Epidemiology of Ductal Carcinoma In Situ

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Rezumat
Carcinomul ductal in situ (CDIS) este considerat a fi precursorul direct al majorităţii cazurilor de cancer mamar, incidenţa lui crescând cu vârsta. Totuşi, impresionanta creştere globală a cazurilor de CDIS este probabil un “artefact” epidemiologic datorat în principal instituirii mamografiei de screening în țările dezvoltate. Mai mult, considerând că de cele mai multe ori nu sunt decelate semne clinice ale bolii, depistarea iniţială a CDIS reprezintă cel mai frecvent un “eveniment” mammografic. Factorii de risc ai CDIS sunt similari cu cei ai cancerului invaziv, inclusiv, printre altele, mutaţiile genelor BRCA, istoricul familial de cancer mamar, nuliparitatea, vârsta avansată la prima naştere, densitatea mamară crescută, istoricul personal de patologii mamare benigne și obezitatea post-menopauzală.

Cuvinte cheie: carcinom ductal in situ, sân, epidemiologie, incidență, factori de risc

Abstract
Ductal carcinoma in situ (DCIS) is thought to be a direct precursor of most cases of breast cancer and its incidence increases with age. However, the globally impressive rise of DCIS cases is probably an epidemiologic “artifact” that is mainly attributed to the establishment of screening mammography in developed countries. Furthermore, considering that usually there are no clinical findings of the disease, the initial detection of DCIS is a mammographic “event” in most cases. The risk factors for DCIS are similar to those for invasive cancer including, among others, deleterious mutations in the BRCA genes, family history of
breast cancer, nulliparity, late age at first birth, increased breast density, personal history of benign breast disease, and postmenopausal obesity.

**Key words:** ductal carcinoma *in situ*, breast, epidemiology, incidence, risk factors

**Incidence**

Ductal carcinoma *in situ* (DCIS) is characterized by regional proliferation of malignant cells within the mammary lumens, without invading the basal membrane towards the adjacent stroma. It is thought to be a direct precursor of most cases of breast cancer and represents an advanced stage of premalignant tumor progression “starting” from hyperplasia and atypical hyperplasia (1).

It was assumed that most breast carcinomas are the terminal “stage” of DCIS. According to a simple model of breast carcinoma growth, it seems that 9 years is the mean time progression from a single cancer cell to an invasive lesion for the slowest growing lesions. For DCIS lesions, 6 years and 3 years are the mean time for intermediate growing and fast-growing lesions respectively to invasive cancer (2).

Ductal carcinoma *in situ* is extremely uncommon in women <30 years old and its incidence increases with age. The disease remains uncommon before age 35-39 (3). Even in the age group 40-49, DCIS is relatively rare (<1 per 1000 screening examinations [%]) and in the age group 70-84, DCIS is found in <1.5‰. Actually, among women diagnosed with DCIS in all ages, women greater than 80 years of age, constitute almost the 6% of the whole sample (4).

Approximately 1 in 33 women was likely to receive a DCIS diagnosis in her lifetime (5) and in all age groups, DCIS is less common than invasive breast cancer, consisting an approximately 20% of all breast malignancies in recent years. According to breast carcinoma *in situ* data deriving from the UK (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-in-situ#heading-One [accessed on May 24, 2021]), average number of new cases per year are concentrated in the age groups 50 to 54. On the other hand, the peak of the incidence rate per 100,000 corresponds to the age groups 65 to 69. It must be noted that as opposed to DCIS, LCIS is an uncommon finding with no specific mammographic features.

Although, during the last fifteen years, the occurrence of the disease reached a plateau, a five-way “increase” in the incidence of DCIS was documented during three decades, from the 1970s (<0.6‰) to 2000s (>3‰). In the United States (US), DCIS incidence rose from 1.87 per 100,000 in 1973-1975 to 32.5 in 2004 (6). In general, the greatest increases in DCIS incidence have been in non-comedo subtypes of DCIS that are not associated with subsequent invasive cancer (7). However, after many years of research, it is still not possible to accurately identify which DCIS lesions are unlikely to progress and, thus, which patients can be managed safely with no treatment beyond the diagnostic biopsy or excision of the lesion (8).

Until recently, approximately 50,000 cases of DCIS were diagnosed each year in the United States (US) which is the country with the highest incidence of DCIS and nowadays, more than 60,000 cases are expected each year in this country (8,9). However, it seems that the globally impressive rise of DCIS cases is an epidemiologic “artifact” that is mainly attributed to the establishment of screening imaging studies (mainly mammography) in developed countries, including US, Europe (10) and the UK. As an example, for breast carcinoma *in situ*, most cases in the UK were identified through the breast screening program. Thus, the incidence peaks when routine screening starts at age
For 2021, the American Cancer Society’s predicts that about 49,290 new cases of DCIS and about 281,550 new cases of invasive breast cancer will be diagnosed in women in the United States (https://www.cancer.org/cancer/breast-cancer/about/how-common-is-breast-cancer.html [accessed on May 21, 2021]). Thus, DCIS in 2021 consists less than 15% of all breast malignancies in USA, showing a probable decline in its incidence. Nevertheless, delays in DCIS treatment could impair the incidence of invasive breast cancer. Considering that in most cases, there are no clinical findings, the initial detection of DCIS is a mammographic “event” in >9 of each 10 cases. By definition, DCIS is a local (in situ) disease. However, in rare cases (less than 1%), local or distant metastases can be identified. In these cases, a comprehensive investigation of the patient could reveal an invasive cancer. Furthermore, in women diagnosed with DCIS and dying from breast cancer, mortality is not necessarily related to in-breast invasive recurrence in their lifetime (11). Finally, although the natural history of DCIS remains uncertain, among other factors, young age and lack of endocrine therapy (tamoxifen or aromatase inhibitors) were identified as risk factors for DCIS progression to invasive cancer (12).

**Risk Factors**

The risk factors for DCIS include deleterious mutations in the BRCA1/BRCA2 genes (DMBRCA), family history of breast cancer, nulliparity, late age at first birth (after age 30), increasing age, increased breast density, personal history of benign breast disease (such as atypical hyperplasia), possibly menarche and/or menopause at younger (before age 12) and/or older age (after age 55) respectively, and (postmenopausal) obesity. A recent multivariate analysis confirmed that age, family history of breast cancer, menopausal status, parity, and first live birth are the main risk factors for DCIS. However, some “new” factors were also included in the final conclusions, as physical activity and height, although the association of these factors with invasive cancer is already known (13).

**Factors Increasing the Risk**

**Mutations in the BRCA1/BRCA2 genes or other genetic mutations**

Mutations in the BRCA1/BRCA2 genes increase the risk of DCIS (https://moffitt.org/cancers/ductal-carcinoma-in-situ/risk-factors/ [accessed at 2021-05-22]) at younger ages. In particular, high-grade DCIS is more common in BRCA1 mutation carriers than in patients without a mutation (14). However, in the past, statistical risk models predicted a low prevalence rate of BRCA1 and BRCA2 in DCIS (15). Similarly, PIK3CA is possibly included in the mutated genes related to DCIS (16).

**Family history of breast cancer**

As mentioned above, a family history of breast cancer is associated with an increased risk of DCIS (https://moffitt.org/cancers/ductal-carcinoma-in-situ/risk-factors/ [accessed at 2021-05-22]), particularly among women with multiple relatives affected at early ages. Furthermore, among women with DCIS, a positive family history increases the risk of contralateral invasive breast cancer (by almost 50%) and the risk of mortality in younger women (17).

**Atypical ductal hyperplasia**

Atypical Ductal Hyperplasia is included in the factors increasing the risk of DCIS (https://moffitt.org/cancers/ductal-carcinoma-in-situ/risk-factors/ [accessed at 2021-05-22]). However, there are breast lesions that have characteristics of both Atypical Ductal Hyperplasia and DCIS with interobserver diagnostic variability and pathologic features that influence clinical outcomes (18). Furthermore, upgrade rates of conventional Atypical Ductal Hyperplasia are reported at ≤30% and rates for Atypical Ductal Hyperplasia bordering on DCIS are reported at ≥45% (19).
Benign breast disease

It was shown that a personal history of benign biopsied breast disease increases the risk of DCIS (20). However, it seems that a personal history of benign breast disease was more strongly associated with higher risk of low-grade DCIS than high-grade DCIS (21).

Increased breast density

It is well established that high mammographic density is a “precursor” of breast cancer and that women with low breast density are relatively protected from the disease. Although little research has been done on the relation of mammographic density and DCIS, it seems that the same relation exists between these two entities. In a logistic regression analysis from limited data, it was observed that breast density of ≥50% was strongly associated with both DCIS and invasive breast cancer compared with breast density of <10%. However, this association was stronger for DCIS, considering that odds ratios for invasive cancer and DCIS were 3.0 and >6.0 respectively (22). As a conclusion, it seems that the comparable strength of association for mammographic density with invasive breast cancer and DCIS supports the hypothesis that both diseases have a shared etiology (23). Furthermore, women with pure DCIS and increased breast density are more likely to be premenopausal, younger at the time of diagnosis, and to present with higher-grade disease (24).

Obesity

(Postmenopausal) obesity is strongly associated with breast cancer development. DCIS could also be implicated in this relation (https://moffitt.org/cancers/ductal-carcinoma-in-situ/risk-factors/ [accessed at 2021-05-22]). However, it was suggested that body mass index has greater influence on disease progression (25). This relation should be differentiated from the weight gain and obesity after breast cancer/DCIS diagnosis (26).

Older age

DCIS is a disease of older ages (13). As an example, in the age group 40-49, DCIS is confirmed in <1 per 1000 screening examinations and DCIS is extremely uncommon in women <30 years old. The youngest ever case of a 23-year-old nulliparous woman with high-grade ductal carcinoma in situ arising within a benign phyllodes tumor was presented a few years ago (27). However, the association of increasing age was found to be stronger with invasive breast cancer (28).

Age at first live birth

Age at first live birth after 30 years (https://moffitt.org/cancers/ductal-carcinoma-in-situ/risk-factors/ [accessed at 2021-05-22]) seems to increase the risk of DCIS compared to live birth before the age of twenty.

Oral contraception

Ten or more years of oral contraception showed a positive association with comedo-type DCIS. However, an inverse association of oral contraception was found for non-comedo DCIS (29).

Age at menopause

It seems that the age at menopause after 55 years increases the risk of DCIS almost 40% in comparison with younger ages (30).

Mammography

Although mammography is not a “real” risk factor for DCIS, having undergone mammography is considered as one of the most prevalent “risk factors” associated with a diagnosis of DCIS (7). The USA, compared to other countries, has the highest utilization of screening mammography and the highest incidence of DCIS. DCIS was not seen in the USA prior to the advent of screening mammography! Thus, it is suggested that probable misconceptions and strategies about DCIS have led to overdiagnosis of the disease (9).
Factors Increasing the Risk of Death after DCIS Diagnosis

It seems that risk factors for death from breast cancer following a DCIS diagnosis include confirmation of the disease before age 35 years and black ethnicity (31).

Factors with Probably no Effect on the Risk

Age at menarche
Data from different sources are not consistent. However, probably, the age at menarche is not associated with the risk of DCIS (29).

Duration of breastfeeding
Data from different sources are not consistent. However, probably, the duration of breastfeeding is not associated with the risk of DCIS (29, 32).

Alcohol consumption
Consumption of two or more alcoholic drinks/day is a known risk factor for invasive breast cancer. However, such a relation was not substantiated for DCIS (20,33,34) although high alcohol intake may be associated with risk of DCIS (19).

Smoking
Available data do not provide consistent evidence of an association of smoking with DCIS. Actually, after adjustment for covariates, smoking status, smoking intensity, duration and pack-years do not provide consistent evidence of an association of smoking with DCIS (32). Considering that some proliferative epithelial disorders could consist precursors of DCIS, the previous conclusion could be strengthened by the fact that cigarette smoking has no overall effects on proliferative epithelial disorders of the breast among postmenopausal women (35).

Raloxifene
Although raloxifene is associated with decreased invasive breast cancer risk, it has no protective role for DCIS (3). Furthermore, across placebo-controlled trials with raloxifene, in situ cancers occurred more often with raloxifene than with placebo or tamoxifen (36).

Menopausal hormone therapy (hormone replacement therapy)

Today, the menopausal hormone therapy is not considered a risk factor for DCIS although older data found such an association (24,37-41) or were inconclusive (42). However, in the updated information of at least one cancer center “taking estrogen-progestin hormone replacement therapy for more than five years after menopause” is included in the risk factors for DCIS (https://moffitt.org/cancers/ductal-carcinoma-in-situ/risk-factors/ [accessed at 2021-05-22]). Whether estrogen-alone use is associated with DCIS requires further investigation (39).

Factors Lowering the Risk for DCIS or Lowering the Risk of Invasive Breast Cancer in the Ipsilateral and/or Contralateral Breast after Surgical Treatment/Radiotherapy for DCIS

It was shown that tamoxifen lowers the risk of DCIS in women of reproductive age. On the other hand, raloxifene, as mentioned above, does not have such a protective role for DCIS (3). For postmenopausal women diagnosed and treated for DCIS, there is a protective role of aromatase inhibitors to lower the risk of invasive breast cancer in the ipsilateral and/or contralateral breast. However, this protection is related to anastrozole and not to letrozole or exemestane, which differs from the protection offered for lobular carcinoma in situ (with equal protective role of anastrozole and exemestane).

An inverse association of oral contraception was found for non-comedo DCIS (28).

As a conclusion, it seems that most risk factors for invasive estrogen (ER)+ breast cancer are also associated with increased risk of ER+ DCIS (24,43). However, some data suggest that high grade DCIS and comedo DCIS have stronger histopathologic and epidemiologic relations with breast cancer, while medium or low-grade DCIS and non-comedo DCIS have few common characteris-
tics with breast cancer or show absolutely different patterns of those related to the invasive disease. The previous relations are very important considering that patients presenting with a DCIS associated with comedo necrosis are more likely to have a microinvasive component in final pathology (44). However, although DCIS appears to be related to the underlying hormonal milieu, the postmenopausal hormone replacement therapy is not included in the risk factors for DCIS although older data found such an association (see above).

Factors Increasing the Risk of Recurrence of DCIS after Treatment

1. African-American race,
2. Larger tumor size, and
3. Close tumor margins (< 2 mm), which are potentially modifiable by the Georgios Iatrakis clinician were more strongly associated with increased risk of DCIS recurrence (45).

Additional modifiable risk factors might be the number of surgical excisions, and the administration of radiotherapy and/or adjuvant endocrine therapy.

Conflict of Interest

No conflicts of interests.

References

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