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The impact of the Covid-19 pandemic on breast cancer early detection and screening

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ABSTRACT

The COVID-19 pandemic affects mortality and morbidity, with disruptions expected to continue for some time, with access to timely cancer-related services a concern. For breast cancer, early detection and treatment is key to improved survival and longer-term quality of life. Health services generally have been strained and in many settings with population breast mammography screening, efforts to diagnose and treat breast cancers earlier have been paused or have had reduced capacity. The resulting delays to diagnosis and treatment may lead to more intensive treatment requirements and, potentially, increased mortality. Modelled evaluations can support responses to the pandemic by estimating short- and long-term outcomes for various scenarios. Multiple calibrated and validated models exist for breast cancer screening, and some have been applied in 2020 to estimate the impact of breast screening disruptions and compare options for recovery, in a range of international settings. On behalf of the Covid and Cancer Modelling Consortium (CCGMC) Working Group 2 (Breast Cancer), we summarize and provide examples of such in a range of settings internationally, and propose priorities for future modelling exercises. International expert collaborations from the CCGMC Working Group 2 (Breast Cancer) will conduct analyses and modelling studies needed to inform key stakeholders recovery efforts in order to mitigate the impact of the pandemic on early diagnosis and treatment of breast cancer.

1. Introduction

As of early February 2021, the COVID-19 pandemic led to over 2.2 million deaths, with 103 million confirmed cases globally (Organization WH, 2021). The Northern Hemisphere winter of 2020–2021 showed increasing rates of infection and deaths particularly in Europe and the Americas (WHO, 2021), leading to widespread disruptions to cancer treatment services (Spicer et al., 2020). While emerging vaccines show

great promise, unequal access and emerging variants of unknown pathogenicity suggest that it will be some time till healthcare, including cancer services, will return to pre-pandemic capacity, usual access and participation to cancer prevention services.

Breast cancer is the most frequently cancer diagnosed worldwide, with 2.3 million cases annually (Sung et al., 2021). Breast cancer is a considerable public health burden, and its primary and secondary prevention requires strengthening globally (IARC, 2021). Early detection of

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breast cancer can reduce mortality and the intensity of treatment required (Cancer IAfRo, 2014). Population breast screening programs reduce breast cancer mortality among women invited for screening by around 20% based on randomized control trials (Marmot et al., 2013). Delays to diagnosis and treatment of breast cancers due to the pandemic are expected to lead to more intensive treatment requirements and, potentially, increased mortality.

Several modelling studies alongside observational data for cancer referrals have noted the widespread impact of COVID-19 on the diagnosis of cancers, including halted screening programs (Dinmohamed et al., 2020a; Feletto et al., 2020; Freer, 2021; Gathani et al., 2020; Maringe et al., 2020; Peng et al., 2020; Sud et al., 2020). Some countries paused their breast screening programs in response to the COVID-19 pandemic. For example, in Canada, the Netherlands, Germany, Italy, the UK and Australia, national screening programs were completely suspended for a period of 1–6 months (Table 1). The impact of these pauses on breast cancer mortality, treatment requirements and the related economic burden on health care systems will depend in part on the usual screening intervals, imaging modalities and targeted ages for breast screening, which vary between settings (Table 1). Even in countries such as Taiwan—where SARS-CoV-2 infection was well contained due to quarantine and early case identification and mammography screening services were not halted—participation in screening was dramatically affected with almost half the number of women attending mammography screening (Peng et al., 2020).

Population breast screening is not available in low- and middle-income countries (LMICs). The Breast Health Global Initiative has developed guidelines (Anderson et al., 2020) to improve early detection and treatment in LMICs. These include risk reduction strategies, improved diagnostic services and cancer care guidelines adapted to resource-constrained settings. Some middle-income countries have opportunistic breast cancer screening, where benefits in downstaging tumors for earlier diagnosis have been noted in at least two independent populations (Murillo et al., 2016; Vale et al., 2019). Other initiatives to diagnose breast cancers earlier in LMICs include breast examination (ideally clinically delivered) (Romanoff et al., 2017), with diagnostic ultrasound and mammography also recommended (Koh et al., 2020; Anderson, 2020). There are also strategies to increase breast awareness and self-breast exam is encouraged in this context. (Ministry of Health K, 2018) These services are also expected to be impacted by COVID-19, and the consequences are not yet known.

Throughout the pandemic, population modelling is playing an important role in anticipating best-and-worst case outcomes to help policy-makers implement optimal public health strategies. Population modelling of breast cancer screening programs was well-established before the pandemic, so that numerous well-validated models are available to help evaluate short- and long-term impacts of COVID-19 on breast cancer screening and treatment services, for a range of scenarios.

The Covid and Cancer Modelling Consortium (CCGMC) (<https://ccgmc.org/about-ccgmc/>) has established a Screening Working Group (Working Group 2) including a group focused on breast cancer screening (CCGMC – WG2 Breast). The aims of this group include to document and estimate disruption of breast screening services and using existing well calibrated and validated model platforms (Table 2) to estimate the impact of breast screening disruptions, in a range of international settings. Outcomes of interest include breast cancer incidence, delayed diagnosis (especially staging via tumor size, nodal involvement), mortality (additional deaths) and impact on referrals to treatment services (in terms of rates and case-mix). In addition, the group aims to compare the impact and cost-effectiveness of various catch-up and recovery strategies, as relevant to specific settings.

To establish a basis for this work, we present some examples of how breast screening models represented in the CCGMC – WG2 Breast group were applied in 2020 to evaluate the impact of COVID-19 on breast

cancer screening outcomes, and propose opportunities for additional modelled evaluations that can provide insights to policy makers aiming to minimize the impact of COVID-19 on breast cancer mortality.

2. Modelled evaluations of COVID-19 impact on breast screening

Modelled evaluations of the impact of the COVID-19 pandemic on breast screening programs and outcomes were conducted in 2020. These differed in the scenarios modelled and outcomes reported and summarized below.

2.1. Australia

In early April 2020, the Australian Government Department of Health commissioned Cancer Council New South Wales to undertake urgent and incremental preliminary modelling and analysis of potential COVID-19 impacts on cancer screening. Model scenarios and evaluation protocols were developed in collaboration with government representatives and screening program managers, aiming to provide information to assist with short-term policy decisions, and the report was produced in May 2020 (Nickson et al., 2020).

The Policy1-Breast microsimulation model was used to estimate the effects of 3-, 6- and 12-month screening pauses (commencing 1 April 2020) on outcomes among women in the target age range for screening (50–74 years). All scenarios assumed services would resume at 100% within one month of screening resumption.

Modelled outcomes include screening intervals, program sensitivity, diagnosis rates, tumor characteristics and 5-year survival. For example, the median screening interval over the period 2020–2021 was estimated to increase from 104 weeks under usual screening to 130 weeks with a 12 month pause. In the short term (the first 12 months following pause commencement), population-level invasive breast cancers were expected to reduce with the duration of the screening pause, so that there would be 244 diagnoses per 100,000 women aged 50–74 for a 3-month pause, or 166 diagnoses per 100,000 women with a 12-month pause. A 12-month pause was predicted to lead to a 10% difference between cancer diagnoses in 2020–2021 (270 per 100,000 women) and 2022–2023 (296 per 100,000 women).

Some stage shifts were predicted, with small increases in tumor size, nodal involvement and high-grade tumors among cancers diagnosed in the short term. For example, over the 12 months following pause commencement, the proportion of population level invasive cancers that are small (≤ 15 mm) was estimated to be 54% for a 3-month pause, or 48% for a 12-month pause. Population level mortality was not estimated, however for women who would usually screen during the first year following the pause at age 50–74 who have a breast cancer diagnosis by end 2023, a 12 month pause in screening was estimated to reduce their 5-year survival following diagnosis from 91.4% to 89.5%.

2.2. Canada

A recent analysis from Yong et al., (Yong et al., 2020) and using the OncoSim model and observed incidence and mortality data from Canada estimated a 3-month pause could increase by 310 the number of breast cancer cases diagnosed at advanced stages and cancer deaths (110 more) in 2020–2029. A six-month interruption could lead to 670 extra advanced cancers and 250 additional cancer deaths. Furthermore, their analysis noted that persistent restrictions in screening volume post-interruption would lead to further excess cancer deaths. A key finding of the modelling showed that even 3- or 6-months interruptions for breast cancer screening in Canada would result in a surge in breast cancer diagnosed cancer cases when screening resumes, whether they are interval or screen-detected will need to be determined in future analyses.

Table 1
Summary of breast cancer screening programs in selected countries and documented COVID-19 disruption.

Country	Screening protocol	National screening program pauses	COVID-19 disruption referencesSource
Australia	Digital mammography, biennial screening from age 40, targeted to 50–74 (some targeted annual screening)	1 month (March–April)	https://www.aihw.gov.au/reports/cancer-screening/cancer-screening-and-covid-19-in-australia/contents/how-has-covid-19-affected-australias-cancer-screening-programs
Brazil	Mammography, biennial screening from age 50–69, opportunistic	Not applicable as not national screening program	https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//nota-tecnica-rastramento-covid-didepre-09-jul-2020.pdf
Canada	Implementation of screening is by provincial and territorial governments and varies between jurisdictions. Broadly, women are screened 50–74 biennially, some programs offer screening for 40–49 (annual or biennial) and some programs offer targeted screening for high-risk women (https://www.partnershipagainstcancer.ca/topics/breast-cancer-screening-environmental-scan-2018/#)	~4 months (March–June) exact start and stop dates dictated by the health ministries of each of the provincial and territorial governments	https://journals.sagepub.com/doi/pdf/10.1177/0846537120928864 https://cbc.ca/en/covid-19-resources
Germany	Digital mammography, biennial screening from age 50–69; invitation-based central organized program	2 months (March–April)	https://www.kbv.de/html/1150_45157.php https://www.aerzteblatt.de/nachrichten/111395/Mammografie-Screening-voruebergehend-ausgesetzt
Italy	Biennial mammography screening age 50–69; also annual screening age 45–49 and biennial age 70–74 in some regions	2 months (March–April) but later resume in some areas since screening program organization is under the responsibility of regional and/or local health authorities	https://www.osservatorionazionalecreening.it/content/ons-la-ripartenza-programmi-screening#monitoraggi http://www.epiprev.it/materiali/suppl/2020_EP5-6S2/344-352_ART-Battisti.pdf
Mexico	Mammography, annual screening from age 40–69, opportunistic	Not applicable as not national screening program	Norma Oficial Mexicana NOM-041-SSA2–2011 (in review) https://www.senado.gob.mx/64/gaceta_del_senado/documento/101991
The Netherlands	Mammography (digital/tomosynthesis), biennial screening from age 50–75; alternative modalities, intervals and age ranges possible	4 months (March–June)	https://doi.org/10.1016/S0959-8049(20)30561-X ; https://jhoonline.biomedcentral.com/articles/10.1186/s13045-020-00984-1
United Kingdom	Breast screening 2-view digital mammography every 3 years in women 50–69 years of age; women over 70 can self refer	6 months; March–August	https://www.clinical-breast-cancer.com/article/S1526-8209(20)30207-X/pdf https://www.gov.scot/news/breast-cancer-screening-to-resume/ https://www.nhs.uk/conditions/breast-cancer-screening/
USA	Multiple, but American Cancer Society guidelines state: Women aged 40 to 44 should have the choice to start mammography screening annually.; women aged 45 to 54 years should be screened with mammography annually. Women aged 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. https://www.cdc.gov/cancer/breast/pdf/breast-cancer-screening-guidelines-508.pdf	Not applicable as not national screening program	Abstract S11–03: Impact of COVID-19 on breast and prostate cancer screening and early detection in a large health care provider group Mara M. Epstein, Devi Sundaresan, Meagan fair, Lawrence Garber, Mary Charpentier, Jerry H. Gurwitz and Terry S. field Clin Cancer res September 152,020 (26) (18 supplement) S11–03; DOI: 10.1158/1557-3265.COVID-19-S11–03

Table 2
Breast cancer screening models currently represented in the CCGMC-WG2 Breast group.

Country or countries modelled	Model name	Reference
Australia	Policy1-breast	https://www.health.gov.au/sites/default/files/documents/2020/09/covid-19-scenario-modelling-for-cancer-screening-programs-the-breastscreen-australia-program.pdf
Canada	Oncosim	Yong, JHE, Nadeau, C, Flanagan, W, et al. the OncoSim-breast cancer microsimulation model. <i>medRxiv</i> . Epub ahead of print 2020. DOI: https://doi.org/10.1101/2020.05.22.20110569 .
The Netherlands	MISCAN (breast)	https://pubmed.ncbi.nlm.nih.gov/3849380 https://pubmed.ncbi.nlm.nih.gov/25895135/ https://pubmed.ncbi.nlm.nih.gov/32484237
The Netherlands	SiMRiSc	https://packages.debian.org/sid/simrisc https://pubmed.ncbi.nlm.nih.gov/19945279/ https://pubmed.ncbi.nlm.nih.gov/29452787/ https://pubmed.ncbi.nlm.nih.gov/32382844/
Australia, Scotland	Stage shift	https://www.medrxiv.org/content/10.1101/2020.05.30.20117630v1 https://cancerhealthservices.shinyapps.io/oncology_stage_shift/
United Kingdom	Life table model –breast cancer	https://jamanetwork.com/journals/jamaoncology/fullarticle/2686812
USA	CISNET (consortium of models applied to the US population)	https://cisnet.cancer.gov/publications/cancer-site.html#breast_header

2.3. Italy

The impact of the suspension and delays in breast cancer screening programmes has been estimated by the National centre for screening monitoring (Mantellini et al., 2020) (National centre for screening monitoring, 2021) applying the expected detection rate to the number of delayed tests for each Region. This analysis showed that at national level the reduction of 37.6% in examinations in women aged 50–69y from January to December 2020, corresponding in a delay of 4.5 standard invitation months, would yield to 3324 delayed breast cancer diagnoses. Using a modelling approach based on data from the Italian cancer registries, Italian Association of Medical Oncology and GLOBOCAN (Bray et al., 2018) Vanni et al., estimated the impact of screening suspension considering the disruption of all early diagnosis pathways also outside organized programmes (Vanni et al., 2020). They estimated that approximately 10,000 patients could have a missed diagnosis during 3 months. Considering a 6-month period the number of patients who will not receive a diagnosis will rise to 16,000.

2.4. The Netherlands

Using cancer registry data in the Netherlands, Dinmohamed et al., highlighted reduced incidence of breast cancers early during the pandemic in 2020 when countries were grappling to reduce infection rates and surging hospitalizations and cancer screening programs were paused in the Netherlands (Dinmohamed et al., 2020b) to alleviate the

pressure on health care services overwhelmed by the upsurge of COVID-19 patients. (Maringe et al., 2020; Bleicher et al., 2016)

An analysis of the Netherlands Cancer Registry on provisional cancer diagnoses from 6 January 2020 and 4 October 2020, was conducted to determine the impact on breast cancer incidence (Dinmohamed et al., 2020a). These analyses showed fewer diagnoses of breast cancer in the early months of the initial COVID-19 outbreak in the Netherlands and not surprisingly most pronounced among the age groups eligible for breast cancer screening programs (which is 50–74 years in the Netherlands). As observed data accumulate MISCAN based modelling will evaluate the impact of different mitigation strategies. A recent study estimated the effects of five restart strategies after the disruption on required screening capacity and cancer burden after a disruption of 6 months. MISCAN was used to simulate five restart strategies, varying in whether screens were caught up or not and, if so, immediately or delayed, and whether the upper age limit was increased. The disruption in screening programs without catch-up of missed screens led to an increase of 2.0 breast cancer deaths per 100,000 women in 10 years. Immediately catching-up missed screens minimized the impact of the disruption but required a surge in screening capacity. Delaying screening, but still offering all screening rounds gave the best balance between required capacity, incidence, and mortality (Kregting et al., 2021).

In separate analyses using the SiMRiSc model, the short-term effects of the 3-month interruption in the Netherlands using showed a comparable decrease in invasive breast cancer diagnoses, and a small increase in interval cancers. In the long-term, the SiMRiSc model expects less screen-detected tumors, an increase in interval cancers, and an increase in cancer deaths (Bock preliminary analysis).

2.5. United Kingdom (UK)

In the UK there have been multiple publications evaluating service disruptions on cancer outcomes including work by Maringe et al. (Maringe et al., 2020). While screening services were completely suspended, urgent referrals for symptomatic cancer patients differ by cancer type. For breast cancer, local NHS Lothian data showed a number of referrals for symptomatic patients came back to usual levels after six weeks, while screening was suspended for nearly 6 months (Unpublished). The incidence of screen-detected breast cancers has increased from 1997 to 2016 (Mesa-Eguiagaray et al., 2020). Prioritization of different cancer health services is necessary during the COVID-19 pandemic and beyond it – should this be re-introduction of screening or protection of symptomatic diagnostic services? To address this topic, an adaptation of the stage-shift extrapolation model of Degeling et al. (Degeling et al., 2020) was applied, using data from the Scottish Cancer Registry (Gray et al., 2019). Excess mortality over 5 years due to delayed diagnosis and treatment initiation was estimated, comparing no disruption to periods of 3, 6, 9 and 12 months of disruption. Breast cancer survival estimates were stratified according to whether cancers were detected by screening. Stage-specific incidence estimates were obtained from all women diagnosed in 2017. Five-year stage-specific survival estimates were based on women diagnosed between 2010 and 2014, stratified by whether the tumors were screen detected or not.

The predicted impact of delays in time-to-treatment initiation on the stage distribution of incident cancers and the resulting excess mortality is displayed in Table 3. As a result of stage-shifts, 6.3% (5.6–6.9) and 22.3% (20.3–24.3) additional deaths were predicted for 3 and 6-month disruptions respectively – broadly similar to the estimates of Maringe et al. (Maringe et al., 2020). Table 4 displays estimated excess mortality for screen-detected and clinically-detected cancers separately. This shows the higher burden for clinically detected tumors for equivalent disruption. However, if the duration of disruption is substantially longer for screen detected tumors, then greater excess mortality would accrue to this group. Using English cancer registry and national audit data support modest but non-negligible effects on mortality due to screening

Table 3

Stage distribution of expected population of cancer cases in 2020 and excess mortality over 5 years in Scotland.

Degree of disruption	Stage (%) – Base case					Excess mortality (N ^a) (95% CI)	Excess mortality (% ^b) (95% CI)
	I	II	III	IV	Unknown		
No delay	40.4	45.9	7.54	5.11	1.07	–	–
3 months	37.8	44.6	9.81	6.65	1.07	32.8 (29.6–36.4)	6.3% (5.6–6.9)
6 months	31.4	41.1	15.77	10.69	1.07	116.8 (106.2–127.4)	22.3% (20.3–24.3)
9 months	22.6	35.4	24.39	16.53	1.07	234.6 (215.4–253.7)	44.8% (41.1–48.4)
12 months	12.4	28	34.9	23.65	1.07	374.8 (347.0–402.8)	71.5% (66.2–76.9)

Expected incident cases 2020 = 4407, expected 5-year mortality = 524.9

^a Number of deaths.^b As a percentage of expected 5-year mortality for incident cases.**Table 4**

Estimated excess mortality among screen-detected and clinically detected groups in Scotland.

Duration of disruption	Screen detected Excess mortality (N) (95% CI)	Clinically detected Excess mortality (N) (95% CI)
3 months	10.4 (9.2–12.0)	22.4 (20.4–24.8)
6 months	37.4 (32.8–43)	79.4 (72.8–86)
9 months	79.3 (67.2–87.2)	166.3 (146.4–170.1)
12 months	127.0 (109.2–140.5)	262.1 (234.9–267.9)

pauses, with the range of additional breast cancer related deaths over the next 10 years ranging from 148 to 687. However, there will be likely variation by region and mitigation of deaths will depend on how well screening services catch up with delayed or missed screening invitations (F. Seedat and S. Duffy Communication, paper in preparation).

3. Future modelling

The modelled evaluations described here were conducted rapidly in the early stages of the pandemic, utilizing or adapting existing modelling platforms to generate estimates for a range of potential scenarios. Common themes included the range of assumed pauses to organized breast screening (e.g., 3, 6, 9 or 12 months) and a focus on tumor staging and mortality as outcomes. Modelled scenarios can be updated based on actual screening program delivery, and feasible scenarios going forward, including ongoing reduced throughput or periods of increased capacity. These scenarios are likely to differ by region more than previously, as the pandemic has impacted these countries differently. For example, as of 4 February 2021 the total number of COVID deaths for the countries modelled ranged from 35 deaths per million in Australia (total 1123 cases per million) to 1606 deaths per million in the UK (total 56,857 cases per million) <https://www.worldometers.info/coronavirus/>.

Modelled estimates in the Netherlands concurred well with emerging observed data, and similar validations are recommended for other settings as cancer registry data becomes available. High quality observed data is key to modelled evaluations. The CCGMC – WG2 Breast group will draw on complementary activities such as the surveys of screening program impacts conducted by the International Cancer Screening Network (ICSN, <https://www.cancer.gov/about-nci/organization/cgh/research/icsn>) and through the ICSN membership identify emerging country-level reports of relevant health data to help specify and validate modelled evaluations.

Australian and Canadian modelling quantified the expected surge in diagnoses following screening resumption, providing useful insights to

help treatment services prepare for changes in the case-mix and throughput of patients beginning breast cancer treatment. Updated estimates will assist with health service resourcing and planning.

Modelling and estimates using English and Scottish data explore the trade-off between prioritizing screening resumption versus protecting symptomatic diagnostic services; this concept is likely to have become a reality given the severity of the pandemic and related morbidity, mortality and health resource requirements in that setting.

High-quality registry data that can account for pathways to diagnosis (including known delays) and tumor staging and subtypes at diagnosis will assist modelled evaluations of the longer-term impacts of delays to diagnosis (and potentially treatment) in the context of the pandemic and, if required, further assessment of the trade-off between directing strained resources at screening versus diagnostic services for women with breast cancer symptoms. Evaluations could also include options for risk-based approaches to screening that direct limited resources to women who will benefit the most, following frameworks for risk-based screening established prior to the pandemic (Pashayan et al., 2020).

Modelled outcomes in the examples shown included incidence, stage shifts and breast cancer mortality, and some outcomes relevant to screening program provision such as screening intervals and program sensitivity. Modelled evaluations should ideally compare the benefits and harms of screening, which can depend in part on the health system in which screening is delivered (Myers et al., 2015). This includes benefits such as reduced treatment intensity and costs due to earlier detection, and harms such as the treatment and psychosocial impact of over diagnosed cancers. Analysis of population specific demographics and diverse populations should be incorporated whenever possible, to capture new or increased inequities in outcomes.

For LMICs, where opportunistic screening and earlier diagnosis campaigns have been encouraged, notable gains in downstaging of breast tumors for improved survival may see setbacks due to changes in healthcare seeking behaviors, travel disruptions and reduced access to cancer care services. Access to care is highly influenced by inequalities including those determined by social status, so that the increased marginalization of some vulnerable groups of women due to the pandemic may in turn deepen the disparities in access to screening and early diagnosis.

For LMICs looking to develop new screening programs and early detection strategies, there are increasing challenges as to how these could be best carried out to surmount barriers evident even before the COVID-19 pandemic. Awareness and uptake of screening services must aim at initially improving awareness. In Kenya for instance, out of 31,079 surveyed in 2014 health survey, only 25% of women aged 15–49 years had performed a self-breast exam and 14% had a clinical breast exam (2014 Demographic and Health Survey Key Findings, 2014). Exploring telehealth and other innovations could help to mitigate some of the barriers around screening and early detection; however, they must however be made to be socially and cultural appropriate (Antabe et al.,

2020). Screening and early detection are not end points themselves and health system strengthening is needed in tandem with appropriate diagnostic, pathologic and treatment support to ensure appropriate and timely management of the breast cancer. High-level modelled evaluations of such scenarios that include these considerations may be feasible with appropriate collaborations, model designs and observed data, and the CCGMC – WG2 Breast group will seek opportunities to progress this work for LMIC's where delayed diagnosis is a major concern.

For all modelled evaluations, ongoing engagement with stakeholders and policy decision-makers is critical to ensure that modelled scenarios are plausible and useful, and the CCGMC – WG2 Breast group includes clinical and health service delivery experts to guide its program of work.

4. Conclusion

As the COVID-19 pandemic continues to impact health and economies globally, timely access to cancer control services is a concern. The public health burden of disruptions to population breast cancer screening and other efforts to diagnose breast cancers early is a global problem requiring a global response. In time we will understand the extent to which delays in breast cancer diagnosis during the COVID-19 pandemic impact on treatment and survival. In the meantime, collaborative modelling through groups such as the CCGMC – WG2 Breast group will continue to play an important role in anticipating best-and-worst case outcomes and thereby assist policy-makers in designing in optimal recovery strategies.

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Declaration of Competing Interest

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