Vaccine effectiveness against COVID-19 breakthrough infections in patients with cancer (UKCCEP): a population-based test-negative case-control study

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Summary

Background People with cancer are at increased risk of hospitalisation and death following infection with SARS-CoV-2. Therefore, we aimed to conduct one of the first evaluations of vaccine effectiveness against breakthrough SARS-CoV-2 infections in patients with cancer at a population level.

Methods In this population-based test-negative case-control study of the UK Coronavirus Cancer Evaluation Project (UKCCEP), we extracted data from the UKCCEP registry on all SARS-CoV-2 PCR test results (from the Second Generation Surveillance System), vaccination records (from the National Immunisation Management Service), patient demographics, and cancer records from England, UK, from Dec 8, 2020, to Oct 15, 2021. Adults (aged ≥18 years) with cancer in the UKCCEP registry were identified via Public Health England's Rapid Cancer Registration Dataset between Jan 1, 2018, and April 30, 2021, and comprised the cancer cohort. We constructed a control population cohort from adults with PCR tests in the UKCCEP registry who were not contained within the Rapid Cancer Registration Dataset. The coprimary endpoints were overall vaccine effectiveness against breakthrough infections after the second dose (positive PCR COVID-19 test) and vaccine effectiveness against breakthrough infections at 3–6 months after the second dose in the cancer cohort and control population.

Findings The cancer cohort comprised 377 194 individuals, of whom 42 882 had breakthrough SARS-CoV-2 infections. The control population consisted of 28 010 955 individuals, of whom 5 748 708 had SARS-CoV-2 breakthrough infections. Overall vaccine effectiveness was 69·8% (95% CI 69·8–69·9) in the control population and 65·5% (65·1–65·9) in the cancer cohort. Vaccine effectiveness at 3–6 months was lower in the cancer cohort (47·0%, 46·3–47·6) than in the control population (61·4%, 61·4–61·5).

Interpretation COVID-19 vaccination is effective for individuals with cancer, conferring varying levels of protection against breakthrough infections. However, vaccine effectiveness is lower in patients with cancer than in the general population. COVID-19 vaccination for patients with cancer should be used in conjunction with non-pharmacological strategies and community-based antiviral treatment programmes to reduce the risk that COVID-19 poses to patients with cancer.

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Introduction

Global COVID-19 vaccine trials have shown that vaccination decreases the incidence of COVID-19 and its associated complications.[1,2] However, people with cancer are at increased risk of morbidity and mortality from COVID-19.[3–5] A cancer diagnosis or cancer treatment has generally been an exclusion criterion for vaccine trials, leading to a paucity of clear evidence of their benefit and some vaccine hesitancy among patients with cancer.[6,7]

Small cohort studies have shown that patients with cancer have an attenuated immune response following COVID-19 vaccination, which could result in lower or absent humoral and cellular responses, compared with groups of healthy volunteers.[8–12] Nevertheless, national and international guidelines recommend vaccinating patients with cancer against COVID-19.[13–15]

Considering the wider issue of waning vaccine effectiveness,[16,17] there is a need to clarify the effectiveness of COVID-19 vaccination in patients with cancer and close crucial evidence gaps.[18,19] Therefore, we aimed to conduct one of the first population-based evaluations of COVID-19 vaccine effectiveness in patients with cancer

Research in context

Evidence before this study

Using the search terms "coronavirus", "COVID-19", "vaccine", "vaccination", "cancer", "effectiveness", and "efficacy", we searched PubMed without language restrictions for studies published between database inception and Jan 25, 2022, related to the efficacy or effectiveness of COVID-19 vaccination in patients with cancer. To our knowledge, there are no studies that have described COVID-19 vaccine effectiveness in patients with cancer at a population level. Several studies have described antibody or cellular immune responses following COVID-19 vaccination or SARS-CoV-2 infection. Leticia Monin and colleagues (2021) reported on immune responses to BNT162b2 (Pfizer–BioNtech) in 152 patients with cancer. Fendler and colleagues (2021) reported on immune responses following SARS-CoV-2 infection in 118 patients with cancer. However, no studies have looked at clinical outcome measures, such as the prevention of SARS-CoV-2 infection or COVID-19-related hospitalisation and death, in patients with cancer.

Added value of this study

To our knowledge, this study is one of the first to evaluate COVID-19 vaccine effectiveness in patients with cancer in a real-world health system at a population level in England, UK. We used the largest cohort of patients with cancer globally, enabling the most comprehensive analysis of the risk of COVID-19 to patients with cancer. We found that COVID-19 vaccination is effective in patients with cancer, albeit less so than in the general control population, with evidence of waning vaccine effectiveness at 3–6 months following the second dose. Patients with lymphoma or leukaemia and those who had received a cancer diagnosis or cancer treatment within the past 12 months had lower vaccine effectiveness.

Implications of all the available evidence

The COVID-19 pandemic continues to have a considerable impact on people with cancer. Although COVID-19 vaccination reduces the risk of infection and poor outcomes for the general population, this protection can be heterogenous for patients with cancer, who then remain at increased risk from COVID-19. COVID-19 vaccination for patients with cancer should be used in conjunction with other non-pharmacological strategies, such as behaviour modification and personal protective equipment, and community-based antiviral treatment programmes to reduce the risk that COVID-19 poses to patients with cancer. Such measures will be crucially important as global health-care and cancer care systems adapt to living with COVID-19 as an endemic disease.

from a real-world health system in England, UK. Our use of the largest cohort of patients with cancer worldwide enabled, to our knowledge, the most comprehensive analysis of the risk that COVID-19 presents to patients with cancer. We describe how cancer subtype, treatment, and patient demographics interact to affect COVID-19 vaccine effectiveness.

Methods

Study design and data sources

The UK Coronavirus Cancer Evaluation Project (UKCCEP) is a subproject of the UK Coronavirus Cancer Monitoring Project and is the next iteration of the UK's COVID-19 pandemic response to monitor, safeguard, and protect patients with cancer. In this population-based test-negative case-control study, we extracted PCR test results, vaccination records, patient demographics, and cancer records (eg, treatment, stage, and subtype) in England from the UKCCEP registry between Dec 8, 2020 (the start of COVID-19 vaccination in England) and Oct 15, 2021 (the study period). This period of analysis coincided with the second COVID-19 wave in the UK, which was principally driven by the delta variant (B.1.617.2).[20]

Patient-level COVID-19 PCR test results, including from community and hospital testing, were obtained for UKCCEP from the Second Generation Surveillance System. National Health Service (NHS) England and NHS Test and Trace use PCR testing for those with symptoms of COVID-19 and lateral flow testing (also known as antigen-detecting rapid diagnostic testing) for the identification of asymptomatic cases. During the study period, confirmatory PCR testing was mandated for individuals testing positive on lateral flow tests. In the NHS, infection and prevention control measures in secondary care required COVID-19 PCR testing of asymptomatic patients before many procedures or treatments. Vaccination records for the UKCCEP registry were obtained from the National Immunisation Management Service. All COVID-19 vaccines licensed in England were considered.

The number of COVID-19 contacts was obtained from individuals who had supplied information as part of the Contact Tracing and Advice Service, which records information about the number of interpersonal contacts before infection or following exposure to COVID-19. Data on COVID-19-related hospitalisation and death were extracted from the Secondary Use Statistics dataset between Dec 8, 2020, and Oct 15, 2021.

From those who had SARS-CoV-2 PCR testing in the Second Generation Surveillance System, we identified adults (aged ≥18 years) with cancer to comprise our cancer cohort via Public Health England's Rapid Cancer Registration Dataset between Jan 1, 2018, and April 30, 2021. This date range was selected to better represent individuals with active cancer, excluding those with a more historical diagnosis. The national Rapid Cancer Registration Dataset includes information about receipt of radiotherapy and systemic anticancer treatments, which is an umbrella term of cancer treatments,

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For more on the **UK Coronavirus Cancer Monitoring Project** see https://ukcoronavirus cancermonitoring.com/

For more on the **Second Generation Surveillance System** see https://www.gov.uk/government/publications/national-covid-19-surveillance-reports/sources-of-covid-19-systems

For more on the **National Immunisation Management Service** see https://www.scwcsu.nhs.uk/services/nhs-immunisation-management-service/

For more on the **Secondary Use Statistics dataset** see https://digital.nhs.uk/services/secondary-uses-service-sus

For more on the **Rapid Cancer Registration Dataset** see http://www.ncin.org.uk/collecting_and_using_data/rcrd

For more on the **UK Policy Framework for Health and Social Care Research** see https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

including cytotoxic (chemotherapy), targeted, immunotherapy, or hormonal treatments. We constructed a control population cohort from adults (aged ≥18 years) with PCR tests in the Second Generation Surveillance System who were not contained within the Rapid Cancer Registration Dataset, excluding those with active cancer. Data linkage between the Second Generation Surveillance System, the National Immunisation Management Service, the Contact Tracing and Advice Service, and the Rapid Cancer Registration Dataset required exact matching of NHS identification numbers.

This study was designed as a public health surveillance analysis to support rapid clinical decision making during the pandemic in accordance with the UK Policy Framework for Health and Social Care Research. The project was supported by the Department of Health and Social Care, with ethical approval from the Health Research Authority (20/WA/0181), and patient consent was waived.

Statistical analysis

The coprimary outcomes of the study were overall vaccine effectiveness (defined relative to breakthrough infections [positive PCR test] following the second dose of COVID-19 vaccine during the period of assessment) and vaccine effectiveness against breakthrough infections at 3–6 months after the second dose. A test-negative case-control method was used to estimate vaccine effectiveness in the cancer cohort and the control population.

Test-negative case-control studies have high concordance with findings from randomised clinical trials and are a standardised measure of vaccine effectiveness for phase 4 surveillance studies.[21,22] Within the test-negative case-control study design, exposure was defined as any positive PCR test result within the study period. Vaccine effectiveness was calculated with the test-negative case-control method formula: 1 minus the ratio of PCR-positive vaccinated to PCR-positive unvaccinated individuals divided by the ratio of PCR-negative vaccinated to PCR-negative unvaccinated individuals. Each datapoint corresponds to a single PCR test and higher vaccine effectiveness would be shown if there were lower numbers of vaccinated individuals among those who had positive tests than among those who had negative tests. The negative tests act as an internal control, comprising individuals who might have symptoms from non-COVID-19 causes. This design addresses challenges that are often present in observational studies, such as differences in health-seeking behaviours or access to testing. Vaccine manufacturers were combined in our evaluation because the focus of our study was a description of vaccine effectiveness and waning in the cancer cohort relative to the control population. Additionally, vaccine effectiveness according to different manufacturers is relatively well described in the literature.[1,2]

Predefined subgroup analyses of overall vaccine effectiveness were done in the cancer cohort by vaccine type (BNT162b2 [Pfizer–BioNtech], ChAdOx1 nCov-19 [AZD1222; AstraZeneca], or mixed and other), cancer type (solid organ *vs* haematological) and subtype (as determined by codes from the tenth revision of the International Classification of Diseases), cancer stage, date of cancer diagnosis (≤12 months *vs* >12 months relative to data cutoff), and receipt of systemic anticancer cancer treatment or radiotherapy (none *vs* any and received ≤12 months ago *vs* received >12 months ago relative to data cutoff). Within the cancer cohort, exploratory multivariable logistic regression with the Wald test was used to describe vaccine effectiveness (overall and at 3–6 months) in the aforementioned predefined subgroups, excluding vaccine type, and was adjusted for the clinically important covariates of age, sex, ethnicity, and Index of Multiple Deprivation (determined by geographical location),[23] which might have acted as confounders, effect modifiers, or both for analysing vaccine effectiveness. Further prespecified exploratory analyses of cancer subtypes, receipt of radiotherapy or systemic anticancer treatment, and time of diagnosis (≤12 months *vs* >12 months relative to data cutoff) were done to identify whether any subgroups were more likely to develop waning vaccine effectiveness at 3–6 months following multivariable correction. Waning vaccine effectiveness was defined as the change in percentage points between vaccine effectiveness over the study period subtracted from vaccine effectiveness at 3–6 months. Wald test z values were used to assess statistical significance.

Variables were either binary (sex, cancer treatments, cancer types, time from diagnosis, PCR status, outcomes and vaccination status) or grouped (age, ethnicity, Index of Multiple Deprivation, cancer subtypes, and stage), with age categorised in 10-year age bands (18–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, 80–89 years, and ≥90 years) in accordance with a previous vaccine effectiveness study.[21] We used information from the Contact Tracing and Advice Service for post-hoc analyses of patient behaviour by patient age band and cancer stage. Contacts included both household and non-household contacts. The mean numbers of contacts and SDs were calculated for each subgroup.

Steps were taken to reduce bias at several study stages, including robust adherence to the data analysis plan, minimising selection bias, and ensuring that the full dataset was reviewed and interpretations were approved by multiple consortium authors. Participants with missing or not specified data were excluded from our analyses.

In further post-hoc analyses, we examined COVID-19 hospitalisation (defined as admission to hospital from 1 day before to 14 days after a positive PCR test) and COVID-19 death (death occurring up to 28 days after a

	Cancer cohort			Control population		
	All (n=1 712 728)	PCR positive (n=56 102)	PCR negative (n=1 656 626)	All (n=75 686 290)	PCR positive (n=5 808 432)	PCR negative (n=69 877 858)
Age, years	69 (58–78)	68 (56–77)	69 (58–78)	45 (29–61)	34 (20–51)	46 (30–62)
Sex						
Female	862 169 (50·34%)	27 266 (48·60%)	834 903 (50·40%)	45 991 583 (60·77%)	3 033 061 (52·22%)	42 958 522 (61·48%)
Male	850 559 (49·66%)	28 836 (51·40%)	821 723 (49·60%)	29 637 195 (39·16%)	2 775 160 (47·78%)	26 862 035 (38·44%)
Other or unknown	0	0	0	57 512 (0·08%)	211 (<0·01%)	57 301 (0·08%)
Ethnicity						
White or White British	1 533 034 (89·51%)	47 856 (85·30%)	1 485 178 (89·65%)	55 551 500 (73·40%)	2 869 777 (49·41%)	52 681 723 (75·39%)
Asian or Asian British	70 859 (4·14%)	3245 (5·78%)	67 614 (4·08%)	5 022 431 (6·64%)	359 812 (6·19%)	4 662 619 (6·67%)
Black or Black British	50 063 (2·92%)	2051 (3·66%)	48 012 (2·90%)	2 611 003 (3·45%)	102 911 (1·77%)	2 508 092 (3·59%)
Mixed or other ethnic group	15 885 (0·93%)	617 (1·10%)	15 268 (0·92%)	1 267 826 (1·68%)	55 454 (0·95%)	1 212 372 (1·73%)
Unknown	42 887 (2·50%)	2333 (4·16%)	40 554 (2·45%)	11 233 530 (14·84%)	2 420 478 (41·67%)	8 813 052 (12·61%)
Index of Multiple Deprivation						
1	129 287 (7·55%)	4280 (7·63%)	125 007 (7·55%)	5 735 964 (7·58%)	364 776 (6·28%)	5 371 188 (7·69%)
2	134 427 (7·85%)	4390 (7·83%)	130 037 (7·85%)	6 073 257 (8·02%)	388 336 (6·69%)	5 684 921 (8·14%)
3	143 823 (8·40%)	4715 (8·40%)	139 108 (8·40%)	6 252 170 (8·26%)	396 746 (6·83%)	5 855 424 (8·38%)
4	151 891 (8·87%)	4339 (7·73%)	147 552 (8·91%)	6 351 129 (8·39%)	391 737 (6·74%)	5 959 392 (8·53%)
5	157 359 (9·19%)	4106 (7·32%)	153 253 (9·25%)	6 296 906 (8·32%)	382 963 (6·59%)	5 913 943 (8·46%)
6	163 835 (9·57%)	4371 (7·79%)	159 464 (9·63%)	6 319 149 (8·35%)	380 069 (6·54%)	5 939 080 (8·50%)
7	168 024 (9·81%)	4450 (7·93%)	163 574 (9·87%)	6 103 357 (8·06%)	369 624 (6·36%)	5 733 733 (8·21%)
8	166 879 (9·74%)	4178 (7·45%)	162 701 (9·82%)	6 102 705 (8·06%)	377 014 (6·49%)	5 725 691 (8·19%)
9	168 813 (9·86%)	4178 (7·45%)	164 635 (9·94%)	5 958 016 (7·87%)	368 232 (6·34%)	5 589 784 (8·00%)
10	160 864 (9·39%)	3913 (6·97%)	156 951 (9·47%)	5 731 492 (7·57%)	350 993 (6·04%)	5 380 499 (7·70%)
Unknown	167 526 (9·78%)	13 182 (23·50%)	154 344 (9·32%)	14 762 145 (19·50%)	2 037 942 (35·09%)	12 724 203 (18·21%)

Data are median (IQR) or n (%).

Table 1: **Baseline characteristics of the cancer cohort and control population**

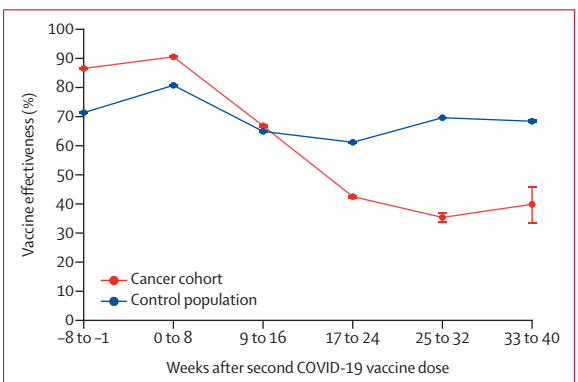

Figure 1: **Vaccine effectiveness over time after the second COVID-19 vaccine dose in the cancer cohort versus the control population**
The error bars represent 95% CIs.

positive PCR test) in the cancer cohort overall and at 3–6 months after the second vaccine dose. These analyses were added to translate the documented positive PCR test into more meaningful clinical outcome measures and provide additional clinical insight.

95% CIs were calculated by Wilson score intervals without continuity correction. Analyses were done in R (version 4.0.3) with epiDisplay (version 3.5.0.1).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

During the study period from Dec 8, 2020, to Oct 15, 2021, 77 399 018 COVID-19 PCR tests for 28 010 955 individuals were done. 491 007 PCR tests were excluded because they were void and 4 084 667 were excluded because they contained no or invalid NHS identifiers. 1 712 728 PCR tests were done for 377 194 individuals identified in the Rapid Cancer Registration Dataset. The cancer cohort comprised 377 194 individuals who had 56 102 positive PCR tests, corresponding to 42 882 individuals infected with breakthrough SARS-CoV-2. The control population consisted of 28 010 955 individuals, of whom 5 748 708 had SARS-CoV-2 breakthrough infections. Baseline characteristics of test-positive cases and test-negative controls in both the cancer and control cohorts are shown in table 1.

Overall vaccine effectiveness following the second vaccine dose against COVID-19 during the study period was 69·8% (95% CI 69·8–69·9) in the control population and 65·5% (65·1–65·9) in the cancer cohort. Vaccine effectiveness at 3–6 months after the second dose was

lower in the cancer cohort (47·0%, 95% CI 46·3–47·6) than in the control population (61·4%, 61·4–61·5). Waning vaccine effectiveness in the cancer cohort reached its lowest point at 24–32 weeks following administration of the second vaccine dose (figure 1; appendix p 6).

See Online for appendix

To ascertain whether predefined subgroups within the cancer cohort showed greater differences in vaccine effectiveness against breakthrough infections, exploratory analyses were done (table 2; figure 2; appendix p 2). In the cancer cohort, vaccine effectiveness was higher in individuals (n=123 060) who had been vaccinated with two doses of BNT162b2 (72·1%, 95% CI 71·6–72·7) than in individuals (n=157 138) who had received two doses of ChAdOx1 nCov-19 (59·0%, 58·5–59·6; table 2).

Cancer subtype analysis identified that vaccine effectiveness (overall and at 3–6 months) was lower

	Overall vaccine effectiveness					Vaccine effectiveness at 3–6 months				
	Exposed (PCR positive)		Not exposed (PCR negative)		Vaccine effectiveness (95% CI)	Exposed (PCR positive)		Not exposed (PCR negative)		Vaccine effectiveness (95% CI)
	Vaccinated (two doses)	Unvaccinated	Vaccinated (two doses)	Unvaccinated		Vaccinated (two doses)	Unvaccinated	Vaccinated (two doses)	Unvaccinated	
All patients with cancer	18 292	31 649	780 054	465 982	65·5% (65·1–65·9)	12 513	31 649	347 414	465 982	47·0% (46·3–47·6)
Cancer stage										
Stage 1	3748	4678	139 476	60 749	65·1% (64·4–65·8)	2551	4678	64 551	60 749	48·7% (47·2–50·1)
Stage 2	2532	3387	104 254	50 455	63·8% (62·9–64·8)	1755	3387	46 566	50 455	43·9% (42·2–45·5)
Stage 3	2203	3649	109 286	58 389	67·7% (66·7–68·8)	1569	3649	48 642	58 389	48·4% (46·6–50·1)
Stage 4	966	3115	69 574	47 760	78·7% (77·5–79·9)	674	3115	30 209	47 760	65·8% (63·7–67·8)
Other or unknown	8843	16 820	357 464	248 629	NA	5964	16 820	157 446	248 629	NA
Vaccine name or manufacturer (doses 1 and 2)										
BNT162b2 (Pfizer–BioNtech)	7050	31 649	372 674	465 982	72·1% (71·6–72·7)	4667	31 649	167 336	465 982	58·9% (58·0–59·9)
ChAdOx1 nCoV-19 (AstraZeneca)	11 192	31 649	402 308	465 982	59·0% (58·5–59·6)	7828	31 649	177 512	465 982	35·1% (34·1–36·1)
Mixed (Pfizer–BioNtech and AstraZeneca) or other	50	0	5072	0	NA	18	0	2566	0	NA
Cancer diagnosis and treatment										
Time of diagnosis										
≤12 months before data cutoff	2807	8286	162 082	164 729	65·6% (64·5–66·6)	1778	8286	63 335	164 729	44·2% (42·2–46·1)
>12 months before data cutoff	15 485	23 363	617 972	301 253	67·7% (67·3–68·1)	10 735	23 363	284 079	301 253	51·3% (50·6–51·9)
Systemic anticancer therapy										
Yes	4633	9024	208 369	158 293	61·0% (60·1–61·9)	3328	9024	92 068	158 293	36·6% (35·1–38·0)
No	13 659	22 625	571 685	307 689	67·5% (67·1–67·9)	9185	22 625	255 346	307 689	51·1% (50·4–51·8)
Received ≤12 months before data cutoff	3061	6509	144 513	121 632	60·4% (59·3–61·5)	2152	6509	62 253	121 632	35·4% (33·5–37·3)
Received >12 months before data cutof	1572	2515	63 856	36 661	64·1% (62·8–65·4)	1176	2515	29 815	36 661	42·5% (40·4–44·6)
Radiotherapy										
Yes	2576	4591	114 754	82 298	59·8% (58·6–60·9)	1823	4591	51 564	82 298	36·6% (34·7–38·5)
No	15 716	27 058	665 300	383 684	66·5% (66·1–66·9)	10 690	27 058	295 850	383 684	48·8% (48·1–49·4)
Received ≤12 months before data cutoff	911	2230	49 023	50 364	58·0% (56·0–60·0)	657	2230	21 194	50 364	30·0% (26·2–33·7)
Received >12 months before data cutoff	1665	2361	65 731	31 934	65·7% (64·6–66·9)	1166	2361	30 370	31 934	48·1% (46·1–50·1)

(Table 2 continues on next page)

	Overall vaccine effectiveness					Vaccine effectiveness at 3–6 months				
	Exposed (PCR positive)		Not exposed (PCR negative)		Vaccine effectiveness (95% CI)	Exposed (PCR positive)		Not exposed (PCR negative)		Vaccine effectiveness (95% CI)
	Vaccinated (two doses)	Unvaccinated	Vaccinated (two doses)	Unvaccinated		Vaccinated (two doses)	Unvaccinated	Vaccinated (two doses)	Unvaccinated	
(Continued from previous page)										
Type of malignancy										
Solid organ malignancy	15 070	26 203	685 675	390 844	67·2% (66·8–67·6)	10 245	26 203	304 288	390 844	49·8% (49·1–50·5)
Haematological malignancy	3222	5446	94 379	75 138	52·9% (51·7–54·1)	2268	5446	43 126	75 138	27·4% (25·6–29·3)
Cancer subtype										
Lip, oral cavity, and pharynx (C00–C14)	441	684	16 718	13 798	46·8% (43·5–50·2)	297	684	7353	13 798	18·5% (12·9–24·2)
Non-colorectal gastrointestinal (C15–C17 and C22–C26)	921	2698	61 577	45 563	74·7% (73·3–76·2)	596	2698	25 495	45 563	60·5% (58·0–62·9)
Colorectal gastrointestinal (C18–C21)	2031	3740	114 874	63 005	70·2% (69·2–71·2)	1399	3740	49 974	63 005	52·8% (51·1–54·6)
Lung (C34)	1228	3344	70 528	49 068	74·5% (73·2–75·7)	820	3344	31 250	49 068	61·5% (59·4–63·5)
Respiratory and intrathoracic organs (C30–C33 and C35–C39)	161	359	7376	5840	64·5% (59·9–68·9)	123	359	3304	5840	39·4% (32·0–46·6)
Bone, mesothelial, and soft tissue (C40–C41 and C45–C49)	283	637	14 976	13 091	61·2% (57·5–64·7)	185	637	6203	13 091	38·7% (32·2–44·9)
Breast (C50)	3774	4877	147 465	70 606	62·9% (62·2–63·7)	2568	4877	66 651	70 606	44·2% (42·8–45·6)
Female gynaecological (C51–C58)	1095	2067	52 094	33 122	66·3% (64·7–67·9)	709	2067	23 001	33 122	50·6% (48·0–53·2)
Male urological (C60, C62, and C63)	234	428	5328	4759	51·2% (46·5–55·8)	133	428	2294	4759	35·5% (28·2–42·6)
Prostate (C61)	3093	3867	108 522	39 592	70·8% (70·1–71·5)	2178	3867	50 373	39 592	55·7% (54·3–57·2)
Urinary tract (C64–C68)	1372	2223	70 547	34 539	69·8% (68·6–71·0)	968	2223	31 654	34 539	52·5% (50·4–54·6)
CNS (C69–C72)	186	789	8127	11 991	65·2% (61·6–69·0)	117	789	3506	11 991	49·3% (41·9–56·0)
Endocrine glands (C73–C75)	251	490	7543	5870	60·1% (56·2–64·0)	152	490	3230	5870	43·6% (41·9–56·0)
Lymphoma (C81–C85)	1806	2427	37 107	27 855	44·1% (42·5–45·8)	1277	2427	16 811	27 855	12·8% (10·4–15·3)
Myeloma (C90)	472	918	29 545	12 921	77·5% (75·8–79·2)	345	918	13 458	12 921	63·9% (60·7–67·0)
Leukaemia (C91–C95)	809	1954	24 555	32 581	45·1% (42·5–47·6)	554	1954	11 333	32 581	18·5% (13·9–23·0)
Other	135	147	3172	1781	NA	92	147	1524	1781	NA

NA=not applicable.

Table 2: **Number of PCR positive and negative test results and vaccine effectiveness in cancer cohort subgroups**

among patients with haematological malignancies than among those with solid organ malignancies, driven principally by those with a diagnosis of lymphoma or leukaemia (table 2; figure 2; appendix p 2). By contrast, we observed that overall and 3–6-month vaccine effectiveness in the myeloma subgroup was high (table 2). Among the solid cancers, vaccine effectiveness was lowest in those with head and neck malignancies (lip, oral cavity, and pharynx; table 2, appendix p 3).

Patients who received systemic anticancer therapy or radiotherapy had a lower vaccine effectiveness overall and at 3–6 months compared with those who had not received these types of treatment (table 2). Patients who received systemic anticancer treatments or radiotherapy

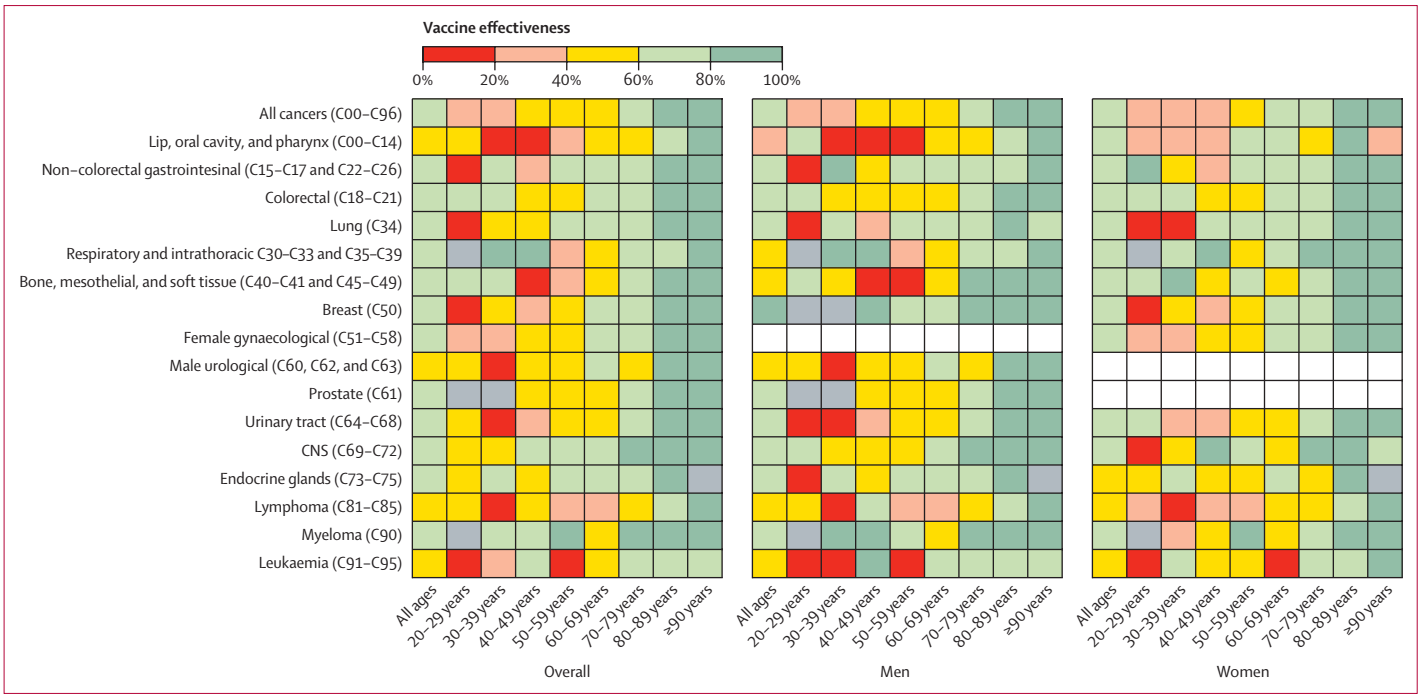

Figure 2: **Heatmap showing overall vaccine effectiveness after the second dose and the interaction of patient age, sex, and cancer diagnosis**
Grey boxes denote insufficient data; white boxes denote inapplicable sections.

within 12 months of data cutoff versus more than 12 months had lower vaccine effectiveness at 3–6 months (table 2). Patients with a more recent diagnosis (≤12 months relative to data cutoff) had a lower vaccine effectiveness at 3–6 months than those with an older diagnosis (>12 months relative to data cutoff; table 2). For every cancer stage, vaccine effectiveness at 3–6 months was lower than overall vaccine effectiveness (table 2).

To examine clinically relevant covariates that might drive these differences in the cancer cohort, a multivariable logistic regression model was fitted to adjust for the effects of the age, sex, Index of Multiple Deprivation, and ethnicity (figure 3; appendix p 7). At 3–6 months, vaccine effectiveness was significantly lower for those who had received systemic anticancer treatments at any time or within the last 12 months, radiotherapy at any time or within the last 12 months, or a cancer diagnosis within the last 12 months compared with those who had not, but was not different between those with versus without haematological malignancies (appendix p 7).

In the adjusted multivariable logistic regression, patients with stage 4 cancers versus all other stages and those aged 70 years or older versus those younger than 70 years had reduced frequencies of breakthrough infections and higher vaccine effectiveness (figures 2, 3). To investigate whether this result might be due to variations in patient behaviour, we did an exploratory post-hoc analysis in which we linked the cancer cohort to the Contact Tracing and Advice Service dataset. We found that patients with stage 4 cancer had fewer mean contacts than those with stage 1 cancer (1·32 [SD 4·36] *vs* 2·04 [7·76]) and that the mean number of contacts was lower for patients older than 70 years compared with those younger than 70 years (appendix pp 4, 8). We identified evidence of an inverse relationship between age group and the number of contacts (appendix pp 4, 8). The greatest levels of waning vaccine effectiveness were observed in those with a diagnosis of lymphoma or leukaemia, in those who were diagnosed within 12 months of data cutoff, and in those who had received systemic anticancer treatments or radiotherapy (figure 4; appendix p 5).

In a post-hoc analysis, we observed that there were higher levels of protection afforded against COVID-19 hospitalisation (84·5%, 95% CI 83·6–85·4) and death (93·5%, 93·0–94·0) than against breakthrough infections in our cancer cohort following the second dose (appendix p 6). Similar to vaccine effectiveness against breakthrough infections, vaccine effectiveness against more severe COVID-19 outcomes waned at 3–6 months (appendix p 6).

Discussion

Patients with cancer initially had high COVID-19 vaccine effectiveness, similar to the control population, but this vaccine effectiveness rapidly waned. Reduced vaccine effectiveness was observed in individuals who had been diagnosed with cancer or had received radiotherapy or systemic anticancer treatments within the preceding 12 months. A diagnosis of lymphoma or leukaemia was also associated with both lower, and more rapidly waning,

	Exposed (PCR-positive)	Not exposed (PCR-negative)	Multivariable-corrected vaccine effectiveness (95% CI)
Cancer stage			
Stage 1	3748/4678	139476/60749	59·5% (57·5–61·4)
Stage 2	2532/3387	104254/50455	58·0% (55·5–60·4)
Stage 3	2203/3649	109286/58389	62·7% (60·4–64·9)
Stage 4	966/3115	69574/47760	72·8% (70·4–75·0)
Time of cancer diagnosis			
≤12 months	2807/8286	162082/164729	54·9% (52·7–57·1)
>12 months	15485/23363	617972/301253	62·9% (62·0–63·8)
Systemic anticancer therapy			
None	13659/22625	571685/307689	61·5% (60·5–62·4)
Any	4633/9024	208369/158293	50·6% (48·5–52·7)
≤12 months	3061/6509	144513/121632	47·8% (45·1–50·4)
>12 months	1572/2515	63856/36661	61·5% (60·5–62·4)
Radiotherapy			
None	15716/27058	665300/383684	60·1% (59·2–61·0)
Any	2576/4591	114754/82298	51·7% (48·8–54·3)
≤12 months	911/2230	49023/50364	46·3% (41·2–50·9)
>12 months	1665/2361	65731/31934	60·2% (59·3–61·0)
Cancer type			
Solid organ malignancy	15070/26203	685675/390844	61·8% (60·9–62·6)
Haematological malignancy	3222/5446	94379/75138	37·7% (34·2–41·1)
Cancer subtype			
Non-colorectal gastrointestinal (C15–C17 and C22–C26)	921/2698	61577/45563	68·2% (65·3–70·9)
CNS (C69–C72)	186/789	8127/11991	65·4% (58·1–71·4)
Colorectal (C18–C21)	3093/3867	108522/39592	64·9% (62·9–66·7)
Prostate (C61)	2031/3740	114874/63005	64·8% (62·6–66·9)
Lung (C34)	1228/3344	70528/49068	64·7% (61·8–67·4)
Bone, mesothelial, and soft tissue (C40–C41 and C45–C49)	1095/2067	52094/33122	63·2% (60·0–66·2)
Female gynaecological (C51–C58)	283/637	14976/13091	63·0% (56·0–69·0)
Respiratory and intrathoracic (C30–C33 and C35–C39)	161/359	7376/5840	61·6% (52·3–69·2)
Breast (C50)	3774/4877	147465/70606	60·4% (58·4–62·2)
Urinary tract (C64–C68)	1372/2223	70547/34539	60·3% (57·1–63·4)
Endocrine glands (C73–C75)	251/490	7543/5870	57·9% (49·8–64·7)
Lip, oral cavity, and pharynx (C00–C14)	441/684	16718/13798	49·1% (41·7–55·5)
Male urological (C60–C63)	234/428	5328/4759	40·7% (28·5–50·8)
Myeloma (C90)	472/918	29545/12921	68·4% (63·9–72·3)
Leukaemia (C91–C95)	809/1954	24555/32581	39·0% (31·9–45·4)
Lymphoma (C81–C85)	1806/2427	37107/27855	19·2% (12·7–25·3)
All patients with cancer	**18292/31649**	**780054/465982**	**58·8% (58·0–59·7)**

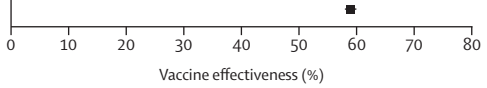

Figure 3: **Forest plot showing multivariable-corrected overall vaccine effectiveness among predefined cancer subgroups**
The error bars represent 95% CIs. Regression models were fitted for the clinically relevant covariates of age, sex, Index of Multiple Deprivation, and ethnicity.

vaccine effectiveness. Our findings reflect published clinical data from a US cohort of 184 485 patients with cancer and a cohort of 2391 patients with cancer from France.[24,25] Waning of vaccine effectiveness at 3–6 months was less pronounced for the outcomes of COVID-19 hospitalisation or death than for breakthrough infections, although we note that these metrics are a lagged indicator of vaccine effectiveness. Although this study cannot address the mechanisms for this drop in vaccine effectiveness, the findings match those of previous studies that have identified reduced levels of protective antibody and T-cell responses after vaccination in this cohort.[8,10] These patients, especially those with lymphoma and leukaemia, might have a limited capacity to maintain immunological vaccine memory, in many cases as a consequence of cancer treatments that specifically suppress immune responses. For patients in the cancer cohort, the BNT162b2 vaccine resulted in higher levels of vaccine effectiveness than the ChAdOx1 nCov-19 vaccine, in keeping with studies in the general population.[21]

We found that the absolute difference in vaccine effectiveness against breakthrough infections in people with cancer compared with the control population was 4·3 percentage points. However, at 3–6 months, this

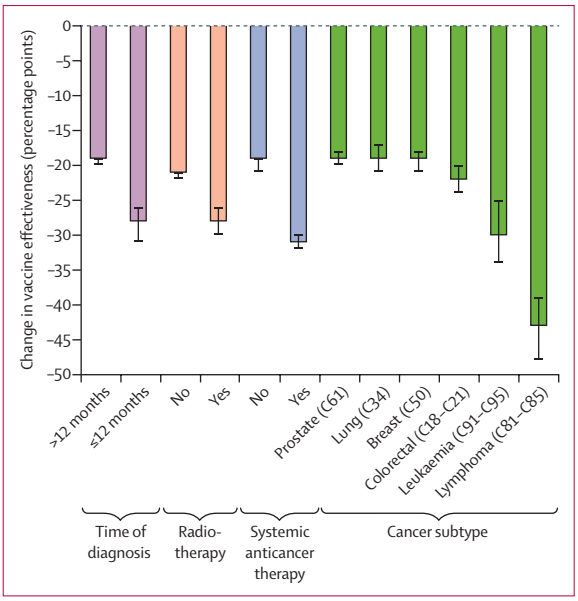

Figure 4: **Waterfall plot showing multivariable-corrected waning vaccine effectiveness at 3–6 months by key cancer subgroups**
The most common solid tumours and haematological malignancies according to Cancer Research UK are shown.

For the **Cancer Research UK list of common cancers** see https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Zero

difference in vaccine effectiveness widened to 14·4 percentage points, representing a reduction in vaccine effectiveness of nearly a third in patients with cancer. Waning vaccine effectiveness has been described in other studies of COVID-19 vaccines in people without cancer.[17,26] In parallel to this work, an analysis of a UK cohort has identified waning vaccine effectiveness against symptomatic disease of 25 percentage points at week 20 after second-dose vaccination for both BNT162b2 and ChAdOx1 nCov-19 in a clinically extremely vulnerable group, which comprised patients with a range of different medical conditions, including trisomy 21, obesity, post-splenectomy, and cancer.[27,28] Our evaluation had the advantage of being done at the population level, reducing the risk of sampling error, and included larger numbers of patients than any previously published analysis on cancer and COVID-19,[29] enabling a more granular cancer subgroup evaluation.

There are some limitations to this analysis. First, we only included patients recorded as having cancer up to April 30, 2021, excluding those who were diagnosed more recently. This restriction is likely to have resulted in underestimation of the reduction in vaccine effectiveness in the cancer cohort, as those who were recently diagnosed were more likely to have been receiving active treatment but will not have been counted among the positive SARS-CoV-2 test results of the cancer cohort. The effect might be additionally compounded by the older median age of the cancer cohort versus the control population; we found that older patients might have had fewer social contacts and therefore fewer potential transmission events. Second, we note that the reduced vaccine effectiveness with radiotherapy might have been driven by concurrent systemic cytotoxic treatment. Third, we are not able to exclude the possibility that the control population might display differences in behaviour compared with patients with cancer. Specifically, there might have been differences in attendance rates for confirmatory PCR following a positive lateral flow test, which might have been exacerbated by patients with cancer being monitored more closely, having tests offered more frequently, and being able to access care more readily. Some of the aforementioned behavioural differences could alter the denominator in test-negative case-control analyses and make it more difficult to make highly certain population inferences. Fourth, we have not corrected our analyses for causes of death other than COVID-19, partly due to the challenges of identifying whether cause of death was due to COVID-19 or associated with COVID-19. Fifth, our analysis comprised patients who had received two doses of COVID-19 vaccine and patients with cancer in England are now routinely offered a third or fourth vaccine booster dose. Sixth, time-to-event analyses were not in the data analysis plan because breakthrough infections occur in waves and vaccination was implemented during several months by age groups. Finally, our analysis also pre-dates the most recent wave of SARS-CoV-2 infection with the omicron variant (B.1.1.529); further follow-up is required to determine whether the same differences in vaccine effectiveness are present between controls and patients with cancer—whether our study is generalisable—in this new situation, although we envisage that findings would be similar.

To conclude, we found that individuals with cancer have demonstrable, albeit impaired, overall vaccine effectiveness against breakthrough infections with SARS-CoV-2. Vaccine effectiveness for those with cancer waned more rapidly than for the control population; this effect was more pronounced in those with haematological malignancies. Put into the wider context of the ongoing emergence of highly transmissible COVID-19 strains, such as omicron, our findings support the global prioritisation and evaluation of vaccination booster types and programmes for people with cancer, including analyses on the impact of different treatments. Patients with cancer should also be encouraged to use non-pharmacological strategies, such as behavioural modifications or personal protective equipment, to prevent transmission when community rates are high; the general population should also be conscious about getting tested before being in contact with high-risk individuals. We have identified groups at high risk of breakthrough infections who can be prioritised for research or pandemic response interventions, early community treatment, or pre-exposure prophylaxis programmes. Such measures will be crucially important as global health-care and cancer care systems adapt to living with COVID-19 as an endemic disease.

Contributors
LYWL, TS, MCI, ML, MT, ART, HSM, LB, MB, SR, TWR, AP, GM, MM, MWF, TF, and PJ contributed to study design; LYWL, MCI, LB, MB, JC, SR, and MP contributed to data acquisition; LYWL, TS, MCI, LB, and MB accessed and verified the data; LYWL, TS, MCI, ML, MT, ART, HSM, YA-H, MB, LB, AB, ELC, JC, JJC, SK, QG, GI, CH-W, RJH, AJXL, PCL, JKHL, MP, JSP, JRP, VAP, AR, ASR, TMR, TWR, RLR, SR, MHT, IW, SW, TI, SML, GM, MM, AP, MWF, TF, and PJ interpreted the data; and LYWL, TS, MCI, ML, MT, ART, HSM, YA-H, MB, LB, AB, ELC, JC, JJC, SK, QG, GI, CH-W, RJH, AJXL, PCL, JKHL, MP, JSP, JRP, VAP, AR, ASR, TMR, TWR, RLR, SR, MHT, IW, SW, TI, SML, GM, MM, AP, MWF, TF, and PJ wrote the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
To comply with data privacy laws, data from this study, including individual participant data, are not available for sharing. Data field definition within the data dictionary is available by reasonable request to the corresponding author. The privacy statement for individuals performing COVID-19 testing provided by the Department of Health and Social Care is available at https://www.gov.uk/government/publications/phe-privacy-information/privacy-information.

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