

RESEARCH ARTICLE

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Clinicopathological Features and Trends in the Incidence of Female Breast Cancer : Results of the Northern Tunisia Cancer Registry (1994–2018)

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Abstract

Introduction: Breast cancer (BC) is the most common cancer in women worldwide and in Tunisia. The objective of this study was to (1) describe the epidemiological characteristics of BC from the Northern Tunisia Cancer Registry (NTCR) in 2018, and (2) analyze trends in the incidence of BC over the period 1994–2018. **Methods:** This was a population-based retrospective study using data from the Northern Tunisia Cancer Registry (NTCR). During the period 1994–2018, a total of 21,673 primary female BC cases were analysed. The NTCR collected, actively and retrospectively, data from all sources of cancer-related care in both public and private healthcare sectors across the Northern Tunisia region. This region encompasses 2,813,900 females. Crude and standardized incidence rates were calculated. Incidence trend analysis was performed using Joinpoint software, version 6.0.1. **Results:** The results of this study showed a significant increase in the incidence of BC in northern Tunisia from 30.0/100,000 in 1994 to 52.4/100,000 in 2018, with an Average Annual Percentage Change (AAPC) of 2.7%; 95% confidence interval (CI) [1.8; 3.6]; $p < 0.05$. The trend in BC incidence across age groups in women showed a significantly increasing trend for the 55–74-year age groups. The proportion of localized BC increased from 28.3% in 1994 to 46.5% in 2018, with an AAPC of 2%; 95% CI [1.4; 2.7]; $p < 0.001$. On the other hand, the trend in the proportion of cases with distant-stage disease showed a downward trend from 17.8% to 14.6%; 95% CI [-1.6; 0.1]; $p = 0.06$. The trend in the mean tumor size of BC during the period 1994–2018 showed a significantly downward trend, from 3.5 cm in 1994 to 2.6 cm in 2018, with an AAPC of -1.57; 95% CI [-2.0; -1.2]; $p < 0.001$. The morphological verification percentage was 97.2%. **Conclusion:** The results of this study suggest the need to strengthen the current strategy for early diagnosis of BC and to improve care with equitable access for all Tunisian women.

Keywords: Breast cancer, Epidemiology, trend, Incidence, Tunisia

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Introduction

Breast cancer (BC) represents the most frequently diagnosed malignancy among women worldwide [1-3]. In 2022, approximately 2.3 million new cases were reported globally, accounting for 11.6% of all newly diagnosed cancers in both sexes [2]. Incidence rates of BC are highest in high-income regions, particularly North America and Europe, where a stabilization or decline has been observed in recent years with a marked decline in mortality rate of BC [3, 4]. In contrast, although incidence rates remain comparatively lower in less developed regions, a sustained upward trend has been documented [5, 6]. BC ranks as the fourth leading cause of cancer-related

mortality worldwide, with an estimated 670,000 deaths in 2022, corresponding to 6.9% of all cancer deaths [4]. Mortality rates are disproportionately higher in low and middle-income countries, particularly in Sub-Saharan Africa and North Africa, largely due to delayed diagnosis, the absence of organized screening programs, and limited access to timely and appropriate treatment modalities [7]. To reduce global disparities, the World Health Organization (WHO) launched the Global Breast Cancer Initiative (GBCI) in 2021. This initiative is based on three fundamental pillars: health promotion and awareness, early diagnosis, and effective and equitable treatment [8]. Tunisia was one of the countries that adhered to the GBCI.

As for the surveillance, Cancer registries are a

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valuable tool for identifying and monitoring trends, gaps, disparities, and barriers related to cancer, for developing, guiding and evaluating comprehensive national cancer prevention and control planning [6, 9]. Cancer surveillance in Tunisia relies on three regional cancer registries (North, Central, and South) that have ensured continuous data collection since 1997 [10, 11]. According to the National Institute of Statistics the northern Tunisia region covers around the half of the Tunisian population a population of 5,700,008 habitants with 2,813,900 female [12].

In Tunisia, epidemiological data on BC remain limited by their retrospective and single-center design with relatively short study periods. This gap hinders an accurate assessment of the current epidemiological profile of BC and limits the evaluation of the existing cancer control strategy. Therefore, this population-based registry study was conducted to provide a more updated epidemiological overview and to generate evidence that may support the optimization of BC control strategies in Tunisia.

The aim of this study was to (1) describe the clinicopathological characteristics of BC cases diagnosed in Northern Tunisia in 2018 and (2) analyze temporal trends in BC incidence between 1994 and 2018

Materials and Methods

Study design

This was a population-based retrospective descriptive study conducted at the Department of Epidemiology of the Salah Azaiez Institute of cancer (SAI). It included all BC cases diagnosed between 1994 and 2018 and recorded in the Northern Tunisia Cancer Registry (NTCR) database. The NTCR is an ongoing registry assuring a continuous surveillance since 1997. Northern Tunisia covers an area of 28,299 km², representing approximately one-fifth of the national territory. The region comprises 11 governorates, grouped into three sub-regions: Greater Tunis (Tunis, Ariana, Ben Arous, Manouba), the northeast (Zaghouan, Bizerte, Nabeul), and the northwest (Béja, Kef, Jendouba, Siliana). According to the National Institute of Statistics (INS, 2020) [13], the northern Tunisia region has a population of 5,700,008 inhabitants and 2,813,900 female, representing nearly 50% of the total Tunisian population. The population pyramid in northern Tunisia in 2018 was described in Figure 1.

Study Population

All cases primary BC registered in the NTCR between 1994 and 2018 were included in this study.

Inclusion Criteria

Female patients diagnosed with primary BC including in situ carcinomas.

Non-Inclusion Criteria

BC in males

Recurrent and metastatic BC were not included.

Exclusion Criteria

Records with incomplete or unusable information were excluded from the analysis.

Data collection

Procedure of data collection

The NTCR employs an active data collection methodology [9, 13]. Cancer registrars retrospectively visited all sources of cancer-related care across northern Tunisia, encompassing both public and private healthcare sectors. These registrars were medical doctors who have received specific training in cancer data collection in accordance with IARC recommendations [13]. Cancer registration procedures, coding, and standardization methods were based on established international guidelines and well-recognized methodological references.

Data were systematically abstracted from patients' medical and histopathological records and recorded using standardized data collection forms. Data entry was performed using EpiData software, and datasets were stored in REC and CSV formats. The Department of Epidemiology at the SAI was responsible for data entry, verification, regular duplicate searches, correction of errors and incompatibilities, coding, and data analysis, in full compliance with IARC guidelines, while ensuring strict confidentiality of all patient information.

Data collection form

The collected data included patient demographic characteristics (age, sex, origin) and tumor-related variables (anatomical site, histological type, histological grade, and disease extension). Certain variables are mandatory, including patient identification details (date and place of birth, full residential address at the time of diagnosis), date of incidence, and the most valid basis of diagnosis (histological confirmation, clinical diagnosis, etc.), tumor topography, tumor morphology, tumor behavior, and sources of information. Concerning histological type, histological classification was based WHO classification of breast tumors. "Invasive carcinoma NOS" refers to BC cases not otherspecified. "othercarcinomas" includemucinous, medullary, tubular, and other rare histologicalsubtypes.

Data quality

To assess completeness of case ascertainment, we calculated the average number of reporting sources per case and the Morphological verification percentage (MV%). As for data validity, the missing case rates for the mandatory variables were calculated for sex variable ,

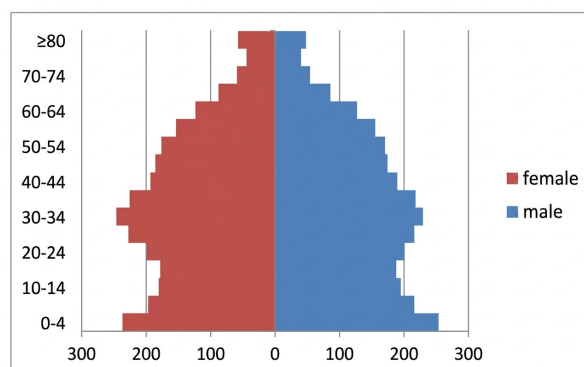


Figure 1. Age Pyramid of the Northern Tunisia Region in 2018

age, primary tumor site and unknown place of residence. In Tunisia, data relating to causes of death are not yet exhaustive, the mortality/incidence ratio could not be calculated.

Tumor Coding

Tumor coding was performed using the International Classification of Diseases for Oncology, for the recording of tumor topography and morphology. According to this classification, BC is coded as "174" or "C50" depending on the version [14].

Data cleaning of the data base

Research for duplicates

Systematic duplicate case ascertainment was conducted both at the time of data entry and at regular intervals thereafter. In the absence of a unique personal identifier in Tunisia, multiple complementary strategies are used to minimize duplicate registrations. These include regular duplicate searches using a matching algorithm that compares key variables such as patient name, sex, date of birth, address, year of incidence, social security number, histology number, and tumor characteristics [9].

Research of errors and incompatibilities

Routine checks for errors and logical incompatibilities specifically age/topography, topography/histology, and age/topography/histology inconsistencies are conducted in accordance with IARC recommendations [9, 13].

Statistical Analysis

Data entry was performed using EpiData software version 2.1b. Statistical analyses were conducted using Microsoft Excel and SPSS software, version 26. Categorical variables were summarized as percentages, whereas quantitative variables were described using means and standard deviations. Some quantitative variables were categorized into predefined groups: the age was divided into 11 categories of five years: [20-29], [30-39], [40-44], [45-49], [50-54], [55-59], [60-64], [65-69], [70-74], [75-79] and ≥ 80 years old and the tumor size was classified into five categories < 1 cm, [1-2 cm[, [2-3 cm[, [3-5 cm[and ≥ 5 cm.

Incidence rates calculations

Incidence rates were calculated as the number of new BC cases occurring during a defined period divided by the corresponding population at risk, expressed in person-years. Population denominators stratified by age group and region were obtained from the National Institute of Statistics for the period 1994–2018.

Crude incidence rates (CIR) were calculated as follow:

$$CIR = \frac{\text{Number of new cases during the period 1994 – 2018}}{\text{number of the population at risk (northern Tunisia region) during the period 1994 – 2018}}$$

The CIR was expressed in terms of person-years.

Age-specific incidence rates (SIR) and age standardized incidence rates (ASIR) were also calculated.

SIR were first calculated for each age group using the following formula:

$$SIR = \frac{\text{Number of new cases in age group } i}{\text{population in age group } i} * 100\,000$$

ASIR were then calculated using the direct standardization method [13], by applying the age-specific rates of the study population to the World Health Organization (WHO) standard population. This method removes the effect of differences in age structure, allowing valid comparisons across populations [15, 16].

$$ASIR = \sum_{i=1}^n (SIR_i \times \text{proportion of age group } i \text{ in the reference population } w_i)$$

where:

n: represents the total number of age groups (corresponding to 11 age groups)

SIR_i: represents the age-specific incidence rate in age group i

w_i: represents the proportion (weight) of age group i in the WHO standard population.

Trend analysis of incidence rates

Trend analysis was performed through joinpoint software [17]. The joinpoint program identifies the simplest model that best fits the observed data by detecting points in time ("joinpoints") where significant changes in trends occur. The minimum and maximum number of joinpoints were set priori at 0 and 3, respectively. Incidence rates were log-transformed prior to analysis to stabilize variance. A constant variance (homoscedasticity) model with uncorrelated errors was assumed. Model selection was based on the Weighted Bayesian Information Criterion (WBIC), which favors a balance between goodness-of-fit and model parsimony. In cases where no meaningful improvement in model fit was observed with additional joinpoints, the most parsimonious model (including zero joinpoints when appropriate) was retained. Trends were expressed as Annual Percent Change (APC) for each segment and Average Annual Percent Change (AAPC) over the entire study period, along with their corresponding 95% confidence intervals. Statistical significance was defined at a two-sided alpha level of 0.05.

Ethical considerations

Confidentiality of patients' personal information was strictly maintained throughout data collection, data entry, and analysis. The cancer registry in Tunisia operates under a specific legal framework established by decree n°2008-846 of March 24, 2008. Furthermore, the Northern Tunisia Cancer Registry (NTCR) received formal authorization from the National Authority for Personal Data Protection on April 27, 2017.

Results

Clinico-pathological features of breast cancer cases in Northern Tunisia in 2018

In 2018, a total of 1688 female BC cases were recorded. The CIR and the ASIR were respectively of 60.0 and 52.4 per 100,000 women per year. The mean age at diagnosis

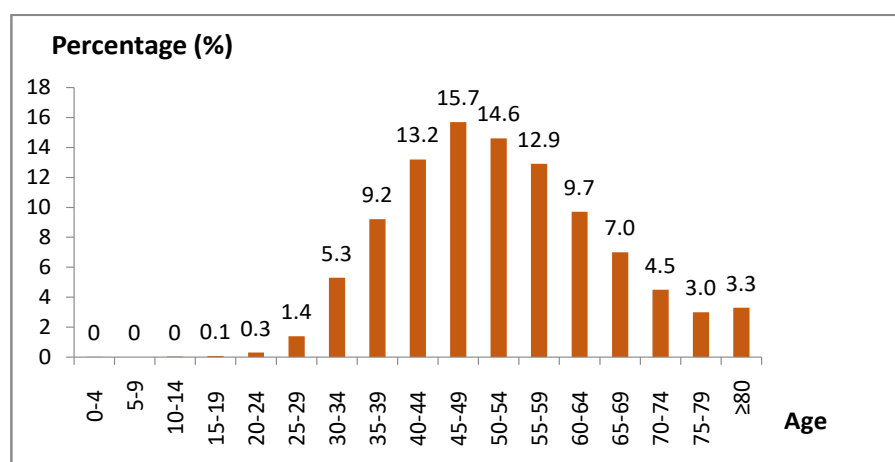


Figure 2. Proportional Repartition of Breast Cancer Cases by Age Group in Northern Tunisia in 2018

was 52.5 ± 13.3 years. More than half of all cases ($n=895$, 53.0%) occurred in women aged 50 years or older, 172 women (7.5%) were under 35 years and 279 (16.5%) were under 40 years (Figure 2). BC was diagnosed at a localized stage in approximately 785 cases (46.5%), at a metastatic stage in 246 cases (14.6%), and at an in situ stage in 88 cases (5.2%). Concerning histological type, invasive ductal carcinoma (IDC) was the predominant histological type, accounting for 1382 BC cases (81.9%). The mean tumor size of BC was $26 \text{ mm} \pm 20.4$ in 2018. The proportional distribution by tumor size showed that 375 BC cases (22.2%) measured between 2 and 3 cm, more than the quarter ranged from 10 to 20 mm ($n=447$, 26.5%), and 371 cases (22%) were between 3 and 5 cm. Left breast involvement accounted for 802 cases (47.5%), and bilateral involvement at diagnosis in 32 cases (1.9%). Tumor differentiation was moderate (grade 2) in 869 cases (51.5%), poorly differentiated (grade 3) in 562 cases (33.3%) (Table 1).

Trends in breast cancer incidence in Northern Tunisia during the period 1994–2018

The ASIR of BC in Northern Tunisia demonstrated a significant increase, from 30.0 per 100,000 in 1994 to 52.4 per 100,000 in 2018, corresponding to an average annual percent change (AAPC) of 2.7% ($p < 0.05$) (Table 2). Trends analysis has also shown that the increase in incidence was less important during 2002–2018 (APC = 2.1) than 1994–2001 (APC = 4.1) with a significant joinpoint ($p < 0.05$) (Figure 3).

Trends in female breast cancer incidence by age group

Analysis by age group indicated a significant upward trend among women aged 55–74 years. In contrast, incidence trends for women aged 20–54 years remained stable (Table 3, Figure 4).

Trends in the proportion of breast cancer extension at diagnosis among females in Northern Tunisia from 1994 to 2018

Analysis of BC extension over the period 1994–2018 revealed a significant upward trend in the proportion of locally advanced disease, increasing from 28.3% in

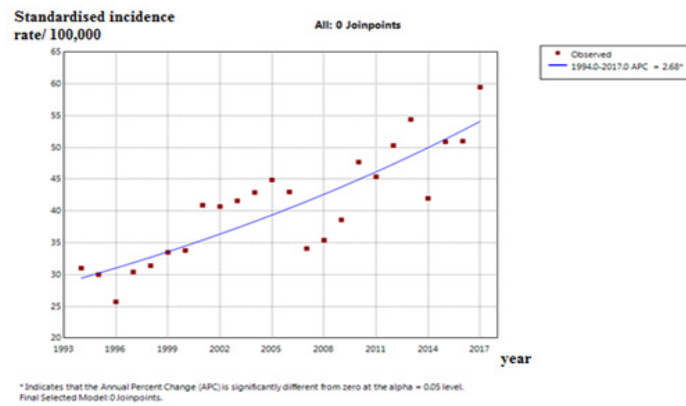
1994 to 46.5% in 2018, with an AAPC of 2.0% ($p < 0.001$). Meanwhile, metastatic extension has significantly decrease from 17.6% in 1994 to 14.6% in 2018 ($p=0.04$) (Table 4, Figure 5).

Trends in breast tumor size among females in Northern Tunisia during the period 1994–2018

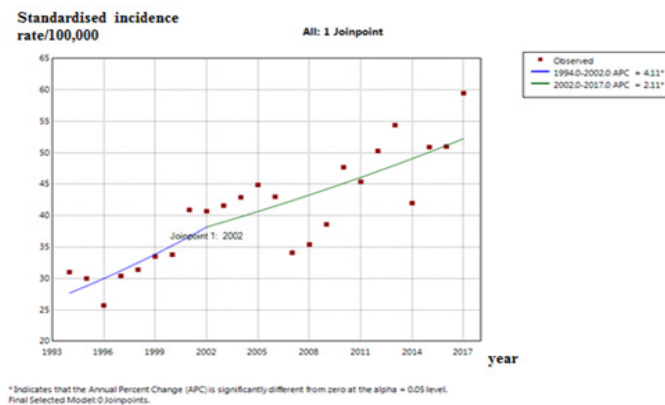
The mean tumor size demonstrated a significant reduction over the study period, declining from 3.47 cm in 1994 to 2.62 cm in 2018, with an AAPC of -0.9% ($p < 0.001$) (Figure 6). The proportion of tumors measuring less than 2 cm increased significantly: tumors <1 cm rose from 3.6% to 21.4% (AAPC = 6.2%), and tumors

Table 1. Clinicopathological Characteristics of Female Breast Cancer Cases in Northern Tunisia in 2018

Variables	number	Percentage (%)
Extension		
In situ	88	5.2
Local	785	46.5
Regional	569	33.7
Metastatic	246	14.6
Tumor size		
<1 cm	361	21.4
1–2 cm	447	26.5
2–3 cm	375	22.2
3–5 cm	371	22.0
≥5 cm	133	7.9
Histological type		
Invasive ductalcarcinoma	1382	81.9
Invasive lobularcarcinoma	52	3.1
Carcinomanototherwisespecified (NOS)	76	4.5
Othercarcinomas (includingmucinous, medullary, tubular, etc.)	54	3.2
Otherhistological types	123	7.3
Diffentiation		
Grade1	257	15.2
Grade2	869	51.5
Grade3	562	33.3



(a)



(b)

Figure 3. Trends in Females Breast Cancer Incidence in Northern Tunisia during the Period 1994–2018 (a: Trends in females breast cancer incidence during the whole period; b: Trends in females breast cancer incidence in Northern Tunisia with a significant joinpoint 2002 ; APC: Annual percentage change in %)

between 1 and 2 cm increased from 23.0% to 26.5% (AAPC = 0.65%). In contrast, tumors measuring 2–5 cm showed a significant decline, with an AAPC of -0.78% for tumors between 2 and 3 cm and -1.45% for tumors between 3 and 5 cm (Table 5, Figure 7).

Trends in the distribution of histological types of breast cancer among females in Northern Tunisia during the period 1994–2018

Analysis of histological subtype trends between 1994 and 2018 revealed a significant reduction in the proportion of lobular carcinomas, declining from 4.8% to 3.1% (AAPC = -3.7% , $p < 0.01$). Conversely, the proportion of other carcinoma subtypes increased from 2.6% to 4.5% (AAPC = 3.0% , $p < 0.04$). The proportion of invasive ductal carcinoma remained relatively stable throughout the study period (Table 6).

Data quality indices

The average number of reporting sources per case was of 1.1 and the Morphological verification percentage (MV%) was 97.2%. Concerning data validity, sex variable was specified for all patients, the percentage of unknown age was 3.8%, the rate of unknown primary tumor site was 2.7% and the percentage of cases with unknown place of

residence was 5% (Table 7).

Discussion

The present study demonstrates a steady and significant increase in the ASIR of BC among women in Northern Tunisia during the period 1994–2018. The specific incidence rate rose from 30.0 per 100,000 in 1994 to 52.4 per 100,000 in 2018, with an AAPC of 2.7% ($p < 0.05$). Trend analyses according to the age revealed a significant upward trend among women aged 55–74 years, whereas incidence rates remained stable among those aged 20–54 years. Analysis of disease extension indicated a significant increase in the proportion of locally confined BC from 28.3% in 1994 to 46.5% in 2018 with an AAPC of 2% ($p < 10^{-3}$), while the proportion of metastatic disease

Table 2. Trend in Female Breast Cancer Incidence in Northern Tunisia during the Period 1994–2018

ASIR (/100,000)	AAPC	CI	p
1994	2018		
30.0	52.4	2.7	[1.8 ; 3.6] < 10-3

ASIR, age-standardized incidence rate; AAPC, average annual percentage change; CI, confidence interval; p, level of significance (5%)

Table 3. Trends in Female Breast Cancer Incidence by Age Group in Northern Tunisia, 1994-2018

Age group (year)	SIR (per 100,000 person- years)		AAPC	CI	P
	1994	2018			
20-29	1.9	2.7	0.2	[-2.1 ; 1.7]	0.82
30-39	9.8	9.4	0.5	[-1.7 ; 0.7]	0.38
40-44	81.7	71.4	0.6	[-1.3 ; 0.2]	0.18
45-49	96.2	83.7	0.1	[-1.1 ; 0.9]	0.77
50-54	103.4	104.5	0.7	[-0.2 ; 1.6]	0.15
55-59	121.6	136.1	1.3	[0.3 ; 2.4]	0.012
60-64	70.8	110.8	1.6	[0.4 ; 2.9]	0.008
65-69	90.6	128.6	2.0	[0.6 ; 3.5]	0.007
70-74	87.4	117.4	1.3	[0.2 ; 2.4]	0.023
75-79	113.7	115.0	0.2	[-1.5 ; 1.0]	0.69
≥ 80	67.3	84.2	1.0	[-1.2 ; 3.2]	0.37

SIR, specific incidence rate; AAPC, average annual percentage change; CI, confidence interval; p, level of significance (5%)

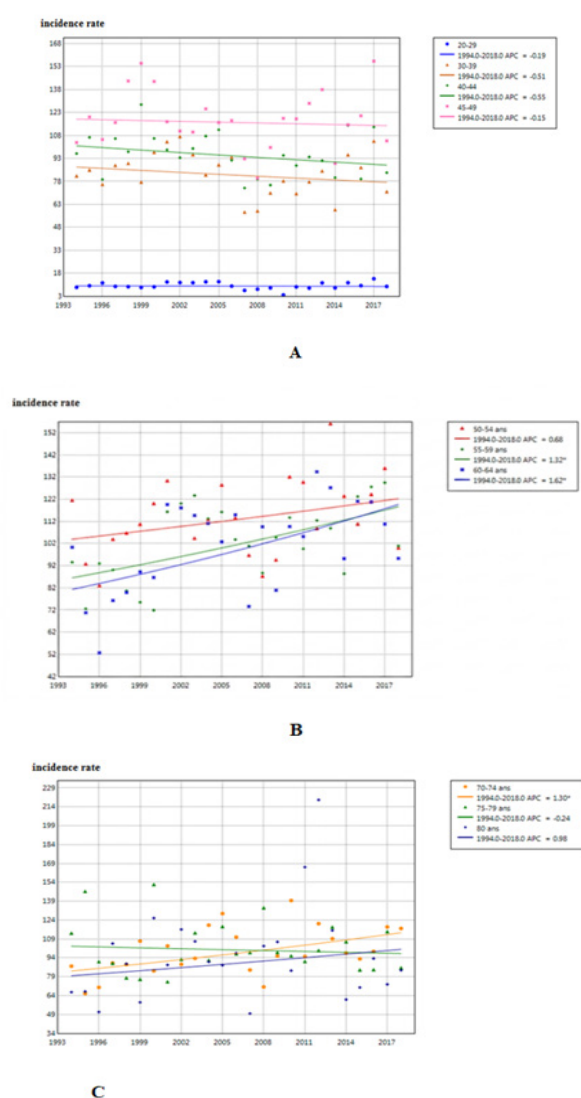


Figure 4. Age-Specific Trends in Female Breast Cancer Incidence (A, B, C) in Northern Tunisia, 1994–2018(A: Age-specific trends in female breast cancer incidence for age groups between 20 and 49 years old; B: Age-specific trends in female breast cancer incidence for age groups between 50 and 65 years old; C: Age-specific trends in female breast cancer incidence for age groups more than 65 years)

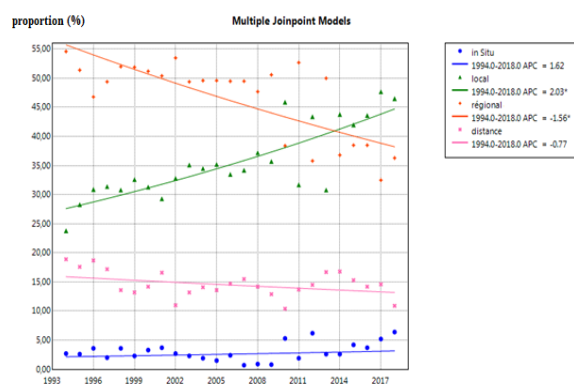
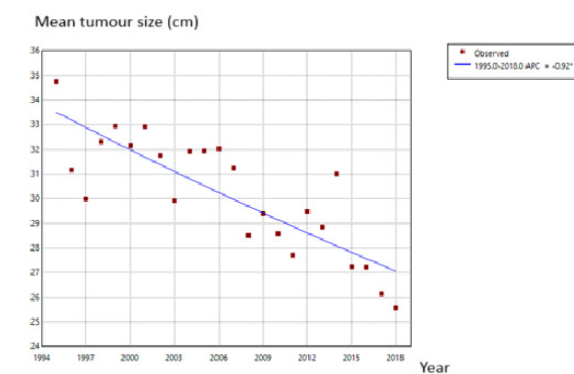


Figure 5. Trends in the Proportion of Breast Cancer Extension at Diagnosis among Females in Northern Tunisia, 1994–2018

significantly decreased from 17.6 in 1994 to 14.6 in 2018 ($p=0.04$). Similarly, the mean tumor size demonstrated a significant reduction, declining from 3.47 cm in 1994 to 2.62 cm in 2018, with an AAPC of -0.9% ($p < 10^{-3}$). Tumors measuring less than 2 cm at diagnosis increased significantly, whereas tumors between 2 and 5 cm showed a significant decrease during the same period. These trends suggest earlier detection and improved diagnostic



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level. Final Selected Model: Joingpoints.

Figure 6. Trends in Mean Breast Tumor Size among Females in Northern Tunisia, 1994–2018

Table 4. Trends in the Proportion of Female Breast Cancer Extension in Northern Tunisia during the period 1994–2018

Extension	Proportion (%)		AAPC	CI	P
	1994	2018			
In situ	3.6	5.2	1.6	[-1.7 ; 5.1]	0.32
Local	28.3	46.5	2.0	[1.4 ; 2.7]	< 0.000
Regional	54.6	36.3	-1.6	[-2.1 ; -1.0]	< 0.000
Metastatic	17.6	14.6	-0.8	[-1.6 ; 0.1]	0.04

AAPC, average annual percentage change; CI, confidence interval; p, level of significance (5%)

Table 5. Trends in the Distribution of Female Breast Cancer Sizes among Females in Northern Tunisia, during the Period 1994–2018

Size	1994	2018	AAPC	CI	P
<1 cm	3.6	21.4	6.20	[4.17;8.31]	< 10-3
1-2 cm	23.0	26.5	0.65	[0.06; 1.24]	0.032
2-3 cm	32.4	22.2	-0.78	[-1.31;-0.26]	0.002
3-5 cm	27.9	22.0	-1.45	[-2.19;-0.71]	< 10-3
≥5 cm	13.1	7.9	-0.9	[-2.30;0.51]	0.188

AAPC, average annual percentage change; CI, confidence interval; p, level of significance (5%)

practices in Northern Tunisia over the past two decades.

Breast Cancer Incidence in Northern Tunisia

In 2018, the standardised incidence of BC in Northern Tunisia was respectively of 52.4 per 100,000 women, placing the region among those with high BC incidence. This observed rate exceeds the GLOBOCAN 2022 estimate of 36.2 per 100,000 in 2022 and aligns with incidence rates reported in neighboring Maghreb countries [3, 4]. For example, the Algerian cancer registry reported an incidence of 54.4 per 100,000 in 2015 [18], while the Casablanca registry in Morocco documented 45.5 per 100,000 women between 2014 and 2017 [19]. Globally, the incidence in Northern Tunisia is comparable to that reported in Türkiye (53.2 per 100,000) and Kuwait (53.0 per 100,000) [20]. However, it remains lower than the highest reported incidence rates worldwide, including Australia, New Zealand, Europe, England, and the United States, where rates exceed 90 per 100,000. Conversely, it is higher than rates reported in sub-Saharan and Eastern Africa, which are generally below 30 per 100,000 [21]. The

Table 6. Trends in the Proportion of Breast Cancer Histological Types among Females in Northern Tunisia during the Period 1994–2018

Histological type	1994	2018	AAPC	CI	P
Invasive ductal carcinoma	80.7	81.9	0.2	[-0.0 ; 0.4]	0.07
Invasive lobular carcinoma	4.8	3.1	-3.7	[-6.5 ; -0.8]	0.01
Carcinoma (NOS)	2.6	4.5	3.0	[0.1 ; 5.9]	0.04

AAPC, average annual percentage change; CI, confidence interval; p, level of significance (5%); NOS, not otherwise specified

relatively high BC incidence observed in Northern Tunisia may reflect enhanced utilization of healthcare services by women, improvements in female education levels, and increased awareness leading to earlier detection. It may also be influenced by greater exposure to established risk factors, including obesity, physical inactivity, and changes in reproductive and lifestyle behaviors [22–25].

Trends in Breast Cancer Incidence in Northern Tunisia, 1994–2018

This study highlights a significant upward trend in BC incidence in Northern Tunisia between 1994 and 2018, with an APC of +2.1% per year ($p < 0.05$). This increasing trend reflects a global phenomenon, historically observed first in developed countries, followed by stabilization. In contrast, developing countries are currently experiencing the highest increases in both BC incidence and mortality [26–28]. Comparable trends have been reported in other Maghreb countries. The Algerian cancer registry documented a 3.7% annual increase in BC incidence between 1990 and 2017 [19]. Similarly, a study from the University Hospital of Marrakech in Morocco reported a 10% increase in BC incidence between 2012 and 2019 [20]. According to the literature, the Middle East and North Africa (MENA) region recorded the highest annual increase in overall BC incidence worldwide between 1990 and 2021, with an average annual increase of 2.38% (95% CI: 2.29–2.47) [27, 28]. This trend has been attributed to

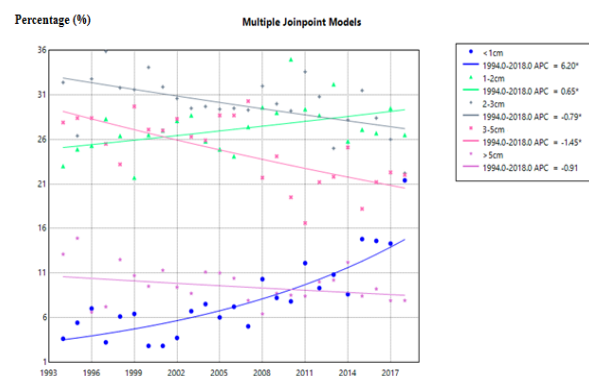


Figure 7. Trends in the Proportion of Breast Tumor Sizes by Categories among Females in Northern Tunisia, 1994–2018

Table 7. Data Quality Indices

Indices	Value
Average number of reporting sources per case	1.1
Morphological verification percentage (MV%)	97.2%
Percentage of Unknown Sex	0%
Percentage of unknown primary tumor site	2.7%
Percentage of unknown place of residence	5%

a complex interplay of genetic, biological, environmental, and behavioral factors [23, 28, 30].

Factors related with the Rising Trend in Breast Cancer Incidence

Several studies in the literature have suggested that changes in reproductive patterns, lifestyle factors, and increasing obesity prevalence may contribute to the rising incidence of BC [31]. These risk factors are particularly relevant in Tunisia, where more than one-third of women (34.6%) are classified as obese, and over half are overweight, according to the national Tunisian Health Examination Survey (THES) [12]. According to the literature, obesity and overweight are associated not only with an increased risk of BC but also with poorer prognosis and higher mortality [32]. Furthermore, only one in five Tunisian women meets the recommended intake of five daily servings of fruits and vegetables, and more than half engage in insufficient physical activity [25]. Reproductive and hormonal factors also play a critical role in modulating BC risk. In Tunisia, the total fertility rate declined from 2.7 in 1994 to 1.8 in 2024, while the mean age at marriage increased to 30 years, and the average age at first pregnancy continues to rise, prolonging exposure to endogenous estrogens and increasing BC risk [6, 33]. Age at menarche and menopause are significant determinants: later menarche (over 15 years) is associated with a reduced risk, whereas early menopause is associated with decreased risk when comparing women who experience menopause at more than 55 years to those before 45 years [6]. Systematic reviews indicate that later menarche and breastfeeding are consistently associated with lower BC risk across all molecular subtypes, whereas later menopause, older age at first childbirth, and nulliparity or low parity increase the risk of luminal A, luminal B, and HER2-positive tumors. Postmenopausal status is additionally associated with an elevated risk of triple-negative and HER2-positive BC compared to luminal A subtypes [33]. Evidence from Tunisian studies were controversial [6, 34, 35] which highlight the need for larger, well-powered studies to clarify the influence of reproductive factors on BC risk in Tunisia. International data further demonstrate the impact of hormonal exposures: in the United States, a substantial reduction in hormone replacement therapy (HRT) prescriptions in the early 2000s was followed by a slight decrease in the incidence of hormone-dependent BC, emphasizing the etiologic importance of HRT [36]. The role of HRT use in Tunisia remains also to be evaluated.

Overall, these data underscore the importance of addressing modifiable risk factors in BC prevention strategies. Nevertheless, according to the WHO, even if all modifiable risk factors were controlled, the potential reduction in BC incidence would be approximately 30%, indicating that primary prevention alone is insufficient to fully mitigate the burden of disease [23, 37].

Breast cancer prevention and control in Tunisia

The Global Breast Cancer Initiative aims to reduce its mortality by 2.5% per year until 2040 [7]. However, many low- and middle-income countries, including those in the

MENA region, still lack comprehensive and reliable data on cancer mortality and survival [7, 28, 38]. In Tunisia, mortality data remain incomplete, limiting the evaluation of national cancer control strategies.

In the present study, several epidemiological indicators suggest a potential shift toward earlier detection over time. Localized-stage BC accounted for nearly half of all cases in 2018, while metastatic cases represented 14.6%. Although this proportion remains relatively high, it is lower than that reported in several neighboring Maghreb regions, where advanced-stage diagnoses exceed 40% [19, 20]. Over the study period, an increasing trend in localized-stage disease was observed, accompanied by a relative decline in metastatic presentations. A parallel shift toward smaller tumor size at diagnosis was also noted, with a reduction in tumors measuring 2–5 cm. These findings may reflect improvements in access to care and diagnostic pathways, although causal inferences cannot be established from this study.

In high-income countries, organized screening programs and universal health care systems are associated with a higher proportion of early-stage diagnoses. In contrast, in resource-limited settings, population-based mammography screening is often constrained by cost-effectiveness considerations and concerns regarding overdiagnosis [38, 40]. In such contexts, early detection strategies based on awareness, clinical breast examination, and timely referral remain relevant approaches.

Overall, these findings support the need for a context-adapted BC control strategy in Tunisia, focusing on strengthening early detection pathways, improving access to diagnostic and treatment services, and ensuring equitable cancer care delivery.

Strengths and Limitations of the Study

This study is distinguished by the depth and reliability of the data analyzed. The utilization of comprehensive records from the Northern Tunisia Cancer Registry over a 25-year period allowed the calculation of precise incidence rates, providing an accurate depiction of temporal trends in BC in the region. Such high-quality, population-based data represent a major strength compared to international estimates derived from statistical modeling, such as GLOBOCAN. The extended observation period further enabled robust analyses of trends by age, histological type, tumor size, and stage at diagnosis. Standardized coding and classification protocols enhanced comparability with international population-based cancer registries. Several limitations should be acknowledged. First, the absence of comprehensive and reliable BC mortality data in Tunisia precludes analysis of survival trends and mortality patterns. Second, the study population is restricted to Northern Tunisia, and extrapolation to the entire country should be made cautiously. Additional limitations include incomplete documentation of tumor stage, molecular markers such as hormone receptor status, and survival outcomes, which may have been affected by variable quality of medical records.

In Conclusion, this study demonstrated an increasing trend in BC incidence in Northern Tunisia. The findings also suggest a shift toward earlier detection, as reflected by

a higher proportion of localized-stage tumors and smaller tumor sizes at diagnosis. Despite these improvements, a substantial proportion of BC patients are still diagnosed at advanced stages, highlighting persistent gaps in early detection and treatment and equitable access to care. Finding of the current study showed the importance of cancer registries to monitor disease trends. Thereby strengthening cancer surveillance systems in Tunisia, and improving the completeness of mortality data are essential to guide effective cancer control policies.

Author Contribution Statement

Conceptualization: H.K. and H.S.; Methodology: H.K., and A.M.; Formal analysis: H.K. and S.S.; Data curation: H.K.; Writing—original draft preparation: B.F.S, S.S., B.A.R and M.N; Writing—review and editing: K.H, S, S; Supervision: K.H., A.M.; Validation: N.M., C.H, B.M.H and H.S.

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Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Jendouba Hospital, Tunisia. Data management complied with Decree No. 2008-846 (March 24, 2008). Authorization from the National Authority for Personal Data Protection was obtained on April 27, 2017. Individual informed consent was waived due to the retrospective registry design; all data were fully anonymized prior to analysis.

All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement

All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data Availability Statement

The datasets analyzed during this study are not publicly available in accordance with national legislation governing cancer registry confidentiality (Article 4, Decree No. 2008-846), but are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no competing interests.

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