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Abstract: Introduction: The aim of this study was to describe breast ductal cancer in situ (DCIS) incidence trends in women in the Girona province during a period of 25 years. The influence of age, use of mammography and implementation of the breast cancer screening programs was explored.

Incidence of subsequent invasive breast cancers (IBC) and DCIS treatment was also considered.

Materials and Methods: Cases diagnosed with primary pure DCIS (n=416) during 1983-2007 were extracted from the population-based Girona Cancer Registry. The estimated annual percent change was estimated using joinpoint analysis.

Results: DCIS incidence showed a sharp rise until 1998, followed by a less marked upward trend.

Among women aged 50-69 the increase was particularly important between 1992 and in 1996, reflecting the spread in mammography use.

Conclusion: The upward trend of DCIS was mainly related to an increase in mammography use either opportunistic or as a result of screening implementation.

Rapid increase in incidence of breast ductal cancer *in situ* in Girona, Spain 1983-2007

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Introduction

Invasive female breast cancer (IBC) is the most frequent tumor in women in Spain. In the 2000-2004 period, IBC incidence was 83.8 per 100,000 women-year and within Spain, Girona had the highest rate (95.5 per 100,000 women-year) (1). It is well known that during the recent decades ductal carcinoma *in situ* (DCIS) incidence has increased

in several countries (2-7). This rising has been associated with the implementation of breast cancer screening programs, but screening does not completely explain the upward trend and other factors might also play a role (2;6). DCIS refers to breast epithelial cells that have become “cancerous” but still reside in the milk ducts. It is thought that most IBC evolve through nonobligatory stages, referred to as hyperplasia, atypical hyperplasia and *in situ* carcinoma. However, the possibility that both DCIS and IBC may develop in parallel it has been also suggested (8;9). DCIS may be presented as a palpable or non-palpable nodule. Screening mammography has increased the detection of non-palpable breast cancer and pre-invasive lesions. Currently the most common DCIS clinical presentation are the impalpable lesions (10;11).

It has been previous reported that risk factors associated with DCIS are similar to those associated with IBC, although some are differently related to various types of DCIS (comedo and non-comedo) (12;13). Women diagnosed with DCIS have an increased risk of developing IBC in the ipsi- or contralateral breast compared with women in the general population. However, the progression into IBC is unknown and it is not possible to identify which DCIS will progress to IBC (6;14). A recent study shows that less than 10% of DCIS patients treated by excisions alone developed IBC after 5 years; while another study demonstrates that about 15% of patients who are initially diagnosed with DCIS on core needle biopsy have IBC identified in the excision or mastectomy specimen. It has been estimated that 14-50% of DCIS lesions would progress to IBC if left untreated. Several studies showed that mortality from breast cancer is low among women diagnosed with DCIS (13-16).

The rising DCIS incidence presents a clinical problem because there is not an effective protocol to distinguishing which women will or will not develop IBC and so, to what extent treatment may benefit a particular patient. Hence, the therapeutic goal is to reduce risk of recurrent disease, particularly IBC. There is some controversy as to whether or not total mastectomy or a lumpectomy with radiation may constitute overtreatment, given that the majority of DCIS patients will not develop invasive disease (5;14;17). Current clinical recommendations indicate that DCIS patients may be treated with lesion excision and radiotherapy and in some cases (multifocality) mastectomy or lumpectomy and radiotherapy should be regarded. Tamoxifen should be considered in patients with positive estrogen receptor tumours (18;19).

Population-based data on incidence trends of DCIS from Spain are not available. To understand the possible extent of overdiagnosis and overtreatment of DCIS, it is important to have information about treatment and incidence of the disease over time. The aim of this study was to describe DCIS incidence trends in women resident in the Girona province during the period from 1983 to 2007, considering the implementation of the population-based mammography screening program. Given the differential impact of breast cancer screening programs on age-specific incidence rates, we also analyzed DCIS trends incidence separately for women younger than 50 years, those aged 50-69 years, and those 70 years or older. Treatment of DCIS diagnosed from 2000 to 2007 was reported and finally, the incidence of IBC subsequent to DCIS was also described.

Materials and Methods

Data

Data were extracted from the population-based Girona Cancer Registry (GCR). The GCR is located in the Northern East of Catalonia, in Spain, covering a population of 339,660 women at the 2007 census. It represents a 9.35% of the Catalan population. Catalan data of female population used for the statistical analyzes were obtained from the *Institut d'Estadística de Catalunya* (20). The GCR collects invasive and *in situ* breast tumors since 1980 and case registration is performed according to the European Network of Cancer Registries (ENCR) recommendations (21;22).

We restricted our analysis to women diagnosed of DCIS during the period from 1983 to 2007. The following ICD-10 classification codes were used; D050-D059 (23). A total of 416 cases were included in the study. Cases diagnosed with lobular in situ carcinoma (n=17), or intraductal carcinoma and lobular in situ (n=1), or intracystic carcinoma (n=2) were excluded. Data of the first tumor in women with bilateral DCIS was recorded. Each woman with DCIS has been followed up to December 31th 2007 to evaluate the occurrence of a subsequent IBC in the ipsi- or contralateral breast. However, in order to have a minimum follow-up of 1 year, women diagnosed with DCIS in 2007 (n=41) were not included in this analysis. Surgical treatment was recorded in women diagnosed with DCIS during the period 2000 to 2007, and classified into the following groups: Conservative surgery alone, including lumpectomy, excision and quadrantectomy; conservative surgery plus radiotherapy; mastectomy, including modified radical mastectomy and simple mastectomy and non-surgery. Molecular and hormonal treatments were not reported.

In Spain there is a National Health System (NHS), financed mainly by taxes, which provides universal health coverage, including early detection of breast cancer. In the Girona province, the Breast Cancer Screening Program (*Programa de Detecció Precoc del Càncer de Mama*, PDPCM) gradually started in the different hospitals during the period 1999 to 2002, providing biennial mammography screening test to women from 50 to 69 years old. PDPCM coverage of the whole Girona province in 2007 was 75.29% with a participation of 63.15%. The Catalan Health Surveys in 1994, 2002 and 2006 describe the percentage of women older than 20 years undergoing mammography periodically in Girona (24-26).

Analyses

Mean age (SD) at diagnosis of DCIS and IBC (codes C500-C509 of the ICD-10) (23) were calculated and compared using t test. DCIS incidence rates were estimated for each 5-year period (1983-1987, 1988-1992, 1993-1997, 1998-2002 and 2003-2007) as the crude rate (CR), the age-standardized to the World standard population rate (ASR_W), and the age-specific rate for 5-year aged (25-29, ..., 80-84, >85). ASR_W was also calculated according to three age groups (<50, 50-69, >69). These age cut points were chosen because PDPCM targets women aged 50-69 years. Epidat software (27) was used to compute CR and ASR_W with the 95% confidence interval (95% CI) by using the direct method. Joinpoint statistical software was used to quantify the evolution of DCIS incidence, as the Estimated Annual Percent Change (EAPC), and to evaluate changes in trends along time in the three broad age groups (28). Median (range) months between DCIS and IBC were calculated for tumors developed in the ipsilateral or in the contralateral breast.

Results

A total of 416 incident cases of DCIS were identified by GCR from 1983 to 2007. Mean age (SD) at diagnosis was 55.82 (12.32) years, ranging from 26 to 89 years. Mean age (SD) at diagnosis of the IBC in the same period was 61.41 (14.83) years, ranging from 21 to 103 years. If only incident cases diagnosed during the screening period (2002-2007 years) were considered, mean age was 55.47 (11.79) years for DCIS and 61.70 (15.05) years for IBC. Differences between mean ages of invasive and *in situ* cancers were statistically significant using t test (P value < 0.001). DCIS accounted for 6.85% of breast carcinomas diagnosed between 1983 and 2007, excluding lobular and intracystic invasive carcinomas.

Table 1 show the incidence expressed as CR and ASR_w per 100,000 women-year. Overall, ASR_w increased during the studied period, from 1.01 in 1983-1987 to 8.24 in 2003-2007. In general, during the 1980s and the beginning of the 1990s incidence rates remained low and began to increase during the 1990s.

As Figure 1 depicts, from 1983 to 1998 DCIS incidence increased rapidly. In 1998 the joinpoint model indicated a statistically significant change in trend (95% CI: 1994 to 2001; P value for the existence of a change point < 0.05). Incidence rates raised by 18.31% (95% CI: 11.86% to 25.14%) per year until 1998 and thereafter the increment was 2.95% and no longer statistically significant (95% CI: -2.74% to 8.98%).

DCIS incidence changed over time according to age (Figure 2). In women under 50 years, DCIS steadily increased at a statistically significant EAPC of 10.31% (95% CI: 7.39% to 13.30%) over the entire period. Among women aged 50-69 years, two statistically significant change points were observed in 1992 (95% CI: 1985 to 1994; P

value for the existence of a change point < 0.05) and in 1996 (95% CI: 1994 to 1998; P value for the existence of a change point < 0.05). In this age group, DCIS incidence increased at a non-statistically significant annual rate of 9.06% (95% CI: -7.72% to 28.89%) until 1992 and then sharply jumped at an annual rate of 59.42% (95% CI: -0.30% to 154.91%) until 1996. From 1996 to 2007, DCIS incidence seemed to level off (EAPC= 2.03%; 95% CI: -1.79% to 6.01%). Finally, among women aged 70 years or older, no change point was observed and the none statistically significant annual increase in incidence was 3.61% (95% CI=-1.18% to 8.64%). During the fully implemented PDPCM screening period (2002-2007 years), 54.9% of all DCIS in women 50-69 years old were screen-detected (n=62), 6.2% were interval cancers (n=7) and 39.0% were DCIS diagnosed outside the program (n=44).

Age-specific rates for the whole period are shown in Figure 3. DCIS increased with age in women aged 25-49 years, peaked at 50-54 years and decreased in those older than 65.

Information regarding the type of surgery was obtained in 75.8% of all DCIS diagnosed between 2000 and 2007 (191 out of 252). Half of them were treated with conservative surgery plus radiotherapy (95 in 191), but a 35.8% of these women were mastectomized. A low percentage (8.4%) was treated with conservative surgery alone and only 2 cases (1%) were not operated.

About 21% of women diagnosed with DCIS until 2006 (n=377) also developed an invasive cancer (n=81) before or/and after DCIS diagnosis. Invasive second cancers were localized in breast, colon, cervix and corpus uteri and thyroid gland. Out of all women included in the study until 2006, 4.0% (n=15) developed an IBC subsequent DCIS. One woman developed bilateral IBC after DCIS. Of all IBC, 50.0% (n=8) occurred in the contralateral breast and 50.0% (n=8) were diagnosed in the ipsilateral

breast. For the contralateral IBC the median of time between DCIS diagnosis and IBC diagnosis was 32.5 month (range, 4 to 124 month), and for ipsilateral was 81.5 month (range, 20 to 211 month).

Discussion

Our results show that DCIS incidence in the Girona province markedly increased from 1983 to the end of 1990s remaining stable afterwards. During the period from 1980 to 1999 in Girona the incidence of IBC increased 2.7% per year (29). Since the PDPCM started in the Girona province in 1999, DCIS incidence had remained stable considering all age groups together. PDPCM was not fully implemented in the whole province until 2002 but DCIS incidence trend markedly changed in 1998. Before PDPCM implementation, women used the mammography as a spontaneous preventive practice, in the public and private health care sectors, as it occurred in other countries (2). Mammography in Catalonia started during 1980s but spread during 1990s. In 1980 only 10 mammography equipments were available, while in 2000 there were already 134 (29). The Catalan Health Survey describes that rates of screening mammography in Girona were lower in 1994 (25.18%) than in 2002 (38.8%) and in 2006 (42.9%) (24-26;30). The observed increment was concurrent with the increased DCIS detection. During the screening period incidence remained high and stable; about half of the women aged 50-69 years were diagnosed by opportunistic mammography and the other half by the screening program. During the entire period studied DCIS incidence trends reflected the mammography use.

Part of the diagnosed DCIS included in the study were asymptomatic and would be undetected if screening had not been performed, given that some DCIS may lack progressive potential. From this point of view screening would be considered as causing overdiagnosis (14;31). Probably, DCIS diagnosed before mammography spread were symptomatic, whereas currently both asymptomatic and symptomatic DCIS are being diagnosed. This is possible because of the widespread use of mammography and the awareness of its role to prevent the disease among the general population and among medical professionals.

Coinciding with a previous study, the most frequent second cancer among women with DCIS is IBC, followed by colon and corpus uteri invasive cancer, among others (32). It has to be considered the possibility that in some cases the DCIS detected would be already invasive, but not diagnosed as such. Women with DCIS were almost all treated and a 35.8% were mastectomized, resulting in a possible overtreatment. However, DCIS treatment was necessary to obtain a low percentage of subsequent IBC if we considered the estimation that 14-50% of DCIS would progress to IBC if left untreated (16). Although screening would cause overdiagnosis and overtreatment, a non-negligible proportion of DCIS progress into IBC.

We observed that changes in DCIS incidence highly differed by age groups. Among women aged 50-69 years, there was an abrupt climb of DCIS incidence in the mid 1990s, whereas among women aged 70 or older and women aged 49 or younger incidence has been gradually increasing. In Spain, IBC in young women is still rising, while in many other developed countries it has stabilized (1;33-35). Our results indicate that DCIS incidence in young women appeared to increase steadily across the entire

study period and it has not completely reached stability, as well as the invasive disease. Although these women are not included in the PDPCM, the widespread use of mammography might nevertheless influenced diagnosis in such women. It was previous reported that there has been an increase in mammography use over time in women in their late 30s or early 40s (31). Taking into account that some risk factors for DCIS are similar to those for IBC, the observed steadily rise of DCIS in young women may be also due to the lifestyle changes experienced by Spanish women in the recent decades. In Spain, fertility had sharply declined, the mean age at menarche had decreased more than in other European countries and the mean age at first child's birth had increased (6;34). On the other hand, DCIS among women aged 70 years or older also showed an upward trend during all the study period, but it was not statistically significant. A previous study showed a gradual stabilization of IBC incidence since 1995 in this age group in Spain (1). Regarding invasive cancers, diagnostic anticipation and treatment of preinvasive lesions could have contributed to reduce incidence. However, the increase in DCIS observed among women older than 69, may be also partly explained by opportunistic mammography after leaving the screening program.

Women aged 50-69 years, was the age group that in 2002 and 2006 reported the highest use of periodic mammograms in the Catalan Health Surveys, followed by the 40-49 age group (31). Unlike IBC, age specific rates of DCIS increased up to 50-54 years and then decreased. This may reflect the mammography use pattern in Girona, which included women from 40 to 75 years. Furthermore, DCIS rates in women 45 to 49 years old appeared to be similar to those observed in the screening age interval.

Results also show that the mean age of women diagnosed with DCIS was significantly lower than the mean age of women diagnosed with IBC. This may be explained by an advanced diagnosis of DCIS respect to IBC due to mammography implementation. A previous study reported that in the U.S.A., between 1975 and 2003, women diagnosed with DCIS were also younger than women diagnosed with IBC (36).

Some limitations must to be considered when interpreting our findings. Firstly, PDPCM was progressively implemented in the population adscribed to the different Screening Radiological Units during 1999-2002. Furthermore, they have different coverage (65.4-87.01% in 2007) and participation rates (47.59-77.96% in 2007). These differences are likely to have influenced breast cancer incidence by increasing heterogeneity within the Girona province. Secondly, it must be taken into account diversity of data used, as they are provided by different hospitals, oncologists and pathologists. Thirdly, improved detection methods may have increased incidence during the recent years (digital mammography). In this regard it should be noted that digital mammography was introduced in Girona in 2005.

Conclusions

The described upward trend of DCIS in the Girona province in 1983-2007 was mainly related to the opportunistic mammography spread and also the PDPCM implementation. This increase was more pronounced in women under 70 years, particularly women aged 50-69 years. Moreover, improved diagnostics and breast awareness resulting from the implementation of screening are also increasing DCIS trends. More research is needed in order to improve breast DCIS diagnostic methods and treatment.

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Conflict of interest statement

None declared

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Ethical Approval

Not required.

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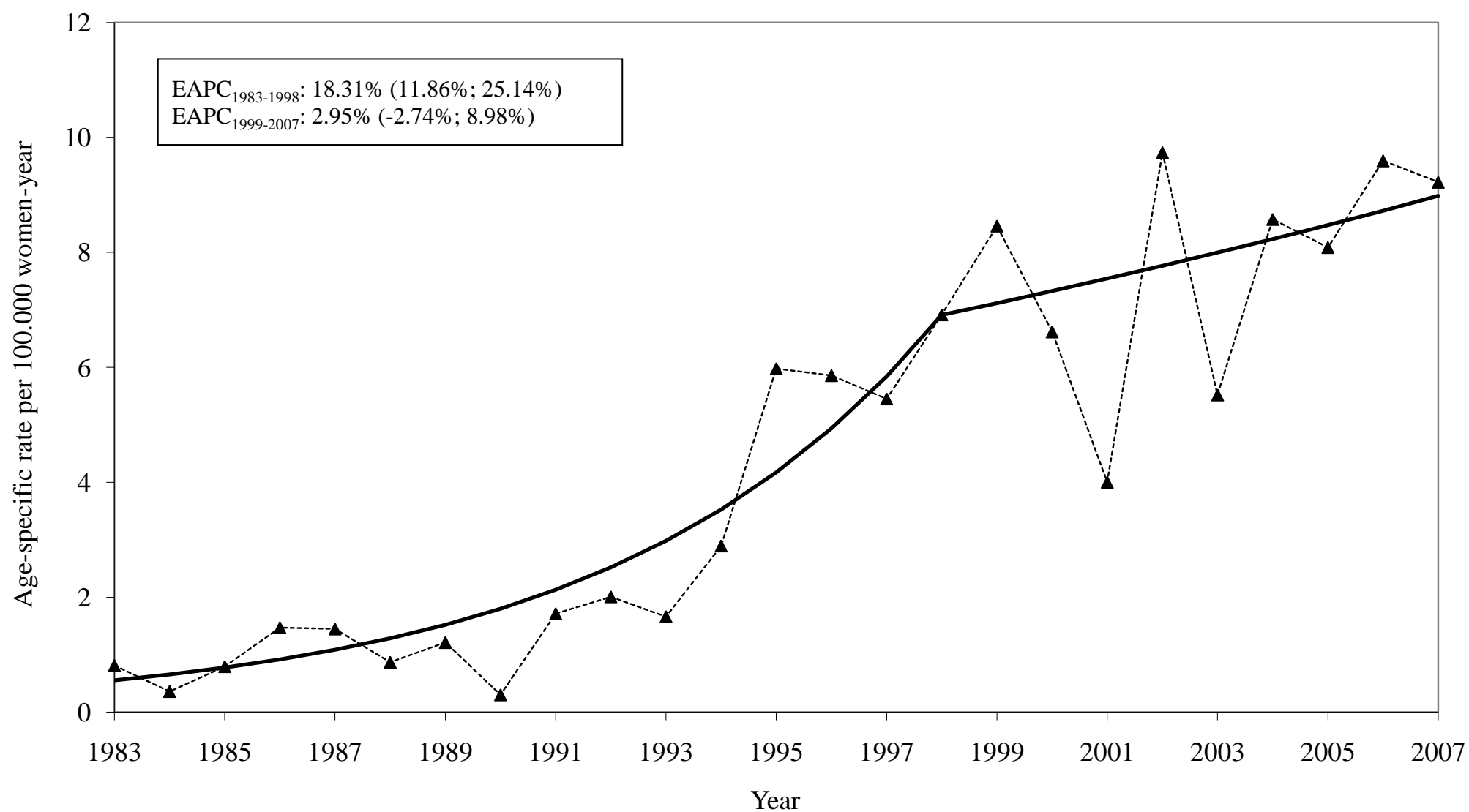
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Table 1. Incidence of breast ductal carcinoma *in situ* in Girona (Spain), 1983-2007.

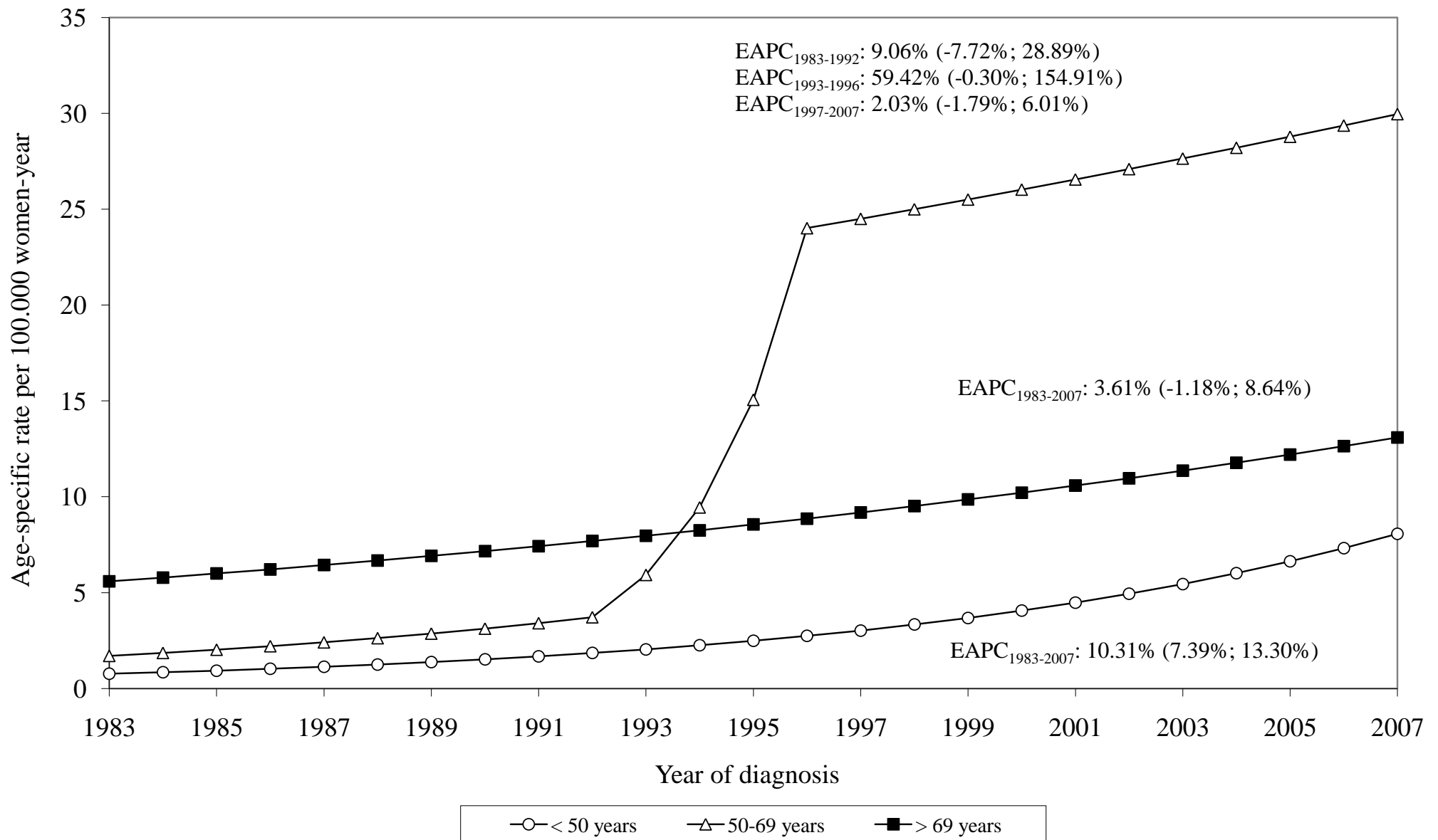
Incidence	1983-1987	1988-1992	1993-1997	1998-2002	2003-2007	Total 1983 - 2007
N	15	20	72	132	177	416
CR	1.33	1.63	5.52	9.61	11.20	6.29
ASR_w (95% CI)	1.01 (0.47-1.55)	1.23 (0.64-1.82)	4.41 (3.36-5.47)	7.17 (5.89-8.44)	8.24 (6.99-9.49)	4.78 (4.30-5.26)

Incidence rated expressed by 100,000 women-year. N: incident cases, CR: crude rate, ASR_w: standardized incidence rate, 95% CI: 95% of confidence interval

Figure 1. Trends in age-adjusted incidence of breast ductal carcinoma *in situ* in Girona (Spain), 1983-2007.

The observed rates (dotted lines) were obtained by using age-adjusted incidence for each year, and the estimated temporal trends (solid lines) were obtained from fitting a joinpoint model (see “Materials and Method”).

Figure 2. Trends in age-specific breast ductal carcinoma *in situ* rates from 1983 to 2007 among women aged <50, 50-69 and >70 years in Girona (Spain)



The estimated temporal trends were obtained from fitting a joinpoint model in women aged < 50, 50-69 and >70 years (see “Materials and Methods”).

Figure 3. Age-specific incidence of breast ductal carcinoma *in situ* by age groups in Girona (Spain), 1983-2007.

