uicc global cancer control

IJC
International Journal of Cancer

Impact of prior cancer history on the overall survival of patients newly diagnosed with cancer: A pan-cancer analysis of the SEER database

Huaqiang Zhou [1,2]*, Yan Huang[1]*, Zeting Qiu[1,2]*, Hongyun Zhao[3]*, Wenfeng Fang[1], Yunpeng Yang[1], Yuanyuan Zhao[1], Xue Hou[1], Yuxiang Ma[3], Shaodong Hong[1], Ting Zhou[1], Yaxiong Zhang[1] and Li Zhang [1]

[1] Department of Medical Oncology, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

[2] Zhongshan School of Medicine, Sun Yat-Sen University, Guangzhou, Guangdong, China

[3] Department of Clinical Research, Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

The population of cancer survivors with prior cancer is rapidly growing. Whether a prior cancer diagnosis interferes with outcome is unknown. We conducted a pan-cancer analysis to determine the impact of prior cancer history for patients newly diagnosed with cancer. We identified 20 types of primary solid tumors between 2004 and 2008 in the Surveillance, Epidemiology, and End Results database. Demographic and clinicopathologic variables were compared by χ^2 test and *t*-test as appropriate. The propensity score-adjusted Kaplan-Meier method and Cox proportional hazards models were used to evaluate the impact of prior cancer on overall survival (OS). Among 1,557,663 eligible patients, 261,474 (16.79%) had a history of prior cancer. More than 65% of prior cancers were diagnosed within 5 years. We classified 20 cancer sites into two groups (PCI and PCS) according to the different impacts of prior cancer on OS. PCI patients with a prior cancer history, which involved the colon and rectum, bone and soft tissues, melanoma, breast, cervix uteri, corpus and uterus, prostate, urinary bladder, kidney and renal pelvis, eye and orbits, thyroid, had inferior OS. The PCS patients (nasopharynx, esophagus, stomach, liver, gallbladder, pancreas, lung, ovary and brain) with a prior cancer history showed similar OS to that of patients without prior cancer. Our pan-cancer study presents the landscape for the survival impact of prior cancer across 20 cancer types. Compared to the patients without prior cancer, the PCI group had inferior OS, while the PCS group had similar OS. Further studies are still needed.

The cancer survivor population is rapidly growing and has shown approximately fourfold growth in the United States over the past 30 years.[1] Almost two-thirds of all survivors have lived beyond 5 years after the initial diagnosis.[1] These improvements have caused an increased prevalence of multiple primary cancer.[2] One-fourth of older adults and >10% of younger adults diagnosed with incident cancer in the United States have a history of prior cancer.[3]

Key words: prior cancer, survival, clinical trial, SEER, outcome, pan-cancer

Additional Supporting Information may be found in the online version of this article.

Conflict of interest: The authors declare that they have no potential conflicts of interest.

L.Z., Y.Z., H.Z., Z.Q. were responsible for the conception and design of the study, interpretation of data, drafting, and writing of the article. Y.H., H.Z., W.F., Y.Y., Y.Z., X.H., Y.M., S.H. and T.Z. were responsible for interpretation of data and revision of the intellectual content. All authors participated in final approval of the article and agreed to be accountable for all aspects of the work

*H.Z., Y.H., Z.Q., and H.Z. contributed equally to this work

Grant sponsor: National Key R&D Program of China; **Grant numbers:** 2016YFC0905500 and 2016YFC0905503; **Grant sponsor:** Science and Technology Program of Guangdong; **Grant numbers:** 2017B020227001 and 2016A020215084; **Grant sponsor:** Science and Technology Program of Guangzhou; **Grant numbers:** 201607020031 and 201400000001-2; **Grant sponsor:** Chinese National Natural Science Foundation project; **Grant numbers:** 81772476, 81572659, and 81602011; **Grant sponsor:** Pearl River Nova Program of Guangzhou; **Grant number:** 201610010048; **Grant sponsor:** National Natural Science Funds for Young Scholars of China; **Grant number:** 81502355

DOI: 10.1002/ijc.31543

History: Received 19 Jan 2018; Accepted 28 Mar 2018; Online 18 Apr 2018

Correspondence to: Yaxiong Zhang, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, People's Republic of China, Tel.: +86-20-87343458, Fax: +86-20-87343535, E-mail: zhangyx@sysucc.org.cn or Li Zhang, Department of Medical Oncology, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, People's Republic of China, Tel.: +86-20-87343458, Fax: +86-20-87343535, E-mail: zhangli6@mail.sysu.edu.cn

What's new?

Prior cancer history often excludes patients from cancer clinical trials. However, whether a prior cancer diagnosis actually interferes with study outcomes is still unknown. In this study, the authors analyzed 20 different cancer types. These cancers fell into two categories: "prior cancer inferior" (PCI), in which patients had lower survival rates than those without prior cancer; and "prior cancer similar" (PCS), in which survival rates were similar. Almost half of the cancer types were PCS. These results suggest that not all prior cancers must be excluded from clinical trials.

Clinical trials are essential for improving their survivorship. However, prior cancer history is one of the most commonly used exclusion criteria in cancer clinical trials, due to concerns about survival impact and prior treatment interference. Given the sizable number of patients with a history of prior cancer, this exclusion criterion may further limit the accrual and generalizability of trials. For instance, over 80% of lung cancer trials sponsored by the Eastern Cooperative Oncology Group (ECOG) have adopted this exclusion criterion.[4] Such a restrictive criterion may unconditionally exclude up to 18% of lung cancer patients from participating in trials.[4] This practice is mainly based on a long-held belief that a prior cancer diagnosis will interfere with study outcomes. However, the validity of this criterion has been barely validated. Until recently, there have been no data that clearly support this assumption for many common cancer types. Notably, Gerber *et al.* found that prior cancer did not adversely impact clinical outcomes in lung cancer trials, most of which used a 5-year prior cancer exclusion window.[3,5,6]

To address these assumptions, we aimed to conduct a pan-cancer analysis to determine the impact of prior cancer history for patients newly diagnosed with cancer, using the Surveillance, Epidemiology, and End Results (SEER) database.

Material and Methods

The SEER program of the National Cancer Institute provides authoritative information on cancer statistics, which covers approximately 30% of the population in the United States (https://seer.cancer.gov/).[7] We extracted data from the SEER database by using the SEER*Stat software version 8.3.4 (accession number: 13693-Nov 2015).[8] We retrieved all records of patients diagnosed with cancers from January 2004 to December 2008. The year 2004 was selected as the first year of the study given that several employed covariates were introduced in SEER in 2004 (American Joint Committee on Cancer: AJCC Staging Manual, 6th edition, http://www.cancerstaging.org).[9] We used International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) Site Recode to identify 20 types of primary solid tumors, including tumors of the nasopharynx, esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, lung and bronchus, bones, joints and soft tissue, melanoma, breast, cervix uteri, corpus and uterus, ovary, prostate, urinary bladder, kidney and renal pelvis, eye and orbit, brain and other nervous system, and thyroid. The exclusion criteria were as follows: (*i*) age at diagnosis younger than 18 years; (*ii*) patients with incomplete survival data and follow-up information; and (*iii*) patients with only autopsy or death certificate records.

We extracted demographic and clinicopathological data, including sex, age, race, marital status, pathology grade, extent of disease, TNM stage, surgery, and radiotherapy, from SEER database. Race was divided into white, black and others. We classified patients as married or unmarried. According to the SEER staging system, disease extension was categorized as localized, regional and distant. The TNM stage was based on the AJCC (6th edition) staging system. The survival data were available in the measurement unit of months, without precise days. Considering the preconditions that no precise survival days were available and that patients with only autopsy or death certificate records were excluded, a survival time of 0 month was recorded as 0.5 months to include patients who died within 1 month of diagnosis but who did not reach the 1-month threshold.[10]

A history of prior cancer was determined from SEER sequence numbers, which indicated the sequence of all primary reportable neoplasms over the lifetime of the patient. The sequence number assigned was "00" when a patient had only one primary cancer. For persons with multiple neoplasms during their lifetimes, the sequence number is "01" for the first cancer, "02" for the second cancer, and so on. We also calculated the timing of the prior cancers using the SEER diagnosis dates of the index cancer and the most recent of any prior cancers. Notably, some prior cancer records may not be registered in the SEER database. These cases accounted for approximately 22% of cases according to our research, so their timing remained uncalculated. The prior cancers with full timing records were used for further study.

The primary outcome of this study was overall survival (OS). OS was defined as the time from diagnosis to the date of death. Patients who were still alive at the follow-up cutoff date were treated as censored observations. We set December 31, 2013 as the follow-up cutoff date to ensure that all included cases (diagnosed at 2004–2008) were followed up for at least 5 years.

For each cancer type, we split patients into two groups based on prior cancer history. Differences in patients' characteristics were assessed by Pearson χ^2 analysis for categorical variables and *t*-test for continuous variables as appropriate. Propensity scores were constructed to minimize the effect of confounding from differences in baseline characteristics

between patients with and without a prior cancer diagnosis. In this study, propensity scores were estimated based on race, sex, age, marital status, TNM stage, pathologic grade, and treatment.[11] Specifically, age is a major confounder for OS, so we matched cases according to age as a continuous variable, rather than by directly dividing cases into two groups according to the mean age. A one-to-one propensity score matching (PSM) with a caliper of 0.2 was performed. The characteristics of the PSM cohort were then compared to ensure that the two groups were balanced. The score-matched pairs were used in subsequent analyses. OS was calculated with the Kaplan-Meier method, and differences between patients with and without a prior cancer history were compared using log-rank tests. Kaplan-Meier curves were also constructed according to the timing of the prior cancer diagnosis and index cancer stage. Finally, we built a multivariate Cox proportional hazards model to identify whether prior cancer impacted the prognosis independently. The common demographic and clinicopathological data, including race, sex, age, marital status, TNM stage, pathologic grade and treatment (radiation and surgery), were entered as covariates. We routinely assessed the proportional hazards assumption and found that the assumption was not met.[12] This issue is common in large dataset analyses because of how easily small departures are detected in a large dataset.[13,14] To investigate the impact of this violation of the assumption, we further included the time-dependent coefficients into the Cox models, by generating time interaction for covariates.[15] Finally, the hazard ratio, demonstrating the impact of prior cancer history was stable with only a subtle change. Statistical significance was set as a two-sided $p < 0.05$. All statistical analyses were performed using R version 3.4.2 software (Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org).

Results

This retrospective study included a total of 1,557,663 eligible patients with cancers diagnosed from 2004 to 2008 in the SEER database. Among these cases, 261,474 (16.79%) had a history of prior cancer. Table 1 shows the proportions of patients with a prior cancer history in terms of the 20 different cancer types. The prevalence of prior cancer ranged from 6.58% to 25.58% according to the cancer type. Patients with the highest prevalence of prior cancer had cancers of the urinary bladder (25.58%); lung and bronchus (21.72%); melanoma (21.61%); kidney and renal pelvis (21.14%); esophagus (20.31%); and colon and rectum (19.08%). All covariables were balanced between groups after the adjustment for propensity scores. There were 200,707 patients (76.76%) with an accurately diagnosed time of prior cancer recorded in the SEER database. More than 65% of prior cancers were diagnosed within 5 years. The time of prior cancer to the time of the newly diagnosed cancer was different across cancer types (median range from 20 to 67 months, mean from 45.65 to 88.25 months).

The impact of prior cancer on prognosis was different across cancers, based on the results of the Kaplan-Meier analysis after PSM, which could be broadly divided into two groups: (*i*) Patients with a history of prior cancer had inferior OS (prior cancer inferior [PCI] group) and (*ii*) the remaining patients showed similar OS (prior cancer similar [PCS] group) to that of patients without prior cancer history. The PCI group mainly comprised tumors involving the following tumor sites: the colon and rectum, bone and soft tissues, melanoma, breast, cervix uteri, corpus and uterus, prostate, urinary bladder, kidney and renal pelvis, thyroid, eye and orbits (Fig. 1). Their Kaplan-Meier curves showed an adverse effect of prior cancer on OS, compared to patients without a prior cancer (log rank tests $p < 0.05$). The OS of patients with a prior cancer history from the PCS group (nasopharynx, esophagus, liver, gallbladder, lung, ovary) was the same as that of patients without a prior cancer ($p > 0.05$), or slightly worse (stomach, pancreas, brain and other nervous system, $p < 0.05$); however, their survival curves visually overlapped without a clinically meaningful difference (Fig. 2).

Propensity-score-adjusted Cox proportional hazards models were constructed to confirm the impact of prior cancer on OS (Fig. 3). Within the PCI group, patients with a prior cancer history had worse OS than patients without a prior cancer history. Cancers with the highest hazard ratios (HRs) were thyroid cancer (HR = 1.56; 95% CI [confidence interval] 1.43–1.69, $p < 0.001$), prostate cancer (HR = 1.55; 95% CI 1.51–1.60, $p < 0.001$), corpus and uterine cancer (HR = 1.34; 95% CI 1.27–1.41, $p < 0.001$), urinary bladder cancer (HR = 1.24; 95% CI 1.21–1.28, $p < 0.001$), and melanoma (HR = 1.23; 95% CI 1.19–1.27, $p < 0.001$). In contrast, prior cancer did not adversely affect survival in the PCS group. The 95% Cis of the HRs for the PCS group cancers were all cover "1" ($p > 0.05$), or slightly <1.

We also performed subgroup analysis of the prior cancer history impact on OS stratified by the timing of prior cancer and AJCC stage after PSM-based log-rank tests in the different cancer cohorts. For analyses by prior cancer timing, we set 24, 36, 60 and 120 months as the exclusion window. Most subgroups of patients had a consistent effect and significance with the previous cohort analysis ($p < 0.05$). There were exceptions in the following PCI subgroups in the specific exclusion window: melanoma, 24 months, $p = 0.33$; melanoma, 36 months, $p = 0.56$; melanoma, 60 months, $p = 0.92$; cervix uteri, 120 months, $p = 0.76$; and kidney, 120 months, $p = 0.36$. The p values were insignificant, but the patients with prior cancer still had a slightly inferior survival curve. Although some p values were significant for some PCS cancers in the specific exclusion window, such as liver (60 months, $p = 0.04$), pancreas and lung cancers (24, 36, 60 months, $p < 0.05$), the patient survival curves were visually overlapped. The PCS subgroups displayed almost the same tendency to that of the non-inferior effect ($p > 0.05$) (Fig. 4, Supporting Information figures).

Table 1. The proportion of prior cancer history in 20 different cancer types

			Cases with timing of prior cancer			
Cancer type	Total	Event (%)[1]	Total[2]	Mean (m)[3]	Median (m)[4]	Event (%)[5]
All cancer types	1,557,663	261,474 (16.79)	200,707			130,947 (65.24)
Nasopharynx	2,667	285 (10.69)	185	61.56	39	115 (62.16)
Esophagus	18,544	3,766 (20.31)	2,658	62.31	43	1,694 (63.73)
Stomach	30,951	5,125 (16.56)	3,647	64.10	43	2,227 (61.06)
Colon and rectum	192,066	36,639 (19.08)	28,381	55.33	32	19,519 (68.77)
Liver	27,278	3,050 (11.18)	2,189	62.99	41	1,395 (63.73)
Gallbladder	4,627	674 (14.57)	436	78.06	48	252 (57.80)
Pancreas	48,517	8,407 (17.33)	5,503	72.21	48	3,218 (58.48)
Lung and bronchus	253,288	55,004 (21.72)	39,392	63.09	43	24,887 (63.18)
Bones, joint and soft tissue	15,200	2,609 (17.16)	1,828	69.13	49	1,048 (57.33)
Melanoma	85,525	18,484 (21.61)	17,269	51.55	36	12,059 (69.83)
Breast	276,867	47,291 (17.08)	39,350	65.05	44	23,709 (60.25)
Cervix uteri	17,375	1,143 (6.58)	772	65.48	34	495 (64.12)
Corpus and uterus	52,819	6,728 (12.74)	4,726	65.13	43	2,829 (59.86)
Ovary	28,666	4,186 (14.60)	2,828	59.25	30	1,864 (65.91)
Prostate	287,632	25,140 (8.74)	18,210	55.40	32	12,479 (68.53)
Urinary bladder	84,392	21,587 (25.58)	16,826	56.71	36	11,386 (67.67)
Kidney and renal pelvis	59,879	12,659 (21.14)	10,043	45.65	20	7,383 (73.51)
Eye and orbit	2,959	321 (10.85)	169	88.25	67	76 (44.97)
Brain and other nervous system	23,600	2,958 (12.53)	2,199	65.71	43	1,370 (62.30)
Thyroid	44,811	5,418 (12.09)	4,096	53.28	26	2,942 (71.83)

[1]The number and proportion of patients with a history of cancer.
[2]The number of patients with accurate diagnosed time of prior cancer recorded in the SEER database.
[3]The mean time (months) of prior cancer to newly diagnosed cancer.
[4]The median time (months) of prior cancer to newly diagnosed cancer.
[5]The number and proportion of patients with prior cancer history within 5 years.

When considered with the different AJCC TNM stages of the index cancers, the majority of PCI patients with stage I, II, and III index cancers had similar adverse survival curves to those of patients with a history of prior cancer ($p < 0.05$). Although the p values were marginally insignificant in the PCI subgroups (prostate, stage I, $p = 0.80$; corpus and uterus, stage II, $p = 0.06$; bone and soft tissues, stage III, $p = 0.77$; cervix uteri, stage III, $p = 0.08$), the patients with prior cancer still had slightly inferior survival curves. The patients in the PCS group with prior cancer showed non-inferior or similar survival to that of patients with no prior cancer, except for the following subgroups: the early stage of esophagus cancer (stage II, $p < 0.01$), stomach cancer (stage I, $p < 0.01$), gallbladder cancer (stage I, $p = 0.04$) and lung cancer (stage I, II, $p < 0.01$). Interestingly, compared with patients with no prior cancer, stage IV patients with prior cancer in the PCI and PCS groups had similar or non-inferior survival, except when they had the following cancers: prostate, pancreas and lung cancer ($p < 0.05$) (Fig. 4, Supporting Information figures).

Discussion

The practice of excluding patients with a prior cancer history is ubiquitous among cancer clinical trials. This exclusion criterion is mainly based on the assumption that prior cancer may interferes with study outcomes. However, there have been no authoritative data to support this assumption until now. In this retrospective study of 1,557,663 patients whose diagnoses were recorded in the SEER database, we classified 20 types of cancers into two groups namely, the PCI and PCS groups, according to the impact of the prior cancer history. The PCI group demonstrated inferior OS among patients with a history of prior cancer, which supports the current exclusion criterion assumption. Patients in the PCS group diagnosed with a prior cancer still displayed non-inferior OS, suggesting that these patients can be considered for enrollment in cancer trials. To our knowledge, this is the first pan-cancer study to evaluate the survival impact of prior cancer across 20 types of cancer systematically. Our results indicate that we need to consider the different impacts of

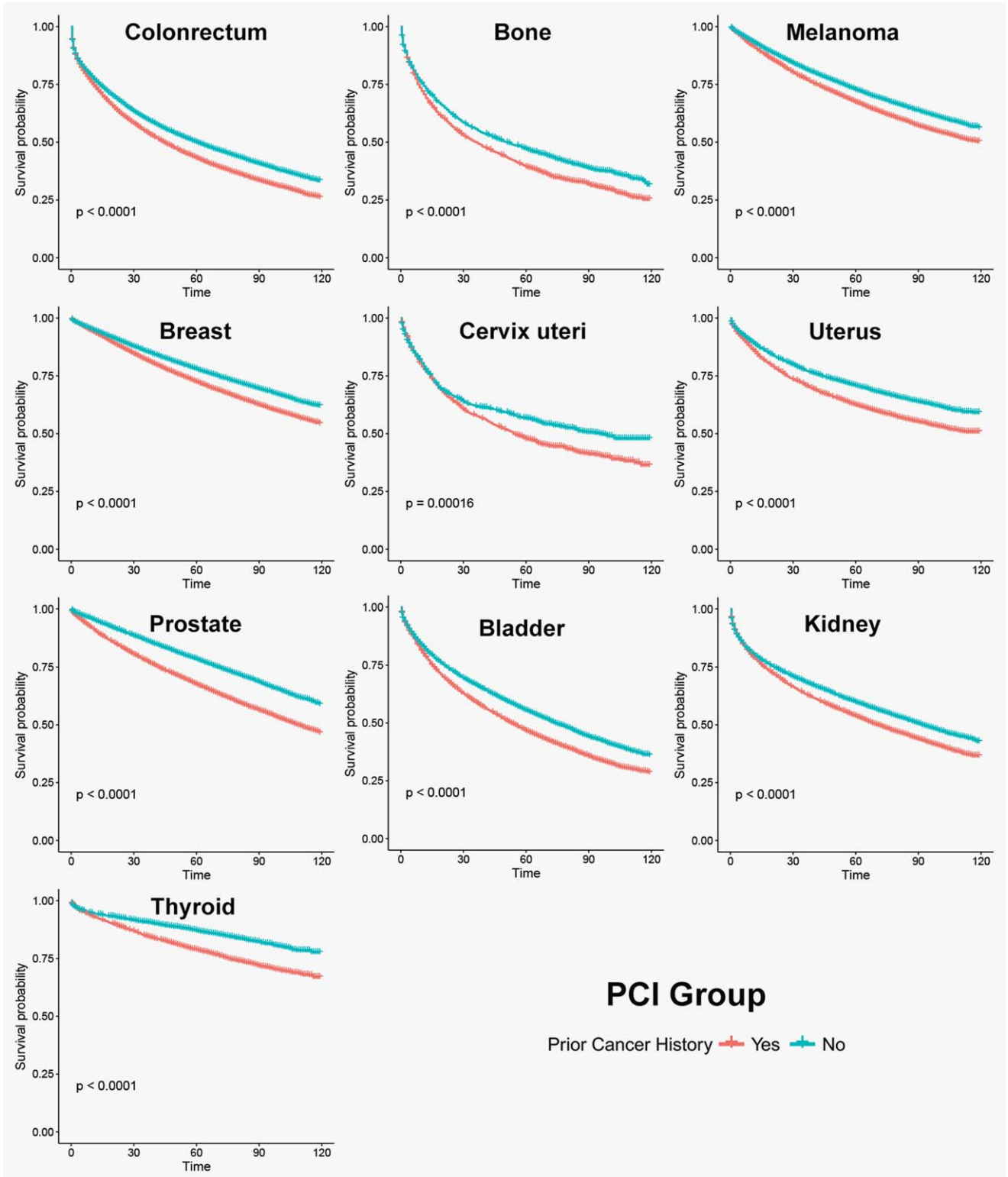

Figure 1. The Kaplan-Meier survival curves of prior cancer history impact on the overall survival in PCI group (prior cancer inferior) after propensity score matching. The overall survival of the PCI group (colon and rectum, bone and soft tissues, melanoma, breast, cervix uteri, corpus and uterus, prostate, urinary bladder, kidney and renal pelvis, eye and orbits, and thyroid) was inferior compared with that of patients without a prior cancer ($p < 0.05$). [Color figure can be viewed at wileyonlinelibrary.com]

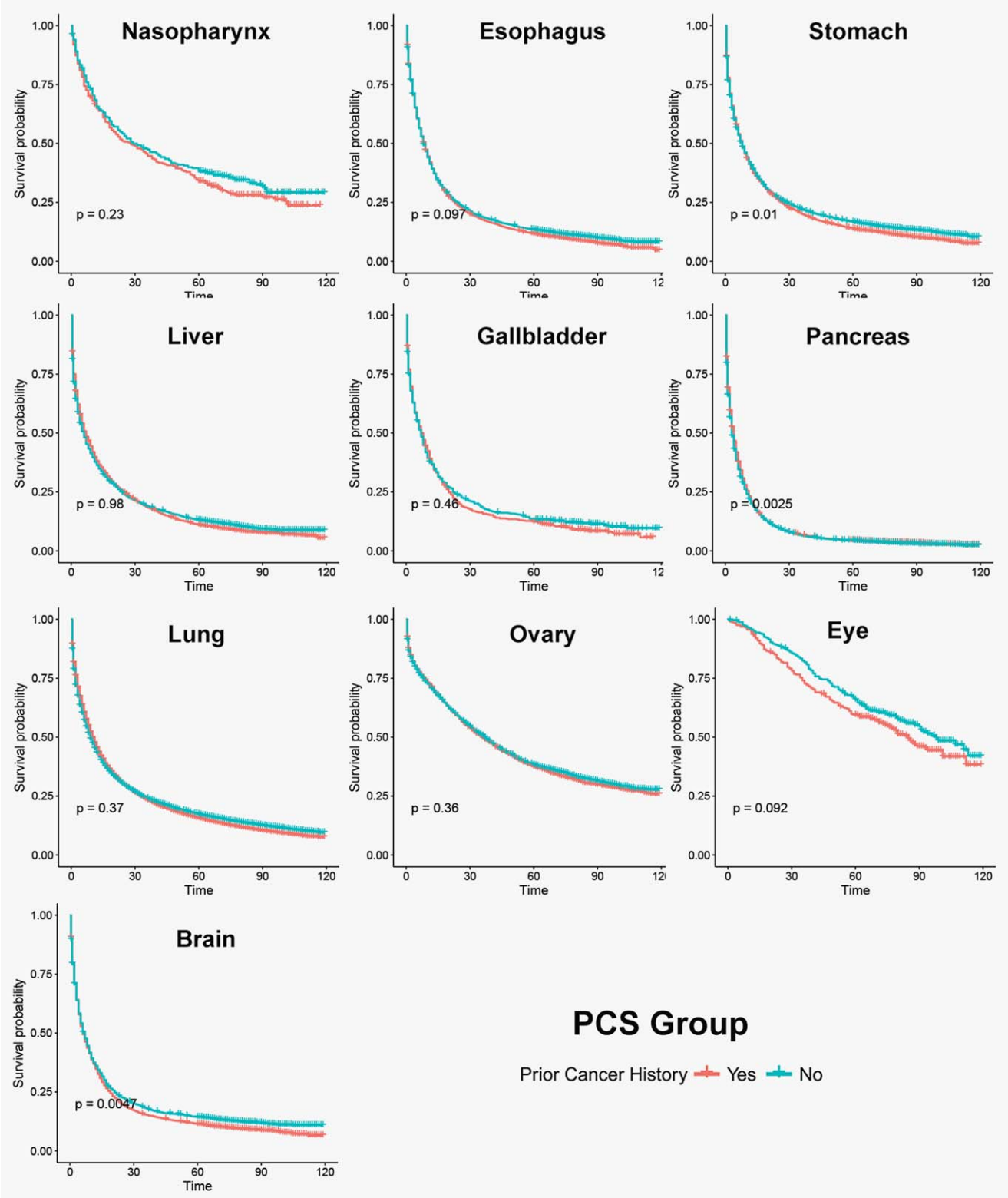

Figure 2. The Kaplan-Meier survival curves of prior cancer history impact on the overall survival in the PCS group (prior cancer similar) after propensity score matching. The overall survival of the PCS group (nasopharynx, esophagus, liver, gallbladder, pancreas, ovary) was similar to that of patients without a prior cancer ($p > 0.05$), or slightly worse (stomach, pancreas, brain and other nervous system, $p < 0.05$), and their survival curves visually overlapped without a clinically meaningful difference. [Color figure can be viewed at wileyonlinelibrary.com]

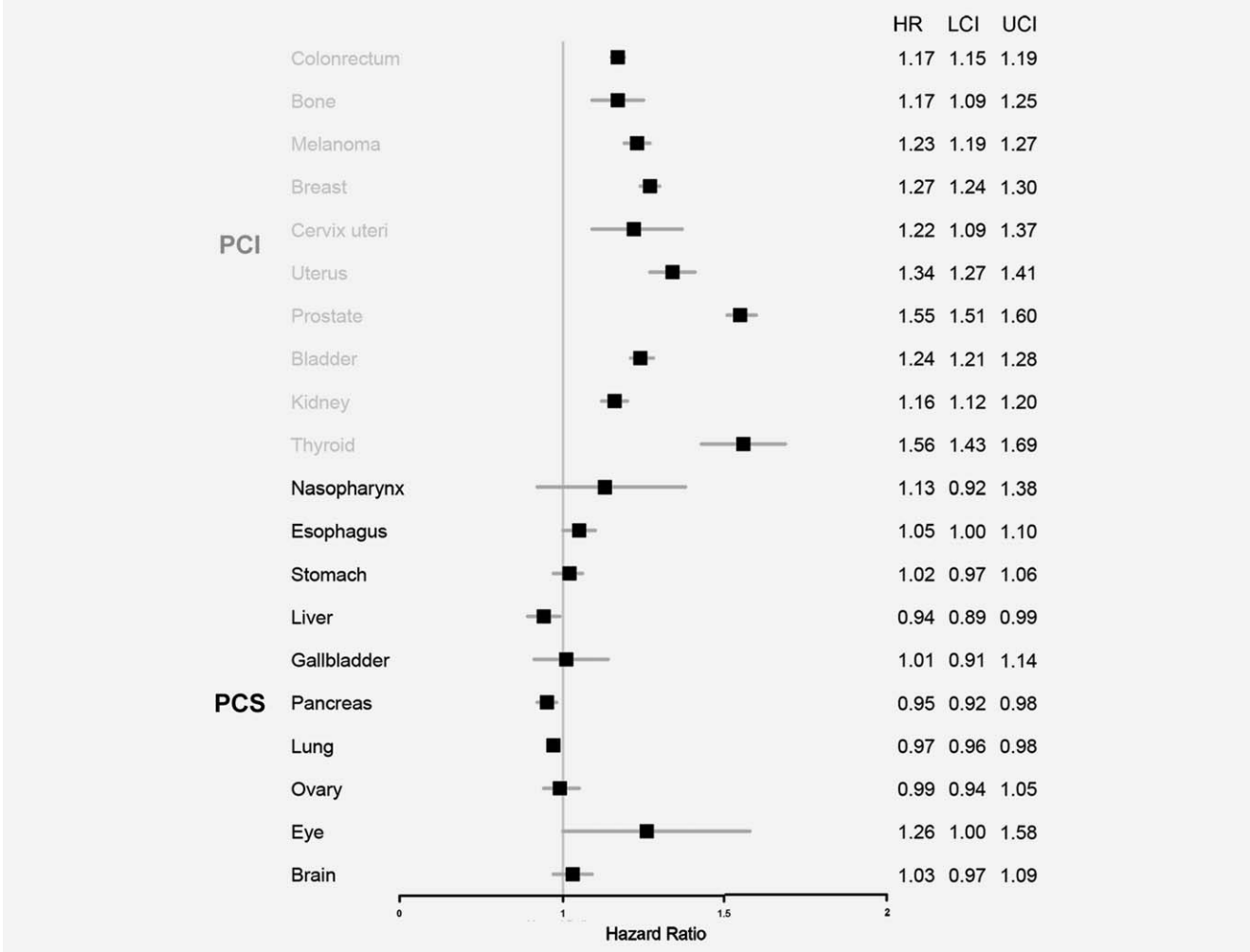

Figure 3. Propensity score match-based Cox proportional hazards regression analysis of prior cancer history impact on the overall survival for patients newly diagnosed with cancer. (*a*) Patients with a history of prior cancer had inferior overall survival (prior cancer inferior, PCI group, grey font); (*b*) those with similar overall survival (prior cancer similar, PCS group, black font).

prior cancer history according to the specific cancer and not take the prior cancer history for granted.

Because the cancer survivor population is rapidly growing, understanding the impact of prior cancer history is critical. Several detailed results have been available for several specific cancer types. Gerber *et al.* have repeatedly found that prior cancer did not adversely impact all-cause or lung cancer specific survival in a series of studies, which was consistent with our results.[4,6,14] Previous studies have also shown that a substantial proportion (18%) of lung cancer patients were excluded from participating in trials because of this stringent criterion, which may substantially limit trial accrual and the generalizability of results.[4] Some researchers identified a higher risk of prostate cancer mortality in patients with a prior cancer, especially in those with higher grade and advanced prostate cancer.[16] This result is similar to our findings, and we may need to be seriously concerned about this "indolent" cancer. When considering gastrointestinal (GI) malignancies, Smyth *et al.* conducted a retrospective single-center study that included 697 GI patients, and the findings were similar to ours; in the former study, GI patients with a prior cancer had similar survival to that of patients with only primary GI cancer.[17] However, there were exceptions. For example, colorectal cancer, which was categorized in the PCI group in our study, had a poor prognosis in patients when diagnosed with a prior cancer. The possible reasons for the discrepancy were the different scales of the study populations and the fact that Smyth *et al.* evaluated all GI cancers. Except for the above cancer types, there is no study that demonstrates the impact of prior cancer on other cancer types. Our pan-cancer study fills this knowledge gap for the first time and provides data to address these issues.

Potential explanations for our findings include lead-time bias.[4,18] In other words, patients with a prior cancer undergoing routine follow-up may be diagnosed with a new cancer at an earlier point for specific cancer types, due to potential differences in routine follow-up. According to Cancer Statistics 2017 and our study results, we found that the 5-year survival

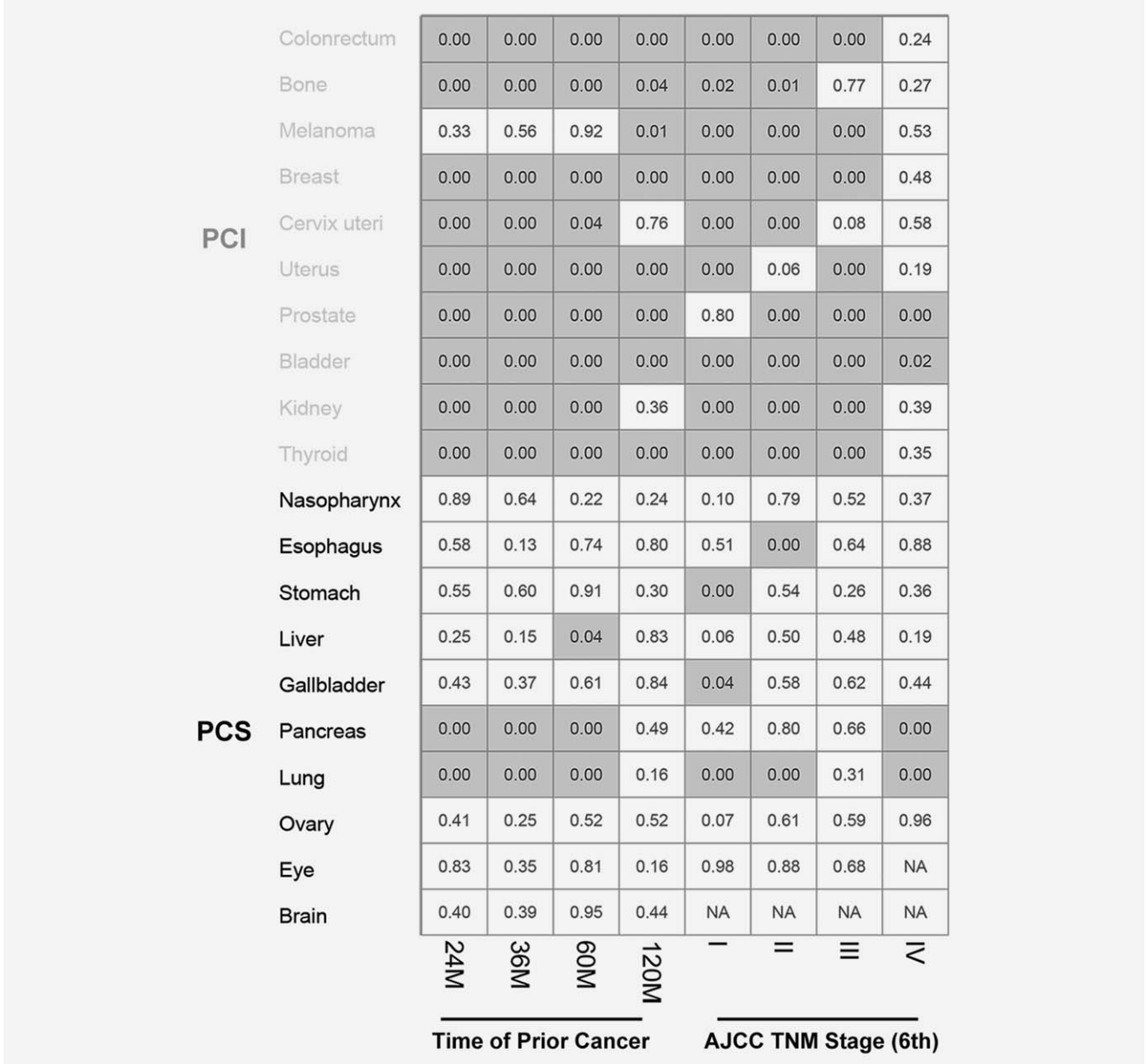

Figure 4. Subgroup analysis of prior cancer history impact on the overall survival stratified by the timing of prior cancer and AJCC stage after propensity score match-based log-rank tests in the different cancer cohorts. The *p* value less than 0.05 was highlighted with grey color. "0.00" means the *p* value less than 0.01, while "NA" for information missing. The prior cancer history has an adverse survival impact on most PCI patients regardless of the timing of prior cancer and AJCC stage. The patients in the PCS group with prior cancer showed a non-inferior or similar survival when compared with patients with no prior cancer. Notably, stage IV patients with prior cancer had similar or non-inferior survival, no matter which group (PCI or PCS) they belong to.

rates of the PCI group (usually >60%) were higher than those of the PCS group (most <20%).[19] Meanwhile, the subgroup analysis by index cancer TNM stage also found that stage IV patients (in both the PCI and PCS groups) with prior cancer showed non-inferior survival compared with patients with no prior cancer. These phenomena indicate that the cancers with relatively good prognoses are more easily affected by prior cancer, whereas the outcomes of aggressive cancers are usually completely unrelated to prior cancer. The dynamic highlights the importance of setting exclusion criteria rationally according to specific PCS cancer types, rather than by directly copying the "standard" criteria from previous trials without thinking.

The timing details of prior cancer diagnoses are an important factor when determining the impact of prior cancer.[5] Most clinical trials use a 5-year exclusion window, and over 65% of prior cancers occur within this time interval in our study.[4] We set 24, 36, 60 and 120 months as options, and tried to find the optimal exclusion window. Finally, we observed that most subgroups of patients had a consistent effect and significance with

those of the previous cohort analysis. Specifically, the impact of prior cancer is independent of timing. From this perspective, if we want to set prior cancer exclusion criteria for the PCI group, 5-year exclusion windows are not enough, and we may need to exclude all patients with prior cancer; however, PCS patients can be considered for enrollment in trials regardless of timing.

In addition to the survival impact, there are other potential reasons why clinicians and investigators usually exclude patients with a history of prior cancer from cancer clinical trials, such as previous exposure to treatments for prior cancer. Previous treatment exposure can disrupt the management approach chosen for the index cancer due to efficacy and tolerability after prior systemic therapies. However, due to the limited treatment data available in the SEER database, we cannot elaborate on this issue in our current analysis.

Undeniably, the present study has several limitations. First, prior cancers diagnosed outside of the registry state are reflected in sequence number only, without detailed prior cancer characteristics. In the current analysis, we only consider the timing of the prior cancer, and not the other clinical features of the prior cancer. Second, our research mainly focuses on the history of prior cancer, without a discussion of the specific prior cancer type. In addition, the SEER database lacks more detailed data on treatments other than radiotherapy or surgery. Adverse events and comorbidities were also unavailable in the database. Thus, we could not match comorbidities in our PSM analyses, and we did not include them in the regression models. Notably, the PSM analysis itself is also vulnerable to hidden biases. Furthermore, we cannot address other concerns of prior cancer, such as the efficacy and tolerability of therapy. Finally, our data mainly cover approximately 30% of the population in the United States, and whether our results are generalizable to other countries remains unknown. Further studies are required to collect more data to confirm our findings.

Conclusions

Our pan-cancer study provides the landscape on the survival impact of prior cancer across 20 cancer types for the first time. More than 16% of patients have a history of prior cancer, and approximately 65% of cases occur within 5 years. These cases can be divided into the PCI group (inferior survival compared with that of patients without prior cancer) and the PCS group (similar survival to that of patients without prior cancer). Our findings suggest that broader inclusion criteria can be adopted for the PCS group. Further studies are still needed to confirm our findings.

Acknowledgements

The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in providing high quality open resources for researchers. The authors thank the editors and the anonymous reviewer for their valuable comments and suggestions to improve the quality of the article. The authors are also grateful to CDMG (SYSU) for assistance.

References

1. de Moor JS, Mariotto AB, Parry C, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol. Biomarkers Prev* 2013;22: 561–70.
2. Hayat MJ, Howlader N, Reichman ME, et al. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. *Oncologist* 2007;12:20–37.
3. Murphy CC, Gerber DE, Pruitt SL. Prevalence of prior cancer among persons newly diagnosed with cancer: an initial report from the surveillance, epidemiology, and end results program. *JAMA Oncol* 2017. doi: 10.1001/jamaoncol.2017.3605
4. Gerber DE, Laccetti AL, Xuan L, et al. Impact of prior cancer on eligibility for lung cancer clinical trials. *J Natl Cancer Inst* 2014;106:dju302.
5. Gerber DE, Pruitt SL, Halm EA. Should criteria for inclusion in cancer clinical trials be expanded? *J Comp Eff Res* 2015;4:289–91.
6. Laccetti AL, Pruitt SL, Xuan L, et al. Prior cancer does not adversely affect survival in locally advanced lung cancer: a national SEER-medicare analysis. *Lung Cancer* 2016;98:106–13.
7. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (1973–2013 varying) - Linked To County Attributes - Total U.S., 1969–2014 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2016, based on the November 2015 submission. Available at: https://seer.cancer.gov/data/, Accessed October 28, 2017.
8. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER*Stat software version 8.3.4, 2017. Available at: http://www.seer.cancer.gov/seerstat, Accessed October 28, 2017.
9. Aizer AA, Chen M-H, McCarthy EP, et al. Marital status and survival in patients with cancer. *J Clin Oncol* 2013;31:3869–76.
10. Shaikh WR, Weinstock MA, Halpern AC, et al. The characterization and potential impact of melanoma cases with unknown thickness in the United States' Surveillance, Epidemiology, and End Results Program, 1989–2008. *Cancer Epidemiol* 2013;37:64–70.
11. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46:399–424.
12. Hosmer DW, Jr., Lemeshow S, May S. Applied survival analysis: regression modeling of time-to-event Data. Hoboken, NJ: John Wiley & Sons, 2011.
13. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. Berlin, Germany: Springer Science & Business Media, 2005.
14. Laccetti AL, Pruitt SL, Xuan L, et al. Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual. *J Natl Cancer Inst* 2015; 107:djv002
15. Verweij PJ, van Houwelingen HC. Time-dependent effects of fixed covariates in Cox regression. *Biometrics* 1995;51:1550–6.
16. Dinh KT, Mahal BA, Ziehr DR, et al. Risk of prostate cancer mortality in men with a history of prior cancer. *BJU Int* 2016;117:E20–E28.
17. Smyth EC, Tarazona N, Peckitt C, et al. Exclusion of gastrointestinal cancer patients with prior cancer from clinical trials: is this justified? *Clin Colorectal Cancer* 2016;15:e53–e59.
18. Sankila R, Hakulinen T. Survival of patients with colorectal carcinoma: effect of prior breast cancer. *J Natl Cancer Inst* 1998;90:63–5.
19. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.