CANCER PREVENTION AND CONTROL

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Impact of COVID-19 in Cervical and Breast Cancer Screening and Systemic Treatment in São Paulo, Brazil: An Interrupted Time Series Analysis

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abstract

PURPOSE COVID-19 caused a disruption in cancer management around the world, resulting in an estimated excess burden secondary to screening disruption and excess lag time for treatment initiation.

METHODS We gathered information from primary reimbursement data sets of the public health system of São Paulo, Brazil, from April 2020 to November 2021, and compared these data with those of the pre–COVID-19 period. We used an interrupted time series model to estimate the effect of the COVID-19 pandemic on the rate of key procedures of breast and cervical cancer health care chain.

RESULTS We estimated that 1,149,727, 2,693, and 713,616 pap smears, conizations, and mammograms, respectively, were missed or delayed during the COVID-19 pandemic, compared with those in the years immediately before the COVID-19 stay-at-home restrictions. Specifically, we observed an acute decrease of procedures after the COVID-19 stay-at-home restrictions, with a trend to recovery in the long term. Regarding the systemic treatment analysis, we observed a 25% reduction in the rate of initiation of adjuvant systemic treatment for early breast cancer (stage I/II). However, we did not find a clear effect on the other settings of systemic treatment for breast cancer. We estimated an excess of 156 patients starting palliative care for cervical cancer after the COVID-19 stay-at-home restrictions.

CONCLUSION The COVID-19 pandemic significantly reduced the performance rate of pap smears, conizations, and mammograms. The initiation of adjuvant treatment for early-stage breast cancer was most susceptible to COVID-19's health system disruption. Furthermore, the downward trend of treatment of advanced cervical cancer was interrupted. Therefore, public health policies are urgently needed to decrease the incidence of advanced cervical and breast cancers caused by delayed diagnosis and treatment initiation.

The COVID-19 control policies resulted in reduction of cancer patients' delivery of care. This study evaluated the pandemic's influence in key procedures of breast and cervical cancer chain of care in São Paulo, Brazil. We observed a substantial reduction in the number of mammograms, pap smears, and conizations performed since the onset of the COVID-19 pandemic. In addition, stage I and II breast cancer adjuvant treatment presented a reduced realization rate, whereas palliative treatment delivered for advanced cervical cancer increased. Our results support the need for public health policies focused on mitigating the long-term effects of COVID-19 in cancer-related mortality.

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ASSOCIATED CONTENT

Appendix

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INTRODUCTION

The ancient dictum of medical ethics, primum non nocere (first, do no harm), permeated the health policies strategies in the fight against COVID-19.[1] The COVID-19 pandemic changed the way that cancers are managed around the world. The initial fear and unfamiliarity regarding the infectious risk in patients with cancer resulted in several protocols focused on the reduction of both patient circulation and treatment aggressiveness.[2-5] In addition, quarantine orders, as a part of COVID-19 control policies, resulted in an important reduction of patients' delivery of care.[6-9] Screening programs were one of the most affected, and we observed pauses in national cancer screening programs in Canada, the Netherlands, Germany, Italy, the United Kingdom, and Australia.[10,11] This decline continued after the end of the quarantine period, as some countries could not return to previous levels of procedures and attendances.[12] Therefore, there was a shift in favor of detecting cancer in more advanced stages caused by delays in cancer diagnosis resulting in an additional burden on the health care systems.[10,11]

Although it is expected longer delays return to pre-pandemic capacity in low- and middle-income

CONTEXT

Key Objective

The COVID-19 control policies resulted in reduction of cancer patients' delivery of care. This study evaluated the pandemic's influence in key procedures of breast and cervical cancer chain of care in São Paulo, the most populous state in Brazil.

Knowledge Generated

We observed a substantial reduction in the number of mammograms, pap smears, and conizations performed since the onset of the COVID-19 pandemic. In addition, stage I and II breast cancer adjuvant treatment presented a reduced realization rate, whereas palliative treatment delivered for advanced cervical cancer increased. In addition, there were no differences in the number of procedures for adjuvant (stage III) and palliative treatment for breast cancer, as well as in the numbers of chemoradiotherapy delivered for cervical cancer treatment.

Relevance

Our results support the need for public health policies and strategies focused on mitigating the long-term effects of COVID-19 in cancer-related mortality.

countries (LMICs), much less studies were reported.[13] Given that disruptive effects of COVID-19 pandemic could further harm cancer health care systems that are already struggling with restricted resources, and the paucity of reports in LMIC, we aimed to systematically describe the effects of COVID-19 pandemic on breast and cervical chain of care in São Paulo (SP), Brazil.

Breast and cervical opportunistic screening and earlier diagnosis campaigns are the core of the Brazilian early detection program. Despite recent advances in important indicators, such as increased access to screening, diagnosis, and treatment involving both conditions, these conditions still pose significant challenges for the Brazilian public health system.[14] In March 2020, after the onset of COVID-19 pandemic in Brazil, an ordinance from the José Alencar Gomes da Silva National Cancer Institute (INCA) recommended that health professionals advise people not to seek health services for cancer screening.[15] In July 2020, this ordinance was revoked because of the heterogeneity of the COVID-19 pandemic situation in the different Brazilian states.[16]

Although there is vast literature forecasting and estimating death excess, there is paucity of literature evaluating its effects on systemic treatment delivery. In this work, we proposed a time series–based analysis of the pandemic's influence in the rates of pap smears, conizations, mammography, and initiation of systemic treatment (stratified by setting of treatment) for breast and cervical cancer in SP, the most populous state in Brazil.

METHODS

Study Design

We performed an interrupted time series model to evaluate the impact of the COVID-19 pandemic on the frequency of screening examinations (pap smear and mammography), conization (defined as both conization per se or Loop Electrosurgical Excision resection for early cervical cancer lesion treatment), and systemic treatment initiation for breast and cervical cancer. We analyzed data from SP, the most populous Brazilian state, which accounts for 20% of the Brazilian population. We evaluated procedures performed between January 2017 and November 2021, and our in-chemotherapy analysis entitled a strict interval (January 2018–November 2021).

Data Sources

We analyzed available information of the procedures performed in the Brazilian public health system, using the electronic address datasus.saude.gov.br to extract the numbers of procedures of pap smears, mammography, and conization performed monthly. In Brazil, complex outpatient procedures are registered in and reimbursed by the Outpatient Information System (SIA), and chemotherapy treatments are registered monthly and are recorded using a specific and detailed reporting form, Authorization of Outpatient Procedures. Because of the strategic position of cervical cancer and breast screening in the national public health policies, mammography and pap smears are also registered in the SIA. Inpatient procedures are registered in a similar, but hospital-based, system called the Hospital Information System. We used both the SIA and Hospital Information System to retrieve information regarding the conization procedures performed in the outpatient and inpatient settings. For the chemotherapy analysis, we accounted for the number of treatments that were initiated; for instance, a patient initiating an adjuvant treatment marked one count, although this could have previously been accounted as a neoadjuvant treatment. This way of analysis (process-based) could better integrate the patient journey in the health system.

In the Brazilian public health system, chemotherapy treatments are reimbursed in monthly installments according to the primary site and purpose of treatment (adjuvant, concomitant, neoadjuvant, curative, and palliative). The Ministry of Health classifies oncology institutions in terms of complexity, and this classification uses as criteria the ability to perform all treatments (surgical, radiotherapy, and chemotherapy) and participation in academic and training programs (residencies, universities, and research).

Specifically for breast cancer, transfers for chemotherapy treatment are subdivided according to clinical stage, human epidermal growth factor receptor 2 (HER2), and hormonal status. In the adjuvant treatment of breast cancer, they are classified according to the clinical stage (I, II, and III), whereas the neoadjuvant treatment is only reimbursable for cases with grouped clinical stage III. Palliative chemotherapy for breast cancer is grouped into first and second (or subsequent) lines, also grouped into HER2 and hormonal subtypes. By contrast, for cervical cancer, there are only two types of reimbursement, one for radical (concurrent) treatment and one for palliative care, regardless of the line of treatment.

We selected patients with stage I-III breast cancer initiating adjuvant systemic therapy, patients with stage II-III cervical cancer initiating definitive chemoradiotherapy, first-line palliative chemotherapy for stage IV cervical and stage IV breast cancer, and neoadjuvant chemotherapy for stage III breast cancer. We divided breast cancer–initiating adjuvant systemic therapy into early (I and II) and locally advanced (III) stages for the construction of the time series model. This selection was performed to ensure classic indications of treatments, with the aim of stabilizing the data. We grouped hormone therapy, anti-HER2 therapy, and cytotoxic chemotherapy as systemic therapy. Patients with a reported clinical stage different from the selection process (eg, stage I-III receiving palliative chemotherapy [recurrence]) and those with a lack of clinical stage information (stage X or absent) were excluded. We used the monthly frequency of procedures as a unit of outcome.

Variables and Model

We performed an interrupted time series model to evaluate the effect of the COVID-19 pandemic on our data. First, we grouped the procedures as mammography, pap smear, conization, early adjuvant breast cancer (stage I and II), locally advanced adjuvant breast cancer (stage III), neoadjuvant breast cancer, palliative breast cancer (first-line palliative), concurrent (with radiotherapy) stage II-III cervical cancer, and palliative cervical cancer (first-line palliative). We performed a sensitivity analysis stratifying chemotherapy initiation according to the complexity of oncologic centers, as defined by the Brazilian health system classification.

Subsequently, we fit a generalized linear model with a quasi-Poisson distribution, adjusting for time, the pandemic start, an interaction term between time and pandemic start, and two pairs of harmonics adjusted monthly to accommodate seasonality. Heteroscedasticity and autocorrelation were visually accessed. Most of our analyzed time series were overdispersed; for those that overdispersion parameter were inferior to 1.0, we fitted an alternative Poisson model. We assessed the effect of the pandemic start as the coefficient term of the categorical variable that defined the pandemic start, and the trend as the coefficient of the interaction term in the fitted model.[17] A pair of harmonics offsets (adjusted by the year month) were used to model the seasonality. This methodology is in accordance with Bernal at al.[18] The Wald test was used to assess statistical significance, with an accepted *P* value $< .05$. Finally, we performed a counterfactual analysis to estimate expected values using the fitted model.

To estimate the difference between the observer and the expected number of systemic treatments initiated, we use the fitted model to predict the expected values in a counterfactual model. Then, we used a Monte Carlo–based bootstrapping to simulate the 95% CI for both the expected procedures (simulation) and the actual procedures performed. We used the functions from the R program[19] for statistical analysis, such as the packages tidyverse(),[20] read.dbc(),[21] tsModel(),[22] MASS(),[23] ciTools(),[24] and broom().[25]

RESULTS

Mammography, Pap Smear, and Conization

A mean number of 186,931 pap smears, 460 conizations, and 103,361 mammography examinations were performed monthly before the COVID-19 stay-at-home restrictions (recommended in March 2020). We found that the pandemic start was significantly correlated with a significant reduction in the realization of both screening examinations (mammography and pap smear), and conization procedures. After March 2020, all these procedures showed immediate reductions in the level (level change), with increasing trends in the slope over time (Fig 1, Table 1). Although mammography and pap smear procedures returned to the levels of the before COVID-19 stay-at-home restrictions, conization performance has not returned to baseline levels by the end of 2021. After the COVID-19 stay-at-home restrictions, we observed a total of 2,448,323 pap smears, 6,211 conizations, and 1,327,087 mammograms, whereas in our counterfactual model, we expected a total of 3,598,050 (95% CI, 3,098,214 to 4,147,108) pap smears, 8,904 (95% CI, 8,055 to 9,816) conizations, and 2,040,703 (95% CI, 1,810,401 to 2,298,773) mammograms. Although the INCA's stay-at-home recommendation was revoked in July 2020, our time series model showed a slow recovery pattern throughout the analyzed period.

Systemic Treatment

Most of our patients analyzed were residents of the metropolitan region of the city of SP, and most were treated in non–high-complexity institutions, except for those undergoing palliative cervical chemotherapy (Table 2). Before the COVID-19 stay-at-home restrictions, we observed that a mean of 461 patients per month initiated adjuvant systemic therapy for early breast cancer (group stage I and II), and 189 patients for locally advanced breast cancer (stage group III). A total of 8,444 (95% CI, 7,890 to 9,064) and

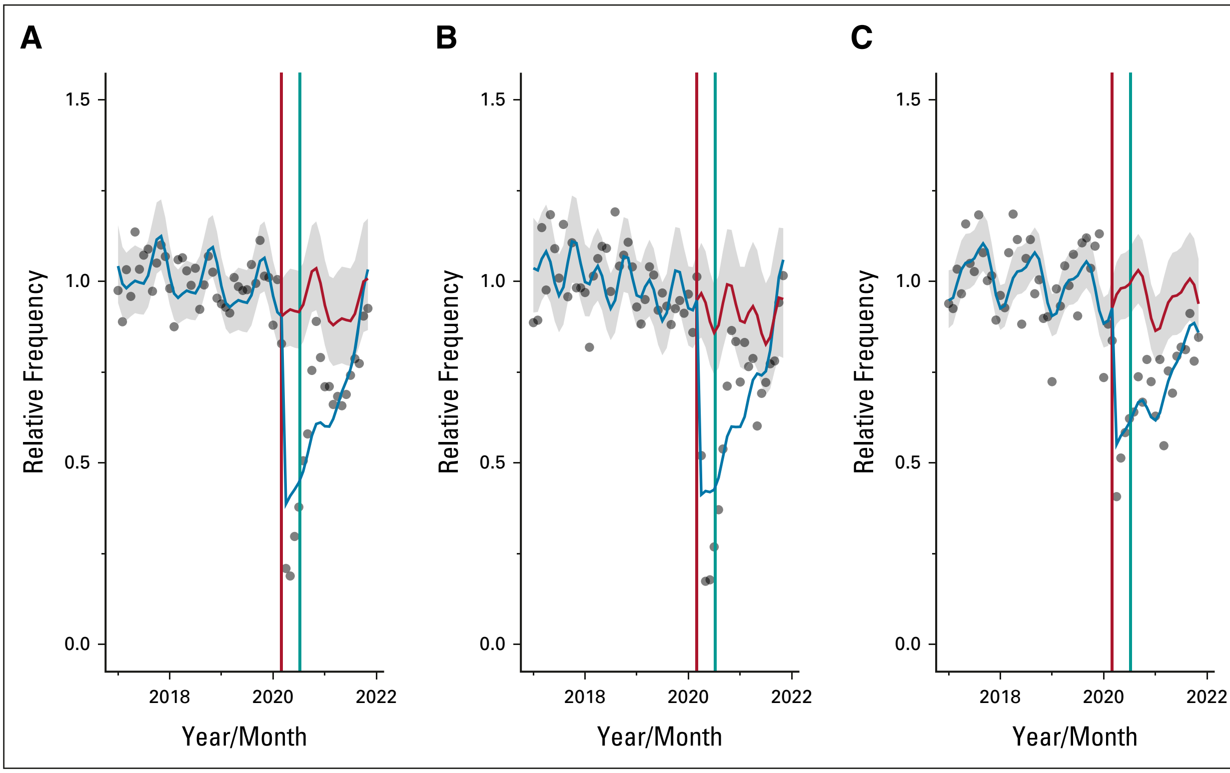

FIG 1. Relative frequencies of (A) mammography, (B) pap smears, and (C) conizations before and after COVID-19 stay-at-home restrictions. Absolute frequency was adjusted by the prepandemic monthly mean, the gray points represent the observed value, the blue line represents the estimated frequency derived by the interrupted time series model, and the red line represents the counterfactual model derived by the interrupted time series model. Red and teal vertical lines represent the stay-at-home recommendation and recommendation lift, respectively.

3,818 (95% CI, 3,613 to 4,032) patients started treatment for early and stage III breast cancer, respectively, while we estimated that 11,268 (95% CI, 9,643 to 13,174) and 3,470 (95% CI, 3,068 to 3,928), respectively, should have started their treatment in our counterfactual model. It is important to note that first-line treatments for local and locoregional breast cancer also include surgery and radiation therapy. However, the impact of the COVID-19 pandemic on these procedures was not studied because these data were not likely to be adequately gathered or not yet mature, respectively. We also noted a mean of 187 patients per month who underwent neoadjuvant systemic treatment for stage III breast cancer and 66 patients for concurrent (with radiotherapy) cervical cancer stage II-III treatment. We observed that 4,550 (95% CI, 4,223 to 4,889) and 1,216 (1,130 to 1,313) patients started neoadjuvant breast cancer treatment and radical cervical cancer treatment, respectively, whereas our simulation estimated 4,514 (95% CI, 3,734 to 5,454) and 1,379 (95% CI, 1,175 to 1,656) patients.

In palliative settings, we noted that a mean of 117 and 32 per month initiated systemic treatment for breast and cervical cancer, respectively, before the COVID-19 stay-at-home restrictions. After the COVID-19 stay-at-home restrictions, we observed that a total of 2,589 (95% CI, 2,389 to 2,791) and 667 (95% CI, 597 to 743) patients started palliative treatment for breast and cervical cancer, respectively, whereas in our model of forecast, a total of 2,517 (95% CI, 2,099 to 3,015) and 511 (95% CI, 398 to 658) patients were expected. We estimated an excess of 156 patients starting palliative care for cervical cancer.

In the interrupted time series models, we found a negative long-term trend (β: –0.015, $P = .007$), indicating a decrease in the early breast cancer (stage I-II) adjuvant treatment start (Fig 2 and Table 3). This trend was more pronounced in non–high-complexity centers (Appendix Figs A1 and A2 and Appendix Tables A1 and A2). We noted a significant increase in the rate of onset of palliative cervical cancer (β: 0.028, $P = .009$), previously described in the summation simulation. We also observed a downward trend before the COVID-19 stay-at-home restrictions in the treatment rate of adjuvant (β: –0.006, $P < .013$) and cervical palliative (β: –0.012, $P = .014$) stage III breast cancer. This trend was more pronounced in high-complexity centers (Appendix Figs A1 and A2 and Appendix Tables A1 and A2). No other statistically significant results were detected (Fig 2, Table 3, Appendix Figs A1 and A2 and Appendix Tables A1 and A2).

DISCUSSION

In our work, we observed a substantial reduction in the number of mammograms, pap smears, and conizations

TABLE 1. Interrupted Time Series Model Analysis of Mammography, Pap Smear, and Conization

Procedure	Model Term	Coefficient (β)	SE	*P*
Mammography	Intercept	11.593	0.0396	< .001
	Pandemic start	–2.721	0.3119	< .001
	Date, month	–0.002	0.0017	.198
	Seasonal harmonic 1	–0.048	0.0241	.052
	Seasonal harmonic 2	–0.029	0.0237	.222
	Seasonal harmonic 3	0.047	0.0244	.059
	Seasonal harmonic 4	0.011	0.0240	.651
	Trend pandemic start: date	0.047	0.0063	< .001
Pap smear	Intercept	12.201	0.0483	< .001
	Pandemic start	–2.872	0.3805	< .001
	Date, month	–0.003	0.0021	.149
	Seasonal harmonic 1	–0.005	0.0293	.871
	Seasonal harmonic 2	–0.053	0.0290	.076
	Seasonal harmonic 3	0.036	0.0300	.239
	Seasonal harmonic 4	–0.012	0.0294	.679
	Trend pandemic start: date	0.051	0.0076	< .001
Conization	Intercept	6.133	0.0320	< .001
	Pandemic start	–1.552	0.2329	< .001
	Date, month	–0.002	0.0014	.180
	Seasonal harmonic 1	–0.059	0.0191	.003
	Seasonal harmonic 2	–0.025	0.0189	.198
	Seasonal harmonic 3	–0.040	0.0196	.049
	Seasonal harmonic 4	–0.017	0.0192	.388
	Trend pandemic start: date	0.025	0.0048	< .001

NOTE. All models were adjusted in a linear generalized model (GLM) for time, pandemic start, two pairs of harmonics for seasonality adjustment, and the time × pandemic interaction. The models were analyzed and stratified by the respective group. Coefficients represent the B term in the GLM model, and the *P* value was derived from a Wald test.

performed since the onset of the COVID-19 pandemic. Notably, these procedures presented an initial trend of decrease in the baseline level, with a recovery trend in the long term. Systemic breast cancer treatment was less affected than screening mammograms in our analysis; however, early breast cancer adjuvant treatment presented a reduction realization rate. We observed no trends in adjuvant advanced and palliative treatment for breast cancer and concurrent chemoradiotherapy for cervical cancer treatment settings. By contrast, we observed an increase in the palliative treatment delivered for advanced cervical cancer. It is important to note that our work is the first to analyze the impact of COVID-19 in breast and cervical cancer screening and treatment chain in Latin America.

The decrease in the performed mammograms, pap smears, and conizations presented similar patterns, that is, started in March 2020 following the INCA recommendations to pause screenings[15] with almost 30% and returned to the normal level by March 2021. Despite the recommendation being revoked in July 2020, the reduction of screening procedures only returned to near-normal numbers in March 2021. Several works worldwide have reported similar reduction realization rates of screening programs, particularly mammography[6,7,26] and pap smears.[27,28] For example, a reduction of 75% was observed for mammograms in Slovenia,[29,30] cervical cytology screening rates per 100 person-months declined approximately 80% in southern California,[27] and there was a 2-month pause in screening program in Italy.[31] However, in striking contrast, the recovery rate in Brazil was much slower than that reported in high-income countries.[27]

Several reasons may explain this discrepancy in recovery delay results. First, the intrinsic differences between an organized screening program, in which reminder systems and tracking persons lost to follow-up are performed, and the Brazilian opportunistic screening program that people seek for the health system spontaneously. Second, during the stay-at-home phase, in Brazil, all nonessential health activities were interrupted. Third, the magnitude of the impact of the COVID-19 pandemic on health systems helps to explain this discrepancy in recovery delay results. For example, in Australia and New Zealand, where efforts to both control and mitigate COVID-19 were highly effective,

TABLE 2. Selected Demographic Characteristics of Patients Submitted to Chemotherapy

Period	Characteristic	Breast Adjuvant Stage I/II	Breast Adjuvant Stage III	Breast Palliative	Breast Neoadjuvant	Cervical Concurrent	Cervical Palliative
Prepandemic	Age, mean (SD)	57.9 (12.2)	55.3 (12.9)	58.2 (14.3)	52.6 (12.9)	49.1 (13.8)	52.5 (14.2)
	Residence in SP metropolis, %	56	49	69	55	54	71
	Treated in high-complexity centers, %	40	42	46	42	47	63
Pandemic	Age, mean (SD)	57.5 (12.1)	54.7 (13.0)	58 (14.1)	53.6 (13.6)	49 (13.9)	52.8 (13.5)
	Residence in SP metropolis, %	57	55	67	61	56	67
	Treated in high-complexity centers, %	33	36	46	35	41	55

Abbreviations: SD, standard deviation; SP, São Paulo.

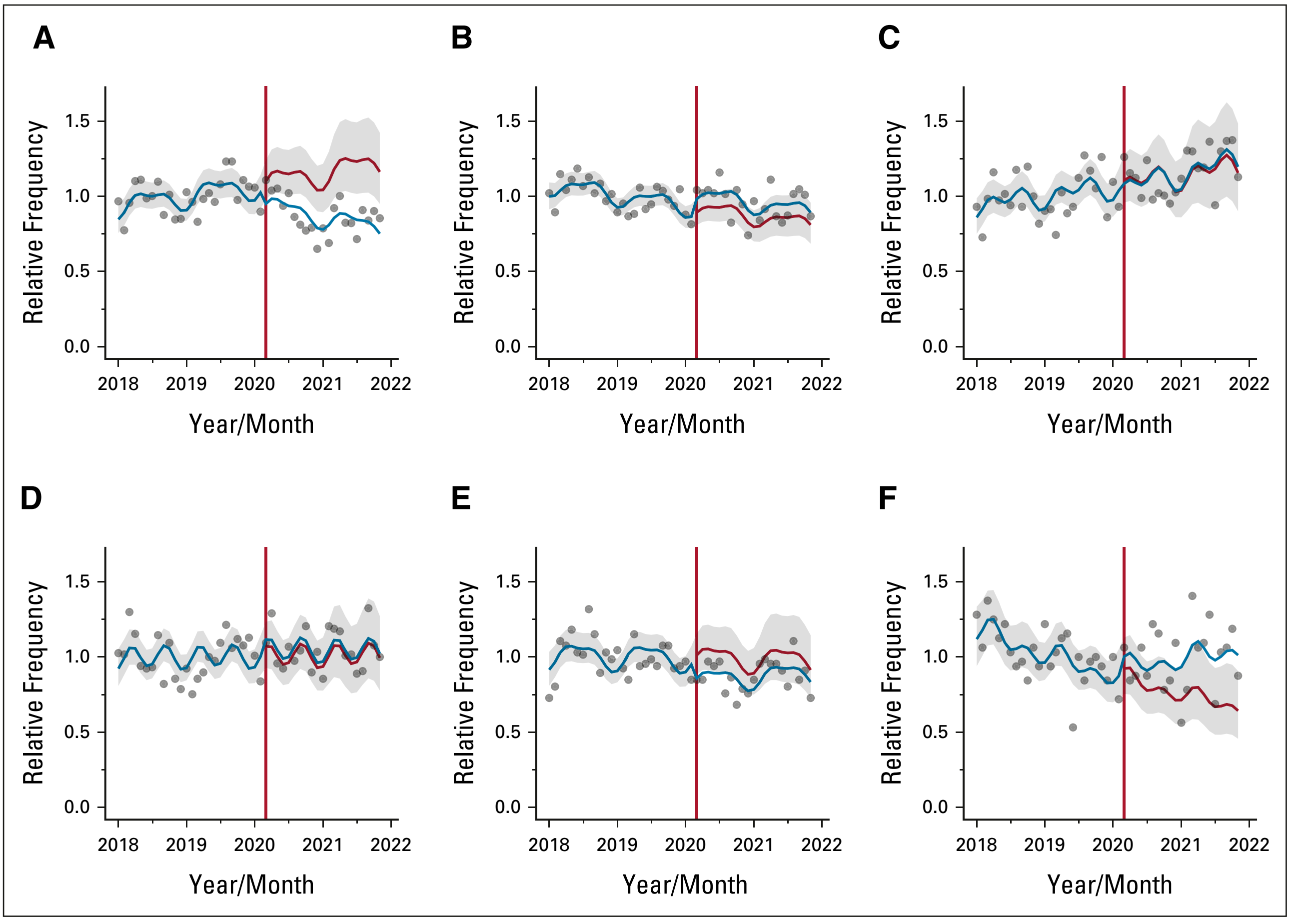

FIG 2. Relative frequencies of systemic treatment initiation. Treatments were stratified as (A) early stage (I/II) breast adjuvant, (B) locally advanced (III) stage breast adjuvant, (C) breast neoadjuvant, (D) breast palliative (stage IV), (E) cervical concomitant, and (F) cervical palliative. Absolute frequency was adjusted by the prepandemic monthly mean, the gray points represent the observed value, the blue line represents the estimated frequency derived by the interrupted time series model, and the red line represents the counterfactual model derived by the interrupted time series model.

there was a rapid screening recovery rate.[32-34] Finally, even after the stay-at-home order lifted, changes in the demand pattern for the health system caused by the fear of contracting COVID-19 were reported.[35,36]

Some authors have identified another factor that could influence the estimated burden in screening disruption as the lag time between the screened lesion and the invasive cancer.[37] Given that mammography detects an already invasive cancer[38,39] and pap smears screen precancerous lesions,[40] we hypothesize this is the reason that only early breast cancer systemic treatment initiation was significantly reduced after the COVID-19 stay-at-home restrictions. Although human papillomavirus polymerase chain reaction–based screened programs could be more resilient, compared with non–polymerase chain reaction–based programs, it has been suggested that a rapid resumption of screening after COVID-19–induced disruption is associated with a small impact on cervical screening.[37] Consistently, we observed that there were no trends in concomitant cervical treatment.

The effect of COVID-19 on cancer treatment has been more uncertain.[41] Baxter et al reported a sharp decrease with a rapid recovery trend in the rate of systemic anticancer treatment in Scotland.[42] A similar finding was also described in Australia.[43] Similar to our findings in cervical palliative setting, Blay et al,[44] in their analysis of French data, reported an increase in the number of patients who initiated palliative treatment. In their analysis of the quantity of treatment and scheme of treatment changes, Eijkelboom et al[45] reported that chemotherapy was less likely to be performed against hormonal therapy for breast cancer treatment. We did not detect changes in the trend of breast cancer palliative treatment.

Although, a recent study reported that delaying 8 weeks for hysterectomy did not result in cervical cancer recurrence,[46] the long prepandemic lines already in place for medical care visits added to the drastic reduction in the number of face-to-face consultation visits in LMICs and may explain the increasing trend in treatment of metastatic cervical cancer. Moreover, the fear of contracting COVID-19 may potentiate the delay in diagnosis.[35,36] The exact burden of COVID-19 in

TABLE 3. Interrupted Time Series Model Analysis of Patients Submitted to Chemotherapy

Chemotherapy Type	Model Term	Coefficient (β)	SE	*P*
Breast adjuvant I/II	Intercept	6.060	0.0458	< .001
	Pandemic start	0.245	0.1634	.142
	Date, month	0.006	0.0029	.057
	Seasonal harmonic 1	–0.011	0.0235	.630
	Seasonal harmonic 2	–0.023	0.0229	.323
	Seasonal harmonic 3	–0.069	0.0242	.007
	Seasonal harmonic 4	–0.025	0.0234	.290
	Trend pandemic start: date	–0.015	0.0051	.007
Breast adjuvant III	Intercept	5.329	0.0362	< .001
	Pandemic start	0.094	0.1282	.467
	Date, month	–0.006	0.0024	.013
	Seasonal harmonic 1	–0.044	0.0190	.027
	Seasonal harmonic 2	–0.021	0.0184	.263
	Seasonal harmonic 3	–0.040	0.0193	.046
	Seasonal harmonic 4	–0.014	0.0187	.468
	Trend pandemic start: date	0.000	0.0040	.992
Breast neoadjuvant	Intercept	5.164	0.0564	< .001
	Pandemic start	–0.094	0.1811	.606
	Date, month	0.005	0.0036	.155
	Seasonal harmonic 1	–0.023	0.0273	.406
	Seasonal harmonic 2	–0.018	0.0266	.512
	Seasonal harmonic 3	–0.043	0.0283	.138
	Seasonal harmonic 4	–0.050	0.0272	.075
	Trend pandemic start: date	0.003	0.0057	.634
Breast palliative	Intercept	4.755	0.0547	< .001
	Pandemic start	0.062	0.1840	.739
	Date, month	0.000	0.0036	.907
	Seasonal harmonic 1	–0.006	0.0273	.823
	Seasonal harmonic 2	–0.029	0.0268	.292
	Seasonal harmonic 3	–0.013	0.0285	.646
	Seasonal harmonic 4	–0.070	0.0274	.015
	Trend pandemic start: date	–0.001	0.0058	.900
Cervical concomitant	Intercept	4.201	0.0511	< .001
	Pandemic start	–0.266	0.1868	.155
	Date, month	–0.001	0.0034	.831
	Seasonal harmonic 1	–0.008	0.0268	.757
	Seasonal harmonic 2	–0.014	0.0260	.603
	Seasonal harmonic 3	–0.079	0.0275	.004
	Seasonal harmonic 4	–0.029	0.0266	.281
	Trend pandemic start: date	0.004	0.0057	.519
Cervical palliative	Intercept	3.645	0.0719	< .001
	Pandemic start	–0.419	0.2605	.116
	Date, month	–0.012	0.0049	.014
	Seasonal harmonic 1	0.037	0.0383	.342

(Continued on following page)

TABLE 3. Interrupted Time Series Model Analysis of Patients Submitted to Chemotherapy (Continued)

Chemotherapy Type	Model Term	Coefficient (β)	SE	*P*
	Seasonal harmonic 2	–0.033	0.0372	.379
	Seasonal harmonic 3	–0.027	0.0393	.491
	Seasonal harmonic 4	–0.042	0.0380	.281
	Trend pandemic start: date	0.019	0.0081	.027

NOTE. All models were adjusted in a linear generalized model (GLM) for time, pandemic start, two pairs of harmonics for seasonality adjustment, and the time × pandemic interaction. The models were analyzed and stratified by the respective group. Coefficients represent the B term in the GLM model, and the *P* value was derived from a Wald test.

cancer mortality is very difficult to estimate. Some models expect substantial increases in breast, cervical, and colorectal cancer death.[8,47] Even a short two-week delay model was associated with an increase in cancer deaths in simulation models.[48]

Our work has some limitations. Although we used a quasi-experimentally based analysis, the retrospective design, time series–based model, and the source of information on the basis of the macro reimbursement system added caution to the interpretation of causality in our data. Furthermore, we did not evaluate the impact of the COVID-19 pandemic on surgery or radiotherapy, which limited our definition of treatment of early breast cancer only to those patients who received adjuvant treatment for stage I/II breast cancer.

The COVID-19 pandemic significantly reduced the rate of pap smears, conizations, and mammograms. In addition, the initiation of adjuvant treatment of early breast cancer and the discontinuation of the downward trend in the cervical cancer treatment for advanced cancer were most vulnerable to the health system disruption caused by COVID-19. The consistency of our findings, in addition to others reported in different countries, clearly show and support the need for public health strategies focused on mitigating the long-term effects of COVID-19 in cancer-related mortality.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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No other potential conflicts of interest were reported.

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APPENDIX

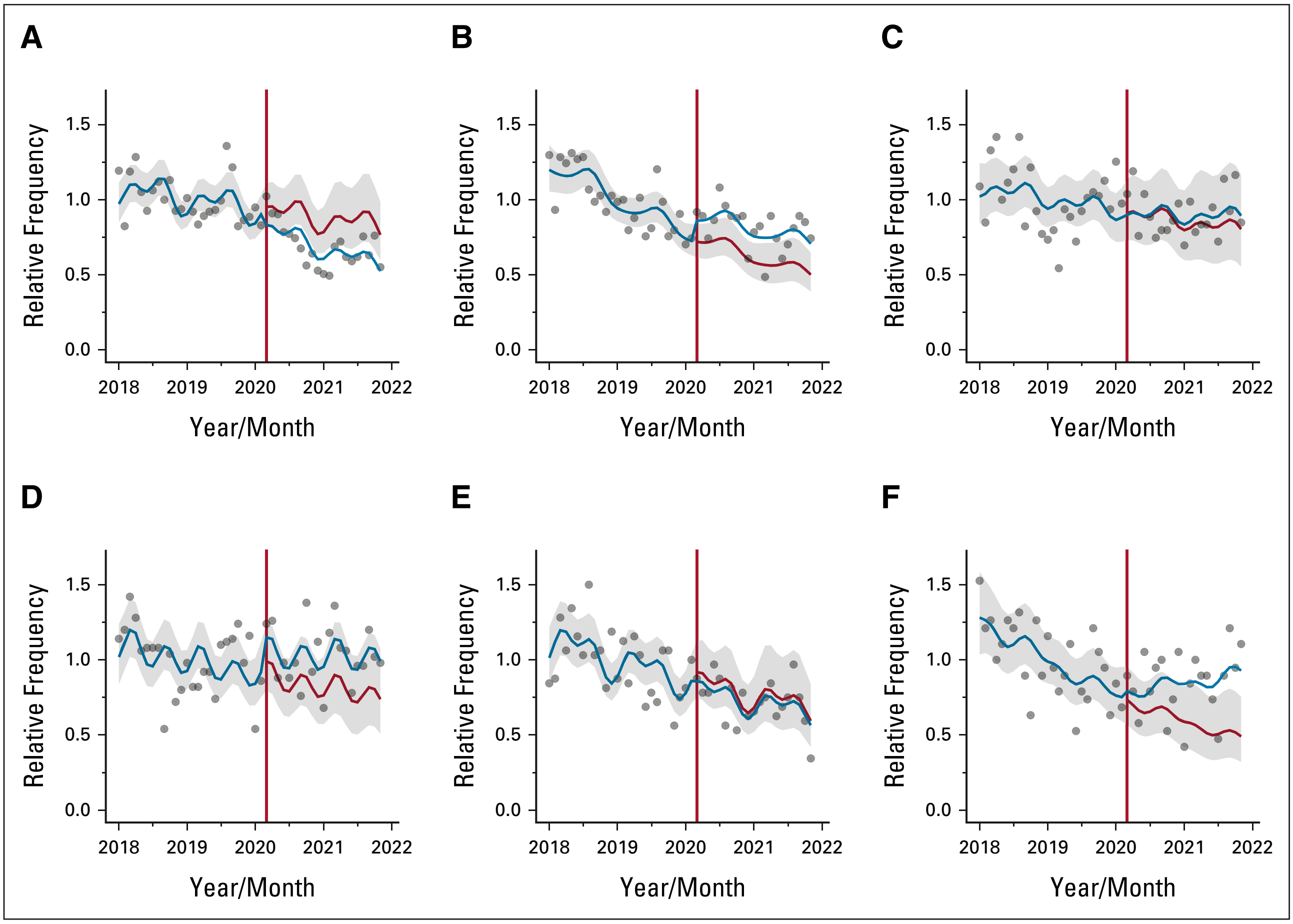

FIG A1. Relative frequencies of systemic treatment initiation in high-complexity hospital. Treatments were stratified as (A) early stage (I/II) breast adjuvant, (B) locally advanced (III) stage breast adjuvant, (C) breast neoadjuvant, (D) breast palliative (stage IV), (E) cervical concomitant, and (F) cervical palliative. Absolute frequency was adjusted by the prepandemic monthly mean, the gray points represent the observed value, the blue line represents the estimated frequency derived by the interrupted time series model, and the red line represents the counterfactual model derived by the interrupted time series model.

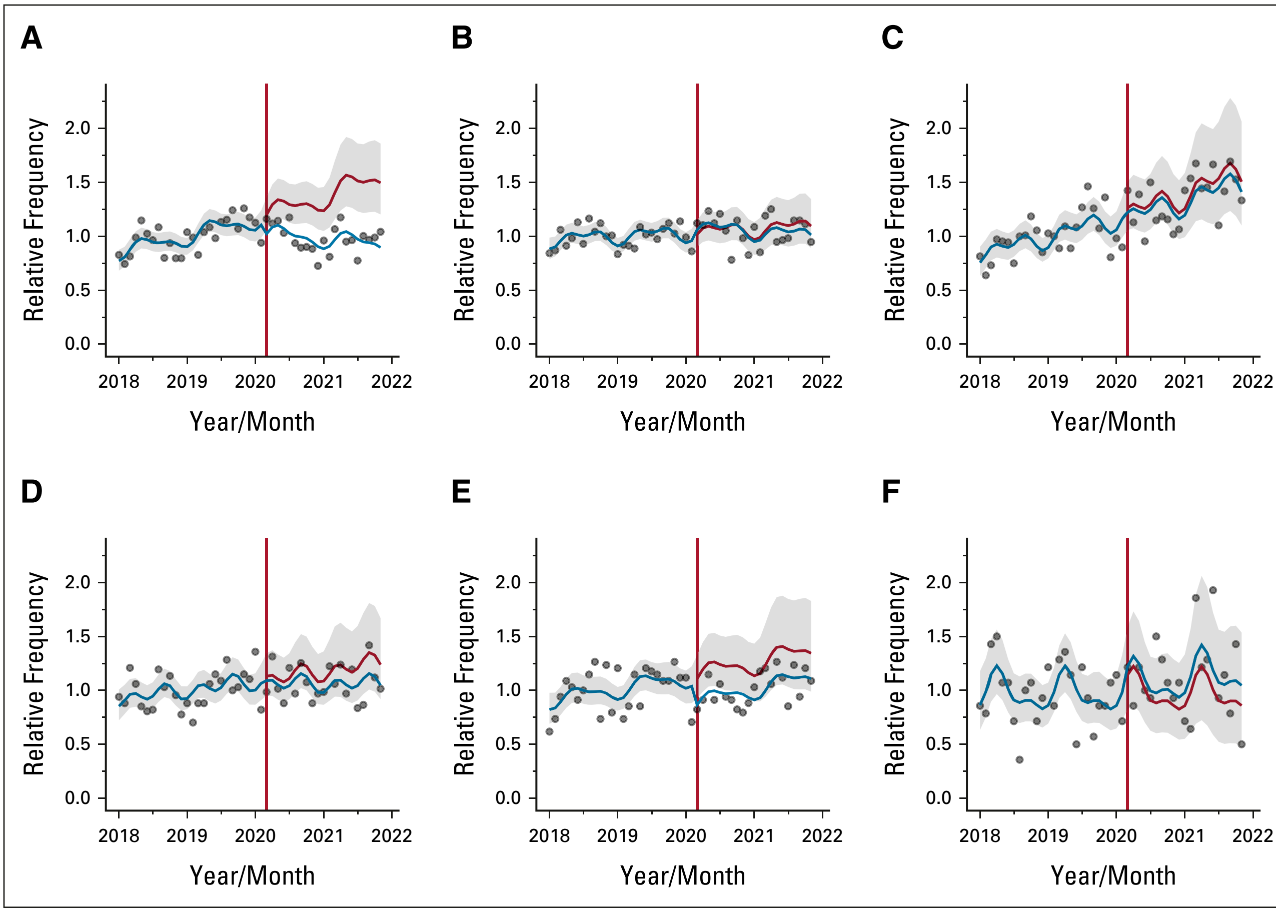

FIG A2. Relative frequencies of systemic treatment initiation in non–high-complexity hospital. Treatments were stratified as (A) early stage (I/II) breast adjuvant, (B) locally advanced (III) stage breast adjuvant, (C) breast neoadjuvant, (D) breast palliative (stage IV), (E) cervical concomitant, and (F) cervical palliative. Absolute frequency was adjusted by the prepandemic monthly mean, the gray points represent the observed value, the blue line represents the estimated frequency derived by the interrupted time series model, and the red line represents the counterfactual model derived by the interrupted time series model.

TABLE A1. Interrupted Time Series Model Analysis of Patients Submitted to Chemotherapy in High-Complexity Hospital

Chemotherapy Type	Model Term	Coefficient (β)	SE	*P*
Breast adjuvant I/II	Intercept	5.255	0.0539	< .001
	Pandemic start	0.191	0.2197	.390
	Date. month	–0.006	0.0036	.104
	Seasonal harmonic 1	–0.035	0.0297	.250
	Seasonal harmonic 2	–0.001	0.0291	.964
	Seasonal harmonic 3	–0.067	0.0310	.038
	Seasonal harmonic 4	–0.063	0.0298	.042
	Trend pandemic start: date	–0.012	0.0067	.078
Breast adjuvant III	Intercept	4.567	0.0521	< .001
	Pandemic start	–0.041	0.2055	.843
	Date, month	–0.020	0.0036	< .001
	Seasonal harmonic 1	–0.063	0.0293	.039
	Seasonal harmonic 2	0.006	0.0283	.833
	Seasonal harmonic 3	–0.034	0.0297	.264
	Seasonal harmonic 4	–0.013	0.0289	.658
	Trend pandemic start: date	0.008	0.0063	.206
Breast neoadjuvant	Intercept	4.467	0.0802	< .001
	Pandemic start	–0.174	0.2944	.557
	Date, month	–0.007	0.0053	.206
	Seasonal harmonic 1	–0.037	0.0425	.390
	Seasonal harmonic 2	–0.023	0.0413	.574
	Seasonal harmonic 3	–0.018	0.0435	.680
	Seasonal harmonic 4	–0.032	0.0422	.454
	Trend pandemic start: date	0.006	0.0091	.516
Breast palliative	Intercept	4.009	0.0802	< .001
	Pandemic start	–0.044	0.2778	.874
	Date, month	–0.008	0.0054	.144
	Seasonal harmonic 1	0.024	0.0412	.569
	Seasonal harmonic 2	–0.040	0.0405	.330
	Seasonal harmonic 3	–0.005	0.0432	.903
	Seasonal harmonic 4	–0.085	0.0414	.047
	Trend pandemic start: date	0.007	0.0087	.416
Cervical concomitant	Intercept	3.597	0.0725	< .001
	Pandemic start	–0.095	0.2915	.745
	Date, month	–0.011	0.0049	.030
	Seasonal harmonic 1	0.009	0.0402	.816
	Seasonal harmonic 2	0.010	0.0394	.801
	Seasonal harmonic 3	–0.097	0.0420	.026
	Seasonal harmonic 4	–0.072	0.0403	.082
	Trend pandemic start: date	0.001	0.0089	.913
Cervical palliative	Intercept	3.220	0.0899	< .001
	Pandemic start	–0.687	0.3563	.054
	Date, month	–0.022	0.0062	.001
	Seasonal harmonic 1	–0.033	0.0505	.514

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TABLE A1. Interrupted Time Series Model Analysis of Patients Submitted to Chemotherapy in High-Complexity Hospital (Continued)

Chemotherapy Type	Model Term	Coefficient (β)	SE	*P*
	Seasonal harmonic 2	–0.001	0.0488	.977
	Seasonal harmonic 3	0.031	0.0513	.539
	Seasonal harmonic 4	–0.032	0.0500	.524
	Trend pandemic start: date	0.028	0.0109	.009

NOTE. All models were adjusted in a linear generalized model (GLM) for time, pandemic start, two pairs of harmonics for seasonality adjustment, and the time × pandemic interaction. The models were analyzed and stratified by the respective group. Coefficients represent the B term in the GLM model, and the *P* value was derived from a Wald test.

TABLE A2. Interrupted Time Series Model Analysis of Patients Submitted to Chemotherapy in Non–High-Complexity Hospital

Chemotherapy Type	Model Term	Coefficient (β)	SE	*P*
Breast adjuvant I/II	Intercept	5.477	0.0508	< .001
	Pandemic start	0.318	0.1689	.067
	Date, month	0.013	0.0032	< .001
	Seasonal harmonic 1	0.000	0.0250	.989
	Seasonal harmonic 2	–0.035	0.0242	.158
	Seasonal harmonic 3	–0.072	0.0256	.008
	Seasonal harmonic 4	–0.005	0.0247	.837
	Trend pandemic start: date	–0.018	0.0053	.002
Breast adjuvant III	Intercept	4.714	0.0459	< .001
	Pandemic start	0.201	0.1524	.194
	Date, month	0.003	0.0030	.396
	Seasonal harmonic 1	–0.034	0.0229	.151
	Seasonal harmonic 2	–0.037	0.0223	.101
	Seasonal harmonic 3	–0.045	0.0235	.063
	Seasonal harmonic 4	–0.014	0.0227	.527
	Trend pandemic start: date	–0.006	0.0048	.224
Breast neoadjuvant	Intercept	4.490	0.0737	< .001
	Pandemic start	0.010	0.2171	.962
	Date, month	0.014	0.0046	.004
	Seasonal harmonic 1	–0.015	0.0334	.649
	Seasonal harmonic 2	–0.015	0.0327	.645
	Seasonal harmonic 3	–0.059	0.0349	.100
	Seasonal harmonic 4	–0.061	0.0334	.076
	Trend pandemic start: date	–0.002	0.0070	.820
Breast palliative	Intercept	4.118	0.0681	< .001
	Pandemic start	0.144	0.2241	.523
	Date, month	0.007	0.0044	.133
	Seasonal harmonic 1	–0.029	0.0333	.393
	Seasonal harmonic 2	–0.021	0.0326	.528
	Seasonal harmonic 3	–0.019	0.0347	.582
	Seasonal harmonic 4	–0.058	0.0333	.090
	Trend pandemic start: date	–0.007	0.0070	.350
Cervical concomitant	Intercept	3.417	0.0730	< .001
	Pandemic start	–0.318	0.2463	.197
	Date, month	0.009	0.0047	.054
	Seasonal harmonic 1	–0.024	0.0364	.504
	Seasonal harmonic 2	–0.032	0.0350	.363
	Seasonal harmonic 3	–0.068	0.0367	.064
	Seasonal harmonic 4	0.007	0.0358	.855
	Trend pandemic start: date	0.003	0.0076	.726
Cervical palliative	Intercept	2.607	0.1267	< .001
	Pandemic start	–0.109	0.4115	.793
	Date, month	0.000	0.0083	.984
	Seasonal harmonic 1	0.117	0.0631	.070

(Continued on following page)

TABLE A2. Interrupted Time Series Model Analysis of Patients Submitted to Chemotherapy in Non–High-Complexity Hospital (Continued)

Chemotherapy Type	Model Term	Coefficient (β)	SE	*P*
	Seasonal harmonic 2	–0.070	0.0615	.261
	Seasonal harmonic 3	–0.099	0.0655	.137
	Seasonal harmonic 4	–0.054	0.0628	.395
	Trend pandemic start: date	0.007	0.0131	.623

NOTE. All models were adjusted in a linear generalized model (GLM) for time, pandemic start, two pairs of harmonics for seasonality adjustment, and the time × pandemic interaction. The models were analyzed and stratified by the respective group. Coefficients represent the B term in the GLM model, and the *P* value was derived from a Wald test.

