Estimating the impact of the COVID-19 pandemic on breast cancer deaths among older women

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Ayşe Arık[a,*], Andrew Cairns[a], Erengul Dodd[b], Angus S Macdonald[a], George Streftaris[a]

[a] *Department of Actuarial Mathematics and Statistics, Heriot-Watt University, and the Maxwell Institute for Mathematical Sciences, UK*
[b] *Mathematical Sciences, S3RI, University of Southampton, Southampton, UK*

Abstract

In this study we investigate the impact of diagnostic delays on breast cancer mortality, caused by public health measures introduced as a response to the COVID-19 pandemic. We establish a Markov model based on available data and medical literature for women aged 65–89 years. We quantify age-specific, short-term excess deaths, for a period up to 5 years, along with years of life expectancy lost and change in cancer mortality by cancer stage, based on an assumption relating to declines in breast cancer diagnosis amid the pandemic. Our analysis suggests a 5–8% increase in BC deaths of women, with no BC, across different ages.

Keywords: Breast cancer; Cancer mortality; COVID-19 pandemic; Excess deaths; Markov model.

1. Introduction

The COVID-19 pandemic has claimed more than 6.2 million deaths worldwide as of May 2022 (WHO, 2022). As a response, since the beginning of the pandemic, the UK entered three national lockdowns, with the first being introduced on 23 March, 2020. Cancer pathways are seriously affected by the changes in health practices due to a halt in cancer screening (from late March 2020 till June 2020), significant increases in the number of patients waiting for key diagnostic tests more than 6 weeks, and significant reductions in the number of patients starting cancer treatment. Cancer Research UK (CRUK) report that there were 3 million fewer people screened for cancer in the UK between March and September 2020 (CRUK, 2021). Moreover, the number of cancer patients starting a cancer treatment decreased by 12% between April 2020 and March 2021 compared to the pre-pandemic levels, whereas the number of people waiting for more than 6 weeks for key diagnostic tests has soared to 215,000 in March 2021 from 67,000 in March 2020. These figures sparked the fear of a shift to later diagnosis for people having the disease but not diagnosed yet. This could restrict the opportunities for feasible treatment and cause a significant impact on cancer survival.

*Corresponding author

Recent published studies based on the National Health Service (NHS) cancer registration and hospital administrative dataset focus on identifying the impact on cancer survival in England of various changes in the availability of cancer treatment and services, in addition to health-seeking behaviour, as a result of national lockdowns. Lai et al. (2020) point out dramatic reductions in the demand for, and supply of, cancer services in response to the COVID-19 pandemic by showing that these reductions could increase excess mortality among cancer patients. Sud et al. (2020) indicate a significant reduction in cancer survival as a result of treatment delay, mostly disruption in cancer surgery. Maringe et al. (2020) also note substantial increases in avoidable cancer deaths in England as a result of diagnostic delays of over a year. Arık et al. (2021) report significant increases in type-specific cancer mortality as a result of diagnostic delays. Alagoz et al. (2021) project a small long-term cumulative impact on breast cancer (BC) mortality in the US over the next decade due to initial pandemic-related disruptions.

It is also documented that COVID-19 is more likely to affect older people and those having comorbidity (Chen et al., 2020; Richardson et al., 2020; Grasselli et al., 2020; Zhou et al., 2020). Furthermore, developing COVID-19 has been shown to be a greater risk for cancer patients depending on type of malignancy, age, and gender (Pinato et al., 2020; Garassino et al., 2020; Lee et al., 2020; Saini et al., 2020). Pinato et al. (2021) reported that cancer patients in the UK have been more severely affected by the COVID-19 pandemic compared to those in continental Europe.

In this study, we focus on BC mortality since it is the most common cancer diagnosed in women, in addition to being one of the leading causes of death for women (ONS, 2019; PHE, 2017). Particularly, we are interested in how a pandemic, such as COVID-19, causing major disruption to the health service, may affect mortality associated with disorders normally treated by the health service. It is assumed that the pandemic may give rise to changes by preventing or delaying the detection or diagnosis of BC. We examine the impact of diagnostic delays up to 5 years, since premature death could happen up to 5 years later as a result of late diagnosis (Maringe et al., 2020). This is motivated by screening programmes and cancer treatments having been largely affected by lockdowns. According to CRUK (2021), 7,200 fewer cases of BC were diagnosed between April–December 2020 compared to the same period in 2019, where 60% fewer cases were diagnosed via screening, whilst 22% fewer patients started treatment from April 2020 till March 2021, compared with the same period in 2019.

Quantifying the impact of cancer diagnosis delays by considering cancer stage is complex in the light of insufficient data, but a Markov approach provides a suitable modelling framework (Lu et al., 2011; Adams et al., 2013; Baione and Levantesi, 2018; Hacariz et al., 2021). We establish a Markov model with multiple states, including observed and unobserved BC cases, based on: (i) available cancer registration and deaths data in England, provided by the Office for National Statistics (ONS); and (ii) published clinical studies. Accordingly, we estimate age-specific, short-term excess deaths, in addition to years of life expectancy lost (YLL) from cancer, with particular emphasis on ages above 65. We also estimate changes in mortality from BC up to 5 years after diagnosis.

This paper is organised as follows. In Section 2 we introduce the model for BC risk. In Section 3 we explain how to calibrate the model in a pre-pandemic scenario. In Section 4 we introduce post-pandemic scenarios. In Section 5 we estimate excess deaths and YLLs under pre-pandemic and pandemic scenarios. In Section 6 we also provide a sensitivity analysis. In Section 7 we discuss our findings and their implications along with strengths

and limitations of our approach.

2. Methodology

2.1. Terminology and definitions of breast cancer stages

At a detailed level, the conceptual model of BC progression is a well-defined staging model:

$$\text{No BC} \rightarrow \text{Stage 1 BC} \rightarrow \text{Stage 2 BC} \rightarrow \text{Stage 3 BC} \rightarrow \text{Stage 4 BC} \rightarrow \text{Dead from BC} \quad (1)$$

in which 'Stage 4' is 'metastatic', meaning that cancer cells have spread from breast to other part(s) of the body (Rutherford et al., 2013; Huang et al., 2020). This progression is assumed to be real and physical, whether observed or not. It is possible that 'transition into Stage 1 BC' is the nearest equivalent in the model to 'onset of BC'. We assume that 'dead from BC' is accessible only from Stage 4, and 'dead from other causes' (not shown above) is accessible from all 'live' states.

Alongside the clinical staging is a model of what is observed. All women free of BC and dead from BC are observed. An individual in one of BC stages 1–4 may be observed to be so, or unobserved, represented by separate states. Transitions are possible:

- forward through stages of BC; and
- from 'No BC' or an unobserved BC state to an observed BC state.

The latter possibility we take to be the same as 'diagnosis'. Thus a woman who is diagnosed with Stage 3 BC makes a transition from either 'Stage 2, Unobserved' or 'Stage 3, Unobserved' to 'Stage 3, Observed' and so on.

In Figure 1, we introduce a model of BC progression, based on the stages described above, but introducing some simplifications (Section 2.3) based on the available data and published clinical studies (Section 3).

2.2. Modelling unobserved breast cancer

We need to distinguish death from BC from other causes of death and define life histories accordingly, keeping in mind that the main focus of this work is on quantifying the impact of BC diagnostic delays. We consider a model involving the following:

- A population of women without BC (State 0).
- Onset of BC, which is clinically diagnosed, where *clinical diagnosis* means detection of the disease (State 1, State 3).
- Onset of BC, which is not clinically diagnosed (State 2).
- Progression to metastatic BC, which we assume is always diagnosed, whether earlier stages were diagnosed or not (State 3).
- Death from other causes (State 4).

- Death from BC (State 5).

Figure 1 shows a schematic representation of a continuous-time model for the life history of a woman at age x. Age-specific transition intensities from state i to state j at age x are denoted by μ_x^{ij}. Stages 1, 2 and 3 of BC combined are represented by States 1 and 2 in the model, State 1 being observed cases and State 2 being unobserved cases. All stage 4 cases of BC are represented by State 3 of the model, and are assumed to be observed. The lexical similarity of 'stage' and 'state' is unfortunate but is hard to avoid.

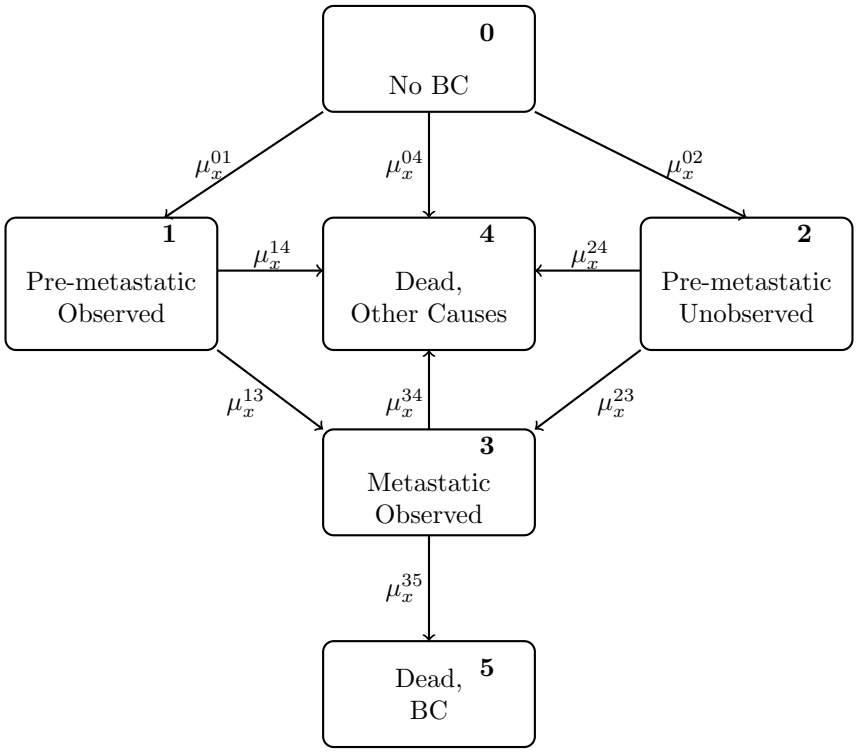


Figure 1: A Markov model in continuous time of observed and unobserved progression to observed metastatic breast cancer and death. Intensities μ may be functions of age x.

2.3. Modelling assumptions

We introduce the following modelling assumptions.

A1: States 1 and 2 both represent stages 1–3 of BC progression, we do not attempt to model progression between these stages explicitly. State 3 represents stage 4 of BC progression. This accords with assumptions in some epidemiological studies (Zhao et al., 2020).

A2: State 5 ('Dead, BC') is accessible only from State 3 ('Metastatic BC'). That is, earlier stages of BC lead to death from BC only by progressing to metastasis.

A3: All individuals in State 3 are observed to be so, whether their progression prior to entering that state was observed or not. That is, death from BC without metastatic BC being noticed pre-mortem is rare enough to ignore (Redig and McAllister, 2013).

We have a state representing unobserved cases of BC, State 2 ('Pre-metastatic Not Observed'). With the pandemic shock in mind, for the purpose of modelling *changes* in BC mortality caused by traumatic changes in the health service, we add two more model assumptions.

A4: Neither the manner in which we observe BC, nor the presence of a pandemic, affect overall new cases of cancer. Therefore we assume the total transition from 'No BC' to BC stays constant. That is

$$\mu_x^{01} + \mu_x^{02} = \mu_x^*,$$

where μ_x^* is independent of any particular pandemic scenario.

A5: Individuals in State 1 ('Pre-metastatic Observed') are assumed to be treated for BC, while individuals in State 2 ('Pre-metastatic Unobserved') are assumed not to be treated. Therefore we assume $\mu_x^{13} < \mu_x^{23}$ for the same age. Moreover, we assume that treatment given while in State 1, e.g. the type of treatment, does not depend on any particular pandemic scenario, so the transition intensities μ_x^{13} and μ_x^{23} also do not depend on any particular pandemic scenario.

A4 and A5 suggest a convenient parametrisation of the model:

$$\mu_x^{01} = \alpha_x\,\mu_x^*, \qquad \mu_x^{02} = (1-\alpha_x)\,\mu_x^*, \qquad\qquad \mu_x^{13} = \beta_x\,\mu_x^{23} \qquad (\beta_x < 1), \tag{2}$$

where $0 < \alpha_x < 1$ quantifies the proportional relationship between μ_x^{01} and μ_x^{02}, and will later be used to determine scenarios. For simplicity, and lacking data to support anything else, we assume $\alpha_x = \alpha$ and $\beta_x = \beta$. We suppose that μ_x^{23} represents the rate of progression to metastatic BC in the absence of treatment, and β measures the effectiveness of treatment. So μ_x^* and β are fixed regardless of the pandemic scenario, and the pandemic affects mortality by reducing α.

3. Calibration of the Markov Model

We calibrate the model mainly based on published clinical studies. We investigate the 6 possible states, where women, within each 5-year age group between 65–69 and 85–89, can be in at any time. The model analysis is initiated at time zero, taken as January 1, 2020.

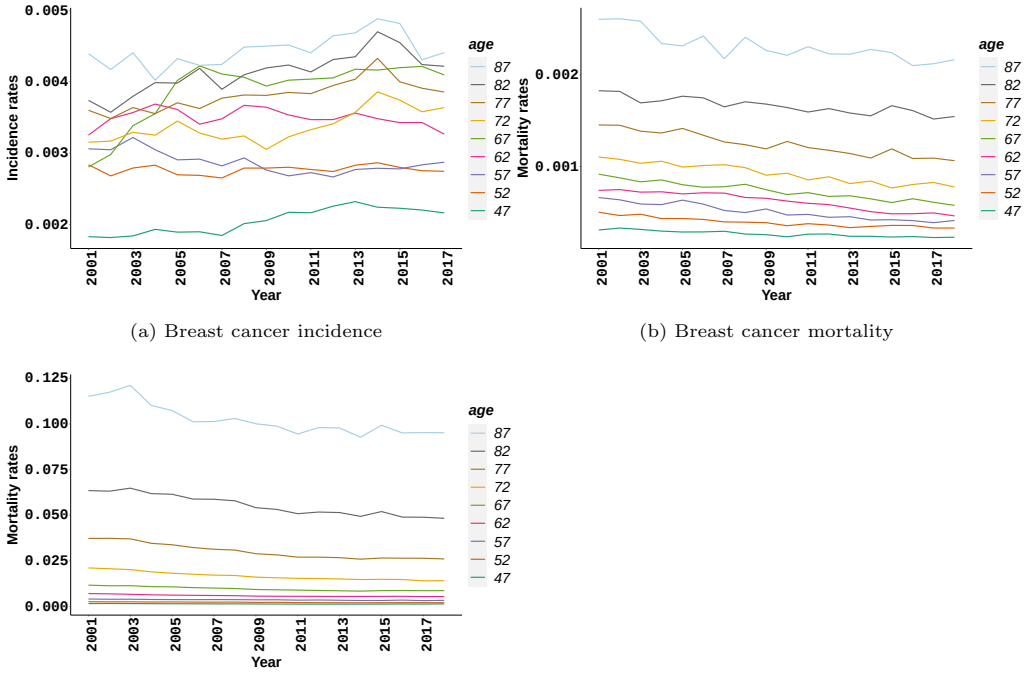
In the following sections we explain available data from different sources for calibration purposes.

3.1. Population incidence and mortality rates of breast cancer

We refer to new cancer diagnoses/registrations and deaths data between 2001–2017 in England, provided by the ONS. Cancer registrations are split by five-year age groups (20–24, 25–29, ..., 85–89), type of tumour, single year, and gender. Cancer deaths data

have similar granularity, up to 2018, where we have causes of death instead of type of tumour. Corresponding mid-year population estimates are available from the ONS.

Figure 2 exhibits available ONS-provided data at various ages, including screening age groups 47–73, from 2001 to 2017. Note that the first screening programme targeted women aged 50–64 and screening was extended to age 70 between 2002–2004, while another extension for ages 47–73 is in operation since announcement made in 2007 (Quinn and Allen, 1995; RAC, 2006; Duffy et al., 2010; NHS, 2021). In Figure 2, five-year age groups are represented by their mid-points. Figure 2a shows BC incidence, which is new cancer registrations divided by mid-year population estimates, and generally shows an increasing trend over calendar time at all ages with higher incidence at older ages, whereas Figure 2b shows BC mortality, which is deaths from BC divided by mid-year population estimates, and points out a decreasing trend. Mortality from other causes, not including BC as a cause, shows a more heterogeneous distribution across different ages with a decreasing trend (Figure 2c).



(a) Breast cancer incidence

(b) Breast cancer mortality

(c) Mortality from other causes (except breast cancer)

Figure 2: Breast cancer incidence, breast cancer mortality, and all-cause mortality (excluding breast cancer) by five-year age groups between 2001–2017/2018 in England

3.2. Clinical diagnosis of breast cancer

We have no empirical data on clinical diagnosis. This is particularly important for defining transitions to State 1 and State 3. We rely on cancer registrations by age and stage for women in the east of England between 2006–2010, reported by Rutherford

et al. (2013, 2015), to define transfers from State 0 to State 1 (Table 1). The mid-year population estimates for the east of England, available from the ONS, during the same interval, are used to represent the exposure in State 0. The resulting transition intensities from State 0 to State 1, μ_x^{01}, are shown in Table 3.

Table 1: Numbers of newly diagnosed BC by age and stage in women living the east of England between 2006–2010, with follow-up on mortality until 15 March 2012. Source: Table 1 in Rutherford et al. (2013, 2015).

Age	BC Stage 1	BC Stage 2	BC Stage 3	BC Stage 4	Total
65–69	1406	896	168	111	2581
70–74	691	769	172	120	1752
75–79	599	856	203	150	1808
80–84	402	694	192	144	1432
85+	345	749	271	121	1486

3.3. De novo and relapsed breast cancer

The term 'De novo' metastatic BC is used in the literature to refer to a (first) diagnosis after developing 'metastatic lesions', which are cancer cells already spread from breast to distant parts of the body. 'Relapsed' BC refers to recurrence of non-metastatic disease, indicating BC that returns after initial treatment.

Colzani et al. (2014) estimate first distant metastasis by age within 10 years of diagnosis of first invasive BC for women in Stockholm and Gotland Swedish counties between 1990–2006, noting fairly stable rates after a peak at about 2 years for women older than 50 years (Figure 3). Note that 'invasive' BC indicates cancer cells spreading from the ducts into the surrounding (breast) tissues, where the two most common types are 'invasive ductal carcinoma' and 'invasive lobular carcinoma'.

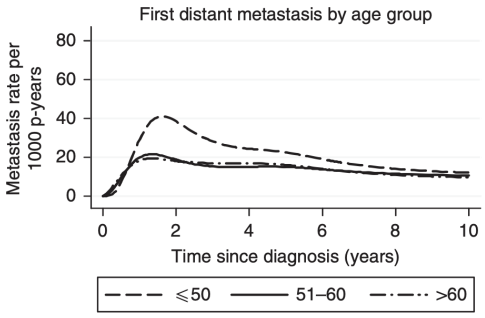


Figure 3: Metastasis rates per 1000 person-years by age. Source: Figure 1, *Estimated rates of first distant metastasis within 10 years of diagnosis of first invasive breast cancer in women diagnosed between 1990–2006 in Stockholm-Gotland Swedish counties, according to age and tumour characteristics*, in Colzani et al. (2014).

Therefore, we assume that the transition intensity from State 1 to State 3, μ_x^{13} in

Table 3, can be given as 19.54 per 1,000 person-years, which is the average of first distant metastasis rates reported in Colzani et al. (2014).

3.4. Tumour growth rate during waiting times

There is no empirical data regarding unobserved BC. However, the existence of State 2 in Figure 1 is essential for being able to quantify the potential impact of a major disruption to the health services on cancer mortality. For modelling purposes we assume that rates of transition from State 1 and State 2 to State 3 can be linked using the β parameter (Eq.(2)).

There is no available data regarding how BC can grow in the lack of treatment, although this is expected to differ by tumour subtypes. This is mainly because patients are required to be treated as soon as they are diagnosed (Nakashima et al., 2018). However, there is information in the literature about tumour growth for patients waiting for surgery. We use this to establish a 'reasonable' value for β.

Lee et al. (2016) quantify tumour growth rates for 1328 women diagnosed with invasive BC, during wait times for surgery, at Seoul National University Hospital between 2013–2014. They report significant changes depending on surrogate molecular subtypes, e.g. larger diameter changes in more aggressive molecular subtypes, and a frequent upgrade from Stage 1 to Stage 2 during wait times for surgery where the median wait time is 31 days. Nakashima et al. (2018) report significant changes in tumours between diagnosis and surgery for 64% of 309 patients diagnosed with invasive BC between 2014–2016, where the mean wait time is 56.9 days. Yoo et al. (2015) report significant increases in tumour sizes of 55% of 957 patients, diagnosed with invasive BC between 2002–2010, where the median time interval between initial and second examination is 28 days. This information suggests a considerable change in BC tumours for more than half of the observed populations during a period of one or two months, and therefore points towards transition intensity μ_x^{23} being much higher than μ_x^{13}, in the absence of any treatment. We assume a value of β as low as 0.1, subject to sensitivity testing. To be precise, we assume μ_x^{23} being 7 times higher than μ_x^{13}, i.e. $\beta = \frac{1}{7}$, in the baseline scenarios, see Section 5, and further check the sensitivity of results to different values of β, e.g. 0.1, in Section 6.

3.5. Metastatic breast cancer related mortality

Survival from metastatic BC can be highly correlated to age, tumour type, and treatment, in addition to other patient- or disease-related factors (den Brok et al., 2017; Purushotham et al., 2014). Zhao et al. (2020) report numbers of BC deaths by age within 12 months of Stage 4 BC diagnosis, using a cohort, between 2010–2015, obtained from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database (Table 2). We define rates of transition to State 5, μ_x^{35}, based on the numbers published by Zhao et al. (2020), assuming these to remain constant during the calculation period.

Table 2: Early deaths, characterised by survival time less than or equal to a year, for patients with Stage IV breast cancer based on the Surveillance, Epidemiology, and End Results (SEER) database. Source: Table 1 in Zhao et al. (2020).

Age	No early death	Total early death	Cancer specific early death	Non-cancer specific early death
<50	2790	645	521	124
50–59	3256	1178	923	255
60–69	3267	1506	1128	378
70–79	1952	1318	940	378
≥ 80	1143	1351	904	447

3.6. Transition intensities in the pre-pandemic scenario

We present the key transition intensities obtained using the available data and published studies in Table 3. We ignore the time trend in BC incidence and mortality rates, or in mortality rates from other causes, over the next five years.

Table 3: Age-specific transition intensities for the BC Markov model based on available literature.

Age	μ_x^{01}	μ_x^{04}	μ_x^{13}	$\mu_x^{35,*}$
65–69	0.00361	0.00867	0.01954	0.28060
70–74	0.00268	0.01516	0.01954	0.36002
75–79	0.00310	0.02779	0.01954	0.40000
80–84	0.00302	0.05416	0.01954	0.49711
85–89	0.00472	0.09857	0.01954	0.50000

We assume that transition intensities to death due to other causes from all 'live' states are equal to each other, particularly equal to μ_x^{04}. Moreover, we define transition intensity to State 5, μ_x^{35}, as

$$\mu_x^{35} = \kappa\, \mu_x^{35,*} \qquad (\kappa \geq 1), \tag{3}$$

where κ is a constant, that is modified in sensitivity analyses, and $\mu_x^{35,*}$ are transition intensities derived by using the reported numbers in Table 2 by Zhao et al. (2020). In our model, transitions to State 5 is restricted to be through from State 3, i.e. not taking into account, for instance, transitions from State 2 to State 5. We assume κ to be greater than or equal to 1, subject to sensitivity testing.

4. Post-pandemic Scenarios

We introduce three pandemic scenarios. Scenario 1 (S1) introduces a significant change in transitions to death from other causes, but does not involve any BC-related assumption. In Scenario 2 (S2) we additionally assume a decline in cancer diagnosis.

S1: The pandemic is assumed to result in increased deaths from other causes. This accords with empirical evidence (Section 4.1).

S2: In addition to the assumption in S1, we further assume a decline in BC diagnosis, i.e. a decline in the number of transfers to State 1 (Section 4.2). This is represented by changing α. Since we assume that the onset of BC remains unchanged before and after the pandemic, we also adjust the total transition intensity into State 2, μ_x^{02}, accordingly (Assumption A4).

4.1. Excess mortality due to COVID-19 in England

The Office for Health Improvement and Disparities (OHID) in England monitors excess mortality by age, sex, Upper Tier Local Authority, ethnic group, level of deprivation, cause of death and place of death since 21 March 2020, in order to have a better understanding of the impact of COVID-19. They also report ratios representing relative changes between registered and expected excess deaths for each group (OHID, 2022). We use these ratios to define the potential increase in transition to death from other causes as follows.

The age-specific transition intensities to death due to other causes, μ_x^{04}, are assumed to increase by a factor of 1.13 for ages 65–84 and 1.12 for ages 85+ from April 2020 until November 2021, while we assume they increase by a factor 1.10 for ages 65–84 and 1.09 for ages 85+ from November 2021 until the end of 2022 (OHID, 2022). Given the gradual decrease in the reported numbers between April 2020 and December 2022, we assume that μ_x^{04} could still be higher than the pre-pandemic levels for an additional period of two years. Specifically, μ_x^{04} is assumed to increase by the following factors: 1.07 for ages 65–84 and 1.06 for ages 85+ in 2023; 1.04 for ages 65–84 and 1.03 for ages 85+ in 2024.

4.2. Changes in breast cancer risk amid COVID-19

There is no evidence suggesting that the COVID-19 pandemic could increase BC incidence. Therefore we assume that overall new cases of cancer are not affected by the pandemic (A4 under Section 2.3). This implies that the onset of BC is assumed to be unchanged by the pandemic, and therefore μ_x^* is not affected. We further assume that there is no time trend in BC risk in the calculation period between 1 January 2020 and 31 December 2024.

However, cancer registrations are known to have reduced during the national lockdown(s) (CRUK, 2021). Particularly, Public Health Scotland (PHS) reported that BC registrations were 19% lower than the 2018/2019 average during the nine months of the pandemic (April–December 2020), as a result of initial health disruptions (PHS, 2021). The fall in BC registrations in the second quarter of 2020 is noted to start returning back to the pre-pandemic levels towards the end of 2020. Based on the available information, we assume that, for all ages, diagnosis of BC, μ_x^{01}, is decreased by 20% from April 2020 until the end of 2020. Following that, it is then assumed to return back to the pre-pandemic levels. The intensity μ_x^{02} is adjusted accordingly, keeping the overall BC onset rate unchanged.

5. Results

In this section we present our main findings for baseline scenarios, associated with pre- and post-pandemic scenarios, where $\alpha = 0.6$, $\beta = \frac{1}{7}$ and $\kappa = 1$. Note that sensitivity

testing is provided for different values of α, β and κ parameters, specifically for $\alpha = 0.4, 0.8$; $\beta = \frac{1}{5}, \frac{1}{10}$ and $\kappa = 0.8, 1.2$ in Section 6.

We estimate age-specific observed and unobserved BC cases along with deaths from BC or other causes in each scenario. Our results are derived based on Kolmogorov equations, shown in Appendix A, using R programming language. A fourth-order Runge-Kutta algorithm is used to discretise Kolmogorov equations, as explained in Appendix B. We also quantify excess deaths and YLL from BC and other causes, and changes in BC mortality by age under various pandemic scenarios.

5.1. Unobserved and observed breast cancer cases

Table 4 presents age-specific occupancy probabilities, denoted by ${}_tp_x^{ij}$, from state i to state j at age x. It shows that, for a woman free of BC at time zero, the probability of having BC and staying undiagnosed, in a 5-year period, ${}_5p_x^{02}$, has increased, around 3%, across different ages, with an exception at the two oldest age groups, in Scenario 2, as a response to the decrease in cancer diagnoses, in comparison to the pre-pandemic scenario. For a woman with no BC at time zero, the probability of being diagnosed with metastatic BC, ${}_5p_x^{03}$, has not changed significantly, in Scenario 2, as compared to the pre-pandemic levels. Scenario 1 mostly points out a decline in both probabilities. The decrease in these states are associated with the increase in deaths from other causes since the transition intensities from States 2–3 to 'Dead, Other Causes' are assumed to be equal to μ_x^{04}. All this is aligned with the fact that cancer patients have been more vulnerable to the SARS-CoV-2 coronavirus and affected worse by the pandemic, compared to the general population (Pinato et al., 2020; Garassino et al., 2020; Lee et al., 2020; Saini et al., 2020). Meanwhile, for a woman free of BC at time zero, the probability of being diagnosed with pre-metastatic BC, ${}_5p_x^{01}$, has decreased, 3–6%, where bigger changes are observed in more advanced ages in Scenario 2, with smaller declines in Scenario 1. It is worth to note that the PHS reported falls in stages 1–2 BC in Scotland along with small increases in stages 3–4 BC in 2020 (PHS, 2021).

Table 4: Occupancy probabilities for women being in different states over 5 years given that they have no breast cancer or clinically diagnosed with breast cancer at time zero in the pre- and post-pandemic scenarios for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$.

	Occupancy Probabilities									
	From State 0						From State 1		From State 3	
Age	${}_5p_x^{00}$	${}_5p_x^{01}$	${}_5p_x^{02}$	${}_5p_x^{03}$	${}_5p_x^{04}$	${}_5p_x^{05}$	${}_1p_x^{15}$	${}_5p_x^{15}$	${}_1p_x^{35}$	${}_5p_x^{35}$
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Pre-pandemic period										
65–69	92.92	1.62	0.82	0.26	4.24	0.14	0.25	4.24	24.37	74.17
70–74	90.65	1.17	0.59	0.17	7.30	0.12	0.31	4.82	30.02	81.26
75–79	84.81	1.27	0.64	0.17	12.97	0.14	0.34	4.91	32.54	82.49
80–84	74.38	1.08	0.55	0.13	23.71	0.14	0.40	5.05	38.21	84.45
85–89	58.73	1.35	0.68	0.16	38.89	0.19	0.39	4.45	37.62	79.34
Post-pandemic period										
Scenario 1										
65–69	92.57	1.62	0.82	0.25	4.60	0.14	0.25	4.23	24.36	74.04
70–74	90.06	1.16	0.59	0.16	7.90	0.12	0.31	4.80	30.00	81.04
75–79	83.79	1.25	0.63	0.17	14.01	0.14	0.33	4.87	32.51	82.11
80–84	72.66	1.06	0.53	0.13	25.48	0.14	0.40	4.97	38.15	83.78
85–89	56.54	1.30	0.66	0.16	41.16	0.19	0.39	4.34	37.52	78.36
Scenario 2										
65–69	92.57	1.57	0.85	0.26	4.60	0.15	0.25	4.23	24.36	74.04
70–74	90.06	1.13	0.61	0.17	7.90	0.13	0.31	4.80	30.00	81.04
75–79	83.79	1.22	0.66	0.17	14.01	0.15	0.33	4.87	32.51	82.11
80–84	72.66	1.03	0.55	0.13	25.48	0.15	0.40	4.97	38.15	83.78
85–89	56.54	1.26	0.68	0.16	41.16	0.20	0.39	4.34	37.52	78.36

5.2. Breast cancer survival

Cancer-specific survival, applied by the ONS, is one of most widely accepted survival measures. It is stated to be a 'net' measure and interpreted as the number of people being alive 'after cancer diagnosis'. This measure is considered to represent a 'hypothetical situation in which the cancer of interest is the only possible cause of death' (Mariotto et al., 2014; Swaminathan and Brenner, 2011; ONS, 2019). For a woman diagnosed with pre-metastatic BC at age x, for instance, cancer-specific survival in t years can be obtained as follows:

$$\frac{100\% - {}_tp_x^{14} - {}_tp_x^{15}}{100\% - {}_tp_x^{14}}.$$

Table 5 compares 1-, 5-, and 10-year survival probabilities in the pre-pandemic scenario by using this definition of cancer-specific survival and our model. In order to obtain survival from BC using the model, we set the transition intensities to 'Dead, Other Causes' after being diagnosed with BC, i.e. μ_x^{14} and μ_x^{34}, to be equal to zero. This allows 'Dead, BC' to be the only cause of death. The survival probabilities for women with pre-metastatic and metastatic BC in our model with these intensities set to zero are ${}_tp_x^{11} + {}_tp_x^{13}$ and ${}_tp_x^{33}$, respectively.

Table 5: 1-, 5-, and 10-year survival probabilities from breast cancer for women with pre-metastatic and metastatic breast cancer in the pre-pandemic scenario for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$, $\mu^{35} = \mu^{35,*}$.

	'Pre-metastatic Observed'			'Metastatic Observed'		
Age	1-year	5-year	10-year	1-year	5-year	10-year
	(%)	(%)	(%)	(%)	(%)	(%)
Pre-pandemic period						
ONS approach						
65–69	99.75	95.57	87.58	75.45	24.10	5.70
70–74	99.69	94.81	86.06	69.60	15.86	2.44
75–79	99.66	94.37	84.91	66.70	12.49	1.48
80–84	99.58	93.42	82.29	60.12	7.00	0.45
85–89	99.57	92.81	78.89	59.36	5.94	0.30
Our model						
65–69	99.75	95.64	87.95	75.53	24.59	6.04
70–74	99.69	94.95	86.81	69.77	16.53	2.73
75–79	99.66	94.66	86.38	67.03	13.53	1.83
80–84	99.59	94.06	85.59	60.83	8.33	0.69
85–89	99.59	94.05	85.57	60.65	8.21	0.67

Table 5 points that cancer survival is worse at older ages. It also suggests that cancer-specific survival probabilities based on the ONS methodology applied to our data are reasonably consistent with those based on our model. Cancer survival probabilities in the post-pandemic environment are not provided in Table 5. This is because survival is conditioned upon diagnosis of BC, which is the event disrupted by the pandemic.

5.3. Breast cancer mortality

For women with clinical cancer diagnosis, i.e. women in either State 1 or State 3, we define cancer mortality as the probability of moving to State 5, for the period under consideration (see ${}_tp_x^{15}$ and ${}_tp_x^{35}$ in Appendix A).

The dependence of BC mortality on age becomes more evident if we consider a longer period after diagnosis, where bigger changes are observed in more advanced ages under a more progressed BC condition (Table 4). For instance, in the pre-pandemic scenario, one-year mortality of a woman aged 65–69 with metastatic BC is estimated as 24.37%, whereas at ages 80+ one-year mortality increases around and above 37%. On the other hand, the variation by age of survival probabilities for women in State 1 is negligible even after 5 years.

Mortality in 5 years after metastatic BC diagnosis is estimated to be between 74.17–84.45%, whereas it is around 4–5% for a woman with pre-metastatic BC diagnosis in the pre-pandemic scenario. However, the relationship between 5-year mortality and age is not straightforward to interpret due to the following reasons:

- We have simplified BC progression using two main model states, with BC Stages 1–3 being combined and included in States 1 and 2, due to the lack of reliable data. Ideally, BC Stage 3, which indicates locally advanced BC, should be treated

differently than Stages 1 and 2, since survival from Stage 3 can be markedly different than that from Stages 1 and 2 (Rutherford et al., 2015; Maringe et al., 2020).

- In the absence of sufficient data, we have assumed constant transition intensities over periods of 5 years. Given the trends of BC incidence and mortality over time in Figure 2, this may not be realistic.
- The probability of metastasis decreases with age. On the other hand, mortality risk increases with age in the presence of any BC-related condition (Purushotham et al., 2014). The net effect of these two forces might be another reason for not seeing a consistent trend by age in 5-year BC mortality rates.

All cause mortality for women with pre-metastatic or metastatic BC is also presented over periods of 5 years, where age dependence is clear (Table C8).

Moreover, across pandemic scenarios, not surprisingly, there is no change in the cancer mortality for women with clinical diagnoses in comparison to the pre-pandemic scenario. This is because we accept that there is no change in the onset of BC before and after the pandemic (Table 6).

Table 6: Age-specific excess number of deaths, years of life expectancy lost, and absolute changes (AC) in cancer mortality at 1- and 5-year after diagnosis, per 100,000 women, in the pandemic scenarios 1-2, as compared to the pre-pandemic scenario, for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$.

	Excess deaths		YLL		AC in cancer mortality from			
	Dead (Other)	Dead (BC)	Dead (Other)	Dead (BC)	Pre-metastatic Observed		Metastatic	
	State 4	State 5	State 4	State 5	State 1		State 3	
					1 year	5 year	1 year	5 year
Scenario 1								
65–69	358	0	6915	−8	0.00	−0.01	−0.01	−0.13
70–74	606	−1	9273	−10	0.00	−0.02	−0.02	−0.22
75–79	1040	−1	12090	−16	−0.01	−0.04	−0.03	−0.38
80–84	1766	−3	14901	−23	0.00	−0.08	−0.06	−0.67
85–89	2274	−6	13282	−34	0.00	−0.11	−0.10	−0.98
Scenario 2								
65–69	358	9	6912	164	0.00	−0.01	−0.01	−0.13
70–74	605	7	9269	106	0.00	−0.02	−0.02	−0.22
75–79	1039	8	12085	87	−0.01	−0.04	−0.03	−0.38
80–84	1765	6	14894	52	0.00	−0.08	−0.06	−0.67
85–89	2272	6	13270	36	0.00	−0.11	−0.10	−0.98

5.4. Excess deaths

The estimated numbers of deaths over 1 and 5 years, by age, due to BC and other causes, can be defined by using ${}_tp_x^{05}$. The estimates of excess deaths, in the corresponding period, are then the differences between estimated numbers of deaths in the pre- and post-pandemic scenarios (Table 6).

Our findings show that deaths from other causes could increase by 5–8%, corresponding 358–2,274 excess deaths at different ages, per 100,000 women, in Scenarios 1–2, compared to the pre-pandemic period over 5 years. Our model also gives a 5–8% increase in deaths from BC in Scenario 2 across different ages, where higher increases are observed for younger ages. This corresponds with 6–9 excess BC deaths at different ages.

5.5. Years of life lost

We calculate age-specific YLL from BC and other causes at a given time t, denoted by $\text{YLL}_{x,t}^{\text{cause}}$, as

$$\text{YLL}_{x,t}^{\text{cause}} = D_{x,t}^{\text{cause}} e_x, \tag{4}$$

where $D_{x,t}^{\text{cause}}$ shows the corresponding excess deaths from a given cause, and e_x is a function that quantifies the number of years lost for deceased people aged x at time of death. Here e_x can be defined as average life expectancy at age x using standard life tables (WHO, 2013). Also, total YLL for all ages, $\text{YLL}_t^{\text{cause}}$, are calculated as

$$\text{YLL}_t^{\text{cause}} = \sum_x D_{x,t}^{\text{cause}} e_x. \tag{5}$$

We refer to standard life tables as a source for the loss function, following WHO (2013). Particularly, we use the 2018–2020 national standard life tables for women in the UK, with the life expectancies for women for ages 65–89, e_x, shown in Table 7 (ONS, 2021).

Table 7: Average life expectancies at various ages, denoted by e_x, in the 2018–2020 national standard life tables. Source: See ONS (2021) for women.

Age	65–69	70–74	75–79	80–84	85–89
e_x	19.31	15.31	11.63	8.44	5.84

Translating excess deaths into total YLL from BC, at 5 years, resulted in an estimated value of 36–164 years of life lost between ages 65 and 89 under Scenario 2. For deaths from other causes, we found 6,912 and 13,282 years of life lost at various ages across Scenarios 1 and 2.

6. Sensitivity Analysis

In this section we assess the sensitivity of our main findings to the model parameters.

6.1. The impact of parameter α

In the baseline scenario(s), Section 5, it was assumed that 60% of women developing BC, would actually be diagnosed with BC, in a given year, by choosing α. Higher

and lower diagnosis rates are represented by $\alpha = 0.8$ and 0.4, respectively (Table C8). Changing α has a significant impact on three states, namely State 2, State 3, and State 5 along with smaller impact on State 0 and State 1. For a woman free of BC, the probability of being in one of the three states after 5 years has changed significantly, increasing for $\alpha = 0.4$ and decreasing for $\alpha = 0.8$.

Changes in cancer mortality, excess deaths and YLL from other causes remain similar to those obtained for $\alpha = 0.6$ (Table 6, Table D9–Table D10). Considering excess deaths from BC, a lower pre-pandemic diagnosis rate of $\alpha = 0.4$ leads to 3–8 excess deaths across different ages, an increase of about 3–4%, as compared to the pre-pandemic levels, whereas a higher diagnosis rate of $\alpha = 0.8$ leads to more excess deaths, 7–9 at the same ages, an increase of about 14% (Table D9–Table D10).

6.2. The impact of parameter β

In the baseline scenario(s), we chose β as low as $\frac{1}{7}$, assuming that the transition from State 2 to State 3, μ_x^{23}, can be 7 times higher than the transition from State 1, μ_x^{13}. This is mainly motivated by the absence of treatment in State 2 along with the potential pace of tumour growth in BC (Section 3.4). All else equal, we vary the value of β by replacing it with $\frac{1}{5}$ and $\frac{1}{10}$. Similar to Case 1, the main impact of changes in β appears to be on three states, specifically State 2, State 3 and State 5. A smaller value of β leads to more transitions to State 3 and State 5, leaving a smaller number of women in State 2 (Table C8). The numbers in these states increase with a decreasing level of β, since this would mean that more women could develop advanced BC (stage 4 BC).

Table E11 and Table E12 show comparable outcomes for excess deaths and YLL from other causes, and cancer mortality. Excess deaths, along with YLL, from BC differ slightly from those in Table C8. BC deaths are around 4–6% higher compared to the pre-pandemic scenario, across different ages, when $\beta = \frac{1}{10}$, where only two age groups, 65–69 and 75–79, have experienced increases when $\beta = \frac{1}{5}$.

6.3. The impact of parameter κ

In the baseline scenario(s), we assumed κ to be equal to 1 in Eq.(3). We now consider κ to be equal to 0.8 and 1.2 in Table F13 and Table F14 respectively. The main effect of a change in κ is on State 3 and State 5, in addition to cancer mortality (Table C8). An increase in the level of κ leads to a decrease in the number of women in State 3 and an increase in State 5. The increase in State 5 is accompanied by significant increases in 1- and 5-year cancer mortality (Table F13, Table F14).

Similarly to Sections 6.1–6.2, varying parameter κ mainly resulted in changes in the number of excess BC deaths, while the changes in other outcomes, e.g. excess deaths from other causes, have remained comparable to the baseline scenarios. An increasing level of κ leads to the numbers of excess BC deaths being increased, by 6% at ages 65–69, with a similar effect on YLL from BC, whereas a smaller κ leads to 5–8% increase in BC deaths at different age groups.

We also obtain cancer survival probabilities, up to 10 years, for different values of κ, provided in Appendix G. Note that different values of α and β are not relevant to this calculation. Consistent with the findings in Table 5, Table G15 and Table G16 point

towards bigger changes in cancer survival for women with metastatic BC up to 5 years, whereas the changes for women with pre-metastatic BC remain smaller.

7. Discussion

During national lockdowns, essential BC diagnostic services were severely affected, along with cancer referral pathways. Health seeking-behaviour has also adversely affected, as only patients with urgent concerns were encouraged to use available services (Maringe et al., 2020). It is therefore important to further examine possible implications of late diagnoses on cancer rates and excess deaths.

We have constructed a Markov model to quantify changes in BC mortality for women aged 65+, for a period up to 5 years, as a result of the impact of COVID-19 on health services. Maringe et al. (2020) noted a 7·9–9·6% increase in the number of deaths due to BC in a 5-year period after diagnosis, assuming that cancers could only be diagnosed through urgent referrals with up to 80% reductions in cancer referrals. We assume 20% reduction in BC diagnosis based on a more recently published report (PHS, 2021). As a result, we found a 5–8% increase in both the number of deaths from BC and other causes at different ages as compared to the pre-pandemic scenario.

7.1. Strengths and limitations

Low availability of suitable data was a major challenge in this study, limiting our ability to make inferences from a realistic model. A related key issue was the incompleteness of BC Stage information in population-based cancer data. Nevertheless, our models, produced useful results, are broadly consistent with the existing literature. Our modelling approach has also provided estimates of excess deaths both from BC and from other causes, separately. As expected, model outputs are sensitive to the choice of certain parameters, e.g. α, where a sensitivity testing is carried out to take into account parameter uncertainty to some extent. However, relative changes in cancer mortality and deaths from different causes obtained under pre- and post-pandemic scenarios have shown consistent results.

Our approach provides a good model, involving the provision of BC diagnostic services and treatment, which will be more valuable as more data become available in time. Availability of more data would help to expand the modelling setting by providing more information in relation to the progression of BC. Also, our model, parametrised by α and β, can be used to represent different levels of BC service availability in normal (non-pandemic) times and therefore provides a method of comparing health service provision in different countries. It can allow to have more insights regarding the impact of pandemic on different health services by changing the levels of α and β parameters, as well.

There are important areas for further research. A more flexible setting may be achieved in a number of ways:

- allowing certain transition intensities, particularly μ_x^{13}, to depend on the duration of stay in the current state, e.g. by using a semi-Markov model;
- extending the existing model into a more detailed model of BC, e.g. by involving 'locally advanced' BC and/or considering treatment and recovery options, which would allow distinguishing between 'relapsed' and 'de novo' metastatic BC;

- considering multi-morbidity as an underlying condition, due to the potential impact on excess deaths;
- introducing time trends over years;
- considering to formally address parameter and model uncertainty.

7.2. Implications of this research

Our study can inform decision makers by increasing the awareness about the continuing impact of the pandemic. The estimated results can be helpful while implementing evidence-based health interventions.

Our findings can also help life insurers understand the impact of late diagnoses or prevented treatment of a major cancer in women, on cancer mortality and survival rates. The modelling framework developed here can be useful for assessing different scenarios of cancer diagnoses not just in pandemics but given different levels of health service provision. Our work can also add value while considering pricing and valuation assumptions.

Increases in population longevity and the relatively and increasingly long BC survival, mean that BC will continue to significantly affect older women (Shachar et al., 2016; BCRF, 2021). In this article we have explored the short-term impact of COVID-19 related diagnostic delays on BC mortality for older population.

Acknowledgements

ED and GS acknowledge funding from the Society of Actuaries, under a research project entitled 'Predictive Modelling for Medical Morbidity Trends related to Insurance'. AA and GS acknowledge funding from SCOR Foundation for Science, under a project entitled 'Estimating The Impact Of The COVID-19 Pandemic On Breast Cancer Deaths - An Application On Breast Cancer Life Insurance'.

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Appendix A Kolmogorov equations for breast cancer Markov model

$$
\begin{aligned}
\frac{d}{dt}{}_tp_x^{00} &= -{}_tp_x^{00}\left[\mu_x^{01}+\mu_x^{04}+\mu_x^{02}\right]\\
\frac{d}{dt}{}_tp_x^{01} &= {}_tp_x^{00}\mu_x^{01}-{}_tp_x^{01}\left[\mu_x^{14}+\mu_x^{13}\right]\\
\frac{d}{dt}{}_tp_x^{02} &= {}_tp_x^{00}\mu_x^{02}-{}_tp_x^{02}\left[\mu_x^{23}+\mu_x^{24}\right]\\
\frac{d}{dt}{}_tp_x^{03} &= {}_tp_x^{01}\mu_x^{13}+{}_tp_x^{02}\mu_x^{23}-{}_tp_x^{03}\left[\mu_x^{35}+\mu_x^{34}\right]\\
\frac{d}{dt}{}_tp_x^{04} &= {}_tp_x^{00}\mu_x^{04}+{}_tp_x^{01}\mu_x^{14}+{}_tp_x^{02}\mu_x^{24}+{}_tp_x^{03}\mu_x^{34}\\
\frac{d}{dt}{}_tp_x^{05} &= {}_tp_x^{03}\mu_x^{35}\\
\frac{d}{dt}{}_tp_x^{11} &= -{}_tp_x^{11}\left[\mu_x^{14}+\mu_x^{13}\right]\\
\frac{d}{dt}{}_tp_x^{13} &= {}_tp_x^{11}\mu_x^{13}-{}_tp_x^{13}\left[\mu_x^{35}+\mu_x^{34}\right]\\
\frac{d}{dt}{}_tp_x^{14} &= {}_tp_x^{11}\mu_x^{14}+{}_tp_x^{13}\mu_x^{34}\\
\frac{d}{dt}{}_tp_x^{15} &= {}_tp_x^{13}\mu_x^{35}\\
\frac{d}{dt}{}_tp_x^{33} &= -{}_tp_x^{33}\left[\mu_x^{35}+\mu_x^{34}\right]\\
\frac{d}{dt}{}_tp_x^{34} &= {}_tp_x^{33}\mu_x^{34}\\
\frac{d}{dt}{}_tp_x^{35} &= {}_tp_x^{33}\mu_x^{35}
\end{aligned}
$$

Appendix B Runge-Kutta method for breast cancer Markov model

Runge-Kutta methods first estimate function values in a given small interval, and then use those values to obtain a better estimate of the function under inspection. A fourth-order Runge-Kutta scheme is based on four recursive estimates of the increment in the function value per time step (Macdonald et al., 2018).

We have a 6-state model in Figure 1, and hence, in full, a 6×6 matrix of occupancy probabilities denoted by ${}_hp_x^{ij} \equiv y_t$ as

$$
y_t = \begin{bmatrix} {}_tp_x^{00} \\ {}_tp_x^{01} \\ {}_tp_x^{02} \\ \vdots \\ {}_tp_x^{55} \end{bmatrix}, \frac{d}{dt}y_t = \begin{bmatrix} \frac{d}{dt}{}_tp_x^{00} \\ \frac{d}{dt}{}_tp_x^{01} \\ \frac{d}{dt}{}_tp_x^{02} \\ \vdots \\ \frac{d}{dt}{}_tp_x^{55} \end{bmatrix} = f(t, y_t).
$$

Now, suppose we would like to solve $\frac{d}{dt}y_t = f(t, y_t)$, $y_{t_0} = y_0$. Then, we could write

$$y_{t_{n+1}} = y_{t_n} + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4),$$

for $t_{n+1} = t_n + h$ and

$$\begin{aligned} k_1 &= f(t_n, y_{t_n}) \\ k_2 &= f(t_n + \frac{h}{2}, y_{t_n} + h\frac{k_1}{2}) \\ k_3 &= f(t_n + \frac{h}{2}, y_{t_n} + h\frac{k_2}{2}) \\ k_4 &= f(t_n + h, y_{t_n} + hk_3). \end{aligned}$$

Here, the four intermediate steps, denoted by k_1, k_2, k_3 and k_4, are also vector quantities such that

$$k_1 = \begin{bmatrix} k_1^{00} \\ k_1^{01} \\ k_1^{02} \\ \vdots \\ k_1^{55} \end{bmatrix}, k_2 = \begin{bmatrix} k_2^{00} \\ k_2^{01} \\ k_2^{02} \\ \vdots \\ k_2^{55} \end{bmatrix}, k_3 = \begin{bmatrix} k_3^{00} \\ k_3^{01} \\ k_3^{02} \\ \vdots \\ k_3^{55} \end{bmatrix}, k_4 = \begin{bmatrix} k_4^{00} \\ k_4^{01} \\ k_4^{02} \\ \vdots \\ k_4^{55} \end{bmatrix}.$$

Appendix C Occupancy probabilities at the end of 5 years in the pre-pandemic period

Table C8: Occupancy probabilities for women being in different states at the end of 5 years given that they have no breast cancer or clinically diagnosed with breast cancer at time zero in the pre-pandemic scenario based on different choices of α, β and κ parameters.

Occupancy Probabilities														
							${}_tp_x^{15}$		${}_tp_x^{35}$		${}_tp_x^{15} + {}_tp_x^{14}$		${}_tp_x^{35} + {}_tp_x^{34}$	
Age	${}_5p_x^{00}$	${}_5p_x^{01}$	${}_5p_x^{02}$	${}_5p_x^{03}$	${}_5p_x^{04}$	${}_5p_x^{05}$	one-year	five-year	one-year	five-year	one-year	five-year	one-year	five-year
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
$\alpha = 0.6$; $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$														
65–69	92.92	1.62	0.82	0.26	4.24	0.14	0.25	4.24	24.37	74.17	1.11	8.41	25.12	76.46
70–74	90.65	1.17	0.59	0.17	7.30	0.12	0.31	4.82	30.02	81.26	1.81	11.98	31.28	84.68
75–79	84.81	1.27	0.64	0.17	12.97	0.14	0.34	4.91	32.54	82.49	3.08	17.62	34.80	88.22
80–84	74.38	1.08	0.55	0.13	23.71	0.15	0.40	5.05	38.21	84.45	5.66	28.25	42.37	93.65
85–89	58.73	1.35	0.68	0.16	38.89	0.19	0.39	4.45	37.62	79.34	9.76	42.55	45.04	94.98
$\alpha = 0.8$; $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$														
65–69	93.62	1.63	0.31	0.13	4.24	0.07	0.25	4.24	24.37	74.17	1.11	8.41	25.12	76.46
70–74	91.16	1.17	0.22	0.08	7.30	0.06	0.31	4.82	30.02	81.26	1.81	11.98	31.28	84.68
75–79	85.36	1.27	0.24	0.09	12.97	0.07	0.34	4.91	32.54	82.49	3.08	17.62	34.80	88.22
80–84	74.85	1.09	0.21	0.07	23.72	0.07	0.40	5.05	38.21	84.45	5.66	28.25	42.37	93.65
85–89	59.31	1.35	0.26	0.08	38.90	0.10	0.39	4.45	37.62	79.34	9.76	42.55	45.04	94.98
$\alpha = 0.4$; $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$														
65–69	91.53	1.61	1.83	0.51	4.24	0.28	0.25	4.24	24.37	74.17	1.11	8.41	25.12	76.46
70–74	89.65	1.16	1.32	0.33	7.29	0.24	0.31	4.82	30.02	81.26	1.81	11.98	31.28	84.68
75–79	83.72	1.26	1.43	0.34	12.96	0.29	0.34	4.91	32.54	82.49	3.08	17.62	34.80	88.22
80–84	73.45	1.08	1.23	0.26	23.70	0.29	0.40	5.05	38.21	84.45	5.66	28.25	42.37	93.65
85–89	57.59	1.33	1.52	0.32	38.86	0.39	0.39	4.45	37.62	79.34	9.76	42.55	45.04	94.98
$\alpha = 0.6$; $\mu^{13} = \frac{1}{5}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$														
65–69	92.92	1.62	0.90	0.21	4.24	0.11	0.25	4.24	24.37	74.17	1.11	8.41	25.12	76.46
70–74	90.65	1.17	0.65	0.13	7.30	0.10	0.31	4.82	30.02	81.26	1.81	11.98	31.28	84.68
75–79	84.81	1.27	0.70	0.14	12.97	0.11	0.34	4.91	32.54	82.49	3.08	17.62	34.80	88.22
80–84	74.38	1.08	0.60	0.11	23.71	0.12	0.40	5.05	38.21	84.45	5.66	28.25	42.37	93.65
85–89	58.73	1.35	0.74	0.13	38.89	0.16	0.39	4.45	37.62	79.34	9.76	42.55	45.04	94.98
$\alpha = 0.6$; $\mu^{13} = \frac{1}{10}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$														
65–69	92.92	1.62	0.72	0.32	4.24	0.18	0.25	4.24	24.37	74.17	1.11	8.41	25.12	76.46
70–74	90.65	1.17	0.52	0.20	7.30	0.15	0.31	4.82	30.02	81.26	1.81	11.98	31.28	84.68
75–79	84.81	1.27	0.57	0.21	12.97	0.18	0.34	4.91	32.54	82.49	3.08	17.62	34.80	88.22
80–84	74.38	1.08	0.48	0.16	23.71	0.18	0.40	5.05	38.21	84.45	5.66	28.25	42.37	93.65
85–89	58.73	1.35	0.60	0.20	38.88	0.25	0.39	4.45	37.62	79.34	9.76	42.55	45.04	94.98
$\alpha = 0.6$; $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = 0.8\mu^{35,*}$														
65–69	92.92	1.62	0.82	0.28	4.24	0.12	0.20	3.66	20.02	66.27	1.06	7.84	20.79	68.83
70–74	90.65	1.17	0.59	0.18	7.30	0.10	0.25	4.23	24.85	74.14	1.75	11.41	26.16	78.04
75–79	84.81	1.27	0.64	0.19	12.97	0.12	0.27	4.33	27.03	75.84	3.01	17.08	29.38	82.43
80–84	74.38	1.08	0.55	0.15	23.71	0.13	0.33	4.52	32.00	78.82	5.60	27.79	36.36	89.55
85–89	58.73	1.35	0.68	0.18	38.89	0.17	0.32	3.98	31.50	73.60	9.70	42.18	39.26	91.74
$\alpha = 0.6$; $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = 1.2\mu^{35,*}$														
65–69	92.92	1.62	0.82	0.24	4.24	0.16	0.29	4.74	28.47	80.15	1.15	8.91	29.20	82.21
70–74	90.65	1.17	0.59	0.15	7.30	0.14	0.36	5.31	34.83	86.28	1.86	12.46	36.05	89.31
75–79	84.81	1.27	0.64	0.15	12.97	0.16	0.39	5.37	37.64	87.06	3.13	18.05	39.82	92.10
80–84	74.38	1.08	0.55	0.12	23.71	0.16	0.46	5.46	43.85	88.13	5.72	28.61	47.83	96.13
85–89	58.73	1.35	0.68	0.14	38.88	0.21	0.45	4.82	43.18	83.28	9.82	42.83	50.27	96.96

Appendix D Excess deaths and years of life expectancy lost at different age groups in Section 6.1

Table D9: Age-specific excess number of deaths, years of life expectancy lost for each pandemic scenario 1–2, and absolute changes (AC) in cancer mortality at 1- and 5-year after diagnosis, per 100,000 women, in the pandemic scenarios compared to the pre-pandemic scenario for $\alpha = 0.8$, $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$.

	Excess deaths		YLL		AC in cancer mortality from			
	Dead (Other)	Dead (BC)	Dead (Other)	Dead (BC)	Pre-metastatic Observed		Metastatic	
	State 4	State 5	State 4	State 5	State 1		State 3	
					1 year	5 year	1 year	5 year
Scenario 1								
65–69	358	0	6916	−4	0.00	−0.01	−0.01	−0.13
70–74	606	0	9274	−5	0.00	−0.02	−0.02	−0.22
75–79	1040	−1	12092	−8	−0.01	−0.04	−0.03	−0.38
80–84	1766	−1	14903	−11	0.00	−0.08	−0.06	−0.67
85–89	2275	−3	13284	−17	0.00	−0.11	−0.10	−0.98
Scenario 2								
65–69	358	9	6913	169	0.00	−0.01	−0.01	−0.13
70–74	606	7	9271	111	0.00	−0.02	−0.02	−0.22
75–79	1039	8	12086	95	−0.01	−0.04	−0.03	−0.38
80–84	1765	7	14896	63	0.00	−0.08	−0.06	−0.67
85–89	2273	9	13271	53	0.00	−0.11	−0.10	−0.98

Table D10: Age-specific excess number of deaths, years of life expectancy lost for each pandemic scenario 1–2, and absolute changes (AC) in cancer mortality at 1- and 5-year after diagnosis, per 100,000 women, in the pandemic scenarios compared to the pre-pandemic scenario for $\alpha = 0.4$, $\mu^{13} = \frac{1}{7}\mu^{23}$ and $\mu^{35} = \mu^{35,*}$.

	Excess deaths		YLL		AC in cancer mortality from			
	Dead (Other)	Dead (BC)	Dead (Other)	Dead (BC)	Pre-metastatic Observed		Metastatic	
	State 4	State 5	State 4	State 5	State 1		State 3	
					1 year	5 year	1 year	5 year
Scenario 1								
65–69	358	−1	6913	−17	0.00	−0.01	−0.01	−0.13
70–74	606	−1	9271	−20	0.00	−0.02	−0.02	−0.22
75–79	1039	−3	12087	−32	−0.01	−0.04	−0.03	−0.38
80–84	1765	−5	14898	−45	0.00	−0.08	−0.06	−0.67
85–89	2274	−12	13280	−67	0.00	−0.11	−0.10	−0.98
Scenario 2								
65–69	358	8	6911	156	0.00	−0.01	−0.01	−0.13
70–74	605	6	9267	96	0.00	−0.02	−0.02	−0.22
75–79	1039	6	12082	71	−0.01	−0.04	−0.03	−0.38
80–84	1764	3	14890	29	0.00	−0.08	−0.06	−0.67
85–89	2272	0	13267	2	0.00	−0.11	−0.10	−0.98

Appendix E Excess deaths and years of life expectancy lost at different age groups in Section 6.2

Table E11: Age-specific excess number of deaths, years of life expectancy lost for each pandemic scenario 1–2, and absolute changes (AC) in cancer mortality at 1- and 5-year after diagnosis, per 100,000 women, in the pandemic scenarios compared to the pre-pandemic scenario for $\alpha = 0.6$, $\beta = \frac{1}{5}$ and $\mu^{35} = \mu^{35,*}$.

	Excess deaths		YLL		AC in cancer mortality from			
	Dead (Other)	Dead (BC)	Dead (Other)	Dead (BC)	Pre-metastatic Observed		Metastatic	
	State 4	State 5	State 4	State 5	State 1		State 3	
					1 year	5 year	1 year	5 year
Scenario 1								
65–69	358	0	6915	−7	0.00	−0.01	−0.01	−0.13
70–74	606	−1	9273	−8	0.00	−0.02	−0.02	−0.22
75–79	1040	−1	12091	−13	−0.01	−0.04	−0.03	−0.38
80–84	1766	−2	14902	−18	0.00	−0.08	−0.06	−0.67
85–89	2275	−5	13283	−27	0.00	−0.11	−0.10	−0.98
Scenario 2								
65–69	358	6	6914	115	0.00	−0.01	−0.01	−0.13
70–74	606	5	9271	74	0.00	−0.02	−0.02	−0.22
75–79	1039	5	12087	60	−0.01	−0.04	−0.03	−0.38
80–84	1765	4	14897	35	0.00	−0.08	−0.06	−0.67
85–89	2273	4	13274	22	0.00	−0.11	−0.10	−0.98

Table E12: Age-specific excess number of deaths, years of life expectancy lost for each pandemic scenario 1–2, and absolute changes (AC) in cancer mortality at 1- and 5-year after diagnosis, per 100,000 women, in the pandemic scenarios compared to the pre-pandemic scenario for $\alpha = 0.6$, $\beta = \frac{1}{10}$ and $\mu^{35} = \mu^{35,*}$.

	Excess deaths		YLL		AC in cancer mortality from			
	Dead (Other)	Dead (BC)	Dead (Other)	Dead (BC)	Pre-metastatic Observed		Metastatic	
	State 4	State 5	State 4	State 5	State 1		State 3	
					1 year	5 year	1 year	5 year
Scenario 1								
65–69	358	−1	6915	−10	0.00	−0.01	−0.01	−0.13
70–74	606	−1	9272	−12	0.00	−0.02	−0.02	−0.22
75–79	1039	−2	12089	−20	−0.01	−0.04	−0.03	−0.38
80–84	1765	−3	14900	−28	0.00	−0.08	−0.06	−0.67
85–89	2274	−7	13282	−43	0.00	−0.11	−0.10	−0.98
Scenario 2								
65–69	358	12	6911	228	0.00	−0.01	−0.01	−0.13
70–74	605	10	9268	147	0.00	−0.02	−0.02	−0.22
75–79	1039	10	12082	122	−0.01	−0.04	−0.03	−0.38
80–84	1764	9	14890	74	0.00	−0.08	−0.06	−0.67
85–89	2271	9	13264	53	0.00	−0.11	−0.10	−0.98

Appendix F Excess deaths and years of life expectancy lost at different age groups in Section 6.3

Table F13: Age-specific excess number of deaths, years of life expectancy lost for each pandemic scenario 1–2, and absolute changes (AC) in cancer mortality at 1- and 5-year after diagnosis, per 100,000 women, in the pandemic scenarios compared to the pre-pandemic scenario for $\alpha = 0.6$, $\beta = \frac{1}{7}$ and $\mu^{35} = 0.8\mu^{35,*}$.

	Excess deaths		YLL		AC in cancer mortality from			
	Dead (Other)	Dead (BC)	Dead (Other)	Dead (BC)	Pre-metastatic Observed		Metastatic	
	State 4	State 5	State 4	State 5	State 1		State 3	
					1 year	5 year	1 year	5 year
Scenario 1								
65–69	358	0	6919	−7	0.00	−0.01	0.00	−0.11
70–74	606	−1	9273	−8	0.00	−0.02	−0.02	−0.22
75–79	1040	−1	12090	−14	0.00	−0.03	−0.03	−0.38
80–84	1766	−2	14902	−20	0.00	−0.07	−0.06	−0.69
85–89	2274	−5	13283	−30	0.00	−0.10	−0.09	−1.02
Scenario 2								
65–69	358	7	6917	141	0.00	−0.01	0.00	−0.11
70–74	606	6	9271	93	0.00	−0.02	−0.02	−0.22
75–79	1039	7	12085	77	0.00	−0.03	−0.03	−0.38
80–84	1765	6	14895	46	0.00	−0.07	−0.06	−0.69
85–89	2273	6	13272	32	0.00	−0.10	−0.09	−1.02

Table F14: Age-specific excess number of deaths, years of life expectancy lost for each pandemic scenario 1–2, and absolute changes (AC) in cancer mortality at 1- and 5-year after diagnosis, per 100,000 women, in the pandemic scenarios compared to the pre-pandemic scenario for $\alpha = 0.6$, $\beta = \frac{1}{7}$ and $\mu^{35} = 1.2\mu^{35,*}$.

	Excess deaths		YLL		AC in cancer mortality from			
	Dead (Other)	Dead (BC)	Dead (Other)	Dead (BC)	Pre-metastatic Observed		Metastatic	
	State 4	State 5	State 4	State 5	State 1		State 3	
					1 year	5 year	1 year	5 year
Scenario 1								
65–69	399	−2	7698	−44	0.00	−0.14	−0.13	−1.40
70–74	657	−3	10058	−50	0.00	−0.28	−0.26	−2.40
75–79	1143	−7	13295	−80	−0.01	−0.51	−0.52	−4.24
80–84	1944	−13	16408	−109	−0.02	−1.03	−1.15	−7.42
85–89	2714	−32	15847	−185	−0.03	−1.72	−2.06	−12.68
Scenario 2								
65–69	398	8	7695	150	0.00	−0.14	−0.13	−1.40
70–74	657	5	10054	78	0.00	−0.28	−0.26	−2.40
75–79	1143	3	13289	33	−0.01	−0.51	−0.52	−4.24
80–84	1943	−3	16400	−29	−0.02	−1.03	−1.15	−7.42
85–89	2711	−19	15834	−109	−0.03	−1.72	−2.06	−12.68

Appendix G Cancer survival at different age groups in Section 6.3

Table G15: 1-, 5-, and 10-year survival probabilities from breast cancer for women with pre-metastatic and metastatic breast cancer in the pre-pandemic scenario for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$, $\mu^{35} = 0.8\mu^{35,*}$.

	'Pre-metastatic Observed'			'Metastatic Observed'		
Age	1-year	5-year	10-year	1-year	5-year	10-year
	(%)	(%)	(%)	(%)	(%)	(%)
Pre-pandemic period						
ONS approach						
65–69	99.80	96.18	88.74	79.82	31.99	10.05
70–74	99.74	95.45	87.15	74.83	22.85	5.07
75–79	99.72	95.03	85.99	72.32	18.81	3.35
80–84	99.65	94.11	83.35	66.55	11.70	1.24
85–89	99.65	93.56	80.19	65.85	10.10	0.85
Our model						
65–69	99.80	96.24	89.08	79.89	32.55	10.60
70–74	99.75	95.57	87.83	74.97	23.69	5.61
75–79	99.72	95.28	87.33	72.61	20.19	4.08
80–84	99.66	94.67	86.40	67.19	13.69	1.87
85–89	99.66	94.66	86.38	67.03	13.53	1.83

Table G16: 1-, 5-, and 10-year survival probabilities from breast cancer for women with pre-metastatic and metastatic breast cancer in the pre-pandemic scenario for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$, $\mu^{35} = 1.2\mu^{35,*}$.

	'Pre-metastatic Observed'			'Metastatic Observed'		
Age	1-year	5-year	10-year	1-year	5-year	10-year
	(%)	(%)	(%)	(%)	(%)	(%)
Pre-pandemic period						
ONS approach						
65–69	99.71	95.06	86.69	71.32	18.16	3.24
70–74	99.63	94.28	85.28	64.73	11.02	1.18
75–79	99.60	93.84	84.13	61.52	8.31	0.66
80–84	99.51	92.89	81.55	54.33	4.20	0.16
85–89	99.50	92.22	77.97	53.53	3.52	0.11
Our model						
65–69	99.71	95.14	87.11	71.41	18.57	3.45
70–74	99.64	94.44	86.08	64.92	11.53	1.33
75–79	99.60	94.16	85.71	61.88	9.07	0.82
80–84	99.52	93.59	85.03	55.07	5.07	0.26
85–89	99.52	93.58	85.01	54.88	4.98	0.25