

MINI-REVIEW

Causative Relationship between Diabetes Mellitus and Breast Cancer in Various Regions of Saudi Arabia: An Overview

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Abstract

The unwarranted connection between diabetes mellitus and breast cancer has gained new ground in recent years. Breast cancer in Saudi females accounts for approximately 21% of all cancers and the prevalence of diabetes mellitus (DM) in Saudi females is also 21.5%. DM is diagnosed in the age group of 30+ years with possible exposure to predisposing factors like hyperinsulinemia and obesity at younger age. Further, 12% of the breast cancer cases are diagnosed in the young females aged 20-34 years. Despite the readily available access to healthcare facilities in the Kingdom, a large number of diabetics, approximately 27.9%, were unaware of having diabetes mellitus. This subpopulation is quite susceptible of developing breast cancer at later age. This review discusses common etiological and predisposing factors for breast cancer and diabetes, regional distribution and possible correlation of diabetes and cancer in Saudi Arabia.

Keywords: Breast cancer - diabetes mellitus - obesity - Saudi Arabia

Asian Pacific J Cancer Prev, 12, 589-592

Introduction

The upcoming reports on an unwarranted and alarming connection between the two of the very complex and heterogeneous and severe diseases of diabetes and cancer are quite disturbing (Cazzaniga et al., 2009; Vigneri et al., 2009; Giovannucci et al., 2010). Cancer and diabetes are diagnosed more frequently within the same individual than would be expected by chance. Both diseases are relatively quite complex with multiple subtypes (Cazzaniga et al., 2009; Vigneri et al., 2009). This scenario could cause havoc in most of the developing countries with high susceptibility to diabetes (Wild et al., 2004; WHO Fact sheet N0312, 2011). One such country is Saudi Arabia where diabetes mellitus is an epidemic and number of people with diabetes is increasing at dangerously alarming rate due to changing and sedentary lifestyles (Nozha et al., 2005). Similar situation is more or less with the female breast cancer incidence in the Kingdom (NCR report, 2003; Al-Sayed et al., 2010). Epidemiological studies clearly indicate that the risk of several types of cancers including pancreas, liver, breast, colorectal, urinary tract, and female reproductive organs is increased in diabetic patients (Cazzaniga et al., 2009; Vigneri et al., 2009).

Cancer in Saudi Arabia

In general the population of Saudi Arabia is quite young. About 30.7% of the total population is females in the age group of 0-24 years while 14.8% females lie in the age group of 25-49 years (NCR Report, 2003).

Cancer is the largest single cause of disease in the World and the largest cause of death in people aged 45–65 years (Smith et al., 2010). As the population grows old, the impact of cancer on the community will also increase. Epidemiological data on cancer incidence in Saudi Arabia is scarce. According to the Cancer Incidence Report (NCR Report, 2003), the overall age-standardized incidence rate (ASR) for all Saudis with a world standard population reference was 67.5/100,000 (68.7/100,000 in males and 66.3/100,000 in females) (NCR Report, 2003). For all sites, the age-specific incidence rate (AIR) increased with age for both males and females. After the age of 64 years, the increase was nearly two folds for males compared to females. The mean age at diagnosis was 53 years for men and 48 years for women. The overall cancers were more predominant in males (51.6%) than females (48.4%) with a male to female ratio of 107:100 (NCR Report, 2003). The total female cancers incidence was highest in the age group of 45-59 years with 13.5% while in males 60-74 years group showed the highest cancer incidence with 16.2%. The five geographic regions with the highest ASR were Eastern region at 100.8/100,000, Riyadh region at 94.8/100,000, Makkah region at 77/100,000, Northern region at 71.3/100,000, and Tabuk region at 66.7/100,000. In the Hail region, ASR of all cancer sites is 49.4 (females) and 32.8 (males) per 100,000 which is below the national average (NCR Report, 2003).

The most common cancers in the whole population irrespective of sex are carcinoma of the breast, lymphoma and leukemia combined and colorectal cancer. In the children of age group of 0-14 years irrespective of sex,

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leukemia is the most common type of cancer affecting 31.5% children. Breast cancer is the leading type of cancer in females while colorectal cancer is the most common cancer in males (NCR Report, 2003).

Breast Cancer in Saudi Arabia

Breast cancer continues to be the public health concern in Saudi Arabia as the commonest cancer among women with overall percentage of 22.4. The most breast cancer incidences in females were found to be in the age group of 20-45 years (NCR Report, 2003). The age-specific incidence of breast cancer is 45 per 100,000 at the age of 45 years. The majority of breast cancer cases were observed in the age group of 30-44 years (21.6%) while 16.3% cases were in the 45-59 years of age group.

Further, analysis of the female breast cancer incidence in various regions shows that the Eastern region has the highest incidence of 28.7% followed by Northern, Makkah and Qassim regions (Table 1). The Najran region reported the least number of breast cancer cases (8.9%) in females while the Hail region has reported 12.5% of breast cancer cases.

Prevalence of Diabetes in Saudi Arabia

WHO (WHO Fact sheet N0312, 2011) predicts that developing countries will bear the brunt of diabetes epidemic in the 21st century. An estimated 285 million people, corresponding to 6.4% of the world's adult population, is currently living with diabetes which is expected to grow to 438 million by 2030, corresponding to 7.8% of the adult population (Wild et al., 2004). Approximately, 70% of the current cases of diabetes occur in low- and middle income countries. India has the world's largest diabetes population with an estimated 50.8 million people living with diabetes, followed by China with 43.2 million. Presently more than 16 million people are living with diabetes in the Eastern Mediterranean Region and this is expected to rise to almost 43 million by the year 2025 (World Diabetes Foundation, 2007). The overall prevalence of Diabetes mellitus has increased alarmingly from 4.3% in 1987 (Fatani et al., 1997) to 23.7% in the

Table 1. Percentage Distributions of Female Breast Cancer Cases and Obesity in Various Regions of Saudi Arabia (extracted from NCR Report, 2003 and Othaimen et al., 2007)

Regions	Breast Cancer	Obesity
Eastern	28.7	
Northern	26.3	
Qassim	25.6	26.5
Makkah	25.2	19.3
Jouf	20.4	
Riyadh	17.1	21.7
Tabuk	16.5	25.2
Jizan	16.0	11.7
Madinah	14.7	15.1
Hail	12.5	33.9
Asir	11.9	16.2
Baha	11.7	
Najran	8.9	

Kingdom (Al Nozha et al., 2004). The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men (Wild et al., 2004).

The prevalence in males and females are 26.2% and 21.5%, respectively. Diabetes mellitus was more prevalent among Saudis living in urban areas of 25.5% compared to rural Saudis of 19.5%. The study by Nozha et al., (2004) indicated a regional prevalence of diabetes mellitus in Northern region (27.9%) followed by Eastern (26.4%), Western (24.7%), Central (23.7%) and Southern regions. The lowest diabetes mellitus prevalence of 18.2% was observed in the Southern region (Nozha et al., 2004). Despite the readily available access to healthcare facilities in the Kingdom, a large number of diabetics (27.9%) were unaware of having Diabetes mellitus (Al Nozha et al., 2004).

Diabetes is one of the major causes of premature illness and death worldwide. Non-communicable diseases including diabetes account for 60% of all deaths worldwide. According to WHO (WHO fact sheet N0312, 2011), diabetes causes approximately 5% of all deaths globally each year and these deaths are projected to increase by more than 50% in the next decade. According to the Diabetes Atlas (2010), 14,105 Saudis were projected to die of diabetes in 2010 while percent cumulative prevalence of diabetes mellitus is 16.8% in the Kingdom.

Since most of the etiological factors are common in both diabetes and breast cancer, it is of utmost importance to take a systematic look on these two diseases in Saudi Arabia. Hyperinsulinemia, obesity, hyperglycemia, and increased oxidative stress may contribute to increased cancer risk in diabetes mellitus patients.

More than 1.6 billion adults are overweight worldwide and almost 30% of them are considered to be obese (WHO fact sheet N0311, 2006; World Diabetes Foundation Press Release October 2007). The obesity rates have been tripled in developing countries in the past two decades mainly due to the overconsumption of oily and fast foods accompanied with the sedentary lifestyles (Al-Othaimen et al., 2007). In the western countries like USA and UK, the percentages of obese and overweight population have sharply increased in the past few decades (Prentice and Jebb, 1995; Flegal et al., 1998; Nozha et al., 2005).

Concurrent with this trend, the prevalence of overweight and obesity is also increasing in Saudi Arabia. The current data demonstrate that approximately three quarters of females and nearly two-thirds of males in the Kingdom are either overweight or obese (Nozha et al., 2005). Since 2000, the prevalence of obesity in the Kingdom has increased from 20.5% to 35.6% in 2005 (Osman and Al-Nozha, 2000; Nozha et al., 2005). The prevalence of overweight was about 36.9% which makes 72.5% of Saudis either overweight or obese. Females are significantly more obese with a prevalence of 44% than 26.4% males (Nozha et al., 2005). Other studies also showed similar trends of higher obesity prevalence in females compared to the males (Al-Nuaim et al., 1997; El-Hamzi and Warsy, 2000).

The causative relationship of obesity in diabetes mellitus is well known (El-Hamzi and Warsy, 1999). Prevalence of obesity was 39.3% among women with

diabetes compared to 18.5% among non-diabetic women. The prevalence of obesity was lower among diabetic men than diabetic women. Men with diabetes had a higher prevalence than non-diabetic men (20.7% and 12.1% respectively). This may be attributed to various predisposing factors including that the females in the Kingdom may be less physically active in comparison to males (Nozha et al., 2005).

Urbanization could also increase the prevalence of obesity and overweight in the Kingdom (Nozha et al., 2005). The lowest obesity rate was found in the south-western province of Jizan where most people live relatively active life due to agricultural work and fishing. Genetic factors, physical activity, healthy dietary habits and rural lifestyle in the southern region may be some of the factors for the lowest prevalence of obesity (Nozha et al., 2005). The highest obesity rate (up to 33.9%) was found in the northern and eastern provinces (Ha'il, Al Sharqiya, Al Qasim and Tabuk). This was probably a result of sedentary lifestyle and the nature of the diet as it is high in fat (Al-Othaimen et al., 2007).

Obesity and Diabetes and Breast Cancer

Despite the inconsistencies and contradictions in the literature with respect to the role of environmental and lifestyle factors in genesis of breast cancer, obesity and diabetes seemed to have a major impact on breast cancer risk (Abulhair, 2009).

The prevalence of breast cancer in various regions of Saudi Arabia showed almost similar patterns except Makkah and Qassim regions which showed the higher cases of breast cancer. The Jizan and Hail regions showed the least prevalence of breast cancer. Interestingly, the percentage prevalence of obesity and diabetes mellitus were also the least in Jizan. In all the other regions, reasonably good correlation seems to exist in the percentage prevalence of diabetes mellitus, breast cancer and Obesity (Figure 1). The correlation between the obesity and diabetes mellitus in the Hail region possibly exists but the correlation between the obesity and breast cancer or breast cancer and diabetes mellitus did not seem to be convincing. The Hail region was reported to be having the highest percentage of obese population

(33.9%) while the breast cancer cases were reported to be only 12.5%. The high incidence of obesity in this region may not be attributable to the high consumption of fast food and oily food since this region is predominantly an agriculture area at the time of the survey reported by Al-Othaimen et al. (2007). Further, the weather is relatively cold which might make most of the population to be indoor and thus making them less physically active. With the massive development of Hail turning into a fast growing sub-urban city, a through epidemiological survey in this region with standard questionnaire for the prevalence of obesity, diabetes mellitus and breast cancer with statistically significant number of population seem to be desirable soon.

Obesity also leads to insulin resistance and increased insulin concentrations which have been correlated with BMI, mortality in breast cancer regardless of estrogen receptor (ER) status (Goodwin et al., 2002; Lorincz and Sukumar, 2006). Insulin is also a growth factor with pre-eminent metabolic but also mitogenic effects, and its action in malignant cells is favored by mechanisms acting at both the receptor and post-receptor level. Insulin and insulin like growth factors (IGFs) can activate ER-alpha transcriptional activity in breast cancer cell lines (Sachdev and Yee, 2001; Moschos and Mantzoros, 2002).

Furthermore, several studies have implicated obesity and diabetes mellitus as risk of developing breast cancer in postmenopausal women (Mink et al., 2002; Michels et al., 2003; Alimova et al., 2009; Cleary and Grossman, 2009; Gonzalez-Angulo and Meric-Bernstam, 2009; Gunter et al., 2009; Hirsch et al., 2009; Rice et al., 2009, Bodmer et al., 2010; Giovannucci et al., 2010). Obesity in postmenopausal women and sedentary lifestyle increase the risk of breast cancer. Current oral contraceptive use, especially by young women, and prolonged use of hormone replacement therapy causes a moderate increase in the risk of breast cancer. Hamilton et al. (1995) quantified the prevalence of obesity in females in the infertility clinic at King Faisal Specialist Hospital in Riyadh: 80% of non-fertile females were either overweight or obese.

However, the risk of breast cancer in premenopausal women with diabetes still needs much attention. There is a recent report by Okail et al., (2009) which describes the obesity and diabetes mellitus as causative factors contributing to the increased breast cancer risk in premenopausal women. Further evidence in this correlation of diabetes mellitus and breast cancer came from the use of anti-diabetic drugs such as metformin to treat various cancers including ovarian and breast cancers (Alimova et al., 2009; Rice et al., 2009; Bodmer et al., 2010; Giovannucci et al., 2010). Epidemiological, preclinical, and retrospective data provide the rationale to study the role of anti-neoplastic metformin for breast cancer therapy in clinical setups (Gonzalez-Angulo and Meric-Bernstam, 2009).

The cancer incidence in Saudi Arabia shows no signs of decline, while in the USA, overall decline in cancer incidences and cancer deaths in both men and women have been observed (Jemal et al., 2009). With an increasing evidence of causative complex relationship of diabetes

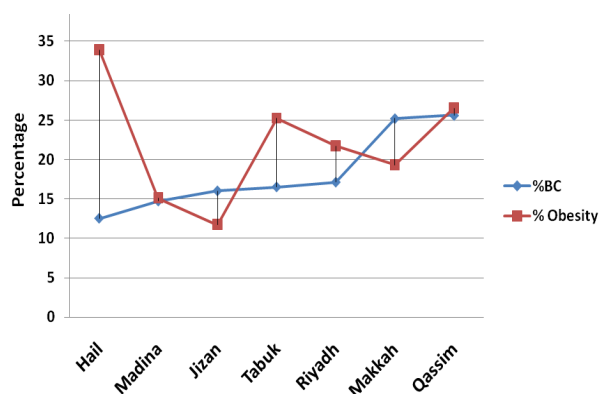


Figure 1. Correlation between the Percentage of Breast Cancer and Obesity in Selected Regions of Saudi Arabia. Data extracted from the NCR Report (2003) and Othaimen et al. (2007)

and cancer, it is now required more clinical attention and better-designed studies in order to culminate this upward trends of cancer and diabetes mellitus in the Kingdom. Obesity which is largely preventable by adopting healthy food and lifestyles seem to be undoubtedly a common reason for both breast cancer and diabetes mellitus. A thorough epidemiological survey throughout the Kingdom may serve in identifying the region-specific etiological causes of these complex diseases. This also will subsequently be helpful in launching countrywide health awareness and public education programs to combat these diseases and save the susceptible population from diabetes and breast cancer

Acknowledgements

There is no conflict of interest with this paper.

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