Cancer Treatment and Research Communications 24 (2020) 100182

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

Young onset breast cancer in Southern China – a 5-year clinico-pathological study from a multi-centre database

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ARTICLE INFO

Keywords:
Breast neoplasm
Risk factors
Epidemiology

ABSTRACT

Aims: Breast cancer onset is known to be younger in China when compared to many westernized countries, the reason remains unknown. This study aims to evaluate the clinical and pathological characteristics of young breast cancer in Hong Kong and Shenzhen, China.

Methods: This is a 5-year retrospective review of a prospectively-maintained region-wide database. Patients treated in Hong Kong and Shenzhen between 2013 and 2017 were analysed.

Results: 1610 breast cancer patients were identified for analysis, 1108 patients were from Hong Kong and 502 patients were from Shenzhen. Median age of breast cancer onset was 60 years old in Hong Kong (Range 21 – 103), while that in Shenzhen was 46 years old (Range 23 – 85). 59 (5.3%) patients from the Hong Kong cohort were younger than 40 years old at the age of diagnosis (i.e. young breast cancer), comparing to 152 (30.3%) patients from the Shenzhen cohort ($p < 0.0001$).

There were more nulliparity, positive family history and use of exogenous hormones in young breast cancer patients in Hong Kong ($p = 0.0043, < 0.0001$ and 0.0022). Pathological characteristics were however comparable between the two cohorts, apart from being more triple negative breast cancers in young breast cancer patients in Hong Kong ($p = 0.05$).

Conclusion: Age of onset of breast cancer tends to be younger in mainland China than in Hong Kong. Personal and familial risk factors were not significantly different. Environmental factor may play an important role.

Introduction

Breast cancer onset is younger in China than many westernized countries [1]. In the United States, approximately 4.8% of all breast cancers diagnosed annually were younger than 40 years old [2], comparing to 13.6% in a recently published report in China [3]. The reason for this phenomenon remains largely unknown. In fact, young onset breast cancer has recently recognized as a distinct clinical entity, it has unique clinical and biological characteristics, which is often more aggressive with poorer overall prognosis [4–7].

Although there is no consensus on the definitions of young onset breast cancer, with various studies arbitrarily or empirically using age cutoffs of 30 to 40 years old. Most studies use 40 years old as cutoff [8].

The aim of this study is to compare the age of breast cancer onset in Chinese population between the two neighbouring cities in Southern China – Hong Kong and Shenzhen; to review the clinical and pathological characteristics of young onset breast cancers, as well as to identify the factors associated with young onset of breast cancers in Mainland China.

Methods

Institutional review board approval was obtained for patient data collection and analysis. Baseline demographic, clinical, and pathological data of patients treated in Hong Kong and Shenzhen from 2013 to 2017 were retrieved from a prospectively-maintained database. Informed consent was obtained from every patient for data collection and storage. All breast cancer patients in both centers were managed under a standard departmental protocol with multidisciplinary approach, in line with the updated National Comprehensive Cancer Network (NCCN) Guidelines.

Patients with non-Chinese ethnicity were excluded from analysis. Clinical and tumour characteristics of young breast cancer patients from Shenzhen were compared to patients >= 40 years old in Shenzhen, as well as young breast cancer patients in Hong Kong. Risks factors for breast cancers were evaluated. Young breast cancer is

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https://doi.org/10.1016/j.ctarc.2020.100182

Table 1
Comparing patient demographics and tumour characteristics of breast cancers in patients aged <= 40 and > 40 treated in Shenzhen, China.

Breast Cancers in Shenzhen, China	Age < 40 (*N* = 152)		Age > = 40 (*N* = 350)		*P-value*
Province of origin (GDP per capita)	High	Low	High	Low	< 0.0001
	72 (47.4%)	80 (52.6%)	242 (69.1%)	108 (30.9%)	
Obesity (BMI > 25)	Non-obese	Obese	Non-obese	Obese	< 0.0001
	142 (93.4%)	10 (6.6%)	278 (79.4%)	72 (20.6%)	
Smoking	Non-smoker	Smoker	Non-smoker	Smoker	0.3889
	150 (98.7%)	2 (1.3%)	348 (99.4%)	2 (0.6%)	
Exogenous hormones	No	Yes	No	Yes	0.3889
	150 (98.7%)	2 (1.3%)	348 (99.4%)	2 (0.6%)	
Personal history of breast cancer	No	Yes	No	Yes	1
	150 (98.7%)	2 (1.3%)	344 (98.3%)	6 (1.7%)	
Personal history of benign breast lesions	No	Yes	No	Yes	0.2461
	150 (98.7%)	2 (1.3%)	338 (96.6%)	12 (3.4%)	
Family history of breast cancer	No	Yes	No	Yes	0.3825
	142 (93.4%)	10 (6.6%)	334 (95.4%)	16 (4.6%)	
Clinical presentation	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	0.4658
	30 (19.7%)	122 (80.3%)	58 (16.6%)	292 (83.4%)	
tumour multiplicity	no	yes	no	yes	0.0873
	132 (86.8%)	20 (13.2%)	280 (80%)	70 (20%)	
Cancer type	DCIS – 26 (17.1%)		DCIS – 86 (24.6%)		0.1863
	IDC – 106 (69.7%)		IDC – 244 (69.7%)		
	Invasive mucinous – 4 (2.6%)		ILC – 10 (2.9%)		
	Others – 16 (10.6%)		Invasive mucinous – 4 (1.1%)		
			Others 6 (1.7%)		
Hormonal receptor	Negative – 40 (26.3%)		Negative – 78 (22.3%)		0.2159
	Positive – 98 (64.5%)		Positive – 260 (74.3%)		
	Unknown – 14 (9.2%)		Unknown – 12 (3.4%)		
HER 2 status	Negative – 92 (60.5%)		Negative – 186 (53.1%)		0.0250
	Positive – 22 (14.5%)		Positive – 84 (24%)		
	Unknown – 38 (25%)		Unknown – 80 (22.9%)		
Triple negative	Yes - 24 (15.8%)		Yes - 14 (4%)		<0.0001
	No - 82 (53.9%)		No - 250 (71.4%)		
	Unknown – (30.3%)		Unknown – 86 (24.6%)		
Cancer grade (Invasive cancers)	Grade 1 – 28 (18.4%)		Grade 1 – 122 (34.9%)		0.0007
	Grade 2 – 66 (43.4%)		Grade 2 – 118 (33.7%)		
	Grade 3 – 12 (7.9%)		Grade 3 – 24 (6.9%)		
	Unknown – 46 (30.3%)		Unknown – 86 (24.5%)		
Ki-67	<= 20% – 46 (30.3%)		< 20% – 146 (41.7%)		0.7295
	>20% – 54 (35.5%)		>20% – 156 (44.6%)		
	Unknown – 52 (34.2%)		Unknown – 48 (13.7%)		
TNM Staging	Stage 0 – 26 (17.1%)		Stage 0 – 40 (11.4%)		0.1557
	Stage 1 – 52 (34.2%)		Stage 1 – 160 (45.7%)		
	Stage 2 – 58 (38.2%)		Stage 2 – 122 (34.9%)		
	Stage 3 – 16 (10.5%)		Stage 3 – 24 (6.9%)		
	Stage 4 – 0 (0%)		Stage 4 – 4 (1.1%)		

(DCIS = Ductal carcinoma in situ, IDC = Invasive ductal carcinoma, ILC = Invasive lobular carcinoma).

defined as onset age < 40 years old, while very young breast cancer is defined as onset age < 30 years old [8]. Chi-square test and Fisher-exact test were used for evaluation of significance of correlation where appropriate. Disease-specific survival was evaluated by Kaplan-Meier method.

Results

1610 breast cancer patients were identified for analysis, 1108 patients were from Hong Kong and 502 patients were from Shenzhen. Median age of breast cancer onset was 60 years old in Hong Kong (Range 21 – 103), while that in Shenzhen was 46 years old (Range 23 – 85). 59 (5.3%) patients from the Hong Kong cohort were younger than 40 years old at the age of diagnosis (i.e. young breast cancer), comparing to 152 (30.3%) patients from the Shenzhen cohort ($p < 0.0001$); while 9 patients from the Hong Kong cohort were younger than 30 years old at the age of diagnosis (i.e. very young breast cancer), comparing to 32 patients from the Shenzhen cohort ($p < 0.0001$).

Mastectomy rate in young breast cancer patients was 44.1% (26/59) in Hong Kong and 52.6% (80/152) in Shenzhen respectively; while breast reconstruction rate in young breast cancer patients was 20.3% (12/59) in Hong Kong and 5.3% (8/152) in Shenzhen respectively.

Clinical and pathological characteristics of young breast cancer patients in Shenzhen were compared to patients older / equal to 40 years old in Shenzhen. While there was no statistical significant difference in family or personal history of breast cancer, as well as documented use of exogenous hormone between breast cancer patients diagnosed <40 and >=40 years old. Young breast cancer patients were more likely to be HER-2 receptor negative ($p = 0.0250$), triple negative ($p < 0.0001$) and of higher nuclear grade in invasive cancers ($p = 0.0007$). (Table 1)

Comparing clinical and pathological characteristics of young onset breast cancer patients between Shenzhen and Hong Kong, young breast cancer patients in Hong Kong were more likely to be nulliparous ($p = 0.0043$), with significant familial risks of breast cancers ($p < 0.0001$) as well as documented use of exogenous hormones ($p = 0.0022$). Pathological characteristics were however comparable between the two cohorts of patients, apart from having more triple negative breast cancers in young Hong Kong breast cancer patients ($p = 0.05$) Table 2.

Genetic test (GT) results were available in 21 young breast cancer patients from the Hong Kong cohort at the time of data analysis. 14 patients had documented negative GT results, while 2 patients had proven BRCA1 mutation, 2 had proven BRCA2 mutation, 2 had

Table 2
Clinical and pathological features of young breast cancer patients from Hong Kong and Shenzhen, China.

Comparing Young Breast Cancers in Hong Kong and Shenzhen, China (Patient demographics)	Hong Kong (N = 59)		China (N = 152)		*p-value*
Family history	Yes	No	Yes	No	<0.0001
	17	42	10	142	
	(28.8%)	(71.2%)	(6.6%)	(73.4%)	
Exogenous hormone (Oral contraceptive pills or hormonal replacement therapy)	Yes	No	Yes	No	0.0022
	7	52	2 (1.3%)	150	
	(11.9%)	(88.1%)		(88.7%)	
Smoking	Yes	No	Yes	No	1
	1 (1.7%)	58	2 (1.3%)	150	
		(98.3%)		(88.7%)	
Nulliparous	Yes	No	No	Yes	0.0043
	28	31	110	42	
	(45.5%)	(54.5%)	(72.4%)	(27.6%)	
In-situ cancer	In-situ	Invasive	In-situ	Invasive	0.2851
	6	53	26	126	
Tumour Histotype	DCIS - 6 (10.2%) IDC - 47 (79.7%) ILC - 1 (1.7%) Mucinous – 2 (3.4%) Others – 3 (5%)		DCIS – 26 (17.1%) IDC – 106 (69.7%) Mucinous – 4 (2.6%) Others – 16 (10.6%)		0.2024
Grade	Grade 1 – 8 (13.6%) Grade 2 – 20 (34.9%) Grade 3 – 15 (25.4%) Not reported – 16 (27.1%)		Grade 1 – 28 (18.4%) Grade 2 – 66 (43.4%) Grade 3 – 12 (7.9%) Not reported – 46 (30.3%)		0.3998
Hormonal receptor status	Negative – 17 (28.8%) Positive – 36 (61.0%) Unknown – 6 (10.2%)		Negative – 40 (6.3%) Positive – 98 (64.5%) Unknown – 14 (29.2%)		0.7250
HER-2 status	Negative – 35 (59.3%) Positive – 14 (23.7%) Unknown – 10 (17.0%)		Negative – 92 (60.5%) Positive – 22 (14.5%) Unknown – 38 (25.0%)		0.2701
Triple negative cancer	Yes	No	Yes	No	0.0500
	17	42	24	128	
	(28.8%)	(71.2%)	(15.8%)	(84.2%)	
Ki-67	<= 20% - 14 (23.7%) >20% - 22 (37.3%) Unknown – 23 (39.0%)		<= 20% - 46 (30.3%) >20% - 54 (35.5%) Unknown – 52 (34.2%)		0.5581
TNM Staging	Stage 0 – 9 (15.3%) Stage 1 – 20 (33.9%) Stage 2 – 20 (33.9%) Stage 3 – 6 (10.2%) Stage 4 – 4 (6.7%)		Stage 0 – 26 (17.1%) Stage 1 – 52 (34.2%) Stage 2 – 58 (38.2%) Stage 3 – 16 (10.5%) Stage 4 – 0 (0%)		0.2981
Genetic tests results	BRCA 1 mutation – 2 (3.4%) BRCA 1 VUS – 1 (1.7%) BRCA 2 mutation – 2 (3.4%) BRCA 2 VUS – 1 (1.7%) HNPCC – 1 (1.7%) GT negative – 14 (23.7%) Not done – 38 (64.4%)		Not done		

(DCIS - Ductal carcinoma in situ; ILC - Invasive lobular carcinoma; IDC - Invasive ductal carcinoma; VUS - Variant of unknown significance; HNPCC - Hereditary Non-polyposis Colonic Cancer; GT - Genetic test).

variance of unknown significance and 1 had documented Hereditary Non-polyposis Colonic Cancer Syndrome. Due to limitation of expertise and GT facilities in Mainland China, GT was not performed in the Shenzhen cohort.

After median follow up interval of 52 months and 38 months respectively, the disease-specific survival rates were comparable at 53/55 (96.4%) and 139/144 (96.5%) in Hong Kong and Shenzhen respectively, with 4 (0.4%) patients lost to follow-up in Hong Kong and 8 (1.6%) patients lost to follow-up in Shenzhen.

Discussion

Hong Kong is a Special Administrative Region (SAR) of China. However, its unique historical background as a former colony of the United Kingdom has substantially influenced its cultural and socio-economic structure. Just across the Shenzhen River lies a totally different, heavily industrialized metropolitan city of China – Shenzhen. Shenzhen is also known as “City of Migrants”, with people coming from all over the country for work. The close geographic relationship and yet markedly different ethnic and socio-economic background enables a detailed epidemiological study of breast cancer of the region.

This is the first study to compare breast cancer epidemiology between two cities in close geographic relationship but markedly different socio-economic background. While Hong Kong is generally considered a “Highly-westernized” financial city, Shenzhen population is largely constituted by a heterogeneous group of working population from different parts of China. In this study, we found that the median age of onset of breast cancer is significantly younger in Shenzhen than in Hong Kong. This can be partly, but not completely, attributed to the fact that average age of population in Shenzhen is younger than that in Hong Kong. Nevertheless, finding from this study is comparable to previous studies suggesting that breast cancer tends to occur younger in China than in Western Countries like in the United States [9]. The reason of such phenomenon is largely unknown. Some postulate that the fall in the fertility rate, partly due to the one-child policy, might have affected the breast cancer risk in premenopausal women in China. [1].

Evaluation of the risk factors for breast cancers in the Shenzhen cohort found that young breast cancer patients in tend to originate from low-income areas in China (Table 1), this is very much different from the traditional belief that breast cancer is a disease of the affluence, closely associated with sedentary lifestyle and high-fat diet [9]. There are studies evaluating the effect of race and poverty on breast cancer in the literature, although most of them were on the effect of race and poverty on breast cancer survival. One study in the United States had found that although breast cancer mortality is also decreasing amongst the African-American women as in the White women, the rates for white women have fallen at a greater pace due to better screening and treatment received [10,11].

Young breast cancer rate in Hong Kong was 5.3% in the current study, which is comparable to that in South Korea [8]. Young breast cancer patients in Hong Kong were more likely to have positive family history of breast cancers, history of use of exogenous hormones, and being nulliparous and yet, young breast cancer rate was almost six-fold lower than that in Shenzhen. Therefore, it is not unreasonable to postulate that, apart from these conventional risk factors exposure, there were additional factors that had resulted in the higher young onset breast cancer rate in China.

In the United States, a report by the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) described the importance of environmental factors in affecting the biological mechanisms that influence the risk of breast cancer. [12]. Environmental factors that are associated with breast cancer carcinogenesis include environmental chemical contamination, excessive hormonal (oestrogen) exposure and dietary contamination. Genotoxicity can be induced by chemicals that are mutagenic (agents that lead to mutations) and/or clastogenic (agents that damage DNA structure). Although some genotoxic chemicals are directly clastogenic (e.g., benzene) or DNA reactive, others can act indirectly via complex signalling pathways involving enzymatic activities and DNA replication [13].

Air pollution has been a major problem due to rapid urbanization

Table 3
List of examples of the recent major food safety incidents in China uncovered by the public media.

Year	Major food safety incidents	Food item	Additives / Contaminants
Multiple 1998–2007	Lean meat powder pork	Pork	Clenbuterol
2004	Contaminated pickles	Pickled vegetables	Insecticide DDVP, industrial-grade salt
2006	Sudan red egg yolk	Egg	Sudan IV
2008	Melamine Milk	Milk	Melamine
2008	Heavy metal rice	Rice	Cadmium
2008	Use of malachite green (MG) in fish farming	Fish	Melachite green
2010	Yardlong bean	Yardlong bean	Pesticide isocarbophos
2010	Toxic take away boxes	Disposible foam boxes	Paraffin
2011	Toxic bean sprout	Bean sprout	Codium nitrite, urea, 6-benzyladenine (Plant hormone)
2011	Leather milk	Milk	Hydrolized leather protein
2010 −2014	Ditch oil	Cooking oil	Recycles oil
2014	Expired frozen meat products	Meat products in fast food chain	Expired meat products
2014	Toxic bean sprout	Bean sprout	6-benzyladenine
2020	Non-baby formula being sold as baby formula	Fake baby formula	Lack of nutrients / essential vitamins required for baby formula

and industrialization in major cities in China, a study in 2007 found that the average air pollution index (API) of Shenzhen and Guangzhou province over 6 years was significantly higher than that of Hong Kong [14]. In fact, several studies have shown associations between the incidence of breast cancer and exposure to benzene and to polycyclic aromatic hydrocarbons, which are commonly found in vehicle and factory emissions [15–18]. Additional environmental factors could have played an important role leading to the tendency of young onset of breast cancer in China.

In this study, use of contraceptive pills and hormonal replacement therapy are the only documented sources of exogenous hormonal exposure. Young breast cancer patients in Hong Kong and Shenzhen have similar rate of exogenous hormonal exposure in the current study, however it is nearly impossible to estimate the exposure to exogenous hormone uptake from daily dietary intake especially when food safety in China is also a concern [19]. Incidents of illegal chemical additives in food products have occurred from time to time and uncovered by mass media, many of which were carcinogenic [19] (See Table 3 for the lists of recent major food safety incidents in China). Apart from illegal addition of oestrogen and growth hormone in poultry, industrial contamination of agricultural source is also a major concern. A study by Nanjing Agricultural University showed that 10% of rice samples collected from six agricultural regions was tainted with Cadmium, a heavy metal that is potentially carcinogenic [20]. Exogenous hormones and environmental carcinogens are one of the major risk factors for breast cancer; However, it is nearly impossible to quantify environmental and dietary exposure.

We recognize the intrinsic weakness of this study of being retrospective in nature which is subjected to confounders and selection bias. In addition, difference in population distribution between the two cities is also an important cofounder. However, all analyses were based on a sizable cohort of more than 1600 patients from a prospectively maintained region-wide multicentre database. This is also the first study to evaluate breast cancer epidemiology in the same ethnicity living in two different social and cultural environments. Our study concluded that breast cancer tends to occur at a younger age in mainland China. However, clinical and pathological characteristics were not significantly different between the two cohorts (Hong Kong and mainland China). Environmental factors may have played an important role in the young onset breast cancer in mainland China. This is an important area that worth further investigation.

Conclusion

Onset of breast cancer is significantly younger in Shenzhen than in Hong Kong, but with less adverse familial or hormonal risk background. Additional risk factors could have resulted in the early onset breast cancer in China.

Clinical practice points

1 Breast tumour biology is more aggressive in young breast cancer patients in China, with higher nuclear grade and more triple negative disease than older patients
2 Young breast cancer patients in China have less significant familial or adverse personal hormonal risk factors than in Hong Kong. Yet, young onset breast cancer rate is higher in Shenzhen, almost six-fold higher than that in Hong Kong
3 Additional environmental factors could have played an important role resulting in the young onset of breast cancer in China

Disclaimers

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

Michael Co – Conceptualization, data collection, data analysis, manuscript preparation
Ava Kwong – Data analysis, manuscript editing
All authors report no conflict of interests
This study is not sponsored by external source of funding

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors would like to thank Mr. Wing Pan Luk, Research Assistant of Medical Physics & Research Department, Hong Kong sanatorium & Hospital for helping with the genetic test data collection.

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