

## Epidemiology of Breast Cancer in Young Women in the Southern part of the Mediterranean Area

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### Abstract

In Northern Africa, the high incidence of breast cancer among young women has been recognized as a particular epidemiologic feature within the region. However, a comprehensive epidemiological overview of the existing data is lacking. Within this present review we aim to: (i) assess the available and reliable epidemiologic data reported from institutional series and registries (ii) investigate the possible impact of demographic or genetic factors on epidemiology and (iii) describe the distinct risk factors and tumour biology of breast cancer in young women presenting in this region of the world.

The evolution of young breast cancer incidence around the Mediterranean area and particularly in the region of Northern Africa will be discussed, as well as its association to the existing demographic context. The issue of possible bias likely to influence the reported incidence rates, as obtained from the regional registries, will be elucidated. We will finally underline that interpretation of data coming from these registries should be cautious, as the concentration of resources within some metropolitan centres (or regions) may induce bias in terms of patients' reporting.

**Keywords:** Breast cancer, Young women, Cancer registry, Epidemiology, Mediterranean area.

### Introduction

Breast cancer is the most common cancer in women worldwide. In the Western world, one out of eight women will develop a breast cancer within her life course [1,2]. Breast cancer incidence increases with age and is more frequent after menopause. Hence, literature from industrialized countries depicts a variable incidence of breast cancers among women aged under 35 years of around 4% [3].

In Northern Africa and the Middle East, breast cancer is also the most common cancer affecting women. It represents between 14 and 42% of all cancer sites in women [4]. The age-standardised incidence rate (ASI) varies between 9.5 and 54 for 10<sup>5</sup> women, thus leading the WHO to consider breast cancer as a public health priority in this region of the world [5]. In addition, the high incidence of breast cancer among young women in this region has been questioned regarding the associated risk factors, as well as its demographic and genetic "particularities".

However, the following points can compromise the quality of evidence and thus the objectivity of the discussion:

From an epidemiological point of view, the data are not exhaustive, and subjected to potential biases according to the inequalities of resources for cancer care in this area.

In terms of risk factors, “the lifestyle westernisation” (occurring namely through a decrease in fertility and breast-feeding, an increase in age at first pregnancy, obesity etc.) hampers the interpretation of such differences.

From a biological and genetic point of view, no reliable evidence is available; however, it might be possible to build several hypotheses that deserve testing by evidence-based research.

In this manuscript, we will highlight the incidence of breast cancer among young women in the demographic context of the three North African countries at the southern part of the Mediterranean area, as well as the different criteria likely to influence the quality of data obtained from existing registries and descriptive studies of the region. We will further discuss the potential impact of genetic predisposition for breast cancer in young women within this area of the world.

## Methodology

The available literature on young breast cancer in Northern Africa has been collected by a systematic search through the MEDLINE database and PubMed (from January 1980 to September 2010) by using keywords, such as “breast cancer, young women, northern Africa, southern Mediterranean area, Morocco, Tunisia, Algeria”. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. Furthermore, authors that seemed to have contributed in the field, as well as citations of important papers, have been further searched and studied. In addition, all registry data from institutional structures and universities or regions have been collected through the Association of Radiotherapy and oncology in the Mediterranean Area (AROME) network comprised of regional leaders and local epidemiologists who provided their national data.

## Results

### Demographic Evolution in Northern Africa

The Algerian population has been growing more quickly than that of Tunisia or Morocco. The Algerian population comprised 35 million inhabitants in 2008 versus 31 millions in Morocco, and 10 millions in Tunisia in 2004. The demographic increase rates of the three above-mentioned countries show an almost identical evolution over a century. For example, in Morocco the population that amounted to 5 million in 1900, experienced a fast growth during the 20<sup>th</sup> century, thus amounting to an increase of more than 3% per year in the 50's. This rate fell to 1.4% in 2004 and then to 1.1% in 2007 (given that this growth rate is equivalent to the global average) [6]. This slowdown corresponds to a very quick decrease of the fertility rate, reduced from 7 children per woman in around 1970 to 2.5 by the 2000's.

In Algeria, the first demographic study in 1970 showed that fertility was over 8 children per woman. In another study published in 1995, on a representative sample of 6000 Algerians, it was shown that the aforesaid fertility rate was then divided by

three, i.e. over a twenty-five year period. In Tunisia, the fertility index was estimated at 2.2 in 1999. Various factors, such as the polygamy ban, the development of contraception, the education of girls, have contributed to the decrease of the fertility rate of women in the area. The key factor of the fertility decrease was however the growth of the average age of women at marriage: i.e. while women used to be younger than twenty years of age at marriage in 1960 in the three countries, this figure went up to over 28 years of age in 2000 [6].

Consequently, the population pyramids of the three aforementioned countries of Northern Africa are disrupted as is the case in the majority of the western countries. Unlike the European Union, where currently the most populated five-year group is that of the 35-39 year olds, in Northern Africa it is the 15-19 year olds [7].

Fertility is not the only criterion of the population pyramid. Life expectancy has increased by almost twenty years between 1975 and 1995. Infant mortality, very high in 1970, considerably declined to 5.5% in Algeria, 5.3% in Morocco and 2.8% in Tunisia in 1996, thus obviously largely contributing to the upheaval of this population pyramid. In 2004, 64% of the Tunisian population was aged between 15 and 59 years old [6].

### Evolution of the Incidence of Breast Cancer in Northern Africa

**Inventory of Registries:** The IACR published “**Cancer incidence in developing countries**” and “**Cancer in Africa**” as well as some monographs as per country in 2003 [8]. Among more than 400 worldwide registries, a small number of registries have been validated in Africa during the last 25 years:

3 registers validated in 1979

11 registers validated in 1986

26 registers validated in 1996

47 registers validated in 2006

With regard to the recording of cancer sites, one notes that Africa is the continent that is least covered by population registries (11% of the population) [8-11].

In Algeria, the first registries of Algiers, Sétif and Oran were created in the 80's. In 2008, the cancer registries covered a population of more than 12 million inhabitants out of the 35 million people in the country. Historically, the first population registry, set up in 1985, was that of Algiers, yet it only recorded digestive cancers before spreading to other cancer sites later in 1992 [12]. It was extended to all cancer sites as from 1993. The cancer registries of Sétif and of Oran were set up in 1987 and 1995 respectively [13,14]. Only these first registries were validated by the IACR, while validation of 11 other population registries is under way [14].

In Tunisia, 3 registries, namely those of the Northern, Central and Southern have been operational since 1987. The data of these

3 registries were published in "Cancer in Africa" in 2003 [8]. The number of cancers rose to 4080 cancers for the period 1993-2001 for the Northern registry, 4042 cancers for the period 1995-1998 for the Centre Registry and 2533 cancers for the period 1997-1999 for the Southern Registry.

In Morocco, there exist 2 cancer registries in Casablanca and Rabat. The first cancer registry of Grand Casablanca was created in 2004. The first edition was published in 2007 with the support of the Lalla SALMA association which also supported the publication of the second edition of the cancer registry of the Grand Casablanca region in 2011, grouping the data recorded between 2005 and 2007 [15]. The second registry, of the city of Rabat, collects the reported incidence of cancer cases diagnosed in 2005 and was published in 2009.

### **Epidemiology of Breast Cancer in Northern Africa**

**Data from registries in Algeria:** Most of the existing cancer registries only include a descriptive evaluation of the epidemiology of breast cancer, except for the Sétif Registry, through its participation in the CONCORD study with 300 cases [16]. The establishment of regional registries in Algeria enabled an almost realistic estimation of the global cancer incidence in the country. Its steady increase over the past decades is real, going up from a global incidence of 100/10<sup>5</sup> inhabitants, to 120/10<sup>5</sup> inhabitants in 20 years [14]. Among women, breast cancer is the first cancer in terms of incidence in the 3 main Algerian registries. Its ASI is of 21.6, 17.03 and 34.49/10<sup>5</sup> women for the 3 registries of Algiers, Sétif and Oran respectively. The ASI of breast cancer is marked by a variation between 1986 and 2005 from 10.4 for the period 1986-1989, to 17 for the period 1993-1997, and to 14.2/10<sup>5</sup> women for the period 2001-2005 [11]. In a recent update of the data of the Sétif Registry between 2000 and 2008, the crude number of breast cancers (including all ages) was 623 with a gross incidence rate and an ASI of 9.5 and 12.2/10<sup>5</sup> women respectively. The higher incidence was observed among the women of the 50-54 year age group, namely with a rate of 40.1/10<sup>5</sup> women, while the ASI among the women aged less than 40 years old was 24.6/10<sup>5</sup> women, the total number of breast cancers being 173 [11]. The data of the Oran Registry of 2006 showed an incidence of 44.2% for breast cancer with an ASI of 34.7/10<sup>5</sup> women. Again, among the population of young women aged less than 40 years, the ASI obtained from the 2 other Algerian registries were 28.3 for Algiers and 24.1/10<sup>5</sup> women for Oran respectively [17,18].

**Data from registries in Morocco:** Out of the 3336 cases of recorded cancers in the Casablanca Registry (2004), 662 new cases were breast cancers (36% of all women's cancers), representing an incidence of 35/10<sup>5</sup> women. The rate of breast cancers among women aged less than 40 years, as compared to the whole, was 22% [15].

In the Rabat Registry, a total number of 763 cases of invasive cancers was recorded during the year 2005. The total number

of new breast cancer cases was 130, corresponding to an ASI of 20.5/10<sup>5</sup> women. The median age at diagnosis was 48 years. The rate of breast cancers among young women aged less than 35 years was 7% of all cases.

In a retrospective series of 3757 cases of breast cancer treated between January 2003 and December 2007 at the National Institute of Oncology in Rabat, 427 were found in women aged less than 35 years, which represents 8.8% of all breast cancers [19].

**Data from registries in Tunisia:** Breast cancer is also the most common type of cancer among Tunisian women, representing 30% of malignant tumours in women, with 2000 new cases annually. Hence its incidence, which used to be around 17/10<sup>5</sup> women, is currently around 30/10<sup>5</sup> women according to the registry data of the Northern, Central and Southern Tunisia. The median age at diagnosis is around 50 years, i.e. 10 years younger compared to Western series and about 10% of the patients are aged less than 35 years [20-22].

In the Northern Registry (Sousse), the number of cancers was 4080 between 1993 and 2001, with a global incidence of 115 and 83/10<sup>5</sup> inhabitants in men and women, respectively. Breast cancer was the most common one in women with 27.8% and an ASI of 28/10<sup>5</sup> women. Among women aged 30-34 years the ASI was 21.7/10<sup>5</sup> women [23,24]. In the Central Registry (Tunis), the number of cancers between 1995 and 1998 was 4042, with a global incidence of 103 and 78/10<sup>5</sup> inhabitants in men and women, respectively. Breast cancer was the most frequent one, representing 30% of the cases with an ASI of 25.3/10<sup>5</sup> women. The incidence among women aged less than 35 years was of 11%. In the Southern Registry (Sfax), the number of cancers was 2533 between 1997 and 1999, with a global incidence of 108 and 79/10<sup>5</sup> inhabitants in men and women, respectively. From 2000 to 2002 the number of recorded cancers was 2713, with a global incidence of 119 and 81/10<sup>5</sup> inhabitants in men and women, respectively. Breast cancer was the most frequent one among women (30% of the cases) with an incidence of 28/10<sup>5</sup> women, an average age of 52 years and affecting women of less than 35 years old in 7.4% of the cases [25].

As in the other countries of Maghreb, the retrospective series published in Tunisia show an incidence of 8 to 12% of breast cancers among women aged less than 35 years, with an incidence rising between 16 and 27 and an ASI of 28.5/10<sup>5</sup> women (Table 1).

## **Discussion**

### **Epidemiological data and breast cancer profiles**

Breast cancer is the most common cancer occurring in women of the Northern African female population. Its ASI rate varies between 9.5 and 54 per 10<sup>5</sup> women. In Northern Africa, the data of the regional registries of Algeria, Morocco and Tunisia show that breast cancer is the most common cancer in women representing ¼ of all cancers [9,10,27,28]. The standardised incidence of breast cancer in Algeria is between 18.8 and 60.5/10<sup>5</sup>

**Table 1:** Retrospective series of young breast cancer in Tunisia

Author (reference)	Year	N	Median age < 35y (%)	OI	ASI
Maalej et al. [37]	1994	689	50	8	16.7
Maalej et al. [21]	2004	1437	51	10.2	27.1 28.5
Ben Ahmed et al. [42]	1990-8	729	50	-	-

N: Number of cases; OI: Overall incidence; ASI: Adjusted standardized incidence /10<sup>5</sup>women

women according to the local registry examined, while in Tunisia it comes to an average of 29/10<sup>5</sup> women and in Morocco one of 35/10<sup>5</sup> women (see Table 2). The extreme rates observed among the young women of the Maghreb aged less than 35 or 40 years are of 7% and 22%. In the Libyan Registry of Benghazi, breast cancer represents 25% of the women's cancers with an age at diagnosis that is largely inferior to that of European women [27,28]. However, all these values have to be interpreted with caution, as the disparities of resources between regions in the same country may highly influence reporting of new cases and thus false the epidemiology profile which is not representative of the whole considered territory.

El Saghier et al. [4] have recently reviewed all of the series published between 1990 and 2000 in Arabic countries and have noted that the standardised incidence by age was between 9.5 and 46.7/10<sup>5</sup> women depending on the particular country in the Middle East and in Northern Africa. They also observed that the median age at presentation in the majority of these countries was 50 years. These data correlate with those retrieved from another paper published by Najjar and Easson in 2010, containing 28 articles devoted to breast cancer in the Arabic world, i.e. Saudi Arabia, Bahrain, Qatar, Kuwait, Emirates, Oman, Yemen, Iraq, Syria, Jordan, Lebanon, Egypt, Libya, Algeria, Tunisia, Morocco, and Sudan. According to this particular report, at the time of diagnosis, the median age was 45.4 years and 2/3 (65.5%) of the patients were aged less than 50 years [29].

Studies carried out more specifically in Northern African countries show corroborating figures. In the Tunisian series, the reported incidences fluctuate between 16 and 27% with an ASI of 28/10<sup>5</sup> women. This standardised incidence has risen from 16.7/10<sup>5</sup> women in 1994 to 28.5/10<sup>5</sup> women in 2004 while the cancer rate among women aged less than 35 years is estimated at 10% [21]. The latter is very close to the rate found in an Algerian series of more than 7000 patients treated between 1995 and 2007 in the Pierre- Marie Curie Centre of Algiers. The authors reported a breast cancer rate of 12% among the patients aged less than 35 years out of whom ¾ were aged between 30 and 35 years

[30]. In Morocco, the data of the Casablanca and Rabat Registries put the incidence standardised to age at 35/10<sup>5</sup> women, with a cancer rate of 7% among the women aged less than 35 years in the Rabat Registry and 22% in the Casablanca Registry [15,31]. The differences in incidences between one region and another, as one can observe in the registries data (Moroccan or Algerian) or in the series published in Northern Africa, can be explained (at least partly) by the overestimations linked to the treatment of a very large number of patients in the regions bearing a high level of available means in terms of patient care (i.e. regions like Algiers, Oran, Constantine) contrasting with an underestimation of the incidence in the regions deprived from treatment centres at the time of the recording (e.g. Sétif).

Epidemiological data reported in Algeria, Tunisia and Morocco come from a limited number of regional registries. Such data is inter-comparable (i.e. among the three aforesaid countries) and refer to well-defined geographic zones. They are therefore not issued from generalised data recording, the quality of which is often poor. Standardised incidences of Northern Africa are currently much more homogeneous than in the past. For example, current figures are much lower in comparison to the former data reported from the Tunisian registries [32,33] and that of Algiers [34] in the 90's. Such incidences are also lower than the figures of other Western registries: French (91.9/10<sup>5</sup> women), Spain (45.8/10<sup>5</sup> women), Denmark or Sweden [7,35]. Moreover, whatever the age groups considered between 20 and 44 years old, the incidence observed in the registries of Northern Africa is 2 to 7 times larger than those of the SEER database (see Table 3). A recent publication has reported data from Egypt, coming from the Egyptian National Cancer Institute. Out of 5408 cases reported 554 were young (<35 years of age) and 45.9% of the patients presented with stage III disease, with a median disease-free survival (DFS) of 60 months [36].

The value of existing cancer registries has been reviewed by Bray and Parkin in 2009 [37]. These authors define *comparability*, *validity* and *timeliness* of cancer registry data in order to provide a means of evaluation of their quality. *Comparability* is defined as a

**Table 2:** Registries data from North Africa countries

Registries	Rabat	Casablanca	Setif	Algiers	Tunis	Sousse	Sfax	Benghazi	Gharbiah	Europe
References	[31]	[15]	[11]	[17]	[23]	[24]	[25]	[27]	[50]	[9,10,26]
Country	Morocco	Morocco	Algeria	Algeria	Tunisia	Tunisia	Tunisia	Libya	Egypt	Europe
Incidence(standardized /age/10 <sup>5</sup> h)	35.8	35.0	18.8	60.5	29.6	29.8	28.0	23.3	42.5	71.5

**Table3:** Incidence by age ranges: comparison between North of Tunisia registry (NTR) and SEER database by Ben Abdallah et al. [22]

Age (Y)	NTR	SEER
20-24	1,7	7,7
25-29	4,8	23,3
30-34	21,8	55,2
35-40	37,2	113,3
40-44	69,8	

comprehensive review of registration routines. *Validity* is defined as the possibility to perform meaningful comparisons with other registries or the same registry over time and is characterized by numerical indices. *Timeliness* remains a less defined feature lacking guidelines. The presented data have not been previously evaluated for these indicators and globally it can be argued that they dispose of limited *comparability*, while their validity remains to be calculated. They dispose of *timeliness*, although as argued in this review all of the three quality features need improvement.

It is likely that the progressive modification of epidemiology and profiles of breast cancer during the next fifteen years will concern the whole of the emerging countries of the Middle East and Northern Africa. The establishment of many screening programs, the “westernisation” of the emerging countries, the modification of eating habits (associated with an increase in obesity and with a lack of physical activity), the increase of life expectancy, the increase in the frequency of late first pregnancies after 30 years of age, the decrease of fertility, and reduced breast-feeding periods are some of the known parameters which could disrupt these data [14].

Compared to Europe and North America, the median age of breast cancer incidence is lower by 12 years on average (i.e. between 48 and 51 *versus* between 61 and 63 years) among the women of the Maghreb. The rate of breast cancer among women aged less than 35 years is between 8 and 12% [21,38]. Besides the population pyramid, the hormonal exposure, the nutritional context, physical activity and other factors are regularly quoted to explain these differences. In Tunisia for example, unlike the data published in 1994 [39] that showed two peaks of incidence for the 45-49 and 60-64 years old age groups, the 2004 data indicated a continuous increase of the incidence between 40 and 55 years old. The epidemiological differences could be explained by the environmental context, the nutritional habits, genetics or other factors such as the increase of age at first pregnancy after 30 years old (12.9% in 1994 against 18.9% in 2004) and of non-parity (14.3% in 1994 against 16.5% in 2004) [21]. All these socio-cultural evolutions will probably induce a cohort or generation effect, as has been shown in studies conducted in Sweden and Hong Kong. According to the Tunisian data [22], one notes a gap between the distribution curves according to age, in comparison to the registries of Bas-Rhin (France), Granada (Spain) and Vila Nova de Gaia (Portugal), which clearly diminished, especially between Tunisian and Portuguese women. This is probably

explained by a generation effect due to the rise in the socio-economic level in Tunisia. According to the authors, the high incidence in women aged less than 35 years is not accounted for by the demographic curves, but rather by the weak incidence of breast cancer in Tunisia, in the age groups over 50 years [22].

Besides the classical forms of breast cancer, age is equally found as a determining factor in cases of inflammatory breast cancer (IBC). The average age of incidence of IBC among Tunisian women is 43 years old, i.e. inferior by 12 years to the data of the 1988-2000 SEER study. Moreover, in Tunisia there is a comparatively high proportion (10%) of young women aged less than 35 years suffering from IBC [40,41].

#### Biology of Young Women Breast Cancer in Northern Africa

Comparatively to Europe and Northern America, the stage and the tumour size at diagnosis of breast cancers in the Maghreb are largely more advanced. Moreover, the pathological profile of breast cancers seems linked to the patients' age. In the Chalabi et al study based on data collected between 2002 and 2007, the Tunisian, Lebanese and Moroccan patients were 10 years younger than the Western patients and suffered more frequently from tumours of luminal B type with more aggressive characteristics: a higher SBR grade and a more important nodal invasion rate. In addition, in this population of the south shore, the common expression of 16 different genes of interest such as MMP9, VEGF, PHB1, BRCA1, TFAP2C, GJA1 and TFF1 [42] was observed.

The Algerian non-BRCA1 tumours are also more frequently of higher grade, non-hormone-sensitive and with a more important nodal damage than the French tumours [43]. The frequency of the tumours of grade II and III in the African populations is high, namely between 65 and 86%. This is perfectly well correlated to the HR status and to the frequency of nodal invasion [44,45]. Obviously, the small proportion of low grade cancers, in comparison to the high grade in these young populations, could be explained by a specific oncogenesis and tumour biology through different pathways, even if the hypothesis of transformation of the low grade tumours into high grade ones during a long delay at diagnosis has long been accepted [46]. Specificities regarding the high grade and the tumour non-hormone-sensitivity, associated with a frequent locally advanced or immediate metastatic presentation, are found among the patients aged less than 35 years in other Mediterranean countries, where age itself is equally considered as an independent factor of

survival [47,48].

### Genetic Predisposition of Breast Cancer in Young Women in Northern Africa

The BRCA1 mutation is responsible for a significant proportion of hereditary breast and ovarian cancers [49]. In the Western populations this mutation confers a risk of 80% to develop a breast cancer in the course of life, with on average 40% of the carriers of the mutated gene who will develop a breast cancer by the age of 50 [50]. Nevertheless, this risk could be modified by environmental factors, life style, the history of reproduction and nutrition. In fact, it has been shown that the carriers of the mutation born after 1940, had a risk to develop a breast cancer largely higher than those born before 1940 [51].

The epidemiologic data of incidence of breast cancer in Northern Africa and the high rates among young women aged less than 35-40 years strongly suggest the contribution of genetic parameters such as the mutation of BRCA1. A quantitative and sequential analysis study of the BRCA1 gene among familial and sporadic cases in Algiers revealed a remarkable frequency of 9.8% of the BRCA1 mutation, observed in the young sporadic cases, against 36.4% in the Algerian family cancer cases (there again against 10.3% in the French family cases of breast and ovarian cancer). This study also showed that the Algerian non-BRCA1 tumours were of significantly higher grade and appeared at a younger age than the French non-BRCA1 tumours [43]. Altogether, this work concluded that the higher frequency of the BRCA1 mutation among the cases of breast cancer in young Algerian women, compared to the European women, could reflect (at least partly) the strong contribution of genetics, revealed within the context of the weak incidence of breast cancer. In another Mediterranean study from Israel, including 60% of patients of Ashkenazi origin, even if the numbers are too limited to draw final conclusions, the BRCA1/2 mutation rate was more frequent in the subgroup of very young patients (i.e. aged less than 35 years old) [47]. The same finding has been confirmed in a recent Algerian study [52].

### Conclusion

Breast cancer is the most common cancer in women from Northern Africa and in Middle East. The incidence is 2 to 3 times lower in comparison to the Western countries. The 3 Northern African countries of Algeria, Tunisia and Morocco have access to regional registries of good quality validated by the IACR. There is, in these registries, a certain disparity of the figures that can be linked to the heterogeneity in terms of availability of reference centres for care of the cancer patient at the regional level.

In addition to the epidemiological characteristics, the tumour profiles observed generally, but also among young patients, are different compared to the Western countries with: more cancers discovered at a late stage, more nodal invasion, more high stages and less hormone-sensitive lesions. The BRCA1 mutation is also more frequently reported, yet this strong contribution of genetics must be considered in the context of the weak incidence of

breast cancer in comparison to the Western world. It is possible that the next fifteen years will be marked by a total upheaval of epidemiology and tumour profiles due to the development of screening methods, a social and cultural “westernisation” evolution of the lifestyle habits and the improvement of life expectancy in this particular region of the world.

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