Critical Assessment of Three Decades of Breast Cancer Research in Yemen: Systematic Review

Al-Naggar RA1, Al-Maktari LAS2, Alshaikhli H3, Trafford J4, Saleh B5 and Mossfer SI6

1Department of Community Medicine, UKM, Malaysia
2Department Haematology, University of Sana’a, Yemen
3School of Public Health and Interdisciplinary Studies, Auckland University of Technology, Auckland, New Zealand
4School of Science and Engineering, Waikato University, Hamilton, New Zealand
5Department of Pharmacology, University of Sana’a, Yemen
6Department of Medicine, Al-Hikmah University, Yemen

Abstract

Objective: This review aims to critically assess three decades (1989 to 2019) of breast cancer research in Yemen and to identify the gaps in, and need for, breast cancer research in Yemen.

Methodology: A search was performed in Web of Science, EMBASE, PubMed, Google Scholar and Ovid to identify articles on breast cancer research in Yemen that were published in the last three decades. The articles were selected and reviewed by experts in this field, based on clinical relevance and future research implications.

Results: This review comprised 19,031 participants, extracted from 27 articles that were included and analyzed. The most common study design was retrospective (N=9), while the least common was Randomized Controlled Trial (N=1). Breast cancer patients in Yemen were commonly diagnosed at an early age of 50 years or younger. Therefore, breast cancer has affected Yemeni women at a younger age, ranging from 40 to 49 years, than the age at which this cancer has affected women in other countries. Overall, awareness of breast cancer among Yemeni women was very poor, and poor knowledge was reported in these studies. Some studies reported that a shockingly low rate of only 11% to 17.4% of Yemeni women practiced Breast Screen Examination (BSE), while another study reported that only 30.3% of Yemeni women performed regular BSE. Only 1.6% of the Yemeni women had been exposed to a mammogram test. The highest performed surgery was a modified radical mastectomy (N=211). Regrettably, 13 patients had refused the surgery. The highest cases of breast cancer were reported in Hadramout (N=956), while the lowest number of only three cases was in Shabowah. The most common histological subtype was invasive ductal carcinoma (N=2695).

Conclusion: Yemen is characterised by three decades of scattered, fragmented and poor-quality breast cancer research. Therefore, there is a need to establish a breast cancer research center in Yemen to research all aspects of breast cancer in Yemen and to build bridges for collaborations in breast cancer research globally.

Keywords: Breast cancer; Yemen; Review; Screening; Diagnosis; Treatment

Introduction

Breast cancer is the most diagnosed cancer, with a high mortality rate, globally. In 2015 there were about 1.7 million confirmed cases of breast cancer, resulting in some 521,900 deaths, worldwide [1]. The highest incidence rates of breast cancer were reported in western countries, while Asia and Africa accounted for the lowest incidence rates [2]. In Yemen, breast cancer is recorded as the commonest cancer among women (30.3%) and the most common of all cancers (16.6%) [3,4].

Delay

Delayed diagnosis of breast cancer is a global problem, especially in developing countries like Yemen. There is strong evidence those patients whose delay in diagnosis is between 3 and 6 months have poorer survival rates than patients whose delay in diagnosis is less than 3 months [5]. Therefore, there is a need to develop local strategies to address the causes of delays in the diagnosis of breast cancer among women in Yemen.

Awareness

Awareness of breast health is both practical and achievable. This includes increasing women’s awareness of the importance of maintaining a healthy weight and regular exercise, as well as cutting down on alcohol consumption. In addition, early-stage detection to control and manage breast cancer risk factors is a very effective measure [6]. Breast cancer risk factors including age, hormone therapy, family history, extensive exposure to radiation and benign breast tumor need to all are well understood among the female population. Early detection of breast cancer will provide the patient with better diagnosis and survival [6-8]. Generally, gaps in evidence-based knowledge, low education and illiteracy are major reasons for late detection [9,10]. One of the strategies for stopping breast cancer is informing women about the risk factors and symptoms of breast cancer [9]. A study that reported the poor knowledge of risk factors...
of breast cancer among the youth of 23 countries [11], signifies the urgency and importance of increasing awareness among the younger population.

**Risk factors**

Breast cancer in Asian women is related to some of the well-known Western risk factors for breast cancer such as early menarche, old age at first full-term pregnancy, women choosing not to breastfeed, women breastfeeding for less time, delayed childbearing, fewer children, late menopause, inactive workforce, as well as diet and lifestyle that follow western patterns [12-15]. In terms of lifestyle factors, soy and high isoflavone be associated with a decreased risk of breast cancer [16], with the greatest protective effects for hormone receptor-positive tumors [17]. Smoking, hypertension, and Diabetes mellitus have been shown to increase breast cancer risk [18,19]. Modifiable health behaviors are thought to be protective against breast cancer, such as maintaining healthy body weight and engaging more in physical activity [20].

**Prevention**

It has been shown that about 30% of all cancer cases can be avoided yearly by following prevention strategies through a healthy lifestyle and a satisfactory working environment [21]. There is strong evidence that obesity, tobacco smoking, diet, drinking alcohol, stress, pollution, sun exposure, physical activity, and infections have an implication for the onset of breast cancer (World Cancer Research Fund, 2007).

There is a relationship between vitamin D deficiency and cancer-related morbidity and mortality [22]. Mediterranean diet has the highest potential to prevent breast cancer development. The rich components of vegetables, fruits, nuts, legumes, whole grains, and fish have been linked to breast cancer prevention, in addition to reducing the consumption of red and processed meats.

The most available literature on different aspects of breast cancer is reported from developed and Western countries. Such research, undertaken in other countries, may not automatically apply in Yemeni settings. Therefore, there is an urgent need to carry out Yemeni studies, mainly in the following areas: psychosocial needs, therapeutic, prognostic, diagnostic, screening, and prevention. Few studies from Yemen have investigated the special risk factors and other aspects of breast cancer research. Therefore, there is a need to conduct a systematic review to establish the gaps and the needs for Breast cancer research in Yemen.

**Methodology**

**Search strategy**

Articles indexed in PubMed, Ovid, EMBASE, Web of Science and Google Scholar were systematically and scientifically searched using the keywords and MeSH terms [Breast Neoplasms” OR “Breast Cancer” OR “Breast Tumor” OR “Breast Tumors” OR “Breast Carcinoma” OR “Breast Carcinomas”) and Yemen]. The references of the included articles were searched manually for further articles. Articles published from 1st January 1989 until 30th March 2019 was included.

Two authors [RAA & HA] separately screened the titles and abstracts of all studies using the inclusion and exclusion criteria. Appropriate studies were retrieved in full-text. Divergences were addressed through discussion with all authors.

**Eligibility**

The following study designs: case-control, cross-sectional, RCTs, non-randomized controlled trials and pre-post were included in this systematic review. Only articles written in the English language were included. Only original, primary articles were included. Studies were excluded from this review if they were review articles, editorials, comments, and letters to authors without information about study details, etc.

**Data extraction and quality assessment**

A data extraction form was used to extract the required information for this systematic review. The data extraction form included: study name, first author’s name, publication year, study design, and the number of participants. Two authors [RAA & HA] autonomously assessed the quality of the included studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist. Studies were then classified into three categories (A, B or C) according to the percentage of criteria met: A >80%, B 50% to 80%, and C<50% of criteria met. Interventional studies were assessed based on their quality using the Effective Public Health Practice Project Quality Assessment Tool. Any differences in the quality assessment were resolved by discussion among all authors.

The flow of the data collection:

1. Records identified through PubMed, Ovid, EMBASE, Web of Science and Google Scholar research (N=42).
2. Records search for inclusion (N=42).
3. Excluded due to non-relevant (N=25) [Review articles=4; Lab study=13; reports=2, Not relevant=6].
4. Full text included [N=17].
5. Further reads identified through hand search in bibliography lists [N=33].
6. Excluded due to non-relevant [N=23] [Arabic abstract only=10; Lab study=5; reports=6; thesis=2].
7. Full text included [N=10].
8. The total number included [N=27].

**Results**

**Characteristics of articles/research studies**

In total, 27 articles were included in the final analyses for this review, comprising a total of 19,031 participants. The characteristics of the studies included are listed in Table 1. The majority of articles had less than 4 authors (N=18). The 27 articles were written by 21 different first authors and published in 17 different medical journals. The most popular journals were: Asian Pacific Journal of Cancer Prevention, Eastern Mediterranean Health Journal and Saudi Medical Journal (Table 1).

The included studies on breast cancer were all published between 1989 and 2018. Most of the studies were conducted in Sana’a (N=12), followed by Aden (N=9) and then Hadramout (N=6). The most common study design was Retrospective (N=9), followed by Descriptive (N=7), Cross-sectional (N=5), Case-control (N=3), and finally Prospective (N=1). Capture-recapture method (N=1), and Randomized Controlled Trial (N=1). None of the articles scored an A using the STORBE checklist, only 12 articles were awarded B scores and 15 articles got C scores (Table 2).
Breast cancer diagnoses

Based on geographical locations within Yemen, the highest number of cases of breast cancer diagnoses were reported in Hadramout (N=956), followed by Sana’a (N=454), then Taiz (N=403), and the lowest was in Shabwah (N=3) (Table 3). In terms of breast cancer stages among Yemeni patients, the highest was stage 2 (N=160) and the lowest was stage 1 (N=60). In terms of tumor size, two studies reported that the patients presented with a large size of (45 ± 12) and the lowest was stage 1 (21.4 ± 1.6) (Table 3) [23,24]. In terms of the type of surgery carried out on the breast cancer patients in Yemen, the highest was modified radical mastectomy (N=211), followed by simple mastectomy (N=53), then lumpectomy (N=43), and lastly radical mastectomy (N=21). Unfortunately, 13 patients refused surgery (Table 3).

In terms of the common breast affected with cancer, 1005 patients were affected in the left breast. In comparison, 787 patients were affected in the right breast. Only 26 patients were affected in both breasts (Table 4). The most common histological subtypes were invasive ductal carcinoma (N=2695), followed by invasive lobular carcinoma (N=120) (Table 5).

Five of the 27 studies looked at awareness of breast cancer in Yemen. The total participants in these studies were 1435 women. Four studies were cross-sectional studies, and one was a case-control. All awareness studies were recent studies, with the oldest conducted in 2009, and followed by one study in 2010, two studies conducted in 2016, and most recently one study in 2018. Two studies were conducted in San'a'a, another two studies were conducted in Hadramout and one study took place in Aden. Overall, the awareness of breast cancer in all studies was very poor, and poor knowledge was reported in these studies. Unfortunately, only 11% to 17.4% of Yemeni women practiced BSE in some studies, while another study reported that only 30.3% of women practiced BSE. Across all five studies, only 1.6% of women had been exposed to a mammogram test, and only 24.7% of female physicians had sent their patients for mammogram screening every year regardless of the patients’ history or symptoms (Table 6).

Discussion

Breast cancer in Yemen

Breast cancer is the most common cancer and the foremost cause of death in women worldwide. In Yemen, breast cancer incidence appears to be increasing, with a reported incidence of 12.6 per 100,000 women in 2010 [1]. The data from recent studies show that the age-adjusted incidence rate of breast cancer in Yemen has increased from 8.1 cases per 100,000 women in 2000 to 13.3 cases per 100,000 women in 2018 [2].

Table 1: Characteristics of included studies (N=27).

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of authors</th>
<th>Type of Journal</th>
<th>Name of the Journal</th>
<th>Characteristics</th>
<th>Year</th>
<th>Number of participants</th>
<th>Governorate</th>
<th>Age (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bawazir et al.</td>
<td>29</td>
<td>Retrospective</td>
<td>Asian Pacific Journal of Cancer Prevention</td>
<td>MEDICINE, IN GENERAL</td>
<td>1989-1993</td>
<td>85</td>
<td>Aden</td>
<td>40-49</td>
</tr>
<tr>
<td>Al-Thobhani et al.</td>
<td>25</td>
<td>Retrospective</td>
<td>Eastern Mediterranean Health Journal</td>
<td>Pan Arab Journal of Oncology</td>
<td>1996-2000</td>
<td>116</td>
<td>Sana'a</td>
<td>(44 ± 12)</td>
</tr>
<tr>
<td>Hamid et al.</td>
<td>26</td>
<td>Retrospective</td>
<td>Saudi Medical Journal</td>
<td>Medical Research and Health Advances</td>
<td>1989-1996</td>
<td>227</td>
<td>Sana'a</td>
<td>40-49</td>
</tr>
<tr>
<td>Bawazir</td>
<td>29</td>
<td>Descriptive</td>
<td>Cancer Epidemiology</td>
<td>Al-Madhaji C</td>
<td>1997</td>
<td>22</td>
<td>Aden</td>
<td>NA</td>
</tr>
<tr>
<td>Honesh et al.</td>
<td>87</td>
<td>Randomized Controlled Trial</td>
<td>European Journal of Pharmaceutical and Medical Research</td>
<td>Al-Thobhani et al.</td>
<td>1998-2002</td>
<td>296</td>
<td>Sana'a</td>
<td>(33 ± 11)</td>
</tr>
<tr>
<td>Bawazir et al.</td>
<td>25</td>
<td>Descriptive</td>
<td>Yemeni Journal of Medical Health Research</td>
<td>Al-Thobhani et al.</td>
<td>1997-2001</td>
<td>773</td>
<td>Sana'a</td>
<td>(51 ± 12)</td>
</tr>
<tr>
<td>Barbha et al.</td>
<td>26</td>
<td>Capture-recapture</td>
<td>Pan Arab Journal of Oncology</td>
<td>Al-Thobhani et al.</td>
<td>All old cases until 2008</td>
<td>134</td>
<td>Hadramout</td>
<td>NA</td>
</tr>
<tr>
<td>Ghouth</td>
<td>95</td>
<td>Retrospective</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2006</td>
<td>48</td>
<td>Hadramout</td>
<td>(45 ± 12)</td>
</tr>
<tr>
<td>Al-Naggar et al.</td>
<td>75</td>
<td>Cross-sectional</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2008-2009</td>
<td>105</td>
<td>Sana'a</td>
<td>(32±7)</td>
</tr>
<tr>
<td>BaSaleem et al.</td>
<td>24</td>
<td>Secondary data</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2002-2006</td>
<td>334</td>
<td>Aden</td>
<td>50-54</td>
</tr>
<tr>
<td>Bafakeer et al.</td>
<td>31</td>
<td>Prospective</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2006-2009</td>
<td>142</td>
<td>Hadramout</td>
<td>40-49</td>
</tr>
<tr>
<td>Ahmed</td>
<td>4</td>
<td>Cross-sectional</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2007-2009</td>
<td>425</td>
<td>Hadramout</td>
<td>(21.4 ± 1.6)</td>
</tr>
<tr>
<td>Al-Kahiry</td>
<td>69</td>
<td>Retrospective</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2008-2011</td>
<td>106</td>
<td>Aden</td>
<td>40-49</td>
</tr>
<tr>
<td>Al-Naggar et al.</td>
<td>75</td>
<td>Cross-sectional</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2008-2011</td>
<td>106</td>
<td>Sana'a</td>
<td>&lt; 55</td>
</tr>
<tr>
<td>Ahmed et al.</td>
<td>4</td>
<td>Case-control</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2010</td>
<td>137</td>
<td>Sana'a</td>
<td>16-80 (43.75)</td>
</tr>
<tr>
<td>El-Zaemey et al.</td>
<td>27</td>
<td>Descriptive</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2004-2010</td>
<td>2654</td>
<td>Sana'a</td>
<td>(46 ± 12)</td>
</tr>
<tr>
<td>Alhaj</td>
<td>76</td>
<td>Case-control</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>April-June 2009</td>
<td>60 cases</td>
<td>Sana'a</td>
<td>40-49</td>
</tr>
<tr>
<td>Badheeb C</td>
<td>4</td>
<td>Retrospective</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2006-2011</td>
<td>494</td>
<td>Hadramout</td>
<td>48-87</td>
</tr>
<tr>
<td>Al-Madhaji C</td>
<td>4</td>
<td>Retrospective</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2006-2010</td>
<td>245</td>
<td>Sana'a</td>
<td>30-50 (49 ± 8)</td>
</tr>
<tr>
<td>Alsanabani</td>
<td>28</td>
<td>Retrospective</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2011-2013</td>
<td>160</td>
<td>Sana'a</td>
<td>44.3</td>
</tr>
<tr>
<td>Al-Sakkaf</td>
<td>94</td>
<td>Cross-sectional</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2008-2011</td>
<td>400</td>
<td>Aden</td>
<td>(26 ± 5)</td>
</tr>
<tr>
<td>Alwabr</td>
<td>86</td>
<td>Case-control</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2011</td>
<td>103 case 103 Control</td>
<td>Sana'a</td>
<td>20-70</td>
</tr>
<tr>
<td>Al-Nabhi et al.</td>
<td>26</td>
<td>Descriptive</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>2007-2017</td>
<td>3782</td>
<td>Sana'a</td>
<td>40-49</td>
</tr>
<tr>
<td>Bawazir et al.</td>
<td>15</td>
<td>Cross-sectional</td>
<td>Al-Madhaji C</td>
<td>Al-Thobhani et al.</td>
<td>1997-2011</td>
<td>6974</td>
<td>Aden, Lahej, Abyan, and Al Dhale</td>
<td>45-49</td>
</tr>
</tbody>
</table>

Table 2: The details of selected studies of breast cancer research in Yemen (N=27).
Table 3: Characteristics of breast cancer in different institutions in Yemen.

<table>
<thead>
<tr>
<th>Breast cancer characteristics</th>
<th>Study 1: Harhra and Basaleem [24] N</th>
<th>Study 2: Alsanabani et al. [28] N</th>
<th>Study 3</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of surgery</td>
<td>Modified radical mastectomy 97</td>
<td>114</td>
<td>-</td>
<td>211</td>
</tr>
<tr>
<td></td>
<td>Simple mastectomy 53</td>
<td>-</td>
<td>-</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Lumpectomy 10</td>
<td>33</td>
<td>-</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Radical Mastectomy 21</td>
<td>9</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>No surgery 13</td>
<td>-</td>
<td>-</td>
<td>13</td>
</tr>
<tr>
<td>Breast cancer based on geographical locations</td>
<td>Study 1: El-Zaemey et al. [27]; No (%)</td>
<td>Study 2: Hamid et al. [29] No (%)</td>
<td>Badheeb</td>
<td>Bafakeer et al. [31]</td>
</tr>
<tr>
<td>Governorates</td>
<td>Hadramout - 3</td>
<td>494</td>
<td>142</td>
<td>317</td>
</tr>
<tr>
<td></td>
<td>Sanāa 454</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Taiz 403</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Aden 218</td>
<td>171</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Ib 238</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Al-Hodidah 273</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Lahej - 29</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Abyan - 17</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Shabwa - 3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Others 1068</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stage of cancer</td>
<td>Stage 1 18</td>
<td>20</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Stage 2 40</td>
<td>72</td>
<td>48</td>
<td>160</td>
</tr>
<tr>
<td></td>
<td>Stage 3 54</td>
<td>84</td>
<td>17</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>Stage 4 64</td>
<td>16</td>
<td>-</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 4: Common breast affected with cancer among Yemeni women.

<table>
<thead>
<tr>
<th>Study</th>
<th>Left breast N (%)</th>
<th>Right breast N (%)</th>
<th>Bilateral N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bafakeer et al. [31]</td>
<td>76(total 142)</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>Alsanabani et al. [28]</td>
<td>77 patients (48.1%)</td>
<td>81(50.6%)</td>
<td>2(1.3%)</td>
</tr>
<tr>
<td>El-Zaemey et al. [27]</td>
<td>408(43.7%)</td>
<td>393(42.1%)</td>
<td>19(2.0%)</td>
</tr>
<tr>
<td>Homesh et al. [87]</td>
<td>147(49.7%)</td>
<td>149(50.3%)</td>
<td>NA</td>
</tr>
<tr>
<td>Al-Thobhani et al. [23]</td>
<td>92(59.4%)</td>
<td>63(40.6%)</td>
<td>NA</td>
</tr>
<tr>
<td>Al-Madhaji et al.</td>
<td>205(83.67%)</td>
<td>38(15.5%)</td>
<td>2(0.82%)</td>
</tr>
<tr>
<td>Total</td>
<td>1005</td>
<td>787</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 5: Distribution of breast cancer cases according to histological subtypes of breast cancer in Yemen.

<table>
<thead>
<tr>
<th>Histological subtypes of breast cancer</th>
<th>Study 1 N</th>
<th>Study 2 N</th>
<th>Study 3 N</th>
<th>Study 4 N</th>
<th>Study 5 N</th>
<th>Study 6 N</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive ductal carcinoma</td>
<td>92</td>
<td>124</td>
<td>123</td>
<td>147</td>
<td>185</td>
<td>2024</td>
<td>2695</td>
</tr>
<tr>
<td>Invasive lobular carcinoma</td>
<td>5</td>
<td>13</td>
<td>-</td>
<td>7</td>
<td>13</td>
<td>82</td>
<td>120</td>
</tr>
<tr>
<td>Intraductal papillary carcinoma</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Infiltrating ductal &amp; lobular carcinoma</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>3</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoma NOS</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Malignant phyllodus</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>6</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Mucinous</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Unspecified</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14</td>
<td>488</td>
<td>502</td>
<td>502</td>
</tr>
</tbody>
</table>

1: Badheeb et al; 2: Ahmed et al. [4]; 3: Bafakeer, Banafa, Aram [31]; 4: Alsanabani, Gilan, AlSaadi [28]; 5: Hamid, Tayeb, Bawazir [26]; 6: El-Zaemey et al. [27]
Breast cancer incidence and screening in Yemen

**Table 6: Characteristics and outcome of breast awareness studies in Yemen.**

<table>
<thead>
<tr>
<th>Author/s</th>
<th>No. of participants</th>
<th>Study Design</th>
<th>Study location</th>
<th>Age (mean)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bawazir et al. [15]</td>
<td>317</td>
<td>Cross-sectional</td>
<td>Hadhramout</td>
<td>31.9 ± 10.2</td>
<td>Only 30.3% were practicing self-breast examination. Only 1.6% had been exposed to a mammogram test.</td>
</tr>
<tr>
<td>Al-Sakkal and Baseleen [15]</td>
<td>400</td>
<td>Cross-sectional</td>
<td>Aden</td>
<td>26.5 ± 5.6</td>
<td>Two-thirds of respondents had poor knowledge, 89% never performed any screening.</td>
</tr>
<tr>
<td>Ahmed [4]</td>
<td>425</td>
<td>Cross-sectional</td>
<td>Hadramout</td>
<td>21.4 ± 1.6</td>
<td>Only 17.4% were performing BSE.</td>
</tr>
<tr>
<td>Al-Naggar et al. [75]</td>
<td>105</td>
<td>Cross-sectional</td>
<td>Sana’a</td>
<td>32.13 ± 7.17</td>
<td>36.6% physician did not send asymptomatic women for mammography screening. In other hand 24.7% physician sent the patients for mammogram screening every year regardless of the patients' history or symptoms.</td>
</tr>
<tr>
<td>Alwabr [86]</td>
<td>103 case</td>
<td>Case-control</td>
<td>Sana’a</td>
<td>20-70</td>
<td>In the control group 83.5% of women not practiced breast self-examination compared to 66%. Practiced by the intervention group.</td>
</tr>
</tbody>
</table>

In Sana’a-Yemen, [25] reported that breast cancer ranked first among Yemeni women and accounted for 8% of all cancers. Another study from the National Oncology Centre (NOC) in Sana’a, carried out from 2007 to 2017, reported that breast cancer was the commonest cancer among Yemeni women (21%) [26]. A large study, which included 2654 breast cancer patients from all governorates in Yemen registered in the National Oncology Centre (NOC), reported that breast cancer represented 22% of all women’s cancer [27]. Yet another study from Sana’a found that breast cancer represented 26.9% of women’s cancer [28].

An early report from Aden-Yemen in 1998 reported that the incidence of breast cancer was 23.3% [29]. A study about breast cancer in Aden-Yemen found the breast to be the most prominent site of cancer among women in Aden [29]. Another population study by the Aden Cancer Registry found 334 women breast cancer patients in Aden (representing 30% of all women’s cancer cases in Aden) [4]. A more recent study from Aden, which analyzed data from across 15-years, reported that breast cancer was top cancer among women with an incidence rate of 30.0% [30].

A study from Hadhramut-Yemen reported that breast cancer accounts for 22.4% of cancer cases in women [31]. Ghouth and Bafageer (2006) reported that breast cancer accounted for 14.37% of all cancer cases registered in Hadhramut, Yemen.

**Breast cancer geographical distribution**

In terms of breast cancer cases based on geographical location, the highest cases were reported in Hadhramut (N=956), followed by Sana’a (N=454), then Taiz (403), while only three cases were reported in Shabowah. This substantial variation in the numbers of breast cancer cases reported across Yemen may be explained by where most of the research was undertaken and where the cancer registries are located. More specifically, 12 of the studies were conducted in Sana’a, 9 studies were conducted in Aden and 6 studies were conducted in Hadramout. Furthermore, there is one cancer registry in Aden called “the Aden Cancer Registry (ACR)”, a second cancer registry in Sana’a called “the National Oncology Center (Sana’a)”, and a third in Hadhramout called the Hadhramout Cancer Registry.

**Breast cancer incidence**

Accurate cancer incidence in Yemen is unknown due to many reasons such as limited pathological and epidemiological resources, as well as the shortage and poor quality of manual medical records. Furthermore, political uncertainty, war, civil war and armed fights, have all contributed to the ambiguity of breast cancer incidence. However, there are a few studies and reports that have estimated the age-standardized rate (ASR) of breast cancer. For instance, Aden’s Cancer Registry reported the five years (2002-2006) Age-Standardized Rate (ASR) of breast cancer as 9.6/100,000 females [4]. The higher rate was reported according to the International Agency for research on cancer that breast cancer incidence rates in Yemen are (20.8/100,000) [32]. The G lobocan has estimated a higher rate of 27.4/100,000 Yemeni females [1]. Jordan has shown a more gradual increase in breast cancer incidence, increasing from 32.8/100,000 in 1997 [33], to 40.1/100,000 in 2005 [34], to 61/100,000 in 2012. Available data for 2013 shows that the ASR rates were 55.9/100,000 women in Bahrain, 50.1/100,000 women in Kuwait, Saudi Arabia (25.5/100,000 women) and Oman (22.4/100,000 women) [35]. The lowest ASR was reported in Mongolia (8.0 cases per 100,000). The highest ASR was reported in Belgium (at 109.4 per 100,000) (Glamočlija and Can, 2013). Pakistan has the second-highest ASR in the Middle East with 50.3 per 100,000 [36,37]. Western Turkey had an ASR of 50 per 100,000 compared to Eastern Turkey with 20 per 100,000. This difference was due to the influence of Western lifestyles, which significantly increase the likelihood of women developing breast cancer [38].

**Cancer registry in Yemen**

Cancer registry persists as the main challenge in Yemen, in the absence of national cancer surveillance. In Yemen there are four cancer registries, each working separately without full coordination and collaboration: the Aden Cancer Registry (ACR), the cancer registry at the National Oncology Center (NOC) (Sana’a), Hadhramout Cancer Registry (Hadhramout), and Taiz Cancer Registry (Taiz). The Aden Cancer Registry was the first cancer registry in Yemen, receiving membership of the IACR (International Association of Cancer Registration) in 1998. In Sana’a, the first oncology center was not established and opened until 2005. The Hadhramout Cancer Registry, starting in 2006, and covers three major governorates: Hadhramout, Shabawah, and Almahrah. Comparatively, Taiz is a very newly established cancer registry. Therefore, there is an urgent need to further strengthen the NOC to become a reliable and reasonable National Cancer Registry.

No comprehensive national study has been conducted in Yemen that includes all of the cancer registries, teaching hospitals and other oncology centers that treat breast cancer patients. No national cancer-specific statistics are available and studies on cancer patterns...
are urgently needed. Furthermore, there is no accurate data-base for breast cancer incidence. Most of the studies conducted in Yemen are hospital-based or in a single cancer registry. Further challenges in Yemen are the advanced stage at presentation, the financial burden of treatment, insufficient medical staff training, and the psychological support of cancer patients.

The higher incidence rates of breast cancer seen in developed countries compared with Yemeni women may be related to diverse reproductive factors such as fertility rates, earlier childbirth and breastfeeding duration [39]. In developed countries, the average age at first birth in 2006 ranged from 25 years in the USA to 29.4 years in Switzerland [40]. However, on average Yemeni women have their first baby at 20 years old, which is approximately a decade younger than women in developed countries (MoPHP, 2003).

There is a significant shortage of health workers in all medical fields, and specifically, there are no national oncology training programs, in Yemen. Also, radiation therapies in Yemen are in high demand. Furthermore, no cancer treatment products have been approved by the Ministry of Health in Yemen. These drugs are manufactured by drug companies in developing countries, so Yemeni people have concerns regarding their effectiveness, safety and immunogenicity [41].

Cancer registries in Yemen often struggle with insufficient health services, transient populations, lack of finances, and lack of qualified workforces, inadequate or imprecise data, and difficulty in establishing a trustworthy and reasonable cancer registry in the nation [21].

Yemen culture and breast cancer

There are special and unique reproductive factors among Yemeni women that may act as breast cancer protective factors: age married, parity and length of time spent breastfeeding. Yemeni women, as a socially accepted practice, tended to marry at a young age. Yemeni women had higher parity, with an average of 6 children per woman, compared to countries like Australia, the USA and the UK where the parity was approximately 2 children per woman [42]. The average woman in Yemen breastfed her child for about 22 months (MoPHP, 2003). Much evidence-based research supported our argument here, that these reproductive factors among Yemeni women may have a protective effect against breast cancer. Epidemiological studies have found that high parity is associated with lower breast cancer risk [43,44]. These differences in fertility may also result in differences in lifetime duration of breastfeeding which have a protective effect. It has been reported that breastfeeding 12 months reduces the risk of breast cancer by 4% (Cancer, 2002) [45] found that each birth will reduce the risk of breast cancer by 11%.

Our own anecdotal evidence suggests that cultural concerns among Yemeni women regarding breast cancer included fear and worry, shyness, seeking traditional medicine, inability to fund travel expenses for treatment abroad and lack of awareness. Other cultural norms in Yemen for not seeking the treatment earlier seem to be illiteracy, cultural shame and the male-dominant culture. For instance, a woman may hide her illness from her husband because of fearing that he may divorce her. The influence of these cultural norms is worthy of further investigation.

Age

The dominant age of Yemeni women with breast cancer is less than 50 years. This is similar to the findings reported in other Eastern countries. The mean age of women diagnosed with breast cancer in Pakistan was 48.6 years [37] and 48 years in Saudi Arabia [46]. A similar finding reported that 75% of Arabic women, following a similar pattern to that reported in our systematic review have presented with breast cancer before 50 years of age. However, only a third of women in developed countries are diagnosed before the age of 50 years [47]. A possible explanation is a larger proportion of younger age groups in developing countries [48].

In developed countries, 50% of all women with newly diagnosed breast cancer are older than 63 years, while in many developing countries women with breast cancer are predominately younger than 50 years of age [49]. This shows that breast cancer presents on average 10 years earlier among women in developing countries, including Arabic countries, compared with women in developed countries. In situ breast cancer has become the most common cancer in developed countries, whereas advanced and metastatic diseases at presentation remain the most common in developing countries [50].

Yemeni breast cancer patients are diagnosed at a young age. Breast cancers diagnosed in young women usually have more aggressive biological behaviors and tend to be at a more advanced stage of cancer at diagnosis, with a poorer overall prognosis, among patients compared with those greater than 40 years of age [51]. Women diagnosed with breast cancer at less than 50 years of age are more likely to have BRCA1 or BRCA2 mutation in up to 15% to 33% of cases, which are regularly associated with aggressive behaviour [52,53].

Evidence shows that breast cancer in younger women is more likely to be at an advanced stage, have a higher pathological grade at diagnosis, and present with more aggressive subtypes, such as having human epidermal growth factor receptor 2 (HER2) positive or triple-negative [54]. These aggressive patterns are particularly obvious among Arabic women since most of these women are diagnosed in their 40s and 50s with breast cancer. The average age at breast cancer presentation in Arabic populations is ten years earlier than in westernized countries [50,55].

Lifestyle and genetic risk factors

There was only one case-control study conducted in Yemen looking at the risk factor of breast cancer patients [56]. This case-control study was conducted among 55 breast cancer patients and 110 women controls. Early menarche, late menopause, family history, stressful life events, and smoking were the risk factors identified in this study. Furthermore, a reduction in breast cancer risk was found among women who breastfed their babies for two years [56]. Many breast cancer risk factors are well-known and well-established in the existing literature such as menarche at an early age, late age at first birth, nulliparity, low parity and late menopause [57-59]. The long duration of breastfeeding has been confirmed as being protective against breast cancer. Physical activity has also been shown to reduce the risk of breast cancer [60]. However, drinking alcohol is one of the risk factors [61]. Furthermore, there is a well-established association between high socioeconomic status women and the risk of breast cancer [62,63].

Other risk factors are dietary fat intake, hormone replacement therapy and oral contraceptives [64]. However, the most significant risk factors for breast cancer are being a woman and growing older. Besides, exposure to artificial light at night is one of the risk factors for breast cancer [65].
Similar risk and lifestyle factors reported in a study from Jorden confirmed that oral contraceptives use, irregular menstruation and increased physiological stress were significantly higher among breast cancer patients [66]. Similar findings were also reported among Lebanese and Jordanian women who followed the western lifestyle related to changes in reproductive factors, changes in dietary habits, obesity and smoking are risk factors [36,67].

**Diagnosis and pathology**

The highest stage of breast cancer among Yemeni patients was stage 2 (N=160) and the lowest was stage 1 (N=60). Two of the studies reported that the patients presented with a large size tumor [23,24]. Similar findings reported that advanced stages are commonly seen among Gulf women [68].

Two studies investigated the pathology of breast cancer in Yemen. The first study was conducted in Aden, Yemen. A total number of 118 patients were investigated in this study with late stages, stage III (n=54) and stage IV (n=64), of breast cancer. The majority of the patients were in their reproductive age, from 30 to 49 years old. In terms of treatment, 42.4% received radiotherapy following chemotherapy, 33.1% received hormonal therapy following chemotherapy, 15.3% received chemotherapy alone, and only 9.3% received chemotherapy and hormonal therapy 69].

The second Yemeni study included data from all fine needle breast biopsies, excisional breast biopsies, and biopsies of mastectomies. The highest case diagnoses were fibroadenoma (30.1%), followed by fibrocystic disease (27.4%), then invasive carcinoma (20.1%) and lastly breast inflammation (13.1%). Fibroadenoma had the highest incidence among younger ages group 11-20. However, carcinoma cases reported the highest incidence in the older age group 41-50 years (34.2%) [70].

**Left breast vs. right breast cancer**

This review shows that the more common breast affected with cancer in the left breast, with 1005 patients affected. Comparatively, 787 patients were affected in the right breast. Only 26 patients were affected in both breasts. Similar studies found that it is a global pattern among breast cancer patients that breast cancer more commonly occurs in the left compared to the right breast [71] and several publications have supported these findings [72,73]. The reason for this phenomenon is not clear, with no reasonable explanations provided for this observation. However, proposed explanations include different sizes of breasts, nurse favoring examination of the left breast, greater convenience for a woman to check her left breast compared to her right breast, brain structure and detection.

**Treatment**

Despite the necessity of the multi-disciplinary team to treat breast cancer women, surgery is still the backbone of breast cancer treatment, alongside radiotherapy, chemotherapy, and hormone therapy. This review reported that the most common type of surgery performed on breast cancer patients in Yemen was the modified radical mastectomy (N=211), followed by simple mastectomy (N=53), then lumpectomy (N=43), and lastly radical mastectomy (N=21). Unfortunately, 13 patients refused surgery. Financial constraints tend to result in lower use of breast conservative surgery in Yemen.

Mastectomy remains an effective surgery in metastatic breast cancer. This is shown by a study that breast surgery lowers the risk of death by 28% [74].

Most Yemeni women are diagnosed with breast cancer at a late stage, so mastectomy is an essential surgery. As mastectomy is a scarring surgery, immediate reconstruction surgery may help Yemeni women to cope with their diseases in terms of body image and feminism. Unfortunately, a few barriers to constructive surgery are of concern such as access to the health care system, cost of surgery and the most painful and important barrier is fear of further surgery.

**Quality of life studies**

Only one study investigated the quality of life among breast cancer patients in Yemen. This study was a cross-sectional study of 106 female breast cancer patient who was chosen randomly from the National Oncology Centre (NOC) Saná, Yemen. The study showed that educational status, BMI, income, histological grade, years after diagnosis, surgery and radiotherapy significantly impacted the quality of life of women with breast cancer [75].

**Histological characteristics**

This review showed that the most common type of breast cancer among Yemeni women is invasive ductal carcinoma, followed by invasive lobular carcinoma. Similarly, for Arabic women, invasive ductal carcinoma is the most frequent followed by invasive lobular carcinoma. This pattern is also reported in developed countries.

**Biomarkers**

Only two studies investigated the biomarkers and hormones among breast cancer women in Yemen. The first study was a case-control study. The Prolactin (PRL) level was measured for all women by AXSYM System (MEIA) technology. The study found that there was a significant increase of the prolactin level in breast cancer patients compared to those healthy women in the control, but this elevation remains within the normal value (3.4 ng/ml to 29.12 ng/ml). Elevated serum levels of PRL (>29.12 ng/ml) were found in 16 of 60 patients (26.7%) and only in 2 healthy women (3.33%). The study suggested a relationship between prolactin levels and breast cancer among Yemeni women [76].

The second study, also a case-control study, assessed the Her 2/neu, ER, PR, and P53 among cases compared to the control group. The study found that there are high rates of positive expression of ER, PR, Her 2/neu, and P53 among ductal carcinoma patients [23].

The subtypes of molecular are influenced by many factors such as ethnicity, age, survival and grade [77,78]. These molecular subtypes were classified using biological markers, including the absence or presence of hormone-either estrogen or progesterone-receptors (HR+/HR) and over expression of a growth-promoting protein called human epidermal growth factor receptor 2 (HER2+/HER2-) [79]. Generally, women with positive cancer receptors (ER+/PR+) tend to have a more positive prognosis and increased response to hormonal therapy (CO, 2015). Although triple-negatives (HR-/HER2-) and increased level of HER2 represent about 12% and 4% of breast cancer (CO, 2015), respectively, women diagnosed with these subtypes are more likely to be younger with poorer disease outcomes (higher stages, grades and shorter survivals) [80].

This systematic review showed that there are high rates of positive expression of ER, PR, Her2/neu and P53 among Yemeni women. The prevalence of HER2 in Yemen was 30.6% [23]. A higher prevalence of HER2 (40%) reported in Emirati women [81]. Lower prevalence of HER2 22% reported in Qatar [82], 7.1% in the US, 5% in Europe and 13.7% in Asia [83-85].
Addressing reasons for the delay

A recent study using data for the period 2007-2009 from the cancer center in Aden indicated that the case fatality rate over that two years was 8.5/100 breast cancer patients with a late-stage presentation. This study suggested several factors that may have contributed to a high percentage of delayed presentation (stage III and IV): low socio-economic conditions, miss-diagnosed cases, and the belief that it is better to ignore the symptoms, seeking traditional medicine, and insufficient facilities and specialists in Yemen [69]. Such late presentation and late diagnosis in Yemen are due to the lack of facilities for early detection and treatment.

Interventional studies

Two intervention studies were found related to breast cancer in Yemen. The first study aimed to determine the impact of interventional education on Yemeni female workers’ knowledge. Intervention health education was given to the case group to determine the impact of such an educational intervention. Improvement in knowledge was reported among the group who received the intervention. Knowledge among the experimental group was higher (46.6%) than in the control group, leading to the conclusion that education significantly improves women’s knowledge of breast cancer [86].

The second study is a respective randomized controlled clinical trial to compare two methods, FNAC and CNB, among Yemeni breast cancer patients. The FNAC sensitivity was 66.66%, with 81.8% specificity and 75.7% accuracy. In comparison, the in-Core Needle Breast (CNB) biopsy sensitivity was 92.3%, 94.8% specificity, 93.4% accuracy. Therefore, CNB showed higher diagnostic accuracy than FNAC [87].

Screening and early detection

The results of this review showed that awareness and knowledge among Yemeni women were very poor regarding breast cancer. Only 11% to 17.4% of Yemeni women practiced BSE in some studies, while other studies reported that only 30.3% of women practiced BSE. Only 1.6% of women performed the mammogram test, and regrettably, only 24.7% of female physicians sent their patients for mammogram screening every year regardless of the patient’s history or symptoms. Similar findings from studies in neighboring countries reported that the motives for less use of breast cancer screening services were inadequate knowledge, stigma and cultural beliefs [88-90].

Regular screening practices such as mammography, clinical breast examination, and breast self-examination have been found to drop morbidity and mortality from breast cancer. This necessitates the availability of high-quality screening and treatment [91,92].

Early detection is the foremost determinant factor of survival, which is reliant on awareness of and screening for breast cancer. However, breast cancer awareness is very poor in Yemen and limited studies have been conducted in different parts of Yemen, Hadhramout, Aden, Al-Mukalla city, and Sanā'a. Several studies have been carried out in Yemen communities in different groups, namely: female physicians, female university students, and women attending reproductive health centers in different parts of Yemen [93,4,94-102,30].

Conclusion and Recommendations

Yemen has been characterised by three decades of scattered, fragmented and poor quality of breast cancer research. Therefore, there is a need to establish a breast cancer research center in Yemen to cover all breast cancer research aspects in Yemen and to build bridges for collaborations globally. The yield of this research reported late presentation and poor knowledge about breast cancer as major issues among Yemeni women. This signals an urgent need to highlight the issue nationally and educate the public through all available and reachable media. It is crucial to improve the basic oncology services for cancer patients, such as providing radiotherapy, chemotherapy and hormone therapy, in all oncology centers in Yemen. Awareness and early diagnosis need to be emphasized and strengthened further. Assessing the psychosocial impact of breast cancer on Yemeni women is urgently needed to support Yemeni women to cope with their cancer and increase their quality of life.

References


