Breast cancer patients in Libya: Comparison with European and central African patients

JAMELA MOSTAFA E. BODER[1,2*], FATHI B. ELMABROUK ABDALLA[1,2*], MOHAMED AHMED ELFAGEIH[3], ABUAGELA ABUSAA[4,5], ABDELBASET BUHMEIDA[6] and YRJÖ COLLAN[1]

[1]Department of Pathology, University of Turku, Turku, Finland; [2]Department of Pathology, Sabratha Teaching Hospital, Sabratha; [3]Department of Surgical Oncology, National Cancer Institute, Misurata; [4]Department of Medical Oncology, and [5]Cancer Registry Unit, African Oncology Institute, Sabratha, Libya; [6]Center of Excellence in Genomic Medicine Research, King Abdul-Aziz University, Jeddah, Saudi Arabia

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Abstract. The present study evaluated the incidence of breast cancer in Libya and described the clinicopathological and demographic features. These features were then compared with corresponding data from patients from sub-Saharan Africa (Nigeria) and Europe (Finland). The study consisted of 234 patients with breast carcinoma, admitted to the African Oncology Institute in Sabratha, Libya, during the years 2002-2006. The pathological features were collected from pathology reports, patient histories from hospital files and the Sabratha Cancer Registry. The demographic differences between the Libyan, Nigerian and Finnish populations were prominent. The mean age of breast cancer patients in Libya was 46 years which was almost identical to that of Nigeria, but much lower than that of Finland. The Libyan breast cancer incidence was evaluated as 18.8 per 100,000 female individuals. This incidence was markedly higher in Finland, but was also high in Nigeria. Libyan and Nigerian breast cancer is predominantly of premenopausal type and exhibits unfavorable characteristics such as high histological grade and stage, large tumor size and frequent lymph node metastases. However, the histological types and histopathological risk features show similar importance regarding survival as European breast cancer cases. Survival in Libya ranks between the rates of survival in Nigeria (lowest) and Finland (highest). In conclusion, in Libya and other African countries, premenopausal breast cancer is more common than postmenopausal breast cancer. However, the opposite is true for Europe. Population differences may be involved, as suggested by the known variation, in the distribution of genetic markers in these populations. Different types of environmental impacts, however, cannot be excluded.

Correspondence to: Dr Fathi B. Elmabrouk Abdalla, Department of Pathology, University of Turku, Kiinamyllynkatu 10, 20520 Turku, Finland
E-mail: fabdalla@utu.fi

*Contributed equally

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Introduction

Globally, breast cancer is the most common form of malignant neoplasia in females, contributing to 23% of all types of cancer (1). Breast cancer accounts for 10-18% of all cancer-related deaths and is the most common cause of cancer-related death in industrialized countries, and the third in developing countries (1-5).

Breast cancer incidence is on the increase worldwide, but it varies from areas of low incidence (Japan and other Asian countries, and Latin American and African countries) to areas of high incidence (US, Western Europe, Northern Europe and Australia). For example, in the US less than 0.9 new cases per 1000 women were reported in the 1990s, and more than 1.4 new cases per 1000 were reported in 2006 (1,2,5). The incidence of breast cancer has also shown a steady increase during the last 30 years in the Nordic countries. The incidence in Finland rose from 63.3 per 100,000 female individuals in 1989 to 87.6 in 2007 (6). In the UK, approximately one in nine female individuals is likely to develop the disease during her lifetime (7). An increase has even been noted in the low incidences of breast cancer in Eastern Europe and Japan (8,9).

Various studies in the US found that female individuals of African descent have a lower breast cancer incidence but higher breast cancer mortality rates than Caucasian women. Poor survival may be related to the fact that female individuals of African descent are more likely to be diagnosed at an early age but with an advanced stage of disease (3,5,10,11). In the sub-Saharan African population low rates of breast cancer exist, and the majority of patients are premenopausal and present at an advanced stage (2).

In Arabic countries studies are not comprehensive. In Morocco, the most frequently occurring cancer in females is cervical uterine neoplasia (35%) followed by breast cancer (22.3%), which is also diagnosed at advanced stages (12). In

Table I. Population data for Libya, Nigeria and Finland.

	Libya	Nigeria	Finland
Total population	6,342,000(07)[a]	144,077,000(07) [a]	5,286,000(07) [a]
Age structure (%)			
0-14 years	30%[a]	44.4%[d]	17.1%[e]
15-64 years	66.2%[a]	52.6%[d]	66.4%[e]
>64 years	3.8%[a]	3.0%[d]	16.5%[e]
Population growth rate (%)	2.3[b,f]	2.67[d]	0.46[e]
Birth rate (births/1.000 population)	26.8[b]	41.3[a]	11.8[e]
Death rate (deaths/1.000 population)	3.5[b,f]	17.2[a]	9.1[e]
Gender ratio (Total population; M/F)	1.05[b]	1.05[a]	0.95[d]
Infant mortality (deaths/1.000 population)	24.6[b]	74.18[d]	3.82[d]
Life expectancy (years)	76.6[b,f]	52.0[c]	79.3[e]
Female	78.8[b,f]	52.0[c]	82.8[e]
Male	74.3[b,f]	52.0[c]	75.8[e]
Total fertility rate	3.34[b]	5.9[a]	1.8[e]
Literacy	84.1%[b]	76.3%[a]	100%[a,c,d,e]
GDP (in US$)	8,298[b,f]	970[d]	21,000[d]

Data on Nigeria and Finland are basically the same as those published in the study of Ikpatt *et al* (13). However, new data, when available, were used for updating (13,15-19). See references 17[a], 16[b], 18[c], 13[d], 19[e], 15[f], respectively.

Egypt, approximately 35% of all female cancer is breast cancer (4). The background of Arabic patients may be related to a greater extent to other African breast cancer patients as compared to European breast cancer patients, although demographic and environmental differences, e.g,. between Libyan, Nigerian and European (Finnish) populations, are prominent (Table I). In this study, various demographic and clinicopathological factors associated with breast cancer in Libya were identified. The Libyan population and breast cancer patients were compared with the Nigerian and the Finnish population and patients as noted in previous studies (13). To the best of our knowledge, such comparisons have not previously been published. An estimate of the incidence of female breast cancer in Western Libya was made based on the Sabratha Cancer Registry Database.

Materials and methods

Libyan data

Clinical and pathological characteristics. A retrospective pathologic study was conducted on 234 patients (Table II). The patients were treated at the African Oncology Institute (AOI) during the 5-year period from 2002 to 2006. The estimated clinical or pathological characteristics included age at presentation, age at first pregnancy, parity, age at menarche, menopausal status at diagnosis, size of tumor, LN status, stage, histological grade, histological type and follow-up history of the patient. Patients were followed-up until they succumbed to the disease or to the end of the observation period in the middle of January 2007. Some patients were lost during follow-up prior to January 2007. For these patients, the last date of contact was defined as the date for the end of follow-up. The follow-up period ranged from 1 to 74 months with an average of 22.0 months. Table II shows all of the breast cancer patients during the years 2002-2006 admitted to the AOI. Table III shows that the number of admissions during the study period varied, and that a complete follow-up record could not be found for all patients. This reflects the situation in local hospitals before the Sabratha Cancer Registry program was initiated. Many patients entered the hospital for a preliminary diagnosis, after which they consulted their families and decided on a treatment. Many patients remained in the hospital until the histopathological diagnosis, usually after the primary surgery was carried out, and then decided on further treatment. Some patients commenced therapy at the AOI, but interrupted the treatment and were lost from follow-up. Finally, approximately half of the patients were diagnosed, treated, followed up, and received further therapy at the Institute. The patients lost to follow-up were generally treated elsewhere (other Libyan hospitals or abroad).

Cancer registration in Libya. The precise number of cancer cases diagnosed each year in Libya is unknown since a complete cancer registry has not yet been established in a number of areas. In 2007, the Ministry of Health created the National Cancer Registry Program, following the commencement of the Sabratha Cancer Registry in 2006. As part of this program, Libya currently has five Cancer Registries (14) (Table III).

Evaluation of breast cancer incidence. Evaluation of breast cancer incidence was based on the 2006 data obtained from the Sabratha Cancer Registry. The histological diagnoses were based on available pathology reports. Two male patients and three non-epithelial malignant cases were excluded. Two patients did not have evidence of a histological diagnosis and

Table II. Breast cancer patients admitted to the African Oncology Institute, Sabratha, Libya, during the years 2002-2006.

Year	No. of breast cancer patients admitted	No. of breast cancer patients with available history and follow-up information	No. of new breast cancer patients in the Sabratha Regional Registry
2002	99	23	41
2003	101	54	42
2004	70	31	44
2005	95	40	54
2006	108	86	50
Total	473	234	231

The fourth column indicates the number of available patients for this study (see text). The data included in the first 4 lines of the third column were collected from patient records of histologically diagnosed cases. The fifth line in column 3 indicates the number of patients in the registry during the first year of operation in 2006.

Table III. Libyan Cancer Registries initiated in 2007[a].

Location of cancer registry	Regions and cities covered by the registry
1. Tripoli	Tripoli, Aljafara, Almergaib, Aljabal Algarbi
2. Benghazi	Benghazi, Albatnan, Darna, Aljabal Alakhader, Almarg, Alwahat, Alkufra, Ejdabiya
3. Sabha	Sabha, Morzuk, Wadi Alhiya, Wadi Shatee, Ghat
4. Musrata	Musrata, Sirt, Aljufra
5. Sabratha	Zawia, Alnikat, Nalut

[a]Presented in the National Cancer Registry program in 2007 (14).

were excluded. The incidence data were consequently based on the histologically confirmed cases for the year 2006, when the Sabratha Registry commenced its first year of operation.

Data from Finland and Nigeria. A portion of the data was previously presented in the study by Ikpatt *et al* (13). Updated data were used, when available (15-19).

Statistical analysis. Variables of the Libyan patients were grouped, and descriptive statistics were calculated for the continuous variables by using SPSS 16.0 for Windows. For survival analysis, Kaplan-Meier curves were plotted, and differences between the curves were analyzed using the log-rank test. Statistical differences among the three countries were determined by the Chi-square test and Student's t-test. $P<0.05$ was considered to be statistically significant. Statistical analyses and graphs were produced by the Excel program.

Results and discussion

Breast cancer incidence. There were 101 breast cancer patients among the 299 female cancer patients (33.7%) admitted to the AOI in 2006. This was in agreement with figures from North African countries; in Egypt, the corresponding percentage was approximately 35% (2,4). The Libyan figure also compares favorably with the European and North American figures (27.3 and 31.3% of cancers in females, respectively) (1).

Of the above-mentioned 101 patients, 50 were from the Sabratha Registry region. The population of this region in 2006 was 542,708, as reported by the Libyan Census Committee (14). The male:female ratio in the Libyan population was 1.05:1 (16). Based on these data, the incidence was 18.89 new cases per 100,000 Libyan females.

Evidence shows that breast cancer in Western Libya is on the increase (Fig. 1). This increase may be attributed to the development in health care, including improved diagnostic facilities. The breast cancer incidences in Libya, Nigeria and Finland were 18.9, 33.6 and 87.6 per 100,000 females, respectively. The incidence in Libya is markedly lower than that in Europe or the US, but is also lower than the incidence in Nigeria. The breast cancer incidence in Nigeria has shown a marked increase from 13.7 per 100,000 in the 1970s, to 33.6 per 100,000 in the 1990s (2,13). Lifestyle differences may be involved, but biological differences as causes cannot be excluded (5,10). The incidence in Libya is in concordance with results published from other North African countries (Tunisia 19.6, Egypt 24.2 and Algeria 23.4) (2,14,20). The apparently slow increase in incidence may be related to improved diagnostic practice (mammography, immunostaining) in the last few years in Libya.

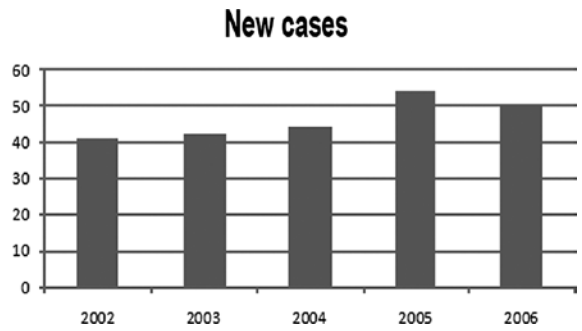

Figure 1. New cases of infiltrative breast carcinoma in the Sabratha Cancer Registry over the 5-year period from 2002 to 2006.

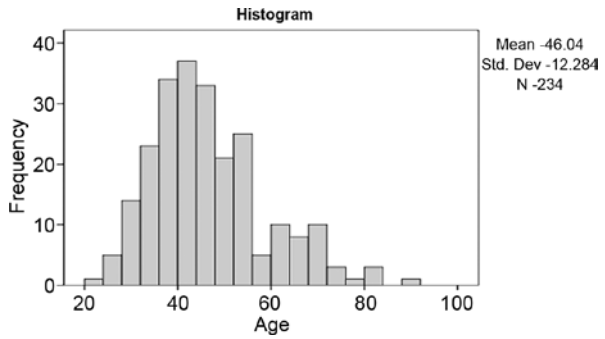

Figure 2. Age distribution at diagnosis of the 234 histologically confirmed breast cancer patients in Western Libya (Sabratha region) from 2002 to 2006.

Table IV. Mean age at diagnosis, mean age at first pregnancy and menopausal status of breast cancer patients in Libya, Nigeria, and Finland.

Variable	Libya	Nigeria[a]	Finland[a]
Mean age at diagnosis (±SD), in years	46.0±12.3	42.7±12.1	58.8±12.5
Mean age at first pregnancy, in years	22.1	20.8	25.6
Menopausal status, n (%)			
Premenopausal patients	160 (68.4)	223 (74.3)	93 (32.6)
Postmenopausal patients	74 (31.6)	77 (21.3)	192 (67.4)

[a]From Ikpatt *et al* (13).

Age at presentation. The occurrence of breast cancer in the female Libyan population is strongly associated with young age with nearly 70.9% of cases arising in female individuals who are 50 years or younger. The median age is 44.0 years, and the mean age, 46.0 years (Fig. 2).

The difference between the mean ages of Libyan and Finnish patients was statistically significant ($p<0.001$), whereas no statistical difference was noted in age at diagnosis between Libyan and Nigerian patients (Table IV). The difference between African and European patients may partly be associated with the age distribution of populations in the respective countries, but biological differences may also be involved.

The variation in genetic marker distribution between Central and North African and European populations is also involved (21), suggesting that in the African population, characterized by 'African' genomic haplotypes, the premenopausal type of breast cancer is more common than the postmenopausal type. In Europe, where the population is characterized by 'European' genomic haplotypes, the contrary is the case.

Age at first pregnancy. Age at first pregnancy was available from 44 out of 234 Libyan breast cancer patients. The average age at first pregnancy was 22.1 years. In addition, there were 40 female individuals without previous pregnancies. The mean age of all of the women at first pregnancy was not available for the female population of Libya. The age at first pregnancy in breast cancer patients in Nigeria was similar to that in the Libyan cases (20,8 years), while Europeans had a higher mean age (25.6 years) (Table IV). Patients with benign breast disease were found to have a lower age at first pregnancy than breast cancer patients (22).

Fertility. Infertility and an unmarried status for females were associated with an increased risk of breast cancer (23). Since the fraction of unmarried female individuals (between ages 34 and 40) was higher among the Libyan breast cancer patients as compared to the North African population in general (23.8% and 15-21%, respectively) (24), childlessness was a risk factor for breast cancer.

Menopausal status. In Libya, almost 68.4% of breast cancer patients were premenopausal, and 31.6% were postmenopausal. The Nigerian data were similar. African breast cancer was markedly different from European cases in this respect. In Europe and among US Caucasian females most patients were postmenopausal (Table IV).

In light of the above findings, breast cancer can principally be divided into two types. The postmenopausal type is more common in Europe and North America, and the premenopausal type is more common in Africa.

Stage. The staging system currently in use for breast cancer is based on the size of the primary tumor, degree of spread to lymph nodes and the presence of systemic metastasis. The TNM classification, adapted by the International Union Against Cancer (16) can also be utilized. The Libyan breast cancer staging in our study was based on the TNM classification of 1997 (25) (Table V). The majority of Libyan patients were

Table V. The frequency of the different stages determined among the 234 breast cancer patients according to the staging manual of the International Union Against Cancer (5th edition).

Clinical stage	Corresponding TNM categories	Frequency	Percentage
0	Tis N0 M0	0	0
1	T1N0 M0	12	5.1
2	T2N0M0 and T0/1N1M0	28	12.0
	T2N1M0 and T3N0M0	75	32.1
3	T1/2/3N2M0 and T3N1M0	60	25.6
	T4NM0 and TN3M0	26	11.1
4	T0-4N0-3M1	33	14.1
Total		234	100.0

The majority of Libyan breast cancer patients were in stages 2B and 3A (combined total of 57.3% of all patients).

Table VI. Comparison of the distribution of tumor size, lymph node status, histological grade and stage in breast cancer patients in Libya, Nigeria and Finland.

Variable	Libya	Nigeria[a]	Finland[a]
Tumor size (cm)			
Diameter (SD)	4.8 (2.1)	4.8 (2.4)	2.6 (1.9)
Range	1.5-12.5	1.0-11.0	1.0-15.0
Lymph node involvement, n (%)			
Positive	173 (73.9)	235 (79.1)	97 (34.0)
Negative	61 (26.1)	62 (20.9)	188 (66.0)
Grade, n (%)			
1	11 (6.6)	44 (14.8)	67 (23.5)
2	104 (62.3)	119 (40.1)	173 (60.7)
3	52 (31.1)	137 (45.1)	45 (15.8)
Stage at presentation, n (%)			
1	12 (5.1)	65 (21.7)	95 (31.25)
2	103 (44.1)	75 (25.0)	171 (56.25)
3	86 (37.6)	97 (32.3)	19 (6.25)
4	33 (14.1)	63 (21.0)	19 (6.25)

[a]From Ikpatt *et al* (13). SD, standard deviation.

in stage 2B and 3A, and approximately 51% were classified in stages 3 and 4.

The large percentage of patients in advanced stages indicates delayed presentation and late diagnosis, as noted in the study by Ikpatt *et al* (13) on Nigerian breast cancer. Mammography was not performed in Nigeria, but has been performed in Libya, although not in screening programs. However, mammography has not been able to improve early diagnosis. The reason includes the difficulties involved in obtaining an early mammographic diagnosis in premenopausal breast cancer (26). The biological aggressiveness of the premenopausal type also appears to limit the value of early screening (27). These results are in agreement with other North African results. In Egypt, breast cancer is largely responsible for cancer-related deaths among females (8.2%), and the majority of tumors are advanced at presentation (2,4). In Tunisia, breast cancer is associated with poor survival due to late diagnosis (2,27). Approximately 55% of the breast cancer patients presenting at the Tunisian Oncology Institute of Salah Aziiz were found to be characterized by rapid disease progression, inflammation and edema (2,28).

Tumor size. In Libya, 15 (6.4%) patients had a tumor size smaller than 2 cm (T1). The average tumor size and tumor range in the Libyan patients were compared with the Nigerian and Finnish patients (Table VI). The Libyan and Nigerian data

Table VII. Histological type of breast cancer among Libyan, Nigerian and Finnish patients.

Histological type, n (%)	Libya	Nigeria[a]	Finland[a]
Ductal	191 (81.6)	252 (84.0)	244 (85.6)
Lobular	17 (7.3)	10 (3.3)	16 (5.6)
Medullary	11 (4.7)	8 (2.7)	2 (0.7)
Tubular	5 (2.1)	8 (2.7)	8 (2.7)
Mucinous	3 (1.3)	5 (1.7)	0 (0.0)
Mixed ductal/tubular	0 (0.0)	3 (1.0)	3 (1.1)
Mixed ductal/lobular	6 (2.6)	5 (1.7)	2 (0.7)
Apocrine carcinoma	1 (0.4)	2 (0.7)	0 (0.0)
Metaplastic carcinoma	0 (0.0)	3 (1.0)	0 (0.0)
Total	234 (100)	297 (100)	285 (100)

[a]From Ikpatt *et al* (13).

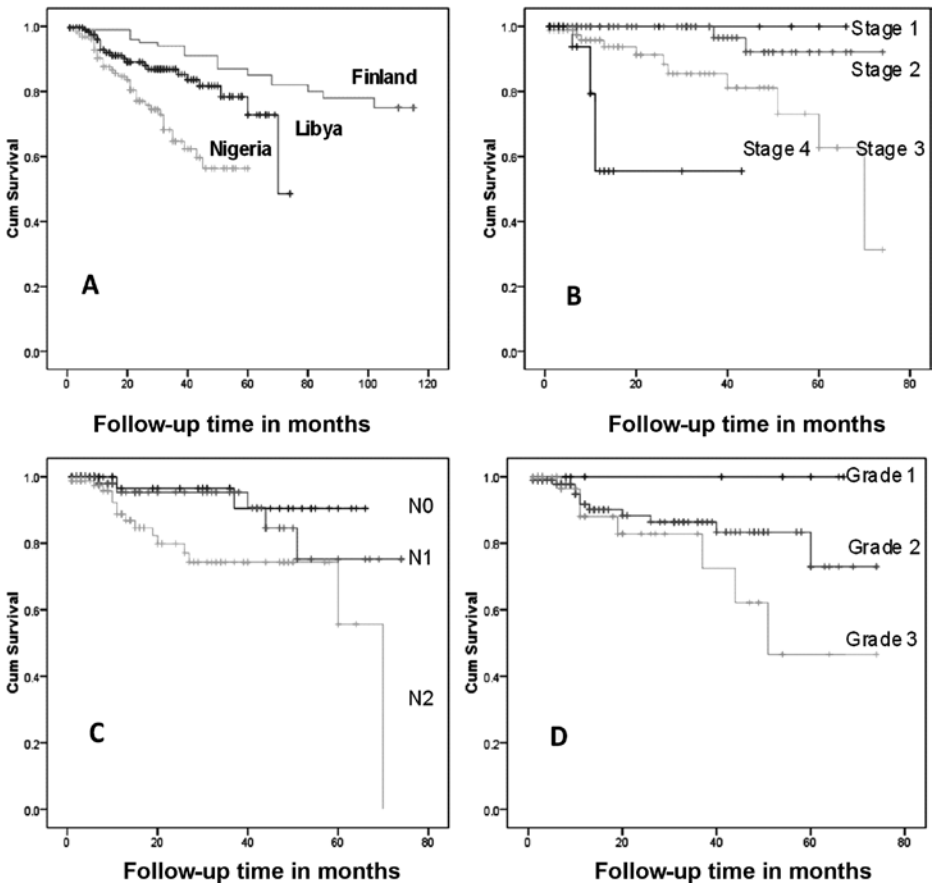

Figure 3. (A) Survival curves of breast cancer patients in Finland, Libya and Nigeria. A more favorable survival is noted in the Libyan patients as compared to the Nigerian patients, but a worse survival is noted when compared to Finnish patients (p<0.0001). (B) Survival curves of Libyan breast cancer patients in different clinical stages. The group of patients with stage 1 had the longest 5-year survival (p<0.0001). (C) Survival curves and lymph node status (N0, N1, N2). The group of patients without lymph node involvement shows a more favorable 5-year survival than the group with N1 and N2 status (p=0.002). (D) Survival and histological grade. G1 (n=11) patients show a more favorable survival than G2 and G3 patients (p=0.09, nearly significant) (167/234 grades available).

are similar, whereas the data from Finland suggest the efficacy of mammography in screening in that population. This suggests that initiation of mammographic screening in peri- and postmenopausal patients should be considered in patients from Libya (26).

Lymph node status and distant metastases. Most Libyan breast cancer patients had regional lymph node involvement at the time of surgery (Table VI); 21.8% (51 out of 234 patients) were in category N2. Distant metastases (to bone and liver) were present in 12.8% of our patients.

In the present study and that by Ikpatt *et al* (13), systemic and regional lymph node metastases were significantly more common in African patients than in Finnish ones (Table VI). This suggests a delay in diagnosis in developing countries and a lack or inefficacy of screening programs. However, the aggressiveness of biological features (such as the dominance of the premenopausal type) in African breast cancer should also be considered.

Histological type. The histological types of the breast cancer cases in Libya, Nigeria and Finland are shown in Table VII. In all three populations, the non-specific variety of invasive ductal carcinoma was the predominant type. Medullary carcinoma was more common in African populations than in European cases. Genetic factors may be involved; however, no evidence currently exists that breast cancer genes (BRCA1 and BRCA2) are more often involved in breast cancer cases in Africa (2).

Histological grade. Libyan and Nigerian patients had a higher tumor grade than Finnish ones (Table VI). Results in African patients are in concordance with those of African-American patients (5,10). One explanation for the grade differences may involve the more active proliferation in the premenopausal type of breast cancer, which is more common in Africa.

Survival. The African breast cancer cases were associated with a worse prognosis than the European breast cancer ones (Fig. 3). However, as regards tumor stage, lymph node involvement and large tumor size, African breast cancer acts in the same manner as the European breast cancer, as shown by the Libyan data (Fig. 3B-D) (29-31). Among Libyan patients the menopausal status, histological type of tumor, and patient age does not appear to affect survival.

A comparison of the survival curves of the patients of 3 countries (Fig. 3A) showed marked differences in survival. The survival curve of the Libyan patients was located between that of the Nigerian and Finnish survival curves.

In conclusion, breast cancer incidence varies considerably with high rates in Western countries, such as Finland, and low rates in African countries such as Libya and Nigeria. African patients are younger than European ones at presentation. The majority of breast cancer patients were found to be premenopausal and at advanced stage at presentation in Africa. African breast carcinoma cases were similar to European ones in terms of histopathologic parameters that are known to be associated with high risk, such as advanced stage, large-sized tumors, lymph node involvement and high grade. The histological predominant types were also similar in African and European breast carcinomas. However, medullary carcinoma was found to be more common in African patients. In Africa, premenopausal breast cancer is more common than postmenopausal breast cancer, while the opposite is the case for European patients.

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