ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

Psychiatric disorders in adolescent and young adult cancer survivors in Korea

S.-M. Jeong[1,2†], D. Kang[3,4,5†], H. Kim[4], K. H. Jeon[6], H. L. Choi[3,7], H. Y. Park[8], S. Kim[3,4], J. Cho[3,4*] & D. W. Shin[3,5,9*]

[1]Department of Medicine, Seoul National University College of Medicine, Seoul; [2]Department of Family Medicine, Seoul National University Hospital, Seoul; [3]Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Science and Technology, Sungkyunkwan University School of Medicine, Seoul; [4]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [5]Center for Trend Monitoring-Risk Modeling, Samsung Medical Center, Seoul; [6]Department of Family Medicine, CHA Gumi Medical Center, CHA University, Gumi; [7]Department of Family Medicine/Executive Healthcare Clinic, Severance Hospital, Yonsei University College of Medicine, Seoul; [8]Department of Psychiatry, Seoul National University Hospital, Seoul National University College of Medicine, Seoul; [9]Department of Family Medicine/Supportive Care Center, Samsung Medical Center, Seoul, Republic of Korea

Available online 27 January 2025

Background: Although adolescent and young adult (AYA) cancer survivors have an increased risk of psychiatric disorders, limited evidence has been suggested. We aimed to determine the risk of psychiatric disorders among AYA cancer survivors.

Materials and methods: A retrospective population-based cohort study based on the Korea National Health Insurance Service database was carried out. All men and women aged 15-39 years diagnosed with cancer between 2006 and 2019 ($N = 88\,965$) were included and matched with controls (1 : 4). The prevalence ratios (PRs) of psychiatric disorders were calculated in cancer patients and compared with those in the control group every 6 months before and after cancer diagnosis.

Results: The mean age of the participants was 32.2 years and the majority were 30-39 years of age (72.9%). There was no difference in the PRs of psychiatric disorders between AYA cancer patients and the control group before cancer diagnosis, but it increased sharply after cancer diagnosis [PR 2.50, 95% confidence interval (CI) 2.42-2.58 in the first 6 months]. During a median follow-up of 6.5 years, 54 733 participants developed psychiatric disorders. The overall risk of psychiatric disorders among AYA cancer survivors compared with the control group had a sub-distribution hazard ratio of 1.42 (95% CI 1.39-1.45) after considering competing risks.

Conclusions: Our study confirmed a 42% increased risk of psychiatric disorders among AYA cancer survivors compared with controls across various cancer types. Our findings suggest that AYA cancer survivors require long-term psychological support following their cancer diagnosis.

Key words: adolescent, young adult, cancer survivors, mental health

INTRODUCTION

Adolescent and young adult (AYA) cancer survivors are those diagnosed with cancer between 15 and 39 years of age. The overall incidence of cancer in this age group has increased over the previous decade.[1] In 2019, there were 1.2 million incident cases, 0.4 million deaths, and 23.5 million disability-adjusted life-years due to AYA cancers globally.[2] Advances in cancer treatment have improved long-term survival rates of the AYA cancer group resulting in an 82.5% 5-year relative survival rate.[3] AYA cancer survivors are more likely to experience mental distress compared with controls.[4] Therefore, it becomes imperative to recognize the risk of psychiatric disorders and provide appropriate management considering their remaining life span, especially because they encounter distinctive developmental and social growth, such as completing their education, achieving an occupational career, and starting their own family.

In contrast to the extensive evidence on mental health problems among childhood cancer survivors,[5-7] few studies have addressed these issues among AYA cancer survivors. According to a systematic review, up to 34% of adolescent cancer survivors were diagnosed for post-traumatic stress

*Correspondence to: Prof. Dong Wook Shin, Department of Family Medicine/Supportive Care Center, Samsung Medical Center, Samsung Comprehensive Cancer Hospital, 81 Irwon-Ro, Gangnam-gu, Seoul 06351, Republic of Korea. Tel: +82.2-6190-5252; Fax: +82.2-3410-2459
E-mail: dwshin.md@gmail.com (D. W. Shin).
Prof. Juhee Cho, Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, 115 Irwon-ro, Gangnam-gu, Seoul 06355, Republic of Korea. Tel: 82-2-3410-1448; Fax: 82-2-3410-6639
E-mail: jcho@skku.edu (J. Cho).

†Co-first authors.

disorder (PTSD), 13% for clinical depression, and 8% for anxiety.[8] A recent meta-analysis of three eligible studies (out of four candidate studies) reported that AYA cancer survivors had higher odds ratios for mood disorders [1.36, 95% confidence interval (CI) 1.19-1.55] and anxiety disorders (1.16, 95% CI 1.05-1.28).[9] A recent retrospective cohort study based on administrative data in Canada reported that AYA cancer survivors experienced a higher rate of outpatient visits for psychiatric disorder (rate ratio 1.29, 95% CI 1.08-1.54) compared with matched controls, mainly due to anxiety and adjustment disorder.[10] However, this study only included AYA cancer survivors aged 15-21 years with six common cancers including lymphoma, leukemia, and sarcoma. Another retrospective study in Canada demonstrated that 61.3% of AYA cancer survivors were diagnosed with at least one of anxiety, depressive, substance use, trauma-and stressor-related, and psychotic disorders 3 years after cancer diagnosis.[11] Although few studies reported an increased risk of psychiatric disorders among AYA cancer survivors, their limitations included weak statistical power due to a relatively small population (less than a few thousand cancer survivors, which hindered subgroup analysis by cancer sites and time since cancer diagnosis),[10-14] narrow age range (such as 15-18 or 15-21 years) of survivors with childhood prevalent cancers,[10,14] and using self-reported information on psychosocial care status.[14] Few studies have compared mental health problems between cancer survivors and control groups before and after the diagnosis, despite suggestions of a genetic susceptibility to both cancer and psychiatric disorders. Only one study adjusted for previous mental health visits to compare the risk ratio of outpatient mental health visits.[10] Furthermore, none of the studies included Asian population, although cultural differences in perception of mental health issues could contribute to epidemiological variation in mental health outcomes.[15] The prevalence and expression of psychiatric disorders can vary significantly across different countries and cultures. Especially, societal attitudes toward mental health, stigma surrounding psychiatric conditions, and access to mental health care differ between Asian and other contries.[16] In fact, the International Guideline Harmonization Group regarding psychological late effects also emphasized the need for further evidence from countries other than North America and Europe.[17]

Therefore, we aimed to assess the risk of psychiatric disorders among AYA cancer survivors compared with matched controls using a large nationwide population-based cohort study in Korea, and to determine the risk of psychiatric disorders according to cancer type and time since diagnosis to help identify high-risk groups. Additionally, we attempted to confirm differences in the prevalence of psychiatric disorders before and after cancer diagnosis.

MATERIALS AND METHODS

Data sources

We carried out a retrospective population-based cohort study using data from the Korean National Health Insurance Service (K-NHIS) database. Korea has a mandatory social insurance system with premiums determined by income level and not by health status. The K-NHIS is a single insurer that covers ∼97% of the population (the remaining 3% are beneficiaries of the Medical Aid Program). Data on the use of medical facilities and prescription records with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) diagnosis codes were gathered by the NHIS; it contains information on demographics, medical treatments, procedures, prescription drugs, diagnostic codes, and hospital use. In addition, the K-NHIS claims database includes data from national health screening examinations, which is a standardized program provided to all insured persons every 2 years.[18] It includes a self-administered questionnaire on medical history and health behavior, including smoking, drinking and physical activity, anthropometric measurements, and laboratory tests.[18] The participation rate among the target population was ∼76%.[18] Vital status and cause of death were obtained from death certification collected by Statistics Korea at the Ministry of Strategy and Finance of South Korea.[19] Use of the K-NHIS database was approved by the NHIS review committee.

Study population

We considered all Korean men and women aged 15-39 years between 2006 and 2019. Data access was restricted by data share policy; we selected all patients with cancer defined as the presence of ICD-10 code C or special copayment reduction code for cancer (V193) between 2006 and 2019 and four times age and sex matched samples of men and women who did not develop cancer during the study period ($n = 3\,352\,310$). To select newly diagnosed cancer as exposure and incident case of psychiatric disorders as outcome, we excluded 199 589 participants who had any cancer ($n = 45\,732$) or any psychiatric disorders before 1 January 2006 ($n = 158\,358$).

Among the eligible participants ($n = 3\,152\,721$), we mimicked sequential emulation of the target trial (detailed methods are presented in the Statistical Analysis section). The number of cloned patients aged 15-39 years between 2006 and 2019 was 61 420 353. During the enrollment process of the new cohort, we excluded participants who had any cancer ($n = 7\,198\,384$) or a history of psychiatric disorders at baseline ($n = 148\,264$). Patients who met the eligibility criteria in the previous cohort were excluded from the next cohort if they were >40 years old, had cancer, history of any psychiatric disorder, or died before the start date of each cohort. These processes were repeated every 6 months until 1 June 2019 ($n = 54\,073\,705$). Among the participants, we generated propensity scores (PS) and the control group was selected in a 1 : 3 ratio using PS matching (control: 265 212; cancer: 88 965) (Figure 1).

The institutional review board approved the study and waived the requirement for informed consent because the K-NHIS data were de-identified (SMC 2022-03-028).

Definition of AYA cancer survivors

The main exposure was incidence of cancer between 15 and 39 years of age. To define incident cancer, we used a special

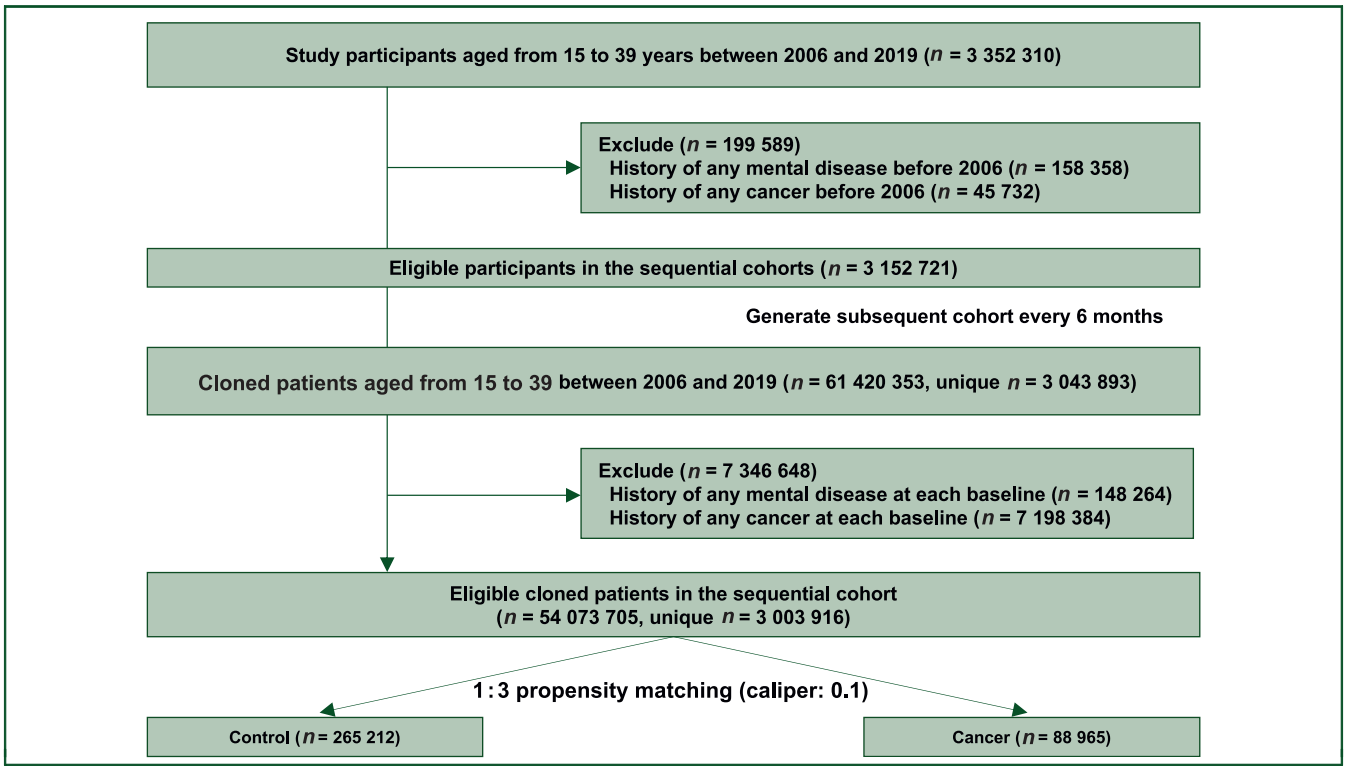

Figure 1. **Flow chart of the study population.**

registration code in addition to the ICD-10 diagnosis code. The NHIS established a special copayment reduction program to enhance health coverage and relieve the financial burden of patients with cancer. Once registered, patients pay only 5% of the total medical bills incurred for cancer-related medical care. As enrollment in this program is indicated by a special copayment reduction code for cancer (V193) and requires a medical certificate from a physician, the cancer diagnoses included in this study are considered sufficiently reliable, and this method has been used in previous studies.[20]

Study outcomes

Psychiatric disorders were identified from diagnostic records according to ICD-10 codes, either outpatient visits or hospitalization. The primary endpoint was composite outcome of major psychiatric disorders including depressive disorder (ICD10 F32, F33), anxiety disorder (ICD10 F40, F41, F4), substance use disorder (ICD10 F10, F11, F12, F13, F14, F15, F16, F17, F18, F19), bipolar disorder (ICD10 F30, F31), PTSD (ICD10 F431), and sleep disorder (ICD10 F510, G470), based on previous studies.[17]

Covariates

Age, sex, comorbidities, income, and residential area at baseline were included as covariates. Comorbidities during the year before baseline were obtained from claims data defined using ICD-10 codes. We included hypertension (with medication), which was defined as the presence of at least one I10-I13 or I15 code during the year before baseline. Income data at the time of the first screening were obtained from the insurance eligibility database. Income level was categorized by percentile groups ($\leq$30th, 31st-70th, and $>$70th percentiles).

For sensitivity analysis, we restricted patients to those who underwent health screening 2 years before baseline, and used body mass index (BMI), alcohol consumption, smoking, and exercise data from the screening examination.

Statistical analysis

To reduce selection and immortal bias, the target trial was emulated several times in a sequence of nested trials to coincide with exposure assignment and the start of follow-up.[21] Emulation of sequential trials is a valid and efficient procedure if participants meet eligibility criteria at several time points.[22] We carried out PS matching (1 : 3, caliper $<$0.1) using the variables age, sex, income, residential area, presence of comorbidities (diabetes mellitus, hypertension, and hyperlipidemia), and having health screening exam data at each cohort entry. These variables were updated based on the first date of each subsequent cohort. Balance between groups was evaluated using standardized mean difference (SMD) between the cancer and control groups with an SMD of $<$0.1 considered indicative of adequate balance (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.104101). The primary endpoint was development of psychiatric disorders. Each endpoint was analyzed separately, and only participants who had not experienced the endpoint before the cohort were included. We followed participants from the baseline of each cohort until the development of psychiatric disorders, death, or

December 2020, whichever occurred first. Finally, we pooled data from all the trials into a single model and included the day at baseline of each cohort.

To determine the peak time of psychiatric disorders in cancer survivors, we calculated the prevalence ratio (PR) of psychiatric disorders in cancer patients compared with the control group every 6 months following cancer diagnosis. In this analysis, we did not include patients who experienced incident psychiatric disorders, which allowed us to evaluate the prevalence of psychiatric disorders from the initial cancer diagnosis to 5 years after the initial incident.

The cumulative incidence of each outcome was estimated using the Kaplan–Meier method, and log-rank tests were applied to evaluate the differences between the groups. Hazard ratios (HR) with 95% CIs for the incidence of clinical outcomes were calculated using the Cox regression model. We examined the proportional hazards assumption using plots of the log–log survival function and Schoenfeld residuals.

For subgroup analysis, we analyzed the incidence of psychiatric disorders according to cancer type, age at diagnosis, and type of treatment. The control group consisted of all participants without cancer at baseline. These subgroup analyses were exploratory analyses to generate hypotheses. Thus, strict control for multiple testing was not carried out.

For sensitivity analysis, (i) we carried out a landmark analysis at 1, 3, and 5 years after cancer diagnosis to evaluate the incidence of psychiatric disorders by time since cancer diagnosis; (ii) to account for competing risks due to mortality, we fitted a proportional sub-distribution hazards regression model[23] with death as the competing event; and (iii) we conducted a sensitivity analysis of participants who underwent a health screening exam. We further adjusted for confounding factors, such as BMI, alcohol consumption, and smoking. The proportional hazards assumption for the competing risks model was also assessed using Schoenfeld residuals, and we found no significant violations of proportionality.

All P values were two-sided, and a P value < 0.05 was considered significant. Analyses were carried out using SAS® Visual Analytics (SAS Institute Inc., Cary, NC) and R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Baseline characteristics (N = 354 177)

	Cancer	Control	SMD
	n = 88 965	n = 265 212	
Age at cancer diagnosis, year [mean (SD)]	32.2 (6.3)	32.2 (6.1)	0.009
Age group, years, n (%)			
15-19	5622 (6.3)	14 870 (5.6)	0.03
20-29	18 475 (20.8)	56 950 (21.5)	−0.017
30-39	64 868 (72.9)	193 392 (72.9)	0.000
Sex, n (%)		—	−0.05
Male	34 356 (38.6)	103 062 (38.9)	
Female	54 609 (61.4)	162 150 (61.1)	
Income, n (%)			
Medical aid	1543 (1.7)	4471 (1.7)	0.004
≤30th	18 785 (21.1)	56 024 (21.1)	0.000
31st-70th	37 845 (42.5)	111 587 (42.1)	0.009
>70th	29 080 (32.7)	87 981 (33.2)	−0.010
Residential area, n (%)			
Rural	25 756 (29.0)	77 189 (29.1)	−0.003
Metropolitan	61 497 (69.1)	182 874 (69.0)	0.004
Comorbidities, n (%)			
Diabetes mellitus, yes	3503 (3.9)	10 349 (3.9)	0.002
Hypertension, yes	5005 (5.6)	14 806 (5.6)	0.002
Hyperlipidemia, yes	7301 (8.2)	21 904 (8.3)	−0.002
Cancer type, n (%)			
Breast	16 943 (19.0)	NA	
Stomach	8726 (9.8)	NA	
Cervix	7546 (8.5)	NA	
Colon/rectal	7140 (8.0)	NA	
Leukemia	6014 (6.8)	NA	
Non-Hodgkin lymphoma	5553 (6.2)	NA	
Brain	4566 (5.1)	NA	
Ovary	4327 (4.9)	NA	
Kidney	2762 (3.1)	NA	
Liver	2666 (3.0)	NA	
Head and neck	2296 (2.6)	NA	
Uterine	2105 (2.4)	NA	
Testis	1955 (2.2)	NA	
Lung	1771 (2.0)	NA	
Hodgkin lymphoma	1133 (1.3)	NA	
Bladder	858 (1.0)	NA	
Pancreas	783 (0.9)	NA	
Gall-bladder	266 (0.3)	NA	
Multiple myeloma	147 (0.2)	NA	
Larynx	66 (0.1)	NA	
Esophagus	54 (0.1)	NA	
Prostate	51 (0.1)	NA	
Other and unspecified	11 237 (12.6)	NA	
Treatment modality, n (%)			
Surgery	33 151 (37.3)	NA	
Chemotherapy	44 354 (49.9)	NA	
Radiotherapy	26 694 (30.3)	NA	
Stem cell transplant	2968 (3.3)	NA	

NA, non-applicable; SMD, standardized mean difference.

RESULTS

The mean age of study participants was 32.2 years and 39% were men (Table 1). At baseline, most cancer survivors were aged 30-39 years (72.9%), and breast cancer was the most common (19.0%). All SMDs of difference between the control and cancer groups were <0.1 (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.104101).

Prevalence ratios

There was no difference in the PRs of psychiatric disorders between AYA patients with cancer and the control group before cancer diagnosis; however, the prevalence sharply increased after cancer diagnosis. The risk of developing any psychiatric disorders after cancer diagnosis was higher in the first 6 months (PR 2.50, 95% CI 2.42-2.58), although it persisted throughout the duration of follow-up (Figure 2A). Overall, sleep disorders were the most prevalent problem in these patients compared with the control group (Figure 2B). For PTSD, the PR of the cancer group increased over time compared with that of the control group (Figure 2B).

Risk of psychiatric disorders

During follow-up (median 6.5 years), 37 924 control and 16 909 AYA cancer survivors developed a psychiatric

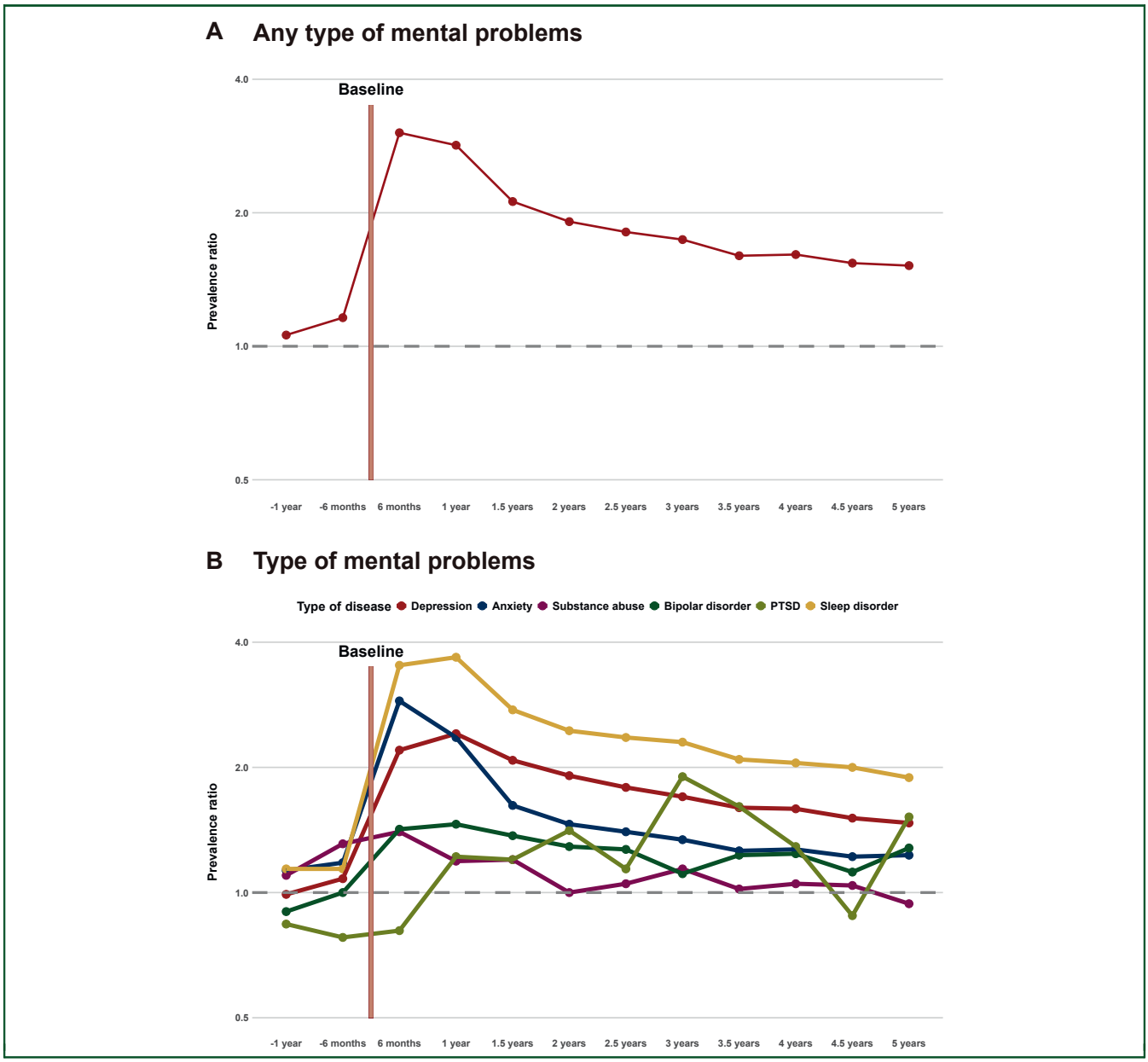

Figure 2. Prevalence ratio of adolescents and young adults for (A) any type of psychiatric disorders and (B) type of psychiatric disorders compared with the control group before and after cancer diagnosis.
PTSD, post-traumatic stress disorder.

disorder, corresponding to 2.0 and 3.3 cases per 100 person-years, respectively. The median time to onset of a psychiatric disorder was 2.6 years (interquartile range 1.0-5.6 years) since cancer diagnosis. Among the psychiatric disorders, anxiety disorder (1.5 cases per 100 person-years) was the most frequent followed by depressive and sleep disorders (Table 2). The fully adjusted HR for overall incident psychiatric disorders among AYA cancer survivors compared with the control group was 1.64 (95% CI 1.61-1.67), and it persisted after competing risks due to mortality were considered [sub-distribution HR (sub-HR) 1.42, 95% CI 1.39-1.45, Table 2]. Sleep disorder had the highest relative risk compared with the control group (sub-HR 1.71, 95% CI 1.67-1.77). Anxiety (sub-HR 1.16, 95% CI 1.13-1.19) and depressive disorders (sub-HR 1.40, 95% CI 1.30-1.50) were also statistically significantly elevated in AYA cancer survivors compared with the control group (Table 2).

Among those who survived at least 5 years, AYA cancer survivors had a statistically significant higher risk of alcohol abuse (sub-HR 1.14, 95% CI 1.00-1.31), opioid abuse (sub-HR 8.99, 95% CI 3.18-25.44), and sedative/hypnotic abuse (sub-HR 1.67, 95% CI 1.05-2.68, Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104101).

Subgroup analysis

Among the subgroups by age at diagnosis, patients diagnosed at an older age experienced an increased risk of developing any psychiatric disorders compared with patients diagnosed at a younger age (Table 3).

Table 2. Hazard ratio (95% confidence intervals) for incident psychiatric disorders associated with cancer ($N = 354\,177$)

	No. of case (100 person-year)		Adjusted HR[a] (95% CI)	Sub-HR[b] (95% CI)
	Control, *n* (%)	Cancer, *n* (%)		
Overall psychiatric disorders	37 824 (2.0)	16 909 (3.3)	1.64 (1.61-1.67)	1.42 (1.39-1.45)
Type of psychiatric disorders				
Depressive disorder	16 204 (0.8)	7333 (1.3)	1.63 (1.59-1.68)	1.40 (1.30-1.50)
Anxiety disorder	22 001 (1.1)	8328 (1.5)	1.35 (1.32-1.39)	1.16 (1.13-1.19)
Substance use disorder	2272 (0.1)	701 (0.1)	1.13 (1.04-1.23)	0.93 (0.86-1.02)
Bipolar disorder	1843 (0.1)	807 (0.1)	1.57 (1.45-1.71)	1.33 (1.23-1.45)
Post-traumatic stress disorder	303 (0.0)	103 (0.0)	1.21 (0.97-1.51)	1.03 (0.82-1.29)
Sleep disorder	12 878 (0.6)	7106 (1.3)	1.98 (1.92-2.04)	1.71 (1.67-1.77)

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, residential area, income, diabetes mellitus, hypertension, and hyperlipidemia.
[b]Sub-distribution hazard ratios for events were modeled with mortality as a competing risk.

When we stratified by type of treatment, patients treated with surgery only had the lowest relative risk than the control group (HR 1.31, 95% CI 1.26-1.36) compared with those in patients treated with combination of surgery, chemotherapy, and radiotherapy (HR 2.80, 95% CI 2.63-2.97, Table 3). However, AYA cancer survivors had a consistently higher risk of psychiatric disorder than the control group regardless of treatment type.

The association between cancer and any psychiatric disorder was consistent across all cancer types (Supplementary Figure S3A, available at https://doi.org/10.1016/j.esmoop.2024.104101). Particularly, those with esophagus (HR 3.83, 95% CI 2.35-6.26), lung (HR 2.44, 95% CI 2.18-2.73), pancreas (HR 2.21, 95% CI 1.83-2.66), breast (HR 2.12, 95% CI 2.05-2.19), multiple myeloma (HR 2.06, 95% CI 1.44-2.95), and brain (HR 2.01, 95% CI 1.89-2.15) cancer had two times more risk of psychiatric disorders compared with the control group. This association was also consistent in all types of cancers among 5-year survivors (Supplementary Figure S3B, available at https://doi.org/10.1016/j.esmoop.2024.104101). Specifically, those with esophagus cancer (HR 3.68, 95% CI 1.53-8.83) had two times more risk of psychiatric disorders compared with the control group. Although the effect size decreased, the risk of psychiatric disorders in the larynx, multiple myeloma, cervical, and lung cancer groups remained higher than that in the control group.

Table 3. Hazard ratio (95% confidence intervals) for incident psychiatric disorders associated with cancer by clinical characteristics ($N = 354\,177$)

	Adjusted HR[a] (95% CI)	Sub-HR[b] (95% CI)
Age at cancer diagnosis, years		
15-19 ($n = 5622$)	1.46 (1.35-1.58)	1.24 (1.14-1.34)
20-29 ($n = 18\,475$)	1.57 (1.50-1.63)	1.34 (1.29-1.40)
30-39 ($n = 64\,868$)	1.69 (1.65-1.72)	1.46 (1.43-1.49)
Type of treatment		
Surgery only ($n = 16\,887$)	1.31 (1.26-1.36)	1.28 (1.23-1.33)
Surgery + chemotherapy ($n = 9257$)	1.99 (1.90-2.09)	1.53 (1.46-1.61)
Surgery + radiotherapy ($n = 1906$)	1.69 (1.52-1.89)	1.56 (1.39-1.75)
Surgery + chemotherapy + radiotherapy ($n = 5107$)	2.80 (2.63-2.97)	2.06 (1.93-2.20)
Chemotherapy only ($n = 15\,757$)	1.89 (1.82-1.96)	1.39 (1.33-1.44)
Radiotherapy only ($n = 5448$)	1.51 (1.42-1.61)	1.36 (1.28-1.45)
Chemotherapy + radiotherapy ($n = 14\,233$)	2.24 (2.16-2.32)	1.72 (1.64-1.80)

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, sex, residential area, income, diabetes mellitus, hypertension, and hyperlipidemia.
[b]Sub-distribution hazard ratios for events were modeled with mortality as a competing risk.

Sensitivity analysis

Among 5-year (at least) survivors, the fully adjusted HR for incidence of any psychiatric disorders between the AYA cancer and control groups was 1.14 (95% CI 1.10-1.18, Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.104101). Among the 5-year survivors, the risk of depression, anxiety, bipolar disorder, and sleep disorders in the cancer group showed a decreasing trend over time, but the risk of substance abuse and PTSD increased over time.

There were no significant differences in BMI, smoking status, drinking status, or physical activity between AYA cancer survivors and controls (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.104101). After adjusting for lifestyle covariates, the results remained consistent with the main findings (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.104101).

DISCUSSION

This large, nationwide, retrospective cohort study provides concurrent evidence to existing literature on the risk of psychiatric disorders among AYA cancer survivors. Our large study population enabled us to confirm the sensitivity of various subgroup analyses (such as by cancer site and age at cancer diagnosis). In addition, a comparison of the time sequence before and after cancer diagnosis could suggest a trend in risk of psychiatric disorders. Before cancer diagnosis, there was no significant difference between cancer survivors and the control group, but the PR sharply increased in the first 6 months after cancer diagnosis and persisted throughout the follow-up period. We found that AYA cancer survivors had a 42% higher risk of psychiatric disorders compared with matched controls, and they had the highest incidence of anxiety disorders, followed by

depressive and sleep disorders. The risk of psychiatric disorders showed a decreasing trend over time since cancer diagnosis, whereas there was an increasing trend in substance abuse and PTSD.

Our study revealed that the increased risk of psychiatric disorders in the AYA cancer group tended to decrease over time after cancer diagnosis. In the first year after cancer diagnosis, anxiety and depression could be common reactions to the diagnosis in itself, the process of diagnosis, staging, histology testing, stressful waiting periods for the results, and anticipated side-effects of intensive anticancer treatment.[24] A recent meta-analysis also provided a downward trajectory of depressive and anxiety symptoms 1 year after cancer diagnosis, consistent with our findings.[25] This study explained that such amelioration may be related to post-traumatic growth and maturity. However, despite this decrease, the higher risk of psychiatric disorders still persisted over time among AYA cancer survivors. In contrast, the risk of PTSD and substance use disorder showed an increasing trend over time, even though the PR of PTSD was lower than that in controls during the first year of cancer diagnosis. Being diagnosed with cancer and active cancer treatment might act as traumatic events,[26] and although it may not be as evident as an acute traumatic event such as car crash, patients can chronically suffer from stress due to fear of recurrence, follow-up visits and test, and physical late effects even 5 years after cancer diagnosis.[27] We found a higher risk of substance use disorders mainly due to alcohol, opioids abuse, sedatives, or hypnotics abuse that is consistent with previous studies.[28,29] Notably, younger cancer survivors had higher rates of opioid misuse.[29] According to a recent survey, opioid use in AYA cancer survivors is attributed to physical pain.[28] This reflects the need for chronic pain control, and recent cancer survivors are more likely to have acute physical symptoms related to cancer treatment and start prescription opioids during early cancer trajectory.

The risk of psychiatric disorders varies with age at the time of cancer diagnosis. We found that young adult cancer survivors (aged 20-39 years) had a higher risk of psychiatric disorders than adolescent cancer survivors (aged 15-19 years). Most studies reported that cancer diagnosis at younger age is associated with higher risk of psychiatric disorders than at older age,[24,30] but these studies were conducted among adult cancer survivors (median age 59 years).[24] Increased disruption of daily life in younger cancer patients might be a potential reason because older patients may already have impairments in physical and cognitive function.[24] Within the AYA age group, the risk of psychiatric disorders by age at cancer diagnosis was rarely evaluated; our findings may be related to different developmental tasks according to age. Young adult cancer survivors face additional social burdens compared with adolescent cancer survivors including disruptions in family and marital relationships, concerns about raising children, work-related challenges, and financial issues.[31]

In subgroup analysis by type of treatment, patients with more severe treatment had relatively much higher risk of psychiatric disorder than the control group. These results were consistent with previous studies in that patients who received all three modalities (chemotherapy, radiotherapy, and surgery) had the highest cumulative burden of psychiatric disorders.[32] According to the type of cancer, the highest risk of psychiatric disorders was consistently observed among AYA survivors of esophageal cancer, followed by those with lung and cervical cancers. A relatively poor prognosis and substantial physical impairment related to cancer treatment can have a detrimental impact on mental health. A poor 5-year survival rate of esophageal cancer (∼33.4% in 2013 in Korea),[33] and prolonged physical effects after esophagectomy, such as muscle loss and difficulty in food intake, negatively affect emotional well-being and health-related quality of life.[34] Certain cancers such as lung and cervical cancer might be associated with stigma due to well-established risk factors (such as cigarette smoking and sexually transmitted human papillomavirus),[35,36] even though genetic factors are largely responsible for cancer incidence in the AYA age group. Social perceptions that cancer survivors' unhealthy lifestyle has brought about their disease might be related to their feelings of guilt and blame. However, less common cancer types may limit the precision of our estimates due to a small sample size. Thus, the findings for less common cancers should be interpreted cautiously, and further study should be conducted.

Our findings indicate the importance of mental health screening and management, particularly in high-risk groups. Co-existing psychiatric disorders among AYA cancer survivors affect treatment compliance as well as health-related quality of life.[37] Ultimately, cancer survivors who have their first episode of psychiatric disorders after cancer diagnosis may have an increased risk of cancer-specific mortality.[38] Accordingly, our findings support the international clinical practice guidelines that strongly recommend regular mental health surveillance for AYA cancer survivors at every visit.[17] We demonstrated that the risk of psychiatric disorders among Asian AYA cancer survivors follows a pattern similar to that in the Western population. However, although the relative risk is much higher (1.64 versus 1.29), the incidence rate was lower (3.3 versus 67 per 100 person-years) than in the previous study.[10,11] The lower incidence of psychiatric disorders in our data might be related to the higher mental health stigma and the relatively lower utilization of mental health services in Korea.[39] Our findings suggest that mental health interventions need to be adapted to cultural contexts. Global mental health strategies should incorporate culturally sensitive approaches to effectively reach AYA cancer survivors. Policies that reduce stigma and improve access to mental health services are critical to ensuring equitable care for diverse populations. Future studies should focus on cross-country comparative analyses to further explore cultural influences on psychiatric outcomes in cancer survivors.

This study showed consistent results through several sensitivity analyses, which reinforce our findings. However, there are several limitations. Firstly, we could not capture

the history of consultation with a psychologist, because it is not covered by national insurance. Additionally, differences in the utilization of medical facilities between AYA cancer survivors and controls could potentially contribute to the disparity in the risk of mental health problems between the two groups. However, universal health coverage in Korea ensures that patients have good access to health care services. Secondly, clinical information on cancer (such as cancer stage and recurrence) was not available because of the use of claims data. Thirdly, we did not specify the difference by treatment modality, even though specific treatments could increase the risk of psychiatric disorders (e.g. cranial irradiation).[40]

In conclusion, AYA cancer survivors are at an increased risk of psychiatric disorders such as anxiety, depression, and sleep disorders, compared with the matched control group across various cancer types, despite the non-significant difference in prevalence before cancer diagnosis. Our findings suggest that AYA cancer survivors may require long-term psychological support following their cancer diagnosis and health care providers should prioritize screening of common psychiatric disorders among AYA cancer survivors.

FUNDING

This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government [grant number NRF-2022R1A2C1013119] and the Institution of Quality of Life in Cancer funded by Samsung Fire & Marine Insurance. The funding source did not involve in the study design, analysis and interpretation of data, writing of the report, and the decision to submit the article for publication.

DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

The data from the Korean National Health Insurance Service (NHIS) can be accessed via the Health Insurance Data Service website (http://nhiss.nhis.or.kr). However, researchers should submit a study proposal for approval from each institutional review board, which is reviewed by the NHIS review committee, to access the database. The raw data cannot be retrieved from the NHIS server.

REFERENCES

1. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin*. 2020;70(6):443-459.
2. Wen YF, Chen MX, Yin G, et al. The global, regional, and national burden of cancer among adolescents and young adults in 204 countries and territories, 1990-2019: a population-based study. *J Hematol Oncol*. 2021;14(1):89.
3. Keegan TH, Ries LA, Barr RD, et al. Comparison of cancer survival trends in the United States of adolescents and young adults with those in children and older adults. *Cancer*. 2016;122(7):1009-1016.
4. Kaul S, Avila JC, Mutambudzi M, Russell H, Kirchhoff AC, Schwartz CL. Mental distress and health care use among survivors of adolescent and young adult cancer: a cross-sectional analysis of the National Health Interview Survey. *Cancer*. 2017;123(5):869-878.
5. Frederiksen LE, Erdmann F, Mader L, et al. Psychiatric disorders in childhood cancer survivors in Denmark, Finland, and Sweden: a register-based cohort study from the SALiCCS research programme. *Lancet Psychiatry*. 2022;9(1):35-45.
6. Abdalla T, Preen DB, Pole JD, et al. Psychiatric disorders in childhood cancer survivors: a retrospective matched cohort study of inpatient hospitalisations and community-based mental health services utilisation in Western Australia. *Aust N Z J Psychiatry*. 2024;58(6):515-527.
7. Hsu TW, Liang CS, Tsai SJ, et al. Risk of major psychiatric disorders among children and adolescents surviving malignancies: a nationwide longitudinal study. *J Clin Oncol*. 2023;41(11):2054-2066.
8. Pineles BL, Hsu S, Park E, Samet JM. Systematic review and meta-analyses of perinatal death and maternal exposure to tobacco smoke during pregnancy. *Am J Epidemiol*. 2016;184(2):87-97.
9. De R, Zabih V, Kurdyak P, et al. Psychiatric disorders in adolescent and young adult-onset cancer survivors: a systematic review and meta-analysis. *J Adolesc Young Adult Oncol*. 2020;9(1):12-22.
10. De R, Sutradhar R, Kurdyak P, et al. Incidence and predictors of mental health outcomes among survivors of adolescent and young adult cancer: a population-based study using the IMPACT cohort. *J Clin Oncol*. 2021;39(9):1010-1019.
11. Rosgen BK, Moss SJ, Fiest KM, et al. Psychiatric disorder incidence among adolescents and young adults aged 15-39 with cancer: population-based cohort. *JNCI Cancer Spectr*. 2022;6(6):pkac077.
12. Ahomäki R, Gunn ME, Madanat-Harjuoja LM, Matomäki J, Malila N, Lähteenmäki PM. Late psychiatric morbidity in survivors of cancer at a young age: a nationwide registry-based study. *Int J Cancer*. 2015;137(1):183-192.
13. Deyell RJ, Lorenzi M, Ma S, et al. Antidepressant use among survivors of childhood, adolescent and young adult cancer: a report of the Childhood, Adolescent and Young Adult Cancer Survivor (CAYACS) Research Program. *Pediatr Blood Cancer*. 2013;60(5):816-822.
14. Dieluweit U, Seitz DC, Besier T, et al. Utilization of psychosocial care and oncological follow-up assessments among German long-term survivors of cancer with onset during adolescence. *Klin Padiatr*. 2011;223(3):152-158.
15. Gopalkrishnan N. Cultural diversity and mental health: considerations for policy and practice. *Front Public Health*. 2018;6:179.
16. Lemon CA, Svob C, Bonomo Y, et al. Priorities for research promoting mental health in the south and east of Asia. *Lancet Reg Health Southeast Asia*. 2024;23:100287.
17. Marchak JG, Christen S, Mulder RL, et al. Recommendations for the surveillance of mental health problems in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol*. 2022;23(4):e184-e196.
18. Cheol Seong S, Kim YY, Khang YH, et al. Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. *Int J Epidemiol*. 2017;46(3):799-800.
19. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol*. 2017;46(2):e15.
20. Yoo JE, Shin DW, Han K, et al. Association of the frequency and quantity of alcohol consumption with gastrointestinal cancer. *JAMA Netw Open*. 2021;4(8):e2120382.
21. García-Albéniz X, Hsu J, Bretthauer M, Hernán MA. Effectiveness of screening colonoscopy to prevent colorectal cancer among Medicare beneficiaries aged 70 to 79 years: a prospective observational study. *Ann Intern Med*. 2017;166(1):18-26.
22. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;79:70-75.
23. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
24. Linden W, Vodermaier A, MacKenzie R, Greig D. Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. *J Affect Disord*. 2012;141(2):343-351.

25. Lee ARYB, Yau CE, Low CE, Li J, Ho RCM, Ho CSH. Severity and longitudinal course of depression, anxiety and post-traumatic stress in paediatric and young adult cancer patients: a systematic review and meta-analysis. *J Clin Med*. 2023;12(5):1784.
26. Cordova MJ, Riba MB, Spiegel D. Post-traumatic stress disorder and cancer. *Lancet Psychiatry*. 2017;4(4):330-338.
27. Leano A, Korman MB, Goldberg L, Ellis J. Are we missing PTSD in our patients with cancer? Part I. *Can Oncol Nurs J*. 2019;29(2):141-146.
28. Ji X, Cummings JR, Mertens AC, Wen H, Effinger KE. Substance use, substance use disorders, and treatment in adolescent and young adult cancer survivors—results from a national survey. *Cancer*. 2021;127(17):3223-3231.
29. Jairam V, Yang DX, Verma V, Yu JB, Park HS. National patterns in prescription opioid use and misuse among cancer survivors in the United States. *JAMA Netw Open*. 2020;3(8):e2013605.
30. Kornblith AB, Powell M, Regan MM, et al. Long-term psychosocial adjustment of older vs younger survivors of breast and endometrial cancer. *Psychooncology*. 2007;16(10):895-903.
31. Naughton MJ, Weaver KE. Physical and mental health among cancer survivors: considerations for long-term care and quality of life. *N C Med J*. 2014;75(4):283-286.
32. Chang WH, Lai AG. Cumulative burden of psychiatric disorders and self-harm across 26 adult cancers. *Nat Med*. 2022;28(4):860-870.
33. Park SY, Kim DJ. Esophageal cancer in Korea: epidemiology and treatment patterns. *J Chest Surg*. 2021;54(6):454-459.
34. Taioli E, Schwartz RM, Lieberman-Cribbin W, Moskowitz G, van Gerwen M, Flores R. Quality of life after open or minimally invasive esophagectomy in patients with esophageal cancer—a systematic review. *Semin Thorac Cardiovasc Surg*. 2017;29(3):377-390.
35. Ostroff JS, Riley KE, Shen MJ, Atkinson TM, Williamson TJ, Hamann HA. Lung cancer stigma and depression: validation of the lung cancer stigma inventory. *Psychooncology*. 2019;28(5):1011-1017.
36. Shepherd MA, Gerend MA. The blame game: cervical cancer, knowledge of its link to human papillomavirus and stigma. *Psychol Health*. 2013;29(1):94-109.
37. Wang Y-H, Aggarwal A, Stewart R, Davies EA. Impact of pre-existing mental health disorders on the receipt of guideline recommended cancer treatments: a systematic review. *Psychooncology*. 2023;32(3):307-330.
38. Zhu J, Fang F, Sjölander A, Fall K, Adami HO, Valdimarsdóttir U. First-onset mental disorders after cancer diagnosis and cancer-specific mortality: a nationwide cohort study. *Ann Oncol*. 2017;28(8):1964-1969.
39. Jang J, Lee SA, Kim W, Choi Y, Park EC. Factors associated with mental health consultation in South Korea. *BMC Psychiatry*. 2018;18(1):17.
40. Friend AJ, Feltbower RG, Hughes EJ, Dye KP, Glaser AW. Mental health of long-term survivors of childhood and young adult cancer: a systematic review. *Int J Cancer*. 2018;143(6):1279-1286.