

Molecular Epidemiology of Breast Cancer in Iran: A Review Article

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ABSTRACT

Breast cancer (BC) was the most common cancer in Iran, accounting for 12.9% of all incident cancer, and was the 5th leading cause of cancer death in 2020. The latest age standardized incidence rate (ASIR) of breast cancer was 35.8 in Iran and is expected to increase to more than 70 per 100,000 by the end of 2030. Incidence of breast cancer had a clustering pattern in Iran, while central provinces had the highest ASIR (72 per 100,000 population), and South East provinces had the lowest ASIR (5-11 per 100,000 population). Numerous studies have shown that the peak incidence of breast cancer was occurred in the age group of 40-49 years in Iran. There has also been reported a rapid increase in the incidence in young women from different regions of the country. Known molecular and cellular processes involved in the development of breast cancer in Iranian BCs have been reported from various studies in recent decades, and the most well-known and prominent genes susceptible to breast cancer were BRCA1 and BRCA2. They acted as tumor suppressor genes and inherited mutations leading to chromosomal instability. However, non-coding RNAs, epigenetic alterations, signaling pathways, immune responses, and antioxidant-related genes are the main molecular processes associated with the progression of breast cancer among Iranian patients. While we are facing a significant increase in the incidence of breast cancer, with a lower survival rate, breast cancer is currently considered as one of the major health problems in Iran, which emphasizes the importance of providing and designing prevention and early detection program of breast cancer.

Keywords: Breast Cancer, Incidence, Mortality, Prognosis, Iran



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1. Introduction

According to the latest cancer incidence and mortality estimates provided by GLOBOCAN in 2020, breast cancer surpassed lung cancer and was the most common cancer worldwide. Breast cancer was the fifth leading cause of cancer death, while the most common cause of cancer mortality in women in less developed countries and the second leading cause of cancer mortality after lung cancer in developed countries (1). There was globally an elevated incidence rates due to dramatic changes in lifestyle, reproductive and hormonal risk factors (2-4). According to the Global Burden of Diseases (GBD) study results, globally, the age standardized incidence rate (ASIR) increased significantly by 17.1%, while the age-standardized mortality rate (ASMR) decreased by 10.6% between 1990 and 2017 (5, 6).

In terms of incidence, there is a significant difference in all regions of the world, so that this rate varies nearly

four times in different parts of the world. This rate is still the highest in developed countries (annual ASIR rates of 90 and 92 per 100,000 in Western Europe and North America) and less common in African countries (annual ASIR 27 per 100,000 in African and Asian countries). There were still low survival rates in transitioning countries like sub-Saharan Africa and Asian countries that was attributed to late-stage diagnosis of breast cancer, and not availability of organized population-based screening modalities (1, 7-9). So, the latest recommendations for breast cancer screening may be performed differently than American and European countries with African and Asian countries, and actually recent guidelines (ACS and NCCN guidelines) didn't work in these countries (10, 11). Efforts to detect breast tumors early by increasing and improving breast cancer awareness, promoting clinical breast examinations by expert health care providers, are key components in improving the

prognosis in low- and low, middle-income countries (1, 12). Recently, however, advances in technology in approaches to genetic and epigenetic alterations have allowed scientists and physicians to have access to early detection and better decision-making in the diagnosis of breast cancer. These approaches, as personalized screening (or precision medicine), are performed for each patient based on specific genetic characteristics, personal and / or family history of breast cancer, and clinical parameters and other risk factors (13, 14). We hope to achieve these personalized screening modalities in the future using consolidated algorithms using "Polygenic Risk Score". However, it is not yet applicable in most low-middle income countries (15-17).

According to the last GLOBOCAN 2020 report, breast cancer was the most common cancer in Iran which accounted for 12.9% of all incident cancer, and 5th leading of cancer death (6.1% of cancer related deaths), with an age standardized incidence rate (ASIR) of 35.8 and age standardized mortality rate (ASMR) of 10.8 per 100,000 (1) This rate has increased compared to previous reports related to 2014, and has been expected to rise to more than 70 per 100,000 by the end of 2030 (18, 19). Since the average age of breast cancer patients in Iran was 49 years, with the majority BCs diagnosed at a younger age, this led to productivity losses from cancer in this age groups, and impact additional economic burden for BCs (20). However, a study from northwestern Iran emphasized that there was no significant difference in the mean age of breast cancer patients in the female group, indicating that breast cancer did not occur earlier in the study population. In fact, the difference between the mean ages in the diagnosis of breast cancer was due to biased results in different ways. The first is that those who are in earlier birth years are less likely to be diagnosed at younger ages. Second, those in the later years of life are less likely to be diagnosed at an older age, and similarly the probability of being caught at a later age is zero for a significant portion of the study population. However, both of these biases are in the same direction; underestimating means diagnosis age for later birth cohorts (21). Also, improving diagnostic facilities and early detection of breast cancer may reduce the average age of diagnosis in recent decades (22, 23).

Although breast cancer is a costly disease worldwide, the economic burden of breast cancer in Iran is remarkable and is expected to rise significantly due to the increase in incidence rates (24-26). The increasing trend of breast cancer in Iran, especially in the population of young women (27), as well as the close relationship between this cancer and risk factors such as significant lifestyle changes with western culture, environmental factors and genetic factors (19), are underlying reasons for the importance of studying emerging trends and increasing the incidence and mortality of this cancer in the country (2, 28-31).

Late-stage diagnosis of breast cancer is another main challenge in Iran, that was associated with patient and system related factors (32-34). According to multi-central studies socio-economic status, place of residence, lack of knowledge and awareness about breast cancer screening modalities were the main reasons leading to late stages of presentation among Iranian women (10, 11, 35). So organized and effective early detection and screening programs are important for reducing breast cancer burden (36, 37). In this article, we aim to review and recognize the latest data on the incidence, survival and molecular approaches of breast cancer from different regions of Iran.

2. Literature search strategy

We searched all available databases including Web of Science (ISI), PubMed, Medline (Ovid), Scopus, Embase, Google Scholar, Journal Citation Reports (JCR), Clinical Key, CINAHL Plus with full text (EBSCO), as English databases, and SID, Magiran, Medlib, and Irandoc as Iranian databases. All manuscripts were screened for eligibility according to our aims and outcomes of interest. We had no restrictions on time, language and type of included manuscripts. The search strategy was based on keywords including: Breast, Malignancy, Cancer, Incidence, Prevalence, Survival, Mortality, Epidemiology, Molecular, Genetic, BRCA1, BRCA2, and Iran. Responsible authors performed the review of the literature and compiled all the results.

3. Incidence of Breast cancer

Although the burden of breast cancer in Iran is low, the incidence and mortality of both has increased in recent years in the country (29, 38, 39). The importance of increasing the incidence of the BC in Iranian women is more important than other Western countries in terms of early disease outbreak, however a very rapid increase in the rate of age-specific incidence in young women (over 25 years old) has been reported from different regions of the country (2, 28-31). Numerous studies revealed that the peak incidence of breast cancer was occurred in 40–49-year age groups in Iran (2, 28-31, 40). This pattern was similar to some other Asian countries, but in contrast with incidence patterns of western countries, where their peak age was in the 6th decade of life (41-43). The incidence of breast cancer had a clustering pattern in Iran (44) The central provinces (Tehran and Alborz) had the highest ASIRs (72 per 100,000 population), while the South East provinces had the lowest ASIRs (Khorasan and Sistan & Balochistan) with ASIR of 5-11 per 100,000 population (28, 44, 45).

Breast Cancer incidence was evaluated in Golestan Province during 2004-2013 by Fazel et al., and 2,106 new breast cancer were diagnosed and recorded. The breast cancer ASIR was increased from 18.3 to 31.7 with an overall ASIR=29.1 per 100,000 during the

study period, and there was significantly increasing in ASIR trend by annual average percentage changes (AAPC) of 4.4% per year (95% CI: 1.2-7.8) during 10 years of study (46). Meanwhile, this study showed that the increasing trend in the incidence of the breast cancer in younger age groups is about 2 times higher, with an AAPC of 10.0 in the age groups of 20-29 compared with AAPC=5.1 among 30-39 years (46). However, a recent ASIRs short term prediction analysis in Golestan indicated an increasing trend in breast cancer incidence by 2025, despite population aging and growth. It has been predicted that breast cancer proportion will be raised from 13.2% (in 2016) to 15.8% (in 2025), and ASIR will be increased from 38.6 to 54.8 per 100,000 women from 2016 to 2025 (30).

These increasing patterns in ASIR breast cancer have been reported from separate surveys. Time trend analysis performed on 4989 registered breast cancer in East Azerbaijan, also showed increased ASIRs from 21.7 in 2007, to 36.9 in 2016 (per 100,000 women), with an overall APC=5.5% and AAPC=6.1% (29, 47). Cancer trends in a province of Southwest of Iran, during 2003–2016 showed that age adjusted incidence rates (ASIRs) of all cancers were increased from 24.48 to 139.43 per 100,000 women, however breast cancer incidence was rising significantly in this region (48).

4. Survival of Breast Cancer

Despite recent efforts for early detection and targeted therapies for breast cancer in Iran, the overall survival rate is much lower than in developed and western countries (29). As a meta-analysis performed on a total of 21 articles from different regions of the country (n=12,195 BCs) one-, three-, five- and ten-year survival rates of breast cancer in Iran were estimated to be 95.8% (94.6-97.0), 82.4% (79.0-85.8), 69.5% (64.5-74.5), 58.1% (39.6-76.6), respectively (49). The most recent Meta-Analysis of breast cancer survival rates in almost 32 studies conducted in Iran showed one-, two-, three-, five-, and ten-year breast cancer-specific survival rates of 94 (92.4–95.6), 88 (81.4–94.6), 80.8 (77.5–84.1), 74.8 (64.4–85), 69 (64.5–73.4), and 59.2 (49–69.4) percent respectively, with better survival rates compared with previous results. Also, these results were compared with other Eastern Mediterranean Region (EMRO) Countries, while Iran had the highest 10-year survival rate, and the lowest was reported from Bahrain (45%). However, one-, two-, three-, five-, and ten-year breast cancer-specific survival rates in Iran were higher than total rates of Eastern Mediterranean Regional countries (93.3, 85.8, 79, 69.2 and 55.5% respectively) (50).

In a study performed by Meshkat et al., (2020) 3184 breast cancer women with a mean age of 49±12 yrs. were studied in Tehran. The average mortality rate was about 17% in different age groups of breast cancer patients, and one, 5, 15, 20, and 25- year survival probabilities of the patients were 95%, 75%, 60%,

47%, 46%, and 46% respectively. Compared to the previous studies conducted in Iran, their results showed an increase in the 5-year survival rate due to an increase in awareness or improvement of treatments in Tehran, the capital of Iran (51).

In another study from North West of Iran, East Azerbaijan, The 10-year crude mortality rate was 3.34 (per 100,000). The one-, two-, three-, five-, and ten-year breast cancer-specific survival rates were 92 (95% CI 0.91-0.93), 88 (95% CI 0.86-0.90), 84 (95% CI 0.83-0.86), 77 (95% CI 0.74-0.80) and 65 (95% CI 0.60-0.70), respectively. Compared to overall survival rates of breast cancer patients in Iran, there was a better breast cancer specific prognosis in East Azerbaijan (29). However, survival rates were increased compared with previous reports from this region (52).

5. Genetic of Breast Cancer in Iran

Breast cancer is a multivariate and heterogeneous disease, while modifiable, relevant and unchanging factors contribute to cancer development (53). Knowing and detecting the molecular changes and genetic susceptibility on the risk of breast cancer may have important impact in developing and establishing risk assessment for breast cancer screening and early detection, as well as implementation of choice treatment guidelines (13, 14, 54, 55). Known molecular and cellular processes involved in breast cancer progression in Iranian BCs have been reported from various studies over the past decades, which were included as: tumor suppressor genes, genes involved in cell cycle control, signaling pathways (EGFR, VEGF), Immune response genes, DNA repair associated genes, and Antioxidant related genes, drug metabolism-related genes, steroid metabolism genes, epigenetic modifications, and miRNAs. Among these, the most well-known and prominent breast cancer susceptibility genes were BRCA1 and BRCA2, which acted as tumor suppressor genes, and inherited mutations in each subject led to chromosomal instabilities (CINs) (56, 57). However, the non-coding RNAs, epigenetic modifications, signaling pathways, immune responses and antioxidant related genes are the main molecular processes associated with breast cancer progression among Iranian BCs (56, 57). Meanwhile, patients with hereditary BC, but BRCA1/2 negative had different putative mutagenic variants in known BC susceptibility genes (58). Large mutational analysis and variant classification on Iranian BCs from different ethnic groups in Iran showed that the frequency of major pathogenic mutations including BRCA1/2 and PALB2 was 10.7% in patients with hereditary BC, compared to average rates reported from other Asian countries. However interestingly, the frequency of BRCA2 mutation is higher than BRCA1 (59). Also, some other studies confirmed that BRCA1 mutations are less common in Iranian BCs (60-63). These results also suggest that offering genetic testing for women with early-onset breast cancer (age at <40) with other

hereditary criteria may not be efficient, and despite NCCN criterion, “Young Age at Onset” alone did not indicate hereditary BC in Iranian women (59).

6. Discussion and Conclusion

While we are facing a significant increase in the incidence and mortality rates of breast cancers in Iran, especially in the younger population, breast cancer is currently considered as one of the major health problems in Iran, which emphasizes the importance of providing and designing prevention and early detection programs of breast cancer in the country (46). It is noteworthy that Iran has a basic health network (PHC). This network is well organized and is credited with improving health outcomes and can provide a high level of coverage of breast cancer awareness and primary care at the first level (64, 65). However, socio-cultural taboos and beliefs, poor knowledge and attitudes, low availability and coverage of screening methods indicate that this system has not been successful so far. Also, full coverage of diagnostic and screening methods in the content of the monitoring system created and implemented in Iran is very important (66, 67).

While there were racial and ethnic disparities in the diagnosis of early-stage breast cancer and stage-specific survival rates based on the molecular subtype, further work and studies are needed to modify these differences that have deep-seated implications for the early detection and survival of breast cancer (68, 69). Knowing the molecular characteristics and gene expression profile of molecular subtypes of breast cancer is the first step in developing the best and reliable diagnostic and therapeutic approaches (69-71). Differentially expressed genes (DEGs) analysis across different subtypes of breast cancer is another approach as an advanced technology for early diagnosis and timely screening of breast cancer (72, 73). However, significant global and geographical differences in the incidence and risk of breast cancer are inevitable (74, 75). Therefore, new approaches and guidelines in breast cancer screening, based on advanced and comprehensive risk assessment models, are moving towards personalized breast cancer screening and prevention methods (76). Known risk factors for breast cancer (positive family history, endocrine exposure, personal history of breast benign and/or malignant masses, lifestyle pattern, age, and breast density) have an accurate potential to develop breast cancer among average – risk women. However, identifying genetic variants, using genome-wide association, provides a polygenic risk score (PRS) for each volunteer (77, 78). This personalized approach will be a promising strategy for early detection and prevention of breast cancer. However, the big question is still: “Are communities ready for personalized breast cancer screening?” (79, 80).

Recently, some good trials were conducted in the country as the “Health Belief Models (HBM)”, which

measured women’s performance regarding breast cancer screening methods, and lifetime risk of breast cancer in Iranian women (81-83). Unfortunately, estimated 5-year and lifetime risk of breast cancer was high among Iranian women and were comparable to Western countries where they had a higher incidence (81). The priority of Iran’s health policy should be to identify the most appropriate risk assessment tool, screening method, and target age group for breast cancer.

The close relationship between breast cancer and risk factors such as dramatic lifestyle, reproductive and hormonal risk factors, as well as environmental and genetic factors are underlying reasons for the importance of studying emerging trends and increasing the incidence and mortality of this cancer in the country.

Declarations

Ethics approval and consent to participate

This study has been approved by the ethics committee of Tabriz University of Medical Sciences as a confirmed research project (Grant Number: IR.TBZMED.REC.1396.524). There was not any patient information and intervention.

Consent for publication

Not applicable, this manuscript does not contain data from any individual person.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors have no conflicts of interest.

Authors' contributions

(1) RD, SD: designed of the study, supervised the project, abstraction data, and analysis of data, prepared the draft of the paper and finalized it based on the comments from the other authors.

(2) MH: participated in the data collection, data linkage

(3) SD, ZS, ND: provided technical support and consultation during the manuscript writing.

All authors reviewed the draft of the manuscript and participated in the interpretation of the results and approved the final version.

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