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ORIGINAL ARTICLE

Antibiotic exposure within six months before systemic therapy was associated with lower cancer survival

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Abstract

Objectives: The objective of the study was to quantify associations between cancer survival and antibiotic exposure before systemic anticancer therapy.

Study Design and Setting: This population-based cohort study compares cause-specific survival according to antibiotic exposure before non−immune checkpoint inhibitor (ICI) systemic therapy in patients diagnosed with single primary cancers in New South Wales between 2013 and 2016. Proportional hazards regression was used to control for confounding, with no antibiotic exposure in the six months before non-ICI systemic therapy serving as the comparator.

Results: After adjusting for tumour spread, cancer site, age, sex and comorbidity, people having antibiotic exposure within 180 days before non-ICI systemic therapy had poorer cancer survival (hazard ratios ranging from 1.21 [95% confidence interval: 1.06−1.39] to 1.58 [1.34−1.87]) for shorter periods since antibiotic exposure ($P < .0001$). Similarly, poorer survival trends applied for localized and metastatic cancer. Of six prevalent cancers studied, lung and breast primaries showed the strongest associations of lower survival with prior antibiotic exposure.

Conclusion: Antibiotic exposure within 180 days before non-ICI systemic cancer treatment is associated with poorer survival. If confirmed in other studies, it provides another reason for vigilant antibiotic stewardship.

Keywords: Antibiotics; Chemotherapy; Systemic therapy; Cancer; Survival; Cancer degree of spread

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Data availability statement: The data underlying this article cannot be shared publicly due to undertakings by authors to protect the privacy of individuals in the study. The data comprise unit records of cancer registrations linked with pharmaceutical supply episodes held in government-run administrative databases subject to secrecy. The data were analyzed in an air-gapped secure research environment in which all information going into and out of the facility is curated according to set privacy protection protocols.

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1. Introduction

Studies of people treated for cancer with immune checkpoint inhibitor (ICI) therapy have reported lower survival and a reduced response to treatment associated with recent exposure to antibiotics [1−5]. A study of 196 people undergoing ICI treatment, which included 119 with non−small-cell lung cancer and 38 with melanoma, reported prior antibiotic use to be correlated with an attenuated treatment response and lower cancer survival, whereas survival was not significantly different between patient groups with concurrent or no prior antibiotic exposure [4]. These findings were supported by a systematic review of 33 studies of antibiotic exposure and ICI treatments which showed that antibiotics taken shortly before and, in addition, up to 60 days after commencing immunotherapy were associated with a poorer prognosis in people with solid tumours [6].

The key questions arising include the following: (1) whether prior antibiotic exposure impacts on outcomes from non-ICI systemic cancer therapy, and if so, (2) whether the effect varies with the timing of the last antibiotic exposure prior to cancer therapy, cancer type, or extent of tumour spread at diagnosis. We undertook a population-based study of the effect of antibiotic exposure prior to systemic therapy using population-wide linked data.

2. Materials and methods

Data for all single primary cancers diagnosed in New South Wales (NSW), Australia, during January 2013 to December 2016, from the NSW Cancer Registry (NSWCR; n = 160,994), were linked to the Australian Pharmaceutical Benefits Scheme (PBS) to identify those undergoing systemic therapy following diagnosis. People with more than one primary cancer were excluded from the study. The NSWCR, in operation since 1972, is a population-based registry that records all malignancies diagnosed in NSW residents. The NSWCR captures incidence, prognostic details, and death details of each diagnosed primary cancer, along with demographic information for each case. The PBS is the Australian government's pharmaceutical subsidy scheme which covers most of the cost of pharmaceuticals for individual patients, including for systemic anticancer therapies as outpatients or inpatients in private facilities. Our cancer cohort excluded 46,055 patients exposed to antibiotics during systemic therapy, leaving 26,660 exposed to antibiotics prior to systemic therapy only or not exposed at all (Appendix, Fig. A1).

Systemic cancer therapy was categorized based on the Anatomical Therapy Chemical (ATC) code categories "L01" to "L04," covering systemic "antineoplastic and immunomodulating agents" [7], as recorded in the PBS. Cancer records were linked to PBS records of any (systemic) antibiotic prescriptions dispensed prior to the systemic therapy, coinciding with the root ATC code "J01," "anti-infectives for systemic use."

Antibiotic exposures were classified based on the most recent exposure prior to commencing systemic cancer therapy (1−30, 31−90, or 91−180 days). Patients who had no antibiotic exposure recorded in the 6 months before systemic therapy served as the unexposed comparison group. All antibiotic and systemic therapy exposure time intervals were based on recorded date(s) of supply.

Cancers diagnosed in 2013−2016 were selected in order to allow a minimum of 6 month look-back time to identify PBS-listed antibiotics regardless of the price subsidy threshold (these data had full coverage only from July 1, 2012). To minimize bias from this source, cancers diagnosed later with longer look-back times in the PBS were censored with respect to antibiotic exposures occurring $>$180 days prior to systemic therapy commencement. People with cancer exposed to antibiotics during systemic therapy were excluded from the analyses.

The outcome was death attributed to cancer, detected up to April 2020 in the National Death Index and linked individually to the 2013−2016 cancer cohort. The median follow-up time of the cohort was 5.5 years.

Survival was analyzed by the following:

1. Systemic treatment subgroup [7]: endocrine therapies (ATC category "L02"), immunostimulants and immunosuppressants (ATC categories "L03" and "L04" considered together), antineoplastic agents (ATC category "L01") minus ICI compounds, and by ICI therapies (shown in the Appendix). Compounds classified as ICI therapies were as follows: ipilimumab (L01XC11), nivolumab (L01XC17), pembrolizumab (L01XC18), durvalumab (L01XC28), avelumab (L01XC31), atezolizumab (L01XC32), and cemiplimab (L01XC33).
2. All cancers were analyzed (n = 26,660; 25,936 without ICIs), and separately, major cancers (not receiving ICI) were analyzed: melanomas (n = 466), breast (n = 7,146), colorectal (n = 3,051), lung (n = 2,370), pancreas (n = 731), and prostate (n = 3,011).
3. Charlson comorbidity index (CCI) [8] scores of 0, 1, 2, and $\geq$ 3 were derived from cancer cohort records linked to NSW Admitted Patients Data Collection. CCI scores were calculated from hospital admissions up to one year prior to cancer diagnosis and during its treatment [9]. Patients not admitted to hospital in that period were assigned a CCI score of zero.
4. The cancer summary degree of spread was based on tumor nodes metastases staging, classified as "localized," "regional spread" (nodal involvement and/or spread to adjacent organ), "distant metastases," and "unknown degree of spread."

What is new?

Key findings

- Exposure to antibiotics prior to anti-neoplastic cancer therapy is significantly associated with lower cancer survival.
- The survival decrement increases with recency of antibiotic exposure prior to commencement of systemic therapy, showing a significant time response relationship.
- Cancers of the breast and lung were affected more than melanomas and cancers of the colon or rectum, pancreas, and prostate.

What this adds to what was known?

- Findings of lower survival from antibiotic exposure have been confined to immune checkpoint inhibitor/blockade (ICI) therapy, but this applies also to non-ICI therapies.

What is the implication and what should change now?

- If confirmed, these findings reinforce the need for careful antibiotic stewardship in the community, given that a subsequent diagnosis of cancer and its outcomes may be influenced by earlier, unrelated antibiotic prescribing.

5. All systemic treatments, excluding ICI therapies in relation to prior antibiotic exposure, were modelled with death from cancer as the outcome using cause-specific proportional hazards regression.

2.1. Statistical analysis

Kaplan−Meier survival curves, with 95% Hall−Wellner bands, were constructed for antibiotic exposure strata occurring before systemic therapy, with a logrank trend test over these strata for a time−response relationship. Non-cancer deaths were censored at the time of death, with survivors censored at the end of the follow-up period. Survival time (in days) was calculated as the difference between the date of death, or the last date of follow-up in survivors, and the date of cancer diagnosis.

Cause-specific proportional hazards regression was used to control for confounders, principally cancer site, age, cancer summary degree of spread, sex, and recorded pre-existing comorbidities at hospital admission. Confounders were modelled as strata, while the exposures of interest were accompanied by an interaction term incorporating survival time, if statistically significant ($P < 0.05$), to account for violations of the proportional hazard assumption. A trend test for a time−response relationship was applied in the regression models by treating the exposure categories as a single ordinal variable (with one degree of freedom), using the *P*-value of the regression estimate to indicate the statistical significance of the hazard ratio (HR) trend across antibiotic exposure categories. All statistical significance tests were two-sided.

Given that deidentified linked data from population data bases were used, no individual consent was required. Use of these data was approved by the NSW Population and Health Services Research Ethics Committee (HREC/15/CIPHS/15) for cancer surveillance of NSW by the Cancer Institute NSW.

3. Results

The cohort ($n = 26{,}660$) comprised 53% women, largely due to the proportion of people diagnosed with breast cancer making up 27% of all cancers in this cohort over the study period (Appendix, Table A1). Excluding prostate and breast cancers, men comprised 55−64% of the remaining cancers. Seven hundred fifty-four patients who received any ICI therapies with or without other compounds (2.7%) were excluded from further analyses (Appendix, Fig. A1). The distribution of the remaining ATC categories was as follows: 48% received non-ICI L01 therapy, 14.4% received endocrine therapy (L02), 3% received immunostimulants/suppressants (L03−L04), and 30.9% received combination therapy. A total of 25,936 patients received systemic therapies other than ICIs across the ATC L01−L04 categories (Table A1). Thirty percent of cancers were localized, 33% had regional spread, 17% were metastatic, and in 20%, the degree of spread was unknown. Eighty-nine percent of the cohort had a zero CCI score, 3% scored one, 7% scored two, and 1% scored three or above.

3.1. Kaplan−Meier survival plots

For cancers overall, survival was significantly less in people undergoing non-ICI systemic therapies exposed to antibiotics administered 0−180 days before commencing therapy, as compared with no exposure or exposure in the 180 days prior to therapy commencing. There was little difference between the three exposure periods (1−30, 31−90, and 91−180 days; Fig. 1, first survival plot). For localized cancers, the period differences were more evident and showed a time−response relationship with the 1- to 30-day exposure group having the lowest survival (second survival plot). Survival in people with regional cancer spread was lower than that for the controls in each of the 0- to 180-day antibiotic exposure groups, with little difference between them (third survival plot). For metastatic cancers, the differences were more apparent, except that antibiotic exposure 30−90 days prior to systemic therapy was associated with lowest survival rather than 1- to 30-day prior exposure (fourth survival plot). For cancers of unknown

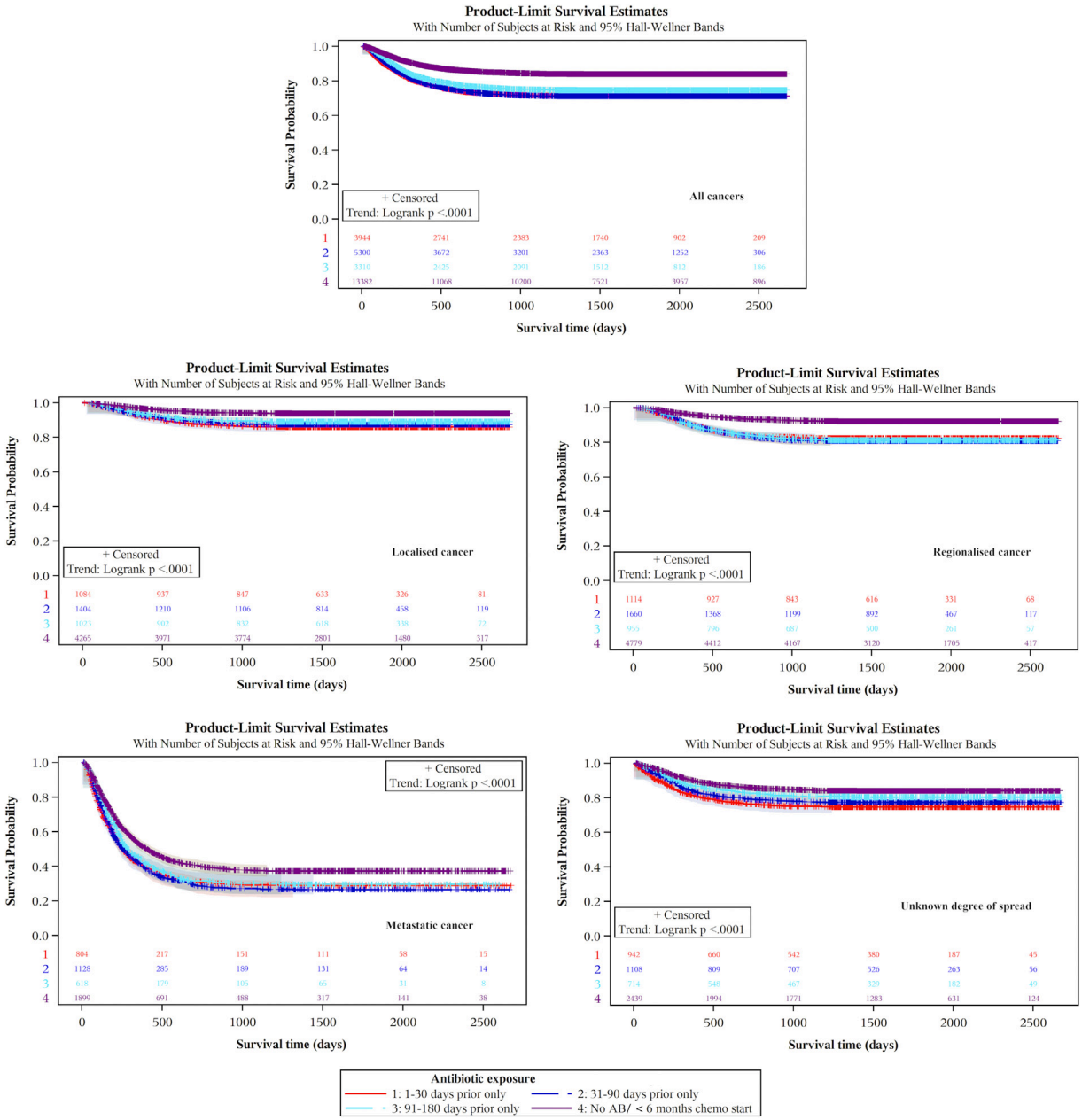

Fig. 1. Survival from cancer cause of death by prior antibiotic exposure, by summary degree of spread, in patients with cancers diagnosed in 2013–2016 undergoing non-ICI therapy, NSW, Australia. ICI, immune checkpoint inhibitor; NSW, New South Wales.

degree of spread, the exposure categories were well differentiated and similar to localized cancer (fifth survival plot).

In subgroups undergoing exclusively a single systemic therapy category, survival was not significantly associated with antibiotic exposure in those undergoing ICI or immunostimulant/suppressor therapies only (Appendix, Fig. A2, first and third plots). The survival differences are more apparent and statistically significant in people having exclusively endocrine or non-ICI ATC L01 agent therapies (Fig. A2, second and fourth plots).

When analyzed separately by CCI scores, similar results are seen for each CCI category (Fig. 2). The time–response pattern is similar and statistically significant for CCI scores $\leq$2, with small numbers preventing meaningful statistical analysis for CCI scores $\geq$3.

Excepting colorectal and pancreatic cancers, antibiotic exposure survival differences were not strictly monotonic but showed broad similarities of lower survival with shorter time since prior antibiotic exposure (Fig. 3). Lung and breast cancers showed the most consistent and statistically significant patterns of lower survival with more recent antibiotic exposure. The patterns for colorectal and prostate cancers were less consistent, despite significantly different survival curves, while melanoma showed the lowest

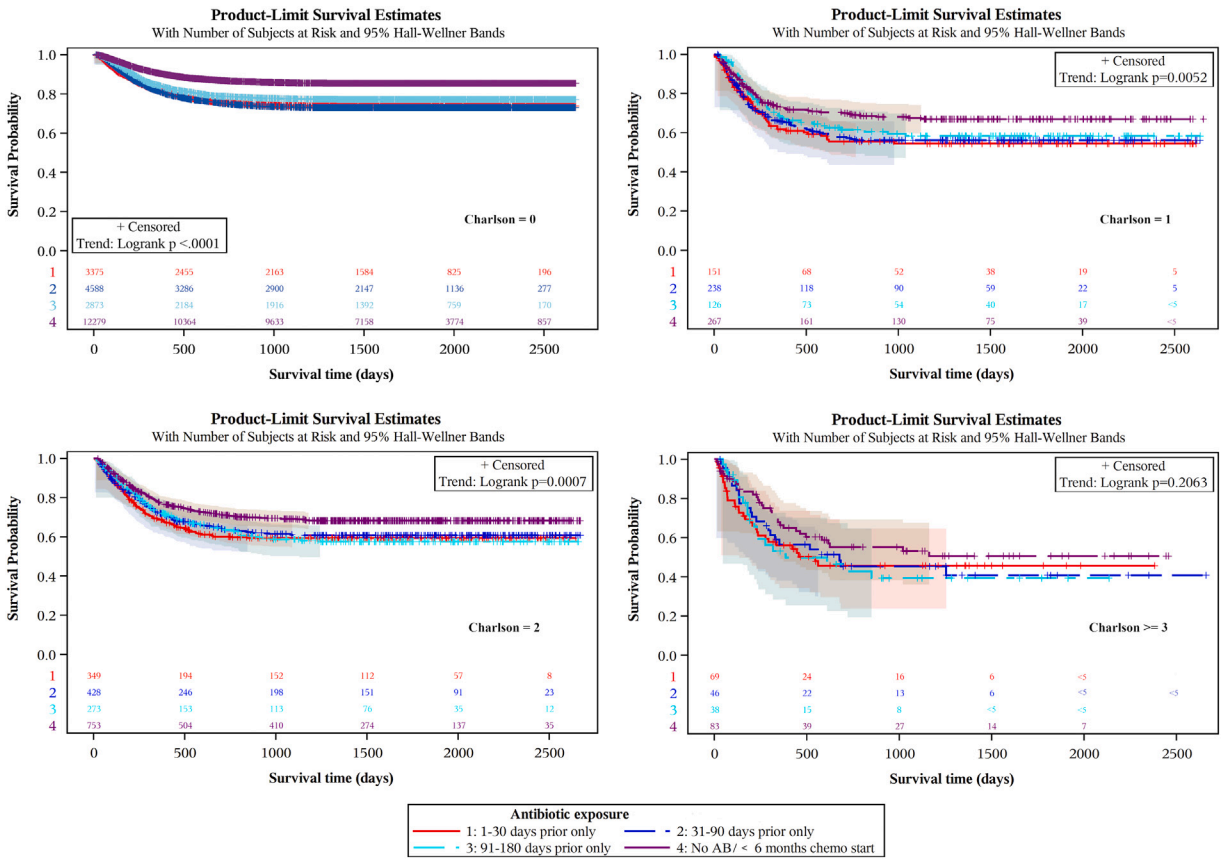

Fig. 2. Survival from cancer cause of death by antibiotic exposure prior to systemic therapy, by Charlson comorbidity score, in patients with cancers diagnosed in 2013−2016 undergoing non-ICI therapy, NSW, Australia. ICI, immune checkpoint inhibitor; NSW, New South Wales.

(nonsignificant) survival differences with the most recent prior antibiotic exposure category.

3.2. Proportional hazards regression models

For all cancers, compared with no antibiotic exposure within the six months prior to systemic therapy commencing, the adjusted HRs for cancer death and exposure to antibiotics were highly statistically significant ($P \leq 0.0044$): 1.58 (95% confidence interval [CI]: 1.34−1.87) for antibiotic exposure 1−30 days prior to any non-ICI systemic therapy (Table 1), 1.36 (95% CI: 1.19−1.55) for antibiotic exposure 31−90 days before, and 1.21 (95% CI: 1.06−1.39) for antibiotic exposure 91−180 days before. The test for trend across these exposure categories was statistically highly significant ($P < .0001$), indicating a time−response relationship between prior antibiotic exposure and cancer survival and adding strongly to the face validity of the findings.

For localized cancer and cancers with unknown degree of spread, the effect sizes were higher than for cancers overall, but similar for people with metastatic disease. Note that these effect sizes are in relation to the baseline survival within each degree-of-spread category, which differs for each, and therefore are not directly comparable with those in other degree-of-spread categories. The time−response relationship was significant for each summary degree-of-spread category.

By cancer diagnostic groups, adjusted HRs for antibiotic exposure were statistically significant for breast and lung cancers only (Table 2).

4. Discussion

These results indicate reduced cancer survival when antibiotics have been used prior to systemic therapy, especially in people with lung or breast cancers. The adverse survival effects apply to cancers undergoing non-ICI systemic therapies but show significant variation by primary site of cancer. For all cancers, lower survival was associated with recent antibiotic exposure regardless of underlying comorbidities, with the signal strongest for the most recent exposure. The present study indicates that the association between antibiotic exposure prior to systemic therapy and survival is not limited to ICI therapy.

When examined in relation to the cancer degree of spread, the prior antibiotic exposure relationship with lower survival from cancer remained. As the associations between antibiotics, systemic therapy, and cancer survival reported here are for a whole population sample of 25,936 single primary cancers undergoing exclusively non-ICI systemic therapy,

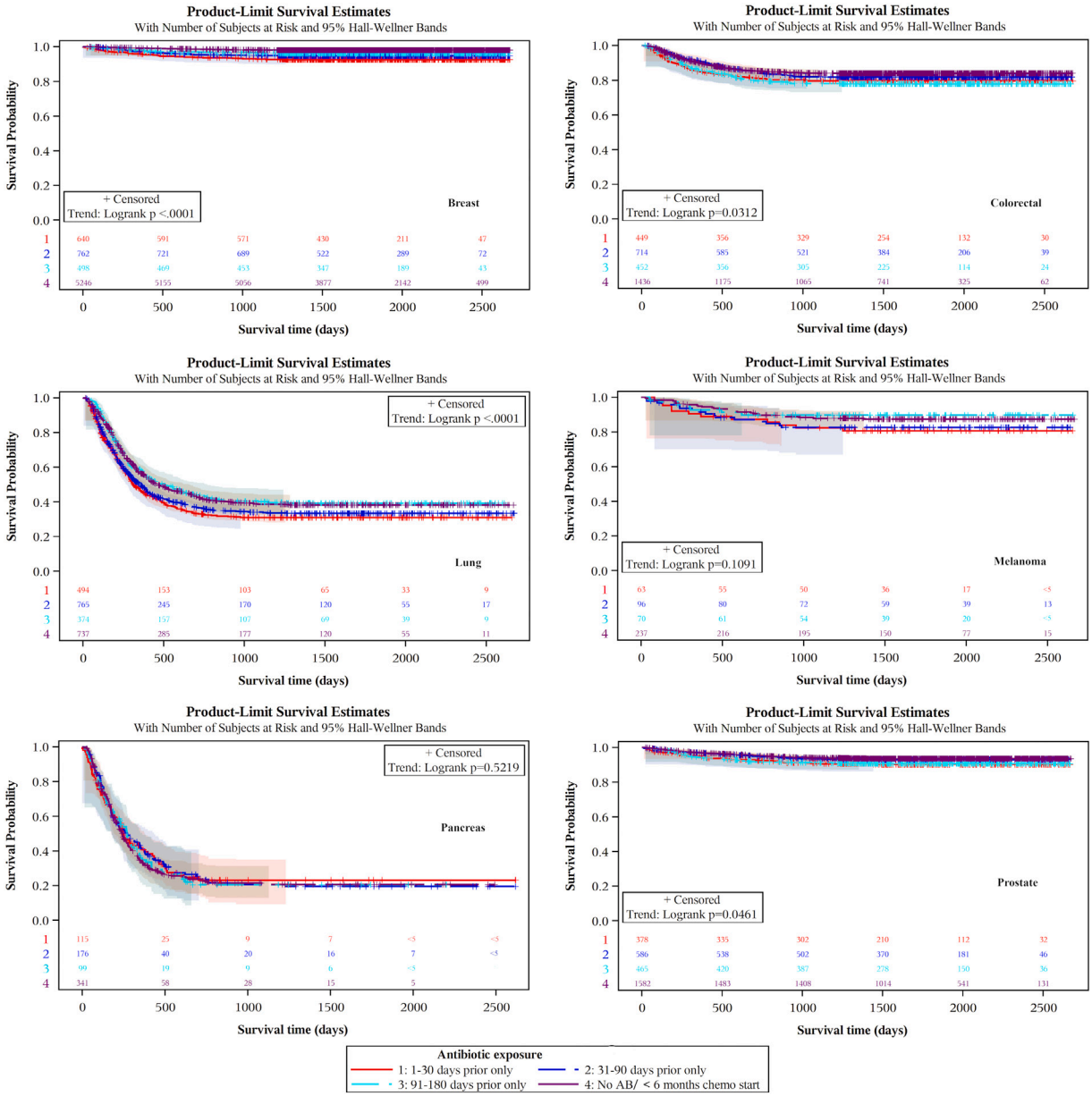

Fig. 3. Survival from cancer cause of death by antibiotic exposure prior to systemic therapy, by cancer type, in patients with cancers diagnosed in 2013–2016 undergoing non-ICI therapy, NSW, Australia. ICI, immune checkpoint inhibitor; NSW, New South Wales.

evidence has emerged of a time–response relationship that would not have been so readily detectable in smaller patient cohorts. Cancer-specific differences in survival by antibiotic exposure are also more evident. In contrast, our cohort was not suitable for analyzing the impact of prior antibiotic exposure to ICI therapies because these therapies were prescribed less often in 2013–2016 in Australia.

Our study has highlighted that the adverse impact of prior antibiotic use does not necessarily apply to all primary cancer sites, such as colorectal, pancreatic, or prostate cancers. It remains to be shown whether this is due to different cancer-specific therapies or different characteristics of the tumours themselves. One of the explanations for our finding could be that prior antibiotic use creates dysbiosis which has an adverse impact on the efficacy of cancer therapies. Patients who also received concurrent antibiotics were excluded here, and it is likely the picture will be more complicated when concurrent antibiotic exposure is taken into account.

Similar to Pinato et al. [4], the association of prior antibiotic exposure with lower cancer survival following the ICI was reported by Derosa et al. [10], who posited a biologically plausible pathway of antibiotics acting on gut microbiota impacting antitumor immune responses, as also put forward by Routy et al. Gopalakrishnan et al., Matson et al., and Pinato et al. and supported by reviews of other studies [11–14].

Table 1. Adjusted[a] cause-specific proportional hazard regression estimates of exposure to antibiotics prior to systemic therapy, cancers diagnosed in NSW from 2013 to 2016 undergoing systemic therapy excluding immune checkpoint inhibitor therapy, overall and by summary degree of spread

Prior antibiotic exposure (days)	Parameter estimate	Standard error	*P*-value	Hazard ratio (95% CI)
All cancers (n = 25,936)				
1–30 days before	0.4587	0.0845	<.0001	1.58 (1.34–1.87)
31–90 days before	0.3063	0.0682	<.0001	1.36 (1.19–1.55)
91–180 days before	0.1931	0.0679	0.0044	1.21 (1.06–1.39)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test[b]		<.0001	
Localized cancer (n = 7,776)				
1–30 days before	0.5135	0.1653	0.0019	1.67 (1.21–2.31)
31–90 days before	0.3676	0.1561	0.0185	1.44 (1.06–1.96)
91–180 days before	0.2276	0.1802	0.2067	1.26 (0.88–1.79)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.0008	
Regionalized cancer[c] (n = 8,508)				
1–30 days before	0.2709	0.1333	0.0422	1.31 (1.01–1.70)
31–90 days before	0.3092	0.1161	0.0078	1.36 (1.09–1.71)
91–180 days before	0.2496	0.1350	0.0643	1.28 (0.99–1.67)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.0110	
Distant metastases (n = 4,449)				
1–30 days before	0.4415	0.1139	0.0001	1.56 (1.24–1.94)
31–90 days before	0.3058	0.0910	0.0008	1.36 (1.14–1.62)
91–180 days before	0.2059	0.0927	0.0262	1.23 (1.03–1.47)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.0002	
Unknown degree of spread (n = 5,203)				
1–30 days before	0.8901	0.2278	<.0001	2.44 (1.56–3.81)
31–90 days before	0.5192	0.1929	0.0071	1.68 (1.15–2.45)
91–180 days before	0.1337	0.1792	0.4557	1.14 (0.80–1.62)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.0071	

Abbreviations: NSW, New South Wales; CI, confidence interval; chemo, chemotherapy.

[a] Adjusted by stratification for stage (all cancers), cancer site, age, Charlson comorbidity index score, and time dependence in antibiotic exposure strata (as an interaction term).

[b] Trend test for time–response relationship between prior antibiotic exposure and survival.

[c] Spread to adjacent organs and/or lymph node involvement.

The ''good'' vs. ''bad'' gut bacteria studies have consistently shown a better response to ICI therapies, where the ratio of the ''good'' to ''bad'' gut bacteria is higher, including for non–small-cell lung cancer, renal cell carcinoma, and melanoma [1–3,11]. Causal evidence for the gut microbiome involvement in therapy response has been provided by studies where faecal microbiota transplantation from patients who responded to immunotherapy to renal tumor–bearing mice improved responsiveness of the mice to PD-1 blockade, compared to transplantation from people who had not had a response to immunotherapy [11,15].

Although antibiotics have been shown to vary widely in their periods affecting gut microbiota, including by antibiotic type, microbiota species and individual [16], we used six months before the commencement of systemic therapy as a pragmatic cut point to indicate nominal ''non-exposure'' to antibiotics. One small study reported that gut microbiota had recovered within 6 months of antibiotic exposure in most participants, although some species remained undetectable [17]. Based on the present findings and assuming a link between antibiotic exposure and composition of the microbiome, a period of >12 months prior to systemic cancer therapy might demonstrate better survival if microbiome recovery time exceeded 6 months. In that case, selecting six months as the cutoff beyond which individuals were considered nonantibiotic exposed would bias our findings towards the null.

Table 2. Adjusted[a] cause-specific proportional hazard regression estimates of exposure to antibiotics, major cancers diagnosed in NSW from 2013 to 2016 undergoing systemic therapy without immune checkpoint inhibitor therapy

Prior antibiotic exposure (days)	Parameter estimate	Standard error	*P*-value	Hazard ratio (95% CI)
Breast (n = 7,146)				
1–30 days before	1.1775	0.2128	<.0001	3.25 (2.14–4.93)
31–90 days before	0.4290	0.2273	0.0591	1.54 (0.98–2.40)
91–180 days before	0.3425	0.3035	0.2591	1.41 (0.78–2.55)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test[b]		<.0001	
Colorectal (n = 3,051)				
1–30 days before	0.0805	0.1579	0.6099	1.08 (0.80–1.48)
31–90 days before	−0.0960	0.1427	0.5011	0.91 (0.69–1.20)
91–180 days before	0.2262	0.1551	0.1446	1.25 (0.93–1.70)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.9849	
Lung (n = 2,370)				
1–30 days before	0.4902	0.1448	0.0007	1.63 (1.23–2.17)
31–90 days before	0.4364	0.1146	0.0001	1.55 (1.24–1.94)
91–180 days before	0.1315	0.1125	0.2425	1.14 (0.92–1.42)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.0002	
Melanoma (n = 466)				
1–30 days before	0.4004	0.8745	0.6471	1.49 (0.27–8.28)
31–90 days before	−0.1575	0.8478	0.8526	0.85 (0.16–4.50)
91–180 days before	−1.1213	1.1841	0.3437	0.33 (0.03–3.32)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.6638	
Pancreas (n = 731)				
1–30 days before	0.2978	0.1963	0.1291	1.35 (0.92–1.98)
31–90 days before	0.0479	0.1789	0.7891	1.05 (0.74–1.49)
91–180 days before	0.0936	0.2233	0.6751	1.10 (0.71–1.70)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.1996	
Prostate (n = 3,011)				
1–30 days before	0.0812	0.2465	0.7418	1.09 (0.67–1.76)
31–90 days before	0.2688	0.2272	0.2367	1.31 (0.84–2.04)
91–180 days before	0.3023	0.2342	0.1968	1.35 (0.86–2.14)
No antibiotics <6 mo prechemo	0.0000	-	-	1.00
	Trend test		0.4016	

Abbreviations: NSW, New South Wales; CI, confidence interval; chemo, chemotherapy.

[a] Adjusted by stratification for stage, age, Charlson comorbidity index score, and time dependence in antibiotic exposure strata (as an interaction term).

[b] Trend test for time–response relationship between prior antibiotic exposure and survival.

A focus on broad- vs. narrow-spectrum antibiotic exposure can test the hypothesis of gut microbiota involvement in the relationship. As broad-spectrum antibiotics affect the more species of gut microbiota than narrow-spectrum varieties, a greater survival decrement would be expected from exposure to broad-spectrum than narrow-spectrum antibiotics prior to systemic therapy.

A drawback of the present study is a lack of clinical information on tumour response to systemic therapy by exposure to antibiotics. Pinato et al. were able to report this key finding to be associated with recent ≤30-day antibiotic exposure, lending credence to the antibiotic survival deficit. While the data used for the present study are clinically coded, information on the tumour objective response rates was not available.

A further limitation of this study is the lack of specificity in combinations of antibiotic agents and systemic compounds associated with reduced survival. Our analysis was limited to exposure to antibiotics prior to the first

systemic therapy episode only, that is, this study was not broken down by first-, second-, or nth-line treatments, nor by particular antibiotics within treatment courses. Data were not available on whether the antibiotic exposure was to treat an active infection or as prophylaxis.

For simplicity, we excluded all cases of multiple primary cancers and exposure to antibiotics during systemic therapy. The results here thus show the need for more detailed analyses that focus on the following:

1. Antibiotic exposures concurrent with systemic therapy and in combination with prior exposures,
2. Specific cancers,
3. Antibiotic classes and the most commonly used individual systemic compounds or combinations, and
4. Appropriate randomized controlled trials to manipulate antibiotic exposure by design, particularly in relation to treatment response as the endpoint, in addition to survival. Trials of supplements to negate gut microbiome dysfunction are also needed.

The present study assumes that antibiotic and systemic therapy exposures are as recorded in the data according to their date of "supply." These data provide no information on the extent that the compounds were consumed. However, at a whole-of-population level, it is not expected that deviations from adherence to prescription medications would account for differences between groups. An additional potential issue is the gap in pharmaceuticals not captured in the PBS, including those supplied or administered in public hospital settings or in clinical trials for experimental therapies. In Australia, most systemic therapies are supplied through the PBS. Clinical trials of experimental compounds comprise a small subgroup, and it is questionable if such cohorts should be included in a general population-based study since they are not receiving standard care.

A potential avenue for further investigation of antibiotic exposure and subsequent survival from systemic therapy is to relate the prescribed dose of antibiotics to the outcome using a standard dosage measure (e.g., the defined daily dose). For antibiotics, this would require careful consideration given the changes in antibiotic prescribing protocols (full course vs. sufficient to clear the infection) and individual patient characteristics (e.g., body weight) that may not be captured at all in population-level data. The data available to the authors were insufficient to capture any individual patient characteristics relevant to antibiotics prescribed.

The CCI (Charlson) score of comorbidity is only a crude measure of comorbid conditions that may lead to lower cancer survival and be associated with antibiotic exposure. Additionally, our CCI estimate relied on conditions recorded at hospital admissions within the previous year. Those with comorbid conditions without a hospital admission in that time period consequently were classified with a zero CCI score. Despite these shortcomings, similar outcomes were found in those with higher CCI scores, indicating that prior antibiotic exposure may be associated with survival independently of comorbidity. These outcomes also remained after adjusting for CCI scores in proportional hazards regression modelling. Improved approaches to ascertaining comorbidity may further refine the models and consequent effect sizes in similar studies.

The findings of the present study are novel and provide a strong signal that further investigation of this association is required. If replicated, this would add further evidence that exposure to antibiotics in the population at large should continue to be minimized, such that in the event of a cancer diagnosis in the coming weeks or months, cancer care will not be compromised. Further work is needed to determine the following:

- Whether particular antibiotic classes are more strongly associated with lower survival in people receiving systemic anticancer therapy,
- Whether antibiotics or specific antibiotic classes impact disproportionately on tumour response to anticancer treatment and need for recurrent courses of anticancer therapy as well as causing mortality,
- The extent to which antibiotic use during chemotherapy may also influence cancer survival and tumour response,
- The relationship between cancer type and antibiotic effects, and
- The biological basis for these observations and potential remedial management strategies.

5. Conclusion

1. Lower survival with antibiotic exposure prior to antineoplastic therapy for cancer appears to extend beyond an association with ICI or blockade therapy alone, but the relationship is not uniform across different primary cancers.
2. Lower survival with antibiotic exposure prior to non-ICI antineoplastic agent therapy is evident for lung and breast cancers, but not for colorectal, pancreatic, or prostate cancers.
3. Lower survival with antibiotic exposure prior to non-ICI antineoplastic agent therapy is evident for cancer by stage, although not reaching statistical significance for people with regional spread of their cancers.
4. Appropriately linked and analyzed administrative health data can indicate disease treatment outcomes not readily discernible from other sources. Our results should be regarded as an alert warranting follow-up examination.
5. These studies can be a valuable complement to clinical studies of therapy outcomes. Such data can generate testable hypotheses for future studies and trials, and their continued use should improve the quality and detail of information available on population-wide outcomes.

6. If confirmed, these findings reinforce the need for careful antibiotic stewardship in the community, given that the subsequent diagnosis of cancer and its outcomes may be influenced by earlier, unrelated antibiotic prescribing.

Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2022.04.003.

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