Clinical outcomes of patients with ductal carcinoma in situ in Hong Kong: 10-year territory-wide cancer registry study

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ABSTRACT

Background: Incidence of ductal carcinoma in situ (DCIS) has increased in recent decades because of breast cancer screening. This study comprised a long-term survival analysis of DCIS using 10-year territory-wide data from the Hong Kong Cancer Registry.

Methods: This study included all patients diagnosed with DCIS in Hong Kong from 1997 to 2006. Exclusion criteria were age <30 years or ≥70 years, lobular carcinoma in situ, Paget's disease, and co-existing invasive carcinoma. Patients were stratified into those diagnosed from 1997 to 2001 and those diagnosed from 2002 to 2006. The 5- and 10-year breast cancer–specific survival rates were evaluated; standardised mortality ratios were calculated.

Results: Among the 1391 patients in this study, 449 were diagnosed from 1997 to 2001, and 942 were diagnosed from 2002 to 2006. The mean age at diagnosis was 49.2±9.2 years. Overall, 51.2% of patients underwent mastectomy and 29.5% received adjuvant radiotherapy. The median follow-up interval was 11.6 years; overall breast cancer–specific mortality rates were 0.3% and 0.9% after 5 and 10 years of follow-up, respectively. In total, 109 patients (7.8%) developed invasive breast cancer after a considerable delay. Invasive breast cancer rates were comparable between patients diagnosed from 1997 to 2001 (n=37, 8.2%) and those diagnosed from 2002 to 2006 (n=72, 7.6%).

Conclusion: Despite excellent long-term survival among patients with DCIS, these patients were more likely to die of breast cancer, compared with the general population of women in Hong Kong.

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New knowledge added by this study

- The incidence of ductal carcinoma in situ (DCIS) has doubled from the late 1990s to early 2000s.
- Most patients with DCIS in Hong Kong undergo mastectomy.
- Breast cancer–specific mortality rates were 0.3% and 0.9% after 5 and 10 years of follow-up, respectively.
- The overall standardised mortality ratio of patients with DCIS was 5.7, compared with the general population of women in Hong Kong.

Implications for clinical practice or policy

- Surgery, with or without radiotherapy, remains the gold-standard treatment modality for patients with DCIS.
- Further investigation is needed regarding the cost-effectiveness of population-wide breast cancer screening implementation.

Introduction

Ductal carcinoma in situ (DCIS) is a premalignant disease in the breast cancer spectrum, in which cancer cells are confined within the basement membrane of the breast ductal system.[1] Because of the enhanced availability of breast imaging and breast cancer awareness, the incidence of DCIS has increased over the past two decades.[2] Although the incidence of invasive breast cancer has declined over the past decade, diagnoses of DCIS have continued to rise.[3]

Although DCIS is the earliest recognised form of breast cancer, its natural history remains largely unknown.[4,5] Long-term survival studies have found that mortality of DCIS could be as low as 3% over 10 years of follow-up.[6] The current gold standard treatment for DCIS is surgery, with or without radiotherapy, according to the type of surgery

performed on a particular patient. To the best of our knowledge, there has been no randomised controlled trial comparing mastectomy and breast-conserving surgery in the context of DCIS treatment; however, a meta-analysis suggested that local recurrence rates were substantially lower among women treated with mastectomy.[7]

In recent decades, the incidence of DCIS has increased due to the widespread use of breast imaging screenings, on the basis of enhanced breast cancer awareness. As in other screening-detected disorders, there is widespread debate regarding whether DCIS is overdiagnosed and overtreated. Some clinicians have advocated a watchful-waiting strategy for DCIS, with the presumption that not all DCIS will progress to invasive cancer.[8]

In contrast to many developed countries, a population-based breast cancer screening programme is not available in Hong Kong. A recent study showed that DCIS is more frequently detected and treated in the private sector in Hong Kong, compared with the public health care system. Notably, DCIS is reportedly detected more frequently among patients in higher social classes due to self-initiated breast screening; more than half of these patients undergo successful treatment with breast-conserving surgery.[9] Here, we present the results of long-term survival analyses based on a territory-wide breast cancer registry.

香港乳腺導管原位癌患者的臨床結果：十年全港癌症登記資料庫研究

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背景：找近幾十年來，乳腺癌篩查使乳腺導管原位癌的發病率有所增加。本研究使用來自香港癌症登記登記資料庫的10年全港數據，對乳腺導管原位癌進行長期活存分析。

方法：本研究納入1997年至2006年在香港診斷為乳腺導管原位癌的所有患者。排除標準為年齡30歲以下或70歲或以上、小葉原位癌、Paget病和並存浸潤癌。將患者分為1997年至2001年診斷組和2002年至2006年診斷組。對5年和10年乳腺癌特異性存活率進行評估，以及計算標準化死亡率。

結果：研究共1391名患者，包括由1997年至2001年診斷的449例以及由2002年至2006年診斷的942例。診斷時的平均年齡為49.2±9.2歲。總體而言，51.2%患者接受乳房切除術，而29.5%患者接受輔助放療。中位隨訪時間為11.6年。隨訪5年和10年後總體乳腺癌特異性死亡率分別為0.3%和0.9%。總計109名患者（7.8%）在相當長時間後才發展為浸潤性乳腺癌。1997年至2001年確診患者（n=37，8.2%）與2002年至2006年確診患者（n=72，7.6%）之間的浸潤性乳腺癌發生率相若。

結論：儘管DCIS患者的長期存活率很高，但與香港普通女性相比，這些患者更容易死於乳腺癌。

Methods

Data source

This was a retrospective analysis of a territory-wide, prospectively maintained database from the Hong Kong Cancer Registry, concerning patients diagnosed during the period from 1997 to 2006; data were censored in December 2015 for retrieval of long-term survival outcomes. The Hong Kong Cancer Registry is a population-based cancer registry managed by the Hong Kong Hospital Authority; this registry has been responsible for collecting basic demographic data, cancer site information, and cancer histology results for all patients diagnosed with cancer in all public and private medical institutions in Hong Kong since 1963. All raw data were validated by various cross-checking procedures involving the locally designed Cancer Case Audit System; they were scrutinised by multiple quality control processes, commensurate with the recommendations by the International Agency for Research on Cancer, a component of the World Health Organization. Queries and "unusual cases" were referred to a clinical oncologist for re-validation.

Cohort selection and statistics

Institutional review board approval was not needed for this retrospective review of a breast cancer registry database. This study included all patients with DCIS who were diagnosed from 1997 to 2006. Exclusion criteria were age <30 years or ≥70 years, lobular carcinoma in situ, Paget's disease, and co-existing invasive carcinoma (ie, diagnosed within 6 months of DCIS onset). Patients were stratified into those diagnosed from 1997 to 2001 and those diagnosed from 2002 to 2006. Five- and 10-year breast cancer–specific survival rates were evaluated; standardised mortality ratios were calculated (with reference to the general population of women in Hong Kong).

Results

From 1997 to 2006, 1391 patients were diagnosed with DCIS and included in the Hong Kong Cancer Registry breast cancer database. In total, 449 patients were diagnosed from 1997 to 2001, while 942 patients were diagnosed from 2002 to 2006. The mean age at diagnosis was 49.2±9.2 years. Most patients (43.5%) were aged 40 to 49 years (Table 1). More than half of the patients (n=712, 51.2%) underwent mastectomy, while 399 (28.7%) underwent breast-conserving surgery. Overall, 410 patients (29.5%) received adjuvant radiotherapy. In addition, 221 patients (15.9%) received risk-reducing hormonal therapy with tamoxifen (Table 1).

The median follow-up interval was 11.6 years; overall breast cancer–specific mortality rates were

TABLE 1. Baseline demographic data

Demographics	All (n=1391)	1997-2001 (n=449)	2002-2006 (n=942)
Age, years	49.2±9.2	48.3±9.2	49.6±9.2
Age-group			
30-34 years	53 (3.8%)	13 (2.9%)	40 (4.2%)
35-39 years	129 (9.3%)	54 (12.0%)	75 (8.0%)
40-44 years	295 (21.2%)	114 (25.4%)	181 (19.2%)
45-49 years	310 (22.3%)	88 (19.6%)	222 (23.6%)
50-54 years	229 (16.5%)	80 (17.8%)	149 (15.8%)
55-59 years	146 (10.5%)	31 (6.9%)	115 (12.2%)
60-64 years	107 (7.7%)	31 (6.9%)	76 (8.1%)
65-69 years	122 (8.8%)	38 (8.5%)	84 (8.9%)
Laterality			
Right	670 (48.2%)	207 (46.1%)	463 (49.2%)
Left	700 (50.3%)	234 (52.1%)	466 (49.5%)
Bilateral	21 (1.5%)	8 (1.8%)	13 (1.4%)
Grade			
Low	276 (19.8%)	54 (12.0%)	222 (23.6%)
Intermediate	326 (23.4%)	80 (17.8%)	246 (26.1%)
High	363 (26.1%)	90 (20.0%)	273 (29.0%)
Unknown	426 (30.6%)	225 (50.1%)	201 (21.3%)
ER status			
Positive	358 (25.7%)	74 (16.5%)	284 (30.1%)
Negative	105 (7.5%)	32 (7.1%)	73 (7.7%)
Unknown	928 (66.7%)	343 (76.4%)	585 (62.1%)
PR status			
Positive	354 (25.4%)	74 (16.5%)	280 (29.7%)
Negative	108 (7.8%)	31 (6.9%)	77 (8.2%)
Unknown	929 (66.8%)	344 (76.6%)	585 (62.1%)
HER2 status			
Positive	136 (9.8%)	25 (5.6%)	111 (11.8%)
Negative	232 (16.7%)	38 (8.5%)	194 (20.6%)
Unknown	1023 (73.5%)	386 (86.0%)	637 (67.6%)
Surgery			
Mastectomy	712 (51.2%)	264 (58.8%)	448 (47.6%)
Wide local excision	399 (28.7%)	121 (26.9%)	278 (29.5%)
Unknown	280 (20.1%)	64 (14.3%)	216 (22.9%)
Radiotherapy			
Yes	410 (29.5%)	98 (21.8%)	312 (33.1%)
No	375 (27.0%)	67 (14.9%)	308 (32.7%)
Unknown	606 (43.6%)	284 (63.3%)	322 (34.2%)
Hormone therapy			
Yes	221 (15.9%)	65 (14.5%)	156 (16.6%)
No	459 (33.0%)	44 (9.8%)	415 (44.1%)
Unknown	711 (51.1%)	340 (75.7%)	371 (39.4%)
Follow-up, years, median (range)	11.6 (0.1-18.9)	15.2 (0.3-18.9)	10.5 (0.1-13.9)
Follow-up interval			
0-4 years	71 (5.1%)	16 (3.6%)	55 (5.8%)
5-9 years	317 (22.8%)	22 (4.9%)	295 (31.3%)
10-14 years	733 (52.7%)	141 (31.4%)	592 (62.8%)
≥15 years	270 (19.4%)	270 (60.1%)	
Subsequent invasive breast cancer			
Yes	109 (7.8%)	37 (8.2%)	72 (7.6%)
No	1282 (92.2%)	412 (91.8%)	870 (92.4%)

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor; SD = standard deviation

* Data are presented as mean±standard deviation or No. (%), unless otherwise stated

0.3% and 0.9% after 5 and 10 years of follow-up, respectively (Table 2). In total, 109 patients (7.8%) developed invasive breast cancer after a considerable delay. Invasive breast cancer rates were comparable between patients diagnosed from 1997 to 2001 and those diagnosed from 2002 to 2006: 37 (8.2%) and 72 (7.6%), respectively (Table 1).

Subgroup analysis revealed higher breast cancer–specific mortality in patients with human epidermal growth factor receptor 2 (HER2)–positive DCIS after 10 years of follow-up, compared with patients who exhibited HER2-negative DCIS (2.9% vs 0%; P=0.0181, Fisher's exact test). In contrast, 10-year breast cancer–specific mortality rates were comparable between patients with low-/intermediate-grade DCIS and those with high-grade DCIS (0.5% vs 0.8%; P=0.6776).

The breast cancer–specific mortality rate (per 100 000) was 2.2 among patients aged 30 to 34 years; this rate slowly increased and peaked at 34.8 among patients aged 60 to 64 years (Table 3). Patients with DCIS were more likely to die of breast cancer, compared with the general population of women in Hong Kong (standardised mortality ratio=5.7; 95% confidence interval=3.1-8.3).

Discussion

Breast cancer is the most common cancer among women in Hong Kong, such that it constituted 26.1% of all newly diagnosed cancers among women in Hong Kong in 2015.[10] Notably, a population-wide breast cancer screening programme is not available in Hong Kong. However, because of improved patient-level and population-level education regarding breast cancer awareness, rates of self-initiated breast cancer screening by ultrasonography and mammography have increased over the past decade.[9] This might well explain the doubling of DCIS incidence from 449 patients (1997-2001) to 942 patients (2002-2006).

The mortality rate of patients with DCIS has substantially declined over the past few decades in the United States: the 10-year breast cancer mortality rate was 3.4% for women who received a diagnosis from 1978 to 1983, then decreased to 1.9% for women who received a diagnosis from 1984 to 1989[11] and 1.1% for women who received a diagnosis from 1988 to 2011.[2] The mortality rate of patients with DCIS in Hong Kong has remained stable during this same period, despite improved detection through self-initiated breast screening. Nevertheless, the 10-year breast cancer–specific mortality rate of 0.9% in the current study is comparable with the findings from Western nations; in particular, the 10-year breast cancer–specific mortality rate was reportedly 1.8% in a randomised trial of 1046 Swedish patients with DCIS, who were diagnosed from 1987 to 1999.[12] The underlying reason for such an improvement in

TABLE 2. Breast cancer–specific mortality

	All (n=1391)	No. of breast cancer deaths in 5 years (n=4)	5-Year breast cancer–specific mortality	No. of breast cancer deaths in 10 years (n=12)	10-Year breast cancer–specific mortality
Age-group	1391	4	0.3%	12	0.9%
30-34 years	53	0	0	0	0
35-39 years	129	0	0	1	0.8%
40-44 years	295	1	0.3%	5	1.7%
45-49 years	310	0	0	2	0.6%
50-54 years	229	2	0.9%	3	1.3%
55-59 years	146	1	0.7%	1	0.7%
60-64 years	107	0	0	0	0
65-69 years	122	0	0	0	0
Laterality					
Right	670	4	0.6%	7	1.0%
Left	700	0	0	5	0.7%
Bilateral	21	0	0	0	0
Grade					
Low	276	0	0	1	0.4%
Intermediate	326	0	0	2	0.6%
High	363	2	0.6%	3	0.8%
Unknown	426	2	0.5%	6	1.4%
ER status					
Positive	358	1	0.3%	3	0.8%
Negative	105	1	1.0%	1	1.0%
Unknown	928	2	0.2%	8	0.9%
HER2 status					
Positive	136	2	1.5%	4	2.9%
Negative	232	0	0	0	0
Unknown	1023	2	0.2%	8	0.8%
Surgery					
Mastectomy	712	2	0.3%	5	0.7%
Wide local excision	399	0	0	3	0.8%
Unknown	280	2	0.7%	4	1.4%
Radiotherapy					
Yes	410	0	0	1	0.2%
No	375	2	0.5%	2	0.5%
Unknown	606	2	0.3%	9	1.5%
Hormone therapy					
Yes	221	1	0.5%	2	0.9%
No	459	1	0.2%	1	0.2%
Unknown	711	2	0.3%	9	1.3%

Abbreviations: ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2

survival is beyond the scope of this study, but we presume that it is multifactorial (eg, earlier detection and improved surgical oncologic treatment for DCIS).[13] However, reports on the improved survival of patients with DCIS (including the current cohort) should be interpreted with care, because this improvement may be the result of overdiagnosis of DCIS.

Overdiagnosis and overtreatment for DCIS have been a major focus of debate over the past

TABLE 3. Standardised mortality ratios of ductal carcinoma in situ

Age-group	Breast cancer–specific mortality rate (per 100 000 population)	Person-years of observation	Expected No. of deaths	Observed No. of deaths	SMR (95% CI)
30-34 years	2.2	586.7	0	0	
35-39 years	5.3	1524.1	0.1	1	12.4 (0.0-36.6)
40-44 years	10.9	3459.2	0.4	6	15.9 (3.2-28.6)
45-49 years	17.7	3601.5	0.6	4	6.3 (0.1-12.4)
50-54 years	25.6	2736.3	0.7	3	4.3 (0.0-9.1)
55-59 years	29.6	1728.6	0.5	1	2.0 (0.0-5.8)
60-64 years	34.8	1266.2	0.4	1	2.3 (0.0-6.7)
65-69 years	29.0	1391.6	0.4	2	5.0 (0.0-11.8)
Total	-	16294.1	3.2	18	5.7 (3.1-8.3)

Abbreviations: 95% CI = 95% confidence interval; SMR = standardised mortality ratio

decade.[12] Several randomised controlled trials, such as the COMET (NCT02926911) and LORIS trials, are currently investigating the feasibility and non-inferiority of active surveillance with or without endocrine therapy for management of low-risk DCIS.

Biological markers such as HER2 receptor and oestrogen receptor statuses have been used for assessment of prognosis and tumour behaviour in patients with invasive breast cancers,[14] but their roles in the context of DCIS may have been previously underestimated. Human epidermal growth factor receptor 2–positive DCIS is considered the most unstable precursor among all molecular subtypes, because of its high invasion rate and frequent association with a discordant phenotype.[15] Our results may provide clinical validation of this postulation, because they demonstrated that the 10-year breast cancer–specific mortality is significantly worse in patients with HER2-positive disease. However, because of the relatively small number of events included in the subgroup analysis, it may be premature to conclude that positive HER2 findings are associated with adverse survival outcome. Oestrogen receptor–positive DCIS was associated with slightly lower 10-year breast cancer–specific mortality (Table 2). Indeed, the use of systemic hormonal therapy with tamoxifen in patients with oestrogen receptor–positive DCIS has been shown to reduce the risk of future invasive cancer.[16]

We acknowledge that this study was limited by its retrospective in nature, because all pathological diagnoses were supplied by the breast cancer database from the Hong Kong Cancer Registry. A formal pathology review might have identified patients whose diagnoses were modified from DCIS (in core biopsy) to invasive cancers (in final pathology); other diagnoses might have been modified from invasive cancers to DCIS. While some researchers reported a 17% exclusion rate after a central pathology review,[17] others reported a much lower exclusion rate of 2% after secondary pathological review of patients with DCIS.[18-20] Nevertheless, our analysis was based on a large territory-wide cancer registry. All data were maintained and validated in a consistent manner. In addition, the extended follow-up period enabled detailed long-term survival analysis for patients with DCIS.

Conclusion

Data from the Hong Kong Cancer Registry revealed that the incidence of DCIS doubled from the late 1990s to the early 2000s. The estimated standardised mortality ratio of patients with DCIS in Hong Kong was 5.7, compared with the general population of women in Hong Kong. Our cohort represents one of the largest DCIS cohorts in the published literature. For locations where population-wide breast cancer screening is not available, as in Hong Kong, we believe that the results of our study support further investigation of the cost-effectiveness of population-wide breast cancer screening implementation.

Author contributions

Concept or design: M Co, A Kwong.
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Critical revision of the manuscript for important intellectual content: A Kwong, RKC Ngan, KH Wong.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Ethics approval

This study was approved by the Hong Kong Hospital Authority West Cluster Research Ethics Committee (Ref UW 09-045). Patient consent was obtained for data collection and analysis.

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