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# Assessment of Tools to Diagnose Cancer in Patients with Early Stage Breast Cancer: A Systematic Review

**Mohsen Pakdaman [1], Hamidreza Dehghan [2], Habibeh Ziadpoor [2*], Firoozeh Abolhasanizade[3], Seyedeh Mahdieh Namayandeh [2]**

[1] Health Policy and Management Research Center, Department of Health service Management, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2] Research Center of Prevention and Epidemiology of Non Communicable Disease, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[3] Department of Surgery, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

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***Corresponding Author:**
Habibeh Ziadpoor
Research Center of Prevention and Epidemiology of Non Communicable Disease, School of Public Health, Shahid sadoughi University of Medical Sciences, Yazd, Iran.

**Email:**
rhziadpoor@gmail.com

**Tel:**
+98-9211915711

***ABSTRACT***

**Background:** Breast cancer is an uncontrolled and unnatural proliferation of cells in different breast tissues. The first measure to diagnose breast cancer is an examination by a surgeon followed by mammography, sonography, sampling, and other diagnosing methods. Given that there are several methods to diagnose breast cancer, and most of them are quite expensive, the present systematic review compares the expenses and effectiveness of different methods to diagnose breast cancer.

**Methods:** The study was carried out as a systematic review through searching databases, i.e., PubMed, Web of Science, Magiran, Scopus, and Embase for articles published from March 1999 to May 31, 2017. The research articles regarding health technology assessment and economic assessment (n = 8) were examined.

**Results:** Generally, conducting MRI screening and digital mammography every six months after the age of 30 are proved to be the most efficient and economical methods to screen carriers of BRCA (BReast CAncer) mutated genes. Besides, implementing both the techniques simultaneously was more cost-efficient with BRCA1 compared to BRCA2. Some studies have revealed that genetic tests and Oncotype tests, in particular, were the most cost-efficient methods to diagnose the disease, especially in its early stages.

**Conclusion:** Consequently, indexing gene expression in individuals with BRCA gene mutation is revealed to more cost-efficient.

**Key words:** BRCA1/2 gene, Breast cancer, Breast cancer diagnosis, Gene expression indexing technology, Cost-effectiveness

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## Introduction

Concepts such as individual and public health are undoubtedly the most important aspects of life and life-long goals for humans (1). Cancer is one of the world-leading diseases causing anxiety and depression in society, especially the patients and their families. It is defined as uncontrolled proliferation of cells. Normally, cell proliferation is controlled by cell division cycle mechanists that are, in turn, controlled by a variety of genes (2).

Breast cancer is one of the major malignant tumors and is affected by environmental factors and genetic damage. Unfortunately, it is the second cause of death in the West, and the prevalence of this cancer has been growing in Asian regions over the past few years. The incidence rate of breast cancer in Iran's female population is 24 cases per 100,000 people (3) and is the most common cause of death in women between 35 and 55 years old. The causes of breast cancer are aging, family history, infertility, first pregnancy after the age of 30, excessive use of animal fat, etc. (3).

Since different cancer treatments and diagnostic methods are available, the authors decided to compare the economic evaluation of gene expression index technology and breast cancer diagnostic tools, especially mammography, in patients with early-stage breast cancer to find the most cost-effective method. Finally, the authors provide the latest information for policymakers to adopt the best program accordingly.

Studies have shown that hereditary and genetic factors can be the facilitators of breast cancers. One-third of the total number of breast cancer patients have a history of positive breast cancer in one or more relatives (4). Since the clinical process of the disease differs from patient to patient, it is not easy to predict the outcome of the disease. However, determining the factors that can predict the outcome either directly or in directly, can help make clinical decisions and choose the right intervention (5).

Changes in BRCA 1/2 genes make some women susceptible to breast and ovarian cancers. While pathogenic changes in these genes increase the risk of breast/ovarian cancer in women by 85 %, researchers try to find additional genes to explain other types of breast cancer (non-hereditary).

Individuals who need a genetic check for breast cancer are those:

- Diagnosed with breast cancer before the age of 50.
- Diagnosed with breast cancer in both breasts (two-side form).
- With one or more family members diagnosed with breast and ovarian cancers simultaneously.
- With two or more cases of breast cancer related to the BRCA gene in one of the family members
- Men with breast cancer (6).

Different factors such as the tumor size, engagement of lymphatic glands, and pathology determine the severity of the disease and the right intervention (7).

Given that there are several methods to determine breast cancer, the present systematic review study examines the economic aspect of breast cancer diagnosing methods. The results can be used to determine the most ethical, cost-efficient, and safest method to diagnose breast cancer.

## Materials and Methods

The study was carried out as a systematic review through searching articles published from March 1999 to May 31, 2017, in PubMed, Web of Science, Magiran, Scopus, and Embase databases. All clinical trial studies (CCT, RCT) related to costs and cost-effectiveness of breast cancer diagnosing methods (genetic consultation, clinical examinations, mammography, genetic tests, and QALY outcomes) were also included. The search was done using the keywords "gene expression, breast cancer, breast neoplasm, the cost-effectiveness of MRI and mammography, BRCA 1/2 and breast cancer, genetic testing for breast, genomic profile of breast, and MRI for breast cancer" and their Farsi equivalents. Specifically, commands such as "OR" and "AND' were used in the search for precise results.

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Quality assessment was done based on CHEC (Consensus on Health Economics Criteria Checklist) (8). The checklist included 20 items that examine perspectives such as the study population, study plan, economics, validity of models and methods, measurability of results, cost-effectiveness, results and follow-up, and ethics observation. The items were scored from 1 to 12. Each item was assigned with a score based on the determined measures that represent the quality of the study.

The selection process for the present study was based on the CHEC checklist (Consensus on Health Economics Criteria**)**, which included 20 items. Accordingly, one article received 19 points, two articles received 17 points, four articles received 16 points, and one article received 15 points.

### Search method

The efficiency of the methodology for systematic review has been supported by other studies. In addition to the search in the mentioned databases, the references of the found articles were used for manual search, and experts were consulted by exchanging information via email.

### Inclusion/exclusion criteria

All the CCT and RCT studies were included in the current study and those that did not have the keywords were excluded. Furthermore, studies that only covered one aspect of the subject and were limited to definitions and costs of genetic tests for breast cancer were excluded as well. IR.SSU.SPH.REC.1396.69.

## Results

The search resulted in 1355 articles, out of which the irrelevant and repetitious articles were excluded based on the titles. Consequently, 382 articles were deleted due to their duplicate article titles, and 973 articles were examined. After their examination, 282 articles were further eliminated in the title screen and abstracts due to their irrelevant content and different purposes. As a result, 691 articles were left out of which 576 articles were further deleted since they examined only one case study of cancer screening methods and that no comparative aspect existed. Out of the remaining 115 articles, 107 articles were additionally excluded because the three keywords, i.e., cost, cost-effectiveness, and quality of life, were not examined simultaneously in the result and discussion section of the articles. As a result, eight articles left were thoroughly checked by one of the reviewers in terms of inclusion and exclusion criteria, and any form of ambiguity was settled by the second reviewer. Eventually, eight articles were selected in the final phase, from which four articles were scored 9, two articles were scored 10, one article was scored 11, and one article was scored 12 according to CHEC (Figure 1).

Following is a brief explanation of the articles selected for the present research work.

A study by Henry J et al. (9) on the effectiveness of mammography, MRI, clinical test, and diagnostic tests explained that genetic tests were cost-effective only in the early stages of breast cancer and young ages. In terms of cost, however, MRI was more economical compared to genetic tests.

Houssami et al. (10) compared three breast cancer screening strategies in the US, UK, and Netherlands and concluded that the strategy adopted in the Netherland was more cost-effective.

Ketil Heimal et al. (11) examined the expenses of genetic consultation, clinical tests, biopsy, and mammography and found that genetic consultation was more cost-effective for patients with a family history.

Similarly, three diagnosing methods, namely MRI, mammography, and gene expression indexing technology, were compared by Eccleston et al. (12). They reported that the former method was more cost-effective in individuals with a mutated BRCA gene.

Other researchers such as Cott Chubiz et al. (13) examined the cost-effectiveness of MRI and digital mammography in individuals with mutated BRCA1/2 gene. They concluded that digital mammography at the age of 25 was the most cost-effective method to determine the gene mutation

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and that both methods were more cost-effective with BRCA2 compare with BRCA1.

Margaret L et al. (14) concluded that genetic tests were more cost-effective than mastectomy and oophorectomy.

In the same line, a study by Katz et al. (15) claimed that the special ward cares for breast cancer were more cost-effective than the cares provided in the general ward. Besides, the ICER of these cares, including medical tests and periodical examination, was 2.13 per QALY (quality-adjusted life year).

Furthermore, a study by Miguel A et al. (16) showed that the MammaPrint test was more cost-effective than a DC test.

**Table1.** Summary of study results

| Year | Author(s) | Goal of study | Costs | Method | Result |
|---|---|---|---|---|---|
| 2017 | Anthony Eccleston, et al. (12) | A Cost-Effectiveness evaluation of Germline BRCA1 and BRCA2 Testing | The index case (full genes):306<br>MRI, per year: 191<br>Mammography, per year:55<br>Total with surgery:13189<br>Total without surgery:9373 | The probability of germline BRCA mutation testing being cost-effective at a threshold of d20,000 / QALYwas99.9 00 %. | BRCA testing compared with no testing, resulting in an ICER of d4,339 / QALY |
| 2015 | Gregory Katz et al. (15) | Economic impact of gene expression profiling in patients with early-stage breast cancer in France | Mean cost of chemotherapy in the private hospital setting: EUR 8,218.<br><br>Mean costs of adjuvant chemotherapy were EUR 10,305 from a societal perspective. | QALY:<br>OncotypeDX: 11.320<br>Standard care:11.160 | ICER from a healthcare payer perspective: EUR 2,134.36 per QALY gained<br><br>ICER from a societal perspective Oncotype DX is dominant to standard care (cost and lifesaving) |
| 2013 | Henry J. Folse1 et al. (9) | Mammography<br>MRI<br>Clinical breast exam diagnostic tests | Costs ($) of mammogram: 35.810<br>MRI:83.716<br>Clinical breast exam:12.169<br>diagnostic tests:32.259<br><br>Note:<br>Screening on a more high-risk people will result in a lower cost per QALY.<br>This is for a test with a cost of only $945, which is much lower than the cost of the BRCA test, which ranges from $3000 to $ 4000. | For people with a risk of 16 % to 28 %, it resulted in a 1.910 % reduction in cancer deaths, saving 0.005 QALY per patient for $163.264<br>Per QALY. These results were sensitive to the age at which the test is given, | The ICER per QALY of the genetic test were $141,415 |

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| Year | Author(s) | Goal of study | Costs | Method | Result |
|---|---|---|---|---|---|
| 2013 | G. H. de Bock et al. (10) | Comparing the Dutch strategies UK strategies US strategies | Cost of: - Ammography (National Breast and Cervical Cancer Early Detection Program (NBCCEDP) | | The ICERs are a few thousand euros per life-year Gained, indicating that the Dutch strategy is cost-effective compared with the UK strategy. |
| 2013 | Niguel ngel Seguı´l et al (16) | Cost-effectiveness analysis from the Spanish National Healthcare System perspective | Cost analysis: Mammaprint:2675<br><br>Oncotype DX:3200<br><br>Chemotherapy: 2825 | QALY: Mamma print: 3.314<br><br>Oncotype DX:3.309 Adjuvant:3.293 | ICER MammaPrint vs Adjuvant: e83,544 / QALY<br><br>ICER MammaPrint vs Oncotype DX: Dominant |
| 2013 | Jessica E Cott Chubiz, et al. (13) | Cost-effectiveness of Alternating MRI and Digital Mammography Screening in BRCA1 and BRCA2 Gene Mutation | Cost: -BRCA1: MRI25:1000 Alt30:2400 BRCA2: MRI25:1400 Alt30:3600 | QALYs*: -BRCA1: (MRI25 / Alt30): 39.440 -BRCA2: (MRI25 / Alt30): 45.590 | ICER: BRCA1(MRI25/Alt30): $226,500 DM25 :Eliminated Alt25 :$978,500<br><br>BRCA2: (MRI25 / Alt30): $554,900 DM25:Eliminated Alt30: $ 215,700 |
| 2009 | Margaret L et al. (14) | Cost-effectiveness of testing for breast cancer susceptibility genes | Cost: Genetic testing:2542 mastectomy:12254 oophorectomy:5011 | QALY: Test-strategy: 22.900 no-test strategy: 22.700 | The ICERof the test strategy was $9k. The costs and effectiveness of both the test and no-test strategies are very similar |
| 1999 | Ketil Heimda et al. (11) | -Genetic counseling -Clinical examinations -Mammography -Biopsy | Cost per item in: -Genetic counseling: 163 -Clinical examinations: 46 -Mammography:61 -Biopsy:76 | In Cancer family clinic strategy, Cost per year saved:753 | The conclusion is that inherited breast cancer may be managed effectively for the cost of Euro 750–1.600 per year earned. |

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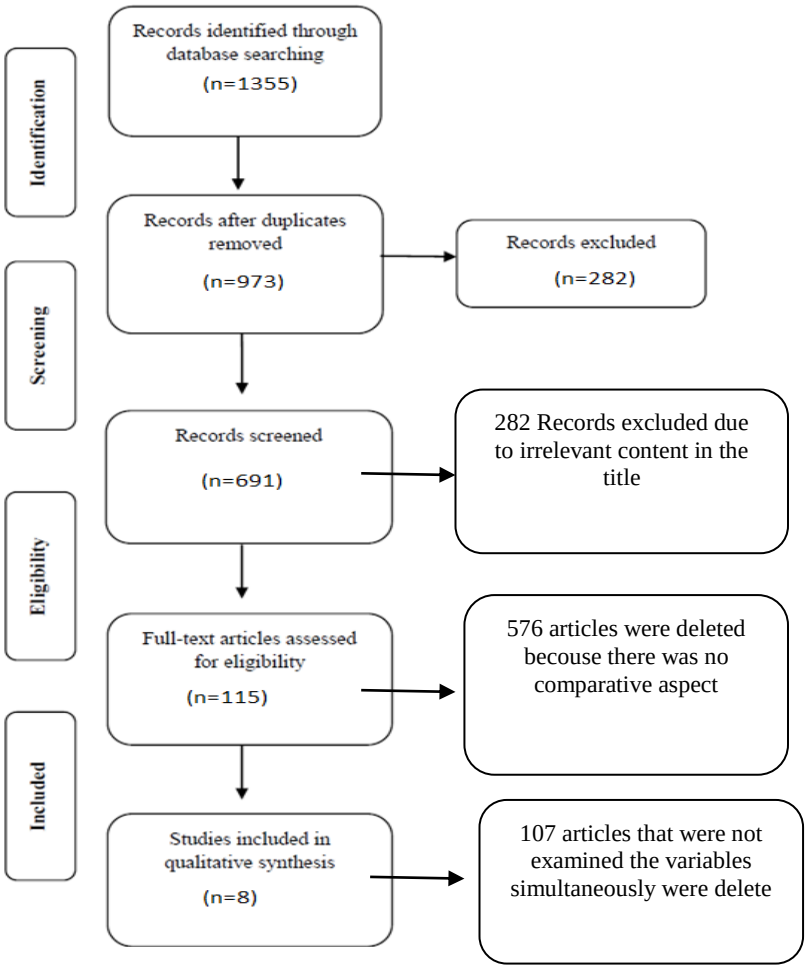


**Figure 1.** The flowchart of the study selection, according to the PRISMA protocol

## Discussion

The present study is part of a health technology assessment program to examine breast cancer diagnosing methods. In this section, the findings of each article are expressed, discussed, and compared.

Henry J Folse et al. (9) reported "cost-effectiveness of genetic tests for breast cancer risk" and the cost of mammography, MRI, clinical breast test, and diagnostic tests as follows:

Cost of mammogram 81/35 (US$), MRI = 716/83 (US$), clinical breast exam = 169.12 (US$), diagnostic test = 259/32 loaded. Therefore, MRI complementary with mammography is recommended for breast cancer screening in women with around 20 - 25 % risk of breast cancer. The cost-effectiveness of a genetic test for each QALY was US$141,415, which was higher than the other methods.

The review of "What strategies are better for women with BRCA 1/2 mutation? (A comparative cost-effectiveness simulation)" conducted by G. H. de Bock et al. (10) concluded that there was no consensus about the best strategy (mammography or MRI). The effectiveness and cost-effectiveness of screening programs implemented in the Netherlands, UK, and the USA (different in terms of period and age group) showed that the three methods were not quite different. There were small differences in terms of cost-effectiveness so and the strategy used in the Netherlands, which were better than the other methods.

Ketil H (11) found that people's attitudes about the cost-effectiveness of genetic tests on mutation

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genes had not changed over the years. In additionally, they found that genetic tests on individuals with a family history were more cost-efficient than those in other individuals diagnosed with breast cancer. These tests on individuals with a family history of breast cancer saved € 750-1600 per patient annually.

Anthony Eccleston et al. (12) examined the cost-effectiveness of BRCA1/2 genes tests and reported that QALY of the BRCA test on all women with ovarian cancer in the UK was equal to 20,000 and ICER was equal to 4.33. By conducting the test on all women, 141 new cases of ovarian cancer and 142 breast cancer can be diagnosed every year, and nearly 77 lives can be saved.

Jessica E et al. (13) examined the cost-effectiveness of MRI and digital mammography tests on women with mutated BRCA1/2 and reported that QALY of BRCA 1 and 2 was 39.44 and 44.59, respectively. Moreover, the cost-effectiveness of BRCA 1 and 2 was 226.50 and 554.90 per QALY, which means that genetic test on mutated BRCA 2 gene was more cost-efficient than that of BRCA 1. On the whole, MRI and digital mammography screening recommended every six months from the age of early 30s was the most efficient method for diagnosing the carriers of BRCA mutated gene.

Margaret L, Holland et al. (14) found that two screening strategies, one with a genetic test and one without a genetic test, were highly similar in terms of general costs. The tests on BRCA 1/2 genes saved six out of 1000 women. The tests were also recommended for individuals with a very low risk of mutation. The cost of genetic cost (US$ 2,54 ) was far less than mastectomy (US$ 12,25 ) and oophorectomy (US$ 5,011 ). On the contrary, QALY of the screening method with and without genetic test was 22.90 and 22.70, respectively, which is not considerably different. In terms of cost-effectiveness, the cost of the strategy without a genetic test was US$ 9,000 which was much higher than the strategy with a genetic test.

Gregory K. et al. (15) focused on the economic effect of gene expression indexing on early-stage breast cancer patients in France and found that the mean cost of chemotherapy in private and state hospitals was € 8.21 and € 10.30 respectively thus, the difference was not considerable.

Miguel A et al. (16) reported that the cost of MammaPrint, DX, and chemotherapy in US dollars was equal to 2, 67, 3, 200, and 2,82 respectively while the QALY of MammaPrint, DX, and chemotherapy was 3.31, 3.30, and 3.20 respectively. The investigation revealed the obvious result that MammaPrint was more cost-effective with ICER with QALY equal to 83.54.

## Conclusion

As a rule of thumb, conducting the MRI and digital mammography screening every six months from the age of early 30s is the most efficient and cost-effective method for the carriers of BRCA mutated gene. Using both the methods simultaneously on BRCA 1 gene was more cost-effective than BRCA 2. From the safety point of view, medical counseling and mammography for individuals suspected of a breast lump are more efficient and safer.

Genetic tests and DX tests, particularly in the early stages of breast cancer, are the most cost-effective method. However, it should be noted that the positive result of a genetic test only indicates that the individual has a malignant mutation in BRCA 1 or 2 and that there is a risk of developing cancer, including breast cancer. However, the exact time of developing the complication and its severity cannot be determined through these tests.

Moreover, all the tests on breast cancer patients need continuous follow-up and screening, periodically if needed.

Different strategies are efficient only when all the required capacity of basic cancer diagnosis, referral services, treatment, and pain alleviation are available. Given the care sensitivities in breast cancer patients, the screening services need to be covered by public medical insurance policies prominently in the case of the more expensive genetic tests.

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## Conflict of interests

The authors declared no conflict of interests.

## Authors' contributions

Ziadpoor H designed research; Abolhasanizade F conducted research; Pakdaman M and Dehghan H and Namayandeh SM analyzed data; and Ziadpoor H wrote manuscript. Ziadpoor H had primary responsibility for the final content. All authors read and approved the final manuscript.

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