

# The Impact of Oral Antibiotics Prior to Cancer Diagnosis on Overall Patient Survival: Findings from an English Population-Based Cohort Study

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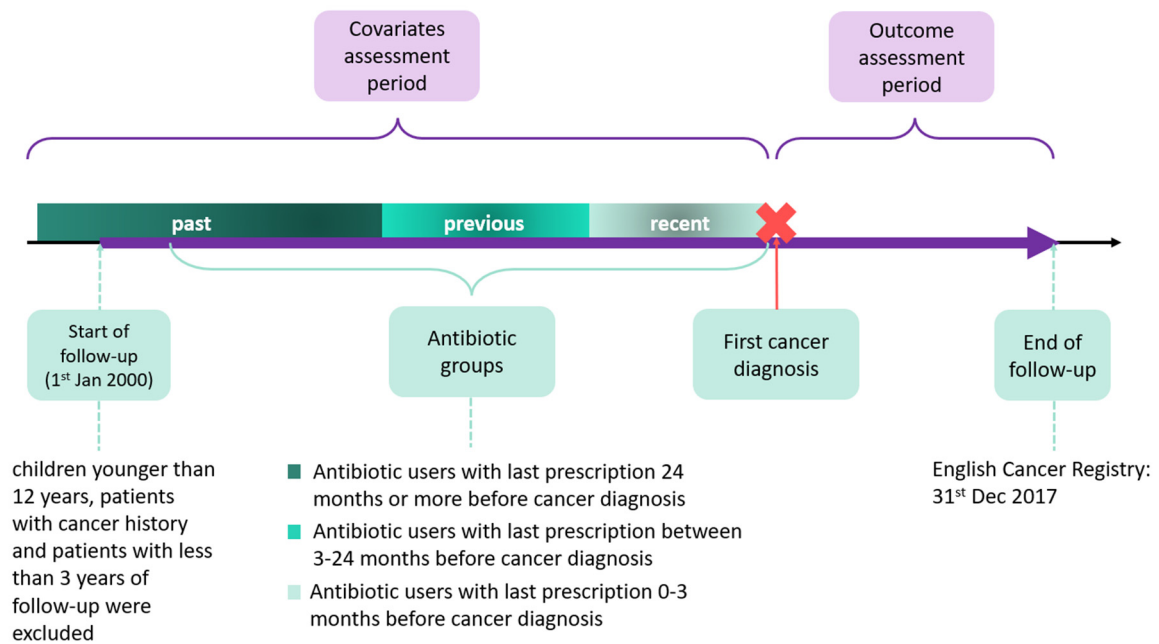
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## Summary

For many cancer types, the survival was significantly lower for patients who received antibiotics shortly before cancer diagnosis, comparing to long past usage. Microbiome may affect cancer therapy outcomes and its potential to act as a new biomarker should be examined.

**Figure S1: Study design - cohorts definition and antibiotic groups**



**Table S1: Cancer types, sequence of treatment and possible alternative therapies.**

Cancer type	Chemotherapy	Surgery	Radiotherapy	Other
Acute lymphoblastic leukaemia (ALL)	√			
Acute myeloid leukaemia (AML)	√			
Breast cancer	√ (b/a s.)	√ (1)	√ (2)	√ (3): Hormone therapy
Chronic lymphocytic leukaemia (CLL)	√	√ †		√ Targeted cancer drugs; Steroids
Chronic myeloid leukaemia (CML)	√ (2)		√	√ (1): Targeted cancer drugs; Bone marrow & stem cell transplant
Colorectal cancer	√ (b/a s.)	√ (1)	√ (2)	
Gastric cancer	√ (b/a s.)	√ (1)	√ (2)	
Hairy-cell leukaemia	√ (1)	√ (3) ‡		√ (2): Targeted cancer drugs
Head and neck cancer	√ (2)	√ (1)	√ (2)	
Hodgkin lymphoma	√		√	√ Steroids; Bone marrow transplantation
Kidney cancer	√ *	√ (1)	√ (2)	√ Cryotherapy; Arterial embolisation; Immunotherapy
Liver cancer	√	√ (1)	√	√ Transplantation
Lung cancer (small cell)	√ (1)	√ (3)	√ (2)	
Lung cancer (non-small cell)	√ (2)	√ (1)	√ (3)	
Melanoma skin cancer	√ (2)	√ (4)	√ (3)	√ (1): Biological therapy
Myeloma	√ (1)			√ (2): Steroids; Biological therapy
Non-Hodgkin lymphoma (NHL)	√	√	√	√ Targeted cancer drugs; Stem cell transplant
Oesophageal cancer	√	√ (1)	√	√ Chemoradiotherapy
Ovarian cancer	√ (b/a s.)	√ (1)		
Pancreatic cancer	√ (u)	√ (r)		
Prostate cancer	√	√	√	√ Hormone therapy; High frequency ultrasound therapy; Cryotherapy
Stomach cancer	√	√ (1)	√	√ Chemoradiotherapy
T cell childhood non-Hodgkin lymphoma (NHL)	√ (1)		√ (2)	
Testicular cancer	√ (a.s.)	√ (1)	√	√ Chemoradiotherapy
Uterus cancer	√ (2)	√ (1)	√ (2)	√ (2): Chemoradiotherapy
Urinary (bladder) cancer	√ (3)	√ (1)	√ (2)	
Vaginal cancer	√ (a. r.)	√ (1; 2)	√ (2; 1)	

† If splenectomy is needed; ‡ Splenectomy; \* usually after immunotherapy/radiotherapy, b/a s.: before/after; a.r.: alongside radiotherapy; a.s.: after surgery; u: unresectable; r: respectable

Each number represents preferable treatment therapy according to clinicians' decision-making process and which depends on cancer's stage, type, spread, position, grade and patient's general health condition. Number (1) alone indicates the most usual type of therapy without excluding the possibility of other therapies. In cases where only √ exists, there are more than one different treatment options for this cancer. Neo-adjuvant and adjuvant therapies are represented by √ (b/a s.) indication. Whenever the same number occurs more than once, there are more than one alternative options. Data has been summarised from Cancer Research UK and American Cancer Society websites.<sup>1,2</sup>

## References

- 1 Cancer Research UK. Your cancer type | All cancer types. 2018. <http://www.cancerresearchuk.org/about-cancer/type>.
- 2 American Cancer Society. Cancer. 2018. <https://www.cancer.org/cancer/all-cancer-types.html>.

**Table S2: Baseline characteristics for cancer patients - results from interlinked Cancer Registry cohort.**

	Leukaemia	Lymphoma	Myeloma	Melanoma	Kidney	Ovary	Bladder	Colorectal	Uterus	Breast	Prostate	Lung	Pancreas	Oesophagus	Stomach
Number of patients	3 303	5 499	2 022	4 701	3 114	2 917	4 894	15 903	3 151	20 635	17 694	17 113	3 641	3 541	3 132
Age (mean) <sup>a</sup>	68	66	71	62	68	65	74	72	67	64	72	72	73	72	73
Sex = Female (%)	1 394 (42.2)	2 636 (47.9)	956 (47.3)	2 607 (55.5)	1 220 (39.2)	2 917 (100.0)	1 477 (30.2)	7 701 (48.4)	3 151 (100.0)	20 495 (99.3)	0 (0.0)	7 683 (44.9)	1 977 (54.3)	1 305 (36.9)	1 151 (36.7)
Diabetes (%)	461 (14.0)	786 (14.3)	305 (15.1)	488 (10.4)	598 (19.2)	311 (10.7)	881 (18.0)	2 765 (17.4)	593 (18.8)	2 136 (10.4)	2 727 (15.4)	2 843 (16.6)	1 013 (27.8)	625 (17.7)	588 (18.8)
COPD (%)	546 (16.5)	942 (17.1)	338 (16.7)	682 (14.5)	548 (17.6)	454 (15.6)	869 (17.8)	2 826 (17.8)	422 (13.4)	3 378 (16.4)	3 032 (17.1)	5 596 (32.7)	688 (18.9)	715 (20.2)	633 (20.2)
Asthma (%)	391 (11.8)	730 (13.3)	255 (12.6)	589 (12.5)	405 (13.0)	386 (13.2)	532 (10.9)	2 064 (13.0)	365 (11.6)	2 844 (13.8)	2 149 (12.1)	2 650 (15.5)	440 (12.1)	485 (13.7)	436 (13.9)
CVD (%)	290 (8.8)	408 (7.4)	150 (7.4)	284 (6.0)	272 (8.7)	175 (6.0)	527 (10.8)	1 462 (9.2)	158 (5.0)	1 121 (5.4)	1 490 (8.4)	2 002 (11.7)	353 (9.7)	399 (11.3)	342 (10.9)
Heart failure (%)	158 (4.8)	227 (4.1)	104 (5.1)	121 (2.6)	176 (5.7)	120 (4.1)	275 (5.6)	845 (5.3)	87 (2.8)	525 (2.5)	756 (4.3)	1 114 (6.5)	179 (4.9)	235 (6.6)	216 (6.9)
Renal disease (%)	344 (10.4)	612 (11.1)	327 (16.2)	380 (8.1)	553 (17.8)	267 (9.2)	798 (16.3)	2 027 (12.7)	353 (11.2)	1 679 (8.1)	2 052 (11.6)	2 224 (13.0)	495 (13.6)	448 (12.7)	412 (13.2)

<sup>a</sup>age at the date of diagnoses, COPD: Chronic Obstructive Pulmonary Disease, CVD: Cardiovascular Disease

**Table S3: Life table based on the Cancer Registry.**

Cancer type	Time period	Patients at risk	Deaths	Censored	Proportion dying	Proportion surviving	Survival probability	% survival
Leukaemia	0-1 year	3 303	1 036	0	0.31	0.69	0.69	69%
	1-5 years	2 267	835	271	0.39	0.61	0.42	42%
	5-10 years	1 161	318	474	0.34	0.66	0.28	28%
Lymphoma	0-1 year	5 499	1 287	0	0.23	0.77	0.77	77%
	1-5 years	4 212	992	628	0.25	0.75	0.58	58%
	5-10 years	2 592	512	1 116	0.25	0.75	0.43	43%
Myeloma	0-1 year	2 022	547	0	0.27	0.73	0.73	73%
	1-5 years	1 475	620	166	0.45	0.55	0.40	40%
	5-10 years	689	282	234	0.49	0.51	0.20	20%
Melanoma	0-1 year	4 701	196	0	0.04	0.96	0.96	96%
	1-5 years	4 505	678	768	0.16	0.84	0.81	81%
	5-10 years	3 059	353	1 440	0.15	0.85	0.69	69%
Kidney	0-1 year	3 114	876	0	0.28	0.72	0.72	72%
	1-5 years	2 238	634	419	0.31	0.69	0.50	50%
	5-10 years	1 185	240	512	0.26	0.74	0.37	37%
Ovarian	0-1 year	2 917	875	0	0.30	0.70	0.70	70%
	1-5 years	2 042	867	208	0.45	0.55	0.39	39%
	5-10 years	967	190	414	0.25	0.75	0.29	29%
Bladder	0-1 year	4 894	1 434	0	0.29	0.71	0.71	71%
	1-5 years	3 460	1 345	310	0.41	0.59	0.42	42%
	5-10 years	1 805	534	601	0.35	0.65	0.27	27%
Colorectal	0-1 year	15 903	4 068	0	0.26	0.74	0.74	74%
	1-5 years	11 835	4 065	1 365	0.36	0.64	0.47	47%
	5-10 years	6 405	1 472	2 615	0.29	0.71	0.34	34%
Uterus	0-1 year	3 151	299	0	0.09	0.91	0.91	91%
	1-5 years	2 852	524	414	0.20	0.80	0.73	73%
	5-10 years	1 914	247	825	0.16	0.84	0.61	61%
Breast	0-1 year	20 635	1 197	0	0.06	0.94	0.94	94%
	1-5 years	19 438	3 165	2 953	0.18	0.82	0.77	77%
	5-10 years	13 320	1 780	5 727	0.17	0.83	0.64	64%
Prostate	0-1 year	17 694	1 306	0	0.07	0.93	0.93	93%
	1-5 years	16 388	3 424	2 629	0.23	0.77	0.72	72%
	5-10 years	10 335	2 170	4 543	0.27	0.73	0.52	52%
Lung	0-1 year	17 113	10 957	0	0.64	0.36	0.36	36%
	1-5 years	6 156	4 052	409	0.68	0.32	0.12	12%
	5-10 years	1 695	783	471	0.54	0.46	0.05	5%
Pancreas	0-1 year	3 641	2 736	0	0.75	0.25	0.25	25%
	1-5 years	905	654	51	0.74	0.26	0.07	7%
	5-10 years	200	107	37	0.59	0.41	0.03	3%
Oesophagus	0-1 year	3 541	1 927	0	0.54	0.46	0.46	46%
continue								

Cancer type	Time period	Patients at risk	Deaths	Censored	Proportion dying	Proportion surviving	Survival probability	% survival
	1-5 years	1 614	1 050	102	0.67	0.33	0.15	15%
	5-10 years	462	168	156	0.44	0.56	0.09	9%
Stomach	0-1 year	3 132	1 754	0	0.56	0.44	0.44	44%
	1-5 years	1 378	849	66	0.63	0.37	0.16	16%
	5-10 years	463	155	139	0.39	0.61	0.10	10%

**Table S4: Hazards ratios (HR) according to cancer type from the Cancer Registry and Primary care records in the CPRD, stratified by recency of issued antibiotic prescriptions (exposure group).**

Cancer type	Exposure group	Cancer Registry		Primary Care	
		crude HR [95% CI]	adjusted HR [95% CI]	crude HR [95% CI]	adjusted HR [95% CI]
Leukaemia	recent	1.34 [1.17-1.52]	1.32 [1.16-1.51]	1.55 [1.37-1.75]	1.53 [1.35-1.73]
	previous	1.12 [0.98-1.26]	1.11 [0.98-1.26]	1.10 [0.98-1.24]	1.17 [1.04-1.32]
	past	reference	reference	reference	reference
Lymphoma	recent	1.26 [1.12-1.41]	1.22 [1.08-1.36]	1.27 [1.16-1.40]	1.16 [1.13-1.30]
	previous	1.13 [1.01-1.26]	1.09 [0.97-1.22]	1.07 [0.98-1.18]	1.09 [0.97-1.22]
	past	reference	reference	reference	reference
Myeloma	recent	1.22 [1.05-1.43]	1.19 [1.04-1.36]	1.32 [1.16-1.51]	1.14 [0.99-1.32]
	previous	1.07 [0.93-1.24]	1.09 [0.96-1.23]	1.06 [0.94-1.19]	1.00 [0.88-1.15]
	past	reference	reference	reference	reference
Melanoma	recent	1.28 [1.11-1.49]	1.28 [1.10-1.49]	1.16 [1.03-1.31]	1.37 [1.21-1.56]
	previous	1.08 [0.95-1.22]	1.08 [0.95-1.23]	1.02 [0.92-1.15]	1.07 [0.96-1.20]
	past	reference	reference	reference	reference
Kidney	recent	1.12 [0.97-1.30]	1.11 [0.96-1.30]	1.37 [1.22-1.54]	1.32 [1.14-1.54]
	previous	0.95 [0.83-1.10]	0.94 [0.82-1.08]	1.05 [0.93-1.18]	1.07 [0.93-1.24]
	past	reference	reference	reference	reference
Ovarian	recent	1.40 [1.22-1.60]	1.34 [1.20-1.50]	1.26 [1.13-1.40]	1.27 [1.11-1.44]
	previous	1.07 [0.94-1.23]	1.02 [0.92-1.14]	1.06 [0.95-1.18]	1.09 [0.96-1.24]
	past	reference	reference	reference	reference
Bladder	recent	1.20 [1.07-1.40]	1.39 [1.25-1.54]	1.28 [1.16-1.40]	1.34 [1.23-1.45]
	previous	1.15 [1.00-1.30]	1.16 [1.04-1.30]	1.12 [1.01-1.23]	1.08 [0.99-1.18]
	past	reference	reference	reference	reference
Colorectal	recent	1.22 [1.14-1.30]	1.20 [1.13-1.28]	1.19 [1.09-1.28]	1.22 [1.14-1.30]
	previous	1.04 [0.98-1.10]	1.03 [0.97-1.09]	1.07 [1.00-1.14]	1.05 [0.99-1.11]
	past	reference	reference	reference	reference
Uterus	recent	1.43 [1.22-1.69]	1.40 [1.18-1.65]	1.29 [1.06-1.57]	1.23 [1.01-1.50]
	previous	1.14 [0.98-1.32]	1.10 [0.95-1.29]	1.07 [0.89-1.28]	1.03 [0.86-1.24]
	past	reference	reference	reference	reference
Breast	recent	1.49 [1.36-1.63]	1.36 [1.23-1.49]	1.39 [1.25-1.54]	1.18 [0.96-1.27]
	previous	1.16 [1.07-1.26]	1.10 [1.01-1.20]	1.13 [1.03-1.24]	1.39 [1.27-1.51]
	past	reference	reference	reference	reference
Prostate	recent	1.10 [1.02-1.20]	1.22 [1.15-1.30]	1.31 [1.22-1.41]	1.20 [1.13-1.28]
	previous	0.95 [0.87-1.03]	1.03 [0.97-1.10]	1.12 [1.04-1.20]	1.00 [0.95-1.06]
	past	reference	reference	reference	reference
Lung	recent	1.12 [1.05-1.21]	1.17 [1.08-1.28]	1.04 [0.97-1.12]	1.10 [1.02-1.18]
	previous	0.98 [0.92-1.06]	1.01 [0.93-1.11]	0.96 [0.89-1.04]	1.05 [0.97-1.14]
	past	reference	reference	reference	reference
Pancreas	recent	1.13 [0.98-1.30]	1.07 [0.93-1.24]	1.14 [1.05-1.23]	1.07 [0.92-1.23]

	previous	1.01 [0.88-1.14]	0.98 [0.86-1.12]	1.02 [0.95-1.11]	1.00 [0.88-1.15]
	past	reference	reference	reference	reference
Oesophagus	recent	1.09 [0.97-1.23]	1.07 [0.94-1.20]	1.06 [0.92-1.22]	1.06 [0.92-1.23]
	previous	0.96 [0.86-1.06]	0.93 [0.84-1.03]	0.98 [0.88-1.10]	0.97 [0.87-1.10]
	past	reference	reference	reference	reference
Stomach	recent	0.94 [0.82-1.08]	1.02 [0.89-1.18]	0.99 [0.86-1.14]	1.13 [1.02-1.25]
	previous	0.86 [0.77-0.96]	0.96 [0.86-1.08]	0.98 [0.88-1.10]	0.99 [0.90-1.07]
	past	reference	reference	reference	reference

## Legends to figures S2-S3

### Figure S2: Kaplan Meier plots for each cancer type – English Cancer Registry (Public Health England).

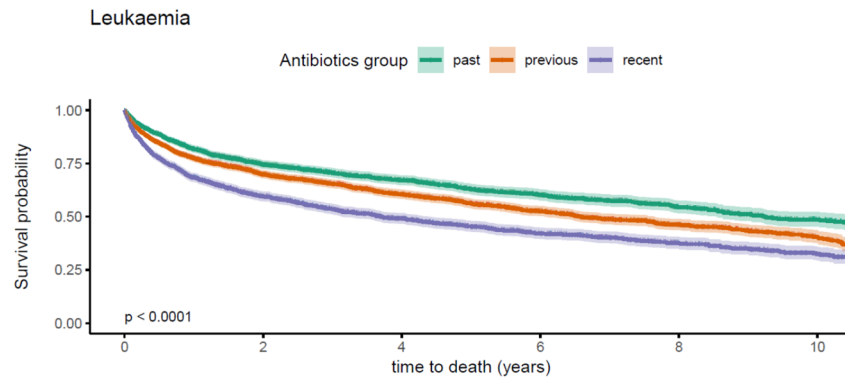
Each curve represents the survival probability for cancer patients who used antibiotics in different time-periods before the cancer diagnosis, according to the expose definition (recent; previous; past). Recent antibiotic users had worst prognoses for all types of cancer in ten-year period except oesophagus, pancreatic and stomach cancer where it is difficult to distinguish the curves due to overlap and long-term follow-up. P-values were calculated from the Log-rank test. Confidence interval is represented in different opacity.

### Figure S3: Kaplan Meier plots - English General Practice Records (Clinical Practice Research Datalink, CPRD).

Each curve represents the survival probability for cancer patients who used antibiotics in different time-periods before the cancer diagnosis, according to the expose definition (recent; previous; past). Recent antibiotic users had worst prognoses for all cancers in ten-year period except lung, pancreatic and stomach cancer where it is difficult to distinguish the curves due to overlap and long-term follow-up. P-values were calculated from the Log-rank test. Confidence interval is represented in different opacity.

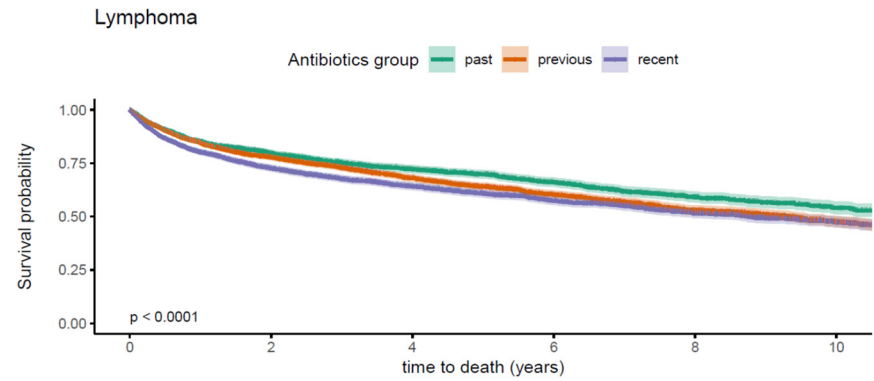


Figure S2



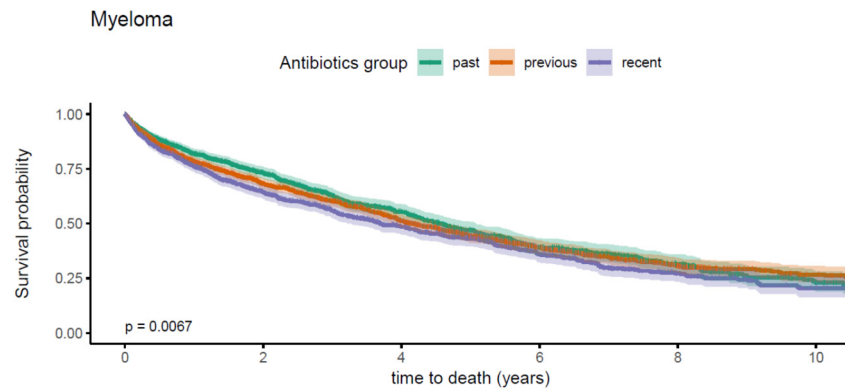
Patients at risk

1902	1090	735	476	272	146
2331	1287	870	542	312	152
1840	870	538	333	190	100



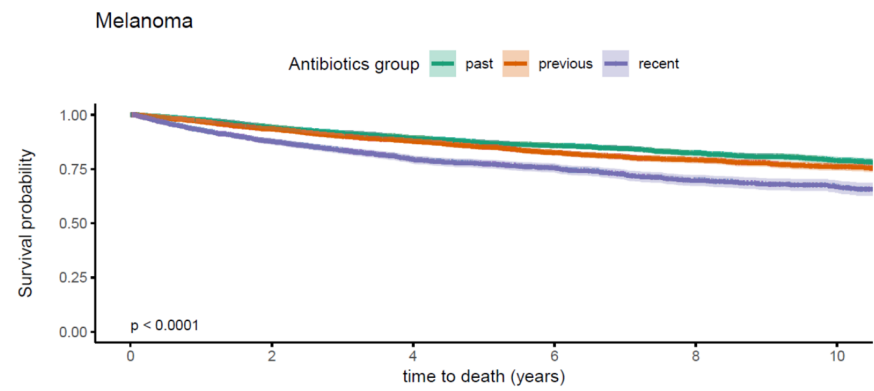
Patients at risk

2340	1461	1049	692	386	213
3096	1947	1301	844	511	291
2778	1631	1115	726	445	254



Patients at risk

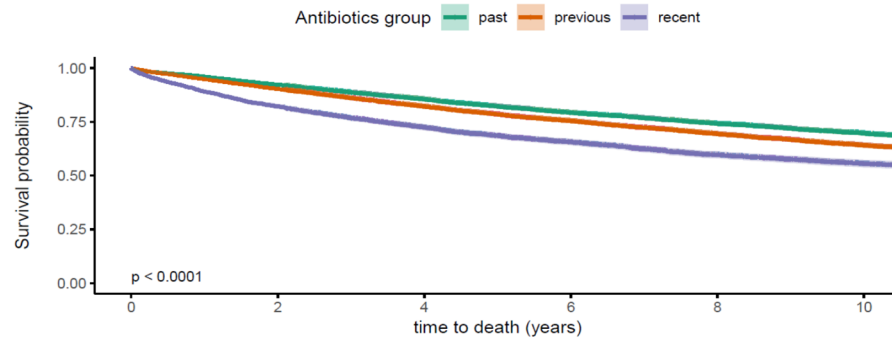
1096	600	319	163	83	35
1521	779	428	237	116	53
1007	473	254	138	64	27



Patients at risk

5340	3872	2729	1827	1167	648
4837	3539	2497	1697	1121	630
2440	1642	1091	735	445	239

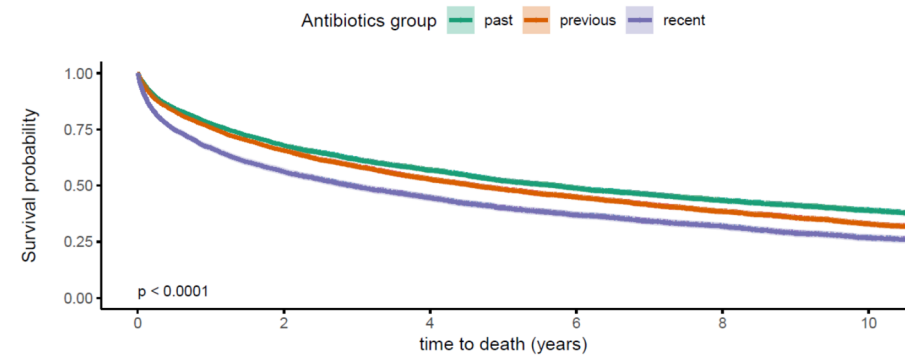
### Breast Cancer



#### Patients at risk

8103	7482	6221	4835	3569	2461
8582	7752	6328	4890	3567	2439
3950	3246	2569	1919	1358	919

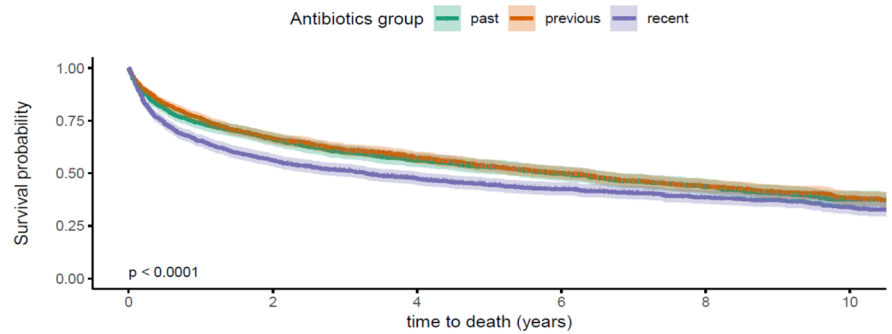
### Colorectal Cancer



#### Patients at risk

6057	4111	3101	2236	1558	1021
6187	4062	2981	2151	1438	864
3659	2057	1468	1023	700	436

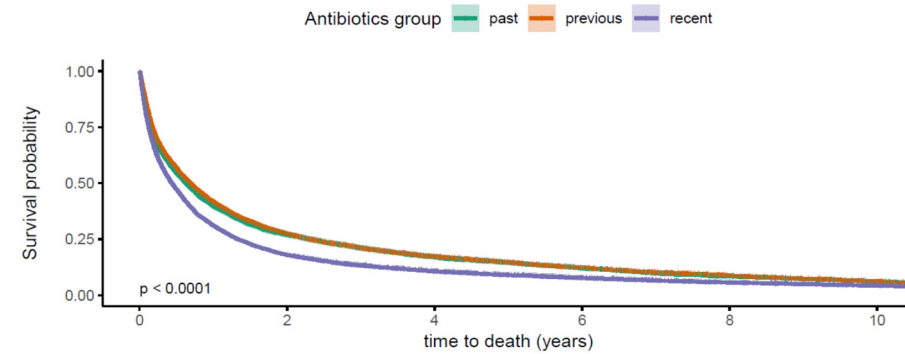
### Kidney Cancer



#### Patients at risk

882	584	432	312	202	125
1188	793	572	399	280	185
1044	586	424	286	192	123

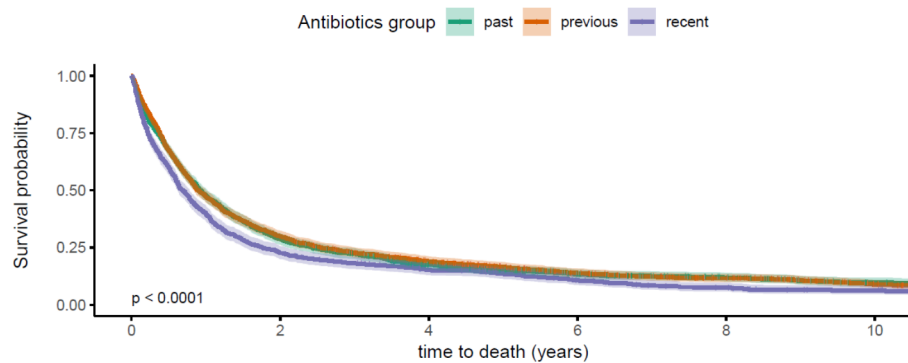
### Lung Cancer



#### Patients at risk

3338	900	520	321	188	117
5097	1403	806	502	298	165
8678	1563	830	492	285	160

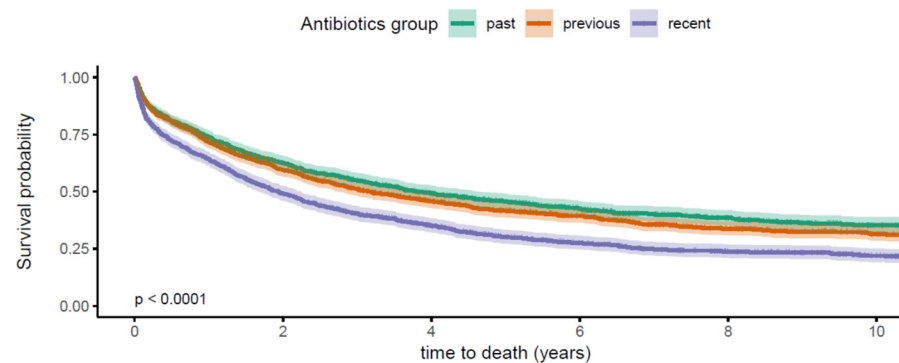
### Cancer of Oesophagus



#### Patients at risk

past	1239	356	197	124	85	48
previous	1455	436	252	156	106	60
recent	847	192	117	72	45	30

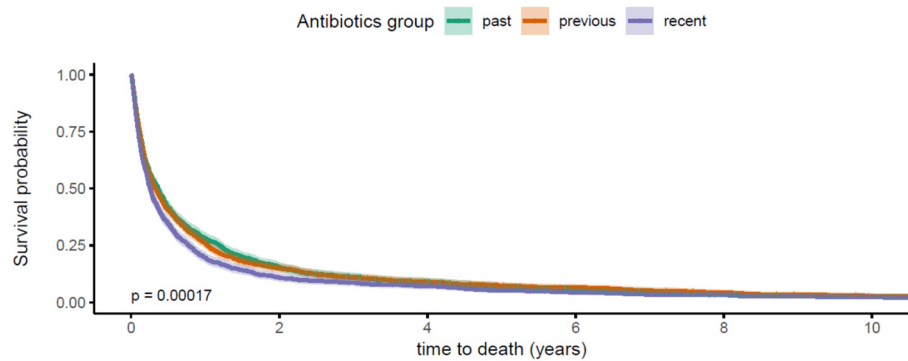
### Ovarian Cancer



#### Patients at risk

past	929	580	417	294	201	131
previous	1061	631	441	323	212	145
recent	927	456	290	191	135	88

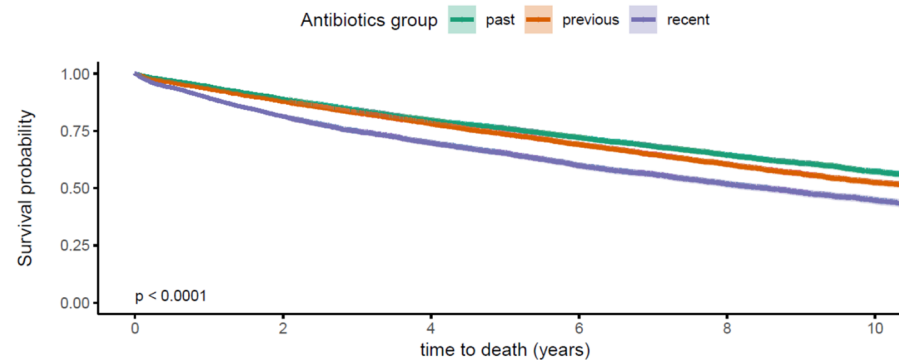
### Pancreatic Cancer



#### Patients at risk

past	1208	188	101	51	28	20
previous	1347	201	110	69	41	23
recent	1086	118	68	38	22	13

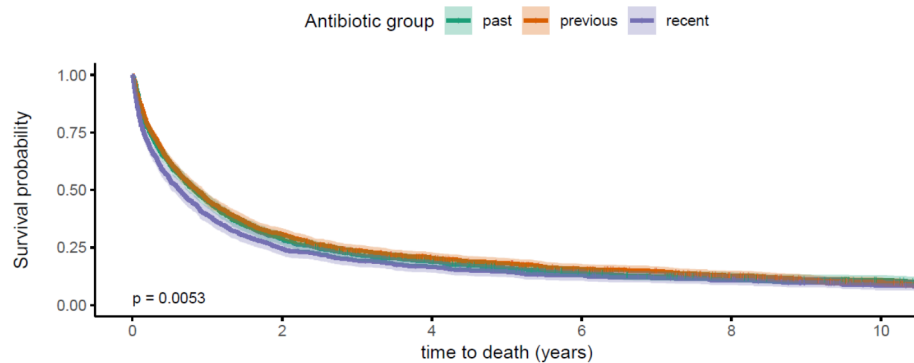
### Prostate Cancer



#### Patients at risk

past	6364	5664	4456	3327	2257	1421
previous	6547	5748	4563	3329	2237	1394
recent	4783	3894	2967	2043	1356	811

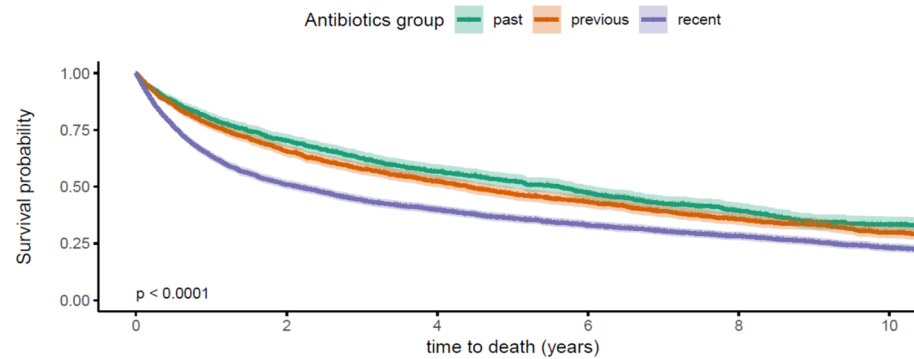
### Stomach Cancer



#### Patients at risk

past	1064	306	192	126	92	67
previous	1315	405	251	173	113	73
recent	753	184	118	82	59	29

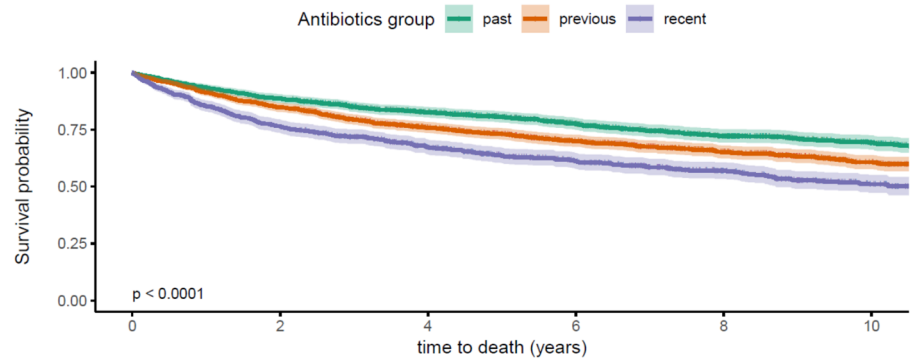
### Urinary Cancer



#### Patients at risk

past	987	694	520	380	249	171
previous	1397	917	672	492	335	220
recent	2510	1278	929	663	460	280

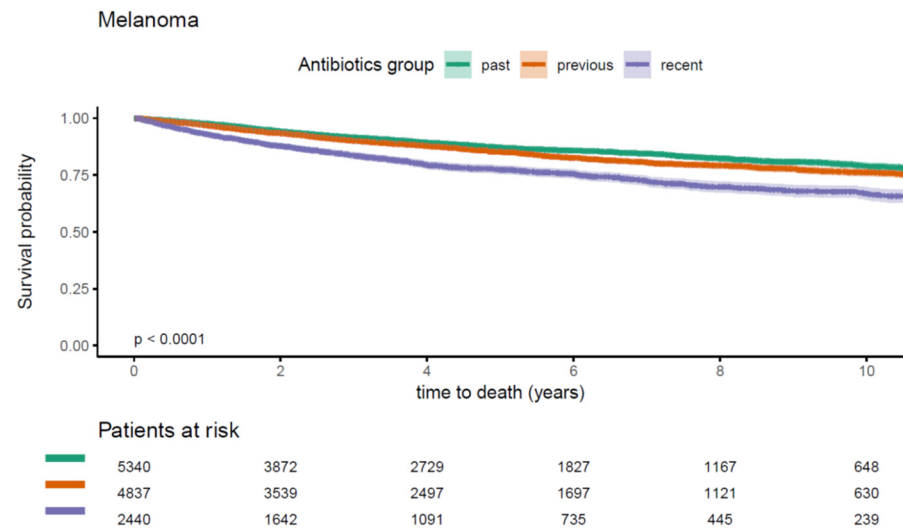
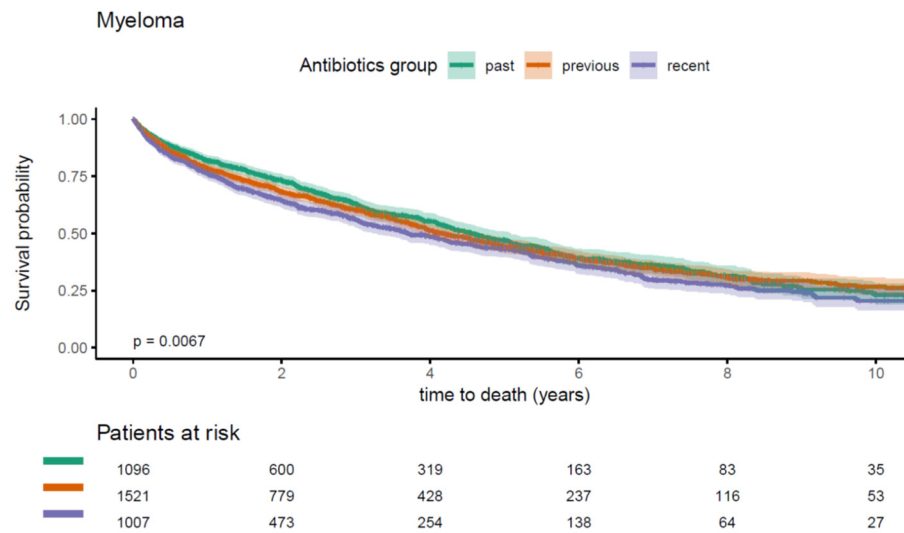
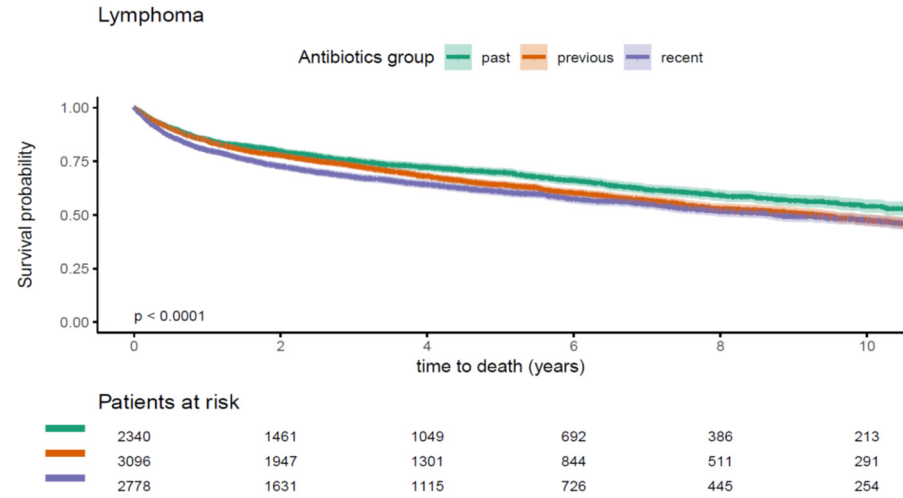
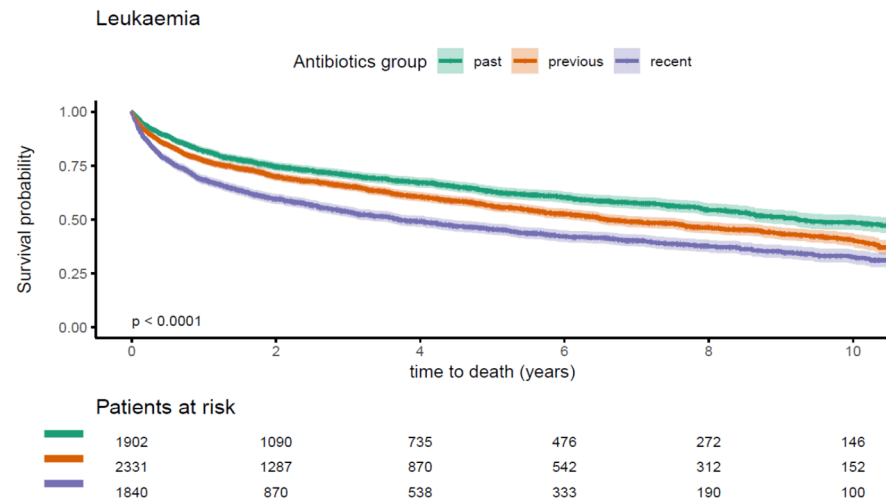
### Cancer of Uterus



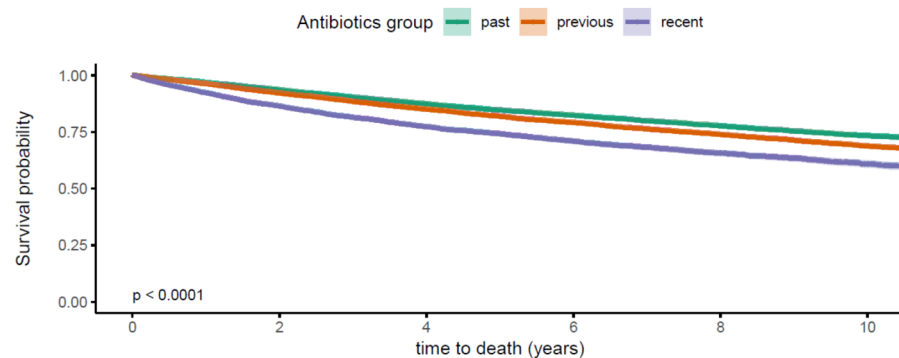
#### Patients at risk

past	1077	954	798	627	474	336
previous	1258	1066	851	673	487	336
recent	816	625	500	378	265	171

Figure S3



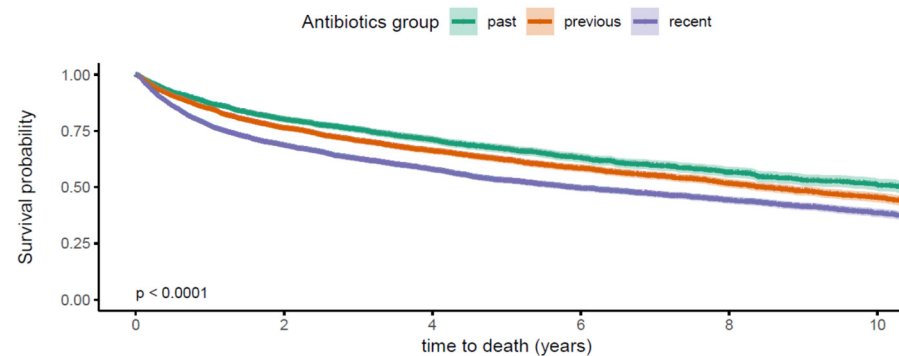
### Breast Cancer



#### Patients at risk

past	15185	11054	7696	5241	3277	1895
previous	15537	11375	7987	5402	3432	1944
recent	7348	5026	3416	2268	1402	769

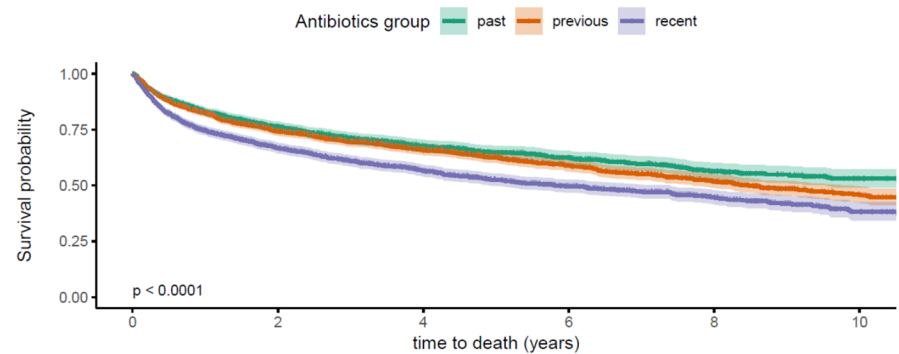
### Colorectal Cancer



#### Patients at risk

past	3056	1917	1273	811	484	269
previous	4599	2785	1821	1212	751	400
recent	6149	3316	2142	1309	741	369

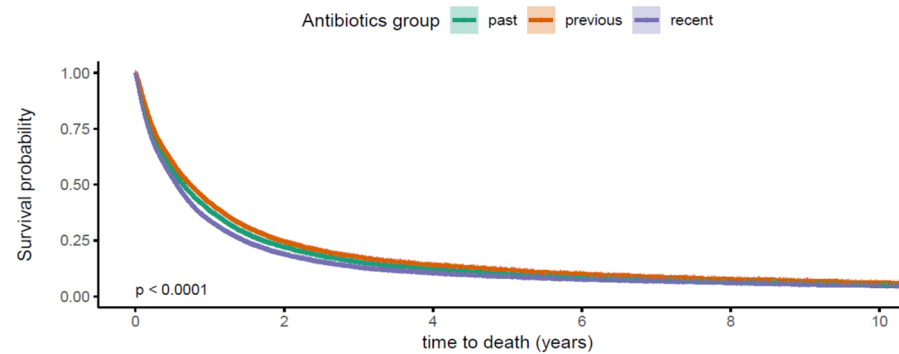
### Kidney Cancer



#### Patients at risk

past	1394	793	478	311	177	91
previous	1933	1107	730	448	259	120
recent	1664	854	540	322	166	62

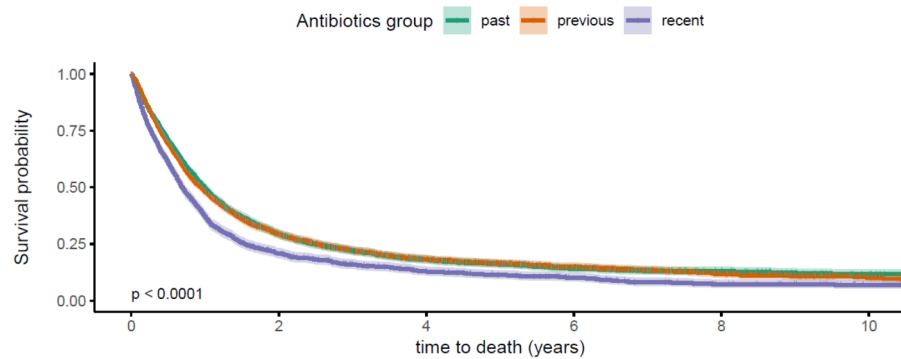
### Lung Cancer



#### Patients at risk

past	4417	694	271	125	66	31
previous	7180	1285	530	257	126	52
recent	12255	1700	660	342	169	73

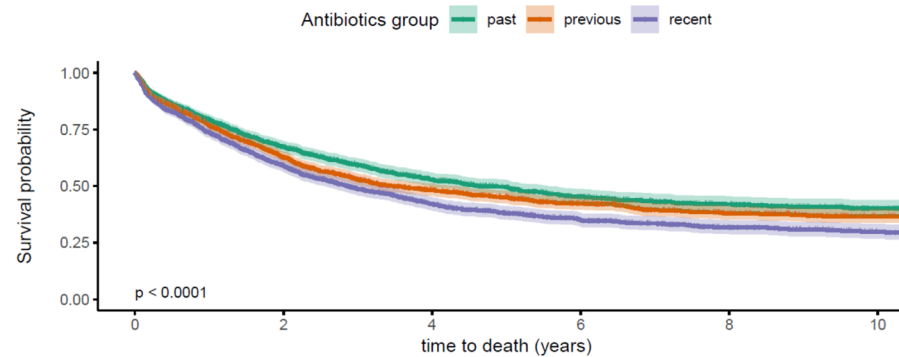
### Cancer of Oesophagus



#### Patients at risk

	2209	481	217	111	69	34
	2350	519	246	140	72	29
	1392	213	105	62	31	13

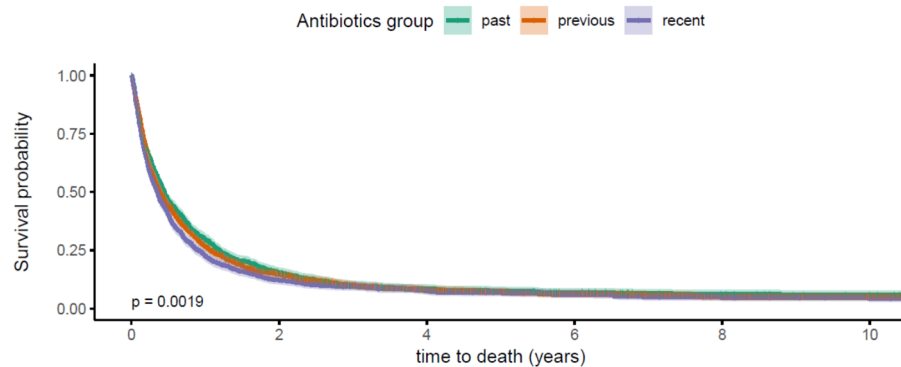
### Ovarian Cancer



#### Patients at risk

	1324	702	419	263	176	91
	1570	800	475	315	197	116
	1382	640	349	222	133	83

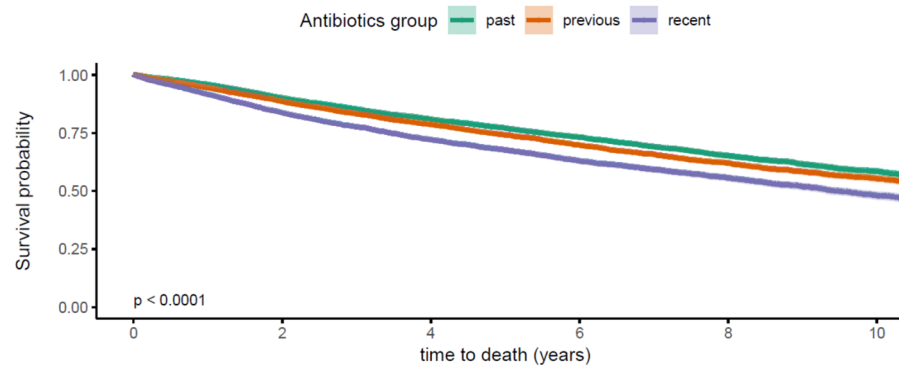
### Pancreatic Cancer



#### Patients at risk

	1443	145	63	38	22	12
	1625	168	62	35	14	9
	1242	105	47	28	16	10

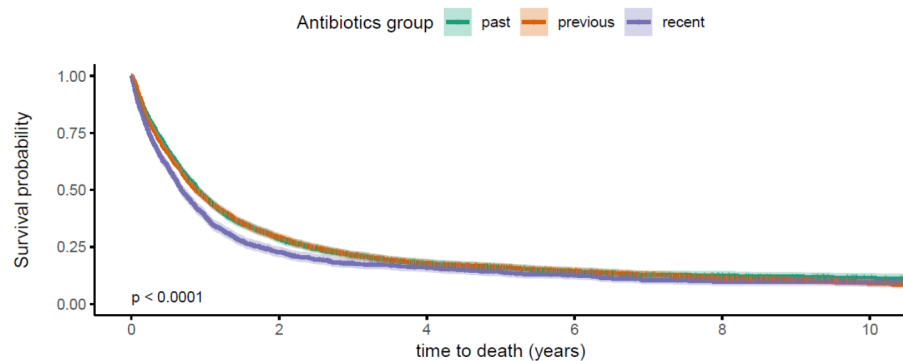
### Prostate Cancer



#### Patients at risk

	10501	7294	4765	2990	1757	887
	10663	7527	5031	3183	1896	977
	7755	5136	3285	2034	1198	595

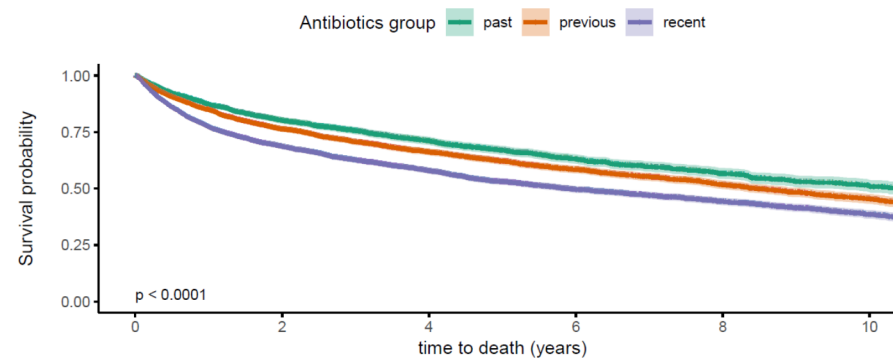
### Stomach Cancer



#### Patients at risk

	0	2	4	6	8	10
past	2296	477	230	128	78	36
previous	2564	583	281	171	92	40
recent	1477	260	142	81	41	23

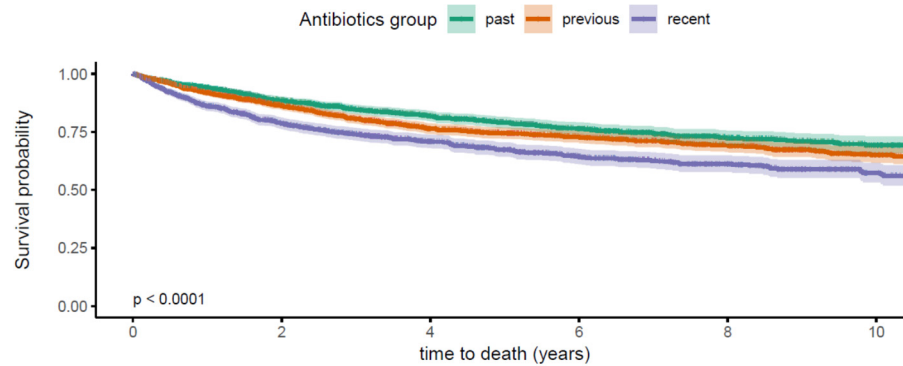
### Urinary Cancer



#### Patients at risk

	0	2	4	6	8	10
past	3056	1917	1273	811	484	269
previous	4599	2785	1821	1212	751	400
recent	6149	3316	2142	1309	741	369

### Cancer of Uterus



#### Patients at risk

	0	2	4	6	8	10
past	1470	998	676	444	254	138
previous	1673	1133	733	504	323	172
recent	1179	732	473	308	180	98



**Table S5: Antibiotics usage for cancer patients that received prescriptions between 0-3 months before cancer diagnosis. Results from the Cancer Registry cohort. Number of recent antibiotic users and percentage (%) per cancer type.**

Antibiotics*	Leukemia	Lymphoma	Myeloma
Amoxicillin (b)-amoxicillin/Ca <sup>†</sup>	397 (38)	703 (38)	231 (41)
Flucloxacillin (b)	110 (11)	220 (12)	44 (8)
Trimethoprim (S)	85 (8)	149 (8)	74 (13)
Erythromycin (M)	83 (8)	127 (7)	27 (5)
Clarithromycin (M)	78 (7)	139 (7)	41 (7)
Phenoxymethylpenicillin (b)	62 (6)	102 (5)	11 (2)
Cephalexin (C)	53 (5)	86 (5)	35 (6)
Doxycycline (T)	52 (5)	87 (5)	24 (4)
Ciprofloxacin (Q)	48 (5)	93 (5)	29 (5)
Cefaclor (C)	18 (2)	17 (1)	9 (2)
Metronidazole (Ni)	15 (1)	35 (2)	4 (1)
All antibiotic users	1043 (100)	1864 (100)	570 (100)

\*Antibiotic route may include oral, intramuscular, intravenous and rectal administration however, 99.9% refer to oral antibiotics; <sup>†</sup>Ca: Clavulanic acid; Antibiotic categories in parentheses: (b) = b-lactam; (S) = Sulphonamides; (M) = Macrolides; (C) = Cephalosporins; (Q) = Quinolones; (T) = Tetracyclines; (Ni) = Nitroimidazole

**Table S6: English Cancer Registry (National Cancer Registration and Analysis Service, Public Health England) - sensitivity analysis. The cohort was stratified to the following groups to test whether this classification has a significant effect on hazards ratio (HR) findings.**

		Leukaemia	Lymphoma	Myeloma
Stratification by	antibiotics group	HR [95% CI]	HR [95% CI]	HR [95% CI]
people younger than 65 years	recent	1.70 [1.30-2.22]	1.29 [1.05-1.60]	1.27 [0.94-1.70]
	previous	1.38 [1.04-1.81]	1.12 [0.90-1.39]	1.24 [0.94-1.62]
	past	reference	reference	reference
people 65 years and older	recent	1.15 [0.96-1.37]	1.06 [0.94-1.21]	1.18 [0.99-1.41]
	previous	1.13 [0.96-1.36]	1.06 [0.93-1.22]	1.01 [0.86-1.19]
	past	reference	reference	reference
gender = male	recent	1.28 [1.08-1.52]	1.18 [1.02-1.38]	1.10 [0.89-1.66]
	previous	1.16 [1.00-1.36]	1.10 [0.95-1.28]	1.08 [0.89-1.31]
	past	reference	reference	reference
gender = female	recent	1.35 [1.10-1.67]	1.13 [0.96-1.34]	1.34 [1.07-1.67]
	previous	1.14 [0.94-1.39]	1.16 [0.99-1.36]	1.09 [0.88-1.35]
	past	reference	reference	reference
follow-up before 2008	recent	1.15 [0.97-1.38]	1.03 [0.87-1.21]	0.88 [0.66-1.18]
	previous	1.08 [0.91-1.27]	1.20 [1.03-1.40]	0.76 [0.57-1.00]
	past	reference	reference	reference
follow-up after 2008	recent	1.21 [1.00-1.47]	1.19 [0.98-1.45]	1.11 [0.87-1.41]
	previous	1.49 [1.22-1.81]	1.06 [0.88-1.29]	1.06 [0.84-1.32]
	past	reference	reference	reference
people without comorbidities*	recent	1.23 [1.01-1.50]	1.06 [0.87-1.29]	1.32 [1.04-1.68]
	previous	1.34 [1.10-1.66]	1.11 [0.92-1.33]	1.16 [0.93-1.44]
	past	reference	reference	reference
people with comorbidities*	recent	1.15 [1.00-1.33]	1.11 [0.97-1.29]	1.09 [0.89-1.33]
	previous	1.58 [1.36-1.83]	1.02 [0.89-1.18]	1.00 [0.82-1.21]
	past	reference	reference	reference

\*People who did not have any recorded comorbidity according to either Charlson Comorbidity Index or QCancer risk tool related variables on which the models were adjusted.

**Table S7: English General Practices (Clinical Practice Research Datalink, CPRD) - sensitivity analyses.**  
**The cohort was stratified to the following groups to test whether this classification has a significant effect on hazards ratio findings.**

		<b>Leukaemia</b>	<b>Lymphoma</b>	<b>Myeloma</b>
<b>Stratification by</b>	<b>antibiotics group</b>	<b>HR [95% CI]</b>	<b>HR [95% CI]</b>	<b>HR [95% CI]</b>
people younger than 65 years	recent	2.04 [1.32-3.35]	1.94 [1.08-3.83]	1.14 [0.87-1.49]
	previous	1.52 [0.91-2.71]	0.98 [0.61-1.88]	1.10 [0.86-1.39]
	past	reference	reference	reference
people 65 years and older	recent	1.35 [1.17-1.56]	1.12 [0.98-1.29]	1.06 [0.92-1.22]
	previous	1.05 [0.92-1.20]	1.10 [0.96-1.25]	0.93 [0.81-1.05]
	past	reference	reference	reference
gender = male	recent	1.68 [1.44-1.96]	1.2 [1.06-1.36]	1.13 [0.95-1.34]
	previous	1.16 [1.00-1.35]	1.04 [0.92-1.18]	0.99 [0.85-1.16]
	past	reference	reference	reference
gender = female	recent	1.36 [1.12-1.66]	1.26 [1.09-1.45]	0.99 [0.82-1.18]
	previous	1.07 [0.88-1.29]	1.11 [0.96-1.28]	0.92 [0.78-1.09]
	past	reference	reference	reference
follow-up before 2008	recent	1.43 [1.22-1.69]	1.21 [1.06-1.38]	1.08 [0.91-1.29]
	previous	1.12 [0.96-1.31]	1.09 [0.96-1.24]	0.97 [0.83-1.14]
	past	reference	reference	reference
follow-up after 2008	recent	1.65 [1.38-1.99]	1.30 [1.13-1.49]	0.99 [0.79-1.23]
	previous	1.12 [0.93-1.33]	1.01 [0.88-1.16]	0.93 [0.76-1.14]
	past	reference	reference	reference
people without comorbidities*	recent	1.72 [1.47-2.02]	1.18 [1.01-1.37]	1.11 [0.91-1.36]
	previous	1.06 [0.91-1.25]	1.12 [0.97-1.30]	0.95 [0.80-1.14]
	past	reference	reference	reference
people with comorbidities	recent	1.46 [1.24-1.71]	1.34 [1.19-1.51]	1.12 [0.96-1.30]
	previous	1.12 [0.96-1.30]	1.05 [0.93-1.18]	1.03 [0.89-1.19]
	past	reference	reference	reference

\*People who did not have any recorded comorbidity according to either Charslon Comorbidity Index or QCancer risk tool related variables on which the models were adjusted.