Predicting the Change in Breast Cancer Deaths in Spain by 2019

A Bayesian Approach

Ramon Clèries,[a,b] *Jose Miguel Martínez,*[c,d,e] *Victor Moreno,*[b,f] *Yutaka Yasui,*[g] *Josepa Ribes,*[a,b] *and Josep Maria Borràs*[a,b]

Background: Breast cancer mortality rates have been decreasing in Spain since 1992. Recent changes in demography, breast cancer therapy, and early detection of breast cancer may change this trend.

Methods: Using breast cancer mortality data from years 1990 to 2009, we sought to predict the changes in the burden of breast cancer mortality during the years 2005–2019 through a Bayesian age-period-cohort model. The net change in the number of breast cancer deaths between the periods of 2015–2019 and 2005–2009 was separated into changes in population demographics and changes in the risk of death from breast cancer.

Results: During the period 1990–2009, breast cancer mortality rates decreased (age-standardized rates per 100,000 women-years 50.6 in 1990–1994 vs. 41.1 in 2005–2009), whereas the number of breast cancer deaths increased (28,149 in 1990–1994; 29,926 in 2005–2009). There was a decrease in the number of cases among women 45–64 years of age (10,942 in 1990–1994; 8,647 in 2005–2009). Changes in population demographics contribute to a total increase of 12.5–12.8% comparing periods 2005–2009 versus 2015–2019, whereas changes in the risk of death from breast cancer contribute to a reduction of 12.9–13.7%. We predict a net decline of 0.1–1.2% in the absolute number of breast cancer deaths comparing these time periods.

Conclusions: The decrease in the risk of death from breast cancer may exceed the projected increase in deaths from growing population size and aging in Spain. These changes may also explain the decrease in the absolute number of breast cancer deaths in Spain since 2005.

(*Epidemiology* 2013;24: 454–460)

Breast cancer was the most common tumor-related death among European women[1] in 2009, with western and northern European countries showing the highest breast cancer mortality rates and eastern and central European countries showing the lowest.[1] Breast cancer mortality trends have been favorable for the past two decades in many countries, mainly owing to the advancements in clinical management and improved prognosis.[1–3] Implementation of breast cancer screening programs has also contributed to an increase in breast cancer incidence, leading to earlier diagnosis and a shift in the tumor stage at diagnosis.[1]

In Spain, a decreasing trend in breast cancer mortality rates was observed during 1992–2001, although this trend was not homogeneous across all age groups.[4] This heterogeneity affected the projection of number of breast cancer deaths; the number of deaths predicted for the years 2002–2016 increased among women older than 50 years,[4] because of population aging, immigration, and increased incidence of breast cancer. However, breast cancer incidence has leveled off in certain Spanish regions.[5] In addition, there are changes in immigration rates and life expectancy among women in Spain.[6] All these factors may affect future time trends of breast cancer mortality. Furthermore, these factors were not taken into account in a previous projection of breast cancer mortality.[4] The aim of this study was to model the burden of breast cancer mortality in Spain for 2010–2019, assessing the role of demographic factors, such as number and age distribution of women in Spain as well as the impact of declines in the risk of death from breast cancer.

METHODS

Data

The National Institute of Statistics of the Spanish Government (INE, http://www.ine.es/) provided data on breast

cancer mortality and age distribution of the female population for the period 1990–2009 by each of the 52 Spanish regions. Breast cancer mortality data were arranged in four 5-year periods (1990–1994, 1995–1999, 2000–2004, and 2005–2009) and twelve 5-year age groups (from 30–34 years to 85–90 years). Projections of future population counts and age distribution for the periods 2010–2014 and 2015–2019 were provided by the Institute, which projects population using rates of mortality, fertility, and migration[7] within a multiregional model.[8] The Institute provides estimates of the age structure of the female Spanish population until 2019. Breast cancer mortality rates presented in tables are age-standardized to the world standard population. We took into account regional variability of breast cancer mortality rates, and we assessed changes in the number of deaths across periods, distinguishing between changes owing to demographic factors and risk of death.

Projections by Bayesian Age-Period-Cohort Modeling

Mortality rates can be analyzed with regard to age at death, period (time of death), and cohort (time of birth).[9,10] Age is a main factor as mortality increases with age.[9] Period effects on mortality arise when changes in mortality are constant across all age groups.[9] Factors that affect mortality rates in a specified birth cohort contribute to the cohort effects.[9] The age-period-cohort (APC) models used for projections incorporate the uncertainty resulting from all these effects and from Poisson error.[11] A model with a high number of parameters may lead to good fit but with large variability in the predictions and therefore less precision in the prediction interval. For some cancers, the use of age and period/cohort effects may result in less variability in the prediction than models that use all three effects.[11] Accordingly, we have assessed three models: age-period (AP), age-cohort (AC), and APC, to determine which model may lead to better projections under a parsimony model selection criterion. Bayesian modeling of the effects that imposes a temporal structure on model parameters improves precision in predicting future rates.[4,11–14] These temporal structures are based on autoregressive smoothing of first order (AR1) or second order (AR2).[12,15,16] Considering age, period, and cohort as time scales, AR1 for a time scale assumes a constant rate of increase or decrease, whereas AR2 assumes a constant absolute change per unit of time.[15,16] As the rise of (the logarithm of) breast cancer mortality rates becomes more than linear with age, we assumed AR2 for age effects.[4,11] However, for period and cohort effects, both types of trends have been observed[4,11–14]; thus, AR1 and AR2 were chosen with respect to the data.[12–14]

The most reasonable hypothesis in making projections is to assume that current and most recent trends will continue unless there is external information to indicate otherwise. The prior temporal structures for the model parameters guarantee that each period (or cohort) parameter is a linear extrapolation of two previous period (or cohort) parameters.

Let λ_{apr} be the observed (age-specific) mortality rate for the age group a in the period p for region r, where $\lambda_{apr} = D_{apr}/N_{apr}$, D_{apr} and N_{apr} being the observed number of deaths and the person-years at risk in the corresponding age group, period, and region. Assuming $D_{apr} \sim \text{Poisson}(N_{apr}\lambda_{apr})$ and age group intervals of the same width as the period intervals, the APC model decomposes $\log(\lambda_{apr})$ additively into an overall level μ, age effects α_a, period effects β_p, and cohort effects γ_c, where the birth cohort c depends on period and age such that $c = p - a$ for c in $\{1, 2,\ldots, 12 + 6 - 1 = 17\}$.[10] Let $\{\alpha_1, \ldots, \alpha_a, \ldots, \alpha_{12}\}$ be the set of age effects, $\{\beta_1, \ldots, \beta_p, \ldots, \beta_6\}$ be the set of period effects, and $\{\gamma_1, \ldots, \gamma_c, \ldots, \gamma_{17}\}$ be the set of cohort effects. These parameters will be adjusted for unstructured regional heterogeneity,[14] ε_{apr}, where $r \in \{1, \ldots, 52\}$ denotes the Spanish regions. The magnitude of the rates can be described by an AP model as

$$\log(\lambda_{apr}) = \mu + \alpha_a + \beta_p + \varepsilon_{apr} \tag{1}$$

by the AC model as

$$\log(\lambda_{apr}) = \mu + \alpha_a + \gamma_c + \varepsilon_{apr} \tag{2}$$

and by the APC model as

$$\log(\lambda_{apr}) = \mu + \alpha_a + \beta_p + \gamma_c + \varepsilon_{apr} \tag{3}$$

Models (1–3) were used to perform projections, using AR1 and AR2 as smoothing priors for the age, period, and cohort effects.[12] For μ, we used a flat prior assigning equal likelihood to all possible values of the parameter,[14] whereas for ε_{apr} we used a Gaussian distribution $\varepsilon_{apr} \sim N(0, \tau_\varepsilon)$ where τ_ε is the precision (inverse of the variance). Let θ represent a vector of age effects α_a, period effects β_p, or cohort effects γ_c. When AR1 is used, $\theta_i \sim N(\theta_{i-1}, \tau_\theta)$ is assumed, and when AR2 is used, $\theta_i \sim N(2\theta_{i-1} - \theta_{i-2}, \tau_\theta)$ is assumed (where τ_θ is the precision). We used independent uniform priors for θ_1 in AR1 and θ_1 and θ_2 in AR2. We also constrained each of the effects to sum to zero to improve numeric stability[12] in the fit of models that use AR1 or AR2.[17] In the APC prediction analysis, the problem of nonidentifiability arises (the same fitted rates are predicted by many different sets of parameter values, because of the linear relationship among age, period, and cohort).[9,10] However, because we are interested only in predicting rates, not interpreting parameters,[18] we have used the sum-to-zero parameter constraints in our models to estimate parameters as previously suggested in the Bayesian framework[12] and predicted rates using these estimates.

We used a prior $\tau \sim \text{Gamma}(a, b)$ for the τ precision parameters,[14,17] where the Gamma density is given by $(b^a / \Gamma(a))\tau^{a-1}\exp(-b\tau)$, with mean a/b and variance a/b^2. We used the values $a = 0.5$ and $b = 0.001$, as evidence suggests that they work well in APC modeling.[14]

Because there is no evidence of which AR scheme works better, and the outcome may depend on the data analyzed,[12,14] we performed projections comparing two scenarios: in the first we assumed AR1 for period and cohort effects, and in the second we assumed AR2 for all effects. Therefore, a total of six models—two AP, two AC, and two APC—were assessed to determine the best predictive model in terms of precision in the predicted counts. The Deviance Information Criterion[19] (DIC), the sum of the posterior deviance and the effective number of model parameters (pD), was used as a Bayesian model selection criterion for prediction.[14] The model with lowest DIC value is considered to be the "best model" to fit data with high out-of-sample predictive power. Models within 1–3 DIC units of the best model are almost as well supported as the best model.[19] We also assessed the relative error (RE) of the prediction,[20] $\text{RE} = \sum_{a=1}^{12} | D_a^{2005-09} - E_a^{2005-09} | / D_a^{2005-09}$, which compares the observed number of breast cancer deaths in 2005–2009, $D_a^{2005-09}$, with the predicted ones (or expected ones, $E_a^{2005-09}$) obtained through each of the models that were fitted to the data from period 1990 to 2004. The RE can be used to measure prediction error and to discriminate among models with similar DIC.

Projections were obtained by fitting AP, AC, and APC models to breast cancer mortality data for the period 1990–2009 (four 5-year periods) and extrapolating the cohort and period parameters into two 5-year future periods (2010–2014 and 2015–2019). For period effects—the β model parameters—the extrapolation was carried out through the AR1 priors, $\beta_5 \sim N(\beta_4, \tau_\beta)$ and $\beta_6 \sim N(\beta_5, \tau_\beta)$, or through the AR2 priors, $\beta_5 \sim N(2\beta_4 - \beta_3, \tau_\beta)$ and $\beta_6 \sim N(2\beta_5 - \beta_4, \tau_\beta)$. Note that a future period effect can be estimated by extending the AR structure into the future, based on the specific AR assumption. The same applies for cohort parameters γ_{16} and γ_{17}. The age effects, α_a, could also be extrapolated, although in our case it was not necessary as data cover all age groups of interest. We also note that the projections have required future population counts, $N_{ap}|\forall a; p \in \{5, 6\}$, which are an offset for these models. The offset is a term added to the Poisson model on the logarithmic scale so that the count of cases can be adjusted for population size.

Working under the Bayesian framework, we obtained a posterior distribution for breast cancer mortality rates in the logarithmic scale and for each model fitted. Making use of the Poisson distribution, the predictive distribution[21] of the number of breast cancer deaths for period 2010–2019 was obtained through simulation as follows. For each age group and region, we used the posterior log-rate mean and its posterior standard deviation for future periods 2010–2014 and 2015–2019, and simulated 1000 values of each log-rate. The antilogarithm transformation was applied to each of these values to obtain the simulated posterior rate. For each of these, we simulated one observation from the Poisson distribution to take into account Poisson variability on the projections of the number of deaths.[22] Therefore, our predictive distribution

for the number of deaths was based on 1000 observations in each age group and region in each of the 5-year future periods. Finally, aggregating the counts by age groups and period, we calculated the total number of deaths in each future period and its 95% prediction interval.

Implementation of the Bayesian Models Using INLA

The Bayesian models were estimated using Integrated Nested Laplace Approximations (INLA),[23] a newly computational alternative to Markov Chain Monte Carlo,[21] through an R-interface (R Development Core Team, 2010). The R code and the dataset to reproduce all the statistical analyses presented in this article can be found in the online supplementary materials (http://links.lww.com/EDE/A673).

Differences in Risk of Death from Breast Cancer Between Periods

To decompose the changes in the number of breast cancer deaths between the two periods into those attributable to changes in population demographics and those attributable to risk of death from breast cancer, we used the method of Bashir and Esteve.[24,25] For example, we can compare the predicted breast cancer mortality in the period 2015–2019, $E_a^{2015-2019}$, with the observed breast cancer mortality in the period 2005–2009, $D_a^{2005-2009}$, through the observed percent net change of the difference in the total number of cases or deaths between both periods, $\text{Net}(\%) = \left(\sum_{a=1}^{12} \left(E_a^{2015-2019} - D_a^{2005-2009} \right) \right) \Big/ \sum^{12} D_a^{2005-2009}$. This net percent change can be separated into two components: (1) deaths because of changes in population size and age distribution and (2) remaining deaths attributable to changes in the risk of death from breast cancer. Therefore, Net (%) = Risk (%) + Population (%) = Risk (%) + Size (%) + Structure (%), the contribution of the risk of death from breast cancer and population demographics (size and age distribution) is equal to the percent net change of the difference between the number of expected cases in 2015–2019 and the observed number of breast cancer deaths in 2005–2009. The effect of population size is easily estimated: if the population is expected to increase by 10%, the expected number of deaths increases by 10%. The effect of population structure is estimated by comparing the estimated mortality rate for 2015–2019 and the mortality rate expected in the 2015–2019 population, the latter obtained by applying the age-specific rates observed in 2005–2009 to the population pyramid for 2015–2019. Finally, the variation in risk is the difference between the percent net change and the percent change explained by population size and age structure.[24,25]

Using the method described above, the statistical analysis has been performed as follows. In the initial analysis, we assessed the differences in the number of deaths between period 1990–1994 (reference) and periods 1995–1999, 2000–2004, and 2005–2009, respectively. After fitting the models (1–3) and obtaining the predicted number of breast cancer

TABLE 1. Age-standardized Breast Cancer Mortality Rates, Number of Breast Cancer Deaths and Women Years at Risk During Period 1990–1994 and 2005–2009 by Specific Age Groups

Period	1990–1994			2005–2009		
Age Group	ASR	N	Women-years	ASR	N	Women-years
All ages	50.6	28,149	58,057,730	41.1	29,926	75,764,833
45–64	48.1	10,942	21,961,100	31.4	8,647	27,155,750
>65	83.5	14,713	16,233,515	74.1	19,361	21,557,043

ASR is age-standardized rate to the world standard population per 100,000 women-years; N is the number of breast cancer deaths.

deaths for 2015–2019, we compared differences in the number of breast cancer deaths between the period 2015–2019 and 2005–2009 (reference period).

RESULTS

The differences in the number of breast cancer deaths and their age-standardized rates, comparing periods 1990–1994 and 2005–2009, are shown in Table 1. Although the age-standardized rates of breast cancer mortality decreased, the number of breast cancer deaths increased between 1990–1994 and 2005–2009 (from 28,149 to 29,926). However, there was a decrease in the number of cases for age groups 45–64 during this time period (from 10,942 to 8647). The Figure depicts the percent change in number of breast cancer deaths in Spain in the four time periods attributable to changes in population structure, changes in population age distribution, and changes in the risk of death from breast cancer. The percent change because of population size increases, whereas the percent change because of risk of death from breast cancer decreases independently of region. Both changes occur at a similar rate but in opposite directions.

Table 2 shows the model fit assessment on the projections of breast cancer mortality rates through the AP, AC, and APC models. The AC and APC models showed similar DIC in the AR1 scenario (11,607.3 and 11,608.4) and AR2 scenario (11,604.1 and 11,605.5). The AC models showed both the lowest relative error (0.4% in AR1 scenario; 0.5% in AR2 scenario) and the lowest posterior standard deviation (180.3 in AR1 scenario; 179.1 in AR2 scenario) of prediction among all models. Using the DIC, the APC model in AR2 scenario and the two AC models in both scenarios were considered as
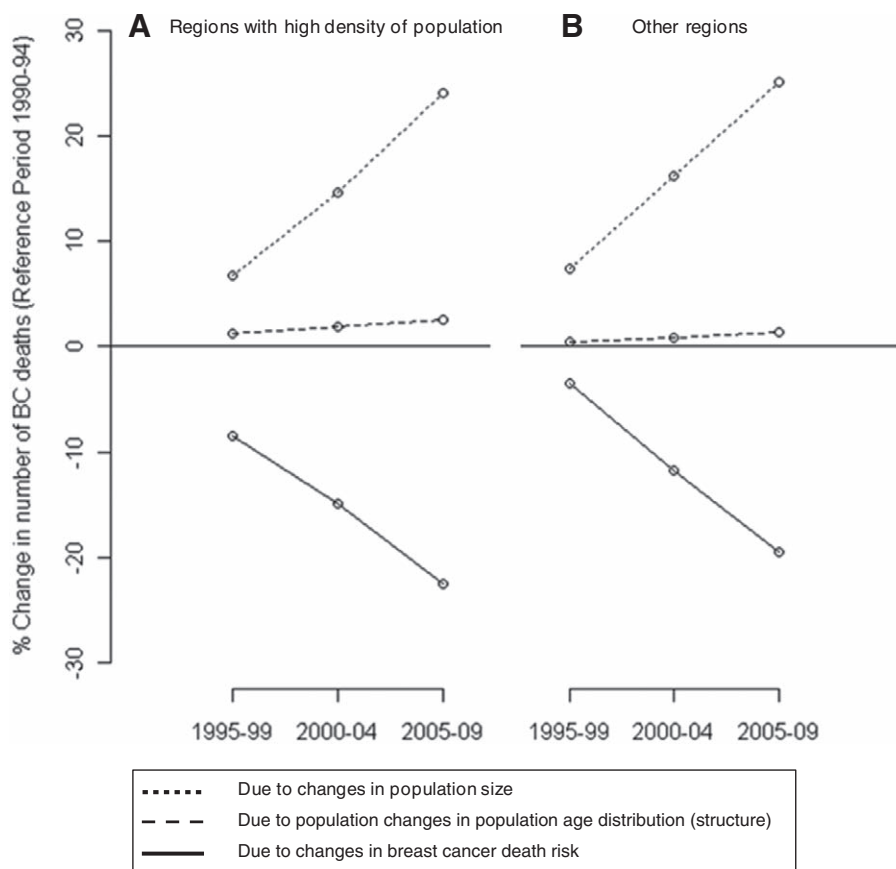
FIGURE. A and B, Percent change in the number of breast cancer deaths in Spanish regions for 1995–1999, 2000–2004, and 2005–2009 versus the reference period 1990–1994 because of changes in population structure, changes in population age distribution, and changes in the risk of death from breast cancer. (Spanish regions with high density of population [more than 300 inhabitants/km²]: Barcelona [northeast], Valencia [east], Murcia [southeast], Seville and Cadiz [south-central], Madrid [central], Navarra and Vizkaia [north-central], and a Coruña [northwest]).

TABLE 2. Model's Selection Procedure: Models Fitted to Breast Cancer Mortality Data During 1990–2004 and Used to Predict Breast Cancer Deaths in Spain for 2005–2009

	Model	DIC	pD	Expected Median	Expected SD	RE %
AR1	AP	11,935.1	62	32,982	282.6	10.2
	AC	11,607.3	73	29,906	180.3	0.4
	APC	11,608.4	74	31,847	294.1	6.4
AR2	AP	11,935.1	62	30,199	215.3	0.9
	AC	11,604.1	70	29,777	179.1	0.5
	APC	11,605.5	70	29,564	224.3	1.2

AR1, models AP and AC made use of an autoregressive smoothing prior of order 1 for period and cohort parameters; AR2, autoregressive smoothing prior of order 2 was used for all parameters; pD, effective number of model parameters; expected, median of the total expected number of breast cancer deaths during 2005–2009 predicted by each of the models; SD, posterior standard deviation of the total expected number of breast cancer deaths during 2005–2009; RE(%), percentage of the relative error between the total observed number of breast cancer deaths during 2005–2009 and the total predicted by each one of the models.

well supported as the better models for projections with similar prediction performance. We also assessed the AP and AC interactions in the full APC model, but these interactions did not improve the projections (see Supplementary Material Section 1, http://links.lww.com/EDE/A673).

The projected numbers of breast cancer deaths for 2015–2019 by age group are shown in Table 3. Note that the number of breast cancer deaths in 2005–2009 was higher (N = 29,926) than the median of the figures predicted for 2015–2019 using the AC models (AR1 scenario: 29,906; AR2 scenario: 29,777) and the APC model of the AR2 scenario (N = 29,564). Therefore, in comparing figures for the period 2015–2019 with those of period 2005–2009, a net decline of 0.1–1.2% in the number of deaths is expected. In this net percent change between these two 5-year periods, population demographics may contribute to an increase of 12.5–12.8%,

whereas the decrease in risk of death from breast cancer may contribute to a decrease of 12.0–13.7%.

DISCUSSION

We have predicted a net decline of 0.1–1.2% in the number of breast cancer deaths in Spain, between 2005–2009 and 2015–2019. This slight decrease can be decomposed into two opposite trends: (1) an increase of 12.5–12.9% because of population increase and aging and (2) a decrease of 13.7–12.9% because of a continuing decline in the risk of death from breast cancer between these two periods. This prediction is based on the time trends of breast cancer mortality rates of the Spanish population during 1990–2009. The projections accounted for different AC and APC models, which lead to similar predicted counts for 2015–2019 and therefore similar conclusions in our results.

Some limitations must be pointed out. The method is based on projecting the most recent breast cancer mortality trend into the future. Several factors[26] could influence future trends in breast cancer mortality and cannot be easily incorporated into predictive models. However, our assumption is supported by the steady fall in breast cancer mortality in Europe.[1] Projections also depend on the estimates of future population counts, which affect the future age distribution of the Spanish population. It would be useful to account for the imprecision of these estimates in our models; however, the government projections do not provide that variability, which is a limitation of our study. Another limitation might be related to changes in the future population distribution because of migration. Barring a large shift in migration, this should not substantially affect our results because breast cancer deaths mostly occur in older age groups, and counts in these age groups are usually not greatly affected by migration.[6] Even so, the lack of estimates of variability in projected breast cancer mortality and demographic changes are additional. Future research in this direction is warranted.[22]

TABLE 3. Predicted Number of Breast Cancer Deaths in Spain for the Time Period 2015–2019, Their 95% Prediction Interval and the Risk of Death from Breast Cancer Comparing the Number of Deaths from 2015–2019 with Those from 2005–2009 by the Three Models That Best Fit the Data

Age Groups	Projections (2015–2019)									Differences in the number of BC Deaths 2015–2019 vs. 2005–2009		
	45–64			>65			All Ages				Contributing Factors to Net Percent Change	
		95% Prediction Interval			95% Prediction Interval			95% Prediction Interval				
Scenario/ Model	Median N	Lower	Upper	Median N	Lower	Upper	Median N	Lower	Upper	Net %	Population %	Risk %
AR1												
AC	8,667	8,463	8,861	19,205	18,915	19,479	29,906	29,551	30,255	−0.1	12.8	−12.9
AR2												
AC	8,616	8,431	8,795	19,215	18,940	19,500	29,777	29,436	30,108	−0.5	12.9	−13.4
APC	8,554	8,333	8,765	19,075	18,717	19,442	29,564	29,131	30,000	−1.2	12.5	−13.7

AR1, models AP and AC made use of an autoregressive smoothing prior of order 1 for period and cohort parameters; RW2, autoregressive smoothing prior of order 2 was used for all parameters; BC, breast cancer.

The Figure shows that changes in risk and demographic factors were similar for breast cancer mortality during 1990–2009 across regions. Some studies at the municipal level in Spain[27,28] have reported positive associations of higher mortality with socioeconomic status and age[6] and negative associations with rurality.[27] This is not relevant to our study, as we are interested in how changes in the risk of breast cancer death and demographic factors affect the levels of breast cancer mortality in Spain as a whole.

Recent studies have shown that risk of death from breast cancer is decreasing in most European countries, whereas an increase in the number of breast cancer deaths might be expected.[24,29] We found that mortality decreased among women between 45 and 64 years of age (target population for breast cancer screening[4,5] programs). In this age group, the decreasing breast cancer mortality trend has occurred at the same time as increased access to mammography screening[30,31] and more effective breast cancer treatments.[1,3,31,32]

Advancements in breast cancer treatment, such as adjuvant antiestrogens therapy and chemotherapy and advancements in radiotherapy and surgery,[2,33–35] have contributed to this decreasing trend. Selective estrogen receptor modulators (such as tamoxifen and raloxifene) have also been assessed for primary prevention of breast cancer[36] although their impact on mortality is likely to be limited because the chemopreventive use of these drugs has been uncommon. The continuous improvement in 5-year relative survival of breast cancer in Spain[37] may reflect advances in treatment, although changes in survival may have also influenced breast cancer screening, with consequent increase in breast cancers with a better prognosis. Detection of breast cancer at an early stage could have less impact than treatment in reducing risk of death from breast cancer,[38] but it presumably contributes to the decreasing breast cancer mortality in Spain.[4] Mortality rates, on the contrary, are not influenced by overdiagnosis because death certification of breast cancer is sufficiently reliable in Spain[39,40] to permit meaningful inference.

We predicted that the number of breast cancer deaths in Spain will decrease in 2005–2019. A previous study used breast cancer mortality data from 1977 to 2001 to project an increasing number of breast cancer deaths to year 2016.[4] That study showed a larger variability in the increase in number of projected breast cancer deaths than the figures presented here. Researchers in that study used different basis periods on the projections (periods 1977–2001, 1982–2001, 1987–2001, and 1992–2001), a different population distribution for the future Spanish population (affected by rising immigration rates), and a single prediction model.[4] We have used data 1990-2009, updating the population distribution used in the past study with significant changes in central age groups[6] and using six prediction models. In addition, we incorporated geographic heterogeneity in our models, and we decomposed the influence of demographic factors and mortality trends.

Models that included age and cohort parameters were those which best fit the data of breast cancer mortality in Spain. We assessed the influence of this cohort effect in the predictions, because some evidence suggests that excluding data from young age groups (in our case 30–44 years of age) might bias projections if there are strong cohort effects.[18] In our modeling, we used data from ages 30 and older, even though data from ages 30 to 44 showed a very small number of deaths and could be considered as unnecessary to the analysis. We found that excluding these age groups may lead to less precision in the predictions (see Supplementary Material Section 2, http://links.lww.com/EDE/A673). We also found certain bias in the predictions when excluding younger age groups because the relative error in the predictions was higher than with the full dataset. Our data showed a strong cohort effect. In Spain, APC analysis of breast cancer mortality across time has consistently shown strong variation associated with the cohort component,[4] following trends observed in the United States[41] and Europe.[42] Changing behaviors may affect the risk of developing breast cancer, for example, patterns of childbearing, breastfeeding, diet, and obesity.[26] Risk factors can also be related to female sex hormones with estrogenic and progestagenic activity, either endogenous or given as hormonal contraceptives or hormone replacement therapy.[43] Although the decline in the use of hormone replacement therapy has been suggested as decreasing breast cancer incidence, its impact on mortality is less clear.[44] The prediction modeling approach used in our study does not take into account different scenarios for all these factors.

Our projections are based on a Bayesian modeling method comparing the predictive performance of six models. Although APC models have been used increasingly for predicting cancer incidence and mortality,[4,11–14,18,20,45–47] projections based on the extrapolation of age, period, and cohort effects require parametric assumptions in non-Bayesian versions of these models.[45] Some models have assumed constant age effects and projected period and cohort effects using a linear regression applied to a fixed number of most recent period and cohort effects.[45] In Bayesian versions of the APC models, period and cohort effects are smoothed and extrapolated by means of smoothing priors,[16] which can be learned from the data.[13] In situations where rates are low, the Bayesian approach to APC models can achieve sensible predictions[47] where other methods may fail.

The projections presented here may be useful as baseline information for public health authorities to investigate possible variations in breast cancer mortality because of early detection and treatment at the national or regional level.

ACKNOWLEDGMENT

REFERENCES

1. Bosetti C, Bertuccio P, Levi F, Chatenoud L, Negri E, La Vecchia C. The decline in breast cancer mortality in Europe: an update (to 2009). *Breast*. 2012;21:77–82.

2. Correa C, McGale P, Taylor P, Wang Y, Clarke M, Davies C. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr*. 2010;2010:162–167.

3. Berry DA, Cronin KA, Plevritis SK, et al; Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353:1784–1792.

4. Clèries R, Ribes J, Esteban L, Martinez JM, Borràs JM. Time trends of breast cancer mortality in Spain during the period 1977–2001 and Bayesian approach for projections during 2002–2016. *Ann Oncol*. 2006;17:1783–1791.

5. Pollán M, Michelena MJ, Ardanaz E, Izquierdo A, Sánchez-Pérez MJ, Torrella A; Breast Cancer Working Group. Breast cancer incidence in Spain before, during and after the implementation of screening programmes. *Ann Oncol*. 2010;21(suppl 3):iii97–iii102.

6. Cleries R, Martínez JM, Valls J, et al. Life expectancy and age-period-cohort effects: analysis and projections of mortality in Spain between 1977 and 2016. *Public Health*. 2009;123:156–162.

7. Instituto Nacional de Estadistica (INE). Long-term projection of Spanish Population 2009–2049. Available at: http://www.ine.es/metodologia/t20/t2030251.pdf. Accessed 10 December 2012.

8. Willekens FJ, Drewe P. A multiregional model for regional demographic projection. In: Heide H, Willekens FJ, eds. *Demographic Research and Spatial Policy*. London: Academic Press; 1984:309–334.

9. Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: age-period and age-cohort models. *Stat Med*. 1987;6:449–467.

10. Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: Age-period-cohort models. *Stat Med*. 1987;6:469–481.

11. Bashir SA, Estève J. Projecting cancer incidence and mortality using Bayesian age-period-cohort models. *J Epidemiol Biostat*. 2001;6:287–296.

12. Knorr-Held L, Rainer E. Projections of lung cancer mortality in West Germany: a case study in Bayesian prediction. *Biostatistics*. 2001;2:109–129.

13. Bray I. Application of Markov chain Monte Carlo methods to projecting cancer incidence and mortality. *Appl Stat*. 2002;51:151–164.

14. Schmid V, Held L. Bayesian extrapolation of space-time trends in cancer registry data. *Biometrics*. 2004;60:1034–1042.

15. Plummer M, Clayton D. Measurement error in dietary assessment: an investigation using covariance structure models. Part I. *Stat Med*. 1993;12:925–935.

16. Berzuini C, Clayton D. Bayesian analysis of survival on multiple time scales. *Stat Med*. 1994;13:823–838.

17. Fong Y, Rue H, Wakefield J. Bayesian inference for generalized linear mixed models. *Biostatistics*. 2010;11:397–412.

18. Baker A, Bray I. Bayesian projections: what are the effects of excluding data from younger age groups? *Am J Epidemiol*. 2005;162:798–805.

19. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde AJ. Bayesian measures of model complexity and fit (with discussion). *J Roy Stat Soc*. 2002;64:583–639.

20. Møller B, Fekjaer H, Hakulinen T, et al. Prediction of cancer incidence in the Nordic countries: empirical comparison of different approaches. *Stat Med*. 2003;22:2751–2766.

21. Gelman A, Carlin JB, Stern H, Rubin DB. Bayesian Data Analysis. 2nd ed. London: Chapman & Hall; 2003.

22. Clèries R, Ribes J, Buxo M, et al. Bayesian approach to predicting cancer incidence for an area without cancer registration by using cancer incidence data from nearby areas. *Stat Med*. 2012;31:978–987.

23. Rue H, Martino S, Chopin N. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations (with discussion). *J Roy Stat Soc*. 2009;71:319–392.

24. Bashir S, Estève J. Analysing the difference due to risk and demographic factors for incidence or mortality. *Int J Epidemiol*. 2000;29:878–884.

25. Valls J, Clèries R, Gálvez J, et al. RiskDiff: a web tool for the analysis of the difference due to risk and demographic factors for incidence or mortality data. *BMC Public Health*. 2009;9:473.

26. Veronesi U, Boyle P, Goldhirsch A, Orecchia R, Viale G. Breast cancer. *Lancet*. 2005;365:1727–1741.

27. Benach J, Yasui Y, Martínez JM, Borrell C, Pasarín MI, Daponte A. The geography of the highest mortality areas in Spain: a striking cluster in the southwestern region of the country. *Occup Environ Med*. 2004;61:280–281.

28. Izquierdo A, González JR, Moreno V, et al. Time trend of breast cancer incidence in Catalonia. *Med Clin (Barc)*. 2006;126:286–289.

29. Bray F, Møller B. Predicting the future burden of cancer. *Nat Rev Cancer*. 2006;6:63–74.

30. Hendrick RE, Klabunde C, Grivegnee A, Pou G, Ballard-Barbash R. Technical quality control practices in mammography screening programs in 22 countries. *Int J Qual Health Care*. 2002;14:219–226.

31. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 European countries. *Eur J Cancer*. 2003;39:1718–1729.

32. Hébert-Croteau N, Brisson J, Latreille J, Rivard M, Abdelaziz N, Martin G. Compliance with consensus recommendations for systemic therapy is associated with improved survival of women with node-negative breast cancer. *J Clin Oncol*. 2004;22:3685–3693.

33. Jatoi I, Miller AB. Why is breast-cancer mortality declining? *Lancet Oncol*. 2003;4:251–254.

34. Clarke M, Collins R, Darby S, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;366:2087–2106.

35. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol*. 2010;28:509–518.

36. Cuzick J, DeCensi A, Arun B, et al. Preventive therapy for breast cancer: a consensus statement. *Lancet Oncol*. 2011;12:496–503.

37. Brenner H, Francisci S, De Angelis R, et al. Long-term survival expectations of cancer patients in Europe in 2000–2002. *Eur J Cancer*. 2009;45:1028–1041.

38. Hutchinson L. Screening: reduced breast cancer mortality rates in Europe are not due to screening. *Nat Rev Clin Oncol*. 2011;8:570.

39. Martinez-Alonso M, Vilaprinyo E, Marcos-Gragera R, Rue M. Breast cancer incidence and overdiagnosis in Catalonia (Spain). *Breast Cancer Res*. 2010;12:R58.

40. Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ*. 2005;83:171–177.

41. Tarone RE, Chu KC. Age-period-cohort analyses of breast-, ovarian-, endometrial- and cervical-cancer mortality rates for Caucasian women in the USA. *J Epidemiol Biostat*. 2000;5:221–231.

42. La Vecchia C, Negri E, Levi F, Decarli A. Age, cohort-of-birth, and period-of-death trends in breast cancer mortality in Europe. *J Natl Cancer Inst*. 1997;89:732–734.

43. Kumle M. Declining breast cancer incidence and decreased HRT use. *Lancet*. 2008;372:608–610.

44. Chlebowski RT, Kuller LH, Prentice RL, et al; WHI Investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med*. 2009;360:573–587.

45. Osmond C. Using age, period and cohort models to estimate future mortality rates. *Int J Epidemiol*. 1985;14:124–129.

46. Clements MS, Armstrong BK, Moolgavkar SH. Lung cancer rate predictions using generalized additive models. *Biostatistics*. 2005;6:576–589.

47. Clèries R, Martínez JM, Escribà JM, et al. Monitoring the decreasing trend of testicular cancer mortality in Spain during 2005–2019 through a Bayesian approach. *Cancer Epidemiol*. 2010;34:244–256.