

Recent Changes in Breast Cancer Incidence in Spain, 1980–2004

Marina Pollán, Roberto Pastor-Barriuso, Eva Ardanaz, Marcial Argüelles, Carmen Martos, Jaume Galcerán, María-José Sánchez-Pérez, María-Dolores Chirlaque, Nerea Larrañaga, Ruth Martínez-Cobo, María-Cres Tobalina, Enrique Vidal, Rafael Marcos-Gragera, Antonio Mateos, Isabel Garau, María-Dolores Rojas-Martín, Rosario Jiménez, Ana Torrella-Ramos, Josefina Perucha, Maria-Eugenia Pérez-de-Rada, Susana González, María-José Rabanaque, Joan Borràs, Carmen Navarro, Esther Hernández, Ángel Izquierdo, Gonzalo López-Abente, Carmen Martínez

- Background** Since the 1980s, Spain experienced two decades of sharply increasing breast cancer incidence. Declines in breast cancer incidence have recently been reported in many developed countries. We examined whether a similar downturn might have taken place in Spain in recent years.
- Methods** Cases of invasive female breast cancer were drawn from all population-based Spanish cancer registries that had at least 10 years of uninterrupted registration over the period 1980–2004. Overall and age-specific changes in incidence rates were evaluated using change-point Poisson models, which allow for accurate detection and estimation of trend changes. All statistical tests were two-sided.
- Results** A total of 80453 incident cases of invasive breast cancer were identified. Overall age- and registry-adjusted incidence rates rose by 2.9% (95% confidence interval [CI] = 2.7% to 3.1%) annually during the 1980s and 1990s; there was a statistically significant change in this trend in 2001 (95% CI = 1998 to 2004; *P* value for the existence of a change point <.001), after which incidence declined annually by 3.0% (95% CI = 1.8% to 4.1%). This trend differed by age group: There was a steady increase in incidence for women younger than 45 years, an abrupt downturn in 2001 for women aged 45–64 years, and a gradual leveling off in 1995 for women aged 65 years or older. Separate analyses for registries that had at least 15 years of uninterrupted registration detected a statistically significant interruption of the previous upward trend in breast cancer incidence in provinces that had aggressive breast cancer screening programs and high screening participation rates, including Navarra (change point = 1991, *P* < .001), Granada (change point = 2002, *P* = .003), Bizkaia (change point = 1998, *P* < .001), Gipuzkoa (change point = 1998, *P* = .001), and Araba (change point = 1997, *P* = .002).
- Conclusions** The recent downturn in breast cancer incidence among Spanish women older than 45 years is best explained by a period effect linked to screening saturation.

J Natl Cancer Inst 2009;101:1584–1591

In the early 1980s, Spain was among the European countries with the lowest incidence of breast cancer (1). However, it experienced a sharp increase in disease incidence over the subsequent decades

Affiliations of authors: Área de Epidemiología Ambiental y Cáncer, Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain (MP, RP-B, EV, GL-A); CIBER Epidemiología y Salud Pública, Spain (MP, RP-B, EA, M-JS-P, M-DC, NL, EV, M-EPdeR, CN, GL-A, CMz); Registro de Cáncer de Navarra, Instituto de Salud Pública de Navarra, Pamplona, Spain (EA, M-EPdeR); Registro de Cáncer del Principado de Asturias, Dirección General de Salud Pública y Participación, Consejería de Salud y Servicios Sanitarios, Oviedo, Spain (MA, SG); Registro de Cáncer de Zaragoza, Departamento de Salud Pública, Instituto Aragonés de Ciencias de la Salud, Zaragoza, Spain (CMs); Registre de Càncer de Tarragona, Fundació Lliga per a la Investigació i Prevenció del Càncer, Tarragona, Spain (JG, JB); Registro de Cáncer de Granada, Escuela Andaluza de Salud Pública, Granada, Spain (M-JS-P, CMz); Registro de Cáncer de Murcia, Departamento de Epidemiología, Consejería de Sanidad, Murcia, Spain (M-DC, CN); Subdirección de Salud Pública de Gipuzkoa, Gobierno Vasco, San Sebastián, Spain (NL); Registro de Cáncer del País Vasco, Subdirección de Sanidad de Araba, Gobierno Vasco, Vitoria, Spain (RM-C); Subdirección de Sanidad de Araba, Gobierno Vasco, Vitoria, Spain (M-CT); Unitat d'Epidemiologia i Registre de Càncer de Girona, Pla Director d'Oncologia,

Departament de Salut, Girona, Spain (RM-G, AI); Registro de Cáncer de Albacete, Consejería de Salud y Bienestar Social, Albacete, Spain (AM); Registre de Càncer de Mallorca, Servei d'Epidemiologia, Direcció General de Salut Pública i Participació, Palma de Mallorca, Spain (IG); Registro de Cáncer de Canarias, Dirección General de Salud Pública, Las Palmas, Spain (M-DR-M); Registro de Cáncer de Cuenca, Consejería de Salud y Bienestar Social, Cuenca, Spain (RJ); Registre de Càncer de Castelló, Direcció General de Salut Pública, Castelló, Spain (AT-R); Registro de Cáncer de La Rioja, Servicio de Epidemiología y Prevención Sanitaria, Logroño, Spain (JP); Universidad de Zaragoza, Instituto Aragonés de Ciencias de la Salud, Zaragoza, Spain (M-JR); Departamento de Salud Pública de Bizkaia, Gobierno Vasco, Bilbao, Spain (EH).

Correspondence to: Marina Pollán, MD, PhD, Área de Epidemiología Ambiental y Cáncer, Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Sinesio Delgado 6, 28029 Madrid, Spain (e-mail: mpollan@isciii.es).

See “Funding” and “Notes” following “References.”

DOI: 10.1093/jnci/djp358

© The Author 2009. Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/2.5/uk/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Advance Access publication on October 26, 2009.

(1–3). A variety of factors were associated with this marked rising trend, including the dramatic decline in fertility (4), the increasing prevalence of obesity (5,6), and the high prevalence of sedentary lifestyle and alcohol consumption in the Spanish population (7).

A downturn in breast cancer incidence in the early 2000s has been reported in several developed countries, including the United States (8–11), Canada (12), Germany (13), Australia (14), New Zealand (15), Norway (16), France (17), and Italy (18). To examine whether a similar downward trend might have occurred in Spain in recent years, we analyzed changes in breast cancer incidence in Spain over the period 1980 through 2004. Given the differential impact of breast cancer screening programs on age-specific incidence rates and the use of hormone replacement therapy (HRT) in postmenopausal women, we also analyzed trends in breast cancer incidence separately for women aged 25–44 years, those aged 45–64 years, and those 65 years or older.

Methods

Data Source

The number of cases of invasive female breast cancer, broken down by 5-year age-at-diagnosis group (0–4, 5–9, . . . , 80–84, and ≥ 85 years) and by the calendar year of diagnosis, was obtained from the 16 population-based cancer registries in Spain that participate in the European Network of Cancer Registries and have collected data for at least 10 consecutive years over the period 1980–2004. Cases of invasive female breast cancer corresponded to code 174 from the *International Classification of Diseases, Ninth Revision* (19) and code C50 from the *International Classification of Diseases, Tenth Revision* (20). Overall, the 16 registries included in this study cover approximately 26% of the total female population of Spain (5 298 119 women covered in 2001) and serve 17 Spanish provinces that are located mainly in the east of the country along an area that runs from the northern Cantabrian coast to the southern Mediterranean region. Estimates of the midyear (ie, July 1) female populations covered by these registries during 1980–2004 were obtained from the Spanish National and Regional Institutes of Statistics.

Statistical Analysis

Age-adjusted breast cancer incidence rates were calculated for each registry and 5-year period (1980–1984, 1985–1989, 1990–1994, 1995–1999, and 2000–2004) by using the direct method (21) and the European standard population as the reference population. We computed the age-adjusted incidence rate ratios and 95% confidence intervals (CIs) for each individual registry with respect to all registries combined in each 5-year period by assuming a Poisson distribution for the number of cases.

Age- and registry-adjusted changes in incidence rates over the study period were evaluated by using log-linear Poisson models (22). More specifically, the number of invasive breast cancer cases, d_{apr} , diagnosed at age a in year p and recorded in registry r was assumed to follow a Poisson distribution with mean $\lambda_{apr}n_{apr}$ and free dispersion parameter ϕ , where λ_{apr} is the underlying incidence rate and n_{apr} is the number of woman-years at risk. The effects of age at diagnosis, calendar year of diagnosis, and registry on the log rate were assumed to be additive,

$$\log(\lambda_{apr}) = \rho_r + \alpha_a + f(p),$$

CONTEXT AND CAVEATS

Prior knowledge

Breast cancer incidence in Spain has increased sharply since the 1980s. However, it is unclear whether Spain is experiencing the recent declines in breast cancer incidence that has been reported in many developed countries.

Study design

Data from all population-based Spanish cancer registries that had at least 10 years of uninterrupted registration over the period 1980–2004 were used to evaluate overall and age-specific changes in the incidence rates of invasive female breast cancer, taking into account the starting year of the corresponding breast cancer screening program for the population covered by the registry and the year in which the screening program achieved full coverage of the target population.

Contribution

Overall incidence rates increased during the 1980s and 1990s by 2.9% annually until 2001, after which incidence declined annually by 3.0%. There was a steady increase in incidence for women younger than 45 years, an abrupt downturn in 2001 for women aged 45–64 years, and a gradual leveling off in 1995 for women aged 65 years or older.

Implications

The recent downturn in breast cancer incidence among Spanish women older than 45 years is best explained by a period effect linked to screening saturation.

Limitations

The observed trends in breast cancer incidence might not be generalizable to all parts of Spain. Regional differences in the timing of breast cancer screening program implementation are likely to have increased the heterogeneity in incidence trends across registries. Data quality differed slightly across registries in terms of case completeness and diagnostic accuracy.

From the Editors

where ρ_r and α_a are the parameters associated with registry r and age group a and whose respective averages (weighted by the corresponding marginal number of woman-years) are constrained to be 0, and $f(p)$ is a predetermined parametric function of the year of diagnosis that includes an intercept term. Two alternative parameterizations were used for the function $f(p)$. First, to describe the observed temporal trend without imposing any particular functional form, this function consisted of the usual indicator variables for each single year of diagnosis. Second, to formally detect and estimate changes in incidence rates over the study period, the function $f(p)$ consisted of two intersecting linear trends with a smooth transition at an unknown change point τ ,

$$f(p) = \beta_0 + \beta_1(p - \tau) + \beta_2\sqrt{(p - \tau)^2 + \gamma^2},$$

where β_0 is the intercept, $\beta_1 - \beta_2$ and $\beta_1 + \beta_2$ represent the period slopes below and above the change point τ , respectively, and γ is a transition parameter that controls the sharpness of the transition between the two linear trends at the change point τ , allowing not only for abrupt changes but also for more gradual transitions. As γ approaches 0, the function $f(p)$ converges to the usual two

intersecting straight lines with a sharp bend at τ ; that is, $f(p) = \beta_0 + (\beta_1 - \beta_2)(p - \tau)$ if $p \leq \tau$ and $\beta_0 + (\beta_1 + \beta_2)(p - \tau)$ if $p > \tau$. This change-point model was fitted by using a grid search over τ and γ , and the asymptotic P value of the test for the existence of a change point was corrected for the search made over τ and γ by applying the improved Bonferroni inequality (23,24). The model provided: 1) the corrected P value of the test for the change point, 2) the estimate and 95% confidence interval for the location of the change point, and 3) the estimates and 95% confidence intervals for the annual percent change in incidence rate before and after the estimated change point. Further details on inference and testing procedures are provided elsewhere (24). A program using R statistical software (R Foundation for Statistical Computing, Vienna, Austria) to fit the above change-point models is available in the Supplementary Material (available online).

Because of the small number of breast cancers diagnosed in women younger than 25 years, this age group was excluded from all trend analyses. The above-described models were also used to evaluate the specific evolution of breast cancer incidence among women aged 25–44 years, those aged 45–64 years, and those 65 years or older. These age cut points were chosen because all Spanish breast cancer screening programs initially targeted women aged 45–64 years or those aged 50–64 years, depending on the region. Finally, to explore possible geographic differences in breast cancer incidence trends, temporal trends were analyzed separately for the nine registries that had at least 15 years of uninterrupted registration. All statistical tests were two-sided. P values less than .05 were considered statistically significant.

Results

A total of 80 453 incident cases of invasive breast cancer were identified among the 100 098 780 woman-years covered by the 16 Spanish registries from 1980 through 2004. Overall, the age-adjusted incidence rate increased sharply from 54.7 cases per 100 000 woman-years in 1980–1984 to 83.8 cases per 100 000 woman-years in 2000–2004 (Table 1). In general, the highest age-adjusted rates were observed in the northeastern provinces of Girona, Tarragona, and Navarra (rate ratios of 1.14, 1.11, and 1.09 with respect to all the registries combined for the period 2000–2004, respectively), whereas the lowest rates were observed in the southeastern provinces of Cuenca, Albacete, Castelló, and Granada (rate ratios of 0.80, 0.85, 0.88, and 0.91, respectively). Nevertheless, these geographic differences in age-adjusted breast cancer incidence rates seemed to be narrowing between 1990–1994 and 2000–2004 (ratio of the 75th to the 25th percentile of breast cancer incidence rate = 1.26 in 1990–1994, 1.18 in 1995–1999, and 1.15 in 2000–2004). Detailed information on biennial age-adjusted rates for all 16 registries is provided in Supplementary Table 1 (available online).

Figure 1 depicts age- and registry-adjusted breast cancer incidence rates by calendar year of diagnosis for women aged 25 years or older included in all Spanish registries, along with the estimated temporal trend obtained by fitting a change-point model. Although the incidence of invasive breast cancer increased steadily during the 1980s and 1990s, it appeared to decline in 2000–2004. The change-point model confirmed this result, with a gradual but sta-

tistically significant change in trend in 2001 (95% CI = 1998 to 2004; P value for the existence of a change point $< .001$). The breast cancer incidence rate increased by 2.9% (95% CI = 2.7% to 3.1%) per year until 2001 and thereafter declined by 3.0% (95% CI = 1.8% to 4.1%) per year.

We next analyzed breast cancer incidence trends by age group. There was no evidence of a change in trend among women aged 25–44 years (P value for the existence of a change point = .99); the annual increase in incidence rate over the entire 1980–2004 period was 1.7% (95% CI = 1.4% to 2.1%) (Figure 2, A). Among women aged 45–64 years, however, we detected a statistically significant and sharp decline in breast cancer incidence in 2001 (95% CI = 2000 to 2002; P value for the existence of a change point $< .001$) (Figure 2, B). In this age group, breast cancer incidence increased at an annual rate of 3.4% (95% CI = 3.1% to 3.6%) until 2001 and then decreased sharply at an annual rate of 2.4% (95% CI = 0.7% to 4.0%). Among women aged 65 years or older, there was a gradual but statistically significant leveling off in breast cancer incidence beginning in 1995 (95% CI = 1992 to 1999; P value for the existence of a change point $< .001$) (Figure 2, C). In this age group, the annual increase in incidence before 1995 was 3.3% (95% CI = 2.8% to 3.7%); after 1995, incidence gradually stabilized (annual percent change = -0.4% , 95% CI = -1.0% to 0.1%).

We also examined temporal trends in age-adjusted incidence rates for registries that had at least 15 years of uninterrupted registration, taking into account the starting year of the corresponding breast cancer screening program for the population covered by the registry and the year in which the screening program achieved full coverage of the target population (Table 2). We detected statistically significant changes in breast cancer incidence trends in Navarra ($P < .001$), Granada ($P = .003$), Bizkaia ($P < .001$), Gipuzkoa ($P = .001$), and Araba ($P = .002$), most of which are provinces that have aggressive breast screening programs (ie, the program reached full screening coverage in only 1 or 2 years). The estimated change point in breast cancer incidence for each of these provinces was very close to the full-coverage year. The annual increases in incidence rates before the change point ranged from 3.3% to 5.1% and were followed by a long-term leveling off or a slight decline in incidence in Navarra, Bizkaia, Gipuzkoa, and Araba and a sharp but short-term decline in Granada. For the remaining provinces in which longer time spans were required to achieve full screening coverage, breast cancer incidence increased steadily by 1.9% to 2.9% per year across the entire study period.

Discussion

Our results show that the steady increase in breast cancer incidence observed in Spain during the 1980s and 1990s has come to a halt in recent years and that changes in incidence in 2000–2004 differed by age group. Among women aged 45–64 years, there was an abrupt downturn in incidence rates in 2001, whereas among women aged 65 years or older, the increasing trend gradually leveled off in 1995 and remained stable thereafter. Among women younger than 45 years, however, breast cancer incidence appeared to increase steadily across the entire study period.

Table 1. Age-adjusted incidence rates of invasive breast cancer (per 100 000 European standard population) by 5-year calendar period and registry*

Cancer registry	Years covered	1980–1984			1985–1989			1990–1994			1995–1999			2000–2004		
		No. of cases	Rate	RR (95% CI)	No. of cases	Rate	RR (95% CI)	No. of cases	Rate	RR (95% CI)	No. of cases	Rate	RR (95% CI)	No. of cases	Rate	RR (95% CI)
Navarra (Navarre)	1980–2004	734	56.6	1.03 (0.97 to 1.11)	900	65.6	1.10 (1.03 to 1.18)	1307	90.6	1.30 (1.23 to 1.37)	1324	86.1	1.10 (1.04 to 1.16)	1536	91.3	1.09 (1.04 to 1.15)
Asturias	1982–2003	982	51.9	0.95 (0.90 to 1.00)	1874	56.2	0.95 (0.91 to 0.99)	2190	63.8	0.91 (0.88 to 0.95)	2538	72.1	0.92 (0.89 to 0.96)	2450	86.1	1.03 (0.99 to 1.07)
Zaragoza	1980–2003	1158	51.2	0.94 (0.89 to 0.99)	1333	55.5	0.93 (0.89 to 0.98)	1616	63.6	0.91 (0.87 to 0.96)	1937	73.4	0.94 (0.90 to 0.98)	1938	86.7	1.04 (0.99 to 1.08)
Tarragona	1980–2002	857	63.8	1.17 (1.10 to 1.24)	976	68.4	1.15 (1.08 to 1.22)	1253	78.7	1.13 (1.07 to 1.19)	1388	82.3	1.05 (1.00 to 1.11)	999	93.0	1.11 (1.04 to 1.18)
Girona	1980–1989, 1992–2004	622	55.9	1.02 (0.95 to 1.10)	839	67.7	1.14 (1.06 to 1.22)	745	84.0	1.20 (1.12 to 1.30)	1364	86.7	1.11 (1.05 to 1.17)	1646	95.5	1.14 (1.09 to 1.20)
Granada	1985–2004	—	—	—	906	47.7	0.80 (0.75 to 0.85)	1107	55.4	0.79 (0.75 to 0.84)	1343	63.3	0.81 (0.77 to 0.85)	1704	75.8	0.91 (0.86 to 0.95)
Murcia	1983–2001	471	51.8	0.95 (0.87 to 1.03)	1357	56.5	0.95 (0.90 to 1.00)	1625	63.0	0.90 (0.86 to 0.95)	2147	76.8	0.98 (0.94 to 1.02)	964	82.4	0.98 (0.92 to 1.05)
Bizkaia (Basque)	1986–2004	—	—	—	1549	63.1	1.06 (1.01 to 1.11)	2248	69.1	0.99 (0.95 to 1.03)	2946	86.5	1.11 (1.07 to 1.14)	3125	86.6	1.03 (1.00 to 1.07)
Gipuzkoa	1986–2004	—	—	—	910	62.6	1.05 (0.99 to 1.12)	1398	72.6	1.04 (0.99 to 1.10)	1787	89.7	1.15 (1.09 to 1.20)	1782	81.6	0.97 (0.93 to 1.02)
Araba	1986–2004	—	—	—	312	60.8	1.02 (0.91 to 1.14)	520	74.4	1.07 (0.98 to 1.16)	696	89.3	1.14 (1.06 to 1.23)	719	82.2	0.98 (0.91 to 1.06)
Albacete	1991–2002	—	—	—	—	—	—	502	69.9	1.00 (0.91 to 1.10)	667	72.6	0.93 (0.86 to 1.00)	422	71.3	0.85 (0.77 to 0.94)
Mallorca	1988–2000	—	—	—	429	67.8	1.14 (1.04 to 1.26)	1196	71.4	1.02 (0.97 to 1.08)	1412	78.0	1.00 (0.94 to 1.05)	341	88.9	1.06 (0.95 to 1.19)
Canary Islands	1993–2004	—	—	—	—	—	—	995	81.5	1.17 (1.10 to 1.24)	2732	79.8	1.02 (0.98 to 1.06)	3342	83.9	1.00 (0.97 to 1.03)
Cuenca	1993–2004	—	—	—	—	—	—	155	63.1	0.90 (0.76 to 1.07)	386	65.4	0.84 (0.75 to 0.93)	414	67.3	0.80 (0.72 to 0.89)
Castelló	1995–2004	—	—	—	—	—	—	—	—	—	1007	76.8	0.98 (0.92 to 1.05)	1096	74.0	0.88 (0.83 to 0.94)
La Rioja	1993–2002	—	—	—	—	—	—	283	91.7	1.31 (1.16 to 1.49)	576	73.4	0.94 (0.86 to 1.02)	376	76.2	0.91 (0.82 to 1.01)
Overall	1980–2004	4824	54.7	—	11 385	59.5	—	17 140	69.8	—	24 250	78.3	—	22 854	83.8	—

* Age-adjusted RRs (and 95% CIs) are for each registry with respect to all the registries combined in the corresponding 5-year period. CI = confidence interval; RR = rate ratio; — = no data available.

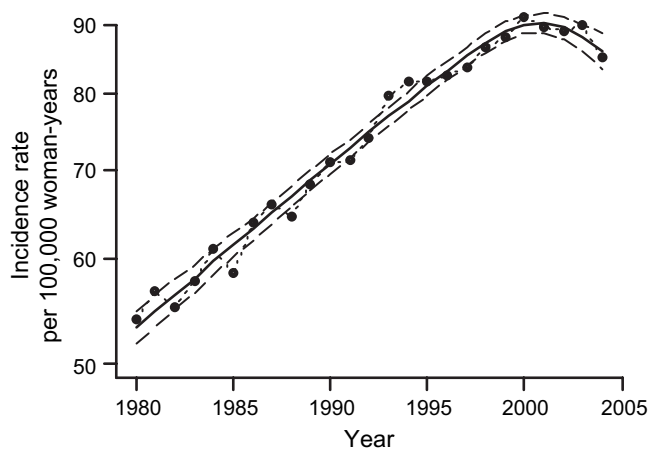


Figure 1. Age- and registry-adjusted incidence rates of invasive breast cancer over the period 1980–2004 among women aged 25 years or older included in all Spanish registries. The observed rates (dotted line) were obtained by using nominal categories for each single calendar year of diagnosis, and the estimated temporal trend (solid line) and its 95% confidence interval (dashed lines) were obtained from fitting a change-point model (see “Methods”).

The results of this study are strengthened by the inclusion of the most recent available data from all population-based Spanish cancer registries with at least 10 years of uninterrupted registration, which resulted in more than 80 000 registered cases of invasive breast cancer, as well as by the use of proper statistical methods to detect trend changes.

Nevertheless, several limitations must be considered when interpreting our findings. First, the populations covered by the included registries are located mainly in the eastern part of Spain. Thus, the observed trends in breast cancer incidence might not be generalizable to the western and central parts of Spain. Second, breast cancer screening programs were implemented in the corresponding populations at different times during the 1990s, and they had highly heterogeneous time spans to achieve full coverage of the target population (1–9 years) and different participation rates (63%–88%). These regional differences are likely to have influenced breast cancer incidence by increasing heterogeneity in incidence trends across registries, and hence the resulting overall trend should be interpreted as a summary of breast cancer incidence trends for the whole country. Third, differences in case completeness and diagnostic accuracy across registries may have distorted the observed trend. This potential problem may be of particular concern in 2000–2004, when we detected the disruption in the former rising trend. However, taking into account the most recent information available regarding the quality of breast cancer registration, the percentage of histologically verified breast cancer cases was high in all Spanish registries during the 1996–2002 period, ranging from 93% to 99%, whereas the percentage of breast cancer cases that were registered solely on the basis of death certificates was between 0.4% and 4% (21). Finally, substantial reporting delays might have produced downwardly biased breast cancer incidence trends for the most recent years of diagnosis. However, in accordance with International Agency for Research on Cancer quality control procedures (21), Spanish registries provided us with data only for the years for which they had complete case ascertainment from all information sources. As a result, the

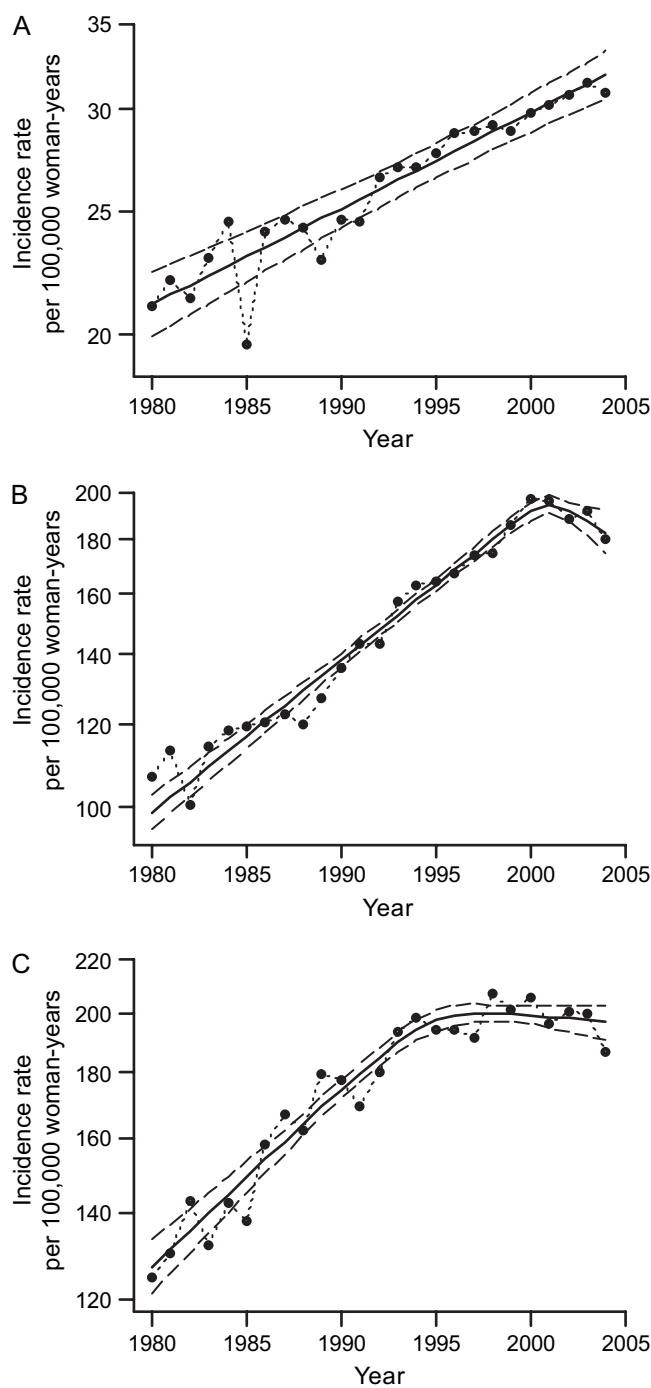


Figure 2. Age- and registry-adjusted incidence rates of invasive breast cancer over the period 1980–2004 among women who were included in all Spanish registries. **A)** Women aged 25–44 years. **B)** Women aged 45–64 years. **C)** Women aged 65 years or older. The observed rates (dotted lines) were obtained by using nominal categories for each single calendar year of diagnosis, and the estimated temporal trends (solid lines) and their 95% confidence intervals (dashed lines) were obtained from a log-linear model (A) and from change-point models (B and C) (see “Methods”).

average percentage of cases added to or deleted from the registries after the closing date for the 1997–2002 period was only 1.3% and ranged from –0.3% in Araba to 3.3% in Girona; hence, case incompleteness was expected to have little influence on the recent downturn in breast cancer incidence.

Table 2. Trends in age-adjusted incidence rates of invasive breast cancer among women aged 25 years or older included in Spanish registries with at least 15 years of uninterrupted registration*

Cancer registry	Years covered	Screening program		Change point, calendar year		Annual percent change (95% CI)		
		Starting year	Full-coverage year	P†	Estimate (95% CI)	Overall	Before change point	After change point
Navarra (Navarre)	1980–2004	1990	1992	<.001	1991 (1989 to 1992)	—	5.1 (3.9 to 6.4)	0.3 (–0.5 to 1.1)
Asturias	1982–2003	1991	2000	.99	—	2.5 (2.1 to 2.8)	—	—
Zaragoza	1980–2003	1999	2006	.83	—	2.8 (2.4 to 3.2)	—	—
Tarragona	1980–2002	1998	2001	.99	—	1.9 (1.4 to 2.3)	—	—
Granada	1985–2004	1998	2003	.003	2002 (2001 to 2003)	—	3.6 (3.0 to 4.2)	–9.0 (–14.7 to –2.8)
Murcia	1983–2001	1995	1999	.46	—	2.9 (2.5 to 3.4)	—	—
Bizkaia (Biscay)	1986–2004	1997	1999	<.001	1998 (1997 to 2000)	—	3.3 (2.6 to 4.1)	–0.9 (–2.3 to 0.6)
Gipuzkoa	1986–2004	1997	1998	.001	1998 (1996 to 1999)	—	3.3 (2.3 to 4.3)	–1.9 (–3.6 to –0.1)
Araba	1986–2004	1995	1997	.002	1997 (1994 to 1998)	—	4.7 (2.9 to 6.5)	–1.8 (–3.9 to 0.3)

* Trend changes were evaluated using change-point models (see “Methods”). Annual percent changes (95% CIs) over the entire covered periods are reported for registries with no evidence of change points, whereas the estimated change point (95% CI), together with the annual percent changes below and above it, is reported for registries with statistically significant trend changes. CI = confidence interval; — = not applicable.

† Corrected asymptotic *P* value of the two-sided test for the existence of a change point in the overall trend (see “Methods”).

In this study we have proposed a new statistical approach to detect and estimate a change point in breast cancer incidence. Trend changes in incidence rates were evaluated by using transition change-point models (24), which afford two methodological advantages over the widely used joinpoint regression approach (25). First, instead of assuming an overall trend comprising intersecting linear segments with a sharp bend at the change point, the change-point model that we used includes a transition parameter that allows for abrupt changes as well as for more gradual transitions between linear trends, the latter of which are more plausible in many epidemiological settings. Second, in transition change-point models, changes in adjusted rates over time are obtained directly by fitting Poisson models to the observed counts, which include a segmented period effect as well as age at diagnosis and registry as adjustment factors, rather than by using a segmented regression on the estimated adjusted rates. Nevertheless, our implementation of these transition models allows for only a single change point and the models should be extended further to enable multiple change points.

To interpret changes in breast cancer incidence, it is important to consider factors that might influence the observed trends. In most developed countries where a downturn in breast cancer incidence has been reported, this decline has been associated with a decrease in the use of HRT (8–11,13–17). HRT use declined after the publication of results from the Women’s Health Initiative, the largest randomized trial ever designed to assess the risks and benefits of HRT that included estrogen plus progestin regimens (26). The trial was halted because more women in the experimental group than in the placebo group developed heart disease and invasive breast cancer (26). It has been argued that too little time has elapsed between the drop in HRT use and the decline in breast cancer incidence for a true causal relationship to be inferred (27,28). Nevertheless, epidemiological data showing sharp decreases in breast cancer risk within 1 year of stopping estrogen plus progestin therapy support a causal link (29,30).

Large differences in HRT use have been reported among postmenopausal women in developed countries: The prevalence of

HRT use was high in the 1990s in North America, Australia, and Western and Northern Europe and low in Central, Eastern, and Southern Europe (31). Although the decline in HRT use seems to be associated with a decrease in breast cancer incidence in several countries (8–11,13–17), changes in HRT use appear to have contributed very little to the breast cancer incidence trends observed in populations in which this treatment was not widespread (18,32,33). A cross-national study in 1996 found that HRT was rarely used in Spain (34). During the 1990s, the prevalence of HRT use among Spanish women aged 45–64 years increased progressively, reaching a high of 5.9% in 1998 (35); however, by 2006, it had declined to 4.2% (36). In addition, a study conducted in Spanish primary care settings in 1998 showed that 56% of postmenopausal women on HRT received estrogens alone, whereas only 42% received combined estrogens with progestins (35). Hence, it is unlikely that variations in HRT use have played a major role in the recent decline in breast cancer incidence among middle-aged Spanish women.

The other important explanatory factor to be considered when interpreting changes in breast cancer incidence is screening saturation (10,27). All of the autonomous regions in Spain implemented breast cancer screening programs during the 1990s, and although these programs mainly targeted women aged 50–64 years, some also included women aged 45–49 years. In accordance with European guidelines (37), most Spanish breast cancer screening programs have recently extended the target population to include women aged 65–69 years (38). The introduction of screening programs perturbs preexisting trends by bringing forward the date of diagnosis, thus resulting in a temporary increase in cancer incidence (39). Once the program is in place and screening coverage of the target population reaches a plateau, incidence rates tend to decrease because the pool of undiagnosed prevalent cases has been reduced (28,39). We found that the change point in breast cancer incidence in Spain occurred in 2001, but this overall trend is likely to be the consequence of changes acting on different age groups and regions at different times. Among women aged 45–64 years, a sharp downturn in breast

cancer incidence was observed in 2001, when screening coverage first exceeded 90% of the target population countrywide (38). Incidence decreased thereafter, probably as a result of the dramatic decline in the pool of prevalent cases following the first screening rounds. In older women, breast cancer incidence stabilized in 1995. This phenomenon may be explained by early diagnosis of screen-detected tumors that otherwise would have been detected later. Moreover, screening also detects *in situ* carcinomas, which are surgically treated to prevent their progression into invasive tumors. Both factors—diagnostic anticipation and detection and treatment of preinvasive lesions—could have contributed to the reduced incidence we observed in the older age groups (28). The same phenomenon has been described in the Netherlands (33).

Our results for Spanish regions with a longer history of cancer registration also confirm the influence of screening on breast cancer incidence trends. A statistically significant interruption in the steady rise in breast cancer incidence was detected before 2000 in Navarra and the three Basque Country provinces of Bizkaia, Gipuzkoa, and Araba. In all of these regions, breast cancer screening programs were fully implemented over fairly short periods and required only 1–2 years to achieve full coverage of the respective target populations. In addition, the overall participation rate in the first and successive screening rounds was 88% in Navarra and 81% in the Basque Country provinces (38), well above the desired level of 75% set by European guidelines to achieve an impact on the population (37). In the remaining regions of Spain, full implementation of screening programs took longer and was achieved only recently, between 1999 and 2006 depending on the region. As a result, screening saturation was not observed during the study period, except in Granada, where it occurred in 2002. Furthermore, in some places where screening programs did not start until the late 1990s, such as in Tarragona, a substantial proportion of women had undergone screening in response to their gynecologist's recommendation (ie, opportunistic screening) and so the screening program had a lower impact in terms of breast cancer incidence.

The recent increase in breast cancer incidence among Spanish women younger than 45 years calls for specific comment because in many other developed countries, breast cancer incidence among women in this age range has stabilized (8,10–14,16,18,40,41). Although women younger than 45 years are not formally included in Spanish screening programs, the widespread use of mammography in gynecological clinics might nevertheless influence diagnosis in such women. According to the 2006 Spanish National Health Survey, only 4% of women aged 25–34 years reported regular use of mammography (ie, at least once every 2 years); among women aged 35–44 years, 19% reported regular mammography use (36). However, these percentages were substantially lower than the prevalence of mammography use of 62% and 84% observed for women aged 45–54 and 55–64 years, respectively, which suggests that regular mammographic examination cannot completely explain the upward trend in incidence observed among women younger than 45 years. A more plausible explanation for the continuous increase in breast cancer incidence among younger women may be the remarkable change in lifestyle that has taken place in Spain during the past two decades. For example, the decline in fertility that has been observed in all European countries

was particularly sharp in Spain, where the average number of births per woman dropped from 2.9 in 1970 to 1.2 in 1995 (4). Furthermore, the mean age at first child's birth was 25 years in 1975, and by 2000, it had increased to 29 years (42). An ecological study conducted in 34 industrialized countries found strong positive correlations above .75 between the average age at first delivery and subsequent breast cancer risk, particularly among women younger than 45 years (43). On the other hand, the mean age at menarche—a risk factor also associated with the development of breast cancer at younger ages (44)—has decreased at a higher rate in Spain than in other European countries (45). In summary, the steadily rising trend in breast cancer incidence among the youngest group of women in Spain may be explained by a cohort effect linked to recent changes in reproductive and lifestyle factors.

At this point, it is difficult to predict whether breast cancer incidence among Spanish women older than 45 years will continue to decrease in the near future, when all Spanish breast cancer screening programs will be fully consolidated and the youngest cohorts of women, who will have experienced these dramatic lifestyle changes, are 60–70 years old. Premenopausal and postmenopausal breast cancers have etiologies that differ somewhat from each other, and epidemiological evidence suggests that there are at least two types of breast tumors with different ages at onset (46). Breast tumors in young women tend to be more aggressive and are characterized by less hormone sensitivity and higher expression of human epidermal growth factor receptor 2 and epithelial growth factor receptor (EGFR), whereas breast tumors that occur in older women tend to have estrogen receptors and lower human epidermal growth factor receptor 2 and epithelial growth factor receptor expression (47). Statistical information systems are an important component of breast cancer control, and the continuous surveillance carried out by Spanish cancer registries will shed light on the evolution of the breast cancer epidemic in the future.

References

1. Parkin DM, Whelan SL, Ferlay J, Storm H. *Cancer Incidence in Five Continents*. Vol 1–8. Lyon, France: IARC; 2005.
2. Parkin DM, Fernandez LM. Use of statistics to assess the global burden of breast cancer. *Breast J*. 2006;12(suppl 1):S70–S80.
3. Botha JL, Bray F, Sankila R, Parkin DM. Breast cancer incidence and mortality trends in 16 European countries. *Eur J Cancer*. 2003;39(12):1718–1729.
4. Bosch X. Investigating the reasons for Spain's falling birth rate. *Lancet*. 1998;352(9131):887.
5. Aranceta-Bartrina J, Serra-Majem L, Foz-Sala M, Moreno-Esteban B. Prevalence of obesity in Spain. *Med Clin (Barc)*. 2005;125(12):460–466.
6. Haftenberger M, Lahmann PH, Panico S, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr*. 2002;5(6B):1147–1162.
7. Ministerio de Sanidad y Consumo. Indicadores de Salud 2005. La Salud de la Población Española en el contexto europeo y del SNS. <http://www.msc.es/estadEstudios/estadisticas/inforRecopilaciones/indicadoresSalud.htm>. Accessed February 1, 2009.
8. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med*. 2007;356(16):1670–1674.
9. Kerlikowske K, Miglioretti DL, Buist DS, Walker R, Carney PA. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst*. 2007;99(17):1335–1339.

10. Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. *Breast Cancer Res*. 2007;9(3):R28.
11. Glass AG, Lacey JV Jr., Carreon JD, Hoover RN. Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst*. 2007;99(15):1152-1161.
12. Kliwer EV, Demers AA, Nugent ZJ. A decline in breast-cancer incidence. *N Engl J Med*. 2007;357(5):509-510.
13. Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. *Breast Cancer Res Treat*. 2008;107(3):427-430.
14. Canfell K, Banks E, Moa AM, Beral V. Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Aust*. 2008;188(11):641-644.
15. Johnston M. Breast cancer drop linked to fall in use of HRT. *New Zealand Herald*. 2006; December 20.
16. Kumle M. Declining breast cancer incidence and decreased HRT use. *Lancet*. 2008;372(9639):608-610.
17. Allemand H, Seradour B, Weill A, Ricordeau P. Decline in breast cancer incidence in 2005 and 2006 in France: a paradoxical trend. *Bull Cancer*. 2008;95(1):11-15.
18. Ponti A, Rosso S, Zanetti R, Ricceri F, Tomatis M, Segnan N. Re: Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst*. 2007;99(23):1817-1818.
19. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, Ninth Revision—ICD-9*. Geneva, Switzerland: World Health Organization; 1977.
20. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision—ICD-10*. 2nd ed. Geneva, Switzerland: World Health Organization; 2004.
21. Curado MP, Edwards B, Shin HR, et al. *Cancer Incidence in Five Continents*. Vol IX: Lyon, France: IARC; 2007.
22. McCullagh P, Nelder JA. *Generalized Linear Models*. London, UK: Chapman and Hall; 1989.
23. Worsley KJ. An improved Bonferroni inequality and applications. *Biometrika*. 1982;69(2):297-302.
24. Pastor-Barriuso R, Guallar E, Coresh J. Transition models for change-point estimation in logistic regression. *Stat Med*. 2003;22(7):1141-1162.
25. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joint-point regression with applications to cancer rates. *Stat Med*. 2000;19(3):335-351.
26. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.
27. Li CI, Daling JR. Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. *Cancer Epidemiol Biomarkers Prev*. 2007;16(12):2773-2780.
28. MacMahon B, Cole P. Is the incidence of breast cancer declining? *Epidemiology*. 2008;19(2):268-269.
29. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*. 2003;362(9382):419-427.
30. Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med*. 2009;360(6):573-587.
31. Lundberg V, Tolonen H, Stegmayr B, Kuulasmaa K, Asplund K. Use of oral contraceptives and hormone replacement therapy in the WHO MONICA project. *Maturitas*. 2004;48(1):39-49.
32. Soerjomataram I, Coebergh JW, Louwman MW, Visser O, van Leeuwen FE. Does the decrease in hormone replacement therapy also affect breast cancer risk in the Netherlands? *J Clin Oncol*. 2007;25(31):5038-5039.
33. Otten JD, Broeders MJ, Fracheboud J, Otto SJ, de Koning HJ, Verbeek AL. Impressive time-related influence of the Dutch screening programme on breast cancer incidence and mortality, 1975-2006. *Int J Cancer*. 2008;123(8):1929-1934.
34. Schneider HP. Cross-national study of women's use of hormone replacement therapy (HRT) in Europe. *Int J Fertil Womens Med*. 1997;42(suppl 2):365-375.
35. Benet RM, Carvajal Garcia-Pando A, Garcia DP, Alvarez RA, Vega AT. Hormonal replacement therapy in Spain. *Med Clin (Barc)*. 2002;119(1):4-8.
36. Ministerio de Sanidad y Consumo. I.N.E. *Encuesta Nacional de Salud de España 2006*. Madrid, Spain: Ministerio de Sanidad y Consumo; 2007.
37. Perry N, Broeders M, de Wolf C, Törnberg S, Holland R, von Karsa L. *European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis*. 4th ed. Luxembourg: Office for Official Publications of the European Communities; 2006.
38. Ascunce N, Ederra M, Barcos A, Zubizarreta R, Fernández AB, Casamitjana M. Situación del cribado de cáncer de mama en España: características y principales resultados de los programas existentes. In: Castells X, Sala M, Ascunce N, Salas D, Zubizarreta R, Casamitjana M, eds. *Descripción del cribado del cáncer en España. Proyecto DESCRIC*. Madrid, Spain: Ministerio de Sanidad y Consumo, Agència d'Avaluació de Tecnologia i Recerca Mèdiques de Catalunya; 2007:31-73.
39. Walter SD, Day NE. Estimation of the duration of a pre-clinical disease state using screening data. *Am J Epidemiol*. 1983;118(6):865-886.
40. Hery C, Ferlay J, Boniol M, Autier P. Quantification of changes in breast cancer incidence and mortality since 1990 in 35 countries with Caucasian-majority populations. *Ann Oncol*. 2008;19(6):1187-1194.
41. Levi F, Te VC, Maspoli M, Randimbison L, Bulliard JL, La Vecchia C. Trends in breast cancer incidence among women under the age of forty. *Br J Cancer*. 2007;97(7):1013-1014.
42. Arroyo A. Fecundidad. In: Arroyo A, eds. *Tendencias demográficas durante el siglo XX en España*. Madrid, Spain: Instituto Nacional de Estadística; 2004:119-162.
43. Soerjomataram I, Pukkala E, Brenner H, Coebergh JW. On the avoidability of breast cancer in industrialized societies: older mean age at first birth as an indicator of excess breast cancer risk. *Breast Cancer Res Treat*. 2008;111(2):297-302.
44. Anderson WF, Matsuno RK, Sherman ME, et al. Estimating age-specific breast cancer risks: a descriptive tool to identify age interactions. *Cancer Causes Control*. 2007;18(4):439-447.
45. Onland-Moret NC, Peeters PH, van Gils CH, et al. Age at menarche in relation to adult height: the EPIC study. *Am J Epidemiol*. 2005;162(7):623-632.
46. Anderson WF, Chen BE, Brinton LA, Devesa SS. Qualitative age interactions (or effect modification) suggest different cancer pathways for early-onset and late-onset breast cancers. *Cancer Causes Control*. 2007;18(10):1187-1198.
47. Anders CK, Hsu DS, Broadwater G, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. *J Clin Oncol*. 2008;26(20):3324-3330.

Funding

Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP) (AC07-005 to M.P., PM07-004 to R.P-B.) and Carlos III Institute of Health (ISCIII-CIBERESP collaborative agreement "Acción Transversal del Cancer").

Notes

M. Pollán and R. Pastor-Barriuso contributed equally to this work.

The study sponsors had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Manuscript received February 16, 2009; revised August 19, 2009; accepted September 14, 2009.