Effectiveness of breast cancer screening campaigns from 2012 to 2017 by analysis of stage at diagnosis, Lebanon

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Abstract

Background: Breast cancer is the most common and costly disease in Lebanon, but data on cancer stage and mortality are scarce.

Aims: This study aimed to assess the effect of mammography screening campaigns in reducing the breast cancer stage at diagnosis.

Methods: A secondary analysis was conducted of data from the Ministry of Public Health’s Cancer Drug Scientific Committee database. The medical files of 3320 newly diagnosed breast cancer patients between 2012 and 2017 were reviewed. Demographic and pathology characteristics, cancer stage at diagnosis and presence of receptors were extracted and analysed.

Results: The median age of the patients was 53 (interquartile range 36–72) years. Most patients had positive estrogen and progesterone receptors. Patients < 35 years mostly lived in South Lebanon, had advanced stages of cancer (III and IV) at diagnosis and were more likely to have triple negative breast cancer than the older groups (31.3% versus 16.7%). Advanced stage at diagnosis was common outside Beirut (60.4% in Bekaa and 54.7% in North Lebanon). In the period 2012–2017, the trend in early stages (I and II) at diagnosis decreased from 55.6% to 41.9%, while advanced stages (III and IV) increased from 44.4% to 57.9%.

Conclusion: Efforts to downstage breast cancer through mammography screening in Lebanon have not succeeded. Implementation of genetic testing and tailored approaches for Lebanese women are recommended for future campaigns.

Keywords: breast cancer, neoplasm staging, hormone receptors, mammography, Lebanon

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Introduction

Breast cancer is the most frequent cancer among women worldwide, affecting 2.1 million women annually and causing the highest number of cancer-related deaths among females (1). One in four of all newly diagnosed cases of cancer in women are breast cancer (24.2% of all female cancers) according to the GLOBOCAN 2018 report (2). Lebanon, a developing Middle Eastern country, has a high breast cancer incidence, accounting for almost 37% of cancer cases in females and 20% of all cancer cases (3).

High-income countries have a higher incidence of breast cancer than low- and middle-income countries. However, the incidence of breast cancer is rising faster in low- and middle-income countries than in high-income countries and the mortality rate is higher (4,5). In 2018, Lebanon had the sixth highest age-standardized incidence rate for breast cancer in the world – 97.6 cases per 100 000 women (6) – and the seventh highest breast cancer mortality rate – 24 per 100 000 women (7).

Implementation of screening programmes in high-income countries was followed by a decrease in advanced breast cancer and mortality rates (8): 10 years after mammography screening was introduced, breast cancer mortality rate had fallen by 20% in high-resource settings but not in limited-resource settings with weak health systems (4).

Lebanon is one of the developing countries that most needs to promote breast cancer awareness and screening. In fact, since 2002, annual breast cancer awareness and screening campaigns have been conducted by the health ministry. These campaigns provide free mammography tests for women 40 years and older with no family history of breast cancer in all Lebanese public hospitals, and in most private medical institutions, the screening is offered at half price.

In parallel, the health ministry has renovated the National Cancer Registry (9). The registry produces yearly ongoing population-based information on cancer incidence, according to sex, age and tumour site. However, it still lacks information on cancer staging and mortality. This gap in knowledge prevents a precise evaluation of the effectiveness of screening campaigns, particularly as the stage of cancer at presentation is one of the most important prognostic factors of survival (10).

Therefore, in order to evaluate the effectiveness of breast cancer campaigns, we collected data on cancer...
stage from the medical files of women receiving cancer treatment from the health ministry between 2012 and 2017. We also collected information on demographic and tumour characteristics.

**Methods**

**Patients and data collection**

This was a secondary analysis of data from the Cancer Drug Scientific Committee database of the health ministry. All women newly diagnosed with breast cancer between 2012 and 2017 were enrolled in the study. A total of 3320 medical files were reviewed.

The health ministry provides breast cancer drug treatment free of charge for uninsured patients, which represents over half of the caseload of breast cancer and is distributed all over the country. Therefore, the sample studied is representative of the Lebanese population.

We reviewed all laboratory, radiology and pathology reports. Information extracted from the medical records included: personal information (demographic characteristics, age at diagnosis and place of residence) and tumour characteristics (presence of estrogen, progesterone and human epidermal growth factor receptors), triple negativity (absence of estrogen, progesterone and human epidermal growth factor receptors), and disease stage at the time of diagnosis.

The patients were divided into three age groups: younger than 35 years (age group 1), 35–50 years (age group 2) and 50 years and older (age group 3).

Pathology was done at local laboratories licensed by the health ministry. Estrogen and progesterone receptors were considered negative if staining was less than 5% positive. The presence of human epidermal growth factor receptors was considered positive if there was strong complete staining of > 30% or in the presence of the human epidermal growth factor receptor gene amplification using fluorescent in situ hybridization. The triple negative breast cancer subtype is characterized by the absence of expression of receptors for estrogen, progesterone and human epidermal growth factor.

Patients were staged according to the TNM (tumour, nodes and metastases) staging system, the most accepted classification (11). Stage at presentation was used for analysis. Clinical staging was used for all patients who had received neoadjuvant pre-operative therapy and pathological staging for all patients post-surgery.

**Statistical analysis**

Data analysed using SPSS, version 24 (IBM Corp., Armonk, New York). All data were entered anonymously to ensure patient confidentiality. The chi-squared test was used to test the statistical significance of differences between categorical variables. Eight variables were included in a univariate analysis: age and cancer stage at diagnosis, governorate of residence, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor status, triple negativity status and trends in stages over the years of the study. Correlation between these variables was also explored. A P-value less than 0.05 was considered statistically significant.

**Ethical concerns**

This study was a secondary analysis of de-identified data.

| Variable | Group 1 (< 35 years) | Group 2 (35–< 50 years) | Group 3 (≥ 50 years) | Total (n = 3320) | P-value* |
|----------|----------------------|--------------------------|----------------------|------------------|----------|
| Median age at diagnosis (IQR), years | 31 (26–33) | 44 (41–46) | 59 (54–77) | 53 (36–72) | 0.001 |
| Governorate | | | | | |
| Beirut | 8 (6.0) | 102 (9.8) | 340 (15.8) | 450 (13.5) | 0.001 |
| Bekaa | 20 (14.9) | 187 (18.0) | 265 (12.3) | 472 (14.2) | 0.001 |
| Mount Lebanon | 21 (15.7) | 187 (18.0) | 158 (27.2) | 792 (23.9) | 0.001 |
| North Lebanon | 35 (26.1) | 244 (23.5) | 397 (18.5) | 676 (20.4) | 0.001 |
| South Lebanon | 50 (37.3) | 317 (30.5) | 563 (26.2) | 930 (28.0) | 0.001 |
| Estrogen receptor | | | | | 0.000 |
| Positive | 78 (58.2) | 769 (74.0) | 1605 (74.7) | 2452 (73.9) | 0.000 |
| Progesterone receptor | | | | | 0.400 |
| Positive | 74 (55.2) | 705 (67.9) | 1418 (66.0) | 2197 (66.2) | 0.400 |
| Human epidermal growth factor receptor | | | | | 0.070 |
| Positive | 31 (23.1) | 233 (22.4) | 461 (21.5) | 725 (21.8) | 0.070 |
| Triple negative breast cancer | | | | | 0.020 |
| Yes | 42 (31.3) | 204 (19.6) | 310 (14.4) | 556 (16.7) | 0.020 |

IQR= interquartile range.

*Comparing demographic and pathology characteristics by age group.
Results

We categorized 3320 breast cancer medical files according to age and stage of the disease at diagnosis over 6 years.

The demographic and pathology characteristics of the cases were classified into three age groups (Table 1). Median age at diagnosis for all patients was 53 years (interquartile range (IQR) 36–72 years). Age group 1 included 134 (4.0%) patients < 35 years with a median age at diagnosis of 26 (IQR 23–33) years, age group 2 included 1038 (31.2%) patients between 35 and 50 years with a median age at diagnosis of 44 (IQR 41–46) years and age group 3 included 2148 (64.8%) patients ≥ 50 years with a median age at diagnosis of 59 (IQR 54–77) years.

The greatest proportion of the cases lived in South Lebanon governorate (28.0%), while 23.9% lived in Mount Lebanon, 20.3% in North Lebanon, 14.2% in Bekaa and 13.5% in Beirut.

There was significant difference in age group between Beirut and other governorates (except for Mount Lebanon) with the lowest number of patients diagnosed younger than 50 years living in Beirut. Compared with other governorates, Bekaa had a significantly higher proportion of patients diagnosed with breast cancer younger than 50 years, and a lower proportion diagnosed older than 50 years compared to Beirut and Mount Lebanon.

Most patients had positive receptors with 73.8% positive for estrogen receptor and 66.1% positive for progesterone receptor. Human epidermal growth factor receptor was overexpressed in 21.7% of the patients. Although, hormone receptor positivity increases with age, no significant differences were found between the different age groups and positivity of the receptors for estrogen, progesterone and human epidermal growth factor. Triple negative breast cancer was present in 16.7% of patients overall, though it was significantly higher (31.3%) in age group 1 (< 35 years old) and decreased with increased patient age (14.4% in age group 3; \( P = 0.02 \)).

Of the 3320 patient records analysed, 314 patients (9.5%) had stage I disease at diagnosis, 1330 (40.1%) had stage II disease, 896 (26.9%) had stage III disease and 779 patients (23.5%) had stage IV disease (Table 2). About 35% of patients in age group 1 (< 35 years old) were diagnosed at stages II and III, while 42.1% in age group 2 and 39.4% in age group 3 were diagnosed at stage II. No statistically significant differences in staging were found between any of the age groups; \( P = 0.235 \) (Table 2).

The association between stage at diagnosis and governorate of residence is shown in (Table 3). No statistically significance differences in staging were found between any of the governorates (\( P = 0.7 \)). However, advanced stages (III and IV) of cancer at diagnosis were mostly seen in areas outside of the capital, in Bekaa (60.4%) followed by North Lebanon (54.7%). On the other hand, early stages (I and II) were mostly seen in Beirut (55.1%) and Mount Lebanon (54.8%).

Distribution of tumour histological characteristics (receptors for estrogen, progesterone and human epidermal growth factor, and triple negative breast cancer) according to disease stages are summarized in Table 4. Human epidermal growth factor receptors were positive in 21.7% of all patients with no significant difference between different stages. Estrogen and progesterone receptors were positive in 73.8% and 66.1% of the patients, respectively, with statistically significant differences between stage I (85.2% positive for estrogen receptor and 78.5% positive for progesterone receptor) compared with other stages (\( P = 0.002 \) for estrogen receptors and \( P = 0.001 \) for progesterone receptors). However, positivity for human epidermal growth factor receptor did not change significantly by stage (\( P = 0.07 \)). In parallel, the frequency of hormone receptor negativity increased with advanced breast cancer stage.

Just 16.7% of patients in the study had triple negative breast cancer; the percentage with triple negative breast cancer was highest in stage I disease (24.7%) and lowest (8.0%) in patients diagnosed at stage IV (\( P = 0.03 \)).

compared the trends of early stage breast cancer on diagnosis to advanced stage from 2012 to 2017, early stages of breast cancer decreased from 55.6% to 41.9%, whereas advanced stages increased from 44.4% to 57.9% (Figure 1).

Discussion

Breast cancer is the most common (9) and most costly disease (12) in Lebanon. The Lebanese health ministry is trying to eliminate the main financial barriers to breast cancer diagnosis and treatment by providing free mammography screening and free cancer drugs (13).

We evaluated the effect of breast cancer campaigns on reducing the stage of the disease at diagnosis and hence

| Stage | Group 1 (< 35 years) | Group 2 (≥ 35–< 50 years) | Group 3 (≥ 50 years) | Total |
|-------|----------------------|-----------------------------|----------------------|-------|
| I     | 11 (8.2)             | 92 (8.9)                    | 211 (9.9)           | 314 (9.5) |
| II    | 47 (35.1)            | 437 (42.1)                  | 847 (39.4)          | 1331 (40.1) |
| III   | 48 (35.8)            | 299 (28.8)                  | 549 (25.6)          | 896 (26.9) |
| IV    | 28 (20.9)            | 210 (20.2)                  | 541 (25.2)          | 779 (23.5) |
| Total | 134                  | 1038                        | 2148                 | 3320   |

\( P = 0.235 \) (comparing cancer stages and age groups).
on breast cancer survival rates by analysing the trends in stage at diagnosis over 6 years.

The median age at diagnosis of our breast cancer patients was 53 years, which is lower than in the United States of America (60 years) (14). While 50% of breast cancer cases in Lebanon occur in women younger than 50 years (15), 78% of the American breast cancer patients are older than 50 years (16). However, the median age in our study was slightly higher than that of the Arab nations (49 years) in a 2010 study (17).

A large proportion (37.3%) of young patients (<35 years old) lived in South Lebanon, outside greater Beirut (Beirut city and suburbs). This result emphasizes the importance of performing genetic mutation analysis and starting to screen women at an earlier age in this region.

In addition to patient age at diagnosis, one of the prognostic factors for breast cancer (16), other markers of prognostic and therapeutic benefits were also identified (18). We found that most patients had positive estrogen (73.8%) and progesterone (66.1%) receptors. This rate of positivity was much lower in the youngest age group – 58.2% for estrogen and 55.2% for progesterone receptors. The occurrence of breast cancer negative for estrogen receptor at earlier ages is greatly associated with tumour aggressiveness (18). In addition to estrogen receptor, human epidermal growth factor receptor, is recognized as an important prognostic factor (18). Human epidermal growth factor receptors were overexpressed in 21.7% of all patients. The most favorable outcomes were seen for hormone receptor-positive tumors followed closely by human epidermal growth factor receptor-positive tumors, with the worst outcomes observed for triple negative breast cancer (18).

Overall 16.7% of the patients had triple negative breast cancer, which is consistent with general literature estimates (19). However, we noticed a higher rate of triple negative breast cancer (31.3%) in patients younger than 35 years. Triple negative breast cancer diagnosed at a younger age has an aggressive biological behaviour with the development of metastasis within 5 years, and an increased mortality rate (20). In addition, there is a possibility of association with BRCA1 mutations in these patients and consequently a need for genetic testing (19). Furthermore, the optimal breast imaging methods should be identified in this age group. As mammography becomes less effective at detecting breast cancer in the presence of increased breast density (21), more suitable approaches are required for screening in young patients. One of such method is the use of ultrasonography which has proven useful and cost-effective for low- and middle-income countries (21). Other new methods for breast cancer screening are also emerging, including annual breast magnetic resonance imaging in young women at high risk, particularly those carrying the BRCA1 mutation (22).

We also found more cases with advanced stages (56.7%) than with early stages (43.3%) in age group <35 years. Breast cancer tends to be more aggressive in young patients with poorer outcomes (23). Studies have shown that a higher proportion of women aged 20–39 years have later stage and higher grade breast cancer at diagnosis than women aged 40–49 years (23). On the other hand, leading organizations and the Lebanese health ministry do not recommend mammography screening for women at average risk before the age of 40. Moreover, educational level and other sociodemographic factors vary according to residence in or outside the greater

| Stage | Group 1 (< 35 years) | Group 2 (≥ 35 – < 50 years) | Group 3 (≥ 50 years) | Total |
|-------|----------------------|-----------------------------|----------------------|-------|
| I     | 11 (8.2)             | 92 (8.9)                    | 211 (9.9)            | 314 (9.5) |
| II    | 47 (35.1)            | 437 (42.1)                  | 847 (39.4)           | 1331 (40.1) |
| III   | 48 (35.8)            | 299 (28.8)                  | 549 (25.6)           | 896 (26.9) |
| IV    | 28 (20.9)            | 210 (20.2)                  | 541 (25.2)           | 779 (23.5) |
| Total | 134                  | 1038                        | 2148                 | 3320 |

P = 0.235 (comparing cancer stages and age groups).

Table 3 Distribution of breast cancer patients in the Lebanese governorates according to stage of the disease at diagnosis

| Governorate       | I     | II    | III   | IV    | Total |
|-------------------|-------|-------|-------|-------|-------|
| Beirut            | 49 (10.9) | 199 (44.2) | 104 (23.1) | 98 (21.8) | 450 (100.0) |
| Bekaa             | 36 (7.6)  | 151 (32.0) | 168 (35.6) | 117 (24.8) | 472 (100.0) |
| Mount Lebanon     | 89 (11.2) | 346 (43.7) | 195 (24.6) | 162 (20.5) | 792 (100.0) |
| North Lebanon     | 61 (9.0)  | 244 (36.1) | 188 (27.8) | 183 (27.1) | 676 (100.0) |
| South Lebanon     | 79 (8.5)  | 390 (41.9) | 239 (25.7) | 222 (23.9) | 930 (100.0) |
| Total             | 314     | 1330   | 894   | 782   | 3320 |

P value = 0.70.
Beirut. Less education, lower socioeconomic status and living outside greater Beirut are associated with lower use of mammography screening (24).

Furthermore, and most importantly, our results show that from 2012 to 2017, the percentage of breast cancer cases diagnosed at an early stage decreased from 55.6% to 41.9%, whereas the percentage diagnosed at an advanced stage increased from 44.4% to 57.9%. These results were not the expected outcomes of the breast cancer campaigns. Therefore, the objective of the campaigns to lower the stage of breast cancer at diagnosis was not met and hence it can be assumed that a decrease in the breast cancer mortality rate was not achieved.

Disparities in access to information and the capacity of the health care system between different governorates are the main reasons for the lack of improvement in staging at diagnosis, and hence breast cancer care. Early stages were mostly seen in Beirut and Mount Lebanon, whereas advanced stages were mostly identified in Bekaa and North Lebanon. These two governorates are geographically far from the capital Beirut and probably the least influenced by screening campaigns. Thus, national campaigns should be scaled up to reach more women all over the country.

According to the World Health Organization, for a mammography screening programme to be effective in reducing mortality, it needs to cover at least 70% of the population at risk (25). Lebanon, is far off this number and only reached 45% of eligible women in 2018 (unpublished health ministry data, 2018).

Wider adoption of mammography screening requires different strategies for delivery of the screening. For instance, using mobile clinics and gathering women for a one-day locally-based mammogram in collaboration with regional municipalities may be an effective strategy to facilitate screening access in remote areas.

In parallel, promoting public education, mainly on the curability of breast cancer and the benefits of repeating mammography screening even if the previous results were negative is essential (24). Using terms appropriate to women’s age and culture is helpful in conveying an accurate message about breast cancer campaigns and can result in increased uptake of mammography screening and repeat screening. Concurrently, it is important to encourage physicians of different specialties, mainly primary care physicians and gynaecologists, to routinely recommend screening to their patients and to keep their records.

One of the main limitations of our study is the lack of data from other similar socioeconomic countries which made comparison difficult.

Our results on the demographic and tumour characteristics of cases of breast cancer may help suggest new approaches in future campaigns to lower tumour stage at diagnosis, and provide a useful framework for the reallocation of the limited health ministry breast cancer budget. We hope our results will encourage the government and health care providers to do more to overcome relevant local barriers and ultimately improve the effectiveness and outcomes of breast cancer campaigns.

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**Competing interests:** None declared.

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Table 4 Distribution of HER2, ER & PR receptors and TNBC according to stage

| Stage | HER2 | ER | PR | TNBC | Total |
|-------|------|----|----|------|-------|
|       | +    | –  | +  | –    | +    | –    | +    | –    | +    | –    |
| I     | 64 (20.5) | 248 (79.5) | 266 (85.3) | 46 (14.7) | 245 (78.5) | 67 (21.5) | 77 (24.7) | 235 (75.3) | 312 |
| II    | 275 (20.8) | 1048 (79.2) | 1007 (76.1) | 316 (23.9) | 913 (69.0) | 410 (31.0) | 298 (22.5) | 1025 (77.5) | 1323 |
| III   | 199 (22.3) | 692 (77.7) | 625 (70.1) | 266 (29.9) | 572 (64.2) | 319 (35.8) | 119 (13.4) | 772 (86.6) | 891 |
| IV    | 184 (23.7) | 594 (76.3) | 554 (71.2) | 224 (28.8) | 467 (60.0) | 311 (40.0) | 62 (8.0) | 716 (92.0) | 778 |
| Total | 722 (21.9) | 2582 (78.1) | 2452 (74.2) | 852 (25.8) | 2197 (66.5) | 1107 (33.5) | 556 (16.8) | 2748 (83.2) | 3304 |

HER2= human epidermal growth factor receptor; ER= estrogen receptor; PR= progesterone receptor; TNBC= triple negative breast cancer.

*Sixteen patients were excluded from the analysis because of missing data on hormone receptors.

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Figure 1. Trends in early stage (I and II) breast cancer and advanced stage (III and IV), Lebanon, 2012–2017

Source: Ministry of Health, Lebanon 2017.
**Efficacité des campagnes de dépistage du cancer du sein de 2012 à 2017 par analyse du stade au moment du diagnostic (Liban)**

**Résumé**

**Contexte :** Le cancer du sein est la maladie la plus fréquente et la plus coûteuse au Liban, mais les données sur le stade du cancer et la mortalité associée sont rares.

**Objectifs :** La présente étude visait à évaluer l'effet des campagnes de dépistage par mammographie sur la réduction du stade du cancer du sein au moment du diagnostic.

**Méthodes :** Une analyse secondaire a été effectuée à partir des données de la base de données du Comité scientifique des médicaments anticancéreux du ministère de la Santé publique. Les dossiers médicaux de 3320 patientes atteintes d'un cancer du sein nouvellement diagnostiqué entre 2012 et 2017 ont été passés en revue. Les caractéristiques démographiques et pathologiques, le stade du cancer au moment du diagnostic et la présence de récepteurs ont été extraits et analysés.

**Résultats :** L'âge médian des patients était de 53 ans (intervalle interquartile 36-72). La plupart des patients présentaient des récepteurs d'œstrogènes et de progestérone positifs. Les patients de moins de 35 ans vivaient principalement au Sud-Liban, étaient à des stades avancés de cancer au moment du diagnostic (III et IV) et étaient plus susceptibles d'avoir un cancer du sein triple négatif que les groupes plus âgés (31.3 % contre 16.7 %). Le stade avancé du diagnostic était courant en dehors de Beyrouth (60.4 % dans la Bekaa et 54.7 % dans le nord du Liban). Au cours de la période comprise entre 2012 et 2017, la tendance des stades précoces (I et II) au moment du diagnostic a diminué, passant de 55.6 % à 41.9 %, tandis que les stades avancés (III et IV) ont augmenté, passant de 44.4 % à 57.9 %.

**Conclusion :** Les efforts visant à réduire le stade du cancer du sein grâce au dépistage par mammographie au Liban n'ont pas abouti. La mise en place de tests génétiques et d'approches adaptées aux femmes libanaises est recommandée pour les campagnes futures.

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