AMERICAN UNIVERSITY OF BEIRUT

TRENDS IN BREAST CANCER STAGING AT DIAGNOSIS ASSOCIATED WITH SCREENING CAMPAIGNS IN LEBANON

by
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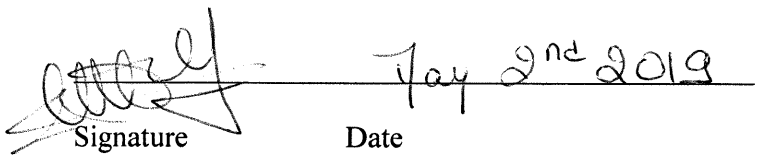

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AN ABSTRACT OF THE THESIS OF

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Mammography screening remains the best policy for early cancer detection, by shifting the disease at diagnosis to more locally confined stages, which carry lighter treatments and better prognoses. Breast cancer awareness campaigns calling for mammography screenings have been on-going in Lebanon since 2002. National guidelines call for an annual mammography starting 40, for women with no known family history of breast cancer. Changes in breast cancer staging at diagnosis as a consequence of documented improvements in mammography uptake remain to be described.

We have reviewed 3501 breast cancer cases treated and/or diagnosed in the American University of Beirut Medical Center between the years 1990 and 2016. After stratifying those cases by age, we have trended the extracted stages versus time. Results were compared between the pre-screening (1990 to 2001) and the post-screening period (2002 to 2016), and then stratified into two age groups (less than 40 and 40 years and older).

Median age at presentation for all the case-series was 51 years, with little changes over the study period. During the post-screening period, stage I accounted for 30%, stage II for 43%, stage III for 15% and stage IV for 12% of the cases. Stage I cases had more than doubled in comparison to the years before the implementation of the awareness campaigns when stage I represented 14% in 1990-2001. Stage III cases displayed a mirror decrease between the two periods, coming down from an initial 35%. The increase in stage I was significantly more prominent in the sub-group of women aged 40 years and above, compared to younger ones. Shifts in staging happened in parallel with a concurrent rise in reported uptake of mammography screening.

Our findings indicate that stages of breast cancer at diagnosis have been steadily and significantly showing a shift upwards towards less advanced stages over a 27-year interval. Trends in earlier detection of the disease are likely associated with the rise of the awareness and screening campaigns, and increasing openness to discuss breast cancer as a public health issue. The Ministry of Public Health should encourage the reporting of breast cancer stage at diagnosis to the National Cancer Registry, so that larger numbers of cases are analyzed from all sources of data across Lebanon. The inclusion of screening history in the routine history taking of breast cancer cases will also result in a valid contribution to the issue of cost-benefit analysis of mammography screening in Lebanon.

ILLUSTRATIONS

TABLES

LIST OF ABBREVIATIONS

AJCC:	American Joint Committee on Cancer
AUBMC:	American University of Beirut Medical Center
BC:	Breast Cancer
BSE:	Breast Self-Examination
CBA:	Cost Benefit Analysis
CBE:	Clinical Breast Examination
GB:	Greater Beirut
GCC	Gulf Cooperation Council
HDF :	Hôtel-Dieu de France
IRB:	Institutional Review Board
MOPH:	Ministry of Public Health
NCR:	National Cancer Registry
TNM:	Tumor size, lymph node involved, metastatic state

CONTENTS

CHAPTER I

INTRODUCTION

1.1. Background

Breast cancer (BC) is by far the most common malignancy in women worldwide and the second most common cancer overall [12]. In Lebanon, BC incidence rates were always on the rise and are expected to increase further [23]. Recent Lebanese BC data provided by the National Cancer Registry (NCR) indicated that in 2011, 2000 new cases of primary BC were reported for all ages, accounting for 38.4% of all female cancers. In fact, BC diagnosis are steadily increasing in Lebanon and 2020 projections predict that BC incidence rates will jump from 46 cases per 100 000 in 2008 to 146 cases per 100 000, constituting around 40% of all cancer incidence in Lebanese women[31].

BC cancer median age at diagnosis among Lebanese women has always been lower compared to Western countries. An analysis conducted by El-Saghir et al. in 2006 indicated that ever since 1998, the median age of diagnosis for BC among Lebanese women had always been around the fifth decade while it has been shown to be 61 years in the United States (2001-2005) and even 63 years in Western Europe. As for other Arab countries, the median age at BC diagnosis was found to be even younger: 47 years in Saudi Arabia (2004), 45 in Kuwait (1993–1998), and 46 in Egypt (2001) [29,32]. The relatively younger median age at diagnosis in Lebanon and other Arab countries compared to Western ones has always been attributed to the age distribution skewed towards younger age-groups in those countries. Nevertheless, the incidence of breast cancer among younger women in Lebanon is higher than in several other, more

developed countries [23]. This higher incidence has been attributed to genetic predispositions in the Lebanese population that are still not well studied [32] .

Fortunately, BC can be screened and diagnosed at early stages, which in turn improves the odds of recovery and of longer survival. Mass BC screening relies essentially on mammography [18]. The main goal of mammography screening is to shift the BC diagnosis from advanced invasive stages to earlier less invasive ones. Early detection minimizes the physical and financial burden of the disease and improves the prognosis [28]. BC staging is usually based on TNM grading from the American Joint Committee on Cancer (AJCC) (Appendix 1). TNM scoring which describes the cancer by the size of the **T**umor, the number of lymph **N**odes affected and whether a **M**etastasis exists or not [38]. Cancer staging helps clinical decision-making and dictates the prognosis of the patient. Moving from stage I to stage IV, the cancer becomes more severe with lower survival [28].

Staging at diagnosis is an important factor of surveillance that illustrates the country's success at capturing malignant diseases earlier [28]. In a systematic review conducted by the WHO European region in 2017, it was recommended to maximize accurate and complete staging data in tumor registries since it played a distinctive role in the evaluation of BC control in low to middle-income countries [8].

Planned efforts to promote BC awareness and screening through regular mammography started in 2002. BC annual campaigns consist of public awareness sessions about screening techniques, in addition to special discounts on mammography nation-wide. Initially, the annual campaigns were confined to the international Breast Cancer month in October of every year. Since 2006, the annual campaigns have been expanded to cover all three autumn months of the year. For several years,

recommendations for mammography screening were left to the discretion of practitioners, who used US, European or other guidelines in their preventive practices. National recommendations were finally published by the Ministry of Public Health (MOPH) in 2009. They were based on accumulated epidemiological data from Lebanon. Recommendations called for an annual mammography for women aged 40 and above with no personal or family history of BC, for as long as a woman is in good health [4].

First utilization of mammography increased slightly between 2002 and 2005 (from 11% to 18%), mainly among women aged between 40 to 49 compared to older age-groups, and more among those residing in the Greater-Beirut (GB) area surrounding the capital city compared to those residing elsewhere [4]. By 2014, the first-time use of mammography had reached 45%, mostly among women around 50 and those of higher socio-economic status [16]. Periodic national sample surveys have shown that mammography uptake has been increasing gradually throughout the years (Figure1).

1.2. Problem Statement and Goal

After more than fifteen years of efforts, it has become important to evaluate the impact of the screening campaigns on the status of BC staging at diagnosis in Lebanon. Changes in staging at diagnosis, if present, may be attributed to the screening campaigns, as about more than half of 1200 women surveyed between 2002 and 2005 indicated that they had heard about the campaigns and were prompted to act as a result[2]. BC treatment costs in Lebanon, like elsewhere, have been steadily increasing over time especially after the introduction of the more expensive immunotherapy [17]. Costs of BC at stages II, III and IV can be 32%, 95%, and 109% higher than stage I [34].

Unfortunately, data on staging at diagnosis are still not directly available from the Lebanese NCR. The evaluation and subsequent cost-benefit analysis (CBA) of mammography screening, which should inform future decisions of health policy-makers has to be obtained indirectly, using available hospital-based case series. This paper performed a historical analysis of BC staging at diagnosis, from the pre-campaign era (1990-2001), up until the year 2016 using data from one large tertiary hospital in Beirut.

1.3. Staging At Diagnosis During The Pre-Campaign Period in Lebanon

The first and only assessment of historical changes in BC staging at diagnosis in Lebanon prior to the initiation of the regular screening programs was conducted by Saghir et. al in 2006 on data derived from cases diagnosed from 1991 to 2001, at the American University of Beirut Medical Center (AUBMC) in Beirut. Visible trends started to appear in the early 2000s showing that proportions of earlier stages (I and II) had started to rise while those of advanced stages (III and IV) were decreasing [29]. There has been no historical description of variations in BC staging at diagnosis at AUBMC ever since that period. In 2015, Chahine et al. examined the characteristics of BC among Lebanese women diagnosed and treated at Hotel-Dieu de France (HDF) hospital in Beirut from 1990 until 2013. Aggregate data showed that BC staging at diagnosis had improved comparing two periods before and after 2002 [11].

1.4. Screening and BC Staging in the Arab World

Literature indicates great diversity in implementation of screening programs across the Arab world, and the impact on BC-related outcomes, including down-staging at time of diagnosis.

In Bahrain, the Cancer Society and the Ministry of Health co-organized a population-based mammography screening program which started in 2005. No evaluation of the impact of those screening campaigns has been achieved so far. Nevertheless, a recent report showed that only one fifth of all breast cancers were diagnosed during the screening periods [6,20].

In other GCC countries, recent mammography campaigns are still not very successful. In Saudi Arabia, a country with free health services, studies have shown that 92% of women had never had a mammogram done in 2014. Saudi women have regularly been diagnosed at more advanced stages, a fact largely attributed to lack of BC awareness and mammography uptake [14]. In Qatar, breast-screening programs were implemented in late 2015. Initial reports indicate that compliance with breast screening recommendations remains low [36].

Good progress in the uptake of mammography has been reported from Jordan and Morocco. Jordan has implemented a BC early diagnosis program since 2007 aiming at spreading BC awareness and improving BC screening practices [1]. By 2009, 26% and 30% of breast cancers were diagnosed in stages I and II, respectively, compared to 7% and 24% in 2005, and stage III proportions had declined from 56% in 2005 to 23% in 2009 [35]. Other reports have found that more than two thirds of BC are diagnosed in stage I and II compared to less than 30% a decade ago [1].

Stages of BC in Morocco were obtained from the Casablanca cancer registry where 28% of the cases were diagnosed at a local stage, 63% regional and 9% distant between 2005 and 2007. In 2011, Morocco established an integrated national BC

awareness and screening program at all levels of the health care system. Subsequently, 75% of captured cases in the screening program were diagnosed in stages I and II [26].

In Egypt, BC awareness and down staging efforts have led to a modest increase in localized BC diagnosis proportions from around 15% to 21% during a 10-year period from 1998 to 2008. Consequently, advanced-stage BC witnessed a significant decline as well [21].

1.5. Research Objectives

The objectives of this study are:

1. To measure the proportions of stages I and II (less advanced disease) compared to stages III and IV (advanced disease) at time of diagnosis, and selected components of staging, within a case-series accumulated at the AUBMC between 2000 and 2016.
2. To describe historical trends over that interval and to relate them to previous ones from 1990-2001.
3. To analyze the correlation of historical trends with the uptake of BC screening available from concomitant serial cross-sectional studies.
4. To analyze trends in BC staging by age-groups at time of diagnosis.

CHAPTER 2

METHODS

2.1. Study Design and Methodological Approach

This study describes historical changes in staging at diagnosis to the occurrence of annual BC awareness campaigns and correlates them to the uptake of mammography screening.

2.2. Data Sources

Data were extracted from de-identified hospital records of all cases of Lebanese female BC diagnosed and/or treated at AUBMC from 2000 until 2016. In parts of the analysis, current data were supplemented by de-identified cumulative data from a previous historical analysis during the years 1990 to 2001 [29]. Staging at diagnosis was not always directly available in all reviewed records, and had to be constructed using clinical and pathological information available.

2.3. Definition of Variables

The main outcome extracted for this data analysis is the BC staging at diagnosis, as defined by the TNM classification of the AJCC. Tumor size, the first component of the TNM staging was considered as a separate outcome. This was done in view of the importance of tumor size in increasing the probability of diagnosis in non-screened women.

1. T: the tumor size was divided into three categories: less than 2 cm, between 2 cm and 5 cm, and more than 5 cm.

2. N: at least one lymph node already involved at time of diagnosis or not.
3. M: presence or not of concomitant metastasis at time of diagnosis

Outcomes were first stratified by three age-groups to examine population characteristics:

1. Women diagnosed at age less than 35 years old
2. Women diagnosed at age between 35 and 49 years
3. Women diagnosed at age 50 years and older

BC staging at diagnosis was later stratified by 2 age-groups, based on the recommended age for initiation of mammography in Lebanon:

1. Women diagnosed at age less than 40 years
2. Women diagnosed at age 40 years and older

2.4. Statistical Analysis

Population characteristics were tabulated and grouped into three age categories for baseline assessment. For the comparative analysis, the relative proportion of each of the four stages and median ages at diagnosis were tabulated for all cases and by age-groups for across the periods studied. Those percentages were plotted independently to assess the significance of their historical changes, starting from data collected in 1990. Different outcome proportions were compared from the period prior to 2002 to that after 2002; and after 2002 in correlational with available national figures of mammography uptake. Differences in proportions were tested using chi-square and the test on the equality of proportions. Mean age differences between different groups were tested using the t-test. Linear regression analysis was carried out in order to analyze the different trends across time. A p-value less than 0.05 was considered significant. All

data were analyzed using STATA. Finally, to enhance generalizability of the findings, our results were compared with published data from a study performed in another Lebanese hospital.

2.5. Ethical Considerations

In this analysis, privacy of subjects and confidentiality of data were preserved through the de-identification of the medical records, and patients were not directly contacted. This study received an exemption because of its nature as a secondary data analysis from the AUB-IRB.

CHAPTER 3

RESULTS

Our study population consisted of 3501 BC cases treated and/or diagnosed in the AUBMC between 1990 and 2016. All individuals included in our results were women of Lebanese nationality. Main outcome studied for all involved patients were the TNM staging components, BC stage at diagnosis, age at diagnosis and the year of diagnosis. Out of the 3501 cases studied, 360 cases (11.46%) were excluded from the analysis because of incomplete data about staging. Baseline characteristics of our patients were presented in table 1, stratified into 3 age-groups. Mean age of diagnosis of all studied cases was 52.3 years (SD= 16.43), while the median age was 51. The majority of our cases were 50 years and older (54.5%) (Table 1).

Differences in tumor size at diagnosis were significant among the three different age-groups ($p= 0.016$). Tumor sizes 2 to 5 cm were most prominently found across all BC cases studied, and across all age-groups. Largest tumor sizes were more proportionally represented in the youngest age-group (15%) while smallest tumor sizes were more represented in the oldest age-group, (36%). There were also significant differences in lymph node involvement across age-groups ($p <0.01$). Most cases in all age-groups presented with lymph nodes already involved (54%), but cases with positive lymph nodes composed 63% of the younger age-group, versus 59% and 57% in the 35-49 and ≥50 age-groups, respectively. Presence of metastases varied between 9% and 11% across the different age-group with no significant differences. Thus, BC staging at

diagnosis differed significantly across age-groups. The majority of cases were diagnosed at stage II (44%), followed by stage I (24%), stage III (23%) and stage IV (9%). In women aged less than 35 years old, stage II was followed by stage III (32%), stage I (15.5%) and finally by stage IV (11%). Same order of staging frequencies was found in cases diagnosed between 35 years and 49 years. However, the order was shuffled in individuals diagnosed at age of 50 and above where stage II fraction was immediately followed by stage I (26.33%), stage III (21.17%) and stage IV (9.45%) respectively (Details presented in Table 1).

3.1. Trends In BC Stages At Diagnosis

Remarkable changes were detected in BC staging at diagnosis over the 27-year interval available for this analysis. The relative proportion of stage I significantly increased from the period preceding the national campaigns in 1990-2001 (14%) to the period after the initiation of the campaigns from 2002 to 2016 (30%) ($p<0.01$). Stage III demonstrated a significant mirror decrease between the two periods, from 35% to 15%. The relative proportion of stage II remained relatively stable over the two periods (45% down to 43% respectively). The proportion of the more advanced stage IV significantly increased from about 6% in the first period to about 12% in the more recent one ($p<0.01$). Details are presented in Table 2.

Figure 2 shows the fitted linear regression for the yearly relative proportion of each BC stage since 1990. Stage I proportions showed increasing trends across time while stage III proportions presented mirroring decreasing trends. Stage II regression line was relatively stable along the years. As for stage IV, the linear regression demonstrated an increase across the large period studied (Figure 2).

3.2. Trends in BC Tumor Size at Diagnosis

Table 2 shows the relative proportions of tumor size categories at diagnosis. In the post-campaign period, this variable was available in the medical records only up to year 2014. Half of the diagnosed BC tumors had a size of less than 2 cm during the post-campaign era, compared to around 19% during pre-campaign era. In addition, 66.5% of diagnosed BC patients had a tumor size between 2 cm and 5 cm versus 42% during the years 2002-2014. As for larger tumors measuring more than 5 cm, the proportion of BC patients diagnosed with such tumor sizes had decreased from 19% to around 6% from the pre-campaign to the post-campaign period. All changes in trends of tumor size categories comparing the two periods were significant (Table 2).

3.3. Trends in BC Stage at Diagnosis Stratified by Age

The mean age at diagnosis of all cases was 53.2 years (SD= 18.4) for patients diagnosed with BC between the years 2002 and 2016, up from 50.7 (SD=12.3) ($p<0.01$). Women were divided in two groups based on the recommended age for initiation of screening, ie 40 years. The relative proportion of diagnosis at an age younger than 40 decreased from about 20% in the 1990-2001 period to 14% to in 2002-2016 ($p = 0.04$). The decrease was significantly marked for stage III; while stage IV actually increased from about 4% to 15%. For women< 40 years, stage I proportions increased from 15% to 21% (p-value= 0.085). The increase of stage I was much more marked in the older age categories, going up from 14% to 31% of ($p<0.01$). The relative proportions of stage II did not significantly fluctuate over time in both age-categories. In the younger age-group, stage III decreased from about 36% to 19%

($p<0.01$). The decrease was even more marked among women aged 40 years and older, from 35% in the pre-campaign period to 14% in the post-campaign ($p<0.01$). The proportions of stage IV, the late stage BC, in women< 40 years increased with time. Moving from the period between 1990 and 2001 to the period between 2002 and 2016, stage IV increased from 4% to 15% ($p<0.01$). Similarly, for women aged 40 years and older, it increased in proportions from 6% to 11% ($p<0.01$) (Details in Table 3).

3.4. Trends in BC Stage Correlated with Mammography Uptake

To further illustrate shifts in BC staging trends happening in parallel with the BC screening campaigns, we have plotted linear regressions of combined early-stages BC (stages I and II) and combined late-stage BC (stages III and IV). Linear regression showed a significant fit of the plotted data for both combined stage-groups. Stages I and II trended upwards across time while stages III and IV trended downwards. In fact, the trend of combined stages I and II shows that for every year, proportions of these early stages increased by 1.17% (95% CI: +0.73% to +1.60%), while trends of combined late stages inversely decreased at the same rate (95% CI: -1.60% to -0.73%). These trends were plotted in parallel with mammography uptake, which had increased gradually with time starting from 14.8% in 2003 to 43.2% in 2016 (figure 4).

CHAPTER 4

DISCUSSION

4.1. Overall Findings

BC incidence and case-load has been increasing year-to-year in Lebanon, suggesting an increase in BC risk factors and diagnostic rates. The existence of a screening program since 2002, in addition to increasing the number of detected cases, is expected to catch earlier stages of the disease, thus improving the prognosis. Such an impact is strongly suggested in this correlational analysis, where increasing uptake of screening mammography after age 40 is mirrored with increasing proportions of stage I and decreasing proportions of stage III at diagnosis. Our findings show that over a 27-year period, the proportions of stage I have more than doubled from pre- to post-screening campaign periods. This increase is mirrored by a historical decrease in stage III proportions at diagnosis.

The move to earlier stages has affected all levels except stage IV. Results indicate that stage II has remained the most frequent one at diagnosis, and had remained relatively stable across time. This apparent stability probably hides internal dynamics by which decreasing proportions of stage III had replaced increasing proportions of stage II moving down to stage I. These internal dynamics in BC diagnosis over time towards less advanced stages can be suspected from studying changes in tumor size, the first and main component of the TNM classification. Results clearly indicated that the average tumor size at diagnosis had been moving steadily smaller, suggesting a down-shift in staging. If those trends remain true, it means that stage III will eventually reach

a lower stable proportion, at which point the proportions of stage II tumors will start decreasing significantly because the downward shift will not be compensated any more. The historical shift towards earlier stages found in the AUBMC series compares favorably with the results obtained from 612 BC patients analyzed as part of the HDF series between 1990 and 2013. In table 4, trends of changes in proportions of BC stages over time are presented and appear as largely similar between the two Lebanese institutions [11].

Trends in staging over the 27-year interval considered in this analysis can be attributed directly and indirectly to the screening uptake. As suggested by graphic representations (Figure 4), the increase in mammography uptake reaching around half of the Lebanese women in recent years can be correlated to down-staging. Indirectly, the annual message on BC screening may have increased the alertness in women and broken the fear associated with cancer diagnosis, thus contributing to earlier detection. At any rate, as the impact of the annual screening campaigns increases across ages and regions in Lebanon, favorable trends in early diagnosis should be sustained.

Findings from this study may be artifacts, associated with improvement in diagnostic techniques over the 27-year span rather than with any other planned variable. However, the consistency of those trends over time, and the absence of sudden short peaks, argue against the potential effects of confounding factors and in favor of the validity of findings. A more serious potential source of errors may be associated with the fact that 11% of the cases eligible for analysis in this paper were found with no data on staging in their medical records. Should all the cases with missing data belong to one specific stage at diagnosis, this may cause a serious selection bias. Nevertheless, conformity with findings from a concurrent analysis in Lebanon, as discussed above,

seems to suggest that there was no specific selection bias among cases with missing data. Finally, it can be argued that cases at AUBMC may not be representative of the entire population of BC cases in Lebanon. Arguably, the majority of cases would be drawn from GB where awareness and accessibility to screening and treatment may differ from elsewhere. Nevertheless, based on NCR data, around 21% of the Lebanese cancer cases in 2010 and around 26% in 2014 were diagnosed and treated at AUBMC (NCR). It can be argued that a center treating one in every four cases in a small country like Lebanon may actually be drawing a sample less severely biased than expected. One may point out that the association between mammography and earlier stages at diagnosis is valid for the case-series involved. If such findings are valid in 25% of cases in Lebanon, there are no reasons to believe that they will not be representative of all Lebanese cases.

4.2. Age and Staging

In this analysis, the most advanced stage IV differed notably as it increased over time. The increase was sharper in women younger than 40, in whom the disease is notably more aggressive even when treatment is sought early [15]. At the same time, the age at diagnosis in Lebanon is slowly shifting towards older age-groups, most likely as a consequence of the ageing process of the population in Lebanon. These reversed trends show that the current recommendations for mammography uptake should not shift to younger ages despite the severity of disease. As ageing trends continue, less cases will be found in younger ages, consequently leading to lower proportions of initial stage IV at diagnosis. Lowering the recommended age for mammography initiation at a time of falling incidence would increase the rate of false-positive readings and add

unneeded costs to the screening program. Improving awareness and education of other screening techniques such as Breast Self-Examination (BSE) and Clinical Breast Examination (CBE) may be more beneficial approaches for early detection in younger age-groups.

The increase in stage IV at diagnosis among women 40 and older was less sharply marked. Still it is surprising that it did not decrease despite advances in screening and detection. This can be largely explained by the fact that AUBMC as an advanced tertiary hospital often captures referred cases that are also the most complicated ones. Referred cases originate in majority from smaller centers in Lebanon, where late diagnosis may be more frequent, but this reality is not evidenced in this analysis or in any other relevant publication. One element suggestive of this attribution are findings showing that mammography uptake is stagnating in several areas away from GB [3].

Age intervenes also on stage I increases over time. The sharpest increase was detected in the group of women eligible for screening (40 and above) as opposed to younger ones (Figure 3). This finding further indicates that screening recommendations calling for an annual mammography starting age 40 are being adopted by Lebanese women and their physicians, and resulting in visible benefits.

4.3. BC Staging and Screening in the Arab World

In the previous two decades, the majority of BC cases in Lebanon have been diagnosed in earlier stages. Published reports from some Arab countries suggest that the predominance of earlier stages in Lebanon may belong to a minority of countries in the region and is attributable to planned screening activities. In fact, percentages of women

aged 40-75 years who had a mammography in Arab countries where advanced BC stages are prevalent were 4.9% in Saudi Arabia, 8.9% in Oman, 13.9% in the UAE and 14.6% in Kuwait [33]. Table 5 lists whether or not staging data were available in parallel with the emergence of screening activities, in Arab countries where such reports were published. In countries where successful screening is being practiced, lower BC stages at diagnosis are being detected. Jordan and Egypt are adequate examples show-casing down-staging benefits of BC awareness and screening campaigns. Nevertheless, even if Morocco BC screening program seemed to be promising since majority of cases screened in that program were early-stage BC, evidence has been showing that detection rates and screening efficiency is low [25], hence the persisting high rates of advanced-stage disease [10]. In Bahrain, stage I proportions were found to be as low as 7% in a series from 1982 to 1994 [19]. Another analysis overlapping the initiation of screening activities in 2005 demonstrated a higher proportion of stage I (28.5%) in a case-series between 2000 and 2010 [20] despite low uptakes of mammography screening [20]. Oman is one of the recent Arab countries to launch national BC screening campaigns in 2018. The need for such campaigns was highly related to the fact that early BC detection in that country is very minimal where stage I represented around 10% of their BC cases and stages III & IV constitute more than half [7,22]. Saudi Arabia and Qatar seem to suffer of relatively higher proportions of advanced BC mainly due to several reports indicating low mammography uptake despite the countries screening efforts [14,27].

Nevertheless, in 2017, the WHO recommended that all countries in the EMR region should improve their BC awareness and screening efforts for timely detection. Because of limited funding, low participation rates and inadequate monitoring of BC

screening and awareness programs in the region, the WHO encouraged program evaluation for more accurate surveillance and documented improvements [36].

CHAPTER 5

CONCLUSIONS AND PRACTICAL IMPLICATIONS

Even though AUBMC is a diverse national institution that captures a representative portion of the Lebanese BC cases, more data derived from other national institutions are needed to complement the information on the eventual national improvement in the fight against BC. Staging data are not routinely collected by the Lebanese NCR, despite their importance in showing the effectiveness of the annual screening campaigns and related public health activities. The current analysis helps in compensating this gap and thus contributes to the cost-benefit analysis of breast cancer screening needed to eventually update the national guidelines. The update is important to ensure adequate resource-allocation to control the growing incidence of BC in Lebanon. Insisting that staging data are easily available at the national level will promote the sustainability of CBA in Lebanon. MOPH should encourage reporting of staging at diagnosis to its NCR as it adds to the completeness of the data and to the accuracy of our surveillance systems.

In daily practice, medical records should routinely include standard staging data which can be easily transferred and compiled nation-wide. In addition, the screening history of each diagnosed cases should be recorded to allow future research on screening impact on individual levels rather than on group levels, as is the case in this analysis.

Our findings endorse the currently available screening efforts as improvement in BC staging was demonstrated. National guidelines calling for annual mammography starting the age of 40 turned out to be adequately followed and effective in Lebanon.

Mammography screening indeed helped with early capture practices especially that the Lebanese MOPH facilitates the access to the procedure free-of-charge during the annual quarterly campaigns. BC campaigns have also aided in spreading awareness and empowering Lebanese women. Ensuring that campaigns are increasingly more successful is one sure way of realizing further progress towards down-grading BC stages at diagnosis. Detailed analyses of mammography intake and stages at diagnosis should be de-accumulated to allow regional particularities to be detected and targeted for specific efforts.

THE END

ILLUSTRATIONS

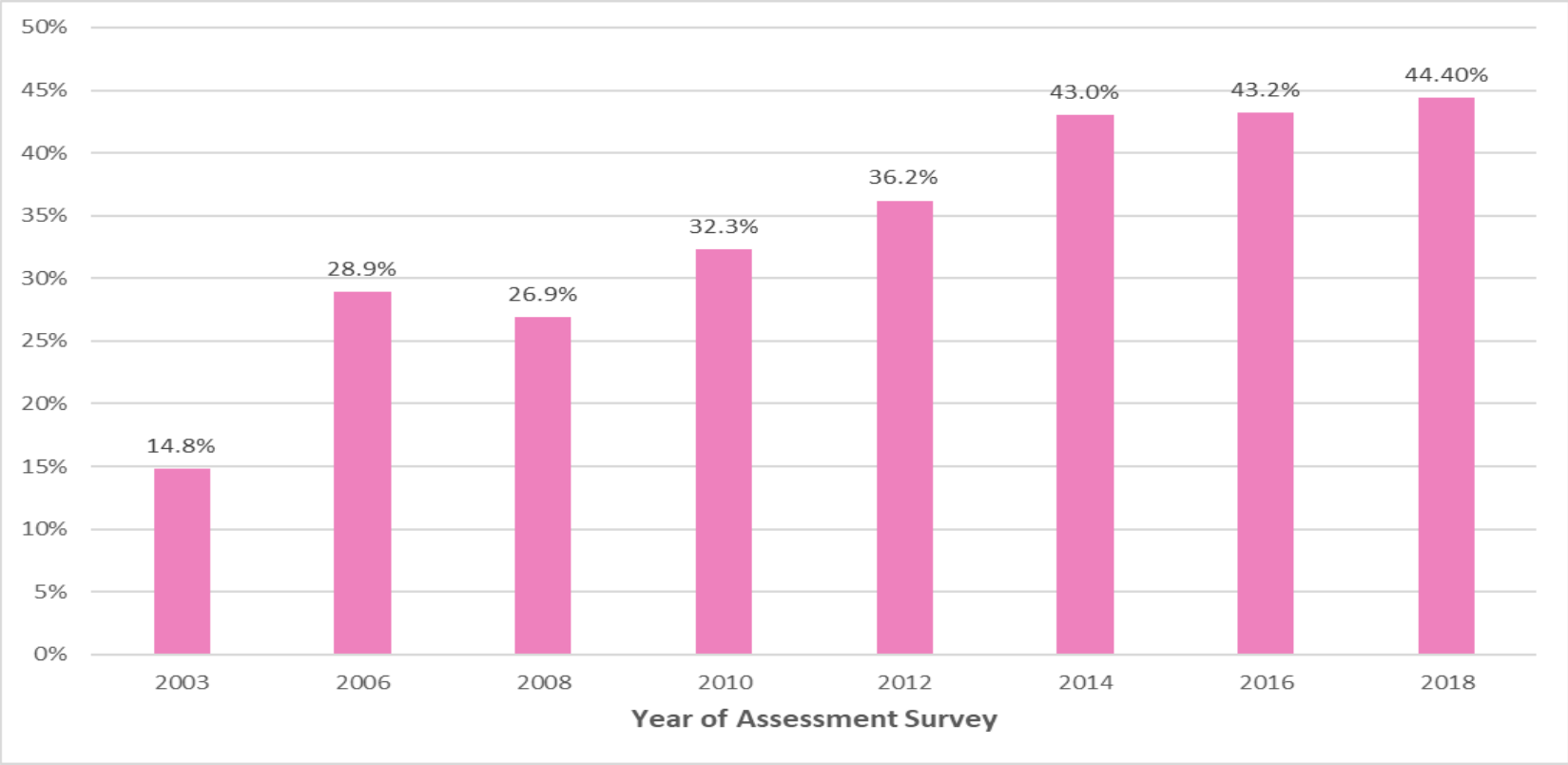


Figure 1: Percentage of mammography uptake in Lebanese women (2003-2018) –

Source: Adib SM. Serial cross-sectional assessment of mammography uptake. Data partially published

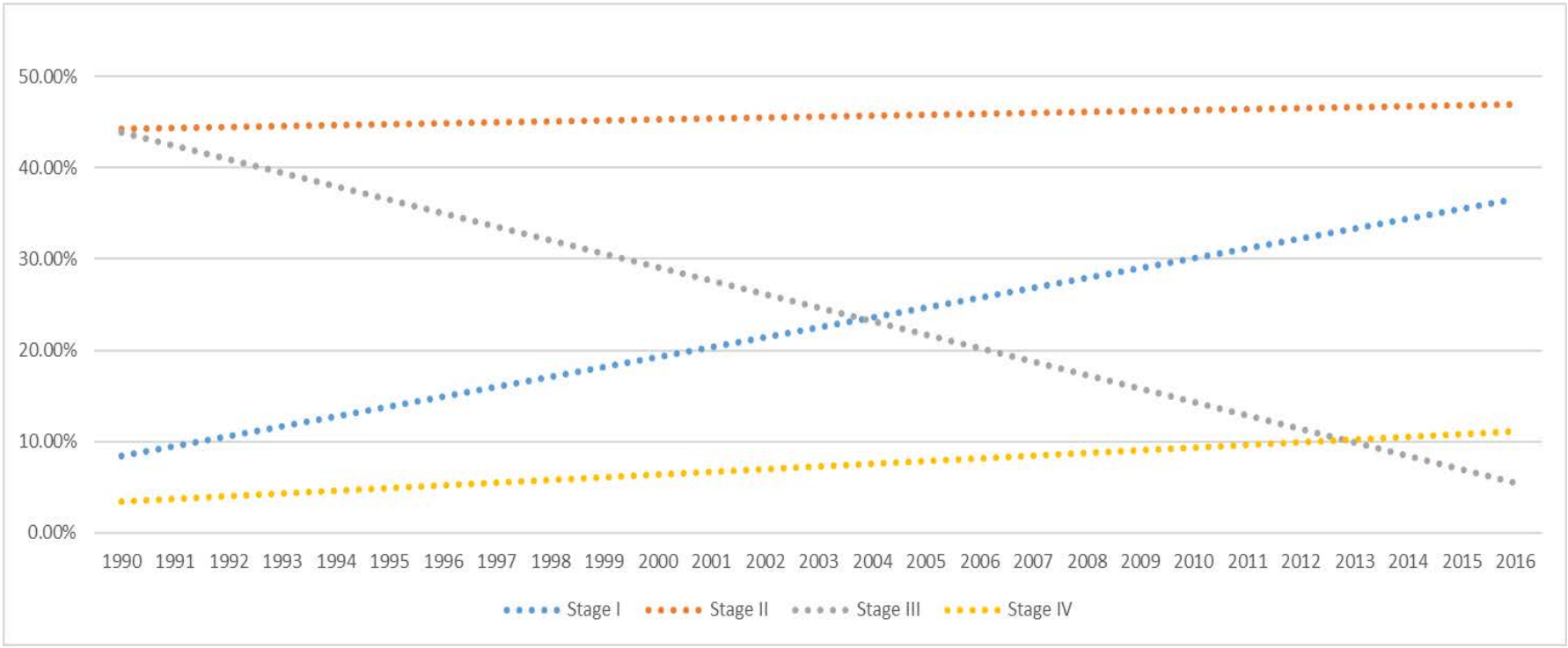


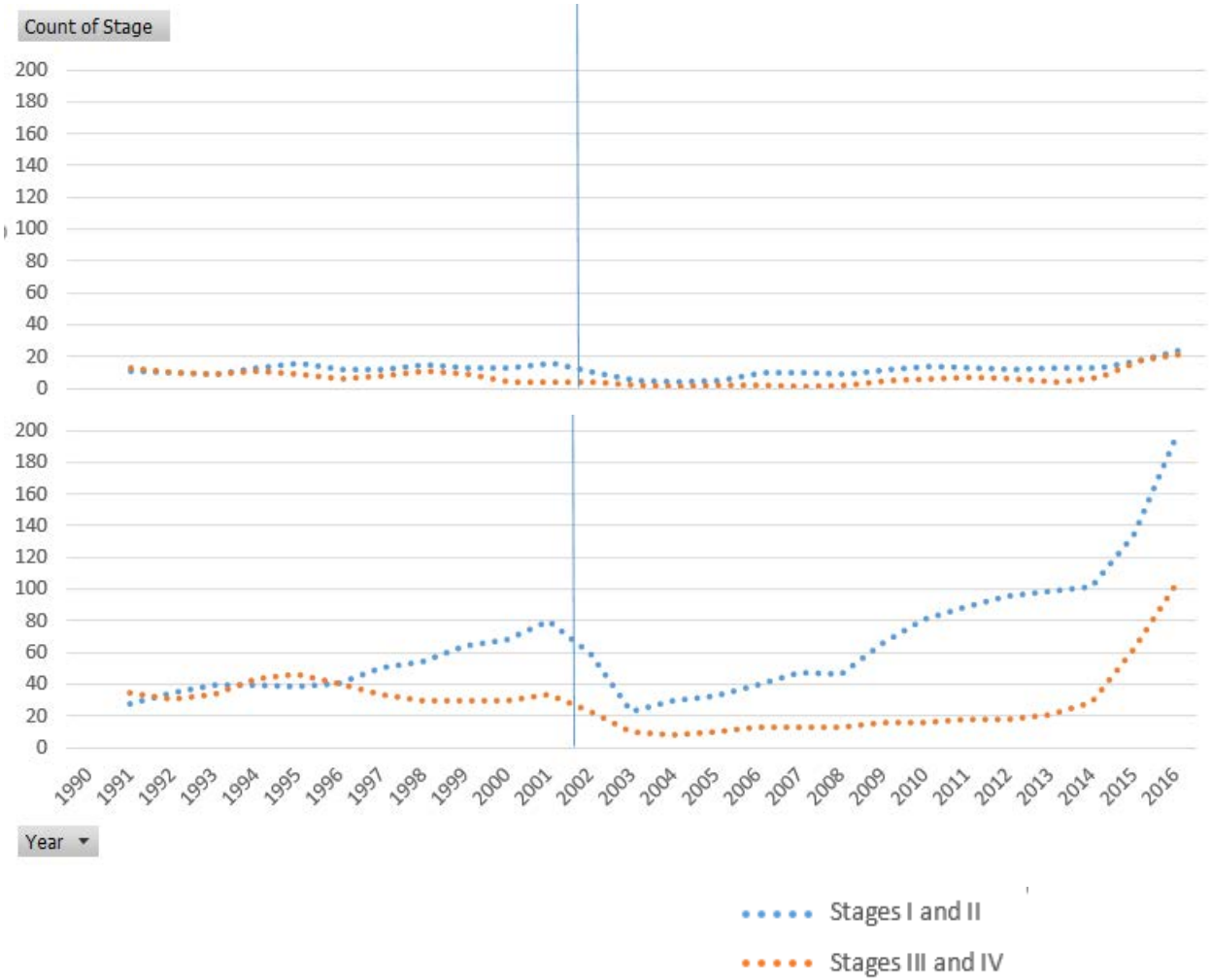
Figure 2: Linear trend of breast cancer stage at diagnosis in Lebanese women from 1990 till 2016

**Stage I: y = 0.10x + 0.07 (95% CI: 0.008 ; 0.013, p-value p<0.01)*

**Stage II: y = 0.001x + 0.44 (95% CI: -0.002 ; 0.004, p-value = 0.55)*

**Stage III: y = - 0.014x + 0.45 (95% CI: -0.018; -0.011, p-value p<0.01)*

**Stage IV: y = 0.002x + 0.48 (95% CI: 0.001 ; 0.004 p-value p<0.01)*



Younger women for whom screening is not recommended (< 40 years old)

Women for whom screening is recommended (≥ 40 years old)

Figure 3: Cases of early stage (combined stages I and II) and advanced stages (combined stages II and IV) by recommended age for screening initiation in Lebanon (AUB Medical Center, Beirut, 1990-2016)

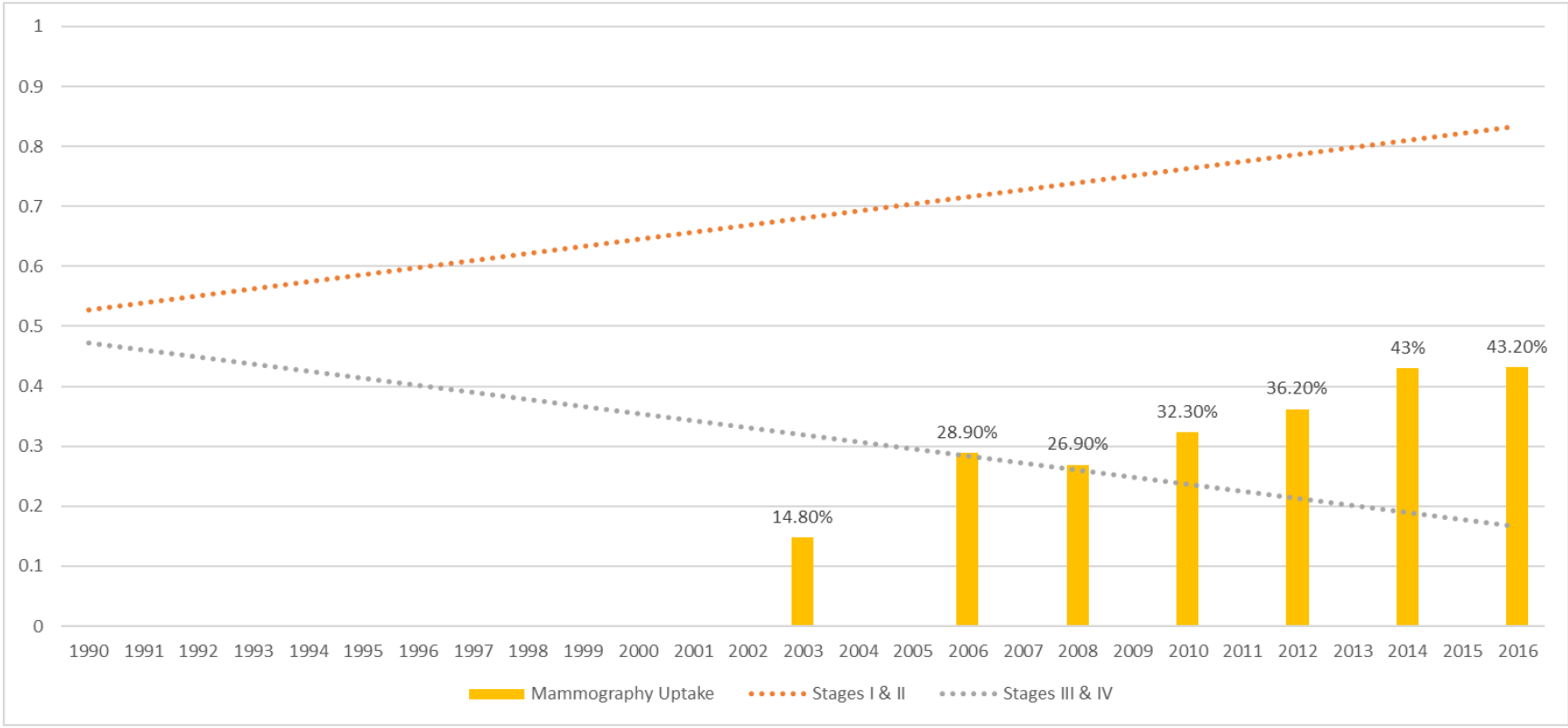


Figure 4: Correlation between trends in early (combined stages I and II) and advanced stages (combined stages III and IV) at breast cancer diagnosis with reported uptake of mammography screening initiated as a national program in 2002 (AUB Medical Center, Beirut, Lebanon, 1990-2016)

**Stages I&II: y = 0.17x + 0.52 (95% CI: 0.73% ; 1.60%, p-value p<0.01)*

**Stages II&IV: y = -0.17x + 0.48 (95% CI: -1.60% ; -0.73% p-value p<0.01)*

TABLES

Table 1: Staging characteristics of breast cancer patients by age at diagnosis (AUB Medical Center, Beirut, Lebanon, 1990-2016)

Age at diagnosis (Median age: 51 years) **n (%)***		**Less than 35** 283 (8.08)	**Between 35 and 49** 1309 (37.39)	**50 and more** 1909 (54.53)	**Total** 3501 (100)	**P-value**
Tumor size n (%)	**Less than 2 cm**	37 (23.72)	294 (32.45)	450 (36.35)	781 (33.96)	**0.016**
	Between 2 and 5 cm	95 (60.90)	504 (55.63)	654 (52.83)	1253 (54.48)	
	More than 5 cm	24 (15.38)	108 (11.92)	134 (10.82)	266 (11.57)	
	Total	156 (100)	906 (100)	1238 (100)	2300 (100)	
Lymph node involvement n (%)						
	Negative (N0)	57 (36.54)	379 (41.15)	630 (43.47)	1066 (45.91)	**<0.01**
	Positive (N1, N2, N3)	99 (63.46)	542 (58.85)	615 (56.53)	1256 (54.09)	
	Total	156 (100)	921 (100)	1245 (100)	2322 (100)	
Metastasis n (%)						
	No (M0)	235 (89.02)	1055 (91.50)	1561 (90.55)	2851 (90.77)	0.4
	Yes (M1)	29 (10.98)	98 (8.50)	163 (9.45)	290 (9.23)	
	Total	264 (100)	1153 (100)	1724 (100)	3141 (100)	
Stage n (%)						
	Stage I	41 (15.53)	245 (21.25)	454 (26.33)	740 (23.56)	**<0.01**
	Stage II	110 (41.67)	532 (46.14)	742 (43.04)	1384 (44.06)	
	Stage III	84 (31.82)	278 (24.11)	365 (21.17)	727 (23.15)	
	Stage IV	29 (10.98)	98 (8.50)	163 (9.45)	290 (9.23)	
	Total	264 (100)	1153 (100)	1724 (100)	3141 (100)	

* Totals do not always add up because of missing or unavailable data over the study period

Table 2: Staging characteristics of breast cancer cases related to the initiation of the national screening program (AUB Medical Center, Beirut, Lebanon, 1990-2016) (N= 3501)

		Pre-screening period (1990 – 2001)	Post-screening period (2002 – 2016)	Total	P-value
Median age at diagnosis (years)		50	51		-
Tumor size n (%)	**Less than 2 cm**	226 (18.97)	555 (50.04)	781 (33.96)	**<0.01**
	Between 2 cm and 5 cm	792 (66.49)	461 (41.57)	1253 (54.48)	**<0.01**
	More than 5 cm	173 (14.52)	93 (8.39)	266 (11.57)	**<0.01**
	Total	1191 (100)	1109 (100)	2300 (100)	
Lymph node involvement n (%)	**Negative (N0)**	426 (35.8)	640 (56.59)	1066 (45.91)	**<0.01**
	Positive (N1, N2, N3)	765 (64.23)	491 (43.41)	1256 (54.09)	
	Total	1191	1131	2322 (100)	
Metastasis n (%)	**No (M0)**	1200 (94.34)	1652 (88.39)	2851 (90.77)	**<0.01**
	Yes (M1)	72 (5.66)	217 (11.61)	290 (9.23)	
	Total	1272 (100)	1869 (100)	3141 (100)	
Stage n (%)	**Stage I**	180 (14.15)	560 (29.96)	740 (23.56)	**<0.01**
	Stage II	572 (44.97)	812 (43.45)	1384 (44.06)	0.40
	Stage III	447 (35.14)	280 (14.98)	727 (23.15)	**<0.01**
	Stage IV	72 (5.66)	217 (11.61)	290 (9.23)	**<0.01**
	Total	1272 (100)	1869 (100)	3141 (100)	3141

* Totals do not always add up because of missing or unavailable data over the study period

Table 3: Relative proportions of breast cancer stages at diagnosis in the pre- and post-screening periods among breast cancer cases diagnosed at AUB Medical Center, Beirut, Lebanon by age-groups (N= 3501)

Age Group	**< 40 years old n (%)**			**≥ 40 years old n (%)**		
Time Period	**Pre-screening period (1990 – 2001)**	**Post-screening period (2002 – 2016)**	**P-value**	**Pre-screening period (1990 – 2001)**	**Post-screening period (2002 – 2016)**	**P-value**
Stage I	38 (15.02)	55 (20.83)	0.085	142 (13.94)	505 (31.46)	**<0.01**
Stage II	115 (45.45)	120 (45.45)	1.00	457 (44.85)	692 (43.12)	0.38
Stage III	91 (35.97)	49 (18.56)	**<0.01**	356 (34.94)	231 (14.39)	**<0.01**
Stage IV	9 (3.56)	40 (15.15)	**<0.01**	64 (6.28)	177 (11.03)	**<0.01**
Total	253 (100)	1869 (100)	**-**	1019 (100)	1605 (100)	**-**
Total per period	253/1272 (19.88)	264/1869 (14.12)	**0.04**	1019/1272 (80.11)	1605/1869 (85.87)	**<0.01**

Table 4: Relative proportions of breast cancer stages at diagnosis between pre-campaign and post-campaign screening periods (1990 – 2001 and 2002 – 2013) as reported in the two largest tertiary hospitals in Lebanon

n (%)	**AUBMC***			**HDF****		
Stage at diagnosis	**Pre-screening period (1990 – 2001)**	**Post-screening period (2002 – 2013)**	**P-value**	**Pre-screening period (1990 – 2001)**	**Post-screening period (2002 – 2013)**	**P-value**
Stage I	180 (15.01)	298 (31.20)	**<0.01**	39 (17.56)	83 (25.69)	**<0.01**
Stage II	572 (47.71)	525 (54.97)	**<0.01**	106 (47.75)	175 (54.18)	**0.04**
Stage III	447 (37.28)	132 (13.83)	**<0.01**	77 (34.69)	65 (20.13)	**<0.01**
Total***	1199	955	-	222	323	-

* American University of Beirut Medical Center (present findings)

** Hôtel-Dieu de France [11]

*** Stage IV was excluded from both groups, as it was an exclusion criterion in the HDF study

Table 5: Staging at diagnosis and screening activities for breast cancer (BC) in selected Arab countries

	Awareness & screening activities	BC stage at diagnosis (%)	Ref
Bahrain	2005	• 1982 - 1994: I (7.5); II (57); III (23.5); IV (19) • 2000 - 2010: local (29); regional (44); metastatic (27)	19,20
Egypt	2004	• 1999: I (19); II&III (64); IV (17) • 2008: I (26); II&III (66); IV (8)	21
Jordan	2007	• 2005: I (7); II (24); III: (56); IV (13) • 2009: I (26); II (30); III (23); IV (21)	35
Lebanon	2002	• 1990 - 2001: I (14); II (45); III (35); IV (6) • 2002 - 2016: I (30); II (43); III (15); IV (12)	*
Oman	2018	• 1996 - 2002: I (9); II (40); III (35); IV (16) • 2003 - 2008: I (6); II (39); III (36); IV (18)	7,22
Morocco	2010	• 2005 - 2007: local (28); regional (63); metastatic (9) • 2004 - 2008: I (15.5); II (52); III (27.5); IV (5) • 2010 - 2015: early (66), locally-advanced (22); metastatic (12)	10,26
Saudi Arabia	2007	• 2002: local (36); regional (50); distant (14) • 2005 - 2012: I (12); II (56); III (21) • 2011 - 2012: I (8.7); II (44); III (46); IV (1.3)	5.37

*Present findings

APPENDIX 1

BREAST CANCER STAGING

Tumor stage is determined by the size of the tumor, number of involved lymph nodes, and whether the cancer has spread to other parts of the body. The TNM staging system classifies cancers based on their T, N, and M stages:

• The letter T followed by a number from 0 to 4 describes the tumor's size and spread to the skin or to the chest wall under the breast. Higher T numbers mean a larger tumor and/or wider spread to tissues near the breast.

• The letter N followed by a number from 0 to 3 indicates whether the cancer has spread to lymph nodes near the breast and, if so, how many lymph nodes are affected.

• The letter M followed by a 0 or 1 indicates whether the cancer has spread to distant organs for example, the lungs or bones.

Once the T, N, and M categories have been determined, this information is combined in a process called stage grouping, as shown below. Cancers with similar stages tend to have a similar outlook and are often treated in a similar way. The stage is expressed in Roman numerals from stage 0 to stage IV. Stage 0 breast cancer (i.e., in situ breast cancer) is characterized by an accumulation of malignant cells that have not invaded into surrounding tissue. Breast tumors designated as stage I, II, III, or IV involve some invasion of tumor cells beyond the basement membrane, and are thus referred to as invasive tumors.

TNM and stages adapted from the AJCC staging companion [37]

Stage	*T*	*N*	*M*
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T0	N1mi	M0
Stage IIA	T1	N1mi	M0
	T0	N1	M0
	T1	N1	M0
Stage IIB	T2	N0	M0
	T2	N1	M0
Stage IIIA	T3	N0	M0
	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

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