*The stratification process*

Simulated women in the model are generated at the age of 38 to allow screening to potentially cancers that generate before the first screening appointment. At age 50, a woman potentially attends her first screening appointment given the uptake for screening in the model. If she attends this appointment, or at the first appointment she does attend, she is assigned a volpara breast density percentage, a ten year risk of breast cancer, and a lifetime risk of breast cancer based on synthetic data created from observations of women’s risk data in the PROCAS2 study. If a stratified screening strategy is selected in the model, the woman is assigned to a risk group based on her ten year risk and the risk cutoffs used in the risk strategy. She is then assigned a vector of screening appointments with a frequency determined by her risk group. At each of these appointments the woman may attend or not attend screening based on the uptake parameters in the model. At the time of risk stratification, a cost of stratification is recorded and added to the total costs for the woman.

Parameters included in the model allow for varying uptake for: 1) risk estimation; 2) attendance at an appointment to receive feedback on breast cancer risk; and 3) changing the frequency of screening based on the risk feedback. In the default model these parameters are all set to 1 (100%) such that it is assumed there is perfect uptake for risk stratification.

*Cancer natural history and screening model:*

One of the most important choices in structuring the model was how to describe the natural history of breast cancer. This was particularly important because the ability of screening to affect health will depend not only on the performance of the test but also on the prevalence of early stage cancers and their characteristics. Natural history models for breast cancer have been developed by other researchers in several published analyses [1–5]. These models, along with published critiques, informed the model created for this evaluation.

The identified previous economic and epidemiological analyses of breast cancer have proposed simplified models of cancer growth. Two general approaches have been taken in the published literature:

1.   State-transition model (also called Markov models): In which, cancers are assumed to grow by advancing through discrete size categories (e.g. 5-10mm) with fixed probabilities of a transition within a discrete time period (e.g. one-year).

2.   Continuous growth model: A growth function is specified that is continuous in time. Tumour growth from starting size can be calculated for any future point in time.

The advantages of state-transition models are that they are potentially easier to use and make calculating model parameters more feasible when available data are in discrete categories (e.g. tumour size data, survival time conditional on tumour size etc). A major disadvantage is the greater approximation because of the introduction of discrete categories for tumour size and time. Another disadvantage is the complexity required to introduce heterogeneity in growth rates. This is because the probability of transition from one size category to the next will then depend on previous transition probabilities. This violates the Markovian (‘memoryless’) property of the health states that makes state-transition models mathematically tractable. The solution requires creating many more health states creating an extremely complex and unwieldy model.

Continuous growth models have the advantage that no approximations are introduced by forcing tumour size into categories with transitions at fixed intervals of time. Usually, fewer parameters will be needed in the model compared with those included in the state transition model (these require transition probabilities estimated for every possible transition). A disadvantage is that a functional form for cancer growth must be assumed. Additional assumptions will be required if the data available to estimate the growth function are discrete.

Variation in growth rates can be simulated in a continuous time model by sampling individual level growth rate parameters from an assumed population distribution. This is simple to achieve mathematically and computationally. The difficulty of achieving variation in individual’s growth rates in a state-transition model gives a clear advantage to continuous growth models.

A more extensive discussion of alternative models of cancer growth for use in cost-effectiveness analysis is available in a paper by Karnon and colleagues [6]. The authors noted that despite the well-known theoretical merits of each modelling approach there has been no empirical investigation of impact on model outputs of such choices in typical cancer screening model scenarios.

To include variation in growth rates, a continuous time and tumour size growth model was used to represent natural history. This approach was implemented using a (individual-level) discrete event simulation (DES) model.

*Diagnosis, Survival and treatment*

Cancers can be diagnosed by screening or through clinical presentation. If a cancer is present at the time of a screening event in the model where the woman attends, a function is run in the model to determine if the cancer is detected given the sensitivity of screening conditional on the size of the cancer and the density of the woman’s breasts. Alternatively, a cancer can be clinically identified if it grows to a large enough size in between screening events.

At time of diagnosis, the size (maximum diameter measured in mm) of the cancer was defined in the model. The model uses cancer stages based on the TNM approach. At diagnosis, cancers were assigned to be of a given stage, or as a DCIS, based on their size using a matrix of the probability of a cancer of a given size being of different stages. Three studies provided input data for this matrix [7–9], providing information on the distribution of lymph node involvement in cancers of different sizes, allowing a stage to be assigned when combined with size.

Survival post cancer diagnosis was simulated based on stage at diagnosis. Survival 10 years post cancer diagnosis was assumed to be the same as the general population. Treatment costs were assigned as a single tariff, with the value conditional on cancer stage, age, and years living with cancer after diagnosis. The costs were applied at the time of cancer diagnosis.

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