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Forecasting age-specific breast cancer mortality using functional data models

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SUMMARY

Accurate estimates of future age-specific incidence and mortality are critical for allocation of resources to breast cancer control programmes and evaluation of screening programmes. The purpose of this study is to apply functional data analysis techniques to model age-specific breast cancer mortality time trends, and forecast entire age-specific mortality functions using a state-space approach.

We use annual unadjusted breast cancer mortality rates in Australia, from 1921 to 2001 in 5 year age groups (45 to 85+). We use functional data analysis techniques where mortality and incidence are modelled as curves with age as a functional covariate varying by time. Data are smoothed using non-parametric smoothing methods then decomposed (using principal components analysis) to estimate basis functions that represent the functional curve. Period effects from the fitted coefficients are forecast then multiplied by the basis functions, resulting in a forecast mortality curve with prediction intervals. To forecast, we adopt a state-space approach and an automatic modelling framework for selecting among exponential smoothing methods.

Overall, breast cancer mortality rates in Australia remained relatively stable from 1960 to the late 1990s, but have declined over the last few years. A set of four basis functions minimized the mean integrated squared forecasting error and account for 99.3 per cent of variation around the mean mortality curve. Twenty year forecasts suggest a continuing decline, but at a slower rate, and stabilizing beyond 2010. Forecasts show a decline in all age groups with the greatest decline in older women.

The proposed methods have the potential to incorporate important covariates such as hormone replacement therapy and interventions to represent mammographic screening. This would be particularly useful for evaluating the impact of screening on mortality and incidence from breast cancer.

KEY WORDS: breast cancer; exponential smoothing; forecasting; functional data analysis; mortality

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INTRODUCTION

Despite an increase in utilization of mammographic screening as a form of early detection, and continual improvements in treatment options, breast cancer remains one of the main causes of mortality and morbidity in women. Regular and accurate estimates of future age-specific incidence and mortality are necessary in making recommendations for the allocation of resources to state, regional and private health care, community-based prevention services and breast cancer control programmes.

At present, most forecasting relies on age–period–cohort methods to estimate mortality (and incidence) from breast cancer [1–3], prostate cancer [1, 4] and cervical cancer [5, 6]. These models are based on regressions with the outcome defined as mortality or incident cases, and modelled using a Poisson error distribution and a log link function for the mean. The mean is modelled using the sum of parameters for age, period effects (variations in time which may apply to the whole population) and cohort effects (variations due to specific birth cohorts). The fitted models are then used to make linear projections of mortality and incidence. Common problems associated with age–period–cohort models for estimating future cancer rates include issues with non-identifiability of the parameters, strong parametric assumptions, and sensitivity of the projections to most recent changes in cohort effects.

Little other progress has been made in developing statistical methodology for cancer projections, with studies concentrating on variations of age–period–cohort statistical methods. Dyba *et al.* [7] and Dyba and Hakulinen [8] proposed linear extrapolation and non-linear Poisson distributed models. Each proposal considered a number of different scenarios with known and linearly extrapolated values for period effects and age-specific rates. Bashir and Esteve [3] used a Bayesian age–period–cohort model with autoregressive smoothing of each of the age, period and cohort components so that the resulting projections are estimated from current and past smoothed trends of the data.

We present an alternative approach to forecasting cancer mortality and incidence. This method was recently developed for demographic forecasting [9] and has not previously been applied to cancer projections. The approach uses functional data analysis techniques, and treats the age-specific mortality curves as the units of analysis rather than the discrete observations. In recent years, functional data analysis has received much attention, particularly in medicine. Ramsay and Silverman [10] provide a comprehensive introduction and have stimulated much additional development of these methods.

The Hyndman–Ullah [9] approach is a generalization of the method of Lee and Carter [11], and has the following advantages: (a) mortality (or incidence) rates are modelled as continuous functions of age so that subtle patterns of variation between years are captured; (b) data are smoothed prior to estimating the basis functions, thus reducing observational error; (c) the approach forecasts the entire function for future time periods with prediction intervals; (d) the method is robust to outlying years; and (e) the flexibility of the approach allows the incorporation of important covariates such as screening and treatment effects into the modelling. The purpose of this study is to demonstrate the utility of this new modelling and forecasting method for estimating future age-specific trends in breast cancer mortality, using unadjusted age-specific data for Australia from 1921 to 2001.

METHODS

Data

In this study we obtained data on mortality from breast cancer in Australian women from the Australian Institute of Health and Welfare (AIHW), an organization that provides deidentified health and welfare data to national and regional government and community organizations. National mortality data are compiled from medical certificates outlining cause of death from the Registrar of Births, Deaths and Marriages located in each state and territory. Additional diagnostic information is also available from the state- and territory-based cancer registries.

At present, breast cancer mortality represents 16 per cent of all cancer deaths in Australian women [12]; 12 per cent of deaths from breast cancer occur in women aged 40–49 years, 38.3 per cent in women aged 50–69 years (the target age group for screening) and 46.2 per cent in women over 70 years of age.

We use crude (unadjusted) age-specific mortality rates, defined as the number of deaths in a particular age group during the year divided by the corresponding population in that age group at 30 June of the same year. The rate is expressed per 100 000 people. Yearly age-specific breast cancer mortality rates were available for the period 1921–2001 and in 5 year age groups (45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85+).

Functional data analysis

With functional data methods, data can be smooth curves or functions. In the case of age-specific mortality, mortality rates are treated as smooth functions of age.

Let $m_t(x)$ denote the mortality rate for age x and year t, $t = 1, \ldots, n$. We model the log mortality, $y_t(x) = \log[m_t(x)]$, and assume that there is an underlying smooth function $f_t(x)$ that we are observing with error. Thus,

$$y_t(x_i) = f_t(x_i) + \sigma_t(x_i)\varepsilon_{t,i} \tag{1}$$

where x_i is the centre of age-group i $(i = 1, \ldots, p)$, $\varepsilon_{t,i}$ is an independent and identically distributed standard normal random variable and $\sigma_t(x_i)$ allows the amount of noise to vary with age x.

The error variance $\sigma_t(x_i)$ is computed as follows. Let $N_t(x)$ be the total population of age x at 30 June in year t. Then $m_t(x)$ is approximately binomially distributed with estimated variance $N_t^{-1}(x)m_t(x)[1 - m_t(x)]$. So the variance of $y_t(x)$ is (via a Taylor approximation)

$$\sigma_t^2(x) \approx [1 - m_t(x)]N_t^{-1}(x)m_t^{-1}(x) \tag{2}$$

Various smoothing techniques are available to estimate the function from the discrete observations. For each year t, we smooth the data $\{y_t(x_i)\}$ over x using weighted local quadratic smoothing with the smoothing parameter (the 'bandwidth') selected using cross-validation [13] and weights set to the inverse variances $\sigma_t^{-2}(x_i)$.

The n smooth curves are our functional observations, $\{f_t(x)\}$ where $x_1 < x < x_p$ and $t = 1, \ldots, n$. For the data considered here, four of these functional observations are shown in Figure 2.

After constructing the functional observations, we fit the model

$$f_t(x) = \mu(x) + \sum_{k=1}^{K} \beta_{t,k}\phi_k(x) + e_t(x) \tag{3}$$

where $\mu(x)$ is the mean log mortality rate across years, $\phi_k(x)$ is a set of orthogonal basis functions, and $e_t(x)$ is the model error which is assumed to be serially uncorrelated.

We wish to estimate the optimal set of K orthogonal basis functions. Specifically, for a given K, we want to find the basis functions $\{\phi_k(x)\}$ which minimize the mean integrated squared error:

$$\text{MISE} = \frac{1}{n}\sum_{t=1}^{n} \int e_t^2(x)\,\mathrm{d}x \tag{4}$$

This is achieved using functional principal components (PC) decomposition [14] applied to the smooth curves $\{f_t(x)\}$ which gives the least number of basis functions, enables informative interpretations and gives coefficients which are uncorrelated with each other.

Hyndman and Ullah [9] proposed a robust method to estimate $\mu(x)$ and a robust approach to obtaining PC when computing the basis functions. However, our data do not exhibit any outliers or other unusual behaviour, and so we estimate $\mu(x)$ using the mean of $\{f_t(x)\}$ over t, and we use standard (functional) PC decomposition.

The PCs can be computed by first constructing the $q \times n$ matrix G with (j,t)th element $f_t(x_j^*) - \hat{\mu}(x_j^*)$ where $\{x_1^*, \ldots, x_q^*\}$ is a fine grid of equally spaced values that span the interval $[x_1, x_p]$. Then the singular value decomposition of G gives $G = \Phi\Lambda V$, where $\hat{\phi}_k(x_j^*)$ is the (j,k)th element of Φ and $\hat{\beta}_{t,k}$ is the (t,k)th element of $B = G'\Psi$. Other values of $\phi_k(x)$ can be computed using linear interpolation.

Applying principal components to $f_t(x)$ rather than $y_t(x)$ makes the principal components more regular and easier to interpret, and we remove some of the variation in the data, thus reducing the noise in the coefficients $\beta_{t,k}$.

Note that Silverman [15] discusses a smoothed version of PC analysis for functional data (compared to our approach of smoothing first, then doing PC analysis). We prefer smoothing $f_t(x)$, rather than $\phi_k(x)$, because it allows us to control the smoothness of $f_t(x)$ directly, and we have more idea of how smooth $f_t(x)$ should be than how smooth $\phi_k(x)$ should be.

It would also be possible to smooth in the t direction. However, the advantage of only smoothing in the x direction is that it provides a method of obtaining forecasts and forecast intervals by forecasting the coefficients, $\{\beta_{t,k}\}$.

To assess the overall goodness of fit, the residuals of the fitted mortality model were displayed using image plots. These showed no evidence of lack of fit. We also checked for autocorrelation in the observational error, $\varepsilon_t(x_i)$, for each x_i; in the smoothing errors $e_t(x)$ for various values of x; and in the one-step forecast errors $f_t(x) - \hat{f}_{t-1,1}(x)$ for various values of x. In all cases, the autocorrelation was either insignificant or sufficiently small to be of no concern.

Forecasting framework

We estimate future values of mortality $y_t(x_i)$ by forecasting the entire function $f_t(x)$ for $t = n+1, \ldots, n+h$ and $x_1 < x < x_p$. The coefficients of the fitted function, $\beta_{t,1}, \ldots, \beta_{t,K}$, are

forecast using time series models. The forecast coefficients are then multiplied by the basis functions, resulting in forecasts of mortality curves.

Let $\hat{\beta}_{n,k,h}$ denote the h-step ahead forecast of $\beta_{n+h,k}$ and let $\hat{f}_{n,h}(x)$ denote the h-step ahead forecast of $f_{n+h}(x)$. Then

$$\hat{f}_{n,h}(x) = \hat{\mu}(x) + \sum_{k=1}^{K} \hat{\beta}_{n,k,h}\hat{\phi}_k(x) \tag{5}$$

To forecast the coefficients in equation (5), a variety of time series forecasting methods are available. In this study we use state-space models for exponential smoothing [16].

Forecasts from exponential smoothing methods are estimated recursively where recent observations are given more weight than historical data. The methods accommodate additive and multiplicative trend in the time series. Makridakis *et al.* [17] present a modelling framework based on the taxonomy proposed by Pegels [18]. The framework is expanded in Hyndman *et al.* [16], who also provide state-space models for each method, and show how models can be automatically selected for a given time series.

Hyndman and Ullah [9] show that the forecast variance can be obtained by adding the variances from each of the terms in equations (1) and (3). Therefore,

$$\mathrm{Var}[y_{n+h}(x) \mid \mathscr{I}, \Phi] = \hat{\sigma}_{\mu}^2(x) + \sum_{k=1}^{K} u_{n+h,k}\hat{\phi}_k^2(x) + v(x) + \sigma_t^2(x) \tag{6}$$

where $\mathscr{I} = \{y_t(x_i);\ t = 1, \ldots, n;\ i = 1, \ldots, p\}$ denotes all observed data, $u_{n+h,k} = \mathrm{Var}(\beta_{n+h,k} \mid \beta_{1,k}, \ldots, \beta_{n,k})$ can be obtained from the time series model, $\hat{\sigma}_{\mu}^2(x)$ (the variance of the smooth estimate $\hat{\mu}(x)$) can be obtained from the smoothing method used, $\sigma_t^2(x)$ is given by (2) and $v(x)$ is estimated by averaging $\hat{e}_t^2(x)$ for each x. A prediction interval is then easily constructed assuming the forecast errors are normally distributed.

We evaluate the accuracy of the mortality forecasts by computing the mean integrated squared forecasting error (MISFE) defined as

$$\mathrm{MISFE}(h) = \frac{1}{n-m+1} \sum_{t=m}^{n} \int [y_{t+h}(x) - \hat{f}_{t,h}(x)]^2 \, \mathrm{d}x \tag{7}$$

where m is the minimum number of observations used in fitting a model. In our implementation, we set $m = 10$.

All analyses were performed using the R implementation of the S language [19].

RESULTS

Descriptives

Figure 1 displays mortality from breast cancer in Australian women by age group for period 1921–2001. Breast cancer mortality rates remained relatively stable for women 45–49 years of age. For older women, there was an increase in mortality between 1921 and 1940, followed by a decline until 1960 for women aged 55 and 80. All age groups had relatively stable mortality rates from 1960 to the late 1990s, and all show a decline in mortality over the last

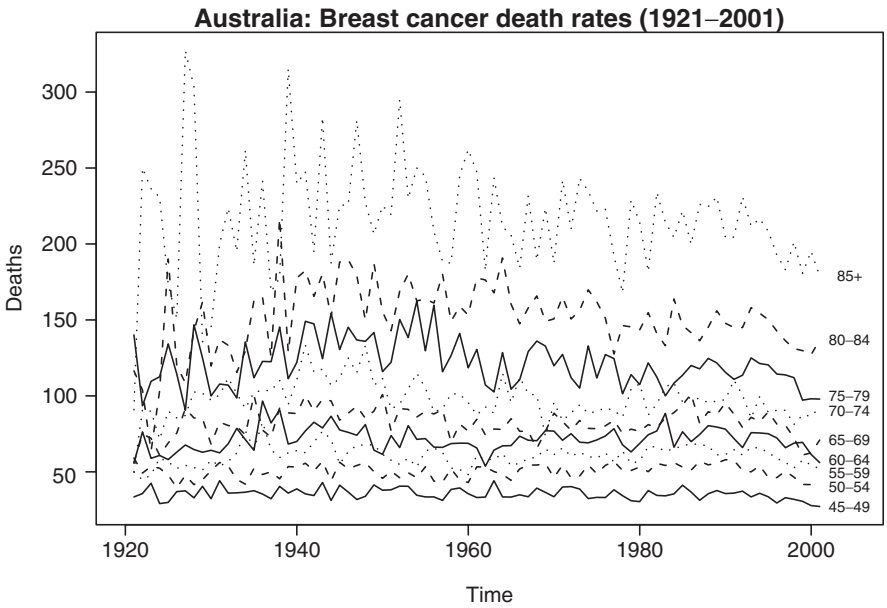

Figure 1. Age-specific mortality from breast cancer, Australia, 1921–2001.

few years. The greatest rate of decline has been in women 65 years and over. In general, mortality increases with age, and in each year, maximum mortality occurred in women over 85 years.

Crude log mortality rates by age for 1941, 1961, 1981 and 2001 are displayed in Figure 2. We smooth the log mortality series by age using loess (locally quadratic) regression with the bandwidth chosen via cross-validation. The fitted smooth curves are overlaid on the observed discrete log mortality rates. Similar trends in the age–mortality relation were observed in each year. Although mortality rates increase with age, the rate of increase varies across age groups. In most years, there is a slight deceleration in the rate of increase for women 60–70 years of age, and a rapid acceleration thereafter.

Functional data analysis

Using functional data analysis techniques and principal component decomposition to estimate the basis functions, a model with $K=4$ basis functions was selected. A set of $K=4$ basis function minimized the MISFE, while estimating an additional basis function did not contribute to a further reduction in the MISFE. The estimated basis functions and corresponding coefficients $\beta_1,\ldots,\beta_4$ are shown in Figure 3. Fitting a functional regression model with $K=4$ basis functions accounts for 99.3 per cent of the variation around the mean log mortality curve. The proportion of variation explained by each basis function is 57.7, 20.0, 14.1 and 7.4 per cent for $k=1,\ldots,4$, respectively.

The first basis function shows decreases in mortality at all ages since about 1950, with the largest changes occurring at the higher age levels. The second basis function describes varia-

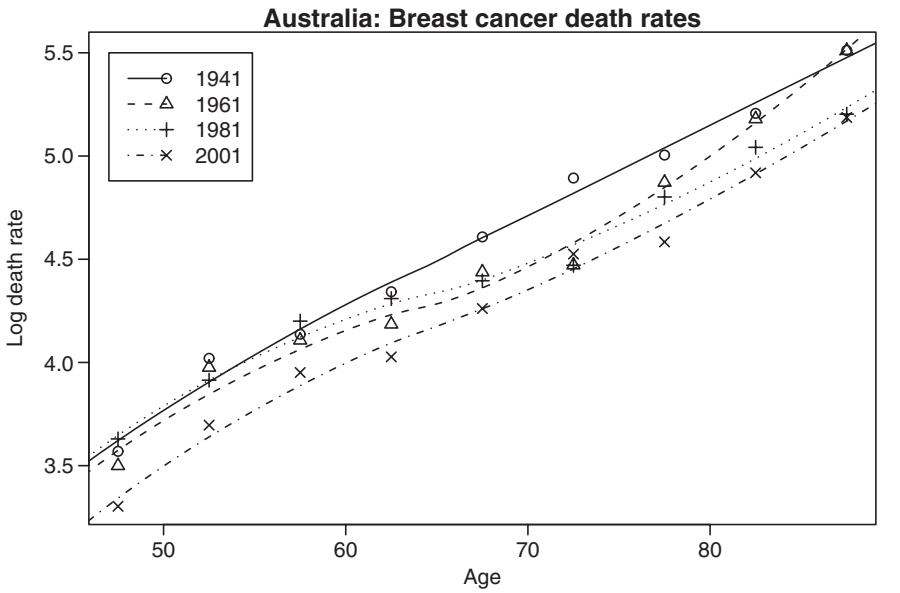

Figure 2. Four years of log mortality from breast cancer by age group in Australia. Loess (locally quadratic) smooth curves are also shown.

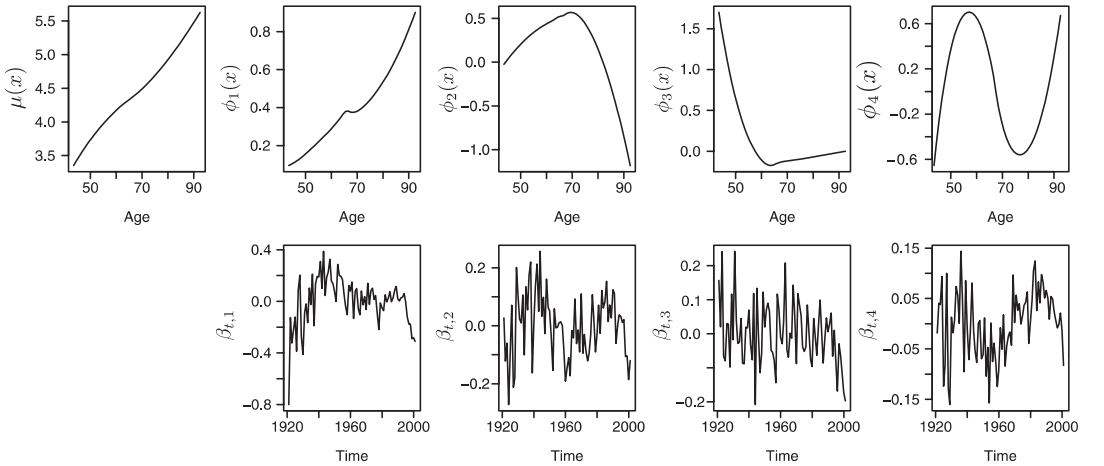

Figure 3. The components from the functional model for breast cancer mortality in Australia. Top line: the mean function and first four basis functions. Bottom line: the coefficients associated with each of the basis functions.

tion in log mortality in women around 70 compared to those much younger and those much older. The third models log mortality in younger women (under 50). The fourth component is complex and contrasts those between 55 and 65 or over 90, with the other ages.

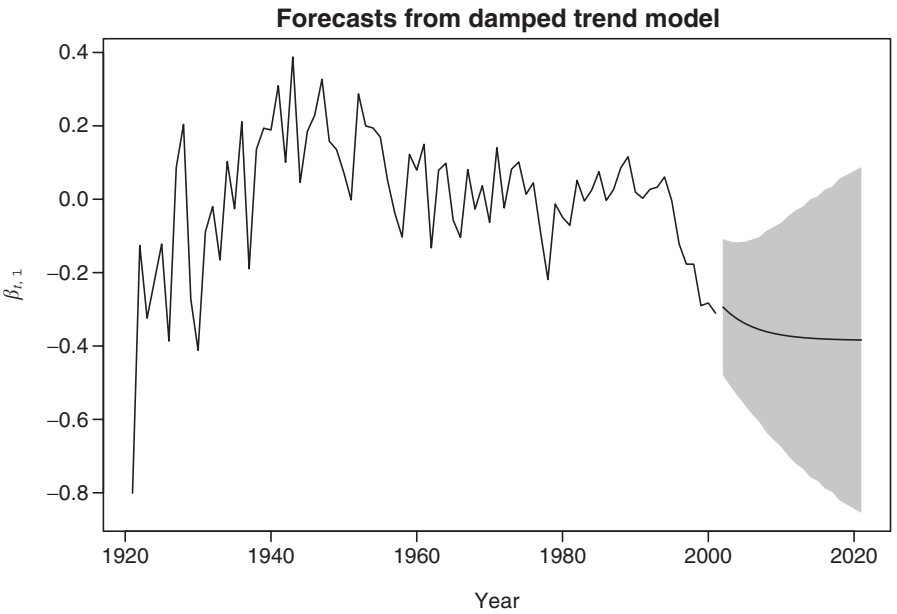

Figure 4. Twenty year forecasts of the first coefficient using a damped trend exponential smoothing model. The shaded region gives 80 per cent prediction intervals.

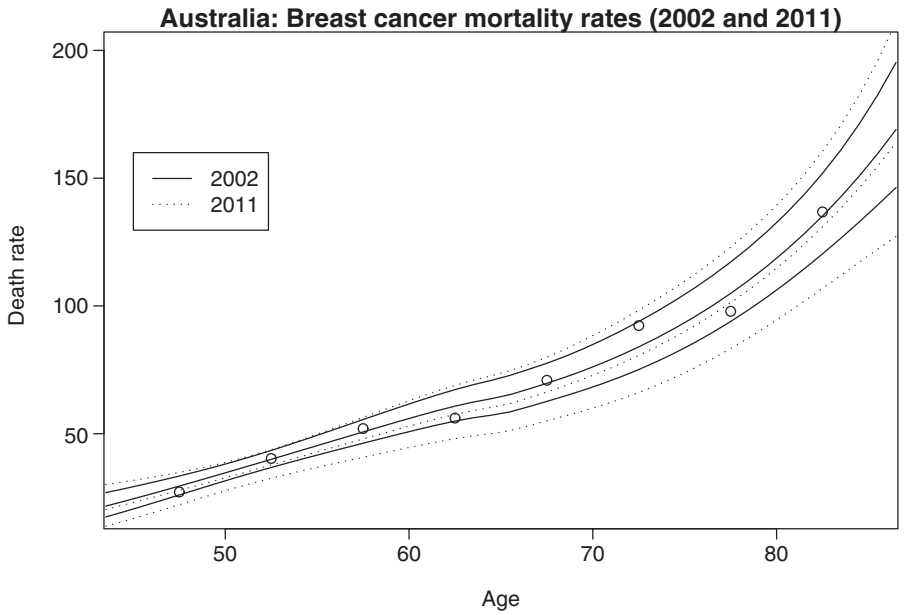

Figure 5. Forecast age-specific breast cancer mortality in Australia for 2002 and 2011, with 80 per cent prediction intervals. Actual values for 2001 are shown as circles. The forecasts show decreasing mortality for all ages, with the greatest decreases for the oldest women.

Forecasting horizon 20 years

We computed 20 year estimates of future age-specific breast cancer mortality using state-space exponential smoothing models as described by Hyndman *et al.* [16]. The automatic model-selection algorithm chose models with additive errors and a damped trend. The model parameters were selected by minimization of the one-step MSE.

Forecasts of $\beta_{t,1}$ are shown in Figure 4 for 2002–2021, along with 80 per cent prediction intervals. This parameter controls the overall change in trend in breast cancer mortality. In Australian women, mortality from breast cancer is expected to continue to decline at a slower rate than that suggested by observed mortality trends during the late 1990s, and expected to level off and stabilize beyond 2010. Note that the wide prediction intervals provide a measure of the uncertainty in the future movements in this coefficient, and even allow for it to increase.

One- and 10-year age-specific breast cancer log mortality forecasts are shown in Figure 5, along with 80 per cent prediction intervals. Very little difference in the overall shape of the age–mortality trends is likely to occur over the forecast horizon. In all age groups, the forecasts show a decline in breast cancer mortality, with the greatest declines in the oldest age groups.

DISCUSSION

At present, statistical methods for mortality projections assume current age-adjusted breast cancer mortality trends will continue into the future, thereby projecting a continual rate of decline in breast cancer mortality in countries such as the U.S., the U.K., Canada, New Zealand and Australia.

In this study of breast cancer mortality in Australian women, we illustrate the utility of a new forecasting method that models mortality using a functional model of age. The model uses basis expansions which highlight important trends in the mortality–age relationship for the period of the study. Future mortality rates are then estimated using all available historical data rather than only the most recent observations.

Using our approach, the forecast horizon suggests a slower rate of decline in breast cancer mortality in Australian women within the next decade, stabilizing beyond 2010. Our data suggest relatively small changes in mortality for women 50–60 years of age who are at the lower end of the target age group for screening, assuming current screening and treatments are unchanged.

In Australia, crude mortality rates have increased during 1920–1940, decreased post-war, remained relatively stable during 1960–1980, followed by a steady decline since the mid-1990s. However, when crude mortality rates are age-standardized to the world population, Australian mortality trends follow a similar pattern to other Western countries such as the U.S., the U.K., Canada and New Zealand [20, 21]. In these countries, mortality rates have shown very little variation beyond 1950 except for the more recent steady decline which began in the 1990s.

The reduction in mortality over the last decade is most likely a result of improvements in treatment regimes such as increased utilization of adjuvant therapy and increased mammographic screening. In the U.S., substantial improvements in survival among postmenopausal

women were observed following new treatment regimes in addition to tamoxifen [22]. The U.K. has adopted tamoxifen treatments in nearly all women over 50 years of age in the early 1990s [23]. Australia has seen similar improvements in adjuvant chemotherapy and hormonal therapy treatment regimes [24] and in 1995 new management guidelines for breast cancer treatment were widely adopted [25].

The more recent reduction in breast cancer mortality rates may in part be explained by the delayed mortality benefit of mammographic screening.

Although the interpretation of randomized control trials of mammographic screening is still subject to some controversy [26], the evidence suggests an approximately 30 per cent reduction in mortality in screened populations due to early detection of tumours. In many countries, participation in mammographic screening has gradually increased since its introduction in the late 1980s and early 1990s. In Australia, 57 per cent of women in the target age group for screening (50–69 years) were screened within a national Breast Screen programme in 2001–2002 [12]. In the U.S, 78.6 per cent of women between 50 and 64 years of age report having a mammogram in the previous 2 years [27].

Blanks *et al.* [2] predicted mortality from breast cancer for England and Wales using the widely used age–period–cohort approach. They provide mortality predictions separately for different age groups in the presence and absence of screening for the period 1990–1999. Although they do not extrapolate beyond 1999, their findings suggest a constant decline in overall mortality, with a slight decline and then levelling off in women 50–65 years of age and an increase in women over 70 years of age.

Verdecchia *et al*. [28] adopted an alternative survival regression-type approach to project breast cancer mortality, incidence and prevalence for the period 1993–2030 by 5-year age groups for women in Connecticut. They report a decrease in projected age-adjusted mortality prior to 2003 and then a levelling off with very little variation beyond 2003. Mortality projections by age suggest a decrease in women 50–69 years of age and a continual increase in women over 70 years of age from 1990, 2000, to 2030. Our forecasts of overall mortality are similar to the findings of Verdecchia *et al*. [28], although we forecast a delay in the levelling off of mortality beyond 2010 and not earlier as they suggest. Our data comprise much longer periods of mortality (1921–2001) and show mortality rates decreasing most rapidly between 1990 and 2001. Our forecasts incorporate these trends.

In this study we adopt a methodological approach which models age as a functional covariate rather than a fixed variable, so that the age-shape of mortality varies over time, thereby enabling the models and forecasts to pick up subtle variations. Other studies in demography have also realized the implications of this phenomenon when modelling all-cause mortality, particularly the acceleration in the rate of mortality decline in older persons [29, 30].

Functional data analysis is an effective exploratory and modelling technique for high-lighting trends and variations in the shape of the age–mortality relationship over time. This analytical approach has a number of strengths. First, in contrast to the common age–period–cohort models used to model trends in mortality, functional data analysis techniques make no parametric assumptions about age or period effects. The shape of the mortality–age curve varies with time, so that at different ages, mortality declines at different rates. This phenomenon is particularly apparent in breast cancer mortality, possibly due to hormonal effects or screening of women in target age groups. To our knowledge, no other study has modelled or forecast from a model with age as a functional covariate of breast cancer mortality over time.

Second, using a functional approach to forecast age-specific mortality models the entire age function and allows the possibility of a damped trend component, thereby providing greater accuracy when forecasting age-specific mortality for future time periods. The damped trend is particularly useful for forecasting breast cancer mortality because in recent years mortality from breast cancer has continued to decrease. Rather than assuming a continual decline into the future, the damping factor decelerates the trend component for the forecast horizon. In other forecasting applications [31], a damped trend model has proved particularly accurate for forecasting.

Functional data analysis methods can be further developed to incorporate interventions such as screening effects and covariates for hormone replacement therapy use. For example, an intervention resulting in a level shift in mortality for all age groups at a given time will show up as a level shift in the coefficient $\beta_{t,1}$ associated with the first principal component. Consequently, it can be handled by allowing a level shift in the time series model for $\beta_{t,1}$.

In addition, the shape of the age–mortality relation can be allowed to vary for different types of cancers and would be particularly useful for forecasting incidence of breast cancer.

A potential limitation of this approach is the assumption that there are only period effects and no cohort effects. Examination of the residuals from the functional fit revealed very little birth cohort effects in breast cancer mortality in Australia. Furthermore, studies of breast cancer mortality in different countries using age–cohort mortality models also support our finding of constant cohort mortality ratios from breast cancer in Australian women [20]. However, birth cohort effects are an important component of modelling mortality trends and studies have shown strong birth cohort effects in mortality trends for the U.K., Canada, the U.S. and Scotland [20, 32, 33].

Often birth cohort effects influence mortality trends in younger and older age groups [34]. Our modelling approach smooths the data prior to fitting the functional regression model, resulting in a smoothed functional age–mortality relation. The smoothing process may reduce much of the variation attributable to outlying observations at younger and older age groups where we expect birth-cohort trends to have the greatest effect. Any remaining birth-cohort trend is saturated in patterns of variation over time. This is not necessarily a problem as it does not hinder the functional age–mortality association over time, which is the focus of these studies. In future work, we intend to extend our model to allow for cohort effects.

In summary, we have demonstrated the utility and flexibility of this newly developed approach to forecast age-specific mortality from breast cancer. Our estimates suggest mortality from breast cancer will continue to decline and then stabilize beyond 2010 with the greatest decline in oldest age groups. These models also have broader application to other cancers and chronic diseases.

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