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The effect of the COVID-19 health disruptions on breast cancer mortality for older women: a semi-Markov modelling approach

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ABSTRACT

Public health measures necessitated by the COVID-19 pandemic have affected cancer pathways by halting screening, delaying diagnostic tests and reducing the numbers starting treatment. Specifically, this moves individuals from observed and treated pathways to unobserved and untreated pathways. We introduce a semi-Markov model that includes both, extending an industry-based multiple state model used for life and critical illness insurance. Our model includes events related to cancer diagnosis and progression based on publicly available population data for women aged 65–89 in England and on relevant medical literature. We quantify age-specific excess deaths, for a period up to 5 years, along with years of life expectancy lost and changes in cancer mortality by cancer stage. Our analysis suggests a 3–6% increase in breast cancer deaths, and a 4–6% increase in registrations of advanced breast cancer, robust under sensitivity analysis. This should be applicable to actuarial work in areas where longevity and advanced age morbidity affect healthcare, retirement and insurance.

KEYWORDS

Breast cancer; cancer insurance; cancer mortality; COVID-19 pandemic; excess deaths; semi-Markov model

1. Introduction

The COVID-19 pandemic has claimed more than 6.2 million lives worldwide as of May 2022 (WHO, 2022). The pandemic has alerted actuaries, epidemiologists and longevity specialists not only because of the increased number of deaths, but also because of the potential future impact of healthcare disruptions resulting from imposed public health measures. During the pandemic the UK entered three national lockdowns, with the first being introduced on 23 March, 2020. Cancer pathways have been 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 for more than 6 weeks, and significant reductions in the number of patients starting cancer treatment. Cancer Research UK (CRUK) has reported that 3 million fewer people were screened for cancer in the UK between March and September 2020. 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 (CRUK, 2021). These figures sparked 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 worsen cancer survival. This has also

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triggered concerns regarding changes in cause-specific mortality, e.g. from cancer, impacting trends of all-cause mortality.

To the best of our knowledge, this is the first actuarial study developed to quantify the impact of healthcare disruptions on cancer mortality. 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.

Early empirical studies suggested that COVID-19 is more likely to affect older people and those with comorbidity (Chen et al., 2020; Grasselli et al., 2020; Richardson 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 (Garassino et al., 2020; Lee et al., 2020; Pinato 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.

Part of the contribution of this work is providing a modelling framework, which goes beyond the aforementioned empirical work, to investigate the impact of a pandemic, such as COVID-19, on BC mortality and morbidity. Our modelling approach also allows the extension of a multiple state model introduced by the UK Continuous Mortality Investigation (CMI) Committee (CMI, 1991) and a critical illness model widely applied by the insurance industry (Reynolds & Faye, 2016). Specifically, the model outlined in CMI (1991) is a 3-state semi-Markov model, consisting of healthy, sick, and all-cause death states, while the model described in Reynolds and Faye (2016) is a 4-state Markov model, consisting of the following states: healthy, sick, death from critical illness causes and death from other causes. Going beyond these models, our model additionally includes states relevant to cancer progression and undiagnosed cases, and it also accounts for changes in diagnostic and treatment services.

Thus, the proposed modelling framework can also be implemented by the insurance industry in the context of critical illness and life insurance applications as demonstrated by Arık et al. (2023). Particularly, we are interested in how the pandemic, 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, as Maringe et al. (2020) state that 'the effect of delayed presentation on patients with cancer is not immediate, and premature death as a result might occur up to 5 years later …' (p. 1024). This is motivated by screening programmes and cancer treatments having been largely affected by lockdowns. This is relevant and important to insurers since BC remains one of the most common conditions amongst female critical illness claims (Aviva, 2015; CMI, 2011). It is worth to noting that a screening programme is available for BC, which plays a crucial role for early diagnosis and increases the chances of BC survival (CRUK, 2020a). However, according to CRUK (2021), 7200 fewer cases of BC were diagnosed between April–December 2020 compared to the same period in 2019, 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 (Adams et al., 2015; Baione & Levantesi, 2018; Buchardt et al., 2015; Castelli et al., 2007; Hacariz et al., 2021; Hubbard et al., 2016; Lu et al., 2011; Soetewey et al., 2022). We establish a semi-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. Our approach presents a more detailed model of BC as compared to existing multiple state models adapted by the insurance industry (CMI, 1991; Reynolds & Faye, 2016). Our model differs from these earlier literature models in two important ways: (i) by differentiating between observed and unobserved cancer cases; and (ii) by introducing cancer stage information.

Furthermore, we focus on mortality at older ages, from 65 years and over. These ages are important for pension plans and healthcare. Besides, in the existence of continuing mortality improvements, relatively high survival from BC would continue impacting older women (Shachar et al., 2016), with further implications on critical illness insurance (Aviva, 2015). 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.

This paper is organised as follows. In Section 2 we introduce the model for BC risk. In Section 3 we calibrate the model in a pre-pandemic environment. In Section 4 we introduce two 'pandemic' scenarios. In Section 5 we estimate excess deaths and YLLs under a pre-pandemic model calibration and pandemic scenarios. In Section 6 we provide a sensitivity analysis for model assumptions. Finally, in Section 7 we discuss our findings and their implications along with strengths and limitations of our approach.

2. Methodology

2.1. Definitions of breast cancer stages

BC mortality is the most common cancer diagnosed in women, in addition to being one of the leading causes of death for women (ONS, 2019a; PHE, 2017). The most common type of BC is known to be 'invasive' BC that indicates cancer cells spreading from the ducts into the surrounding (breast) tissues, with the two most well-known ones are 'invasive ductal carcinoma' and 'invasive lobular carcinoma'. Invasive BC can be described from early to advanced stage BC (CRUK, 2020c). The clinical model of BC progression is a well-defined staging model of the form:

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

where a higher stage number shows that cancer tumour is bigger or has spread from breast to distant parts of the body, also known as 'metastasis'. This staging model, namely TNM, categorises cancer from Stage 1 to Stage 4 based on the tumour (T) size, that can be between 1–4 with 1 for small tumours and 4 for large tumours; whether or not lymph nodes (N) have cancer cells, that can change between 0–3; and whether or not the cancer cells move to other parts of the body (M), that can be either 0 or 1 (CRUK, 2020b; ONS, 2017).

The progression from Stage 1 to Stage 4 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.

The clinical staging model above takes no account of what is observed or unobserved, i.e. all women free of BC and dead from BC are observed. In reality, 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' event, that is the first occurrence of BC observed. 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.

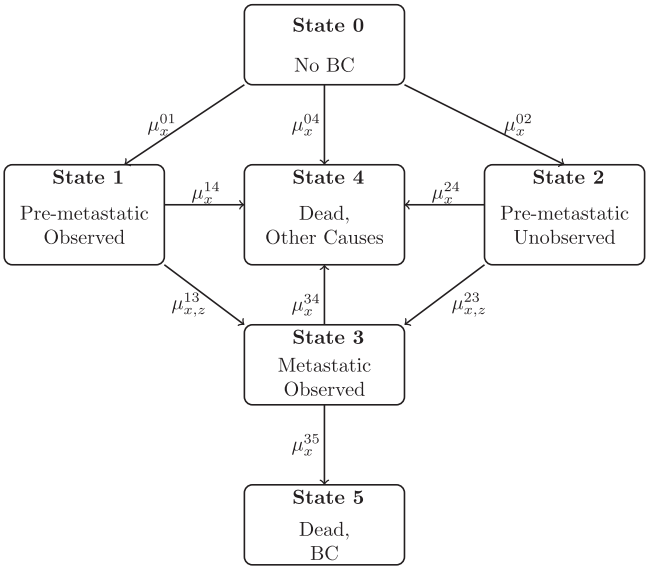

Figure 1. A breast cancer semi-Markov model in continuous time.
Note: Intensities μ may be functions of age x and/or duration z.

2.2. Modelling unobserved breast cancer

We distinguish BC death from other causes of death and define life histories accordingly, keeping in mind that the main focus of this work is providing a methodology on quantifying the impact of BC diagnostic delays.

In Figure 1, we introduce a model of BC progression, based on the stages described in Section 2.1, but introducing some simplifications (Section 2.3) based on the available data and published clinical studies (Section 3). 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 are denoted by μ_x^{ij}, where x is age-at-entry to state i. Age- and duration-dependent transition intensities at age x and duration z from state i to state j are denoted by $\mu_{x,z}^{ij}$. 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. We note here that 'stage' and 'state' are distinct concepts in this paper.

In the semi-Markov model considered here, Figure 1, the usual Kolmogorov equations in a Markov model are replaced by a system of integral-differential equations, with integrals over duration being required for certain states. Often such integrals can be intractable. In our model, which has no more than one duration-dependent transition in any possible life history, the required integrals are of low dimension and the modified Kolmogorov equations can be solved numerically using standard methods (Appendix 1). In particular, we apply a fourth-order Runge–Kutta scheme to solve the modified Kolmogorov equations under consideration (Macdonald et al., 2018). The Runge-Kutta scheme is outlined in Appendix 2. We also note that a trapezium rule is employed to approximately calculate related integrals in the modified Kolmogorov equations. The related algorithms for the (modified) Kolmogorov equations are developed in the R programming language.

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 transitions from State 2 to State 1, or progression between Stages 1–3 explicitly as this is not supported by available data. Note that Stages 1–3 BC have a similar pattern for one-year survival (ONS, 2016b). 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 first progressing to metastasis.

A3: All individuals entering State 3 are observed to do 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 & McAllister, 2013).

The model also includes 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 dramatic changes in the health service, we add two more model assumptions relating to State 2:

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

$$\mu_x^{01} + \mu_x^{02} = \mu_x^*, \tag{1}$$

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 are assumed not to be treated. Therefore, we assume $\mu_{x,z}^{13} < \mu_{x,z}^{23}$ 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 $\mu_{x,z}^{13}$ and $\mu_{x,z}^{23}$ also do not depend on any particular pandemic scenario.

A4 and A5 suggest a convenient parametrisation of the model:

$$\mu_x^{01} = \alpha_x \mu_x^*, \qquad \mu_x^{02} = (1-\alpha_x)\mu_x^*, \quad \mu_{x,z}^{13} = \beta_{x,z}\mu_{x,z}^{23} \quad (0 < \beta_{x,z} < 1), \tag{2}$$

where $0 < \alpha_x < 1$ quantifies the proportional relationship between μ_x^{01} and μ_x^{02}, and will later be used to determine pandemic scenarios. For simplicity, and lacking data to support other assumptions, we assume $\alpha_x = \alpha$ and $\beta_{x,z} = \beta$. We suppose that $\mu_{x,z}^{23}$ represents the rate of progression to metastatic BC in the absence of treatment, and β measures the effectiveness of treatment. So, our approach assumes that μ_x^* and β are fixed regardless of any pandemic scenario.

3. Calibration of the model

The overall aim is to estimate occupancy probabilities for each model state at future times. Calibrating the model involves estimating the age distribution in State 0 between 1 January 2020 and 31 December 2024, and the transition intensities in the model. The model is partly calibrated based on estimates of the population of women in England, in age groups 65–69, …, 85–89. These population estimates are the closest available data to represent exposure in State 0, which consists of women free of BC. However, we note that these population estimates do not distinguish between BC free and undiagnosed BC cases, and could therefore represent potentially higher exposure in State 0. We also use data information from published clinical studies and a set of cancer data collected by the ONS. We describe the various data sources in the following sections.

Table 1. Age-specific transition intensities for the semi-Markov model in Figure 1.

Age	μ_x^{01}	μ_x^{04}	μ_x^{35}
65–69	0.00333	0.00878	0.28060
70–74	0.00286	0.01521	0.36002
75–79	0.00324	0.02693	0.40000
80–84	0.00355	0.05142	0.49711
85–89	0.00377	0.09684	0.50000

Note: μ_x^{01} and μ_x^{04} are based on the ONS data, μ_x^{35} is based on a published study.
Source: See Section 3.1 and Zhou et al. (2020).

Table 2. Transition intensities and the corresponding modelling assumptions for the semi-Markov model in Figure 1.

Transition intensity	μ_x^{01}	μ_x^{02}	$\mu_{x,z}^{13}$	$\mu_{x,z}^{23}$	μ_x^{35}	μ_x^{04}	μ_x^{14}	μ_x^{24}	μ_x^{34}
Modelling assumption	$\alpha\mu_x^*$	$(1-\alpha)\mu_x^*$	$\beta\mu_{x,z}^{23}$	$\mu_{x,z}^{23}$	μ_x^{35}	μ_x^{04}	μ_x^{04}	μ_x^{04}	μ_x^{04}

Note: Refer to (2) regarding the relationship between μ_x^{01} and μ_x^{02}.

3.1. Available data: population incidence and mortality rates of breast cancer

We consider new cancer diagnoses/registrations and deaths data between 2001–2020 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 calendar year, and gender. Causes of death data have similar granularity, up to 2021. 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 2020 for cancer incidence and up to 2021 for mortality. Note that the first screening programme was introduced in 1988, targeting women aged 50–64. Later, the screening was extended to age 70 between 2002 and 2004, including the age groups 47–73 at which screening takes place since an announcement made in 2007 (Advisory Committee on Breast Cancer Screening, 2006; Duffy et al., 2010; NHS, 2021; Quinn & Allen, 1995). In Figure 2, five-year age groups are represented by their mid-points. Figure 2(a) shows BC incidence, which is calculated as new cancer registrations divided by mid-year population estimates. BC incidence generally shows an increasing trend over calendar time at all ages with higher incidence at older ages, up to 2019. There is a sharp decline in 2020, due to the national lockdowns introduced as a response to the COVID-19 pandemic, representing a decrease in BC incidence as low as 25% from age 65 onwards, compared to the same period in 2019. Figure 2(b) shows BC mortality, which is calculated as deaths from BC divided by mid-year population estimates, and points out a decreasing trend. In this study, our focus is on older age groups, with an emphasis on those aged 65 and above, as we are mainly interested in quantifying the immediate effects of early health disturbances on BC mortality. Figure 2(b) shows an overall increase in BC mortality in 2020, with a particular surge among women aged 65 and older, which has been as high as 7% compared to the same period in 2019. Mortality from other causes, not including BC as a cause, shows a more heterogeneous distribution across different ages with a decreasing trend, apart from the last two calendar years (Figure 2(c)).

3.2. Key transition intensities

This section outlines assumptions and sources used to calibrate the overall process. For obtaining the transition intensities in Figure 1, and in the absence of a large-scale study covering all necessary transitions, we determine the key transition intensities after a number of simplification in the modelling framework. The key transition intensities are determined based on available data and published studies, as shown in Table 1.

Table 2 summarises all transition intensities in Figure 1, along with the related modelling assumptions (see Section 2.3).

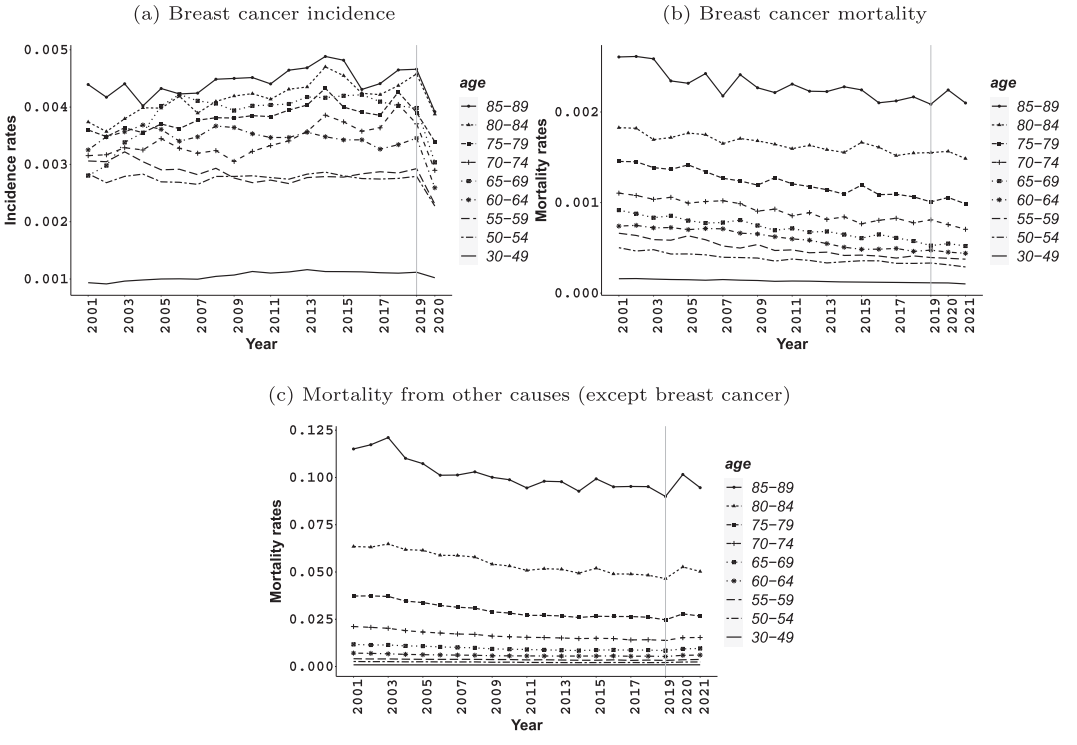

Figure 2. Breast cancer incidence, mortality, and all-cause mortality (excluding breast cancer). Note: The data is by five-year age groups between 2001–2017/2018 in England.

Survival probabilities from other causes for BC patients could vary depending on cancer stage, in comparison to the general population (Cho et al., 2013). However, in the absence of comprehensive data, as indicated in Table 2, 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}, i.e.:

$$\mu_x^{14} = \mu_x^{24} = \mu_x^{34} = \mu_x^{04}. \tag{3}$$

Note that we ignore any time trend in BC incidence and mortality rates, or in mortality rates from other causes, in the calculation period (1 January 2020 to 31 December 2024). Also, to the best of our knowledge, there is no available literature regarding the level of α and β, which are used to determine μ_x^{02} and $\mu_{x,z}^{23}$, respectively, in (2). Hereby, we carry out sensitivity analyses to measure the impact of parameters α and β on model findings. Specifically, we consider a range of values between 0.4 and 0.8 for α and between $\frac{1}{5}$ and $\frac{1}{10}$ for β. We also investigate the impact of different values of μ_x^{35}, that is 20% lower, or 20% higher, than the rates in Table 1 (Section 6).

3.2.1. Determining μ_x^{01}: clinical diagnosis of breast cancer

We do not have suitable empirical data on clinical diagnosis by age and stage. This is particularly important for determining transitions to State 1 and State 3. Available data include BC registrations by stage in England for year of diagnosis 2012–2015 (ONS, 2016a). However, it is not recommended to use this yearly information (ONS, 2016b), due to issues relating to the potential incomplete nature of the data. Therefore, we determine the transition intensities μ_x^{01}, based on 81% of overall cancer registrations, provided by the ONS, as suggested in ONS (2016b) (Table 1). For consistency with the μ_x^{35} intensities, which were obtained based on data between 2010–2015 (see Section 3.2.5), we also determine μ_x^{01} based on the same time period. The ONS mid-year population estimates for England,

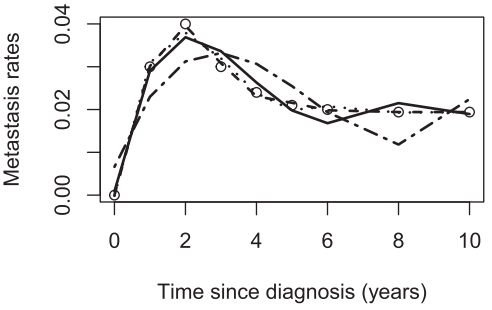

Figure 3. Rates of transition from State 1 to State 3.
Note: Circles are observed values and lines are fitted values from 3rd (two dash), 4th (solid), 6th (dotted), and 7th (dashed) degree polynomials.
Source: Figure 1 in Colzani et al. (2014).

Table 3. Rates of transition from State 1 to State 3 in different durations (years).

time	0	1	2	3	4	5	6	8	10
$\mu_{x,z}^{13}$	0	0.03	0.04	0.03	0.024	0.021	0.02	0.0194	0.0194

Note: The values are determined based on Figure 1 in Colzani et al. (2014).

during the same time period, are used to calculate the exposure in State 0. The resulting transition intensities μ_x^{01} are shown in Table 1, along with other key transition intensities.

We note that an alternative source for defining μ_x^{01} could be cancer registrations reported by Rutherford et al. (2013); Rutherford et al. (2015) (See Table 1 in Rutherford et al. (2013); Rutherford et al. (2015)). Although this data is more granular than the ONS data, stratified by both age and stage for women in the east of England between 2006–2010, the corresponding exposure is not available from the same source. Therefore, we have chosen to use the ONS data for our results.

3.2.2. Determining μ_x^{04}: other-cause mortality

Other causes of deaths and related mid-year population estimates are available between 2001 and 2018 in England (see Section 3.1). Hereby, the transition intensity from State 0 to State 4, μ_x^{04}, is determined using deaths from other causes from 2010 to 2015 in England, divided by the corresponding mid-year population estimates in the same years. The time period is chosen so that it is consistent with the time period of other transition intensities.

3.2.3. Determining μ_x^{13}: developing metastatic breast cancer

Colzani et al. (2014) estimate risk of developing 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).

We assume that the transition intensity from State 1 to State 3, $\mu_{x,z}^{13}$, follows a functional form, indicating a steep increase in the first two years with stable rates afterwards, based on Colzani et al. (2014). Figure 3 shows observed values, taken from Figure 1 in Colzani et al. (2014), and fitted values based on some polynomial functions.

Here, we define $\mu_{x,z}^{13}$ as a function of duration only, using a 4th degree polynomial, given as

$$\mu_{x,z}^{13} = 0.00088644 + 0.04191138z - 0.01574062z^2 + 0.00207282z^3 - 0.00008998z^4, \qquad (4)$$

for a given age x and $0 \leq z < 10$. This function is not suitable for extrapolation to durations $z > 10$. Parameters are estimated from the data in Table 3.

We also consider a special case of the semi-Markov model in Figure 1, i.e. a Markov model, assuming $\mu_x^{13} = 0.01954$. This is an estimate of first distant metastasis rates reported in Colzani et al. (2014),

Table 4. Proportionality constants applied to transition intensities in the pandemic scenarios.

	μ_x^{01}/μ_x^{02}	μ_x^{04}	
Pandemic period	α	65–84	85–89
April–Nov. 2020	0.8	1.13	1.12
Dec. 2020–Nov. 2021	1	1.13	1.12
Dec. 2021–Dec. 2022	1	1.10	1.09
Jan.–Dec. 2023	1	1.07	1.06
Jan.–Dec. 2024	1	1.04	1.03

Note: Proportionality constants are the same across all ages in both pandemic scenarios.

based on a population study involving 14,188 women diagnosed with first invasive BC from 1 January 1990 to 31 December 2006 (see Figure 3 and also Table 1 in Colzani et al. (2014)).

Note that rates of transition from State 2 to State 3, $\mu_{x,z}^{23}$, in the semi-Markov model are determined based on a polynomial function in the form of (4), following (2). In the case of the Markov model, rates of transition from State 2 to State 3, μ_x^{23}, are not duration dependent and are determined based on (2), where duration z is ignored, with $\mu_x^{13} = 0.01954$.

3.2.4. Determining β: measure of treatment effectiveness

State 2 is important in our model for being able to quantify the potential impact of a major disruption to health services on cancer mortality. However, there is no empirical data regarding unobserved BC. For modelling purposes we assume that rates of transition from States 1 and 2 to State 3 are related through parameter β, which represents a measure of treatment effectiveness, as shown in (2). There is no available data regarding how a BC tumour can grow in the absence 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 that can be used as a proxy for the tumour growth in the lack of treatment leading to a more advanced BC stage. 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 waiting times for surgery, where the median waiting 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 waiting 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 the transition intensity $\mu_{x,z}^{23}$ being considerably higher than $\mu_{x,z}^{13}$, in the absence of any treatment. We consider a range of values between $\frac{1}{5}$ and $\frac{1}{10}$ for β in the absence of empirical data and literature information.

3.2.5. Determining μ_x^{35}: 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 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. We define rates of transition to State 5, μ_x^{35}, based on the numbers shown in Table 1 in Zhao et al. (2020). Note that 'No early death' shows the number of patients that survived for 12 months, whilst 'Total early death' displays the number of patients deceased within

12 months in that study. Thus, we use a Uniform Distribution of Deaths assumption, to define the exposure under 'Total early death' (Hossain, 1994). Specifically, we assume that 'No Early Death' contributes a full year and each 'Early Death' half a year on average to the exposure. The resulting rates, μ_x^{35}, presented in Table 1, are assumed to remain unchanged during the calculation period from 1 January 2020 to 31 December 2024. Note that we add small increments to the rates at ages 75–79 and 85–89 where these are rounded to 0.4 and 0.5, respectively.

4. Pandemic scenarios

We consider two pandemic scenarios. Scenario 1 (S1) introduces a significant change in transitions to death from other causes, but does not involve any BC-related assumption. Thus, it reflects what would have been expected if the pandemic-related health disruptions had not affected BC diagnosis. In Scenario 2 (S2) we additionally assume a decline in cancer diagnoses.

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 the level of a given α in (2) based on Table 4. Since we assume that the onset of BC remains unchanged before and after the pandemic, see (1) and (2), we accordingly adjust the total transition intensity into State 2, μ_x^{02} (Assumption A4).

Table 4 summarises the assumptions made in relation to some of the key transition intensities in the pandemic scenarios. These assumptions are explained in Sections 4.1–4.2. Note that a one-day time step is employed to facilitate algorithms associated with the (modified) Kolmogorov equations (Appendix 1). Specifically, one year is considered as 360 days whereas one month is represented as 30 days.

4.1. Scenario 1: excess mortality due to COVID-19 in england

There is evidence suggesting that the COVID-19 pandemic has caused an increase in excess mortality, which can be linked to Scenario 1. 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 report ratios representing relative changes between registered and expected excess deaths for each group (OHID, 2022). We use a set of ratios, shown in Table 4, to define the potential increase in transition to death from other causes.

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 excess mortality 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. Scenario 2: changes in breast cancer risk amid COVID-19

There is no evidence suggesting that the COVID-19 pandemic increased 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 over the next five years.

However, cancer registrations are known to have reduced during national lockdowns (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 number of 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. This is achieved by reducing the level of α by 20% (see pandemic scenario S2 in Section 4). Following that, it is then assumed that they are restored back to pre-pandemic levels. The intensity μ_x^{02} is adjusted accordingly, keeping the overall BC onset rate unchanged (see (2) and Table 4).

5. Results

In this section we quantify the impact of initial health disruptions caused by the COVID-19 pandemic on BC mortality based on two pandemic scenarios, using the semi-Markov model developed in Figure 1 and also a simplified Markov modelling setting. We present the main findings based on different scenarios, associated with a pre-pandemic model calibration and pandemic scenarios S1 and S2. These findings are obtained for selected values of α and β, which are $\alpha = 0.6$ and $\beta = \frac{1}{7}$. Note that α is associated with the level of BC diagnosis whereas β is related to the availability of BC treatment (see (2) in Section 2.3). We further note the lack of suitable data for determining the values of these parameters. Therefore, we test for sensitivity of the results to changes in α and β in Section 6.

Table 5 compares age-specific occupancy probabilities, denoted by ${}_tp_x^{ij}$ from state i to state j at age x, based on the semi-Markov BC model, Figure 1, over one and 5 years from 1 January 2020. As a special case of the model in Figure 1, we also present results with a Markov model, which is determined by removing duration dependency in rates of transition from State 1 to State 3, $\mu_{x,z}^{13}$, and accordingly in $\mu_{x,z}^{23}$, as well. Therefore, in the Markov model, we determine constant values for μ_x^{13} and μ_x^{23} over both age and time (Section 3.2.3). This simplified model is more in line with relevant critical illness models in the insurance literature (CMI, 1991; Reynolds & Faye, 2016) can therefore facilitate further comparisons. In addition, contrasting to the semi-Markov model allows assessment of the impact on BC risk of the possibly more realistic assumption of duration dependence after a pre-metastatic BC diagnosis.

5.1. Observed and unobserved breast cancer cases: ${}_5p_x^{01}$, ${}_5p_x^{02}$, and ${}_5p_x^{03}$

Table 5 shows that for a woman free of BC at time zero, 1 January 2020, the probability of being diagnosed with pre-metastatic BC over the following 5 years, ${}_5p_x^{01}$, has decreased by 3–6%, across different ages, in Scenario 2, as compared to the pre-pandemic calibration. The results show bigger changes at older ages in Scenario 2, consistent in both models. The decline in ${}_5p_x^{01}$ has remained less than 3% in Scenario 1. At the same time, the probability of having BC and staying undiagnosed, ${}_5p_x^{02}$, increases by 1–3% over 5 years in Scenario 2 based on the Markov model. The increase is mostly higher at younger ages. The increase in the same probability, ${}_5p_x^{02}$, is less than 2% under the semi-Markov model.

Meanwhile, results under both models show that for a woman with no BC at time zero, the probability of being diagnosed with metastatic BC over the following 5 years, ${}_5p_x^{03}$, increases at certain ages, for instance, by 5% to 6% at ages 80–84 in Scenario 2, as compared to the pre-pandemic calibration. An increase in ${}_5p_x^{03}$, up to 4%, occurs at ages 65–69 and 70–74 based on the semi-Markov model.

In Scenario 1 the modelling mostly reveals a decline in ${}_5p_x^{02}$, up to 3%, as compared to the pre-pandemic levels based on both models, and no considerable changes in ${}_5p_x^{03}$, apart from the decrease in the youngest age in the Markov model. The decrease in ${}_5p_x^{02}$ and occasional decrease in ${}_5p_x^{03}$ in Scenario 1 can be 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}.

Table 5. Occupancy probabilities for women (%) being in different states over 5 years.

	Occupancy probabilities (%)														
	From State 0										From State 1				From State 3	
	${}_5p_x^{00}$	${}_5p_x^{01}$		${}_5p_x^{02}$		${}_5p_x^{03}$		${}_5p_x^{04}$	${}_5p_x^{05}$		${}_1p_x^{15}$		${}_5p_x^{15}$		${}_1p_x^{35}$	${}_5p_x^{35}$
Age	M	M	S-M	M	S-M	M	S-M	M	M	S-M	M	S-M	M	S-M	M	M
							Pre-pandemic calibration									
65–69	93.09	1.50	*1.47*	0.76	*0.68*	0.24	*0.31*	4.29	0.13	*0.16*	0.25	*0.16*	4.24	*5.98*	24.36	74.15
70–74	90.49	1.25	*1.22*	0.63	*0.57*	0.18	*0.23*	7.32	0.13	*0.16*	0.31	*0.20*	4.82	*6.82*	30.02	81.25
75–79	85.07	1.33	*1.31*	0.67	*0.61*	0.18	*0.24*	12.59	0.15	*0.19*	0.34	*0.22*	4.92	*6.97*	32.56	82.61
80–84	75.07	1.29	*1.26*	0.65	*0.59*	0.15	*0.20*	22.66	0.17	*0.21*	0.40	*0.26*	5.09	*7.21*	38.26	84.79
85–89	59.71	1.09	*1.07*	0.55	*0.50*	0.13	*0.17*	38.36	0.16	*0.19*	0.39	*0.25*	4.47	*6.29*	37.65	79.54
							Pandemic scenarios									
S1																
65–69	92.73	1.49	*1.46*	0.75	*0.68*	0.23	*0.31*	4.66	0.13	*0.16*	0.25	*0.16*	4.23	*5.96*	24.36	74.03
70–74	89.90	1.24	*1.22*	0.63	*0.56*	0.18	*0.23*	7.93	0.13	*0.16*	0.31	*0.20*	4.80	*6.79*	30.00	81.03
75–79	84.09	1.32	*1.29*	0.67	*0.60*	0.18	*0.23*	13.60	0.15	*0.19*	0.33	*0.22*	4.88	*6.91*	32.53	82.24
80–84	73.42	1.26	*1.24*	0.64	*0.57*	0.15	*0.20*	24.36	0.17	*0.21*	0.40	*0.26*	5.02	*7.10*	38.20	84.15
85–89	57.53	1.05	*1.03*	0.53	*0.48*	0.13	*0.17*	40.61	0.15	*0.19*	0.39	*0.25*	4.36	*6.12*	37.55	78.56
S2																
65–69	92.73	1.45	*1.42*	0.78	*0.70*	0.24	*0.32*	4.66	0.14	*0.17*	0.25	*0.16*	4.23	*5.96*	24.36	74.03
70–74	89.90	1.20	*1.18*	0.65	*0.58*	0.18	*0.24*	7.93	0.14	*0.17*	0.31	*0.20*	4.80	*6.79*	30.00	81.03
75–79	84.09	1.28	*1.25*	0.69	*0.62*	0.18	*0.24*	13.60	0.16	*0.20*	0.33	*0.22*	4.88	*6.91*	32.53	82.24
80–84	73.42	1.22	*1.20*	0.66	*0.59*	0.16	*0.21*	24.36	0.18	*0.22*	0.40	*0.26*	5.02	*7.10*	38.20	84.15
85–89	57.53	1.02	*1.00*	0.55	*0.49*	0.13	*0.17*	40.61	0.16	*0.20*	0.39	*0.25*	4.36	*6.12*	37.55	78.56

Notes: Women have no breast cancer or clinically diagnosed with breast cancer at time zero, 1 January 2020. Results are based on Markov (M) and semi-Markov (S-M) models in the pre-pandemic model calibration and the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$.

These findings are aligned with documented information that cancer patients have been more vulnerable to the SARS-CoV-2 coronavirus and affected worse by the pandemic, compared to the general population (Garassino et al., 2020; Lee et al., 2020; Pinato et al., 2020; Saini et al., 2020). It is also worth noting 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).

5.2. Breast cancer mortality: ${}_5p_x^{05}$, ${}_5p_x^{15}$, and ${}_5p_x^{35}$

For women with clinical cancer diagnosis, i.e. women in either State 1 or State 3 at time zero, 1 January 2020, we define cancer mortality as the probability of moving to State 5, for the period under consideration.

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 for women with metastatic BC, consistent in both models (Table 5). For instance, in the pre-pandemic calibration, one-year mortality for a woman aged 65–69 with metastatic BC is estimated as 24.36%, whereas at ages 80+ one-year mortality is around and above 37%. On the other hand, the variation in mortality, with respect to different ages, for women in State 1 is very small even after 5 years.

The results in Table 5 also show that mortality in 5 years after metastatic BC diagnosis is estimated to be between 74.15–84.79%, whereas the mortality for a woman with pre-metastatic BC diagnosis differs in the presence of duration dependence: (i) around 4–5% under the Markov model; and (ii) 6–7% under the semi-Markov model.

Meanwhile, 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 states, with BC Stages 1–3 being combined and included in States 1 and 2, due to 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 (Maringe et al., 2020; Rutherford et al., 2015).
- 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, while 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, including death from BC, for women with pre-metastatic or metastatic BC is also presented over periods of 5 years, where age dependence is clear (Tables A1 and A2).

There is a relative decline in the cancer mortality, less than 2%, across different ages in the pandemic scenarios in comparison to the pre-pandemic calibration under both models. This decline is as a result of increases in excess mortality (Section 4.1). However, across pandemic scenarios, our modelling shows no change in the cancer mortality for women with clinical diagnoses (Table 5). This is because our approach assumes that there is no change in the onset of BC before and after the pandemic, and the corresponding probabilities are conditional on BC diagnosis.

The models also allow us to obtain cancer survival rates. Cancer-specific survival, as used 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; ONS, 2019b; Swaminathan & Brenner, 2011). We refer to this as the 'ONS approach'. For a woman diagnosed with pre-metastatic BC at age x, for instance, cancer-specific

survival in t years can be obtained based on the ONS approach as follows:

$$\frac{1 - {}_tp_x^{14} - {}_tp_x^{15}}{1 - {}_tp_x^{14}}, \tag{5}$$

where ${}_tp_x^{14}$ represents mortality from other causes, while ${}_tp_x^{15}$ represents mortality from BC.

Table 6 compares 1-, 5-, and 10-year survival probabilities based on both Markov and semi-Markov models in the pre-pandemic calibration using (5) based on the ONS approach and an adjustment of our models. We adjust the models developed here by setting the transition intensities to 'Dead, Other Causes' after being diagnosed with BC or having BC without a clinical diagnosis, i.e. μ_x^{14}, μ_x^{24} and μ_x^{34}, equal to zero. This allows 'Dead, BC' to be the only cause of death.

Table 6 shows that cancer survival is worse at older ages. It suggests that cancer-specific survival probabilities based on the ONS methodology applied to our data are reasonably consistent with those based on the adjusted models. The main difference between the models has risen for women with pre-metastatic BC, with and without a clinical diagnosis, where lower estimates are obtained in the longer term based on the semi-Markov model. The estimates across ages change to a slightly higher degree in the longer term based on the ONS methodology as compared to the adjusted models.

We note that our findings for women with pre-metastatic and metastatic BC are broadly agreement with the ONS statistics, where 5- and 10-year age standardised survival rates (aged 15 to 99 years) for women diagnosed with BC between 2011-2015 were reported to be above 80% and 50%, respectively. Whilst very few excess deaths for women diagnosed with Stages 1–2 BC were observed, compared with general population, after the first year of diagnosis, one-year age standardised survival rate for women diagnosed with Stage 4 BC in 2015, followed up to 2016, was noted to be 65.8% (ONS, 2017). Furthermore, we found that cancer survival has worsened significantly in the absence of any treatment, in State 2, as compared to those where medical treatments were available in State 1. For instance, 10-year cancer survival of women with pre-metastatic BC at ages 65–69 would have declined from around 84–87% to 34–42%, with higher rates in the Markov model, if these women could have stayed undiagnosed and taken no medical care during the 10 years. This is aligned with the existing medical literature (Joseph et al., 2012; Verkooijen et al., 2005).

Cancer survival probabilities in the pandemic scenarios are not provided in Table 6. This is because survival is conditioned upon diagnosis of BC, which is the event disrupted by the pandemic.

5.3. Excess deaths

The estimated numbers of deaths over 5 years, by age, due to BC and other causes, can be determined by using ${}_5p_x^{05}$ and ${}_5p_x^{04}$, respectively. Estimates of excess deaths, in the corresponding period, are then calculated as the differences between estimated numbers of deaths in the pre-pandemic calibration and the pandemic scenarios (Table 7). We note that the time trend in mortality is ignored.

Our findings show that deaths from other causes increase by 5–8%, with higher changes at younger ages, corresponding to 363–2,255 excess deaths, per 100,000 women at different ages, in Scenarios 1–2, compared to the pre-pandemic calibration under both models. Our model also gives a 3–6% increase in deaths from BC across different ages in Scenario 2 based on both settings, with higher increases for younger ages. This corresponds to 5–8 excess BC deaths at different ages under the Markov model, and 6–10 excess deaths under the semi-Markov model.

5.4. Years of life lost

We calculate age-specific years of life lost (YLL) from BC and other causes at a given time t, denoted by $\mathrm{YLL}_{x,t}^{\mathrm{cause}}$, as

$$\mathrm{YLL}_{x,t}^{\mathrm{cause}} = D_{x,t}^{\mathrm{cause}} e_x, \tag{6}$$

Table 6. 1-, 5-, and 10-year survival probabilities (%) for women from breast cancer.

	Cancer Survival (%)														
	From State 1						From State 2						From State 3		
	1-year		5-year		10-year		1-year		5-year		10-year		1-year	5-year	10-year
Age	M	S-M	M	S-M	M	S-M	M	S-M	M	S-M	M	S-M	M	M	M
								ONS approach							
65–69	99.75	*99.84*	95.57	*93.76*	87.57	*84.44*	98.32	*98.90*	74.75	*67.52*	42.95	*34.87*	75.45	24.09	5.70
70–74	99.69	*99.79*	94.81	*92.65*	86.06	*82.65*	97.90	*98.61*	70.62	*62.15*	37.67	*29.50*	69.60	15.86	2.44
75–79	99.66	*99.77*	94.38	*92.06*	84.95	*81.32*	97.68	*98.47*	68.47	*59.45*	34.70	*26.66*	66.71	12.52	1.49
80–84	99.58	*99.72*	93.46	*90.75*	82.48	*78.35*	97.18	*98.13*	63.96	*53.89*	29.13	*21.58*	60.16	7.06	0.46
85–89	99.57	*99.72*	92.83	*89.97*	79.04	*74.17*	97.13	*98.10*	61.52	*51.41*	24.22	*17.45*	59.38	5.98	0.31
								Adjusted model							
65–69	99.75	*99.84*	95.64	*93.85*	87.95	*84.93*	98.33	*98.90*	75.08	*67.88*	43.94	*35.84*	75.53	24.59	6.04
70–74	99.69	*99.80*	94.95	*92.84*	86.81	*83.60*	97.91	*98.62*	71.26	*62.84*	39.40	*31.13*	69.77	16.53	2.73
75–79	99.66	*99.78*	94.66	*92.40*	86.38	*83.11*	97.70	*98.48*	69.66	*60.71*	37.75	*29.48*	67.03	13.53	1.83
80–84	99.59	*99.73*	94.06	*91.53*	85.59	*82.23*	97.23	*98.16*	66.46	*56.46*	34.87	*26.70*	60.83	8.33	0.69
85–89	99.59	*99.73*	94.05	*91.50*	85.57	*82.21*	97.22	*98.15*	66.38	*56.35*	34.80	*26.64*	60.65	8.21	0.67

Note: Results are for women with pre-metastatic and metastatic breast cancer, and for women with undiagnosed breast cancer based on Markov (M) and semi-Markov (S-M) models, using (5), in the pre-pandemic calibration for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$.

Table 7. Age-specific excess number of deaths and years of life expectancy lost (YLL), per 100,000 women.

	Excess deaths				YLL			
	Dead (Other)		Dead (BC)		Dead (Other)		Dead (BC)	
	State 4		State 5		State 4		State 5	
Age	M	S-M	M	S-M	M	S-M	M	S-M
S1								
65–69	363	*363*	0	0	7003	*7010*	−8	0
70–74	608	*607*	−1	−1	9301	*9293*	−11	−15
75–79	1012	*1012*	−1	−2	11767	*11770*	−16	−23
80–84	1700	*1700*	−3	−4	14350	*14348*	−25	−34
85–89	2255	*2255*	−5	−6	13167	*13169*	−27	−35
S2								
65–69	363	*363*	8	*10*	7000	*7010*	152	*193*
70–74	607	*607*	7	*9*	9298	*9293*	113	*138*
75–79	1011	*1012*	8	*10*	11762	*11770*	92	*116*
80–84	1699	*1699*	7	*9*	14342	*14340*	63	*76*
85–89	2253	*2253*	5	*6*	13158	*13158*	29	*35*

Note: Results are based on Markov (M) and semi-Markov (S-M) models in the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), as compared to the pre-pandemic calibration, for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$.

Table 8. Average life expectancies at various ages, denoted by e_x.

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

Note: The values are based on the 2018–2020 national standard life tables.
Source: See ONS (2021) for women.

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 is determined 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

$$\text{YLL}_t^{\text{cause}} = \sum_x D_{x,t}^{\text{cause}} e_x. \tag{7}$$

We refer to standard life tables as a source for the years 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 8 (ONS, 2021).

Table 7 shows that the semi-Markov model gives more years of life lost due to BC, as compared to the Markov model. This is a direct result of the former model estimating higher numbers of death due to BC. For deaths from other causes, we found 7,000–14,350 years of life lost across Scenarios 1 and 2 under the Markov model, with almost identical results under the semi-Markov model (Table 7).

6. Sensitivity analysis

In this section we assess the sensitivity of our main findings to the values of certain model parameters. Table 9 shows different parametrisation for pre-pandemic model calibration and pandemic scenarios.

6.1. Impact of parameter α

In the pre-pandemic calibration and the pandemic scenarios in Section 5, it was assumed that 60% of women developing BC, would actually be diagnosed with BC, in a given year, by choosing $\alpha = 0.6$ (Section 5). We now vary the value of α, while keeping all other model characteristics fixed in the pre-pandemic calibration and pandemic scenarios. Higher and lower diagnosis rates are represented by

Table 9. Parameter values applied in different sections.

Parametrisation in Section 5	$\alpha = 0.6, \beta = 1/7$
Parametrisation in Section 6	$\alpha = 0.4, \beta = 1/7$
	$\alpha = 0.8, \beta = 1/7$
	$\alpha = 0.6, \beta = 1/5$
	$\alpha = 0.6, \beta = 1/10$
	$\alpha = 0.6, \beta = 1/7$, 20% lower value for μ_x^{35}
	$\alpha = 0.6, \beta = 1/7$, 20% higher value for μ_x^{35}

assuming $\alpha = 0.8$ and $\alpha = 0.4$, respectively. Changing α mainly affects transitions to State 2 and State 3, along with smaller impacts on State 0 and State 5. For a woman free of BC, the probabilities of being in States 2–3 over 5 years have changed considerably as compared to the pre-pandemic calibration when $\alpha = 0.6$ (Table A1). Specifically, we observe an increase, mostly around 2 times higher, when $\alpha = 0.4$ and a decline, by 70% in ${}_5p_x^{02}$ and 50% in ${}_5p_x^{03}$, when $\alpha = 0.8$. Changes in State 0 and State 5 are more evident in the presence of lower diagnosis under both modelling settings.

Changes in excess deaths and YLL from other causes remain similar to those obtained for $\alpha = 0.6$ (Tables 7, A3 and A4). Considering excess deaths from BC, a lower pre-pandemic diagnosis rate of $\alpha = 0.4$ leads to an increase of about 2%, corresponding 7 or less deaths across different ages, as compared to the corresponding pre-pandemic calibration, in the Markov model, whereas the semi-Markov model suggests a slightly higher increase, about 3%, around and less than 10 deaths at the same ages. Meanwhile, a higher diagnosis rate of $\alpha = 0.8$ leads to a more dramatic increase in BC deaths, which is about 9–12%, corresponding 7–11 excess deaths, for the same ages under both models.

6.2. Impact of parameter β

In the pre-pandemic calibration and the pandemic scenarios in Section 5, we assumed β as low as $\frac{1}{7}$, assuming that the transition from State 2 to State 3, $\mu_{x,z}^{23}$, can be 7 times higher than the transition from State 1 to State 3, $\mu_{x,z}^{13}$. This is mainly motivated by the absence of treatment in State 2, along with the potential pace of BC tumour growth (Section 3.2.4). All else being equal, we vary the value of β by replacing it with $\frac{1}{5}$ and $\frac{1}{10}$. Note that there is no change in $\mu_{x,z}^{13}$, with $\mu_x^{13} = 0.01954$ in the Markov model, or determined by (4) in the semi-Markov model (Section 3.2.3). Similar to Section 6.1, the main impact of changes in β appears to be on State 2 and State 3, with higher changes occurring when $\beta = \frac{1}{10}$. A smaller value of β leads to more transitions into State 3, leaving a smaller number of women in State 2 in the relevant pre-pandemic model calibration (Table A1). The numbers in State 5 increase with a decreasing level of β over time, because of the higher numbers of women with advanced BC (Stage 4 BC) in State 3.

Tables A5 and A6 show comparable outcomes for excess deaths and YLL from other causes. Excess deaths, along with YLL, from BC differ slightly from those obtained when $\beta = \frac{1}{7}$. For a relatively higher value of β, $\frac{1}{5}$, BC deaths are around 2–5% higher across different ages, indicating 3–7 excess deaths, as compared to the corresponding pre-pandemic calibrations, in both modelling settings. For a smaller value of β, $\frac{1}{10}$, deaths are around 3–6% higher than the relevant pre-pandemic calibrations, corresponding to 7–14 excess deaths at different ages.

6.3. Impact of transitions to death from breast cancer μ_x^{35}

In the pre-pandemic calibration and the pandemic scenarios in Section 5, we assumed the transition to death from BC, μ_x^{35}, to follow the rates reported in Table 1. We now consider μ_x^{35} to be 20% lower, or 20% higher, than the rates in Table 1, where the pre-pandemic model calibrations in these cases are shown in Table A1. The main effect of a change in this particular transition intensity is on cancer mortality (State 5), and on State 3. For instance, an increase in the level of μ_x^{35} leads to a decrease

in the number of women in State 3 and an increase in State 5. A considerable increase in 5-year cancer mortality, ${}_5p_x^{15}$ and ${}_5p_x^{35}$, corresponding less than 11% and 8% increase across different ages, respectively, is also observed as a result of a higher level of μ_x^{35}. This leads to a higher level of overall mortality, as well. The changes in cancer mortality are more evident for women with advanced BC.

Similarly to Sections 6.1–6.2, varying rates of μ_x^{35} mainly results in changes in the number of excess BC deaths, while other outcomes, e.g. excess deaths from other causes, have remained comparable to the ones in Section 5. An increasing level of μ_x^{35} leads to higher number of excess BC deaths, 5–12 deaths across different ages, whereas a decreasing level of μ_x^{35} results in smaller number of BC deaths, 4–9 excess deaths at the same ages, with a similar effect on YLL from BC. However, the relative increase across ages, in comparison to the relevant pre-pandemic calibration, has remained the same, 3–6%, independent of the level of μ_x^{35}, under both models (Tables A7 and A8).

We also obtain cancer survival probabilities, up to 10 years, for different values of μ_x^{35}, provided in Appendix 7. Note that different values of α and β are not relevant to this calculation. Consistent with the findings in Tables 6, A9 and A10 point towards higher changes in cancer survival for women with pre-metastatic BC using different modelling settings, with these changes becoming more profound in time. Although an increasing level of μ_x^{35} results in lower cancer survival for women with metastatic BC, our model still suggests smaller differences between cancer survival at the oldest and youngest age groups in comparison to ONS methodology.

7. Discussion

During national lockdowns, essential BC diagnostic services were severely affected, along with cancer referral pathways. Health-seeking behaviour was 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.

In this paper we have developed a versatile modelling framework for measuring the impact of the COVID-19 related initial health disruptions on BC risk. Our approach is based on well-established and practised Markov multiple-state modelling methodology, and incorporates insightful calibration in the presence of limited relevant data. The semi-Markov model developed here allows for a generally realistic assumption of duration dependence in transition rates between certain cancer states, as also suggested in other literature. It also significantly enhances related models in insurance literature and practice, by accounting for states relevant to cancer progression, undiagnosed cases, and changes in diagnostic and treatment 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 substantial impact due to initial health disruptions, with a 3–6% increase in the number of deaths from BC at different ages, and a 5–8% increase in deaths from other causes, in comparison to the pre-pandemic calibration. For BC deaths in particular, this represents a material effect, considering that BC mortality has been decreasing steadily over recent years in many countries (CRUK, 2022; Verdecchia et al., 2007). Our results are also aligned with earlier literature (Maringe et al., 2020; Sud et al., 2020), pointing out the need for policy interventions to cope with additional cancer deaths caused by diagnoses delays. Nonetheless, further evaluation of cancer survival will be necessary as more data become available in the future. Also, our results showed considerable differences among certain occupancy probabilities, e.g. ${}_5p_x^{15}$, between the semi-Markov and Markov models, highlighting the significance of assuming duration dependence in the modelling.

7.1. Strengths and limitations

Low availability of suitable data was a major challenge in this study, limiting our ability to make data-driven inferences and to quantify uncertainty through appropriate statistical measures. A related key

issue was the incompleteness of BC stage information in population-based cancer data. Nevertheless, our models are based on a pragmatic combination of available data, literature information and modelling assumptions. The models have produced insightful findings, while the results are broadly consistent with existing literature. Our modelling approach has also provided estimates of excess deaths both from BC and from other causes. Furthermore, sensitivity testing has been carried out to take into account parameter uncertainty to a certain extent. As expected, model outputs are sensitive to the choice of key model parameters. Importantly, sensitivity to parameter α demonstrates the model's ability to capture the impact of health-service disruptions to BC mortality. Relative changes in cancer mortality and deaths from other causes have shown consistent results based on different parametrisations in various pre-pandemic model calibrations and pandemic scenarios.

Our approach provides a valuable model, relating to delays in the provision of BC diagnostic and treatment services, which can be more accurately calibrated as more data become available. Availability of more data can help expand the modelling setting by providing more information in relation to the progression of BC. Our model can also be used to represent different levels of BC service availability in non-pandemic times and therefore also provides a framework for comparing health service provision in different countries. It can allow further insights regarding the impact of a pandemic on different health services by changing the levels of α and β parameters.

There are important areas for further research. The modelling framework can be extended in a number of ways, including the following:

- employing a more detailed clinical model for BC, e.g. by involving locally advanced BC and/or considering treatment and recovery options, which would allow distinguishing between recurrence of non-metastatic BC and developing of metastatic BC;
- considering multi-morbidity as an underlying condition, allowing for the potential impact on excess deaths;
- introducing time trend for BC mortality and morbidity over years;
- formally measuring parameter and model uncertainty.

7.2. Implications of this research

Our study can inform decision makers by increasing awareness about the continuing impact of the COVID-19 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 under pandemic circumstances, but also given different levels of health service provision.

Our work can add value while considering insurance pricing and valuation assumptions related to ages of 65 years and over, which is also important for pension plans and healthcare at advanced age. Our model can be particularly relevant to critical illness and life insurance. For example, BC is one of the most common causes of critical illness claims among women, accounting for 44% of all claims in 2014 in the UK (Aviva, 2015; CMI, 2011). In addition, our approach provides a more detailed modelling framework, as compared to one currently used by the insurance industry (Reynolds & Faye, 2016), and can therefore provide better insights in relation to insurance cash flows. For instance, Arık et al. (2023) show that accounting for duration-dependent rates in BC progression can have an impact on actuarial net premiums, affecting short and long-term insurance products differently, while a semi-Markov model leads to intuitive results aligned with the medical literature. Furthermore, a detailed comparison between the semi-Markov model in Figure 1 and the industry-based model in Reynolds and Faye (2016) is provided in Arık et al. (2023).

Increases in population longevity, together with the relatively and increasingly long BC survival, mean that BC will continue to significantly affect older women (BCRF, 2021; Shachar et al., 2016).

In this article we have explored the short-term impact of COVID-19 related BC diagnostic delays on related mortality in an older population.

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Appendices

Appendix 1. Modified Kolmogorov equations with duration dependence for breast cancer model

Modified Kolmogorov equations for the 6-state BC model, in Figure 1, are given as below. Note that more details can be found in CMI (1991), based on a 3-state multiple model, allowing recovery from the disease under inspection along with duration dependence. Here, in order to make integrals clearer, we introduce actuarial selection notation. For instance, $\mu^{13}_{x,z}$ is shown based on select attained age $[x]$ with duration z, specifically $\mu^{13}_{x,z} = \mu^{13}_{[x]+z}$.

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{00}_x = -{}_tp^{00}_x\left(\mu^{01}_{x+t} + \mu^{02}_{x+t} + \mu^{04}_{x+t}\right) \tag{A1a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{01}_x = {}_tp^{00}_x\mu^{01}_{x+t} - {}_tp^{01}_x\mu^{14}_{x+t} - \int_{u=0}^{t} {}_up^{00}_x\mu^{01}_{x+u}{}_{t-u}p^{11}_{[x+u]}\mu^{13}_{[x+u]+t-u}\,\mathrm{d}u \tag{A1b}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{02}_x = {}_tp^{00}_x\mu^{02}_{x+t} - {}_tp^{02}_x\mu^{24}_{x+t} - \int_{u=0}^{t} {}_up^{00}_x\mu^{02}_{x+u}{}_{t-u}p^{22}_{[x+u]}\mu^{23}_{[x+u]+t-u}\,\mathrm{d}u \tag{A1c}$$

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{03}_x &= \int_{u=0}^{t} {}_up^{00}_x\mu^{01}_{x+u}{}_{t-u}p^{11}_{[x+u]}\mu^{13}_{[x+u]+t-u}\,\mathrm{d}u \\ &\quad + \int_{u=0}^{t} {}_up^{00}_x\mu^{02}_{x+u}{}_{t-u}p^{22}_{[x+u]}\mu^{23}_{[x+u]+t-u}\,\mathrm{d}u - {}_tp^{03}_x\left(\mu^{34}_{x+t} + \mu^{35}_{x+t}\right)\end{aligned} \tag{A1d}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{04}_x = {}_tp^{00}_x\mu^{04}_{x+t} + {}_tp^{01}_x\mu^{14}_{x+t} + {}_tp^{02}_x\mu^{24}_{x+t} + {}_tp^{03}_x\mu^{34}_{x+t} \tag{A1e}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{05}_x = {}_tp^{03}_x\mu^{35}_{x+t} \tag{A1f}$$

We note that the select notation on age $[x]$ is kept in the equations below, where this is based on the assumption of being in the relevant initial state.

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{11}_{[x]} = -{}_tp^{11}_{[x]}\left(\mu^{13}_{[x]+t} + \mu^{14}_{[x]+t}\right) \tag{A2a}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{13}_{[x]} = {}_tp^{11}_{[x]}\mu^{13}_{[x]+t} - {}_tp^{13}_{[x]}\mu^{34}_{[x]+t} - {}_tp^{13}_{[x]}\mu^{35}_{[x]+t} \tag{A2b}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{14}_{[x]} = {}_tp^{11}_{[x]}\mu^{14}_{[x]+t} + {}_tp^{13}_{[x]}\mu^{34}_{[x]+t} \tag{A2c}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{15}_{[x]} = {}_tp^{13}_{[x]}\mu^{35}_{[x]+t} \tag{A2d}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{22}_{[x]} = -{}_tp^{22}_{[x]}\left(\mu^{23}_{[x]+t} + \mu^{24}_{[x]+t}\right) \tag{A2e}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{23}_{[x]} = {}_tp^{22}_{[x]}\mu^{23}_{[x]+t} - {}_tp^{23}_{[x]}\left(\mu^{34}_{[x]+t} + \mu^{35}_{[x]+t}\right) \tag{A2f}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{24}_{[x]} = {}_tp^{22}_{[x]}\mu^{24}_{[x]+t} + {}_tp^{23}_{[x]}\mu^{34}_{[x]+t} \tag{A2g}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{25}_{[x]} = {}_tp^{23}_{[x]}\mu^{35}_{[x]+t} \tag{A2h}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{33}_{[x]} = -{}_tp^{33}_{[x]}\left(\mu^{34}_{[x]+t} + \mu^{35}_{[x]+t}\right) \tag{A2i}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{34}_{[x]} = {}_tp^{33}_{[x]}\mu^{34}_{[x]+t} \tag{A2j}$$

$$\frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{35}_{[x]} = {}_tp^{33}_{[x]}\mu^{35}_{[x]+t}. \tag{A2k}$$

Appendix 2. Runge-Kutta method for breast cancer model in Figure 1

Runge-Kutta methods 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 ${}_hp^{ij}_x \equiv y_t$ as

$$y_t = \begin{bmatrix} {}_tp^{00}_x \\ {}_tp^{01}_x \\ {}_tp^{02}_x \\ \vdots \\ {}_tp^{55}_x \end{bmatrix}, \quad \frac{\mathrm{d}}{\mathrm{d}t}y_t = \begin{bmatrix} \frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{00}_x \\ \frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{01}_x \\ \frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{02}_x \\ \vdots \\ \frac{\mathrm{d}}{\mathrm{d}t}{}_tp^{55}_x \end{bmatrix} = f(t, y_t).$$

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

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

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

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

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

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

Appendix 3. Occupancy probabilities over 5 years in pre-pandemic model calibration

Table A1. 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, 1 January 2020, based on Markov (M) and semi-Markov (S-M) models in the pre-pandemic model calibration using different choices of α, β parameters and μ^{35}.

	From State 0										From State 1				From State 3		From State 1				From State 3	
	${}_5p_x^{00}$	${}_5p_x^{01}$		${}_5p_x^{02}$		${}_5p_x^{03}$		${}_5p_x^{04}$	${}_5p_x^{05}$		${}_1p_x^{15}$		${}_5p_x^{15}$		${}_1p_x^{35}$	${}_5p_x^{35}$	${}_1p_x^{14}+{}_1p_x^{15}$		${}_5p_x^{14}+{}_5p_x^{15}$		${}_tp_x^{34}+{}_tp_x^{35}$	
Age	M	M	S-M	M	S-M	M	S-M	M	M	S-M	M	S-M	M	S-M	M	M	M	S-M	M	S-M	M, $t=1$	M, $t=5$
											$\alpha=0.6;\ \mu^{13}=\frac{1}{7}\mu^{23}$											
65–69	93.09	1.50	*1.47*	0.76	*0.68*	0.24	*0.31*	4.29	0.13	*0.16*	0.25	*0.16*	4.24	*5.98*	24.36	74.15	1.12	*1.03*	8.47	*10.18*	25.12	76.47
70–74	90.49	1.25	*1.22*	0.63	*0.57*	0.18	*0.23*	7.32	0.13	*0.16*	0.31	*0.20*	4.82	*6.82*	30.02	81.25	1.82	*1.71*	12.00	*13.96*	31.29	84.68
75–79	85.07	1.33	*1.31*	0.67	*0.61*	0.18	*0.24*	12.59	0.15	*0.19*	0.34	*0.22*	4.92	*6.97*	32.56	82.61	2.99	*2.88*	17.27	*19.24*	34.75	88.17
80–84	75.07	1.29	*1.26*	0.65	*0.59*	0.15	*0.20*	22.66	0.17	*0.21*	0.40	*0.26*	5.09	*7.21*	38.26	84.79	5.40	*5.27*	27.26	*29.22*	42.22	93.56
85–89	59.71	1.09	*1.07*	0.55	*0.50*	0.13	*0.17*	38.36	0.16	*0.19*	0.39	*0.25*	4.47	*6.29*	37.65	79.54	9.61	*9.47*	42.05	*43.62*	44.94	94.94
											$\alpha=0.8;\ \mu^{13}=\frac{1}{7}\mu^{23}$											
65–69	93.73	1.50	*1.47*	0.29	*0.26*	0.12	*0.16*	4.29	0.07	*0.08*	0.25	*0.16*	4.24	*5.98*	24.36	74.15	1.12	*1.03*	8.47	*10.18*	25.12	76.47
70–74	91.04	1.25	*1.23*	0.24	*0.21*	0.09	*0.12*	7.32	0.06	*0.08*	0.31	*0.20*	4.82	*6.82*	30.02	81.25	1.82	*1.71*	12.00	*13.96*	31.29	84.68
75–79	85.65	1.34	*1.31*	0.25	*0.23*	0.09	*0.12*	12.60	0.08	*0.09*	0.34	*0.22*	4.92	*6.97*	32.56	82.61	2.99	*2.88*	17.27	*19.24*	34.75	88.17
80–84	75.63	1.29	*1.27*	0.25	*0.22*	0.08	*0.11*	22.66	0.09	*0.11*	0.40	*0.26*	5.09	*7.21*	38.26	84.79	5.40	*5.27*	27.26	*29.22*	42.22	93.56
85–89	60.18	1.09	*1.07*	0.21	*0.19*	0.07	*0.09*	38.37	0.08	*0.10*	0.39	*0.25*	4.47	*6.29*	37.65	79.54	9.61	*9.47*	42.05	*43.62*	44.94	94.94
											$\alpha=0.4;\ \mu^{13}=\frac{1}{7}\mu^{23}$											
65–69	91.80	1.49	*1.46*	1.69	*1.52*	0.47	*0.61*	4.29	0.26	*0.32*	0.25	*0.16*	4.24	*5.98*	24.36	74.15	1.12	*1.03*	8.47	*10.18*	25.12	76.47
70–74	89.42	1.24	*1.22*	1.41	*1.27*	0.35	*0.46*	7.32	0.26	*0.32*	0.31	*0.20*	4.82	*6.82*	30.02	81.25	1.82	*1.71*	12.00	*13.96*	31.29	84.68
75–79	83.93	1.32	*1.30*	1.50	*1.35*	0.35	*0.46*	12.59	0.30	*0.37*	0.34	*0.22*	4.92	*6.97*	32.56	82.61	2.99	*2.88*	17.27	*19.24*	34.75	88.17
80–84	73.97	1.28	*1.25*	1.46	*1.31*	0.30	*0.40*	22.65	0.34	*0.42*	0.40	*0.26*	5.09	*7.21*	38.26	84.79	5.40	*5.27*	27.26	*29.22*	42.22	93.56
85–89	58.78	1.08	*1.06*	1.23	*1.10*	0.26	*0.34*	38.34	0.31	*0.38*	0.39	*0.25*	4.47	*6.29*	37.65	79.54	9.61	*9.47*	42.05	*43.62*	44.94	94.94
											$\alpha=0.6;\ \mu^{13}=\frac{1}{5}\mu^{23}$											
65–69	93.09	1.50	*1.47*	0.83	*0.76*	0.19	*0.26*	4.29	0.10	*0.13*	0.25	*0.16*	4.24	*5.98*	24.36	74.15	1.12	*1.03*	8.47	*10.18*	25.12	76.47
70–74	90.49	1.25	*1.22*	0.69	*0.64*	0.14	*0.19*	7.32	0.10	*0.13*	0.31	*0.20*	4.82	*6.82*	30.02	81.25	1.82	*1.71*	12.00	*13.96*	31.29	84.68
75–79	85.07	1.33	*1.31*	0.74	*0.68*	0.15	*0.20*	12.59	0.12	*0.15*	0.34	*0.22*	4.92	*6.97*	32.56	82.61	2.99	*2.88*	17.27	*19.24*	34.75	88.17
80–84	75.07	1.29	*1.26*	0.71	*0.66*	0.13	*0.17*	22.66	0.14	*0.17*	0.40	*0.26*	5.09	*7.21*	38.26	84.79	5.40	*5.27*	27.26	*29.22*	42.22	93.56
85–89	59.71	1.09	*1.07*	0.60	*0.55*	0.11	*0.14*	38.36	0.12	*0.16*	0.39	*0.25*	4.47	*6.29*	37.65	79.54	9.61	*9.47*	42.05	*43.62*	44.94	94.94

Table A1. Continued.

	From State 0										From State 1				From State 3		From State 1				From State 3	
	${}_5p_x^{00}$	${}_5p_x^{01}$		${}_5p_x^{02}$		${}_5p_x^{03}$		${}_5p_x^{04}$	${}_5p_x^{05}$		${}_1p_x^{15}$		${}_5p_x^{15}$		${}_1p_x^{35}$	${}_5p_x^{35}$	${}_1p_x^{14} + {}_1p_x^{15}$		${}_5p_x^{14} + {}_5p_x^{15}$		${}_tp_x^{34} + {}_tp_x^{35}$	
Age	M	M	S-M	M	S-M	M	S-M	M	M	S-M	M	S-M	M	S-M	M	M	M	S-M	M	S-M	M, $t=1$	M, $t=5$
$\alpha = 0.6$; $\mu^{13} = \frac{1}{10}\mu^{23}$																						
65–69	93.09	1.50	*1.47*	0.67	*0.58*	0.29	*0.37*	4.29	0.17	*0.20*	0.25	*0.16*	4.24	*5.98*	24.36	74.15	1.12	*1.03*	8.47	*10.18*	25.12	76.47
70–74	90.49	1.25	*1.22*	0.56	*0.49*	0.22	*0.28*	7.32	0.16	*0.20*	0.31	*0.20*	4.82	*6.82*	30.02	81.25	1.82	*1.71*	12.00	*13.96*	31.29	84.68
75–79	85.07	1.33	*1.31*	0.59	*0.52*	0.22	*0.28*	12.59	0.19	*0.23*	0.34	*0.22*	4.92	*6.97*	32.56	82.61	2.99	*2.88*	17.27	*19.24*	34.75	88.17
80–84	75.07	1.29	*1.26*	0.57	*0.50*	0.19	*0.24*	22.66	0.22	*0.26*	0.40	*0.26*	5.09	*7.21*	38.26	84.79	5.40	*5.27*	27.26	*29.22*	42.22	93.56
85–89	59.71	1.09	*1.07*	0.49	*0.42*	0.16	*0.21*	38.35	0.20	*0.24*	0.39	*0.25*	4.47	*6.29*	37.65	79.54	9.61	*9.47*	42.05	*43.62*	44.94	94.94
$\alpha = 0.6$; $\mu^{13} = \frac{1}{7}\mu^{23}$; μ^{35} is 20% lower than the baseline level																						
65–69	93.09	1.50	*1.47*	0.76	*0.68*	0.26	*0.33*	4.29	0.11	*0.14*	0.20	*0.13*	3.66	*5.14*	20.02	66.26	1.07	*1.00*	7.90	*9.36*	20.80	68.85
70–74	90.49	1.25	*1.22*	0.63	*0.57*	0.19	*0.26*	7.32	0.11	*0.14*	0.25	*0.16*	4.23	*5.96*	24.84	74.13	1.76	*1.67*	11.43	*13.13*	26.15	78.04
75–79	85.07	1.33	*1.31*	0.67	*0.61*	0.20	*0.26*	12.59	0.13	*0.16*	0.28	*0.18*	4.34	*6.12*	27.04	75.96	2.93	*2.84*	16.72	*18.43*	29.32	82.35
80–84	75.07	1.29	*1.26*	0.65	*0.59*	0.17	*0.23*	22.66	0.15	*0.19*	0.33	*0.21*	4.56	*6.43*	32.04	79.18	5.34	*5.22*	26.79	*28.53*	36.18	89.42
85–89	59.71	1.09	*1.07*	0.55	*0.50*	0.15	*0.19*	38.36	0.14	*0.17*	0.32	*0.21*	4.00	*5.60*	31.52	73.80	9.54	*9.43*	41.68	*43.06*	39.15	91.67
$\alpha = 0.6$; $\mu^{13} = \frac{1}{7}\mu^{23}$; μ^{35} is 20% higher than the baseline level																						
65–69	93.09	1.50	*1.47*	0.76	*0.68*	0.22	*0.29*	4.29	0.15	*0.18*	0.29	*0.19*	4.73	*6.70*	28.47	80.14	1.16	*1.06*	8.95	*10.89*	29.21	82.23
70–74	90.49	1.25	*1.22*	0.63	*0.57*	0.16	*0.21*	7.32	0.15	*0.18*	0.36	*0.24*	5.31	*7.53*	34.83	86.28	1.87	*1.75*	12.48	*14.65*	36.06	89.32
75–79	85.07	1.33	*1.31*	0.67	*0.61*	0.16	*0.22*	12.59	0.17	*0.21*	0.39	*0.26*	5.39	*7.65*	37.65	87.18	3.04	*2.92*	17.71	*19.88*	39.76	92.07
80–84	75.07	1.29	*1.26*	0.65	*0.59*	0.14	*0.18*	22.66	0.19	*0.24*	0.46	*0.31*	5.51	*7.82*	43.90	88.46	5.46	*5.32*	27.63	*29.76*	47.68	96.08
85–89	59.71	1.09	*1.07*	0.55	*0.50*	0.12	*0.15*	38.36	0.17	*0.21*	0.45	*0.30*	4.85	*6.83*	43.21	83.46	9.66	*9.52*	42.34	*44.04*	50.18	96.93

Table A2. Occupancy probabilities (%) for women being in different states at the end of 1 year given that they have no breast cancer or clinically diagnosed with breast cancer at time zero, 1 January 2020, based on Markov (M) and semi-Markov (S-M) models when $\alpha = 0.6$; $\mu^{13} = \frac{1}{7}\mu^{23}$.

	From State 0										From State 1				From State 3		From State 1				From State 3	
	${}_1p_x^{00}$	${}_1p_x^{01}$		${}_1p_x^{02}$		${}_1p_x^{03}$		${}_1p_x^{04}$	${}_1p_x^{05}$		${}_1p_x^{15}$		${}_5p_x^{15}$		${}_1p_x^{35}$	${}_5p_x^{35}$	${}_1p_x^{14} + {}_1p_x^{15}$		${}_5p_x^{14} + {}_5p_x^{15}$		${}_tp_x^{34} + {}_tp_x^{35}$	
Age	M	M	S-M	M	S-M	M	S-M	M	M	S-M	M	S-M	M	S-M	M	M	M	S-M	M	S-M	M, $t = 1$	M, $t = 5$
Pre-pandemic calibration																						
65–69	98.58	0.33	*0.33*	0.21	*0.21*	0.02	*0.01*	0.87	0	*0*	0.25	*0.16*	4.24	*5.98*	24.36	74.15	1.12	*1.03*	8.47	*10.18*	25.12	76.47
70–74	98.02	0.28	*0.28*	0.18	*0.18*	0.01	*0.01*	1.51	0	*0*	0.31	*0.20*	4.82	*6.82*	30.02	81.25	1.82	*1.71*	12.00	*13.96*	31.29	84.68
75–79	96.82	0.31	*0.31*	0.20	*0.20*	0.01	*0.01*	2.66	0	*0*	0.34	*0.22*	4.92	*6.97*	32.56	82.61	2.99	*2.88*	17.27	*19.24*	34.75	88.17
80–84	94.43	0.33	*0.33*	0.21	*0.21*	0.02	*0.01*	5.01	0	*0*	0.40	*0.26*	5.09	*7.21*	38.26	84.79	5.40	*5.27*	27.26	*29.22*	42.22	93.56
85–89	90.20	0.34	*0.34*	0.21	*0.22*	0.02	*0.01*	9.23	0	*0*	0.39	*0.25*	4.47	*6.29*	37.65	79.54	9.61	*9.47*	42.05	*43.62*	44.94	94.94
Pandemic scenarios																						
S1																						
65–69	98.49	0.33	*0.33*	0.20	*0.21*	0.02	*0.01*	0.96	0	*0*	0.25	*0.16*	4.23	*5.96*	24.36	74.03	1.21	*1.12*	8.81	*10.52*	25.19	76.56
70–74	97.88	0.28	*0.28*	0.17	*0.18*	0.01	*0.01*	1.66	0	*0*	0.31	*0.20*	4.80	*6.79*	30.00	81.03	1.96	*1.85*	12.58	*14.53*	31.39	84.78
75–79	96.56	0.31	*0.31*	0.20	*0.20*	0.01	*0.01*	2.91	0	*0*	0.33	*0.22*	4.88	*6.91*	32.53	82.24	3.24	*3.13*	18.22	*20.17*	34.92	88.31
80–84	93.96	0.33	*0.33*	0.21	*0.21*	0.02	*0.01*	5.49	0	*0*	0.40	*0.26*	5.02	*7.10*	38.20	84.15	5.88	*5.74*	28.87	*30.78*	42.51	93.70
85–89	89.42	0.33	*0.34*	0.21	*0.22*	0.02	*0.01*	10.02	0	*0*	0.39	*0.25*	4.36	*6.12*	37.55	78.56	10.39	*10.26*	44.17	*45.68*	45.43	95.12
S2																						
65–69	98.49	0.28	*0.28*	0.25	*0.26*	0.02	*0.01*	0.96	0	*0*	0.25	*0.16*	4.23	*5.96*	24.36	74.03	1.21	*1.12*	8.81	*10.52*	25.19	76.56
70–74	97.88	0.24	*0.24*	0.21	*0.22*	0.01	*0.01*	1.66	0	*0*	0.31	*0.20*	4.80	*6.79*	30.00	81.03	1.96	*1.85*	12.58	*14.53*	31.39	84.78
75–79	96.56	0.26	*0.26*	0.24	*0.25*	0.02	*0.01*	2.91	0	*0*	0.33	*0.22*	4.88	*6.91*	32.53	82.24	3.24	*3.13*	18.22	*20.17*	34.92	88.31
80–84	93.96	0.28	*0.28*	0.26	*0.26*	0.02	*0.01*	5.49	0	*0*	0.40	*0.26*	5.02	*7.10*	38.20	84.15	5.88	*5.74*	28.87	*30.78*	42.51	93.70
85–89	89.42	0.28	*0.29*	0.26	*0.27*	0.02	*0.01*	10.02	0	*0*	0.39	*0.25*	4.36	*6.12*	37.55	78.56	10.39	*10.26*	44.17	*45.68*	45.43	95.12

Appendix 4. Excess deaths and years of life expectancy lost at different age groups in Section 6.1

Table A3. Age-specific excess number of deaths and years of life expectancy lost (YLL), per 100,000 women, based on Markov (M) and semi-Markov (S-M) models in the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), as compared to the pre-pandemic calibration, for $\alpha = 0.8$, $\mu^{13} = \frac{1}{7}\mu^{23}$.

	Excess deaths				YLL			
	Dead (Other)		Dead (BC)		Dead (Other)		Dead (BC)	
	State 4		State 5		State 4		State 5	
Age	M	S-M	M	S-M	M	S-M	M	S-M
S1								
65–69	363	*363*	0	*0*	7004	*7010*	*−4*	*0*
70–74	608	*608*	0	*−1*	9302	*9308*	*−5*	*−15*
75–79	1012	*1012*	*−1*	*− 1*	11769	*11770*	*−8*	*−12*
80–84	1701	*1700*	*−2*	*−2*	14352	*14348*	*−13*	*−17*
85–89	2255	*2255*	*−2*	*−3*	13168	*13169*	*−13*	*−18*
S2								
65–69	363	*363*	8	*10*	7001	*7010*	155	*193*
70–74	607	*608*	8	*10*	9299	*9308*	118	*153*
75–79	1011	*1011*	9	*11*	11764	*11758*	100	*128*
80–84	1700	*1699*	9	*11*	14344	*14340*	76	*93*
85–89	2253	*2253*	7	*9*	13159	*13158*	43	*53*

Table A4. Age-specific excess number of deaths and years of life expectancy lost (YLL), per 100,000 women, based on Markov (M) and semi-Markov (S-M) models in the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), as compared to the pre-pandemic calibration, for $\alpha = 0.4$, $\mu^{13} = \frac{1}{7}\mu^{23}$.

	Excess deaths				YLL			
	Dead (Other)		Dead (BC)		Dead (Other)		Dead (BC)	
	State 4		State 5		State 4		State 5	
Age	M	S-M	M	S-M	M	S-M	M	S-M
S1								
65–69	363	*363*	*−1*	*−1*	7001	*7010*	*−15*	*−19*
70–74	607	*607*	*−1*	*−2*	9299	*9293*	*−21*	*−31*
75–79	1012	*1011*	*−3*	*−3*	11764	*11758*	*−33*	*−35*
80–84	1700	*1699*	*−6*	*−8*	14346	*14340*	*−51*	*−68*
85–89	2254	*2255*	*−9*	*−11*	13165	*13169*	*−53*	*−64*
S2								
65–69	362	*363*	7	*10*	6999	*7010*	143	*193*
70–74	607	*607*	7	*8*	9295	*9293*	102	*122*
75–79	1011	*1011*	6	*8*	11759	*11758*	75	*93*
80–84	1699	*1698*	4	*6*	14337	*14331*	38	*51*
85–89	2253	*2253*	0	*1*	13155	*13158*	3	*6*

Appendix 5. Excess deaths and years of life expectancy lost at different age groups in Section 6.2

Table A5. Age-specific excess number of deaths and years of life expectancy lost (YLL), per 100,000 women, based on Markov (M) and semi-Markov (S-M) models in the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), as compared to the pre-pandemic calibration, for $\alpha = 0.6$, $\mu^{13} = \frac{1}{5}\mu^{23}$.

	Excess deaths				YLL			
	Dead (Other)		Dead (BC)		Dead (Other)		Dead (BC)	
	State 4		State 5		State 4		State 5	
Age	M	S-M	M	S-M	M	S-M	M	S-M
S1								
65–69	363	*362*	0	*−1*	7003	*6990*	*−6*	*−19*
70–74	608	*608*	*−1*	*0*	9301	*9308*	*−8*	*0*
75–79	1012	*1011*	*−1*	*−2*	11768	*11758*	*−13*	*−23*
80–84	1700	*1701*	*−2*	*−3*	14351	*14356*	*−20*	*−25*
85–89	2255	*2255*	*−4*	*−5*	13168	*13169*	*−21*	*−29*
S2								
65–69	363	*362*	6	*7*	7001	*6990*	106	*135*
70–74	607	*608*	5	*7*	9299	*9308*	79	*107*
75–79	1012	*1011*	5	*7*	11764	*11758*	63	*81*
80–84	1700	*1700*	5	*7*	14345	*14348*	42	*59*
85–89	2254	*2253*	3	*4*	13161	*13158*	18	*23*

Table A6. Age-specific excess number of deaths and years of life expectancy lost (YLL), per 100,000 women, based on Markov (M) and semi-Markov (S-M) models in the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), as compared to the pre-pandemic calibration, for $\alpha = 0.6$, $\mu^{13} = \frac{1}{10}\mu^{23}$.

	Excess deaths				YLL			
	Dead (Other)		Dead (BC)		Dead (Other)		Dead (BC)	
	State 4		State 5		State 4		State 5	
Age	M	S-M	M	S-M	M	S-M	M	S-M
S1								
65–69	363	*362*	*−1*	*−1*	7002	*6990*	*−10*	*−19*
70–74	607	*608*	*−1*	*−1*	9300	*9308*	*−13*	*−15*
75–79	1012	*1011*	*−2*	*−2*	11766	*11758*	*−21*	*−23*
80–84	1700	*1700*	*−4*	*−5*	14349	*14348*	*−32*	*−42*
85–89	2255	*2255*	*− 6*	*−7*	13167	*13169*	*−34*	*−41*
S2								
65–69	362	*362*	11	*13*	6999	*6990*	210	*251*
70–74	607	*607*	10	*13*	9295	*9293*	157	*199*
75–79	1011	*1011*	11	*14*	11759	*11758*	128	*163*
80–84	1699	*1698*	11	*13*	14337	*14331*	90	*110*
85–89	2252	*2252*	7	*9*	13153	*13152*	43	*53*

Appendix 6. Excess deaths and years of life expectancy lost at different age groups in Section 6.3

Table A7. Age-specific excess number of deaths and years of life expectancy lost (YLL), per 100,000 women, based on Markov (M) and semi-Markov (S-M) models in the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), as compared to the pre-pandemic calibration, for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$, $\mu^{35} = 0.8\mu^{35}$.

	Excess deaths				YLL			
	Dead (Other)		Dead (BC)		Dead (Other)		Dead (BC)	
	State 4		State 5		State 4		State 5	
Age	M	S-M	M	S-M	M	S-M	M	S-M
S1								
65–69	363	*362*	0	*−1*	7003	*6990*	*−7*	*−19*
70–74	608	*608*	*−1*	*−1*	9301	*9308*	*−9*	*−15*
75–79	1012	*1012*	*−1*	*−1*	11768	*11770*	*−14*	*−12*
80–84	1700	*1700*	*−3*	*−3*	14351	*14348*	*−22*	*−25*
85–89	2255	*2255*	*−4*	*−5*	13168	*13169*	*−24*	*−29*
S2								
65–69	363	*362*	7	*8*	7001	*6990*	130	*154*
70–74	607	*608*	6	*8*	9298	*9308*	99	*122*
75–79	1011	*1012*	7	*9*	11763	*11770*	81	*105*
80–84	1699	*1699*	7	*9*	14343	*14340*	56	*76*
85–89	2253	*2254*	4	*6*	13159	*13163*	26	*35*

Table A8. Age-specific excess number of deaths and years of life expectancy lost (YLL), per 100,000 women, based on Markov (M) and semi-Markov (S-M) models in the pandemic scenarios, Scenario 1 (S1) and Scenario 2 (S2), as compared to the pre-pandemic calibration, for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$, $\mu^{35} = 1.2\mu^{35}$.

	Excess deaths				YLL			
	Dead (Other)		Dead (BC)		Dead (Other)		Dead (BC)	
	State 4		State 5		State 4		State 5	
Age	M	S-M	M	S-M	M	S-M	M	S-M
S1								
65–69	363	*363*	0	*0*	7003	*7010*	−9	*0*
70–74	608	*608*	*−1*	*−1*	9301	*9308*	*−12*	*−15*
75–79	1012	*1012*	*−2*	*−2*	11767	*11770*	*−18*	*−23*
80–84	1700	*1700*	*−3*	*−4*	14350	*14348*	*−28*	*−34*
85–89	2255	*2255*	*−5*	*−7*	13167	*13169*	*−29*	*−41*
S2								
65–69	362	*362*	9	*12*	7000	*6990*	170	*232*
70–74	607	*608*	8	*10*	9297	*9308*	125	*153*
75–79	1011	*1012*	9	*11*	11761	*11770*	101	*128*
80–84	1699	*1699*	8	*11*	14340	*14340*	68	*93*
85–89	2253	*2253*	5	*7*	13156	*13158*	31	*41*

Appendix 7. Cancer survival at different age groups in Section 6.3

Table A9. 1-, 5-, and 10-year survival probabilities (%) for women from breast cancer.

	Cancer Survival														
	From State 1						From State 2						From State 3		
	1-year		5-year		10-year		1-year		5-year		10-year		1-year	5 − *year*	10 − *year*
Age	M	S-M	M	S-M	M	S-M	M	S-M	M	S-M	M	S-M	M	M	M
								ONS approach							
65–69	99.80	*99.87*	96.18	*94.63*	88.74	*85.84*	98.63	*99.11*	78.12	*71.93*	47.69	*39.94*	79.82	31.98	10.05
70–74	99.74	*99.83*	95.45	*93.59*	87.14	*83.91*	98.28	*98.87*	74.10	*66.73*	41.71	*33.63*	74.83	22.85	5.06
75–79	99.72	*99.82*	95.04	*93.01*	86.03	*82.56*	98.10	*98.75*	71.99	*64.06*	38.38	*30.31*	72.33	18.85	3.37
80–84	99.65	*99.77*	94.14	*91.75*	83.52	*79.54*	97.68	*98.47*	67.44	*58.39*	32.03	*24.26*	66.58	11.79	1.26
85–89	99.65	*99.77*	93.59	*91.05*	80.33	*75.62*	97.63	*98.44*	65.15	*56.01*	26.96	*19.88*	65.87	10.15	0.86
								Adjusted model							
65–69	99.80	*99.87*	96.24	*94.71*	89.08	*86.27*	98.64	*99.11*	78.41	*72.25*	48.66	*40.92*	79.89	32.55	10.60
70–74	99.75	*99.83*	95.57	*93.74*	87.83	*84.78*	98.29	*98.87*	74.68	*67.36*	43.42	*35.30*	74.97	23.69	5.61
75–79	99.72	*99.82*	95.28	*93.32*	87.33	*84.20*	98.12	*98.76*	73.07	*65.23*	41.44	*33.22*	72.61	20.19	4.08
80–84	99.66	*99.78*	94.67	*92.43*	86.40	*83.14*	97.72	*98.49*	69.74	*60.83*	37.84	*29.56*	67.19	13.69	1.87
85–89	99.66	*99.78*	94.66	*92.40*	86.38	*83.11*	97.70	*98.48*	69.66	*60.71*	37.75	*29.48*	67.03	13.53	1.83

Note: Results are for women with pre-metastatic and metastatic breast cancer, and for women with undiagnosed breast cancer based on Markov (M) and semi-Markov (S-M) models, using (5), in the pre-pandemic calibration for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$, $\mu^{35} = 0.8\mu^{35}$.

Table A10. 1-, 5-, and 10-year survival probabilities (%) for women from breast cancer.

	Cancer Survival														
	From State 1						From State 2						From State 3		
	1-year		5-year		10-year		1-year		5-year		10-year		1-year	5 — *year*	10-year
Age	M	S-M	M	S-M	M	S-M	M	S-M	M	S-M	M	S-M	M	M	M
								ONS approach							
65–69	99.71	*99.81*	95.06	*93.01*	86.69	*83.41*	98.02	*98.70*	71.93	*63.81*	39.54	*31.34*	71.32	18.15	3.24
70–74	99.63	*99.76*	94.28	*91.89*	85.28	*81.76*	97.53	*98.37*	67.82	*58.45*	34.93	*26.81*	64.73	11.02	1.18
75–79	99.60	*99.73*	93.86	*91.28*	84.19	*80.45*	97.29	*98.20*	65.69	*55.81*	32.26	*24.34*	61.53	8.34	0.66
80–84	99.51	*99.68*	92.93	*89.98*	81.75	*77.55*	96.72	*97.81*	61.34	*50.49*	27.26	*19.94*	54.37	4.24	0.17
85–89	99.50	*99.67*	92.25	*89.12*	78.12	*73.15*	96.65	*97.77*	58.78	*47.95*	22.48	*15.97*	53.55	3.55	0.11
								Adjusted model							
65–69	99.71	*99.81*	95.14	*93.11*	87.11	*83.94*	98.03	*98.70*	72.28	*64.19*	40.53	*32.28*	71.41	18.57	3.45
70–74	99.64	*99.76*	94.44	*92.09*	86.08	*82.78*	97.55	*98.37*	68.50	*59.18*	36.65	*28.40*	64.92	11.53	1.33
75–79	99.60	*99.74*	94.16	*91.67*	85.71	*82.36*	97.31	*98.21*	66.96	*57.13*	35.29	*27.09*	61.88	9.07	0.82
80–84	99.52	*99.68*	93.59	*90.83*	85.03	*81.62*	96.78	*97.84*	63.97	*53.15*	32.97	*24.95*	55.07	5.07	0.26
85–89	99.52	*99.68*	93.58	*90.81*	85.01	*81.60*	96.76	*97.83*	63.90	*53.05*	32.91	*24.91*	54.88	4.98	0.25

Note: Results are for women with pre-metastatic and metastatic breast cancer, and for women with undiagnosed breast cancer based on Markov (M) and semi-Markov (S-M) models, using (5), in the pre-pandemic calibration for $\alpha = 0.6$, $\mu^{13} = \frac{1}{7}\mu^{23}$, $\mu^{35} = 1.2\mu^{35}$.