REVIEW ARTICLE
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NATURAL HISTORY OF DUCTAL CARCINOMA *IN SITU*

História natural do carcinoma ductal *in situ*

Nayara Alves de Freitas Lemos[1], Ruffo Freitas-Junior[2]*, Marise Amaral Rebouças Moreira[3], Fábio Francisco Oliveira Rodrigues[4]

ABSTRACT

Ductal carcinoma *in situ* (DCIS) has been detected more frequently in the last decades using the mammographic screening. The objective of the present study was to review the epidemiological aspects of DCIS. A bibliographic narrative review was carried out focusing on the following aspects: the epidemiology of DCIS to discuss subtypes; natural history; screening; and survival. It was possible to verify that the DCIS is currently considered a precursor lesion of breast cancer, presenting a considerable and uneven increased incidence between developed and developing countries, probably due to the inclusion of mammographic screening programs. There are controversies regarding the benefit or not of its detection, diagnosis, treatment and survival of patients with DCIS. It is concluded that the considerable increase in the incidence of DCIS raises an important discussion about the real need for its diagnosis as well as its real biological significance.

KEYWORDS: noninfiltrating intraductal carcinoma; breast neoplasms; epidemiology; incidence; carcinoma *in situ*.

RESUMO

O carcinoma ductal *in situ* (CDIS) tem sido detectado com maior frequência nas últimas décadas a partir do rastreamento mamográfico. O objetivo do presente estudo foi revisar os aspectos epidemiológicos do CDIS. Foi realizada uma revisão bibliográfica narrativa enfocando os aspectos do CDIS: epidemiologia, para discussão a respeito dos subtipos; história natural; rastreamento; e sobrevida. Foi possível verificar que o CDIS é atualmente considerado como uma lesão precursora do câncer de mama e apresenta aumento considerável e desigual em sua incidência entre países desenvolvidos e em desenvolvimento, devido, provavelmente, à inclusão dos programas de rastreamento mamográfico. Há controversas quanto ao benefício ou não da detecção, do diagnóstico, do tratamento e da sobrevida de pacientes que apresentam o CDIS. Conclui-se que o aumento considerável da incidência do CDIS levanta importante discussão sobre a necessidade real de seu diagnóstico, bem como do seu real significado biológico.

PALAVRAS-CHAVE: carcinoma intraductal não infiltrante; neoplasias da mama; epidemiologia; incidência; carcinoma *in situ*.

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[1]Rede Goiana de Pesquisa em Mastologia – Goiânia (GO), Brazil.
[2]Universidade Federal de Goiás – Goiânia (GO), Brazil.
[3]School of Medicine, Universidade Federal de Goiás – Goiânia (GO), Brazil.
[4]Instituto do Câncer Dr. Arnaldo Vieira de Carvalho – São Paulo (SP), Brazil.
***Corresponding author:** ruffojr@terra.com.br
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DUCTAL CARCINOMA *IN SITU*

Ductal carcinoma *in situ* (DCIS) comprises heterogeneous lesions resulting from abnormal cell proliferation in the mammary ducts, characterized by non-invasion of the basement membrane; its differentiation from atypical ductal hyperplasia (ADH) is complex, taking into account the number of layers of proliferated cells and the wide variety of interobserver interpretation due to the proliferation of the number of cell layers[1]. Although a different terminology was proposed for DCIS, the World Health Organization (WHO), in their last consensus, in 2012, chose to maintain the classical nomenclature of intraductal proliferative lesions[2]. According to the TNM classification of the Union for International Cancer Control (UICC), DCIS is defined as Tis (DCIS) ductal carcinoma *in situ*, stage 0 (TisN0M0)[3]. Based on its architectural characteristics, the DCIS is classified into four morphologies: micropapillary, cribriform, solid and comedo[1].

EPIDEMIOLOGY

DCIS has been detected more frequently in the last decades, which calls the attention of medical surgeons, pathologists and researchers. Of rare occurrence in the mid-1970s, since the introduction of mammographic screening programs, it has accounted for approximately 20% of breast cancer cases detected in countries where there is organized population screening[4]. This increase has been most observed among women over 50 years of age (Table 1)[5].

The prevalence is higher in White women, followed by Hispanic Whites, Black and Asians in the Pacific region[6]. The incidence of DCIS, when adjusted for age, is higher among Caucasian women, followed by African American and Asian women in the Pacific region, compared to Latin American women[7]. In Brazil, little information has been published on the epidemiology of carcinomas *in situ*[8]. It is estimated that its incidence varies between 6.6 and 8.9%[9-11]. In Goiânia, data from the Population-Based Cancer Registry showed a significant increase in carcinoma *in situ* cases, from 0.2 to 6.2% between 1989 and 2003[10].

MAMMOGRAPHY SCREENING

Because DCIS is not specifically screened, it is diagnosed more frequently as a consequence of screening for invasive breast cancer. As its etiology is presumably heterogeneous, prognostic evaluation based on pathology and imaging findings is highly variable[12].

If, on the one hand, the mammography screening allows a considerable increase in the diagnosis of initial tumors and a substantial increase in the number of DCIS cases, on the other, this strategy of secondary prevention has also led to an increase in the so-called superdiagnosis[13]. This term is used for DCISs that would not evolve into the invasive variant and are nevertheless detected by screening exams[14]. Cases of superdiagnosis are reported more frequently on low-grade nuclear DCIS[15,16] in which active surveillance and individualization of treatments should be based on prospective studies[13].

Although there is controversy, the benefit of the mammography screening in terms of saved lives is greater than the excess of diagnoses, since for each case of superdiagnosis, three lives are saved in groups of women submitted to the screening[17].

In Brazil, the connection between the adequate mammography screening and the incidence of DCIS can be indirectly verified, with data from the population screening program in the Barretos region: there is a 20% incidence of DCIS among all tumors detected between 2003 and 2010[18]. Table 2 summarizes the prevalence of DCIS reported in Brazil between 2000 and 2014.

RISK FACTORS

Regarding risk reduction factors related to breast cancer, Inumaru et al.[19] highlighted lactation and the practice of physical activities, both pre- and post-menopausal. The change in women's lifestyle has been indicated as an important factor related to the increase in the incidence of breast cancer[20]. Currently, women schedule less pregnancies, breastfeed for a shorter period, or even choose not to have children; when they do so, it usually is later on. In addition, they adopt unhealthy lifestyle habits, which lead to an increased body mass index, also considered a risk factor[12]. In less developed countries, the incidence of breast cancer is higher in premenopausal women, because the female population is younger and postmenopausal risk factors are not present[21]. Decreased use of postmenopausal hormone therapy has been suggested as responsible for the decline in the incidence of invasive breast cancer since 2003[22].

For DCIS, the association with the use of hormones (estrogen and progesterone), or even an increase in the estimation of time-dependent risk, would be uncertain[23]. However, a study conducted in Norway involving 681 cases of DCIS, registered a 1.61% risk related to the long-term use of combinations of estrogen and progesterone[24].

Table 1. New estimated cases of female breast cancer and deaths by age in the United States, 2013.

Age	In situ cases	Invasive cases	Deaths
<40	1,900	10,980	1,020
<50	15,650	48,910	4,780
50–64	26,770	84,210	11,970
65+	22,220	99,220	22,870
All ages	64,640	232,340	39,620

Table 2. Prevalence of cases of ductal carcinoma ***in situ*** in Brazil until 2014.

City – State	Period/year	Total of DCIS cases	DCIS prevalence (%)
São Carlos – SP	2000 to 2004	106	6.6
São Paulo – SP	2012 to 2014	288	8.1
Lavras – MG	2008 to 2013	112	8.9

DCIS: ductal carcinoma ***in situ***.

NATURAL HISTORY

Evidence on the natural history of the progression of invading DCIS refers to different malignant changes in the ductal epithelium[25], which is associated with different stages in the progression to a subsequent invasive carcinoma. However, the proportion of untreated DCIS that will develop to invasive breast cancer is unknown[12].

It is observed that the cells most prone to invasion are located at the end of the duct which is regulated, preferably, by the mechanisms of adhesion and cellular contractility. During the progression of breast cancer, there are cellular morphological alterations in which the cribriform and comedo subtypes represent the final stages of DCIS[26]. Figures 1 to 3 illustrate the DCIS in different nuclear grades and histological subtypes.

Neoplastic cells in DCISs and in invasive ductal carcinomas show similarities at molecular levels that translate into similar global profiles of gene and immunophenotypic expression[27]. The biological differences between DCIS and invasive breast carcinoma have not yet been adequately identified[28], and the main known molecular phenotypes found in invasive breast cancer are similar, but different in prevalence[29]. Estrogen receptor expression is strongly associated with low grade DCIS, whereas HER2 overexpression is linked to high grade DCIS[27].

Current evidences suggest that the transition from carcinoma *in situ* to invasive breast cancer depends on microenvironmental interactions, since the levels of change in DCIS genomic copy numbers correlate positively with the presence of immune cells, and that the invasive disease could require a number of copies leading to tumor "immunosuppression"[30]. The expression of tumor-infiltrating lymphocytes is higher in high-grade nuclear DCIS, with comedo necrosis, negative RE and positive HER2[30].

In many cases, myoepithelial cells are abnormal presenting loss of function of tumor suppressor genes[31]. In addition, the interaction between stromal and epithelial cells contributes to the phenomenon of tumor cells invasion[31].

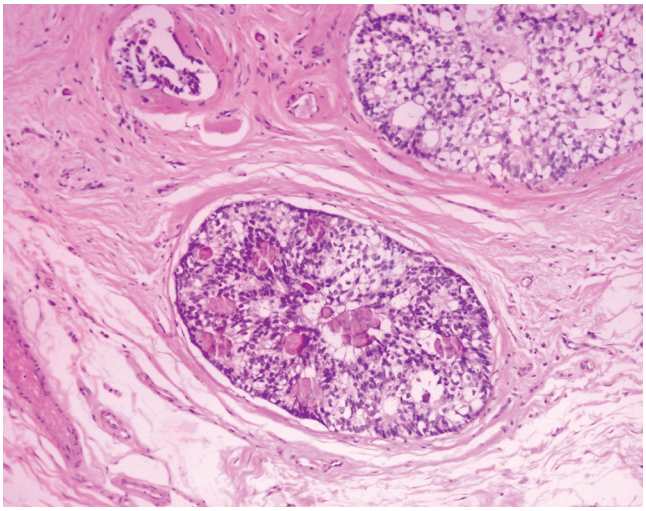

Figure 1. Ductal carcinoma *in situ* stage I, cribriform with foci of calcification (HE 100x).

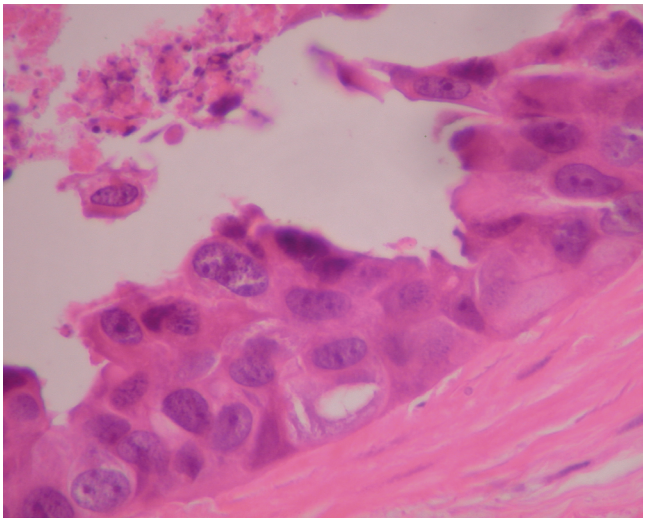

Figure 2. Ductal carcinoma *in situ* stage III, comedocarcinoma (HE 400x).

SURVIVAL

Women with a diagnosis of DCIS have high global survival rates and are close to 100%[32-35], as shown in Table 3. These studies relate

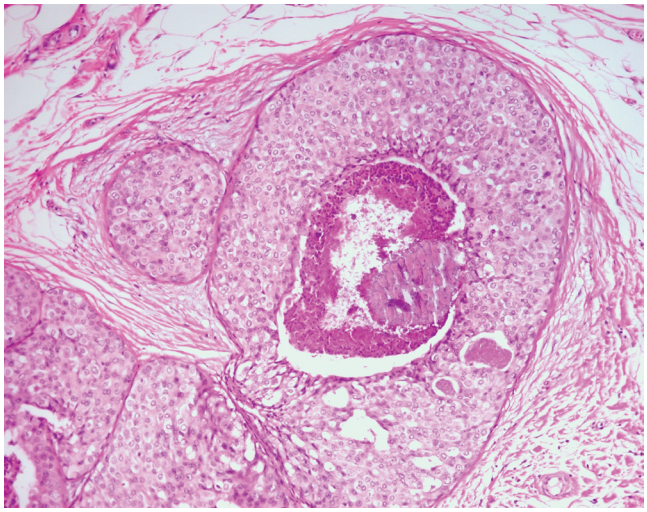

Figure 3. Ductal carcinoma *in situ* stage II (HE 200x).

Table 3. Surviv al rates reported for women with ductal carcinoma *in situ*.

	Sagara et al., 2015 (%)	Shikama et al., 2015 (%)	Worni et al., 2015 (%)	Wadsten et al., 2016 (%)
Cancer-specific survival	98.4	91	–	97
Global survival	89.3	97	98	–

the following factors of higher local survival: low nuclear grade DCIS; conservative surgery associated with radiotherapy; and free surgical margins[36,37].

The benefit of surgery for low nuclear grade DCIS is lower than in intermediate and high grade cases, compared to the results of a large study using data from Surveillance, Epidemiology, and End Results Program (SEER). Patients with low nuclear grade tumors who did not receive surgical treatment presented as little chance of evolution as those who received it, unlike women with high nuclear grade DCIS[32].

In prospective studies, there are increased rates of disease-free survival in patients with DCIS who have used Tamoxifen, especially when associated with conservative surgery and radiotherapy, as well as in young patients with positive estrogen receptors[36,37].

The number of invasive relapses is lower when DCIS cases are detected by screening methods compared to symptomatic DCIS, in addition to patients having longer disease-free survival[37]. Low recurrence rates are found in patients treated with mastectomy[38].

The rates of DCIS relapse are of the order of 10 to 35%, considering risk factors: high nuclear grade; compromised margins; and women younger in age[16,38,39], in this scenario about 35% occur in an invasive manner[40].

From the review, there is controversy regarding the detection of DCIS. On the one hand, greater survival, on the other, superdiagnosis. Thus, it is necessary for the DCIS to be considered with special attention in order to know its natural history, which would change the understanding for its approach and reduce the need for screening.

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