. Meanwhile, malignancy remains the dominant cause of disease-linked death among these age groups in most studies.⁶⁻⁸ These populations do not benefit equally from these advances, owing to discrepancies in the age of clinical occurrence, malignancy type, disease stage (in solid tumor), anatomical position, geological region, or variations within regions. Discrepancies are particularly evident in resource-restricted settings, but also apply to socioeconomic groups in developed countries, although to a lesser but detectable degree.⁹ In undeveloped countries, survival rates of cancer-bearing AYAs and children are dismal and lower than 10%.¹⁰ In high-income countries, the survival rates of AYAs with cancer have improved, while the survival of younger pediatric patients and older adult patients have deteriorated because of inaccessibility to medical care and health insurance, as well as disparities in race/ethnicity and neighborhood socioeconomic status (SES).¹¹ American AYAs are the least likely to be covered by health insurance, and they tend to choose no insurance or public insurance.¹² Recent research implies that insurance deficiency is positively related to delayed diagnosis and later stage (and less treatable) disease in children and AYAs with cancer.¹³ Insured young adults tend to undergo definitive cancer therapy and are therefore, less likely to die.¹³ Additionally, lower neighborhood SES, minority race/ethnicity, public or deficient insurance, and other sociodemographic factors are all related to a greater risk of death¹⁴ among AYAs, in addition to delayed diagnoses and undertreatment.¹³

However, the effect of health insurance on the risk of mortality in cancer-bearing AYAs (age 15–39 years) and children (age 0–14 years) has not been clearly described because of inconsistent findings.^{15,16} In particular, some undetected confounders may have been neglected by model adjustment and contributed to bias. Given these concerns, we aimed to verify these findings through a systematic review.

Material and Methods

Search scheme and inclusion criteria

This study adheres to the PRISMA statement standards of quality for reporting systematic reviews. Two independent investigators searched PubMed, Wiley Cochrane Central Register of Controlled Trials, Econlit, CINAHL, Web of Knowledge, PsychInfo, Business Source Premier, ProQuest Dissertation & Theses Database, and SCOPUS with starting and ending date from inception to February 29, 2020 and with no language restriction. The combinations of terms searched included: 'insurance', 'Medicaid', 'Medicare', or 'cooperative medical scheme' and 'infant', 'child*', 'adolescent', 'youth*', 'puberty', 'prepuberty*', 'pediatric*', or 'paediatric*' and 'cancer', 'oncolog*', 'neoplas*', 'carcinom*', 'tumor*', 'malignan*', 'tumour*', 'leukemi*', 'lymphom*', 'sarcom*', 'osteosarcoma', 'nephroblastom*', 'neuroblastoma', 'rhabdomyosarcoma', 'teratom*', 'hepatom*', 'hepatoblastom*', 'medulloblastom*', 'retinoblastom*', 'meningioma*', or 'gliom*' and 'mortality', 'mortalit*', or 'survival'. The titles and abstracts of papers as-searched were reviewed. The search scheme was elaborated in Supplementary Information. The references of these papers were hand-searched using the snow-ball technique to ensure no potential articles were missed. Disagreements were resolved through mutual consensus. When detailed information needed for the analysis was unavailable, the original authors were contacted through e-mail to obtain the missing information. All authors agreed upon the final selection of included studies.

The inclusion criteria were as follows: (i) observational studies (cohort or registry), (ii) provision of endpoint for overall survival or all-cause mortality in malignancy patients aged 0–39 years with different health insurance status, and (iii) report of effect estimates: hazard ratio (HR), relative risk (RR), or Odds ratios (OR) and available relevant raw data for recalculation.

The exclusion criteria were: (i) case report, comment, editorial, letter, quasi-experiment (non-random subject assignment), or unpublished study and (ii) abstract or conference proceeding. Of two or more articles from the same team or organization, only the latest publication or the report with the largest sample size was selected.

Data isolation and quality assessment

Two investigators independently extracted all information of interest in a standardized form, including the study design, name of first author, title, country, publication year, follow-up duration, endpoints, sample size, adjustment level, mean age, gender, analysis strategy (statistical models and adjustment factors), and effect magnitude, including HRs, RRs, or ORs, as well as relevant raw data for re-calculation.

Study quality was evaluated by two independent investigators using the *Effective Public Health Practice Project Quality Assessment Tool for Quantitative Studies*.¹⁷ Any inconsistencies were addressed via discussions. This quality assessment tool rates the study procedures as 'strong', 'moderate', or 'weak' using eight scales (selection bias, study design, confounders, blinding, data collection methods, withdrawal/dropouts, intervention integrity, and analyses). We scored a paper as overall 'strong' or 'high quality' if no 'weak' item score existed and if at least four of the eight items were 'strong'. A paper of overall 'moderate quality' was one with only one 'weak' item score, with otherwise only 'strong' and 'moderate' item scores. The remaining studies were rated as 'weak' or 'low quality' overall.

Statistical analyses

The primary outcome measure was overall survival (freedom from all-cause mortality)¹⁸ or all-cause mortality. Dichotomous outcomes were synthesized using HRs, RRs, or ORs, with 95% confidence interval (CIs). The percent of between-study variability due to between-study heterogeneity was estimated using I^2 statistic¹⁹

and was classified as high, modest, and low with $I^2 \geq 50\%$, $<50\%$, and $<25\%$, respectively. A CI for I^2 was identified using the iterative non-central chi-square method.²⁰ RRs were converted to natural logarithms, and logRRs and standard errors were pooled by DerSimonian and Laird's approach in a random- or fixed-effect model as per the heterogeneity evaluated by Cochran's Q and I^2 statistics.

One-study-removed analysis was also performed to test sensitivity. Regarding the a-priori discrepancy of all-cause mortality, we conducted subgroup analyses by age (0–21 years, 15–39 years, and 0–39 years) according to the patient population of the enrolled studies. Publication bias was quantified by Egger's test (regression asymmetry) and Begg's test (rank correlation). All analyses were conducted using Stata statistical 15.0 (Stata Corp LP), at the α level of 0.05. P was set as two-sided. The 95% CI with null '1' indicated no clinical significance even if $P < 0.05$.

Results

Study selection, characteristics, and quality assessment

The initial search found 3867 potentially feasible articles, and after title and abstract screening, 52 articles were retrieved for full-text assessment. Finally, 14 studies^{11,14-16,21-30} were included (Fig. 1). Of the 14 studies, the dates of publication were between 2009 and 2019, the sample size varied between 19 and 80,855 patients, and there were four resources. Four studies were conducted among children, six among AYAs and four included both groups. Patient demographics, tumor characteristics, and treatments are shown in Table I.

Eleven of the 14 identified programs were assessed as moderate via the global rating, three as weak, and none as strong (Table II). Study design and confounders were the main weaknesses.

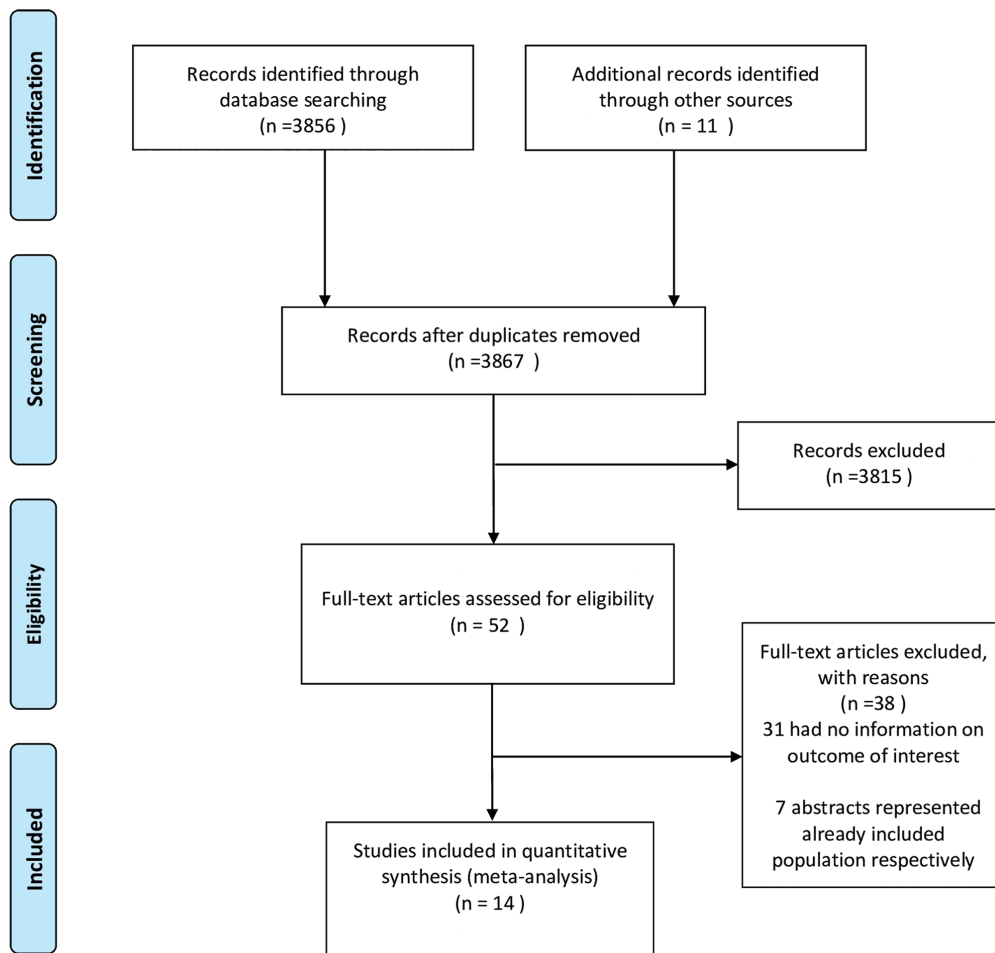


Fig. 1. Flow-diagram of study selection for the systematic literature review.

Effect of health insurance status on all-cause mortality in malignancy in patients aged 0–39 years

In 10 studies which examined the relationship between insured and uninsured patients, the pooled RR of all-cause mortality for insured versus uninsured was 0.78 (95% CI, 0.71-0.86; $p < 0.001$) in a fixed-effects model without heterogeneity ($I^2=33.7\%$, $p=0.138$; Fig. 2). A stratified analysis by contingency revealed the presence of positive outcome regarding all-cause mortality in studies among children and AYAs (HR 0.76, 95% CI 0.68-0.84; $p < 0.001$; Fig. 3). Since Egger’s test showed evidence of publication bias ($p=0.012$, Fig. 4), rather than replacing potential missing data, we performed a trim-and-fill sensitivity analysis and found basically similar results.

In 10 studies reporting the relationship between private and nonprivate insurance, the pooled RR of all-cause mortality for private insurance versus nonprivate insurance was 0.70 (95% CI 0.60 to 0.82; $p < 0.001$) in a random-effect model with severe heterogeneity ($I^2=83.3\%$, $p < 0.001$; Fig. 5). Heterogeneity was analyzed via the sensitivity test. However, heterogeneity remained after the exclusion of single studies. The funnel plots showed evidence of systematic bias in the analysis of all-cause mortality (Begg test, $p=0.21$; Egger’s test, $p=0.005$; Fig. 6). In the exploration of possible publication bias via the trim-and-fill approach, we did not substitute the probable missing data and found generally identical results.

Table I. Detailed demographic characteristics of studies included in the meta-analysis.

Study	Region	Study design	Baseline years	Sample size	Age (years)	Sex (% female)	Malignancy	Malignancy Stage	Data Resource
Kent et al (2009)	American	Retrospective Cohort	1996–2005	7,688	~39	42.1	Leukemia	NR	CCR
Fintel et al (2015)	American	Retrospective Cohort	1973-2010	574	18-30	36.0	ALL	NR	SEER
Abrahão et al (2016)	American	Retrospective Cohort	1988-2011	3,935	~39	46.5	AML	NR	CCR
Akhavan et al (2015)	American	Retrospective Cohort	1998-2011	3,658	~30	51.4	Renal cell carcinoma	NR	NCDB
Keegan et al (2015)	American	Retrospective Cohort	1988-2010	16,827	15-39	82.8	thyroid cancer	NR	CCR
Keegan et al (2016)	American	Retrospective Cohort	1988-2011	9,353	15-39	48.8	Hodgkin lymphoma	NR	CCR
Lee et al (2017)	American	Retrospective Cohort	1998–2012	3,295	15-39	42.5	Rectal Cancer	NR	NCDB
DeRouen et al (2017)	American	Retrospective Cohort	2001–2011	80,855	15-39	59.8	Cancer ^a	NR	CCR
Martijn et al (2017)	Kenya	Retrospective Cohort	2010-2012	63	~16	29.0	non-Hodgkin's lymphoma	NR	MTRH
Garner et al (2017)	American	Retrospective Cohort	1998-2012	9,585	~21	82.6	Thyroid Cancer	None insurance: stage I57.3%; stage II42.7% Government insurance: stage I59.3%; stage II40.7% Private insurance: stage I69.1%; stage II30.9%	NCDB
Njuguna et al (2017)	Kenya	Retrospective Cohort	2010-2012	39	~16	51	Wilms Tumor	NR	MTRH

HR: adjusted hazard ratio, CI: confidence interval, OR: odds ratio, NR: Not Reported, OS: overall survival, ASM: all-cause mortality, NHIF: National Hospital Insurance Fund, ALL: Acute Lymphoblastic Leukemia, AML: acute myeloid leukaemia, CCR: California Cancer Registry, NCDB: National Cancer Database, MTRH: Mot Teaching and Referral Hospital, NOS: not otherwise specified, CNS: central nervous system, ICC: International Classification of Childhood Cancer

^a including breast cancer, thyroid cancer, melanoma, testicular cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, cervical cancer, colorectal cancer, sarcoma, central nervous system cancers and ovarian cancer;

^b denoted as COX HR, reported in paper; ²denoted as extracting HR from Kaplan–Meier curves

Table I. Continued.

Study	Region	Study design	Baseline years	Sample size	Age (years)	Sex (% female)	Malignancy	Malignancy Stage	Data Resource
Bownes et al (2018)	American	Retrospective Cohort	1998-2012	3,125	15-39	100	ovarian germ cell tumors	None insurance: stage I56.1%; stage III10.0%; stage III25.8%; stage IV8.1% Government insurance: stage I59.2%; stage II5.6%; stage III27.4%; stage IV7.8% Private insurance: stage I63.8%; stage II8.4%; stage III24.4%; stage IV3.5%	NCDB
Penumarthy et al (2020)	American	Retrospective Cohort	2000-2015	1,106	~39	41.7	bone and soft tissue sarcomas	Low-income public insurance: local 36.0%; regional 26.9%; metastatic 21.3%; unknown 15.9% Private insurance: local 45.4%; regional 24.2%; metastatic 12.5%; unknown 17.8%	CCR
Mitchell et al (2020)	American	Retrospective Cohort	2000-2015	9,577	~19	45.7	central nervous system tumours	NR	SEER

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Table I. Continued.

Study	Observation group vs. control group	Survival Rates(%)	Outcome	Effect estimates ^b
Kent et al (2009)	None/unknown insurance vs. Any insurance	NR	OS	OS:HR ¹ (95%CI): 1.31 (1.16–1.47)
Fintel et al (2015)	Insured vs. Uninsured	Insured: 61 Uninsured:50	OS	OR (95%CI):1.60(0.98-2.63)
Abrahão et al (2016)	Unknown/NOS vs. Private; Uninsured vs. Private; Public vs. Private	None insurance:37.9 Public insurance:43.8 Private insurance:46.5 Unknown/NOS:37.1	OS	Unknown/NOS vs. Private, HR ¹ (95%CI):1.27(1.07-1.51); Uninsured vs. Private, HR ¹ (95%CI):1.34(1.01-1.78); Public vs. Private, HR(95%CI):1.05(0.93-1.19)
Akhavan et al (2015)	Government vs. Private Insurance; Uninsured vs. Private Insurance;	NR	ASM	Government vs. Private Insurance, HR ¹ (95%CI):2.64(1.34-5.20); Uninsured vs. Private, Insurance, HR ¹ (95%CI):2.77(0.62-12.50) OS:HR ¹ (95%CI): 2.56 (1.39–4.71)
Keegan et al (2015)	Public insurance/no insurance/unknown vs. Private/military insurance	Private/military insurance:99.4 Public insurance/no insurance/unknown:98.3	OS	OS:HR ¹ (95%CI): 2.56 (1.39–4.71)
Keegan et al (2016)	Public insurance/no insurance vs. Private/military insurance;	Private/military insurance:94.9 Public insurance/no insurance:88.4 unknown:93.9	OS	Public insurance/no Insurance vs. Private/military insurance:HR ¹ (95%CI):2.05 (1.58–2.66); Public insurance/no unknown vs. Private/military insurance, OS:HR ¹ (95%CI): 1.25 (0.70–2.24)
Lee et al (2017)	No insurance vs Private; Medicaid/Medicare/ Government vs. Private	NR	OS	No insurance vs. Private, HR ¹ (95%CI): 1.71 (1.08–2.70); Medicaid/Medicare/Government vs. Private, HR ¹ (95%CI):1.86 (1.33–2.59)

HR: adjusted hazard ratio, CI: confidence interval, OR: odds ratio, NR: Not Reported, OS: overall survival, ASM: all-cause mortality, NHIF: National Hospital Insurance Fund, ALL: Acute Lymphoblastic Leukemia, AML: acute myeloid leukaemia, CCR: California Cancer Registry, NCDB: National Cancer Database, MTRH: Moi Teaching and Referral Hospital, NOS: not otherwise specified, CNS: central nervous system, ICC: International Classification of Childhood Cancer
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^b ¹denoted as COX HR, reported in paper; ²denoted as extracting HR from Kaplan–Meier curves

Table I. Continued.

Study	Observation group vs. control group	Survival Rates(%)	Outcome	Effect estimates ^b
DeRouen et al (2017)	Public/ uninsured vs. Private/military Unknown vs Private/military	15-24 years: Private/military 97.7; Public/none 94.1 24-34 years: Private/military 94.5; Public/none 88.5 35-39 years: Private/military 93.4; Public/none 88.8	OS	Public/uninsured vs.Private/military,HR ¹ (95%CI): 1.57 (1.36-1.80) Unknown vs Private/military,HR ¹ (95%CI): 1.22(1.11-1.34)
Martijn et al (2017)	NHIF vs. No NHIF	NR	ASM	OR(95%CI):0.29(0.03-2.51)
Garner et al (2017)	None vs. Private Government vs. Private	NR	OS	None vs. Private, HR ² (95%CI):2.05(0.12-34.98) Government vs. Private, HR ² (95%CI):2.32(0.14-37.63)
Njuguna et al (2017)	NHIF vs. No NHIF	NR	ASM	OR(95%CI):1.2(0.27-5.4)
Bownes et al (2018)	Government vs No insurance; Private vs No insurance	NR	OS	Government vs. No insurance, HR ¹ (95%CI):. 0.82 (0.41-1.01); Private vs No insurance, HR ¹ (95%CI): 0.70 (0.33-1.18)
Penumarthy et al (2020)	Low-income public insurance vs. Private insurance	Low-income public insurance: 49 Private insurance:63	OS	HR ¹ (95%CI): 1.27 (1.02-1.57)
Mitchell et al (2020)	Insured (Medicaid) vs. Insured (Private); Insured (unknown type) vs. Insured (Private); No insurance vs. Insured (Private); Unknown vs. Insured (Private)	Insured (private): 76.1 Insured (Medicaid):70.3 Insured (unknown type):80.9 No insurance:76.0	OS	Insured(Medicaid) vs. Insured (Private), HR ¹ (95%CI): 1.01(0.87-1.16); Insured (unknown type) vs Insured (Private), HR ¹ (95%CI): 0.82(0.66-1.02); No insurance vs Insured (Private),HR ¹ (95%CI): 0.97(0.61-1.53); Unknown vs Insured (Private),HR ¹ (95%CI): 1.36(0.94-1.96)

HR: adjusted hazard ratio, CI: confidence interval, OR: odds ratio, NR: Not Reported, OS: overall survival, ASM: all-cause mortality, NHIF: National Hospital Insurance Fund, ALL: Acute Lymphoblastic Leukemia, AML: acute myeloid leukaemia, CCR: California Cancer Registry, NCDB: National Cancer Database, MTRH: Mot Teaching and Referral Hospital, NOS: not otherwise specified, CNS: central nervous system, ICC: International Classification of Childhood Cancer
^a including breast cancer, thyroid cancer, melanoma, testicular cancer, non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, cervical cancer, colorectal cancer, sarcoma, central nervous system cancers and ovarian cancer;
^b denoted as COX HR, reported in paper; ²denoted as extracting HR from Kaplan-Meier curves

Table II. Ratings of methodological quality by effective public health practice project quality assessment tool.

Study	Selection bias	Design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Intervention integrity	Analyses	Global rating*
Kent et al. (2009)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Fintel et al. (2015)	Strong	Weak	Weak	Moderate	Strong	Strong	Strong	Strong	Moderate
Abrahão et al. (2015)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Akhavan et al. (2015)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Keegan et al. (2015)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Keegan et al. (2016)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Lee et al. (2017)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
DeRouen et al. (2017)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Martijn et al. (2017)	Weak	Weak	Weak	Moderate	Strong	Strong	Strong	Strong	Weak
Garner et al. (2017)	Strong	Weak	Weak	Moderate	Strong	Strong	Strong	Strong	Weak
Njuguna et al. (2017)	Weak	Weak	Weak	Moderate	Strong	Strong	Strong	Strong	Weak
Bownes et al. (2018)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Penumarthy et al. (2020)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate
Mitchell et al. (2020)	Strong	Weak	Strong	Moderate	Strong	Strong	Strong	Strong	Moderate

*: strong; no weak ratings, moderate; one weak rating, weak; two or more weak ratings.

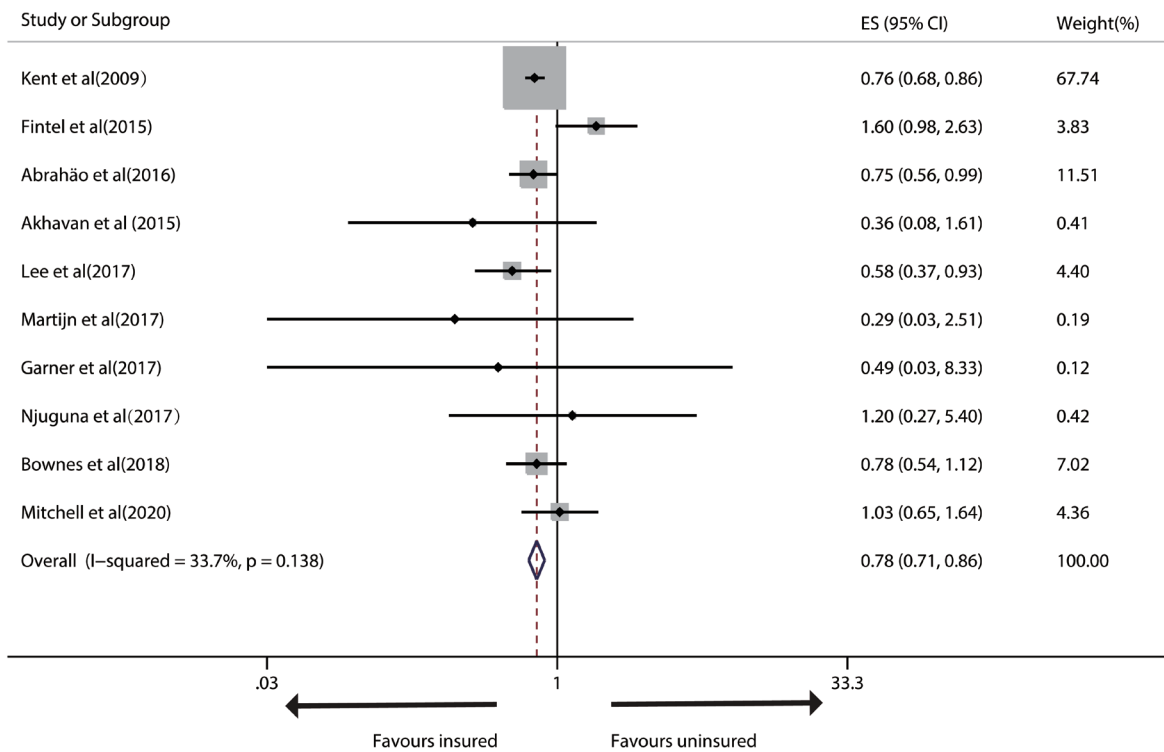


Fig. 2. Forest plot of the risk of all-cause mortality between insured and uninsured cancer patients aged 0-39 years.

Discussion

This systematic review found that uninsured malignancy patients, aged 0–39 years, relative to private insurance, had a higher risk of all-cause mortality. Many factors (such as disease stage and delayed diagnosis) related to healthcare availability may have modulated the association between deficient or public insurance and survival,³¹ which in turn resulted in a later stage diagnosis (and resulting in the cancer being untreatable), delays, lower therapy reception, termination,¹³ Medicaid service inhibitions, or limited accessibility of information and support services among patients and survivors.³² The AYA Health Outcomes and Patient Experience research found that insurance shortage was related to a lower quality of life among new patients.³³ Similarly, contacts with health care services may promote adherence to therapy and follow-up instructions, which are factors that were reportedly connected with poor outcomes among AYAs.

However, the race and SES differences in survival identified among privately insured AYAs imply that broadening insurance coverage alone may not eliminate all outcome differences. Insurance coverage has often been shown to be a key modulator of race and SES differences in survival. This is supported by recent studies, including ours, on relationships between no or public insurance and cancer outcomes among AYAs after race and SES adjustments.³⁴ Our results verified the significance of insurance coverage, and suggested that considerable race and SES disparities still exist even among those with private insurance. Our results agree with recent findings that severe financial stress is related to a cancer diagnosis for those who are relatively young in age, lower SES, or non-white race/ethnicity, irrespective of insurance conditions.³⁵ For those with private insurance, financial stress can originate from out-of-pocket costs related to co-payments, co-insurance, deductibles, and out-of-network costs, that may dictate treatment plans and termination, and

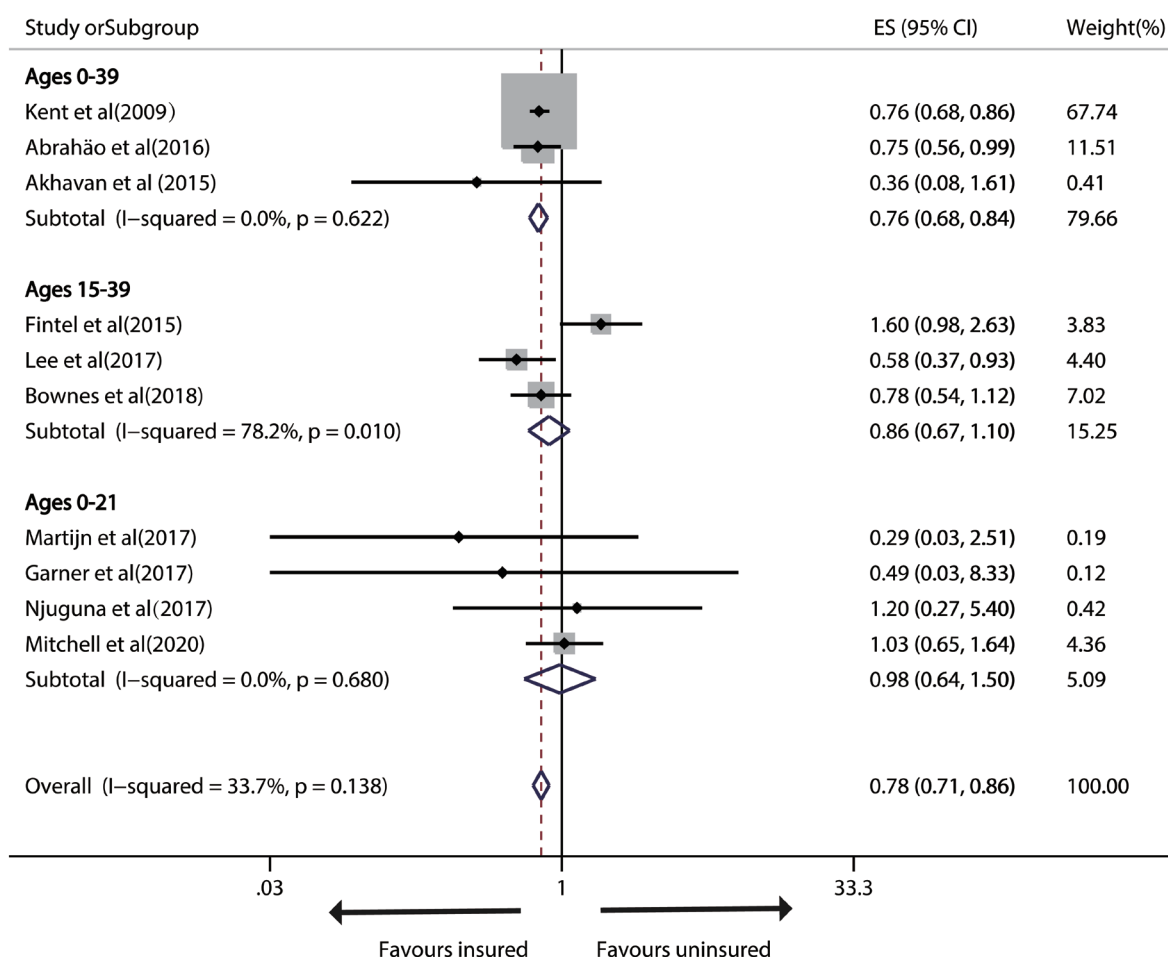


Fig. 3. Forest plot of the risk of all-cause mortality between insured and uninsured cancer patients aged 0-39 years, according to study population.

general well-being.³⁶ For instance, for all age groups, African Americans and low-SES citizens are less likely to undergo standard medical therapy than their Caucasian counterparts, even when they have the same insurance coverage. This disparity has been noted by other studies on specific cancer care.³⁷

Race bias may affect care use (regardless of insurance condition), and chronic burden due to bias affects health outcomes.³⁸ Severe racial/ethnic differences for cancers resulting in some groups being more prone to avoidance of therapy indicate that disparities in socioeconomic resources (social capital) may contribute to and intensify the residual racial/ethnic disparities in cancer survival.³⁹ Financial concerns among minorities and low-SES groups, even with

private insurance, may critically contribute to racial/ethnic and SES differences in therapy and therefore, survival. Moreover, biological divergences in cancer subtypes are probably related to some cancers. For example, African-American AYAs are more susceptible to breast cancer of specific molecular subtypes, and these are related to more adverse prognoses.⁴⁰ In addition, when considering molecular subtypes and insurance types in survival models, these decrease the relationship of a certain race/ethnicity with a severe risk of death.⁴¹

Our analyses have some notable limitations. First, we did not examine the roles of specific sociodemographic characteristics (e.g., income, education, and access to medical care). There may also have been some undetected

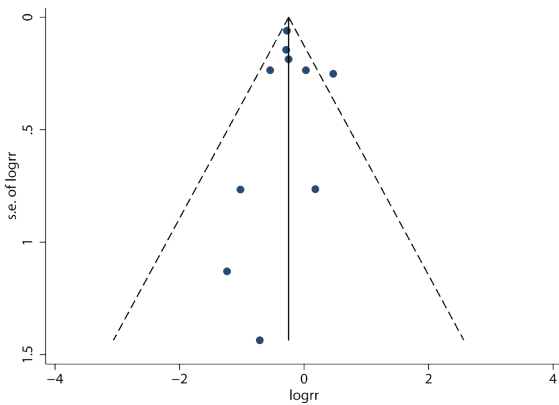


Fig. 4. Funnel plot of the risk of all-cause mortality between insured and uninsured cancer patients aged 0-39 years.

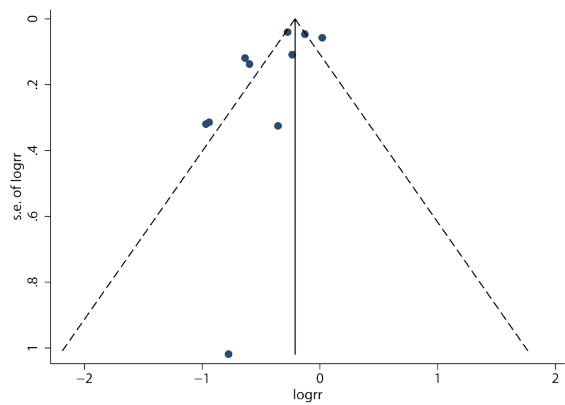


Fig. 6. Funnel plot of the risk of all-cause mortality between private and nonprivate insurance cancer patients aged 0-39 years.

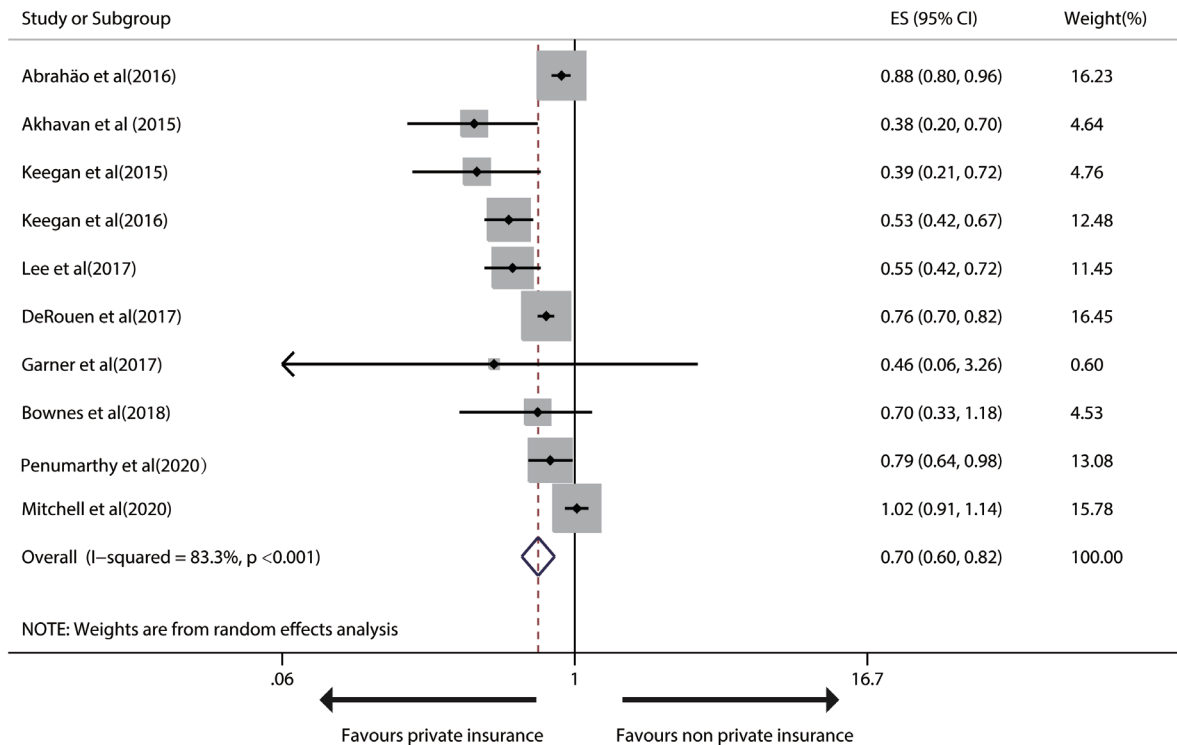


Fig. 5. Forest plot of the risk of all-cause mortality between private and nonprivate insurance cancer patients aged 0-39 years.

confounding factors that we did not account for in our findings. Second, we ignored therapeutic indices, which were often inconsistent and/or incomplete. This omission is likely to weaken our findings because we cannot clarify the extent to which the divergences in survival may be induced by differences in treatment

(which are also probably related to insurance coverage). Third, we were unable to detect causality in a cross-sectional analysis and there were uncertainties regarding whether deficient or private insurance may lead to delayed diagnoses. Fourth, since insurance status was reported at diagnosis, we cannot explain the

changes in insurance status over the follow-up period. As a result, uninsured patients may be misclassified as Medicaid patients at baseline, which may lead to a lower observed survival rate among Medicaid patients.⁴² We are not inferring that Medicaid is less 'protective' than private insurance. Rather, our concern is that any shortage of insurance upon diagnosis may be related to a higher risk and that patients coded as 'Medicaid-insured' may actually be uninsured before diagnosis. Fifth, any survival superiority for privately insured patients may be ascribed to lead-time bias, which was suggested as a reason for survival differences by insurance conditions among adults.⁴² For instance, the lead-time of later diagnoses may give a false impression of longer survivals among privately insured patients than among uninsured or Medicaid patients. In addition, as anticipated in any systematic review, the cohort studies demonstrated remarkable heterogeneity for all-cause mortality between uninsured and privately insured patients. Moreover, Egger's test uncovered a potential publication bias, which was difficult to identify. These results suggest that we may have exaggerated the exact effect if some studies, such as abstracts or conference proceedings being a potential resource for grey literatures were excluded.

In conclusion, results from our systematic review suggest that limited or deficient insurance is heavily related to all-cause mortality in AYAs with malignancy. Strategies aimed at identifying causality and reducing disparities are warranted.

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Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SH, CH; data collection: HH; analysis and interpretation

of results: CH, LJ; draft manuscript preparation: CH, HL. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that they have no competing interest.

Supplementary information is available at:

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REFERENCES

1. Pritchard-Jones K, Pieters R, Reaman GH, et al. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. *Lancet Oncol* 2013; 14: e95-e103.
2. Bleyer A. The adolescent and young adult gap in cancer care and outcome. *Curr Probl Pediatr Adolesc Health Care* 2005; 35: 182-217.
3. Global Burden of Disease Child and Adolescent Health Collaboration, Kassebaum N, Kyu HH, Zoeckler L, et al. Child and adolescent health from 1990 to 2015: findings from the global burden of diseases, injuries, and risk factors 2015 Study. *JAMA Pediatr* 2017; 171: 573-592.
4. Patton GC, Coffey C, Sawyer SM, et al. Global patterns of mortality in young people: a systematic analysis of population health data. *Lancet* 2009; 374: 881-892.
5. Abdul-Razak S, Azzopardi PS, Patton GC, Mokdad AH, Sawyer SM. Child and adolescent mortality across Malaysia's epidemiological transition: a systematic analysis of global burden of disease data. *J Adolesc Health* 2017; 61: 424-433.
6. Heron M. Deaths: leading causes for 2010. *Natl Vital Stat Rep* 2013; 62: 1-96.
7. Sidebotham P, Fraser J, Fleming P, Ward-Platt M, Hain R. Patterns of child death in England and Wales. *Lancet* 2014; 384: 904-914.
8. Bleyer A, Ferrari A, Whelan J, Barr RD. Global assessment of cancer incidence and survival in adolescents and young adults. *Pediatr Blood Cancer* 2017; 64.
9. Mogensen H, Modig K, Tettamanti G, Erdmann F, Heyman M, Feychting M. Survival after childhood cancer-social inequalities in high-income countries. *Front Oncol* 2018; 8: 485.

10. Stones DK, De Bruin GP, Esterhuizen TM, Stefan DC. Childhood cancer survival rates in two South African units. *S Afr Med J* 2014; 104: 501-504.
11. Keegan TH, Grogan RH, Parsons HM, et al. Sociodemographic disparities in differentiated thyroid cancer survival among adolescents and young adults in California. *Thyroid* 2015; 25: 635-648.
12. James SL, Castle CD, Dingels ZV, et al. Global injury morbidity and mortality from 1990 to 2017: results from the Global Burden of Disease Study 2017. *Inj Prev* 2020; 26(Suppl 1): i165.
13. Aizer AA, Falit B, Mendu ML, et al. Cancer-specific outcomes among young adults without health insurance. *J Clin Oncol* 2014; 32: 2025-2030.
14. Keegan TH, DeRouen MC, Parsons HM, et al. Impact of treatment and insurance on socioeconomic disparities in survival after adolescent and young adult Hodgkin lymphoma: a population-based study. *Cancer Epidemiol Biomarkers Prev* 2016; 25: 264-273.
15. Fintel AE, Jamy O, Martin MG. Influence of insurance and marital status on outcomes of adolescents and young adults with acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2015; 15: 364-367.
16. Kent EE, Sender LS, Largent JA, Anton-Culver H. Leukemia survival in children, adolescents, and young adults: influence of socioeconomic status and other demographic factors. *Cancer Causes Control* 2009; 20: 1409-1420.
17. Docrat S, Besada D, Cleary S, Lund C. The impact of social, national and community-based health insurance on health care utilization for mental, neurological and substance-use disorders in low- and middle-income countries: a systematic review. *Health Econ Rev* 2020; 10: 11.
18. Takagi H, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. Worse survival after transcatheter aortic valve implantation than surgical aortic valve replacement: a meta-analysis of observational studies with a propensity-score analysis. *Int J Cardiol* 2016; 220: 320-327.
19. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-1558.
20. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. *Psychol Methods* 2001; 6: 203-217.
21. Abrahão R, Keogh RH, Lichtensztajn DY, et al. Predictors of early death and survival among children, adolescents and young adults with acute myeloid leukaemia in California, 1988-2011: a population-based study. *Br J Haematol* 2016; 173: 292-302.
22. Akhavan A, Richards M, Shnorhavorian M, Goldin A, Gow K, Merguerian PA. Renal cell carcinoma in children, adolescents and young adults: a National Cancer Database study. *J Urol* 2015; 193: 1336-1341.
23. Lee DY, Teng A, Pedersen RC, et al. Racial and socioeconomic treatment disparities in adolescents and young adults with stage II-III rectal cancer. *Ann Surg Oncol* 2017; 24: 311-318.
24. DeRouen MC, Parsons HM, Kent EE, Pollock BH, Keegan THM. Sociodemographic disparities in survival for adolescents and young adults with cancer differ by health insurance status. *Cancer Causes Control* 2017; 28: 841-851.
25. Martijn HA, Njuguna F, Olbara G, et al. Influence of health insurance status on paediatric non-Hodgkin's lymphoma treatment in Kenya. *BMJ Paediatr Open* 2017; 1: e000149.
26. Garner EF, Maizlin II, Dellinger MB, et al. Effects of socioeconomic status on children with well-differentiated thyroid cancer. *Surgery* 2017; 162: 662-669.
27. Njuguna F, Martijn HA, Kuremu RT, et al. Wilms tumor treatment outcomes: perspectives from a low-income setting. *J Glob Oncol* 2017; 3: 555-562.
28. Bownes LV, Stafman LL, Maizlin II, et al. Socioeconomic disparities affect survival in malignant ovarian germ cell tumors in AYA population. *J Surg Res* 2018; 222: 180-186.e3.
29. Penumarthy NL, Goldsby RE, Shiboski SC, Wustrack R, Murphy P, Winestone LE. Insurance impacts survival for children, adolescents, and young adults with bone and soft tissue sarcomas. *Cancer Med* 2020; 9: 951-958.
30. Mitchell HK, Morris M, Ellis L, Abrahão R, Bonaventure A. Racial/ethnic and socioeconomic survival disparities for children and adolescents with central nervous system tumours in the United States, 2000-2015. *Cancer Epidemiol* 2020; 64: 101644.
31. Smith EC, Ziogas A, Anton-Culver H. Delay in surgical treatment and survival after breast cancer diagnosis in young women by race/ethnicity. *JAMA Surg* 2013; 148: 516-523.
32. Keegan TH, Tao L, DeRouen MC, et al; AYA HOPE Study Collaborative Group. Medical care in adolescents and young adult cancer survivors: what are the biggest access-related barriers? *J Cancer Surviv* 2014; 8: 282-292.
33. Smith AW, Bellizzi KM, Keegan TH, et al. Health-related quality of life of adolescent and young adult patients with cancer in the United States: the adolescent and young adult health outcomes and patient experience study. *J Clin Oncol* 2013; 31: 2136-2145.

34. Gorey KM, Luginaah IN, Holowaty EJ, Zou G, Hamm C, Balagurusamy MK. Mediation of the effects of living in extremely poor neighborhoods by health insurance: breast cancer care and survival in California, 1996 to 2011. *Int J Equity Health* 2013; 12: 6.
35. Yabroff KR, Dowling EC, Guy GP Jr, et al. Financial hardship associated with cancer in the United States: findings from a population-based sample of adult cancer survivors. *J Clin Oncol* 2016; 34: 259-267.
36. Zafar SY, Peppercorn JM, Schrag D, et al. The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *Oncologist* 2013; 18: 381-390.
37. Wu XC, Lund MJ, Kimmick GG, et al. Influence of race, insurance, socioeconomic status, and hospital type on receipt of guideline-concordant adjuvant systemic therapy for locoregional breast cancers. *J Clin Oncol* 2012; 30: 142-150.
38. Chae DH, Nuru-Jeter AM, Adler NE, et al. Discrimination, racial bias, and telomere length in African-American men. *Am J Prev Med* 2014; 46: 103-111.
39. Tehranifar P, Neugut AI, Phelan JC, et al. Medical advances and racial/ethnic disparities in cancer survival. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 2701-2708.
40. Keegan TH, DeRouen MC, Press DJ, Kurian AW, Clarke CA. Occurrence of breast cancer subtypes in adolescent and young adult women. *Breast Cancer Res* 2012; 14: R55.
41. Keegan TH, Press DJ, Tao L, et al. Impact of breast cancer subtypes on 3-year survival among adolescent and young adult women. *Breast Cancer Res* 2013; 15: R95.
42. Bradley CJ, Gardiner J, Given CW, Roberts C. Cancer, medicaid enrollment, and survival disparities. *Cancer* 2005; 103: 1712-1718.