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Temporal changes in the incidence of ductal carcinoma *in situ* in Goiânia, Brazil: a population-based study

Nayara Alves de Freitas-Lemos[1], Ruffo Freitas-Junior[1,2]*, Carleane Maciel Bandeira e Silva[3], Marise Amaral Rebouças Moreira[4], Élbio Candido de Paula[5], Nilceana Maya Aires Freitas[6], Edesio Martins[1], José Carlos de Oliveira[3], Carolina Maciel Reis Gonzaga[1], Marcus Nascimento Borges[1], Julio Roberto Macedo Bernardes Junior[7], Ricardo Francalacci Savaris[8], Régis Resende Paulinelli[1], Luiz Fernando Pádua Oliveira[1], Leonardo Ribeiro Soares[1], Rosemar Macedo Sousa Rahal[1]

ABSTRACT

Introduction: Mammography screening has resulted in a considerable increase in the diagnosis of early-stage tumors in various countries. However, most available data refer to high-income countries, hospital-based studies, or studies with limited follow-up. Therefore the aim of this study was to determine the incidence of ductal carcinoma in situ (DCIS) in Goiânia, Brazil. **Methods:** Ecological study among residents of the city of Goiânia, Brazil. We included all the DCIS cases registered at the Goiânia population-based cancer registry between 1994 and 2010. Crude incidence and age-standardized incidence rates (using the world standard population) were calculated. Poisson regression was used to analyze temporal changes, with the average annual percent change (AAPC) in the crude and age-standardized incidence rates being calculated. **Results:** There were 261 cases of DCIS, with an annual incidence rate that ranged from 0.58 to 4.21 per 1,000 women (crude and standardized) over the period. The number of cases of DCIS in the 40–49 and 60–69-years age groups increased significantly (p<0.01). The AAPC of the crude incidence rate for the period was 11.88% per year (95%CI 9–15; p<0.01) and the standardized rate was 11.89% per year (95%CI 9–15; p<0.01). **Conclusions:** The incidence of DCIS in Goiânia increased between 1994 and 2010, possibly due to improved mammography screening. The present study, which was conducted in a consolidated population-based cancer registry (PBCR) and involved an extensive follow-up time, could contribute towards increasing epidemiological knowledge on DCIS and its variations around the world.

KEYWORDS: breast carcinoma in situ; breast neoplasms; incidence; epidemiology; cesium.

INTRODUCTION

Ductal carcinoma *in situ* (DCIS) is a form of breast cancer characterized by abnormal cell proliferation confined within the basement membrane. It may present with extensive ductal involvement and lesions that render differential diagnosis difficult.[1,2] Since DCIS is considered a precursor lesion, a reduction was expected in breast cancer incidence and mortality following the advances made in the approach to DCIS over recent decades. However, even with an estimated 50,000–60,000 surgical procedures performed annually to resect DCIS, controversies remain regarding the progression of the disease and its epidemiological variations.[3,4]

The incidence of DCIS has increased expressively over recent years, perhaps as the result of the consolidation of population-based mammography screening programs and of the advances made in diagnostic methods.[2,5,6] Nevertheless, there are major

[1]Universidade Federal de Goiás, Advanced Center for Diagnosis and Treatment for Breast Cancer – Goiânia (GO), Brazil.
[2]Associação de Combate ao Câncer de Goiás, Hospital Araújo Jorge, Gynaecology and Breast Unit – Goiânia (GO), Brazil.
[3]Associação de Combate ao Câncer de Goiás, Goiânia Population-Based Cancer Registry – Goiânia (GO), Brazil.
[4]Universidade Federal de Goiás, Pathology Department – Goiânia (GO), Brazil.
[5]Association for the Combat of Cancer in Goiás, Hospital Araújo Jorge, Surgical Pathology Department – Goiânia (GO), Brazil.
[6]Association for the Combat of Cancer in Goiás, Hospital Araújo Jorge, Radiotherapy Department – Goiânia (GO), Brazil.
[7]Santa Casa de Misericórdia, Breast Department – Goiânia (GO), Brazil.
[8]Universidade Federal do Rio Grande do Sul, Surgical Sciences – Porto Alegre (RS), Brazil.
***Corresponding author:** ruffojr@terra.com.br
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differences in the rates found in different countries, with less developed countries tending to have relatively lower values. However, in less developed countries, most of the data on DCIS originate from retrospective, hospital-based studies, with incidence rates that range from 2.5 to 24.4%.[7-9] In this respect, the lack of data originating from population-based studies hampers understanding of the disease and the creation of specific public policies.[8]

Since PBCRs record incident cases of cancer in a defined population over a period of time, their use in real-world studies allows a wider exploratory data analysis to be conducted and includes the possibility of external validation. The city of Goiânia, situated in midwestern Brazil, has the longest continuously operating PBCR in the country.[10] Therefore, the objective of the present study was to determine the temporal changes in the incidence of DCIS at a PBCR in midwestern Brazil.

METHODS

An ecological study was conducted between January 1994 and December 2010 on women with DCIS. This period was chosen due to the completeness of the 10-year overall survival data, which will be reported in another study. The cases were extracted from the database of the Goiânia PBCR where data on all new cases of cancer in the municipality are collected and recorded. This PBCR was developed in 1986, and has uninterruptedly been registering all new cases of cancer in residents of the municipality of Goiânia since its creation.[10]

Cases

All cases registered as DCIS that were diagnosed in the city of Goiânia between 1994 and 2010 were included in the study. Following analysis, cases in which the women had only moved to the city after being diagnosed (untrue city residents), cases for which there was a bias in data collection (inconclusive information), and any cases in which DCIS was associated with an invasive or micro-invasive carcinoma were excluded from the study sample.[11]

Variables

The patients were divided into the following age groups: 30–39 years, 40–49 years, 50–59 years, 60-69 years and ≥70 years. Data regarding the size of the lesion (taking into consideration the largest measurement in centimeters) and nuclear grade were obtained from the surgical pathology reports. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expressions were classified as positive or negative with respect to the initial *in situ* lesion, in accordance with the description on the immunohistochemical report.

Statistical analysis

The database was created using Excel, version 2003 (Microsoft Corporation, Redmond, WA, USA). The frequency of all the variables was determined and the analysis of central tendency was performed whenever pertinent.

The crude incidence rate was defined as the ratio between the number of new cases of breast cancer *in situ* diagnosed annually and the number of women exposed to the risk of developing the disease at the midpoint of the respective year, with the result being expressed as a coefficient per 100,000 women.[12] The female population of Goiânia considered to have been exposed to the risk of cancer was calculated for each respective year based on the population census data for 1991, 2000 and 2010 and on the intercensal data for the other years.[13] The annual standardized incidence rate was calculated for each age group based on the world standard population according to Doll and Cook.[14]

The temporal changes in the incidence of DCIS were analyzed using Poisson jointpoint regression model (JoinPoint Regression, version 4.3.0, the National Cancer Institute, USA).[15] The average annual percent change (AAPC) in the crude incidence rate and in the age-standardized incidence rate was calculated. The 95% confidence intervals (95%CI) were calculated and p-values<0.05 were considered statistically significant. Statistical Package for the Social Sciences (SPSS) for Windows, version 13.0 (IBM Corp, Armonk, NY, USA) was used for the other statistical analyses.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Institutional Ethics Committee approved the study protocol with the register number 1.940.921 (CAAE 64258216.5.0000.5078). This study fully complies with the current law of the country in which it was conducted.

RESULTS

Characterization of the sample

Between 1994 and 2010, 376 cases of carcinoma *in situ* were identified; however, 115 of these cases (44%) were excluded either because they did not comply with the classification of DCIS or due to missing data. A total of 261 cases of DCIS were included in the analysis (Figure 1).

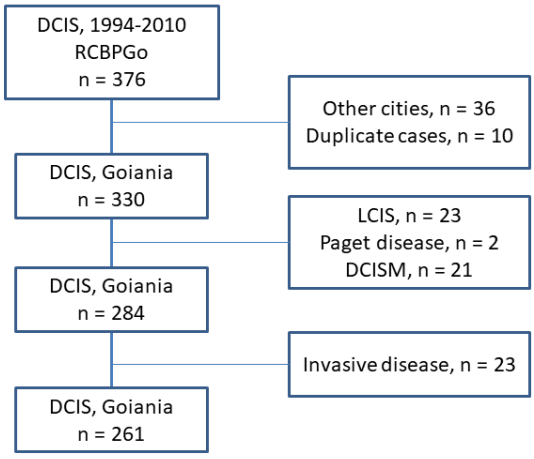
Most of the cases of DCIS registered in Goiânia occurred in women of 40 to 49 years of age (n=80), with peak registration occurring in 2009 (n=38). Tumor size was described in 51% of the surgical pathology reports, with mean size being 1.4 cm. The classification of nuclear grade was described in 68% of the reports, with 19% of the cases of DCIS being classified as grade I, 44% as grade II, and 37% as grade III. Immunohistochemical reports were available from 139 cases (49%). Of these, 56% were estrogen receptor (ER) and/or progesterone receptor (PR) positive, 26% were HER-2 positive, and 4% were triple-negative (Table 1).

Incidence

While in the 1994-2010 period 5,277 cases of invasive breast cancer were registered, with an increase from 155 cases in 1994 to 425 in 2010, there were four cases of DCIS in 1994 and 21 in 2010. For the cases of DCIS, an increase of 425% was found in relation to the first year, while cases of invasive breast cancer had an increment of 174% over the same period (Figure 2). Considering the total number of cases, the relative rate of DCIS was 4.94% (261/5,277). This increase was confirmed from the AAPC, both for DCIS and for invasive carcinomas, corresponding to 15.5 (95%CI 12.5–18.7) and 7.2 (95%CI 6.0–8.5), respectively (p<0.01).

The crude annual incidence rate of DCIS was 1.33/100,000 in 1994, and 4.21/100,000 in 2010. The incidence rate adjusted for the Doll and Cook[14] world standard population was 0.58/100,000 in 1994, and 1.85/100,000 in 2010. There was an annual increase both in the crude incidence rate of 11.93% (95%CI 9–15; p<0.01) and in the standardized rate of 11.94 (95%CI 9–15; p<0.01).

Stratifying the incidence for each 10-year age group, a significant growth was found in the number of cases of DCIS for the 40-49 years and 60-69 years age groups (p<0.01). The crude incidence rates and those standardized according to age are shown in Table 2 for 1994 and 2010 according to age groups and with the respective AAPC for each rate.



DCIS: ductal carcinoma *in situ*
RCBPGo: Registro de Câncer de Base Populacional de Goiânia
LCIS: Lobular Carcinoma *in situ*

Figure 1. Flowchart of patients included in the study.

Table 1. Characteristics of the primary tumor as retrieved from the surgical pathology and immunohistochemical reports.

Characteristics	n (%)
Age (years)*	54.21±12.30
Tumor size (cm)*	1.39±1.69
Nuclear grade	
Low (I)	31 (18.3)
High (II/III)	138 (81.7)
Total	169
Estrogen receptor	
Positive	94 (75.8)
Negative	30 (24.2)
Total	124
Progesterone receptor	
Positive	80 (66.1)
Negative	41 (33.9)
Total	121
HER2	
Positive	36 (30.8)
Negative	81 (69.2)
Total	117

*Mean±standard deviation. HER2: human epidermal growth factor receptor 2.

DISCUSSION

The incidence of DCIS has increased expressively in recent years, possibly as a result of the consolidation of population-based mammography screening programs and the advances made in diagnostic methods.[2,6,8] In Brazil, according to a telephone survey conducted with almost 268,000 individuals, mammography coverage in the country increased from 71% to 78% between 2007 and 2016.[16] Nevertheless, there is a huge difference between the rates found in different countries, with low-to-middle income countries tending to have a relatively low incidence rate compared to developed countries.[3,7-9] The present study, which was conducted in a consolidated PBCR and involved an extensive follow-up time, could contribute towards elevating epidemiological knowledge on DCIS and its variations around the world.

In the United States, according to data from the Surveillance, Epidemiology and End Results (SEER) program, the incidence of DCIS had a rapid growth following the introduction of mammography screening in the 1980s. Nevertheless, despite the stabilization

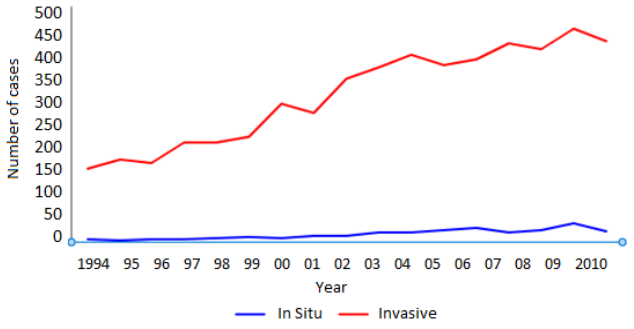


Figure 2. Evolution of the number of cases of carcinoma in situ and invasive carcinoma, in residents of Goiânia, over the years studied.

Table 2. The average annual percent change in the crude incidence rate and in the age-standardized incidence rate of ductal carcinoma *in situ* in the city of Goiânia (GO) between 1994 and 2010.

Age group (years)	Crude rate by age group*				Age-standardized incidence rate*			
	1994	2010	AAPC (95%CI)	p-value	1994	2010	AAPC (95%CI)	p-value
30–39†	1.24	1.71	-	-	0.15	0.21	-	-
40–49	1.99	5.23	6.19 (2.0–10.5)	<0.01	0.24	0.63	6.21 (2.0–10.6)	<0.01
50–59	6.06	6.36	7.46 (-0.3–15.8)	0.07	0.55	0.57	7.49 (-0.3–15.9)	0.07
60–69	0	12.40	10.35 (4.3–16.8)	<0.01	-	0.87	10.35 (4.2–16.8)	<0.01
≥70	0	12.69	10.13 (-2.5–24.4)	0.11	-	0.51	10.31 (-2.5–24.8)	0.09

AAPC: average annual percent change; 95%CI: 95% confidence interval; *Incidence rates per 100,000 women; †For the 30-39 years age group, analysis of the AAPC proved impossible since no cases were registered in some of the periods analyzed; There was only one case under 30 years of age over the entire period evaluated, making analysis of the AAPC impossible.

of screening rates over the past ten years, an AAPC of 0.8% was seen in the incidence of DCIS between 1992 and 2011.[3] In the present study, an increase of 425% was found in the standardized incidence rate of DCIS, which ranged from 0.58/100,000 in 1994 to 1.85/100,000 in 2010. Over the same period, the incidence of invasive carcinoma increased 174%. Possible explanations for this difference in proportion include the transition from analogical mammography to digital mammography and the improvement of other diagnostic methods, which could have increased the detection of early lesions.[2,3] In low-to-middle income countries, this improvement in technology occurred much later and is still occurring in some regions, explaining the elevated trend of a rise in relation to the US data for the same period.[3] Furthermore, expanded knowledge on the histology of the disease and other initiatives involving quality control in mammography could also have contributed to this increase in incidence between 1994 and 2010.[1,2,17]

The incidence of DCIS also varied according to age, race and other clinical factors. In the United States, where there is less racial miscegenation compared to the Brazilian population, a different distribution of prognostic factors was found between the racial groups analyzed, together with different incidence rates.[3,5] In the evaluation by age group, the correlation between the reduction in DCIS in women of 50-69 years of age between 2002 and 2006 and the reduction in the prescription of combined hormone replacement therapy following publication of the Women's Health Initiative (WHI) study merits particular attention.[3,18] In the same period, there was no statistically significant difference in the incidence curve in women of 40 to 49 years of age.[18] These data differ from those found in the present study, possibly due to different genetic factors or risk exposures.[19] Furthermore, the occurrence of DCIS in the over-70s (9.5%), an age group that is excluded from the majority of screening guidelines worldwide is also noteworthy.[20,21] Despite questioning on over-diagnosis and overtreatment in this population,[22] this is a very heterogenous group in which screening should be individualized in accordance with clinical status rather than chronological age alone.[23]

Considering age at diagnosis, women with DCIS also tend to be diagnosed at a younger age compared to those with an invasive carcinoma. While invasive disease is more prevalent in the 50 to 59-year age group,[9,24] DCIS appears to be more prevalent in women of 40 to 49 years of age. These data reinforce the theory that DCIS is a precursor lesion that could take up to ten years to invade the basement membrane and the breast stroma. Nevertheless, the possibility that the carcinogenesis of DCIS is different from that of invasive carcinoma and that different factors could sometimes affect the biological behavior of these pathologies cannot be ruled out.[1,2,25]

Another interesting point in the incidence of DCIS in the city of Goiânia involves the radioactive contamination accident that occurred in 1987 and the possible increase in cancer cases resulting from exposure to ionizing radiation.[26-28] Considering a latency time of 10 years, peak incidence would be expected to occur in 1997, and this was not seen. Furthermore, the incidence rate of DCIS in the city of Goiânia was found to be similar to that of the other Brazilian state capital cities where the higher incidence over time has occurred gradually.[29] These data, along with the findings of other epidemiological studies conducted in the region, suggest that there is no association between the accident involving cesium-137 and the incidence of breast cancer and DCIS.[27,28]

In recent years, in addition to the growth in the incidence rates of DCIS, a favorable change has also been seen in tumor stage at the time of diagnosis. Different studies have evaluated breast cancer staging in Brazil and, despite the inherent limitations of retrospective studies, a wide variation was found in the effectiveness of mammography screening. In the city of Barretos,[8]

which has the best organized screening system in the country, the incidence rate of DCIS was much higher than that seen in the cities of Curitiba[7] and São Paulo,[30] with rates of 16.5%, 2.9% and 8.1%, respectively. In Goiânia, the relative rate of DCIS was only 5%, which is also proportional to the poor mammography coverage (14.7%) within the public healthcare system in the mid-western region of the country.[31]

The limitations of the present study include its retrospective design and the loss of 44% of the sample due to missing or contradictory data in the Goiânia PBCR database. These limitations, however, are inherent to population-based studies,[14,32] and do not affect the credibility or the relevance of the results found. On the other hand, the strongpoints of the study were the long follow-up time and the secondary verification of the surgical pathology data that give greater robustness and innovativeness to the study.

CONCLUSIONS

The incidence of DCIS in the city of Goiânia increased between 1994 and 2010, possibly due to improved mammography screening. This increase differed as a function of the age groups analyzed and was relatively higher than the increase in the incidence of invasive carcinoma. Finally, the observed incidence was similar to the average in other regions, according to the literature.

AUTHORS' CONTRIBUTION

NAFL: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. RFJ: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing. CMBS: Conceptualization, Data curation, Formal analysis, Project administration, Software, Validation, Visualization, Writing – review & editing. MARM: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – review & editing. ECP: Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – review & editing. NMAF: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing. JCO: Conceptualization, Methodology, Project administration, Software, Validation, Visualization, Writing – review & editing. CMRG: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. MNB: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. JRMBJ: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. RFS: Conceptualization, Formal analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing. RRP: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. LFPO: Conceptualization, Data curation, Methodology, Validation, Writing – review & editing. LRS: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. RMSR: Conceptualization, Data curation, Methodology, Validation, Supervision, Writing – review & editing.

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