



ORIGINAL RESEARCH

EPIDEMIOLOGICAL AND BIOLOGICAL PROFILING OF BREAST CANCER IN SOUTHERN MOROCCO

Fatima Zahra AZNAG ^{1*} , Ezohra ELOUILAMINE ^{1*}, Mohammed Amine BASSELAM ¹, Smail CHADLI ^{1 2}, Mostafa AIT EL CADI ³, El hassan IZAABEL ³

* These authors contributed equally to this work

¹ Laboratory of Cellular Biology and Molecular Genetics; Faculty of Sciences, Ibn Zohr University , Agadir, Morocco.

² Higher Institute of Nursing Professions and Health Techniques, Agadir, Morocco.

³ Regional Center of Oncology and Radiotherapy, Agadir, Morocco.

ABSTRACT

Breast cancer is one of the most frequent cancers that affect women. Risk factors include a combination of multiple factors such heredity, age and environment. The frequency of breast cancer in Morocco increased significantly in recent years, and it is now a major public health concern.

A retrospective epidemiological study was produced for a cohort of 1559 patients attending the regional center of oncology and radiotherapy in Agadir, during a period comprised between January 2010 and December 2015.

Our data shows that the average age of the patients is 48 years, the majority of them present grade II tumors 66.38%. The immunohistochemical analysis of tumors revealed that 64% of them are positive for hormone receptors. With 67.07% is positive for ER and 61.01% positive for RP, while 29.17% of tumors overexpress HER2 protein. The distribution of molecular subtypes of breast cancer shows that luminal A has the highest percentage 50.96% followed by basal-like 20.26%.

To clarify the young epidemiological profile and the etiology of breast cancer a regional cancer registry is required. Furthermore, the awareness campaigns are crucial to avoid having patients with aggressive form of the disease. Therefore, to improve survival and reduce morbidity of breast cancer's patients.

KEY WORDS: Breast cancer, epidemiology, Human epidermal growth factor receptor 2 (HER-2), histological grade, hormone receptors, southern Morocco.

CORRESPONDING AUTHOR:

Fatima Zahra AZNAG, Laboratory of Cellular Biology and Molecular Genetics; Faculty of Sciences, Ibn Zohr University, Agadir, Morocco. E-mail: Fatimazahra.aznag@edu.uiz.ac.ma

COPYRIGHT © 2018 Aznag Fatima Zahra et al.

This is an open access article distributed under the Creative Commons Attribution 4.0 International, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Female Breast Cancer is a worldwide major health problem. It is the second leading cause of cancer death (7.04 % of the total cancer deaths) [1]. In Morocco, breast cancer is the first malign tumour among women and the second one of all registered cancer cases [1].

The frequency of breast cancer in Morocco increased significantly in recent years 20.73 % [1], which makes it a major public health concern. Since 2005, the date of creation of the Lalla Salma Foundation for cancer (ALSC), cancer care in Morocco has notably improved and became a public health priority.

Risk factors for this type of cancer include a combination of multiple factors among which the most prominent ones are the patient age, familial history, age at first birth and environment [2].

The understanding of the etiologic heterogeneity of different subtypes of breast cancer has increased recently.

A better identification of prognostic factors is crucial for clinical and prognostic purposes, including the age at the onset of the disease, the histological type and the grade of the tumor (SBR). The young age is considered as a principal factor of poor prognostic [3], beside the knowledge of the hormone receptor status has become very important, with an arrangement according to the presence of receptors for oestrogen, progesterone and human epidermal growth factor 2 (Her2).

We produced a retrospective study during a period comprised between January 2010 and December 2015, conducted for the first time in southern Morocco, on patients with breast cancer, with the collaboration of the regional centre of oncology and radiotherapy of Agadir.

Our study focused on a number of parameters in relation to the selected population, including their geographical distribution, the age at the onset of the disease, the

histological type of tumors, the grade of the tumor (SBR), the expression of hormonal receptors, and the level of expression of the HER-2 protein. Therefore, the aim is to assess the epidemiological and biological profiling of breast cancers in southern Morocco (2010-2015).

MATERIALS AND METHODS

Patients

This study was performed in the centre of oncology and radiotherapy of Agadir, which is the main oncology centre in southern Morocco. Using data of the 1559 patients diagnosed with breast cancer, aged between 21 and 98 years old, attended the centre of oncology and radiotherapy were diagnosed along six years, from January 2010 to December 2015, we excluded from the study patients with missing data.

Data source

To recapitulate the complete history of each patient's disease we collect information on age and gender from the clinic registration records. Data on tumor histology, grade, hormonal and HER2 receptors status were obtained from pathology reports.

Statistical methods

To evaluate the epidemiologic profile, data from different clinical records of each patient were analysed with the Epi-info 7.1.5.2 software [4]. The statistical data for different variables were performed using the χ^2 test and Fleiss 95% LCL.

Results

It's widely accepted that establishment of the epidemiological profile of breast cancer is essential to provide hypothesis for understanding the etiology of the disease. The study involved 1559 patients recruited between January 2010 and December 2015. The geographical distribution of patients showed that a high frequency is observed in the province of Agadir with 671 patients compared to other provinces, followed by Taroudant with 326 patients. Saharan cities (Tantan and Sidi Ifni Dakhla) account for only 110 of all cases. We also note the presence of other cities outside the southern area of Morocco (Marrakesh, Tanger Casablanca, Beni Mellal and El Jadida) (Figure 1).

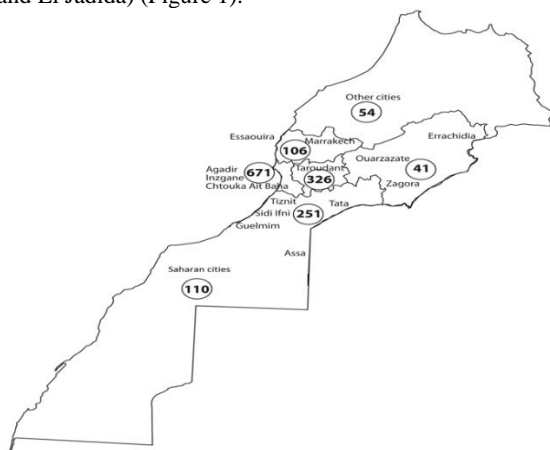


Figure 1: Geographic distribution of breast cancer in the Moroccan southern area.

Women diagnosed with breast cancer are aged between 21 and 98 years old, and the mean age at diagnosis is 48 ± 11 . Therefore this population is characterized by a young age. The age range distribution showed that the highest percentage 35.02% is found in women aged between 40-50 years, the second highest group is between

50-60 years old 25.86%, while women between 20-40 and 60-100 years old represent only 18.73% and 20.40% respectively (Figure 2).

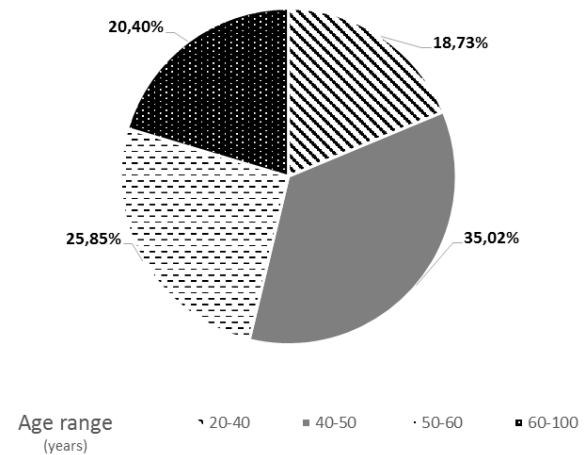


Figure 2: The age range distribution of breast cancer patients.

Histopathological analyses show that invasive ductal carcinoma is the predominant type of breast cancer and represents 84.25% of cases, whereas invasive lobular carcinoma affects only 8.45% of women and medullary carcinoma 2.18%. The remaining tumours are represented by rare cases of papillary carcinoma infiltrating, apocrine carcinoma, metastatic carcinoma and undifferentiated. Histological grade is one of the basic pathological information that typically conditioner the treatment choice, SBR grade is determined for 1270 patients from 1559 patients admitted in the center. 30.39% were grade III, grade II tumors were in the majority, and they represented 66.38% of cases, the grade I tumors accounted for only 3.23% of cases.

Breast cancer is a complicated disease, characterized by the accumulation of multiple molecular alterations that give each tumor a specific phenotype that can be used as a molecular signature to reach a personalized therapy. Guided to a correct control of the expression of estrogen (ER), progesterone receptors (PR) and the HER2 protein (Human Epidermal growth factor Receptor).

The study of immunohistochemical analysis of patients revealed that 64% of tumors are positive for hormone receptors: 67.07% are positive for ER and 61.01% positive for PR, while 29.17% of tumors overexpress HER2 protein.

The expression of ER increases with age, rising from 19.48% in patients aged 20-40 years to 36.36% among patients aged 40-50 years. Similarly, the expression of PR represents 19.12% and 37.14% respectively in the age group of 20-40 and 40-50. An identical profile was observed for the overexpression of the HER2 protein. The major peak of expression of hormone receptors and HER2 were detected in the group between 40-50 years old while we found a decrease of the hormonal receptors overexpression as well as the HER2 after the age of 50 (Figure 3).

Figure 4 showed that, regardless of age, the proportion of SBR grades II and III is high among all age groups, the percentage ranges from 62 to 68% for SBR II and 28 to 33% SBR III. The percentage of grade I tumours is very low and represented only 4.88% among the age group 20-40 years and 2.17% of the age group 50-60 years.

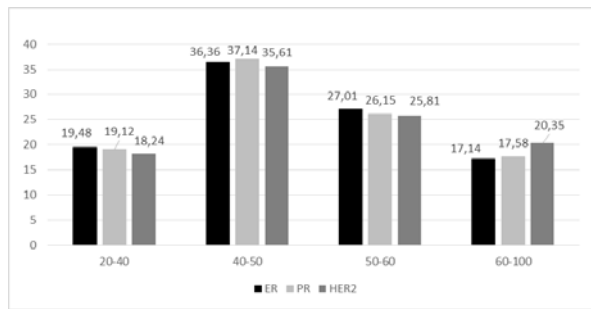


Figure 3: Expression of hormone receptors and HER2 according to age groups

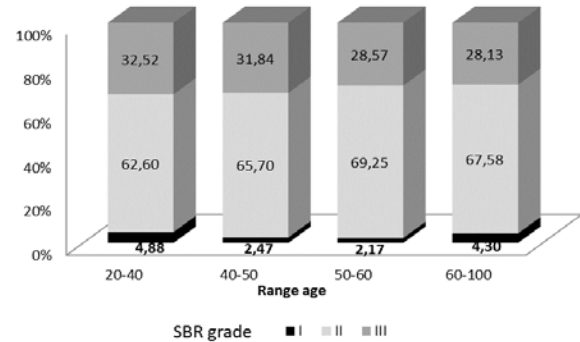


Figure 4: Histological grade of breast cancer depending on age groups of patients.

The molecular classification of breast carcinomas proposed by a study conducted in 2006 [5], defined several immunohistochemical (IHC) subtypes. In this study breast cancer is classified into four groups based on IHC profile ER/PR and Her2/neu expression, positive (+) and/or negative (-) luminal A, B and basal-like and HER2/neu.

The distribution of molecular subtypes of breast cancer (Table 1) shows that luminal A has the highest percentage of all 50.96% followed by basal-like 20.26%, while luminal B and HER2/neu subtypes had respectively 18.35%, 10.43%.

Table 1: The percentage of immunohistochemical subtypes of breast cancer.

IHC subtypes	IHC profile ER/PR and Her2/neu expression	Percentage
Luminal A	ER+ and/or PR+ ER-/PR+	50,96
Luminal B	ER+ and/or PR+ ER-/PR+	18,35
Basal-like	ER-, PR-	20,26
HER2/neu	ER-, PR-	10,43

The research on immunohistochemistry of the status ER / PR / HER2 in tumors has detected eight biological subtypes which we ranked in the order of better survival time as has been described in the literature [6]. ER+/PR+/HER2-, ER+/PR-/HER2-, ER+/PR+/HER2+, ER+/PR-/HER2+, ER-/PR+/HER2-, ER-/PR+/HER2+, ER-/PR-/HER2-, ER-/PR-/HER2+.

Our population is characterized by the following subtypes (table 2), ER+ / PR + / HER2- represents the majority of cases 32.78% followed by subtype ER- / PR- / HER2- with 14.95% while subtypes ER+ / PR- / HER2 -, ER+ / PR - / HER2+ and ER - / PR + / HER2 - are poorly represented 3.78%, 2.18% and 1.03% respectively.

Table 2: Biological subtypes frequencies.

Immunohistochemical classification	Statut ER/PR/HER2	Frequency	Percent %	Cum. Ercent %	Fleiss 95% LCL	Fleiss 95% LCL
Luminal A	ER+/PR+/HER2-	511	32,78	62,86	30,46	35,18
	ER+/PR-/HER2-	59	3,78	27,90	2,92	4,89
	ER-/PR+/HER2-	16	1,03	23,67	0,61	1,70
Luminal B	ER+/PR+/HER2+	170	10,90	73,77	9,42	12,58
	ER+/PR-/HER2+	34	2,18	30,08	1,54	3,07
Basal Like	ER-/PR+/HER2+	7	0,45	24,12	0,20	0,97
	ER-/PR-/HER2-	233	14,95	14,95	13,23	16,83
HER2/neu	ER-/PR-/HER2+	120	7,70	22,64	6,45	9,16
	Missing	409	26,23	100,00	24,08	28,51
	TOTAL	1559	100,00	100,00		

The classification of these biological subtypes based on age range still shows a predominance of subtype ER + / PR + / HER2- followed by subtype ER - / PR- / HER2- . The sub-types ER- / PR- / HER2 + and ER + / PR + / HER2 + are represented by small percentages, particularly for patients under 50 years. The proportion of other subtypes ER/ PR / HER ranges from 1 - 6% regardless of age group. The tumours overexpressing the HER2 protein are said to

be of poor prognosis and results in higher recurrence and decreased survival (Figure 5).

DISCUSSION

We report in this paper the first study of breast cancer epidemiology in the Moroccan southern area after the clinical records from patients attending the center of oncology and radiotherapy of Agadir.

The high percentage of patients from Agadir is explained by the center approximation, whereas the province of Taroudant had also the highest percentage, must probably due to the proximity from the major center which is Agadir, and also to other environment factors. The province is well known by agriculture activities, which in turn may expose its population to pesticides. According to the literature it has been shown that exposure to pesticides plays a role in increasing risk of hormone-dependent cancers, including breast cancer [7,8]

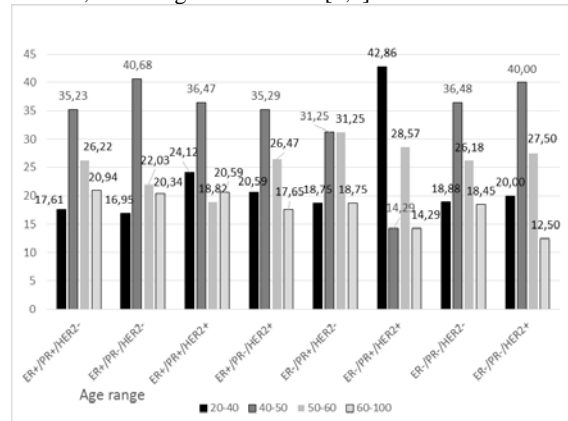


Figure 5: Correlation of the biological sub-type and the age range.

While the low percentage of patients from the Saharan cities is likely due to the fact that they are far from Agadir and also have a preference to move to private centers or centers of Casablanca and Rabat.

The mean age at diagnosis is 48 years, with 53.75% of our patients diagnosed before the age of 50. In comparison to CRC (Cancer Registry of the Greater Casablanca) and CRR (Cancer Registry of Rabat), the mean age at diagnosis is 49.5 and 50 years respectively (CRC, 2012; CRR, 2012). On the other side, Abbas and colleagues showed in a cohort of 265 women with breast cancer in the Fez region, that the median age was 45 years [9]. Overall, the mean age at diagnosis in Morocco is nearly the same in Algeria, which presents a mean age at diagnosis of 47 years [10] and European western countries where the average age of onset of breast cancer is 55 years old [11]. In concordance with Arab reports, our data shows that invasive ductal carcinoma is the most prevalent pathology type followed by invasive lobular carcinoma and ductal carcinoma in situ [12,13]. Otherwise, the percentage of tumours grade I at diagnosis is very low 3.23% instead of 14% in Fez, while in Europe it goes as high as 30%. Whereas grade III had a similar percentage we had 30.39% instead of 30.5% in Fez and 30% in Europe. Grade II is more frequent, more marked in our population with 66.38% instead of 55.5% in Fez and 42% in Europe [9, 11]. Regardless of age, the proportion of SBR grades II and III is high among all age groups, while the percentage of grade I tumours is very low. The importance of poor prognostic factors, found in the tumors of patients in southern Morocco could be explained by the lack of awareness of breast cancer risks and to a late diagnosis.

The expression of both ER and PR and also HER2, increases with age. We summarized that the age group between 40-50 years represents the peak of expression of hormone receptors and HER2, but we can also detect a decrease of the hormonal receptors overexpression as well as the HER2 after the age of 50.

The molecular subtypes of breast cancer may be affected by ethnicity, age and grade [14,15]. Our patients are estrogen-receptors positive in 67.07% of the cases, progesterone-receptors positive in 61.01% of the cases and HER2 is overexpressed in 29.17% of all patients whilst in general Arab women are negative for estrogen-receptor and overexpress HER2 [16]. The age group between 40-50 years represents the peak of expression of hormone receptors and HER2. This can be explained by the physiological changes related to the onset of the menopausal process when a decrease of the hormonal receptors overexpression as well as the HER2 is expected after the age of 50.

IHC-based classification of both ER/PR and Her2 status in our population shows that luminal A is the most prevalent form accounting to 50.96%, followed by basal-like 20.26%, luminal B were 18.36% and HER2/neu were 10.43%. Similarly in a retrospective study from Tunisia [17], 51% of breast cancers were luminal A, 23% were triple-negative, 13% were luminal B, and 13% were HER2/neu. The same profile was found in Lebanon [18], luminal A represents 35.4%, followed by the triple negative subgroup and luminal B at 11.6 and 8.4% respectively. By contrast a study realized at Fez in Morocco [19] showed that women with breast cancer had luminal B subtype most prevalent 42%, followed by luminal A 31%, basal-like 14%, HER2/neu 9%. The same pattern appears in Saudi Arabia [20], 4% were luminal A subtypes, 16% were luminal B, 17% were HER2, 10% were basal.

All these biological and molecular markers are supposed to conditioning the appropriate choice of treatments and help the practitioner in the choice of the best treatment for each case.

The implementation of regional cancer registry is necessary to understand the etiology of the disease, and to explain the very young epidemiological profile of breast cancer. On the other hand, large and extensive public awareness campaigns should be conducted for early diagnosis of breast cancer, to avoid having patients with aggressive form and advanced tumor's stages, by consequences, improve survival and reduce morbidity of breast cancer's patients.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals](#) of the [International Committee of Medical Journal Editors](#). Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

ETHICS

This work has obtained approval from the ethics committee of Mohamed VI University Hospital, University Cadi Ayyad Marrakech, Morocco.

SPONSORSHIP

Declared none.

COMPETING INTERESTS

The authors declare no competing interests.

REFERENCES

- [1] F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, "Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries," *CA. Cancer J. Clin.*, Sep. 2018.
- [2] E. Washbrook, "Risk factors and epidemiology of breast cancer," *Women's Heal. Med.*, vol. 3, no. 1, pp. 8–14, Jan. 2006.
- [3] F. Molinié, S. Billon-Delacour, C. Allieux, S. Blais, P. Bercelli, and P. Lombraïl, "Incidence and prognostic factors of breast cancer diagnosed within and outside of the organised screening program in the department of Loire-Atlantique (1991–2002)," *Rev. Epidemiol. Sante Publique*, vol. 56, no. 1, pp. 41–49, Feb. 2008.
- [4] S. K. Dean AG, Arner TG, Sunki GG, Friedman R, Lantinga M, Sangam S, Zubieta JC and F. R. M, Brendel KA, Gao Z, Fontaine N, Shu M, Fuller G, Smith DC, Nitschke DA, "CDC - Epi InfoTM - Training Resources," *Epi InfoTM*, a database Stat. Progr. public Heal. Prof. CDC, Atlanta, GA, USA., 2011.
- [5] L. A. Carey et al., "Race, Breast Cancer Subtypes, and Survival in the Carolina Breast Cancer Study," *JAMA*, vol. 295, no. 21, p. 2492, Jun. 2006.
- [6] C. A. Parise, K. R. Bauer, M. M. Brown, and V. Caggiano, "Breast Cancer Subtypes as Defined by the Estrogen Receptor (ER), Progesterone Receptor (PR), and the Human Epidermal Growth Factor Receptor 2 (HER2) among Women with Invasive Breast Cancer in California, 1999-2004," *Breast J.*, vol. 15, no. 6, pp. 593–602, Nov. 2009.
- [7] B. A. Cohn et al., "DDT Exposure in Utero and Breast Cancer," *J. Clin. Endocrinol. Metab.*, vol. 100, no. 8, pp. 2865–2872, Aug. 2015.
- [8] C. Fenga, "Occupational exposure and risk of breast cancer," *Biomed. reports*, vol. 4, no. 3, pp. 282–292, Mar. 2016.
- [9] F. Abbass et al., "Epidemiological and biologic profile of breast cancer in Fez-Boulemane, Morocco/Le profil epidemiologique et biologique du cancer du sein a Fes-Boulemane (Maroc)," World Health Organization, 2011. .
- [10] A. Bounedjar, "Epidemiology and Characteristic of Breast Cancer in CHU Blida, Algeria," *Pan Arab J. Oncol.*, vol. 9, no. 2, 2016.
- [11] R. W. Blamey et al., "ONCOPOOL – A European database for 16,944 cases of breast cancer," *Eur. J. Cancer*, vol. 46, no. 1, pp. 56–71, Jan. 2010.
- [12] A. E. Fakhro, B. E. Fateha, N. al-Asheeri, and S. A. al-Ekri, "Breast cancer: patient characteristics and survival analysis at Salmaniya medical complex, Bahrain," *East. Mediterr. Health J.*, vol. 5, no. 3, pp. 430–9, May 1999.
- [13] J. Zidan, N. Sikorsky, W. Basher, A. Sharabi, E. Friedman, and M. Steiner, "Differences in pathological and clinical features of breast cancer in Arab as compared to Jewish women in Northern Israel," *Int. J. Cancer*, vol. 131, no. 4, pp. 924–929, Aug. 2012.
- [14] M. L. Telli et al., "Asian ethnicity and breast cancer subtypes: a study from the California Cancer Registry," *Breast Cancer Res. Treat.*, vol. 127, no. 2, pp. 471–478, Jun. 2011.
- [15] R. H. Jack et al., "Differences in breast cancer hormone receptor status in ethnic groups: a London population," *Eur. J. Cancer*, vol. 49, no. 3, pp. 696–702, Feb. 2013.
- [16] L. Chouchane, H. Boussen, and K. S. R. Sastry, "Breast cancer in Arab populations: molecular characteristics and disease management implications," *Lancet Oncol.*, vol. 14, no. 10, pp. e417–e424, Sep. 2013.
- [17] A. Fourati et al., "Descriptive analysis of molecular subtypes in Tunisian breast cancer," *Asia. Pac. J. Clin. Oncol.*, vol. 10, no. 2, pp. e69–e74, Jun. 2014.
- [18] G. Chahine et al., "Characteristics of incident female breast cancer in Lebanon, 1990–2013: Descriptive study of 612 cases from a hospital tumor registry," *Cancer Epidemiol.*, vol. 39, no. 3, pp. 303–306, Jun. 2015.
- [19] H. El Fatemi et al., "Luminal B tumors are the most frequent molecular subtype in breast cancer of North African women: an immunohistochemical profile study from Morocco," *Diagn. Pathol.*, vol. 7, p. 170, Dec. 2012.
- [20] D. M. Al Tamimi, M. A. Shawarby, A. Ahmed, A. K. Hassan, and A. A. AlOdaini, "Protein expression profile and prevalence pattern of the molecular classes of breast cancer - a Saudi population based study," *BMC Cancer*, vol. 10, no. 1, p. 223, Dec. 2010.