Matched Case Control Analysis of Breast Cancer-Specific Factors Affecting Risk of Developing SARS-CoV-2 Infection

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ABSTRACT

Introduction: In this retrospective matched case control study, we aim to identify breast cancer-related risk factors associated with developing COVID-19 and describe outcomes of patients with breast cancer diagnosed with COVID-19.

Methods: Women with breast cancer treated at the Medical College of Wisconsin and diagnosed with COVID-19 from March through December 2020 served as cases, and those without COVID-19 within the same timeframe served as controls. Univariate and multivariate comparisons were performed.

Results: Twenty-five cases and 77 controls were identified. All cases were fully matched by age, obesity, county, and race. Mean age was 54.6 versus 54.9, body mass index 31.0 versus 31.6, 48% lived in Milwaukee County, and 68% were White. Regarding COVID-19 outcomes, 24.0% (n = 6) of cases were hospitalized, median length of stay was 2 days, 8% (n=2) needed oxygen, 4% (n = 6) were intubated, and 4% (n = 6) died. COVID-19 led to treatment delays in 40% of cases. On univariate analysis, there was no statistically significant difference in hormone receptor status or breast cancer stage. Being on active chemotherapy (OR 5.8, *P* = 0.043) significantly increased the likelihood of developing COVID-19.

Conclusions: In this matched case control study of patients with breast cancer, active chemotherapy was significantly associated with an increased likelihood of developing COVID-19, with a trend seen for triple negative disease. These findings support continued strict precautions for those on active chemotherapy and warrant further analysis in those with triple negative disease.

INTRODUCTION

In December 2019, a novel coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in the Wuhan province of China. It rapidly spread across the world, causing a clinical syndrome of viral infection known as coronavirus disease 2019 (COVID-19).[1–3] In addition to the unparalleled toll on global health care systems as a direct result of these infections, COVID-19 has had drastic secondary consequences for routine care of all kinds, including the regular care of patients with cancer.[4] COVID-19 has been shown to disrupt all aspects of cancer care, including screening, surgical management, systemic chemotherapy administration, and routine follow-up.[5–10]

In 2020, breast cancer surpassed lung cancer and is now the most commonly diagnosed cancer worldwide, with an estimated 2.3 million new cases diagnosed per year.[11] Particularly in the beginning of the pandemic, well-established screening programs for breast cancer were disrupted, leading to fewer women being diagnosed.[6,8,9] It has been reported previously that up to 54% of breast cancer patients have experienced treatment delays as a result of the COVID-19 pandemic.[7] Such treatment delays in breast cancer have been associated with worse overall survival.[5] It is unknown to what extent and what types of treatment delays have occurred in our own center.

Patients with cancer often are more vulnerable to infections due to the immunosuppressive effects of treatment and their underlying malignancy.[12] To date, most published literature on the outcomes of patients with cancer who were diagnosed with COVID-19 do not differentiate based on cancer type. Additionally, there are varying accounts on the association between cancer-specific risks such as recent chemotherapy treatment and patient out comes with COVID-19 infection.[13–20] It is unknown whether the outcomes of patients with breast cancer and SARS-CoV-2 infection differ from the general population.

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The risk of severe illness from SARS-CoV-2 is known to increase with age.[21] This association seems to persist in patients with and without cancer.[14,17,19,20] For patients newly diagnosed with breast cancer, the median age at diagnosis is 62, putting a majority of patients with breast cancer at increased risk of severe illness due to age alone.[3,22] However, data also suggest that women are at decreased risk compared to men of developing severe illness from SARS-Cov-2.[3] We aim to describe the characteristics and outcomes of patients with active breast cancer diagnosed with SARS-CoV-2 infection at our own academic medical center. Our goal is to identify risk factors associated with SARs-CoV-2 infection specific to breast cancer patients.

METHODS

After institutional review board approval, patient data were gathered retrospectively from the electronic medical record. Data collected included tumor pathology, cancer stage, demographic characteristics, comorbidities, types of treatment received (surgery, radiation, chemotherapy and/or endocrine therapy), treatment disruptions (as defined by ≥1 day delay in active treatment), method of determination of SARS-CoV-2 infection, COVID-19 symptoms, hospitalization, and severity of COVID-19 infection (need for hospitalization, need for intensive care unit [ICU] stay, supplemental oxygen, intubation status, disposition from hospital).

Women with breast cancer treated at the Medical College of Wisconsin and diagnosed with COVID-19 from March through December 2020 served as cases. Women with breast cancer with at least one clinic visit from January through July 2020, but without COVID-19 diagnosis within the same time frame were identified as potential controls. Controls were chosen by matching for age (≥60 vs <60), obesity (BMI <30 vs ≥30), county (Milwaukee vs suburban), race (White vs non-White), and diabetes with 3:1 matching planned. These variables were chosen for matching as they have been known to affect outcomes of COVID-19 infection.[1-3,21] The same control could be used for multiple cases. For calculation of summary statistics, controls were weighted by the inverse of the number of matches for the case. Univariate comparisons between cases and controls were done via Rao-Scott stratified chi-square test for categorical outcomes and stratified *t* test for continuous variables. Conditional logistic regression was performed to evaluate the joint effect of multiple characteristics on the odds of being a COVID-19 case. The multivariable analysis included predictors that were significant at the 0.1 level in the univariate analysis.

RESULTS

Twenty-five cases and 77 controls were identified. All cases were fully matched by age, obesity, county, and race. Three cases were not able to be matched for diabetes. Full demographic information is included in Table 1. Mean age at diagnosis of COVID-19 was 54.6 years, mean BMI was 31.0, 48% of cases lived in Milwaukee County, and 68% of cases were in White patients. Breast cancer-specific information is included in Table 2. Fifty-two percent of cases had stage I disease at time of COVID-19 diagnosis, 64% had estrogen receptor (ER)/progesterone receptor (PR) positive cancer, 12% had human epidermal growth factor receptor 2 (HER2) positive cancer, and 28% had triple negative disease. Seventy-two percent were on active treatment at the time of COVID-19 diagnosis, 44% were receiving endocrine therapy, and 20.8% were on active chemotherapy at the time of COVID-19 diagnosis. All patients had received surgery for their breast cancer, 76% had received chemotherapy, and 60% had received radiation therapy.

Of the 25 patients diagnosed with COVID-19, 6 (24%) needed hospitalization, with a median length of hospital stay of 2 days. Two patients (8%) required supplemental oxygen, and 1 patient (4%) required intubation. Of the 6 hospitalized patients, 4 (16%) received only supportive care, 1 patient (4%) received hydroxychloroquine, and 1 patient (4%) received convalescent plasma and

Table 1. Demographic Information of COVID Cases and Matched Controls

Patient Characteristics	Case (n=25)	Control (n=77)
Mean age at diagnoses of COVID, or last follow-up if control (SE)	54.6 (2.4)	54.9 (0.8)
Mean body mass index (SE)	31.0 (1.4)	31.6 (0.7)
Residence		
Milwaukee County	48%	48%
Suburban county	52%	52%
Diabetes	16%	4%
Tobacco use	40%	37.2%

Abbreviation: SE, standard error.

Table 2. Univariate Analysis of COVID-19 Cases and Controls

	Case (n=25)	Control (n=77)	*P* value
Stage at Last Contact			
0 – I	52.0%	66.0%	0.433
II	16.0%	12.7%	
III – IV	32.0%	21.3%	
ER/PR positive	64%	74.7%	0.309
HER2 positive	12%	20.3%	0.340
Triple negative	28%	13.4%	0.103
Active treatment at time of COVID diagnosis, or last contact if control	72%	74%	0.850
On chemotherapy at time of COVID diagnosis, or last contact if control	20.8%	4%	0.007
On endocrine therapy at time of COVID, or last contact if control	44%	52%	0.488
Breast cancer radiation prior to COVID, or at last contact if control	60%	63.3%	0.763

Controls are weighted to match the number of cases.
Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor.

remdesivir. COVID-19 diagnosis resulted in a treatment delay for 10 patients (40%).

As reported in Table 2, univariate analysis of cases versus controls showed 64% versus 74.7% were ER/PR positive ($P = 0.31$), 12% versus 20.3% HER2 positive ($P = 0.34$), and 28% versus 13.4% triple negative ($P = 0.10$). There was no statistically significant difference in breast cancer stage. At time of COVID diagnosis, or their last contact with clinic if a control, 16% versus 14% had active disease ($P = 0.81$), 72% versus 74% were on active treatment ($P = 0.85$), with 20.8% versus 4% being on chemotherapy ($P = 0.007$) and 44% versus 52% on endocrine therapy ($P = 0.49$). On multivariate conditional logistic regression, current treatment with chemotherapy significantly increased the risk of COVID-19 infection (OR 5.66, $P = 0.044$) as shown in Table 3. There was a trend toward triple negative disease, but it did not cross the boundary of statistical significance (OR 2.69, $P = 0.08$).

Table 3. Multivariate Conditional Logistic Regression for Odds of Being a COVID-19 Case

Predictor	Comparison	Univariate OR (95% CI)	Univariate *P* value	Multivariate OR (95% CI)	Multivariate *P* value
Stage at last contact	II vs 0 – I	1.81 (0.44 – 7.41)	0.4084		
	III – IV vs 0 – I	2.10 (0.67 – 6.61)	0.2052		
Previous radiation	yes vs no	0.86 (0.34 – 2.14)	0.7410		
ER/PR-positive	yes vs no	0.59 (0.22 – 1.58)	0.2963		
HER2-positive	yes vs no	0.50 (0.14 – 1.84)	0.2994		
Triple negative	yes vs no	2.69 (0.88 – 8.20)	0.0813	2.65 (0.78 – 9.03)	0.1186
Active treatment at time of COVID diagnosis, or last contact if control	yes vs no	0.89 (0.32 – 2.43)	0.8143		
Active chemotherapy at time of COVID diagnosis, or last contact if control	yes vs no	7.50 (1.46 - 38.66)	0.0160	5.66 (1.05 – 30.43)	0.0435
On endocrine therapy at time of COVID diagnosis, or last contact if control	yes vs no	0.71 (0.28 - 1.80)	0.4685		

Abbreviations: OR, odds ratio; ER, estrogen receptor; PR, progesterone receptor; HER, human epidermal growth factor receptor.

DISCUSSION

Existing literature on breast cancer and COVID-19 is limited. We set out to identify and describe breast cancer-specific risk factors for developing COVID-19 infections and to describe our institutional experience. Our cohort of cases was relatively representative in terms of both cancer stage and hormone receptor status, with perhaps triple negative breast cancer overrepresented in comparison to our patient population as a whole. Of all cancer-specific patient factors, we found that only current treatment with chemotherapy was significantly associated with developing COVID-19. One potential mechanism for this finding is the common neutropenia experienced with cytotoxic chemotherapy and more frequent clinic visits.

Chemotherapy has been implicated inconsistently as a risk factor for severe COVID-19 and/or death in previous studies, but to our knowledge, it has not been described as a risk factor for development of COVID-19 itself. Multiple cohort studies have suggested that advanced age and comorbidities are associated with increased mortality from COVID-19 but that recent chemotherapy was not.[14,16] Unfortunately, those studies have included all types of cancer, which can impact cancer-specific attributions. A French cohort study by Vuagnat et al prospectively described breast cancer patients diagnosed with COVID-19 and found that age and hypertension were associated with higher risk of ICU stay and/or death, while current treatment with chemotherapy was not associated with patient outcomes.[15] In contrast to these studies, multiple retrospective cohort studies from China have identified recent chemotherapy as a risk factor for developing severe COVID-19 infection and/or death.[17–19]

Similar to previously reported pandemic-related treatment delays, 40% of our patients experienced cancer treatment delays as a result of COVID-19 infection. A recent population study of the impact of timely treatment on breast cancer-specific survival by Ho and colleagues found that delayed first treatment (as defined by more than 90 days from time of diagnosis) was associated with worse overall survival in both the nonmetastatic and metastatic settings.[5] In addition to the deleterious effect on patient survival, treatment delays can contribute to significantly worse patient-reported outcomes. One study in China found that 46.2% of patients with breast cancer had to modify planned, necessary anticancer treatment, and these changes were associated with significant anxiety, depression, and overall distress.[23] Additionally, a European registry enrolling adult patients with cancer and COVID-19 infection found that as a result of sequelae from SARS-CoV-2 infection, 38.2% of patients required a systemic therapy regimen or dose adjustment, and 15% of patients permanently discontinued anticancer therapy.[24] Thus, COVID-19 infection can have lasting repercussions for cancer patients.

It has been established that cancer patients are at higher risk of developing infections, including COVID-19. We endeavored to elucidate risk factors specific to patients with breast cancer in the development of COVID-19 infection. While our study found no association between hormone receptor status or breast cancer stage with the development of COVID-19, there was an association between COVID-19 infection and recent chemotherapy treatment.

One limitation of our study is that it was conducted prior to widespread availability of COVID-specific therapeutics and

COVID-19 vaccination. However, there are some data to suggest that COVID-19 vaccination in patients with solid tumors receiving cytotoxic chemotherapy results in less immunogenicity and therefore lower immune response.[25-28] Thus, this highlights a continued need for further protective measures for this patient population.

CONCLUSIONS

COVID-19 infection represents a significant risk to the health of patients with breast cancer and a substantial disruption to their routine care. We found that factors specific to breast cancer, such as hormone receptor status and endocrine therapy, had no bearing on the risk of developing COVID-19 but that recent treatment with cytotoxic chemotherapy significantly increased risk of infection. The percentage of patients experiencing treatment delays as a result of COVID-19 infection was similar to previously published values.

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