Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

Parallel evolution and differences in seroprevalence of SARS-CoV-2 antibody between patients with cancer and health care workers in a tertiary cancer centre during the first and second wave of COVID-19 pandemic: canSEROcov-II cross-sectional study

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Seroprevalence;
Cancer center;
Health care workers;
Cancer patients

Abstract ***Background:*** Patients with cancer are a population at high risk of severe infection from SARS-CoV-2. Patients with cancer regularly attend specialised healthcare centres for management and treatment, where they are in contact with healthcare workers (HCWs). Numerous recommendations target both patients with cancer and HCWs to minimise the spread of SARS-CoV-2 during these interactions.
Objective: To investigate the parallel evolution of the COVID-19 epidemic in these 2 populations over time, we studied the seroprevalence of anti-SARS-CoV-2 antibodies after both the first and second waves of the pandemic, and in both cancer patients and HCWs from a single specialised anti-cancer centre. Factors associated with seropositivity were identified in both populations.
Methods: We conducted a cross-sectional study after the second wave of the COVID pandemic in France. All participants were invited to undergo serological testing for SARS-CoV-2 and complete a questionnaire collecting data about their working conditions (for HCWs) or medical management (for patients) during this period. Results after the second wave were compared to those of a previous study among 1011 patients with cancer and 663 HCWs performed in the same centre after the first wave, using the same evaluations.
Findings: We included 502 HCWs and 507 patients with cancer. Seroprevalence of anti-SARS-CoV-2 antibodies was higher after the second wave than after the first wave in both HCWs (15.1% versus 1.8%; $p < 0.001$), and patients (4.1% versus 1.7%; $p = 0.038$). By multivariate analysis, the factors found to be associated with seropositivity after the second wave for HCWs were: working in direct patient care ($p = 0.050$); having worked in a dedicated COVID-19 unit ($p = 0.0036$); contact with a person with COVID-19-positive in the workplace ($p = 0.0118$) or outside of the workplace ($p = 0.0297$). Among patients with cancer, only a contact with someone who tested positive for COVID-19 was found to be significantly associated with positive serology. The proportion of reported contacts with individuals with COVID-19-positive was significantly lower among patients with cancer than among HCWs (7.6% versus 40.7%, respectively; $p < 0.0001$)
Interpretation: Between the first and second waves of the epidemic in France, the seroprevalence of anti-SARS-CoV-2 antibodies increased to a lesser extent among patients with cancer than among their HCWs, possibly due to better self-protection, notably social distancing. The risk factors for infection identified among HCWs plead in favour of numerous intra-hospital contaminations, especially for HCWs in contact with high-risk patients. This underlines the compelling need to pursue efforts to implement strict hygiene and personal protection measures (including vaccination) to protect HCWs and patients with cancer.

1. Introduction

COVID-19, caused by SARS-CoV-2, has led to a global pandemic since its emergence in China in December 2019 [1]. By July 2021, it was estimated that the pandemic had affected 194 million individuals and caused more than 4 million deaths worldwide. In Europe, France was among the hardest-hit countries, with more than 7 million cases and around 117,000 deaths [2], with a first epidemic wave (March–June 2020), followed by a second (October 2020–January 2021), both necessitating nationwide lockdown of the population.

Several diagnostic techniques are available to estimate the extent of the pandemic in the population, including RT-PCR, used to identify SARS-CoV-2 genomic material in the upper respiratory tract during the initial phase of infection [3]. Serological testing represents a complement to RT-PCR, by showing the presence of anti-SARS-CoV-2 antibodies, which generally persist long after infection [4]. By identifying seropositive subjects, serology is a useful tool for epidemiological tracking of the spread of disease [5] and identifying the proportion of individuals who have acquired a specific immune response among given populations, including subjects who are asymptomatic during the acute phase of infection [6,7].

Among the most vulnerable populations, patients with cancer, and especially those undergoing active treatment, have been the focus of much attention, as they are theoretically at higher risk of severe infection due to immunosuppression caused by their disease or its treatments. The incidence of COVID-19 among patients with cancer varies across studies [8–15] but nonetheless seems to be higher than in the general population [8,10,16], with an increased risk of severe forms of disease and death [17–25].

Among other populations of interest, healthcare workers (HCWs) have also been the focus of numerous studies [26–31], with a view to estimating the spread of infection within hospitals or determining the risk factors for infection in HCWs in direct contact with frail, hospitalised patients. Importantly, the majority of large studies investigating seroprevalence among HCWs were performed in 2020 during the first wave of the pandemic. For example, some studies in the general hospital setting [26,32], or specifically in oncology units or anti-cancer centres [9,12,15,33], reported low seroprevalence rates, similar to those observed in the general population [26,32], and also similar to those observed in the oncology patients that these HCWs were caring for [9,12,15,33]. Other studies, like that of van Dam [34] conducted in Belgium during the first wave showed a higher seroprevalence in HCWs than in patients with cancer (in whom the seroprevalence were very low and close to those observed in healthy volunteers).

Conversely, to the best of our knowledge, no study has been conducted in parallel among both patients with cancer and the HCWs caring for them, in the same centre, during both waves of the pandemic. This information is of major potential interest since the second wave was of greater magnitude in many countries (including France) and occurred after international professional societies of oncology had issued recommendations for the optimal protection of patients with cancer [35–37].

Immediately after the first wave, we performed a first cross-sectional study in our centre (CanSeroCov [12]), among patients with cancer and HCWs, and showed that the prevalence of anti-SARS-CoV-2 antibodies was similar in both populations and very low at 1.7% and 1.8%, respectively. In the present work, we performed a second cross-sectional study (CanSeroCov II) in the same populations, after the second wave of the pandemic. Our working hypothesis was that patients with cancer would have taken more stringent measures to protect themselves, especially social distancing, than the HCWs caring for them.

2. Methods

The location of our cancer care centre, the epidemiology of SARS-CoV-2 in the region and the safety measures implemented at our institution are described in detail in the Supplemental Appendix.

2.1. Sampling strategy and sample size calculation

In view of the low seroprevalence observed in HCWs and patients with cancer in our institution after the first wave, we hypothesised that seropositivity in both populations would be higher overall after the second wave, and twice as high in HCWs as inpatients, due to a greater risk of exposure. Based on the hypothesis of a seroprevalence rate of around 5% among patients and 10% among caregivers, using a two-sided Fisher's exact test, with an alpha risk set at 5%, a total of 474 subjects per group would achieve 80% power to detect such a difference in proportions between the groups. Assuming a rate of incomplete or unexploitable data of 5%, a total of 498 patients per group was considered necessary, and we rounded this up to 500 per group.

2.2. Study questionnaires

The study was approved by the internal scientific committee of the Georges-Francois Leclerc Cancer Centre, and by its Ethics Committee, as well as by a national Ethics Committee (CPP Sud-Ouest et Outremer 1). All questionnaires destined for the staff and patients were developed jointly by an expert group comprising oncologists, biologists and epidemiologists from our centre, specifically for the purposes of our first cross-sectional study [12]. The same questionnaires were used for the present second study. For the first cross-sectional study [12], blood tests for staff took place from 11th May 2020 (date of the end of the first national lockdown) to 25th May 2020 and from 25th May to 30th June 2020 for patients with cancer.

For this second cross-sectional study, for the recruitment of staff, all employees of the cancer centre received an email on their nominative work email address, providing information about the study and inviting them to participate. Blood tests for staff for the purposes of the present study took place from 12th January 2021 (after the end of the second national lockdown) to 22nd January 2021. The second national lockdown was in place from 28th October to 15th December 2020. For the patients, participation was proposed to all patients of the Medical Oncology department (patients seen in consultation, in the outpatient unit, and inpatients) from 25th January to 26th February 2021. For all patients, data relating to their cancer and treatment were retrieved from the medical files.

2.3. Blood samples, serological tests and serum bank

All serum samples were analysed in the clinical biology unit of the Georges-Francois Leclerc cancer centre, using the same tests as in the first study [12], in order to enable comparison and paired testing since a majority of HCWs participating in the present study had already participated in the first study.

SARS-CoV-2 total antibodies were measured on the fully-automated cobas e411 analyser (Roche Diagnostics) using Elecsys® Anti-SARS-CoV-2 electrochemiluminescence immunoassay (Roche Diagnostics) for the qualitative detection of SARS-CoV-2 antibodies in human serum and plasma. The IVD CE-marked Elecsys® assay uses a modified double-antigen sandwich immunoassay using recombinant nucleocapsid protein

(N), which is geared towards the detection of late, mature, high-affinity antibodies independent of the subclass. It is a total SARS-CoV-2 antibody assay (IgA, IgM and IgG) detecting predominantly but not exclusively, IgG. This test was validated (amongst others) by the French national reference centre on 21st May 2020 [38]. Measurement of anti-SARS-CoV-2 antibodies was performed following the manufacturer's instructions. Results are reported as numeric values in the form of a cutoff index (COI; signal sample/cutoff) and as a qualitative result, i.e. non-reactive (COI <1.0; negative) or reactive (COI ≥ 1.0; positive).

2.4. Statistical analysis

Quantitative variables were described as mean ± standard deviation or median + range and were dichotomised according to the median or a clinically relevant threshold. Qualitative variables were described as number (percentage). The number of missing data is indicated for each variable. The prevalence of seropositivity was expressed as a percentage with the associated 95% Confidence Interval (CI). Univariate comparisons between groups were performed as appropriate using Chi2, Fisher, Student T-test or Wilcoxon Mann–Whitney tests. Paired tests were used to compared seroprevalence among individuals who participated in both studies. Factors associated with seropositivity among staff members and then among patients were investigated using univariate and multivariate logistic regressions. All variables with a p-value <0.05 by univariate analysis were included in the multivariate models. The best multivariate model was chosen according to the best AUC. All analyses were performed by the Methodology & Biostatistics Unit of the Georges-Francois Leclerc cancer centre using SAS version 9.4 (SAS Institute Inc., Cary, NC). Tests were 2-sided. P-values <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study population: HCWs

In total, 502 staff members participated in this study; of these, the majority (N = 422, 84.1%) had already participated in the first study, of whom 10 had had positive serology in the first study. The recruitment of voluntary HCWs was closed when the required number of subjects was reached. For the first study which called on all the voluntary HCWs, the number of participants (n = 663) represented 80.3% of the HCWs at the cancer centre.

The main characteristics of the participating HCWs and their serological results are presented in Table 1 and Fig. 1. There were 401 women (79.9%) and 101 men (20.1%); the mean age was 39.2 years. Overall, 220 (43.8%) were caregivers (Fig. 1A). The other most widely represented staff categories were medicotechnical staff (16.3%), research staff (13.5%), secretarial (11.4%) and administrative staff (8.4%) (Fig. 1A). Among the participating HCWs, 87 HCWs (18%) had worked in a unit dedicated to caring for patients suffering from COVID-19. Three hundred and forty HCWs (71.3%) declared that they had daily contact with patients in the course of their work (Table 1). Regarding the working conditions during the pandemic, the majority of HCWs (79.6%) reported that they worked on-site as normal during the pandemic, while 102 participants (20.4%) worked from home (Fig. 1B).

Overall, 201 HCWs (40.7%) reported that they had been in contact with one or more persons who tested positive for COVID-19, and these contacts took place in

Table 1
Characteristics of the healthcare workers (N = 502).

Characteristics	Positive Serology (N = 76)	Negative Serology (N = 426)	P value	Test	Overall (N = 502)
Sex			0.1826	Chi-Square	
Female	65 (85.5%)	336 (78.9%)			401 (79.9%)
Male	11 (14.5%)	90 (21.1%)			101 (20.1%)
Age (years)			**0.0031**	Wilcoxon	
N	76	423			499
Mean (SD)	35.5 (9.8)	39.8 (11.5)			39.2 (11.4)
Median [min - max]	34.0 [22.0–56.0]	38.0 [19.0–81.0]			38.0 [19.0–81.0]
Contact with patients in the course of daily work			**0.0007**	Chi-Square	
No	8 (11.6%)	129 (31.6%)			137 (28.7%)
Yes	61 (88.4%)	279 (68.4%)			340 (71.3%)
Missing values	7	18			25
Worked in the COVID-19 unit during lockdown			**<0.0001**	Chi-Square	
No	42 (60.0%)	354 (85.7%)			396 (82.0%)
Yes	28 (40.0%)	59 (14.3%)			87 (18.0%)
Missing values	6	13			19

SD, standard deviation; min, minimum; max, maximum. P value is in bold when statistically significant.

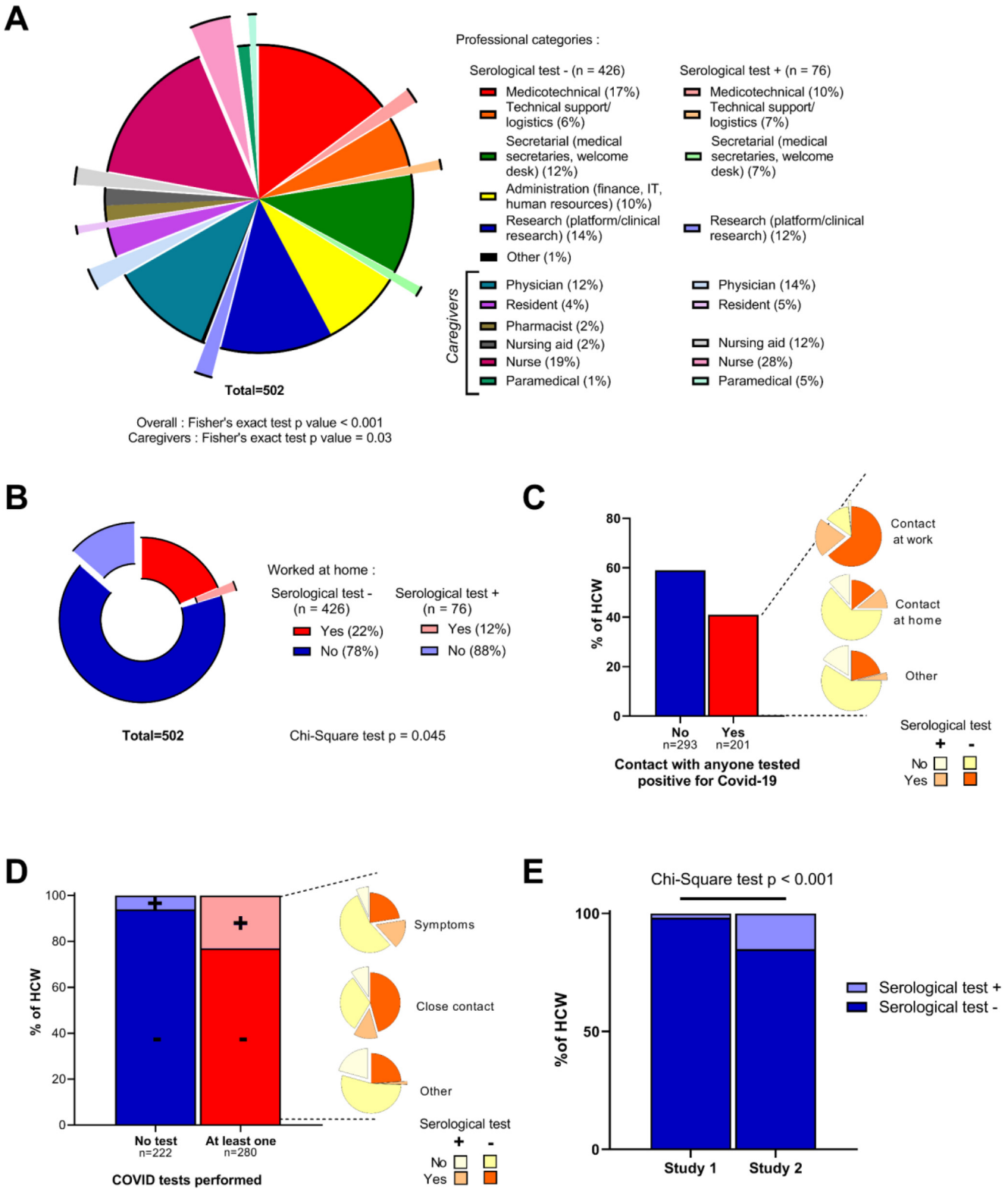

Fig. 1. **A**–**B**. Pie chart for professional categories of employees (A) and working conditions (B). Light (dark) colors represent employees with positive (negative) COVID-19 tests at the time of the study. **C**. Bar chart showing the proportion of employees who had (no) contact with anyone who tested positive for COVID-19, in red (blue). For employees who had contact a COVID-19-positive person, the type of contact is represented using pie charts. Light (dark) colors represent employees with positive (negative) COVID-19 tests at the time of the study. **D**. Bar chart showing the proportion of employees who had (or had not) at least one test for COVID-19 in red (blue) color. For employees who performed at least one test, the origin of the contact is indicated using pie charts. Light (dark) colors represent employees with positive (negative) COVID-19 tests at the time of the study. **E**. Bar chart showing the proportion of employees with a positive (light) or negative (dark) test in both studies.

Table 2
Univariate and multivariate analysis of the factors associated with positive serology among healthcare workers.

Variable	Serology positive/Total	Univariate analysis			Multivariate analysis		
		OR	95%CI	P value	OR	95%CI	P value
Age at time of lockdown (years)				**0.0172**			
Age >38	26/234	1					
Age≤38	50/265	1,86	[1.116–3.101]				
Caregiver				**0.0001**	1.893	[0.99–3.59]	**0.0505**
No	27/282	1					
Yes	49/220	2,706	[1.628–4.498]				
Contact with patients in the course of daily work				**0.0013**			
No	8/137	1					
Yes	61/340	3,526	[1.639–7.584]				
Worked in hospitalisation units				**<0.0001**			
No	37/358	1					
Yes	32/119	3,191	[1.880–5.417]				
Worked in the COVID-19 unit during lockdown				**<0.0001**	2.684	[1.37–5.22]	**0.0036**
No	42/396	1					
Yes	28/87	4	[2.304–6.947]				
Worked from home				**0.0493**			
Yes	9/102	1					
No	67/399	2,085	[1.002–4.339]				
Contact with COVID-19 case				**<0.0001**			
No	26/293	1					
Yes	47/201	3,13	[1.86–5.26]				
Contact with COVID 19 case at work				**<0.0001**	2.25	[1.19–4.25]	**0.0118**
No	30/322	1					
Yes	37/151	3.15	[1.86–5.35]				
Contact with COVID 19 case outside of work				**0.0031**	2.55	[1.09–5.93]	**0.0297**
No	57/436	1					
Yes	17/61	2.569	[1.375–4.80]				

P value is in bold when statistically significant.

the workplace in 84.8% of cases, at home in 25% and in other locations in 25% (Fig. 1C).

Since the beginning of the pandemic, 280 individuals (55.8%) had undergone at least one RT-PCR (nasal swab test). The average number of PCR tests per HCW was 1.8 [1–11], either because they presented suggestive symptoms (38.2%), had contact with a COVID-positive person (58.6%) or for other reasons (25.7%) (Fig. 1D). A total of 57 HCWs (11.4%) declared having had at least one positive RT-PCR (nasal swab test). One HCW reported having been hospitalised for COVID-19 and had required oxygen support during the hospital stay.

3.2. Seropositivity rates and factors associated with seropositivity among HCWs

In total, 76 HCWs (15.1%) had a positive serology result. Compared to the previous study among 663 HCWs after the first wave, the seropositivity rate increased significantly (from 1.8% to 15.1%; $p < 0.001$) (Fig. 1E). All the HCWs who had had a positive serology in the first study (N = 10) remained positive in the present study; 53 HCWs who were negative in the first study were positive in the present study, while there were an additional 13 seropositive individuals in this study who had not participated in the first study. Regarding symptoms, all those with positive serology more frequently reported having experienced symptoms than seronegative HCWs (71.1% versus 32.9%; $p < 0.0001$). The symptoms most commonly reported by seropositive HCWs were fever, shivers, loss of smell and taste, cough, breathlessness, cramps and fatigue (supplemental Figure 1).

Seropositive HCWs more frequently had RT-PCR tests than their seronegative counterparts (83% versus 51%). A total of 57 HCWs declared having had a positive RT-PCR test since the beginning of the pandemic, and of these, 53 (93%) were seropositive at the time of our study, while 4 (7%) were seronegative. A further 13 patients with a positive serology (17% of all seropositive HCWs) had never had a nasal swab test before the serological test performed for the purposes of the present study (Fig. 1D).

Among the variables studied, seropositive HCWs (N = 76) were significantly younger ($p = 0.0031$) (Table 1), were more often caregivers (N = 49; $p < 0.0001$) (Fig. 1A), (especially those in close contact with patients, i.e. nurses, nurses' aides or paramedical staff); more often had daily contact with patients

(N = 61; p = 0.0007), more often worked in medical wards (N = 32; p = 0.0016), especially the unit dedicated to the care of patients with COVID-19 (N = 28; p < 0.0001) (Table 1).

Conversely, administrative staff (p = 0.0034) (Fig. 1A) or those who worked from home during the pandemic (p = 0.045) (Fig. 1B) had lower seropositivity rates.

By univariate analysis, younger age (≤38 years), being a caregiver, having daily contact with patients, working in a medicine ward, working in the COVID-19 unit and working on-site (versus from home) were also associated with a higher likelihood of seropositivity (Table 2).

Beyond the working conditions, contact with a COVID-19 positive individual, be it in the workplace, or outside the workplace, was also associated with a higher risk of seropositivity (Table 2).

By multivariate analysis, being a caregiver (OR: 1.89, 95%CI [0.99–3.59], p = 0.0505), working in the unit dedicated to caring for patients with COVID-19 (OR: 2.68, 95%CI [1.37–5.22], p = 0.0036), having been in contact with a COVID-19-positive individual outside of the workplace (OR: 2.55, 95%CI [1.09–5.93], p = 0.0297) or within the workplace (OR: 2.25, 95%CI [1.19–4.25], p = 0.0118) were the factors independently associated with seropositivity (Table 2).

3.3. Characteristics of the study population: patients with cancer

A total of 507 patients participated in the present study (398 women (78.5%) and 109 men (21.5%)), of whom 153 (30.1%) had previously participated in the first study. The median age was 61 years [26–98] (Table 3). More than half the patients were being followed for breast cancer (N = 307; 60.6%); the distribution of other cancer types is detailed in Fig. 2A. A total of 54% had metastatic disease and 461 (91.1%) were receiving active treatment, which was chemotherapy in 54.9%, immunotherapy in 12.1%, targeted therapy in 39.7% and hormone therapy in 16.1% (Table 3). The majority were being treated as outpatients (N = 376; 74.2%), and 131 were being followed-up in consultations (N = 131; 25.8%) (Fig. 2B). The majority (83.1%) attended our institution during the second lockdown either for consultations (77.5%), a hospital admission (25.2%), a surgical intervention (41.7%), radiotherapy (11.6%) or to receive other treatment (74.6%).

Only 37 patients (7.6%, versus 40.7% among HCWs; p < 0.0001) reported that they had been in contact with someone who tested positive for COVID-19. These contacts were either in the patient's home (N = 17) or outside both the home and hospital (N = 19). For only 1 patient, the contact was during a stay in our institution (Fig. 2C).

This patient profile reflects the usual population of patients in our centre and was comparable to the population that participated in the study after the first wave (N = 1011), especially concerning the forms of cancer and the types of active treatment (Supplemental Table 1). There were more metastatic cancers (60.8% versus 54%) and a slightly higher proportion of men (30.2% versus 21.5%) in the first study.

Table 3
Patient characteristics (N = 507).

Characteristic	Positive Serology (N = 21)	Negative Serology (N = 486)	P value	Test	N (%) (N = 507)
Sex			0.4192	Fisher	
Female	6 (28.6%)	103 (21.2%)			109 (21.5%)
Male	15 (71.4%)	383 (78.8%)			398 (78.5%)
Age			0.7252	Wilcoxon	
N	21	486			507
Mean (std)	59.8 (10.9)	60.6 (13.4)			60.6 (13.3)
Median [min - max]	62.0 [34.0–78.0]	61.0 [26.0–98.0]			61.0 [26.0–98.0]
Metastatic cancer			0.4552	Chi-Square	
No	8 (38.1%)	225 (46.4%)			233 (46.0%)
Yes	13 (61.9%)	260 (53.6%)			273 (54.0%)
Missing values	0	1			1
Active anti-cancer treatment			0.242	Fisher	
No	0 (0.0%)	45 (9.3%)			45 (8.9%)
Yes	21 (100.0%)	440 (90.7%)			461 (91.1%)
Missing values	0	1			1
Ongoing treatment			0.0502	Fisher	
Chemotherapy	8 (38.1%)	182 (37.4%)			190 (37.5%)
Chemotherapy & Immunotherapy	0 (0.0%)	3 (0.6%)			3 (0.6%)
Chemotherapy & targeted therapy	6 (28.6%)	54 (11.1%)			60 (11.8%)
Endocrine therapy	0 (0.0%)	38 (7.8%)			38 (7.5%)
Immunotherapy	5 (23.8%)	48 (9.9%)			53 (10.5%)
No systemic treatment	0 (0.0%)	46 (9.5%)			46 (9.1%)
Radiotherapy	0 (0.0%)	3 (0.6%)			3 (0.6%)
Targeted therapy	2 (9.5%)	112 (23.0%)			114 (22.5%)

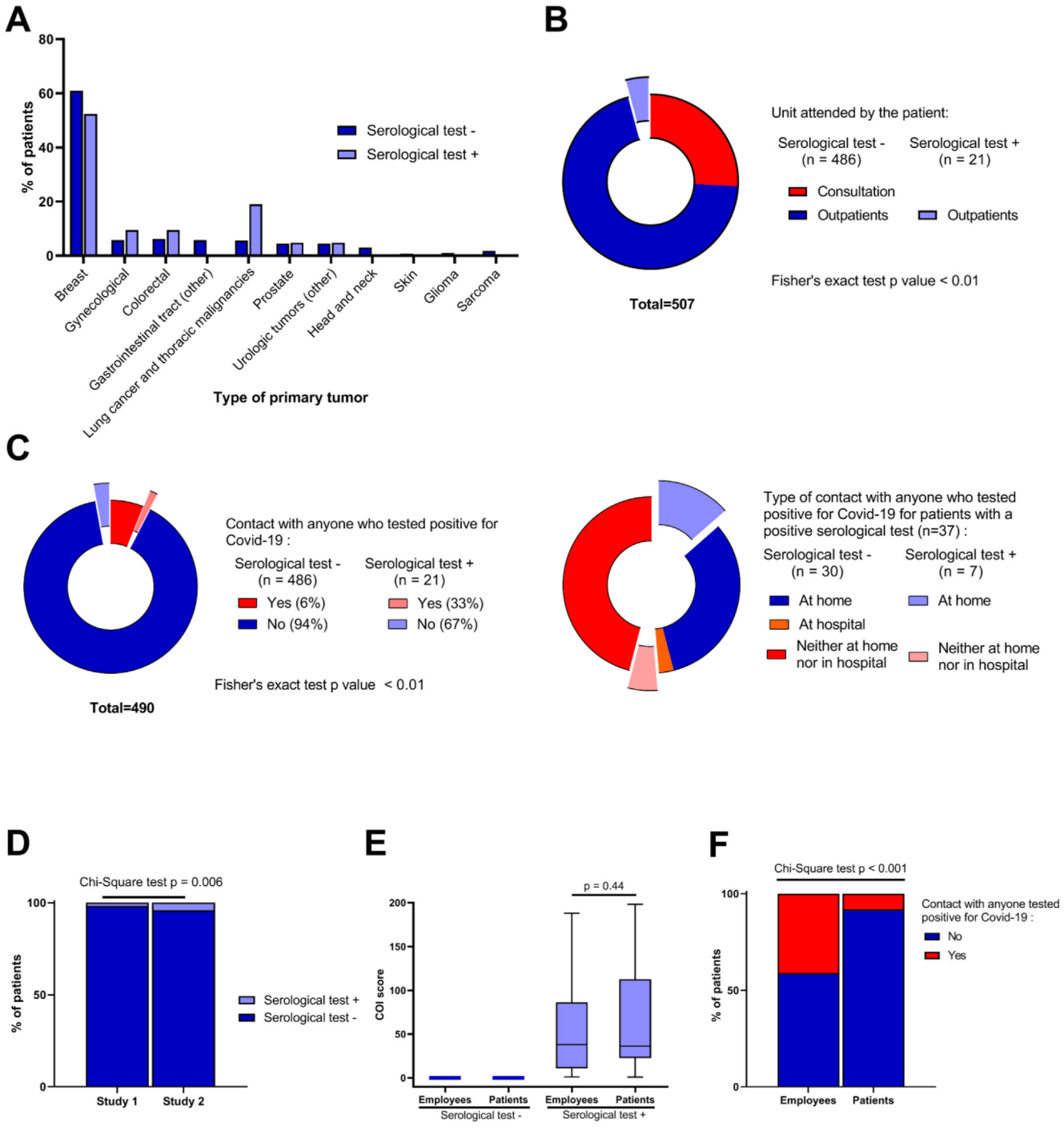

Fig. 2. **A**. Bar chart showing the percentage of patients with positive (light) or negative (dark) tests according to the type of primary tumor. **B**. Pie chart showing the proportion of patients recruited from the consultations (blue) or outpatient (orange) services. Light (dark) colors represent patients with positive (negative) COVID-19 tests at the time of the study. **C**. Left: Pie chart showing the proportion of patients who had (or did not have) contact with someone who tested positive for COVID-19, in red (blue). Light (dark) colors represent patients with positive (negative) COVID-19 tests at the time of the study. Right: For patients who had contact with a COVID-19-positive individual, the type of contact is indicated using pie charts (right). **D**. Bar chart showing the proportion of patients with a positive (light) or negative (dark) test in both studies. **E**. Box plots showing the distribution of the COI score among patients and HCWs, according to whether they had positive (light color) or negative (dark color) COVID-19 tests at the time of study. **F**. Bar chart showing the proportion of employees (left) and patients (right) who had (or did not have) contact with someone who tested positive for COVID-19 in (blue) red color.

For both studies, the recruitment of patients with cancer was closed when the required number of subjects was reached. The rate of screen failure was low but it was not recorded.

3.4. Seropositivity rates and factors associated with seropositivity among patients with cancer

Overall, 21 patients (4.1%) had positive serology. Compared to the 1011 patients included in the first study performed after the first wave, the seropositivity rate increased significantly (1.7 versus 4.1%; $p = 0.038$) (Fig. 2D) but remained significantly lower than the seropositivity rate among HCWs ($p < 0.0001$).

Regarding the 153 patients who had previously participated in the first study, 147 patients (96.1%) were still seronegative, 5 patients (3.3%) had acquired anti-SARS-CoV-2 antibodies since the previous study, and 1 patient (0.7%) had a very low-level seropositive result in the first study was seronegative in this study. Regarding symptoms, seropositive patients more frequently reported fever, loss of smell and cough (Supplemental Fig. 2).

Among the variables tested, only contact with a COVID-19 positive person was significantly associated with seropositivity (OR: 7.31, 95%CI [2.7–19.4]; $p < 0.0001$) (Fig. 2C).

Of note, patients reported contact with a COVID-19 positive person much less frequently than HCWs (7.6% versus 40.7% respectively; $p < 0.0001$) (Fig. 2F). Interestingly, no characteristics relating to the disease, stage of disease or treatments were significantly associated with seropositivity.

Finally, the cut-off index (COI) for seropositivity did not differ significantly between patients with positive cancer and positive HCWs (Fig. 2E).

4. Discussion

This is the second of two cross-sectional studies performed in a French cancer care centre and shows the parallel evolution of seroprevalence for anti-SARS-CoV-2 antibodies in both HCWs and patients with cancer between the end of the first wave and the end of the second epidemic wave in France. During and after the first wave, several professional societies in oncology issued recommendations for measures to protect patients with cancer against COVID-19 infection [35–37]. We hypothesised that thanks to these measures, as well as self-protection implemented by the patients themselves, especially regarding social distancing, the second wave of the epidemic would affect HCWs more than it would affect patients with cancer. Our results confirm that the second wave resulted in a much wider spread of SARS-CoV-2 among HCWs than among patients with cancer. At the end of the first wave, our first cross-sectional study found a seropositivity rate that was similarly very low in both groups[12], in line with what has since been reported in other similar studies conducted around the same time [9,15,33]. The seropositivity rate was so low in the first study that it precluded multivariate analysis to identify factors significantly associated with infection. This second study is original, in that it was conducted among the same two groups, in the same centre, but after the second wave. It provides insights into the dynamics of the virus' spread in HCWs and how this compares with the spread among patients, but given the higher seropositivity rates after the second wave, it also enabled us to identify factors significantly associated with the risk of infection.

It is evident from these analyses that among HCWs, the risk of contamination is primarily linked to their profession, with a significantly increased risk of infection observed in caregivers in daily contact with patients, especially those working in medicine units, and in particular, the dedicated COVID-19 unit. Two parallel observations among the staff support the hypothesis of an increased risk of contamination within the hospital, for all professional categories. First, the observation that administrative staff and those who worked from home during the second wave had a significantly lower seropositivity rate than staff who worked on-site. Second, the seropositivity among non-caregiving staff remained significantly higher than that observed among patients (9.5% versus 4.1%). These results are congruent with the literature, notably a recent meta-analysis [39], and indicate that the risk of contracting SARS-CoV-2 is associated with the type of work performed, the number of contacts and, thus, exposure to the virus.

In further support of this, our multivariate models showed that HCWs who were caregivers and those who had contact with a COVID-19-positive individual (within or outside of the workplace) were at significantly higher risk of being seropositive. Interestingly, when we analysed the frequency of these contacts, we noted that HCWs had significantly more contacts with COVID-infected individuals than patients, and most HCWs reported that these contacts had occurred at work. This information is of paramount importance for orienting preventive policies within anti-cancer centres, especially regarding the importance of vaccination (initial and booster doses) for younger HCWs, who were not priority groups for vaccination when it was first rolled out but who are generally in more frequent contact with patients.

Concerning the patients, we found that the seropositivity rate in this study was significantly higher than at the end of the first wave, although it remained significantly lower than that of HCWs. The only factor found to be associated with seropositivity among the patients was the fact of having been in contact with a COVID-19-positive individual. Contacts with infected persons occurred much less often for patients than for the

HCWs, suggesting that the patients spontaneously respected strict social distancing measures. It is nonetheless noteworthy that these self-imposed preventive measures were not applied at the cost of their anti-cancer therapy since the majority of patients were receiving active treatment and regularly attended our centre at the time when the serological testing was performed.

Interestingly, among the patients, we did not observe any link between SARS-CoV-2 seropositivity and the type of cancer, stage of disease or treatment. The impact of active cancer and its treatment by immunomodulating agents (cytotoxic chemotherapy, immunotherapy, radiotherapy) on the efficacy of spontaneous immune response to SARS-CoV-2 infection remains debated. Large-scale studies, including several meta-analyses, seem to suggest that severe (including fatal) forms of COVID-19 are more common among patients with, and treated for, cancer [24,40].

Even though our patients with cancer appear to have taken steps to protect themselves against infection with COVID-19, the increase in seropositivity in this population compared to the end of the first wave underlines the importance of achieving optimal vaccine uptake in these patients, in line with current recommendations [41–44], as they are at risk of severe forms of the disease. With the advent of vaccines against SARS-CoV-2, the question will inevitably arise regarding the degree of protection afforded by vaccination in these patients undergoing treatment for cancer. Indeed, in recent studies of vaccinated patients undergoing anti-cancer therapy, the humoral immune response appeared to be of lesser magnitude in certain groups of oncology patients, notably those receiving chemotherapy or immunotherapy [45–50], and above all, patients receiving treatment for haematological malignancies, notably receiving anti-CD20 therapy [51–53]. This, like other factors (type of cancer, age, type of test used, etc.), is also likely to explain a certain degree of variability in the seropositivity of patients with cancer. However, our 2 consecutive studies were relatively homogeneous concerning the characteristics of the patients included, did not include patients with haematological malignancies, and used the same serological tests.

Our study has several strengths, especially from a methodological viewpoint, with pre-defined study hypotheses and the necessary statistical power to have confidence in the robustness of the differences observed. To the best of our knowledge, this is the largest seroprevalence study to date in oncology (1674 subjects in the first study and 1009 in the second). It is also important to note that the serological testing in this study was performed before the start of vaccination roll-out in France and is therefore not biased by the possible existence of vaccinated individuals during the study period. Finally, the biological assays used to test seroprevalence were the same here as in the first study, thus enabling a confident comparison of the seroprevalence rates at the end of both waves.

Our study also has some limitations. The variables recorded were self-reported, thus leaving the potential for declaration bias. However, in view of the nature of the variables recorded in this study, there was no other reliable way to obtain the information. Regarding the patients with cancer, the population included was largely composed of different patients than in the previous study, contrary to the HCWs, where a majority participated in both evaluations. Nevertheless, there was a 30% overlap in the patients and no change in patient recruitment in our centre between the two studies, and the comparison of both populations showed no significant differences, particularly for the main characteristics of the disease and treatment. We, therefore, believe that the patient populations in both studies are comparable. Concerning the recruitment, for the 2 studies we called on the HCWs who were voluntary, and for the patients, those who agreed to have serology and complete the questionnaire. We cannot, therefore, exclude recruitment bias linked to this volunteering, but we do not think that this influenced the results of the studies because we had very few screening failures.

We did not have available RT-PCR test results at the time of serological testing for all subjects. The availability and ease of large-scale access to RT-PCR had improved dramatically at the time of the second wave (as shown by the high proportion of HCWs and patients with at least one test), and the number of persons diagnosed by this technique was much higher in the second wave. In this context, serological testing makes it possible to judge whether the higher number of cases diagnosed corresponds to a real increase in the prevalence of the disease (as was found to be the case in the populations studied here). Concerning serological testing, even when using assays with excellent performance, the seropositivity rate remains above all epidemiological measure of infection and provides little indication of the actual level of protection afforded by the antibodies detected against the virus. Indeed, other components of the immune response, especially memory T-cell response, seem to be determinant, including among seronegative individuals [54,55].

In conclusion, this is the first study, to the best of our knowledge, to have evaluated seropositivity for anti-SARS-CoV-2 antibodies in parallel in patients with cancer and HCWs in a single comprehensive cancer care centre, at two key timepoints during the COVID-19 pandemic. These epidemiological findings provide insights that will improve our understanding of the dynamics of the pandemic in specific populations with different levels of exposure and risk. Our results provide further arguments in favour of preventive health policies for vulnerable populations such as patients with

cancer and HCWs in this setting. Vaccination remains a priority for both patients and HCWs to break the chain of contamination in cancer care centres.

Authors' contributions

Sylvain Ladoire, Vincent Goussot, Emilie Rederstorff, Aurélie Bertaut, and François Ghiringhelli performed literature search, study design, data collection, data analysis, data interpretation, and writing the paper.

Sylvain Ladoire, Nathalie Briot, Elise Ballot, and Caroline Truntzer made the figures.

Siavoshe Ayati, Leila Bengrine-Lefevre, Nathalie Bremaud, Bruno Coudert, Isabelle Desmoulins, Laure Favier, Cléa Fraisse, Jean-David Fumet, Roxana Hanu, Audrey Hennequin, Alice Hervieu, Silvia Ilie, Courèche Kaderbhai, Aurélie Lagrange, Nils Martin, Irina Mazilu, Didier Mayeur, Rémi Palmier, Anne-Laure Simonet-Lamm, Julie Vincent, and Sylvie Zanetta performed data collection.

Emilie Rederstorff, Sophie Parnalland, Charles Coutant, and Laurent Arnould organised the research work and the logistics.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Appendix A. Supplementary data

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