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Patterns of care of breast cancer patients in Morocco – A study of variations in patient profile, tumour characteristics and standard of care over a decade

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ABSTRACT

Guided by a national cancer plan (2010–19), Morocco made significant investments in improving breast cancer detection and treatment. A breast cancer pattern-of-care study was conducted to document the socio-demographic profiles of patients and tumour characteristics, measure delays in care, and assess the status of dissemination and impact of state-of-the-art management. The retrospective study conducted among 2120 breast cancer patients registered during 2008–17 at the two premier-most oncology centres (Centre Mohammed VI or CM-VI and Institut National d'Oncologie or INO) also measured temporal trends of the different variables.

Median age (49 years) and other socio-demographic characteristics of the patients remained constant over time. A significant improvement in coverage of the state-financed health insurance scheme for indigent populations was observed over time. Median interval between onset of symptoms and first medical consultation was 6 months with a significant reduction over time. Information on staging and molecular profile were available for more than 90% and 80% of the patients respectively. Approximately 55% of the patients presented at stage I/II and proportion of triple-negative cancers was 16%; neither showing any appreciable temporal variation. Treatment information was available for more than 90% of the patients; 69% received surgery with chemotherapy and/or radiation. Treatment was tailored to stage and molecular profiles, though breast conservation therapy was offered to less than one-fifth. When compared using the EUSOMA quality indicators for breast cancer management, INO performed better than CM-VI. This was reflected in nearly 25% difference in 5-year disease-free survival for early-stage cancers between the centres.

Introduction

Breast cancer is highly curable when detected early and managed appropriately. The CONCORD study estimated the 5-year age-standardized net survival from breast cancer to be as high as 85% in higher resourced countries [1]. Though breast cancer survival has significantly improved in the last two decades due to improved access to diagnosis and wider use of multi-modality treatment, huge variations still exist between and within the countries [2].

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Morocco belongs to the medium human development index (HDI) category (HDI value 0.647) with a total population of 36.5 million in 2019 [3]. According to the report published by Greater Casablanca Cancer Registry of Morocco in 2016 breast cancer was the most frequent cancer among Moroccan women, accounting for 35.8% of all new cancers in females [4]. Majority (67%) of female breast cancers diagnosed at the capital city of Rabat between 2005 and 2008 were at stages II or III [5]. However, no recent data is available. The five-year overall survival rate reported for breast cancer patients aged 40–65 years during the same time was 83% [5].

The Ministry of Health (MoH), guided by the National Cancer Control plan (2010–2019), made significant investments to improve diagnostic and therapeutic facilities for common cancers, including breast cancer [6]. A nationwide breast cancer screening programme was launched in 2010 and gradually scaled up across all the regions. Women belonging to 40 years–69 years of age are screened every two years with clinical breast examination (CBE). A highly visible awareness campaign promoting breast cancer screening is performed all throughout the month of October. Women are screened at the primary health centres by trained nurses and general practitioners. The CBE positive women are referred to dedicated cancer early detection centres with facilities for mammography, ultrasound and core biopsy. The national cancer treatment guideline was initially published in 2011 and updated biennially. Specialized units to comprehensively manage breast cancer patients were established in 2013 at the two largest public-funded oncology centres, *Centre Mohammed VI pour le traitement des cancer (CM-VI)* situated in Casablanca and *Institut National d'Oncologie* (*INO*) situated in Rabat (the capital city).

The International Agency for Research on Cancer (IARC) collaborated with the MoH and the Lalla Salma Foundation for Prevention and Treatment of Cancer to conduct a pattern of care (POC) study in breast cancer to assess how far the state-of-the-art cancer diagnostics and therapy had disseminated into routine practice. The retrospective study based on abstraction of data from the case records of breast cancer patients registered at CM-VI and INO over a decade (2008–17) aimed to document the following:

- Temporal variations in socio-demographic profiles of patients and their tumour characteristics
- Delays in accessing diagnosis and treatment, their determinants and trends over time
- Improvement in practices related to breast cancer treatment, especially after establishment of the specialized breast units in 2013
- Disparities in quality of care between the two oncology centres
- Impact of such disparities on disease-free survival (DFS) from breast cancer

Methods and analysis

Case records of all breast cancer patients registered at CM-VI and INO during a two-month period of each year, starting from 2008 and ending in 2017, were reviewed. Patients with a confirmed diagnosis of breast cancer were included in the study. The bimonthly sampling cycle started in January–February of 2008, kept on shifting to the next two months every year, and restarted in January–February after six years (Supplementary Table 1). Patients registering at the centres after receiving any cancer-directed treatment outside were also included. Only those with a documented recurrence at the time of registration were excluded. Trained investigators used a pretested data-collection form to abstract patients' information (including demographic and social profiles, longest interval between symptom onset and first medical consultation, clinical and pathological staging, tumour differentiation, and immunochemistry details, treatment received and details of follow-up after treatment) from the medical records.

Distribution of the patient characteristics was presented as proportions and stratified by the period of diagnosis (2008–2012 and 2013–2017). The longest symptom duration was further categorized into 1–5, 6–11 and 12+ months to evaluate its distribution in terms of proportions for each category of the different patient characteristics. To assess the effect of patient characteristics on symptom duration, the continuous variable of the longest duration with symptoms was assumed to follow an exponential distribution and was used as the response variable in the exponential Bayesian regression model. The effect estimates of the patient characteristics on the longest duration, presented as risk ratios (RRs), were obtained from median and their confidence intervals from the 2.5 and 97.5 percentiles of the posterior distribution of the Bayesian regression model.

The American Joint Committee on Cancer (AJCC) composite staging was calculated using the pathological TNM stage information first and then using clinical TNM stage information for patients with missing pathological stage [7]. Depending on the expression status of hormonal receptors (estrogen receptor or ER and progesterone receptor or PR) and human epidermal growth factor receptor 2 (HER2), breast cancers were categorized into four subsets – ER and/or PR positive and HER2 negative, ER and/or PR positive and HER2 positive, ER and PR negative and HER2-positive and triple-negative [8]. The effect of different patient characteristics on advanced stage (stage-III/IV) at diagnosis was assessed and presented as odds ratios (ORs), obtained from posterior distribution median and their confidence intervals from the 2.5 and 97.5 percentiles of the Bayesian logistic regression model.

Evaluations of treatment received were presented separately for the two centres. Disease relapse or recurrence after treatment was the only outcome that could be assessed in the survival analysis. Overall survival could not be estimated as majority of the deaths happened outside the oncology centres and the information was not captured in the case records. The endpoint in the disease-free survival (DFS) analysis was defined as being found alive with disease (relapse) during follow-up. The follow-up time for the DFS was measured starting from the date of treatment initiation for all patients. The end date was the date of relapse for the patients who experienced the endpoint, or the date of death or date last seen, whichever was first, for patients who did not experience the endpoint. Bayesian Cox proportional hazard regression models were used to assess the effect of the patient characteristics on DFS. Kaplan-Meier estimates were presented for the probability of relapse over the study duration.

The frequencies for the patient characteristics assessed and Kaplan Meier curves were done in Stata 15.1 (StataCorp LP, Texas, USA), whereas the Bayesian regression models were carried out using Just Another Gibbs Sampler (JAGS) software [9,10]. JAGS was used in order to additionally model for the missing data in the outcomes and/or explanatory variables [11].

The study was approved by the ethics committees at IARC and the participating institutions. A waiver of informed consent was obtained.

Results

Data were abstracted for 915 confirmed breast cancer patients registered at CM-VI and 1205 patients registered at INO. Socio-demographic characteristics of the patients stratified by the centres and time period are shown in Table 1. The median age at registration at either centre was 49 years [Inter-quartile range

(IQR): 42–57 years], without any significant change observed over time. Proportion of urban, ever married and post-menopausal patients and patients with insurance coverage was significantly higher at INO, compared to CM-VI. Rabat being the administrative capital, patients covered by an employee's insurance were two-fold higher at INO as compared to CM-VI. Only significant change in patient characteristics observed with time was the proportion of patients being covered by a health insurance scheme. A state-financed subsidized insurance scheme *(Régime d'assistance Médicale; RAMed)* for the economically disadvantaged populations was piloted in 2010 and scaled up nationally in 2012 [12]. Proportion of insured patients drastically increased from 33.8% in 2008–2012 to only 90.2% in 2013–2017 as the number of beneficiaries of RAMed increased.

At the time of registration, 47.0% and 64.7% of the patients registered at CM-VI and INO respectively had a pathologically confirmed diagnosis of cancer, and the proportion increased significantly over time (Table 1). The median interval between the date of onset of symptoms and that of first medical consultation leading to referral for cancer diagnosis (defined by the World Health Organization as access delay) was 6 months (IQR: 3–12 months) at either centre [13]. A significant shortening of the interval was observed over time after adjusting for other parameters (Table 2). The interval increased significantly with advancing age of the patients. The median interval between disease confirmation and registration at the oncology centre was 1.5 months (IQR: 0.8–2.9 months) at CM-VI and 0.7 months (IQR: 0.3–1.8 months) at INO.

Overall, 90.7% of the patients registered at CM-VI and 94.9% of those registered at INO had adequate information to estimate the AJCC anatomic stage. Pathologic T and N status was available for nearly 85% of the patients. Early-stage cancer (stage-I/II) was detected among 56.6% patients registered at CM-VI, with proportions remaining almost similar over time (2008–10: 56.4%; 2011–14: 55.9% and 2015–17: 57.6%). Early cancers were detected among 52.5% patients registered at INO, with improvement observed since 2011 (2008–10: 47.7%; 2011–14: 55.4% and 2015–17: 53.3%). In the adjusted logistic regression model, the likelihood of being diagnosed in advanced stages increased significantly with increasing access delay (Table 3).

ER/PR status were available for 78.4% patients at CM-VI and 91.1% patients at INO. HER2 status was documented in 70.3% patients at CM-VI and 85.5% patients at INO. HER2-positive and triple-negative cancers comprised of 30.1% and 18.1% of the CM-VI patients with known receptor status; the similar proportions among those registered at INO were 29.1% and 13.9% (Table 4). No significant difference was observed in molecular profiles of the patients with early and late-stage cancer. Patients with poorly differentiated cancer had higher proportion of triple-negative types (30.9% at CM-VI and 24.2% at INO) compared to those with well-differentiated (7.7% and 4,3% respectively) or moderately differentiated (12.9% and 8.9% respectively) cancers.

All cancer patients were routinely referred to a multi-disciplinary tumour board (MDT) at INO, whereas only selected cases at CM-VI were referred to the board. Cancer-directed treatment was received by 85.8% (785/915) of the patients registered at CM-VI and 96.0% (1157/1205) of those registered at INO. Initial treatment was performed at other hospitals for 68.3% (484/915) of the patients registered at CM-VI and 36.5% (418/1205) of those registered at INO. Treatment performed at the outside hospitals was limited to surgery alone in nearly 97% of the patients at either centre.

Overall, 70% (549/785) of the treated patients at CM-VI and 86.2% (997/1157) of those at INO received either breast conservative surgery (BCS) or mastectomy. Only 23.9% (188/785) of the treated patients at CM-VI received a combination of surgery, radiation-therapy (RT) and chemotherapy (CT). The proportion was much higher (57.7%; 668/1157) at INO. CT was tailored to stage and molecular profile of the patients at both centres. For example, neo-adjuvant or adjuvant CT was used to treat 57% of ER and/or PR positive but HER2-negative, 83% of HER2-positive and 100% of triple-negative cancers with stage-I disease at CM-VI (data not shown). The proportion of stage-I patients receiving CT at INO was 67%, 95% and 92% for ER and/or PR positive but HER2-negative, HER2-positive and triple-negative cancers respectively. Overall, 53% (320/605) of the patients treated with CT at CM-VI and 68% (682/1004) of those at INO had *taxane* included in the regimen. The median number of cycles of CT received by patients (excluding those treated with palliative intent) was six at either centre, indicating a high compliance to CT. None of the patients at CM-VI and only 3.6% of those at INO required hospitalization during RT.

The European Society of Breast Cancer Specialists (EUSOMA) identified a set of quality indicators to assess the standard of breast cancer treatment [14]. We used some of these indicators and their minimum standards to assess quality of care at the Moroccan oncology centres (Table 5). Nearly half of the patients at either centre initiated treatment within 6 weeks of registration (EUSOMA minimum standard – 80%); no significant improvement being observed over time. Proportion of patients operated for primary tumour was close to the EUSOMA minimum standard of 80% at INO, but lower at CM-VI. Frequency of breast conservative therapy (BCT) was significantly less at both CM-VI and INO compared to the ESMO benchmark of 70%. EUSOMA stipulated that at least 90% of the patients undergoing BCS should receive post-operative RT; the proportion was 75.3% at INO, but only 38.3% at CM-VI. Proportion of patients with ER-negative (T > 1 cm or node-positive) breast cancers who received chemotherapy was around 65% at both the centres; significantly lower than the EUSOMA minimum standard of 85%. Proportion of patients with HER2-positive cancer (T > 1 cm or node-positive) treated with CT at either centre was close to the EUSOMA standard of 85%. While frequency of the ER and/or PR positive patients receiving endocrine therapy was close to the EUSOMA benchmark of 85% at INO, it was much less at CM-VI. Proportion of patients with HER2-positive cancer (T > 1 cm or node-positive) treated with CT and trastuzumab was 44.4% at CM-VI and 66.3% at INO. The EUSOMA benchmark for this indicator is 85%.

Follow up information was available for 74.5% of the treated patients at CM-VI and 92.1% of the treated patients at INO (data not shown in the tables). High rate of follow up and systematic documentation of the disease status at last follow up permitted us to estimate the DFS. Both 3-year and 5-year DFS of the patients registered at INO were significantly higher compared to those registered at CM-VI for early as well as advanced stage. In Fig. 1, the 5-year DFS for early-stage cancers at CM-VI was 60.5%, while it was 86.1% at INO. Patients with advanced-stage had 5-year DFS of 41.4% and 51.8% at CM-VI and INO respectively. Patients with advanced-stage had 5-year DFS of 41.4% and 51.8% at CM-VI and INO respectively. Almost all the deaths happened either at the patients' homes or at hospitals close to their residence. Due to lack of reliable information on the date of death, we could not estimate the overall survival.

Discussion

Based on analysis of the patient profiles, tumour characteristics and treatment details for a representative sample of 2120 breast cancer patients registered at two oncology centres in Morocco, our study demonstrated that quality of treatment makes a significant difference in breast cancer survival, even when there is no

Table 1
Patient characteristics by oncology centre and period of diagnosis.

Characteristics	All patients		Oncology centre					Period of diagnosis				
			CM-VI, Casablanca		*INO*, Rabat		Chi^2	2008–2012		2013–2017		Chi^2
	n (%)		n (%)		n (%)		p-value	n (%)		n (%)		p-value
Patients assessed	2120		915		1205			880		1240		
Period of diagnosis												
2008–2012	880	(41.5)	383	(41.9)	497	(41.2)	0.777					
2013–2017	1240	(58.5)	532	(58.1)	708	(58.8)						
Age at diagnosis (years)												
<30	43	(2.0)	23	(2.5)	20	(1.7)	0.816	17	(1.9)	26	(2.1)	0.152
30-39	336	(15.9)	149	(16.3)	187	(15.6)		158	(18.0)	178	(14.4)	
40-49	723	(34.2)	307	(33.6)	416	(34.6)		308	(35.0)	415	(33.6)	
50-59	602	(28.5)	259	(28.3)	343	(28.6)		243	(27.6)	359	(29.0)	
60-69	288	(13.6)	123	(13.5)	165	(13.7)		108	(12.3)	180	(14.6)	
70+	123	(5.8)	53	(5.8)	70	(5.8)		45	(5.1)	78	(6.3)	
Total	2115	(100.0)	914	(100.0)	1201	(100.0)		879	(100.0)	1236	(100.0)	
Missing	5	(0.2)	1	(0.1)	4	(0.3)		1	(0.1)	4	(0.3)	
Residence												
Urban	1687	(79.6)	672	(73.4)	1015	(84.2)	<0.001	689	(78.3)	998	(80.5)	0.074
Semi-urban	182	(8.6)	114	(12.5)	68	(5.6)		90	(10.2)	92	(7.4)	
Rural	251	(11.8)	129	(14.1)	122	(10.1)		101	(11.5)	150	(12.1)	
Total	2120	(100.0)	915	(100.0)	1205	(100.0)		880	(100.0)	1240	(100.0)	
Missing	0	(0.0)	0	(0.0)	0	(0.0)		0	(0.0)	0	(0.0)	
Health insurance coverage												
None	582	(31.0)	295	(35.9)	287	(27.2)	<0.001	468	(66.2)	114	(9.8)	<0.001
RAMed	997	(53.2)	439	(53.5)	558	(52.9)		140	(19.8)	857	(73.4)	
Employee's insurance	296	(15.8)	87	(10.6)	209	(19.8)		99	(14.0)	197	(16.9)	
Total	1875	(100.0)	821	(100.0)	1054	(100.0)		707	(100.0)	1168	(100.0)	
Missing	245	(11.6)	94	(10.3)	151	(12.5)		173	(19.7)	72	(5.8)	
Profession												
Housewife	1622	(94.4)	655	(94.4)	967	(94.4)	0.962	667	(94.2)	955	(94.6)	0.759
Others	96	(5.6)	39	(5.6)	57	(5.6)		41	(5.8)	55	(5.4)	
Total	1718	(100.0)	694	(100.0)	1024	(100.0)		708	(100.0)	1010	(100.0)	
Missing	402	(19.0)	221	(24.2)	181	(15.0)		172	(19.5)	230	(18.5)	
Marital status												
Single	311	(15.7)	144	(17.1)	167	(14.7)	<0.001	130	(15.6)	181	(15.8)	0.273
Married	1333	(67.3)	519	(61.5)	814	(71.7)		569	(68.1)	764	(66.8)	
Widow	208	(10.5)	106	(12.6)	102	(9.0)		93	(11.1)	115	(10.1)	
Separated	128	(6.5)	75	(8.9)	53	(4.7)		44	(5.3)	84	(7.3)	
Total	1980	(100.0)	844	(100.0)	1136	(100.0)		836	(100.0)	1144	(100.0)	
Missing	140	(6.6)	71	(7.8)	69	(5.7)		44	(5.0)	96	(7.7)	
Parity												
None	439	(23.3)	192	(23.7)	247	(22.9)	0.360	194	(23.9)	245	(22.8)	0.182
1-2	499	(26.4)	219	(27.0)	280	(26.0)		207	(25.5)	292	(27.1)	
3-4	521	(27.6)	231	(28.5)	290	(26.9)		210	(25.9)	311	(28.9)	
5+	429	(22.7)	168	(20.7)	261	(24.2)		201	(24.8)	228	(21.2)	
Total	1888	(100.0)	810	(100.0)	1078	(100.0)		812	(100.0)	1076	(100.0)	
Missing	232	(10.9)	105	(11.5)	127	(10.5)		68	(7.7)	164	(13.2)	
Menopause status												
No	1043	(54.4)	461	(57.1)	582	(52.4)	0.045	442	(52.1)	601	(56.2)	0.077
Yes	875	(45.6)	347	(42.9)	528	(47.6)		406	(47.9)	469	(43.8)	
Total	1918	(100.0)	808	(100.0)	1110	(100.0)		848	(100.0)	1070	(100.0)	
Missing	202	(9.5)	107	(11.7)	95	(7.9)		32	(3.6)	170	(13.7)	
Family history of breast cancer												
No	1654	(87.5)	696	(87.5)	958	(87.4)	0.928	732	(87.5)	922	(87.5)	0.989
Yes	237	(12.5)	99	(12.5)	138	(12.6)		105	(12.5)	132	(12.5)	
Total	1891	(100.0)	795	(100.0)	1096	(100.0)		837	(100.0)	1054	(100.0)	
Missing	229	(10.8)	120	(13.1)	109	(9.0)		43	(4.9)	186	(15.0)	
Diagnosed before registration at oncology centre	1210	(57.1)	430	(47.0)	780	(64.7)	<0.001	473	(53.8)	737	(59.4)	0.009

CM-VI: Centre Mohammed VI pour le traitement des cancers; INO: *Institut National d'Oncologie*; RAMed: *Régime d'Assistance Médicale.*

Table 2
Interval between date of onset of symptoms and the date of first medical consultation that led to referral for cancer diagnosis (access delay) and its determinants.

Characteristics	Longest duration of symptoms (months)						Crude			Adjusted*		
	1–5		6–11		12+		Risk ratio (95% CI)			Risk ratio (95% CI)		
	n (%)		n (%)		n (%)							
Patients with symptoms	850		433		549							
Centre												
CM-VI, Casablanca	370	(46.2)	183	(22.8)	248	(31.0)	1.00			1.00		
INO, Rabat	480	(46.6)	250	(24.2)	301	(29.2)	0.98	(0.88 -	1.07)	0.95	(0.86 -	1.03)
Period of diagnosis												
2008–2012	337	(40.3)	224	(26.8)	275	(32.9)	1.00			1.00		
2013–2017	513	(51.5)	209	(21.0)	274	(27.5)	0.79	(0.72 -	0.86)	0.76	(0.67 -	0.85)
Age at diagnosis (years)												
<30	19	(52.8)	9	(25.0)	8	(22.2)	1.00			1.00		
30-39	145	(49.0)	87	(29.4)	64	(21.6)	1.14	(0.78 -	1.59)	1.19	(0.83 -	1.67)
40-49	321	(50.6)	140	(22.1)	173	(27.3)	1.11	(0.96 -	1.27)	1.12	(0.96 -	1.28)
50-59	226	(43.4)	117	(22.5)	178	(34.2)	1.25	(1.07 -	1.43)	1.22	(1.01 -	1.44)
60-69	99	(41.1)	59	(24.5)	83	(34.4)	1.38	(1.15 -	1.62)	1.33	(1.05 -	1.60)
70+	39	(37.9)	21	(20.4)	43	(41.7)	1.54	(1.21 -	1.92)	1.50	(1.13 -	1.90)
Residence												
Urban	672	(46.5)	346	(23.9)	428	(29.6)	1.00			1.00		
Semi-urban	73	(44.8)	38	(23.3)	52	(31.9)	0.99	(0.84 -	1.16)	1.01	(0.86 -	1.19)
Rural	105	(47.1)	49	(22.0)	69	(30.9)	0.97	(0.84 -	1.11)	1.03	(0.89 -	1.19)
Health insurance coverage												
None	214	(39.6)	146	(27.0)	180	(33.3)	1.00			1.00		
RAMed	422	(51.0)	174	(21.0)	232	(28.0)	0.83	(0.74 -	0.92)	1.02	(0.89 -	1.17)
Employee's insurance	120	(48.0)	55	(22.0)	75	(30.0)	1.01	(0.86 -	1.17)	1.13	(0.96 -	1.31)
Marital status												
Never married	129	(46.9)	62	(22.5)	84	(30.5)	1.00			1.00		
Ever married	669	(45.9)	354	(24.3)	433	(29.7)	1.02	(0.89 -	1.15)	1.05	(0.88 -	1.24)
Parity												
None	181	(45.8)	92	(23.3)	122	(30.9)	1.00			1.00		
1-2	196	(45.4)	121	(28.0)	115	(26.6)	0.97	(0.83 -	1.12)	0.92	(0.78 -	1.10)
3-4	232	(50.4)	95	(20.7)	133	(28.9)	0.84	(0.73 -	0.97)	0.82	(0.69 -	0.96)
5+	174	(44.8)	95	(24.5)	119	(30.7)	0.96	(0.82 -	1.10)	0.84	(0.69 -	0.99)
Menopause status												
No	465	(50.0)	225	(24.2)	240	(25.8)	1.00			1.00		
Yes	334	(42.7)	182	(23.2)	267	(34.1)	1.27	(1.15 -	1.40)	1.13	(0.99 -	1.30)
Family history of breast cancer												
No	693	(46.7)	350	(23.6)	440	(29.7)	1.00			1.00		
Yes	98	(44.5)	58	(26.4)	64	(29.1)	1.13	(0.97 -	1.31)	1.14	(0.98 -	1.32)

CM-VI: Centre Mohammed VI pour le traitement des cancers; INO: Institut National d'Oncologie; RAMed: Régime d'Assistance Médicale; CI: Confidence Interval; * Adjusted for all the variables listed in the table.

significant difference in tumour characteristics.

Breast cancer is the leading cause of cancer mortality among women in Morocco, causing nearly 3700 deaths per year [15]. The frequency of early-stage cancers in the two major oncology centres in Morocco (~55%) was comparable to that reported from other Mediterranean countries with higher resources (53% in Saudi Arabia and 58% in Bahrain) [16]. The breast cancer screening programme in Morocco could account for the significant reduction in access delay observed over time. A formal evaluation of the performance of the programme by IARC revealed that the opportunistic programme screened 1.1 million and 1.5 million women in the years 2015 and 2016 respectively, thus achieving a coverage of 62.8% of the annual target population [17]. Downstaging of breast cancer at INO since 2011 (but not at CM-VI) could also be ascribed to the screening programme. However, a median access delay of 6 months and a waiting time exceeding six weeks for nearly half of the patients to initiate treatment at the oncology centres show that there is a significant room for improvement in diagnostic and therapeutic services. Steps should be taken to limit the interval between symptom onset and treatment initiation to below 3 months, which by itself may raise 5-year survival from breast cancer by at least 10% [18]. A systematic situational analysis is needed to document the patient-, provider- and system-related factors responsible for the access, diagnostic and treatment delays in Morocco. The large number of cancer early detection centres built across the country to investigate patients referred through the screening programme should be utilized to examine women with symptoms suggestive of breast cancer. A clearly defined referral pathway linking various service facilities is necessary to ensure prompt diagnosis and treatment.

Detecting breast cancer at an early stage can have a positive impact only when standardized treatment would be delivered with quality and equity. The national cancer plan of Morocco was instrumental in making significant vertical investments to improve oncology infrastructure.[4] Comprehensive cancer care in public sector is being delivered through 11 regional oncology centres in the country. The number of external beam RT machines (8/10,000 cancer patients) in the country is significantly higher than that reported from most low- and middle-income countries (LMICs) [19,20]. The benefit of the strategy adopted in 2013 to provide oncopathology and treatment services as a comprehensive package is reflected in the fact that a high proportion of patients had complete pathology diagnosis, staging information and molecular profiles. Non-availability of reliable immunohistochemistry (IHC) is a major

Table 3
Determinants of presentation in advanced stage (stage III-IV) at diagnosis.

Characteristics	Patients assessed	Patients with advanced stage (III-IV)		Crude odds ratio (95% CI)			Adjusted* odds ratio (95% CI)		
	n	n (%)							
Patients with staging information	1973	903	(45.8)						
Centre									
CM-VI, Casablanca	829	360	(43.4)	1.00			1.00		
INO, Rabat	1144	543	(47.5)	1.18	(0.98 -	1.40)	1.20	(0.99 -	1.43)
Period of diagnosis									
2008–2012	846	403	(47.6)	1.00			1.00		
2013–2017	1127	500	(44.4)	0.88	(0.72 -	1.04)	0.95	(0.75 -	1.17)
Age at diagnosis (years)									
<30	40	18	(45.0)	1.05	(0.47 -	1.88)	1.05	(0.50 -	1.95)
30-39	305	133	(43.6)	1.00			1.00		
40-49	679	309	(45.5)	1.08	(0.80 -	1.39)	1.05	(0.78 -	1.39)
50-59	569	266	(46.7)	1.14	(0.82 -	1.46)	1.07	(0.73 -	1.46)
60-69	269	130	(48.3)	1.21	(0.84 -	1.64)	1.10	(0.70 -	1.60)
70+	108	47	(43.5)	0.99	(0.61 -	1.49)	0.84	(0.44 -	1.32)
Residence									
Urban	1572	712	(45.3)	1.00			1.00		
Semi-urban	170	77	(45.3)	1.00	(0.70 -	1.34)	1.01	(0.71 -	1.37)
Rural	231	114	(49.4)	1.18	(0.88 -	1.53)	1.20	(0.89 -	1.56)
Health insurance coverage									
None	550	257	(46.7)	1.00			1.00		
Covered	1195	528	(44.2)	0.91	(0.73 -	1.09)	0.93	(0.72 -	1.19)
RAMed	925	418	(45.2)	0.94	(0.76 -	1.15)	1.01	(0.76 -	1.29)
Employee's insurance	270	110	(40.7)	0.78	(0.57 -	1.03)	0.77	(0.54 -	1.03)
Marital status									
Never married	286	118	(41.3)	1.00			1.00		
Ever married	1571	726	(46.2)	1.22	(0.95 -	1.57)	1.10	(0.74 -	1.47)
Parity									
None	411	176	(42.8)	1.00			1.00		
1-2	472	219	(46.4)	1.16	(0.87 -	1.48)	1.13	(0.79 -	1.52)
3-4	491	228	(46.4)	1.15	(0.88 -	1.49)	1.15	(0.82 -	1.56)
5+	399	195	(48.9)	1.28	(0.96 -	1.66)	1.22	(0.84 -	1.68)
Menopause status									
No	975	436	(44.7)	1.00			1.00		
Yes	836	393	(47.0)	1.10	(0.91 -	1.31)	0.99	(0.76 -	1.27)
Family history of breast cancer									
No	1600	1490	(93.1)	1.00			1.00		
Yes	228	221	(96.9)	0.93	(0.69 -	1.22)	0.91	(0.65 -	1.19)
Interval between symptoms onset and first consultation (months)				1.03	(1.02 -	1.04)	1.03	(1.02 -	1.04)

CM-VI: Centre Mohammed VI pour le traitement des cancers; INO: Institut National d'Oncologie; RAMed: Régime d'Assistance Médicale; CI: Confidence Interval; * Adjusted for all the variables listed in the table.

hindrance to provide tailored breast cancer management in most LMICs. A recently published survey among the laboratories from 17 countries participating in the African Cancer Registry Network (AFCRN) observed that only half of these laboratories had IHC facilities [21]. The sub-optimal quality of IHC at such laboratories is evident from the unusually high (as much as 50%) frequency of triple-negative breast cancers reported in African studies [22,23]. The proportion of different molecular sub-types of breast cancer reported in our study was consistent with what has been reported from comprehensive oncology centres in other Mediterranean countries, which possibly indicates the reliability of IHC services in Morocco [24].

Introduction of innovative insurance schemes to financially protect vast majority of the Moroccan population against catastrophic expenditure often incurred during cancer treatment is a significant public health achievement. Patients and their families are also entitled to free accommodation during treatment at the Houses-of-life (‘*Maison de vie*’) built close to the oncology centres. These free accommodations save significant indirect out-of-pocket expenditure for the patients, and at the same time reduce demand for in-patient admissions. Regular procurement and uninterrupted supply of common chemotherapeutic drugs (including *trastuzumab*) at the public hospitals was ensured by including them in the updated national list of essential drugs [25]. The consequences of these benevolent public health measures are evident from the high proportion of breast cancer patients being covered by health insurance in the recent years, very few requiring hospitalizations for RT and high proportion of patients being treated with combination chemotherapy.

While highlighting the achievements made by Morocco in improving breast cancer care, our study also identified the prevailing gaps in services and the inequality that exists between the two oncology centres. The standard-of-care for breast cancer favours increasing use of BCS, polychemotherapy (including *taxane*) and/or RT for patients with higher risk of recurrence, endocrine treatment for ER and/or PR positive cancers and targeted therapy

Table 4
Distribution of molecular subtypes of breast cancer by stage at diagnosis and tumour differentiation.

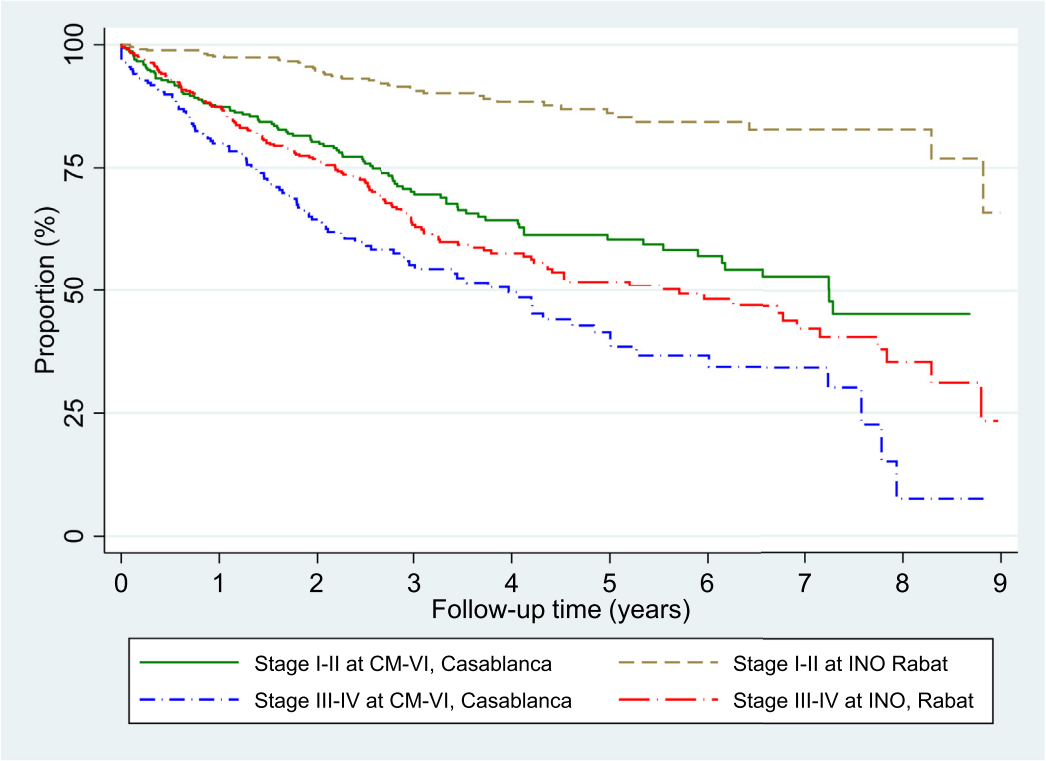
	CM-VI, Casablanca								INO, Rabat							
	Patients assessed	ER, PR and HER2 combinations							Patients assessed	ER, PR and HER2 combinations						
		ER and/or PR positive, and HER2 negative		ER and/or PR positive, and HER2 positive		ER and PR negative, and HER2 positive		Triple negative		ER and/or PR positive, and HER2 negative		ER and/or PR positive, and HER2 positive		ER and PR negative, and HER2 positive		Triple negative	
Distribution of molecular subtypes	635	329	(51.8)	137	(21.6)	54	(8.5)	115	(18.1)	1020	581	(57.0)	211	(20.7)	86	(8.4)	142	(13.9)
Stage at diagnosis - n (%)																		
I	76	47	(61.8)	11	(14.5)	6	(7.9)	12	(15.8)	92	58	(63.0)	14	(15.2)	8	(8.7)	12	(13.0)
II	278	142	(51.1)	56	(20.1)	22	(7.9)	58	(20.9)	435	244	(56.1)	90	(20.7)	34	(7.8)	67	(15.4)
III	197	97	(49.2)	50	(25.4)	20	(10.2)	30	(15.2)	348	208	(59.8)	73	(21.0)	31	(8.9)	36	(10.3)
IV	43	25	(58.1)	7	(16.3)	3	(7.0)	8	(18.6)	111	57	(51.4)	24	(21.6)	9	(8.1)	21	(18.9)
Unknown	41	18	(43.9)	13	(31.7)	3	(7.3)	7	(17.1)	34	14	(41.2)	10	(29.4)	4	(11.8)	6	(17.6)
Tumour differentiation - n (%)																		
Well differentiated	26	16	(61.5)	3	(11.5)	5	(19.2)	2	(7.7)	94	65	(69.1)	22	(23.4)	3	(3.2)	4	(4.3)
Moderately differentiated	340	202	(59.4)	76	(22.4)	18	(5.3)	44	(12.9)	540	341	(63.1)	110	(20.4)	41	(7.6)	48	(8.9)
Poorlydifferentiated	181	70	(38.7)	34	(18.8)	21	(11.6)	56	(30.9)	335	148	(44.2)	69	(20.6)	37	(11.0)	81	(24.2)
Others	3	0	(0.0)	1	(33.3)	0	(0.0)	2	(66.7)	3	1	(33.3)	1	(33.3)	1	(33.3)	0	(0.0)
Unknown	85	41	(48.2)	23	(27.1)	10	(11.8)	11	(12.9)	48	26	(54.2)	9	(18.8)	4	(8.3)	9	(18.8)

CM-VI: Centre Mohammed VI pour le traitement des cancers; INO: *Institut National d'Oncologie*; ER: Oestrogen receptors; PR: Progesterone receptors; HER2: human epidermal growth factor receptor 2.

Table 5
Selected quality indicators in breast cancer care and their minimum standards identified by the EUSOMA Working Group and their values observed in the two oncology centers in Morocco over two time periods.

	EUSOMA minimum standard	CM-VI, Casablanca		INO, Rabat	
		2008–12	*2013–17*	*2008–12*	*2013–17*
Proportion of invasive cancer cases for which the following prognostic/predictive parameters have been recorded: histological type, grading, ER and HER-2 (PR/Ki67 optional)	>95%	64% (246/383)	49% (258/532)	80% (399/497)	74% (522/708)
Time interval of ≤6 weeks, from the date of registration at oncology centre to the date of surgery or start of other treatment.	80%	53% (140/266)	51% (123/239)	55% (263/475)	49% (303/614)
Proportion of patients (with treatment information available) who received an operation (lumpectomy/mastectomy) for the primary tumour	80%	63% (212/337)	72.3% (324/448)	86% (426/496)	84% (558/661)
Proportion of patients with breast cancer not greater than 3 cm who underwent BCT (lumpectomy + RT) as primary treatment	70%	20% (34/174)	11% (23/215)	23% (59/261)	27% (89/326)
Proportion of patients who received postoperative radiation therapy (RT) after Breast conservation surgery	90%	65% (61/94)	23% (39/167)	81% (82/101)	71% (110/154)
Proportion of patients with involvement of axillary lymph nodes (≥pN2a) who received post-mastectomy radiation therapy to the chest wall and all (non-resected) regional lymph-nodes	90%	56% (15/27)	27% (14/51)	86% (96/112)	66% (83/125)
Proportion of patients with involvement of up to three axillary lymph nodes (pN1) who received post-mastectomy radiation therapy to the chest wall and non-resected axillary lymph-nodes,	70%	57% (20/35)	32% (12/37)	85% (77/91)	71% (81/114)
Proportion of patients with ER negative (T > 1 cm or Node positive) invasive carcinoma who received adjuvant chemotherapy	85%	71% (133/187)	61% (151/248)	71% (248/350)	63% (270/429)
Proportion of patients with HER2 positive invasive carcinoma (T > 1 cm or Node positive) treated with chemotherapy	85%	92% (47/51)	75% 43 (/57)	99% (73/74)	94% (102/109)
Proportion of patients with ER and/or PR positive invasive cancer who received endocrine therapy	85%	67% (153/228)	45% (135/301)	84% (309/367)	82% (403/490)
Proportion of patients with HER2 positive invasive carcinoma (T > 1 cm or Node positive) treated with chemotherapy who received adjuvant trastuzumab	85%	36% (17/47)	53% (23/43)	63% (46/73)	69% (70/102)

CM-VI: Centre Mohammed VI pour le traitement des cancers; INO: *Institut National d'Oncologie.*



Stage and survival period	CM-VI, Casablanca			INO, Rabat		
	Number at risk	Number of failures	Survival proportion (%)	Number at risk	Number of failures	Survival proportion (%)
Stage I-II						
3-year	125	75	70.2	219	33	91.0
5-year	66	14	60.5	105	8	86.1
Stage III-IV						
3-year	69	82	55.3	135	124	63.5
5-year	29	13	41.4	74	20	51.8

Fig. 1. Kaplan Meier's curve showing disease-free survival to relapse after treatment among breast cancer patients treated during 2008–2015 at *Centre Mohammed VI pour le traitement des cancers (CM-VI)*, Casablanca and *Institut National d'Oncologie* (*INO*), Rabat by stage at diagnosis.

for cancers expressing HER2 [26–30]. Both CM-VI and INO have adopted many of these best practices and the overall quality of treatment (as evident from the high proportion of patients being treated, tailoring of treatment based on molecular profile, high compliance to CT, achieving EUSOMA standards at least for some of the indicators etc.) was superior to what is generally reported in most countries with limited resources [31,32]. However, the frequency of BCS at either oncology centre needs to improve considerably. Earlier studies have noted that the surgeons in the Arab world are generally reluctant to practice breast conservation even when indicated [33]. As majority of the surgeries for the patients registered at CM-VI and INO were performed outside, the surgeons at these other hospitals need to be oriented to the evidence-based practices. Allowing the external surgeons to participate in the MDTs (e.g., through virtual consultation) at any of the oncology centres and discuss their patients prior to surgery may improve their adherence to the standard practice guidelines that already exist in Morocco.

As reflected in our study and a quality issue that has already been identified by the oncologists in Morocco, the proportion of patients (57% at CM-VI and 67% at IN) with hormonal receptor positive, HER2-negative with stage I cancers receiving chemotherapy is unexpectedly high. A significant number of the patients could have other risk factors (lymph node positivity, poorly differentiated cancer etc.). The proportion is still on the higher side. The latest national guideline in Morocco recommends more conservative and rational use of chemotherapy in the treatment of breast cancer [34].

The high quality of care at INO was reflected in the high survival rates comparable to that reported in high HDI countries in the Mediterranean region [35]. The survival rates for patients registered at CM-VI were significantly lower than that observed at INO in spite of the two centres having patients with similar age distribution, tumour characteristics and stage. The difference in the quality of care could explain this inequality. Services at CM-VI were not as comprehensive as at INO (e.g., CM-VI had to depend on Casablanca University Hospital located in the same compound for pathology and radiology services or in-patient chemotherapy administration).

Significantly higher proportion surgeries were performed at other hospitals for the patients registered at CM-VI compared to those at INO. Proportion of patients not receiving RT even when indicated (especially those undergoing BCS) was higher at CM-VI. Though CT was administered to almost equal proportion of patients at CM-VI and INO, the regime included *taxane* less frequently at the former centre. A smaller proportion of patients at CM-VI had information on receptor status or underwent endocrine or *trastuzumab* therapy. Similar intra-country disparity in survival with the patients in capital cities being more privileged has recently been reported from Kenya and Zimbabwe [36].

The major limitation of our study is its retrospective nature and dependence on the quality of documentation. In general, high quality of clinical documentation, completeness of the diagnostic examinations carried out and careful maintenance of records over many years at the oncology centres permitted us to gather reasonably adequate information for this study. Some of the information essential to understand quality of care like proportion of patients completing treatment could not be assessed as it was not clearly documented in the records. The radiation therapy department at either oncology centre maintained its own digitized database of the patients since 2016. It is possible that some of the RT data was missing from the case notes for the patients registered in 2016–17. This could explain the apparent decline in RT performance in the later period at CM-VI, in particular. Prescriptions of drugs for hormone therapy were often not recorded in the case-notes, leading to a possible under-reporting.

The results of our study may not reflect the standard of breast cancer care across all oncology centres in Morocco. In fact, during the study period these two institutions incorporated in our study were the main public-funded comprehensive oncology centres. The MoH is currently establishing one public oncology centre in each region, and they should try to emulate the high standard of care being delivered at the two existing centres, especially at INO.

Conclusion

The breast cancer pattern-of-care study in Morocco certainly highlights the great progress made in the country to organize oncology services with quality. The standard of breast cancer treatment and survival outcome at INO were comparable to that observed in many high-resourced countries. However, the disparity between the two oncology centres was also revealing of the inequality that exists within the country. Regular monitoring of the delays in care and assessing adherence to the evidence-based guidelines should be an integral part of the quality improvement process. Continued effort is needed to address the gaps identified in our study, minimize the inequalities and consolidate the gains achieved from a pragmatic cancer control policy, as Morocco moves towards being an exemplar LMIC in cancer control.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.07.009.

Authors contributions

PB designed the study, oversaw the implementation, drafted first version of the manuscript, participated in subsequent revisions, and contributed to the final version of the manuscript. HM, CS, AB, KB and FS were involved in study implementation, data collection and data analysis, and contributed extensively to the revision of the initial drafts. LAl, RM and EL contributed to data management, data analysis and manuscript preparation. YC, PV, LAb, AC, MB, HE, RS and RB were involved in study designing, supervising implementation and finalization of the manuscript.

Authors declare no conflict of interest

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