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COVID-19 Pandemic Effects on Breast Cancer Diagnosis in Croatia: A Population- and Registry-Based Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. COVID-19 • SARS-CoV-2 • Coronavirus • Pandemic • Breast cancer • Lockdown

Abstract

Background. Our objective was to assess the effects of COVID-19 antiepidemic measures and subsequent changes in the function of the health care system on the number of newly diagnosed breast cancers in the Republic of Croatia.

Subjects, Materials, and Methods. We performed a retrospective, population- and registry-based study during 2020. The comparator was the number of patients newly diagnosed with breast cancer during 2017, 2018, and 2019. The outcome was the change in number of newly diagnosed breast cancer cases.

Results. The average monthly percent change after the initial lockdown measures were introduced was −11.0% (95% confidence interval − 22.0% to 1.5%), resulting in a 24% reduction of the newly diagnosed breast cancer cases in Croatia during April, May, and June compared with the same period of 2019. However, during 2020, only 1% fewer new cases were detected than in 2019, or 6% fewer than what would be expected based on the linear trend during 2017–2019.

Conclusion. It seems that national health care system measures for controlling the spread of COVID-19 had a detrimental effect on the number of newly diagnosed breast cancer cases in Croatia during the first lockdown. As it is not plausible to expect an epidemiological change to occur at the same time, this may result in later diagnosis, later initiation of treatment, and less favorable outcomes in the future. However, the effect weakened after the first lockdown and COVID-19 control measures were relaxed, and it has not reoccurred during the second COVID-19 wave. Although the COVID-19 lockdown affected the number of newly diagnosed breast cancers, the oncology health care system has shown resilience and compensated for these effects by the end of 2020. ***The Oncologist*** 2021;26:e1156–e1160

Implications for Practice: It is possible to compensate for the adverse effects of COVID-19 pandemic control measures on breast cancer diagnosis relatively promptly, and it is of crucial importance to do it as soon as possible. Moreover, as shown by this study's results on the number of newly diagnosed breast cancer cases during the second wave of the pandemic, these adverse effects are preventable to a non-negligible extent.

Introduction

The first cases of infection with the SARS-CoV-2 virus, a new strain of RNA coronavirus, in humans were detected in December 2019 in Wuhan, Hubei Province, China [1]. By February 15, 2021, 108.9 million cases and 2.4 million deaths from the effects of coronavirus disease 2019 (COVID-19) had been globally confirmed [2]. In the Republic of Croatia, the first case of infection was confirmed on February 25, 2020, and by February 15, 2021, there were 237,725 detected cases (58,481 per million inhabitants) and 5,339 deaths (1,313 per million inhabitants). Measures

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taken to limit the spread of the infection, to stabilize and "flatten the curve" of hospitalizations in the intensive care units, and to better match available resources were, in principle, based on the measures of social distancing ("lockdown"). On March 15, 2020, the Croatian government implemented lockdown measures with a reorganized health care system to optimally manage the COVID-19 outbreak. All around the globe, similar measures of postponing health services of lower urgency such as breast reconstruction surgery [3], performing evaluations and consultations via telephone or video during virtual check-ups, allocation of protective equipment [4], earlier discharges, limiting outpatient visits [5], redeployment of health care professionals, change in treatment from longer to shorter duration, changes of intravenous to subcutaneous or oral treatments, refill of prescriptions without the patient coming to the clinic, home delivery of medications, reduction of nonessential follow-up visits, and rescheduling of appointments to reduce waiting time have been introduced [6]. The consequences of the lockdown measures could have a significant impact on cancer outcomes worldwide. In Croatia, as well as in many other countries [7], national secondary prevention programs were halted during the pandemic, and recent gains in the early diagnosis of breast cancer could have been undermined in the short term [8]. Diagnosing breast cancer in COVID-19-reprogrammed health systems became markedly more challenging. As a consequence, delay of the diagnosis may become more frequent, underpinning poorer outcomes [8].

Breast cancer is the most frequent malignancy in women globally, with more than 2.1 million newly diagnosed cases in 2018 [9]. Late diagnosis and potentially upward stage migration could, together with other COVID-19-associated oncology specificities (not optimal multidisciplinary work, suboptimal therapy, and insufficient follow-up procedures as well as lack of diagnostics opportunities), result in a significant increase in breast cancer morbidity and mortality.

Our objective was to assess the effects of COVID-19 on the number of patients with newly diagnosed breast cancer in the Republic of Croatia.

Subjects, Materials, and Methods

Study Design

We performed a retrospective, population- and registry-based study during 2020. The comparator was the number of patients with newly diagnosed breast cancer in the same registry during 2017, 2018, and 2019. The study was approved by the Ethics Committee of Clinical Hospital Centre Split, School of Medicine, University of Split, Split, Croatia, and was performed in accordance with the World Health Organization Declaration of Helsinki of 1975 as revised in 2013 [10] and the International Conference on Harmonization Guidelines on Good Clinical Practice [11]. We fully protected the patients' anonymity and did not collect any data on individual patients. The study was not preregistered.

Study Population

The targeted population was patients with newly diagnosed breast cancer. Diagnosis was performed by tissue sample pathohistological analysis. Tissues were obtained by needle, stereotactic, or open tumor biopsy or surgery.

Sample Type and Needed Sample Size

We analyzed the total population from 25 Croatian hospitals that cover >95% of all Croatian breast cancer cases.

Endpoints

The endpoint was the difference in the number of patients with newly diagnosed breast cancer between comparable periods in 2017, 2018, and 2019 and in 2020 after the COVID-19 outbreak. We collected the data from hospital pathohistological databases on the total number of newly diagnosed patients in each of the participating institutions on any given day without recording individual patient data.

Statistical Analysis

We performed the main analysis using segmented or joinpoint regression and permutation tests with 10,000 permutations and fit the autocorrelated errors model based on the data, to identify changes in trends [12]. We described the detected trends using the average annual percent change as the summary measure, with their 95% confidence intervals (CIs). We set two-tailed statistical significance at $p < .05$ and calculated all CIs at the 95% level. We controlled the false-positive rate using the Benjamini-Hochberg procedure with the false discovery rate (FDR) set in advance at FDR < 5%. We performed statistical analysis using StataCorp 2019 (Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX) and the joinpoint regression using the Joinpoint Regression Program, version 4.8.0.1 - April 2020 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, USA).

Results

During 2017, 2018, and 2019, we did not detect any significantly different trends in the number of newly diagnosed breast cancer monthly, and these numbers were best described by single linear trends over the entire years (Table 1). The slope of this linear trend was not significantly different from zero during 2017 when the annual percent change was 1.2% (95% CI −0.9% to 3.3%; $p = .128$; FDR > 5%). These single linear trends were significantly different from zero during 2018 and 2019 with the annual percent changes 1.7% (95% CI 0.3% to 3.1%; $p = .001$; FDR < 5%) and 2.9% (95% CI 1.6% to 4.1%; $p < .001$; FDR < 5%), respectively. In contrast, during 2020, we detected two distinct, significantly different trends in the change of patients with newly diagnosed breast cancer, separated by one joinpoint in May (Fig. 1). The slope of the first trend (January to May) was at the edge of significance but with FDR <5% (Table 1). The annual percent change of the first trend was −11.0% (95% CI −22.0% to 1.5%; $p = .052$; FDR < 5%). The second trend was reversed and significantly different from zero with the average weekly percent change

Table 1. Detection of trends in the number of newly diagnosed breast cancer cases annually by joinpoint regression

Year	No. of new diagnoses	No. of joinpoints	APC	95% CI	*p* value
2017	2,535	0	1.2	−0.9 to 3.3	.128
2018	2,651	0	1.7	0.3 to 3.1	.001[a]
2019	2,875	0	2.9	1.6 to 4.1	<.001[a]
2020	2,848	1	0.4[b]	−4.3 to 5.4	.423
2020 (January to May)	1,132		−11.0	−22.0 to 1.5	.052[a]
2020 (June to December)	1,716		7.6	2.2 to 13.3	.007[a]

[a]FDR <5%
[b]Average APC.
Abbreviations: APC, annual percent change; CI, confidence interval; FDR, false discovery rate.

7.6% (95% CI 2.2% to 13.3%; p = .007; FDR < 5%). After the introduction of hospital lockdown on March 15, 2020, the number of newly diagnosed breast cancer cases during April decreased by 33% compared with March. During April, May, and June 2020, 167 (24%) fewer cancer cases were newly diagnosed as compared with the same period in 2019. During the entire year of 2020, 27 (1%) fewer new cases were detected than during 2019. Based on the linear trend in the number of newly diagnosed cases during 2017–2019, the expected number in 2020 was supposed to be 3,027, which is 179 (6%) more patients than have actually been diagnosed during the year 2020.

Discussion

We have detected a significant decrease in the number of patients with newly diagnosed breast cancer since the detection of the first Croatian COVID-19 case on February 25, 2020, and since the consecutive lockdown antipandemic measures were introduced. This decrease was significantly different from the trend during the year before (2019) and during 2017 and 2018, while there was no reason to expect any sudden epidemiological change. Therefore, the basic assumption is that the number of new breast cancer cases remained comparable to the number of new cases in the previous year, that is, before the outbreak of the COVID-19 pandemic, but during the follow-up period, fewer of these new cases were successfully diagnosed. This could lead to a later diagnosis in the natural course of the disease and the later initiation of the treatment. The longer the duration of undetected breast cancer, the higher the risk that it will be in an advanced stage at the time of diagnosis [13]. In addition to that, it was estimated that each month's delay in diagnosis is associated with a 1.8% higher probability of a more advanced cancer stage [14] and that 3 months' delay of the primary surgery resulted in decreased overall survival [15]. This effect of the national lockdowns may be additionally detrimental in low- and middle-income countries where locally advanced or metastatic disease was already more common among newly diagnosed breast cancer and where we have been experiencing significant challenges in delivering optimal breast cancer care [16, 17], even before COVID-19. Whether these diagnostic delays and later initiation of the treatment will have relevant negative consequences in terms of outcomes and prognosis depends on their duration. A delay of 3–6 months has been associated with worse long-term prognosis and shorter survival [14, 18]. However, shorter delays may have no relevant consequences [19]. A delay of 3 months from surgery to adjuvant chemotherapy is associated with a 60% higher hazard for a shorter overall survival [19]. Taking all this into account, it is crucial to get the system back to normal as quickly as possible so that we

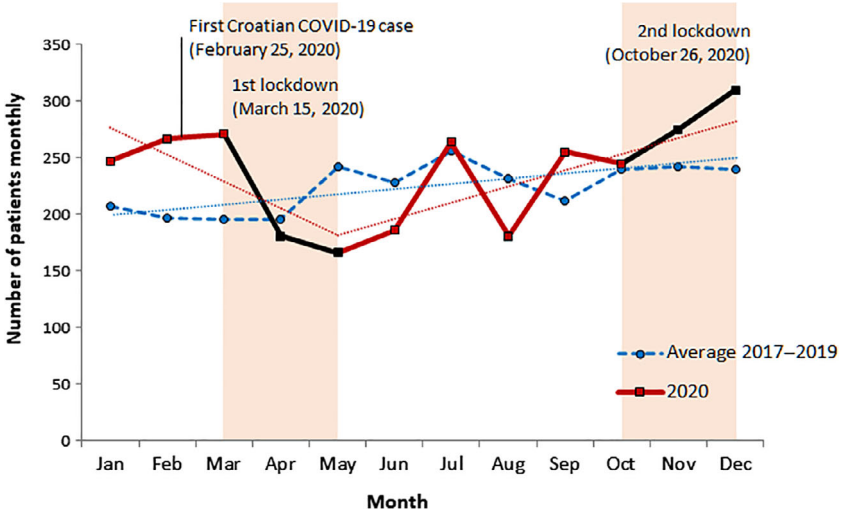

Figure 1. The number of newly diagnosed breast cancer cases monthly during the year 2020 (solid red line), and the average of 2017, 2018, and 2019 (dashed blue line); dotted trend lines represent joinpoint regression lines.

may still be able to avoid, or at least minimize, the worst consequences.

In addition to the described possible immediate consequences on the diagnosis of breast cancer and oncology care, the COVID-19 pandemic will also have a detrimental effect on the economy, with lower tax revenues and available resources for public health care, leading to the possible decrement of overall investment in cancer care and health care in general [20]. These effects may be particularly severe in the transitional countries of Central and Eastern Europe, where the expenditure on oncology drugs per cancer case was already 2.5 times lower than that in Western Europe before the COVID-19 outbreak [21]. This is important because the expenditure on oncology drugs is negatively correlated with the mortality-to-incidence ratio, particularly in breast cancer [21]. More generally, socioeconomic well-being indicated by a human development index, living standard, or gross national income per capita are all highly negatively correlated with the breast cancer mortality-to-incidence ratio [22], and a poor general economic situation is associated with a later-stage diagnosis of breast cancer [16]. Moreover, different socioeconomic factors, that could or will likely be affected by the effects of COVID-19 on the economy, have an impact on the breast cancer stage at the time of diagnosis and, consequently, overall survival [23].

Equally important is the fact that during the second lockdown we did not experience a decrease in the number of newly diagnosed breast cancer cases. The most probable reason lies in the fact that medical systems, as well as the general population, were better prepared and more organized and resilient during the second lockdown.

Conclusion

It seems that national health care system measures for controlling the spread of COVID-19 had a detrimental effect on the number of newly diagnosed breast cancer cases in Croatia. As it is not plausible to expect an epidemiological change to occur at the same time, this may result in later diagnosis, later initiation of the treatment, and less favorable outcomes in the future. However, the effect has weakened after the first lockdown when COVID-19 control measures were more relaxed, and it has not reoccurred during the second COVID-19 wave, defining a better and more organized health system during the second part of 2020. Hence, although the formal lockdown of hospitals affected the number of newly diagnosed breast cancers, the oncology health care system has shown resilience and compensated for these effects by the end of 2020.

Author Contributions

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Disclosures

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References

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433.

2. Center for Systems Science and Engineering at Johns Hopkins. COVID-19 Dashboard. Coronavirus Resource Center. 2021. Available at https://coronavirus.jhu.edu/map.html. Accessed February 15, 2020.

3. Rocco N, Montagna G, Micco R et al. The impact of the COVID-19 pandemic on surgical management of breast cancer: Global trends and future perspectives. ***The Oncologist*** 2021;26: e66–e77.

4. Soran A, Gimbel M, Diego E. Breast cancer diagnosis, treatment and follow-up during COVID-19 pandemic. Eur J Breast Heal 2020;16: 86–88.

5. Dietz JR, Moran MS, Isakoff SJ et al. Recommendations for prioritization, treatment, and triage of breast cancer patients during the COVID-19 pandemic. The COVID-19 pandemic breast cancer consortium. Breast Cancer Res Treat 2020;181: 487–497.

6. NHS. Guidance for trusts on the management of non-coronavirus patients requiring acute treatment: Cancer. Spec. Guid. 2020. Available at https://https://www.nice.org.uk/media/default/about/covid-19/specialty-guides/cancer-and-covid-19.pdf. Accessed June 3, 2020.

7. Dinmohamed AG, Visser O, Verhoeven RHA et al. Fewer cancer diagnoses during the COVID-19 epidemic in the Netherlands. Lancet Oncol 2020; 21:750–751.

8. Vrdoljak E, Sullivan R, Lawler M. Cancer and coronavirus disease 2019; how do we manage cancer optimally through a public health crisis? Eur J Cancer 2020;132:98–99.

9. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68: 394–424.

10. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA 2013;310:2191–2194.

11. Dixon JR. The International Conference on Harmonization Good Clinical Practice Guideline. Qual Assur 1998;6:65–74.

12. Kim HJ, Fay MP, Feuer EJ et al. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19:335–351.

13. Richards M, Westcombe A, Love S et al. Influence of delay on survival in patients with breast cancer: A systematic review. Lancet 1999; 353:1119–1126.

14. Unger-Saldaña K, Miranda A, Zarco-Espinosa G et al. Health system delay and its effect on clinical stage of breast cancer: Multicenter study. Cancer 2015;121:2198–2206.

15. Johnson BA, Waddimba AC, Ogola GO et al. A systematic review and meta-analysis of surgery

delays and survival in breast, lung and colon cancers: Implication for surgical triage during the COVID-19 pandemic. Am J Surg 2020 [Epub ahead of print].

16. Ginsburg O, Yip C, Brooks A et al. Breast cancer early detection: A phased approach to implementation. Cancer 2020;126:2379–2393.

17. Vrdoljak E, Bodoky G, Jassem J et al. Cancer control in Central and Eastern Europe: Current situation and recommendations for improvement. ***The Oncologist*** 2016;21:1183–1190.

18. Kothari A, Fentiman IS. 22. Diagnostic delays in breast cancer and impact on survival. Int J Clin Pract 2003;57:200–203.

19. Lohrisch C, Paltiel C, Gelmon K et al. Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 2006;24:4888–4894.

20. McKee M, Stuckler D. If the world fails to protect the economy, COVID-19 will damage health not just now but also in the future. Nat Med 2020;26:640–648.

21. Vrdoljak E, Bodoky G, Jassem J et al. Expenditures on oncology drugs and cancer mortality-to-incidence ratio in Central and Eastern Europe. ***The Oncologist*** 2019;24:e30–e37.

22. Hu K, Lou L, Tian W et al. The outcome of breast cancer is associated with National Human Development Index and Health System Attainment. PLoS One 2016;11:e0158951.

23. Coughlin SS. Social determinants of breast cancer risk, stage, and survival. Breast Cancer Res Treat 2019;177:537–548.