Systematic Review of the Use of Biomarkers in Early Breast Cancer Diagnosis

Ana Pedro[1], rod tucker[2]

1 University of Hull

2 The Robert Gordon University

Abstract

Early detection of breast cancer improves prognosis. Unfortunately, in many instances patients' tumours are diagnosed following metastasis, thus making treatment more difficult and worsening their prognosis. The development of a specific biomarker for the early detection of breast cancer could potentially allow more women to be successfully treated yet at present there no validated biomarkers available. Only a few biomarkers (such as HER-2/neu, estrogen receptor, and progesterone receptor) have a limited utility for diagnosis and prognosis. Thus, there is a great need for new biomarkers for breast cancer. Here we review the current state of the art relative to the use of biomarkers in early breast cancer screening and diagnosis.

Definitions

Validation of circulating biomarkers for breast cancer screening

Defined by Ana Pedro

True positive fraction

Defined by Margaret Pepe

True negative fraction

Defined by Margaret Pepe

Introduction

Worldwide breast cancer (BC) affects around 8 million women with the most common form, accounting for 70%, being estrogen-receptor positive (ER+)[1][2].

Currently, women with suspected breast cancer are referred for mammography screening (MS) and a subsequent biopsy for confirmation of the diagnosis. However, MS is not diagnostic and can result in up 80% false positives so that only around one in 4 women with an abnormal result will be found to have cancer after further inspection of abnormal areas with diagnostic mammography (DM) and eventually a biopsy[3][4]. Early detection of BC is associated with a better prognosis[5], with the 5-year survival for stage 1 BC being 90% but only 13% for stage 4[2]. However, in up to 5% of patients, when the disease is detected the cance has metastasised, which is associated with a worse prognosis[6].

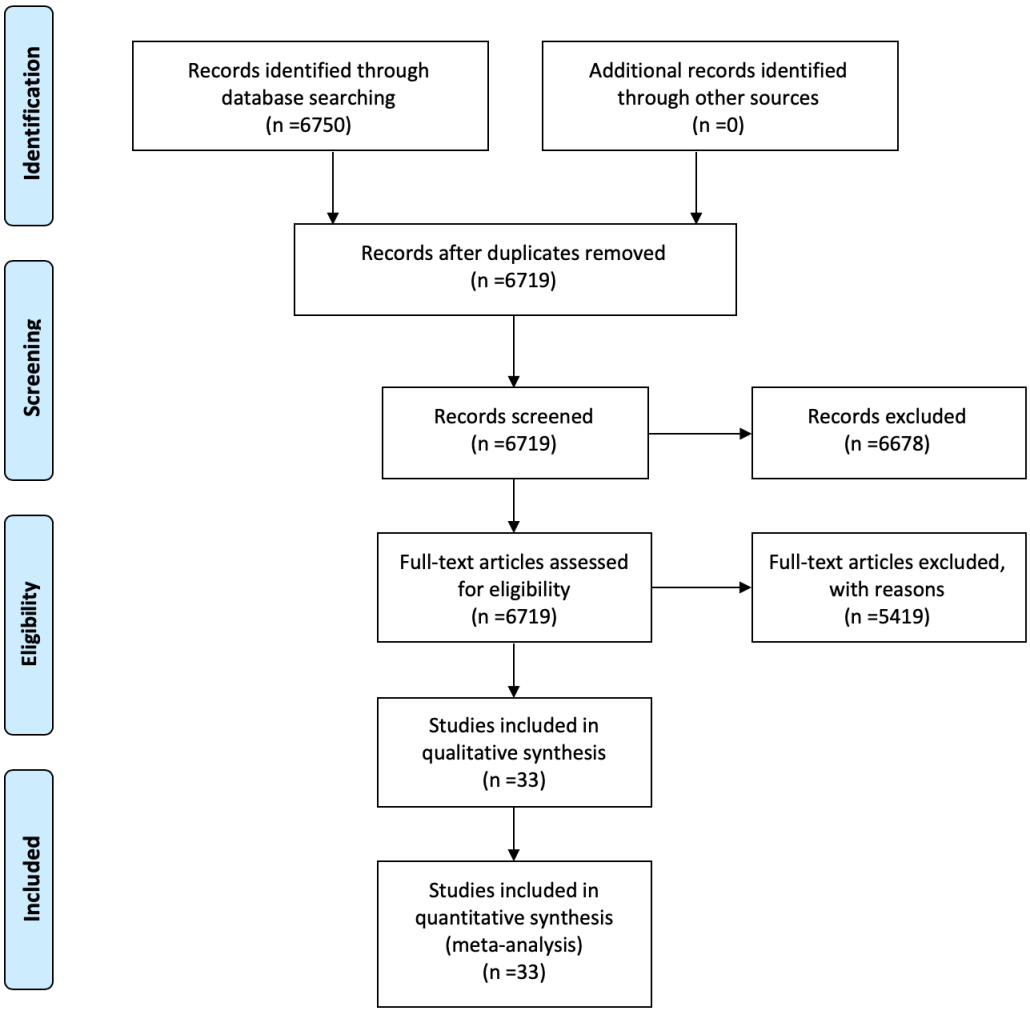
The use of disease specific specific biomarkers offers the potential of earlier detection of BC and a timelier access to treatment which would improve prognosis, however, to date, no such validated biomarkers exist. Although current markers (such as HER2/neu, estrogen receptor (ER) and progesteron receptor (PR)) are useful prognostic tools that assist with disease management, they are not sufficiently discriminatory as although these markers are significantly raised in BC are also present in normal breast cells. Thus, there is a need for biomarkers which are only present in patients with BC[7] and not in healthy women or women suffering from other pathologies such as ovarian cancer[8], endometrial carcinoma[9], endometriosis[10], fibroids[11][12], cardiovascular disease[13], Alzheimer's disease[14] or colorectal cancer[15] where these markers maybe raised as well. Also, these markers may detect ER+ or HER2+ BC, but they can't neither detect triple-negative BC or distinguish between lymph node negative (LN-) or lymph node positive (LN+) or metastatic BC.

A growing number of early diagnostic biomarkers are currently under investigation whereas others are targeted at prediction of metastatic behaviour and selection of therapy[16], though at present none of these are used in clinical practice.

Here, we review the current data on biomarkers intended for the early detection of BC.

Methods

Searches were conducted using Pubmed, Scopus, CAB abstracts, Cochrane Library, Web of science core collection, NCRI cancer research database, Google Scholars, Embase and CINAHL, for articles published in the last 5 years.



PRISMA 2009 Flow Diagram

Results and Discussion

As shown in the Prisma flow diagram, the search using the different databases and the criteria mentioned above yielded the articles mentioned in *Table 1*. Most of the developed biomarkers are proteins, RNA or DNA and a small proportion are based on tumor mechanical properties. Most came from studies in plasma/serum/blood and a minority from tissues, nipple fluid, urine or saliva. The biomarker which is closest to clinical use is the one described by Shimomura et al, 2016[17] but is not yet validated and is based on miRNA detection what makes difficult to develop a simple lateral flow assay because miRNA needs to be isolated, amplified and labelled prior to testing it in the lateral flow assay strip[18][19].

Also, the use of protein panels that detect multiple biomarkers may enhance sensitivity and specificity in a clinical setting[20], however none of the multiple biomarkers shown in *Table 1* was also yet validated.

In addition, most of the tests do not distinguish between LN- or LN- cancers or have been validated by the inclusion of advanced BC samples for comparison or specify the BC subtypes analysed what does not make possible to distinguish those cancers that are prone to progress and need treatment.

The ideal test would be specific for biomarkers that could be incorporated in a lateral flow assay and be developed to test a single drop of blood or other fluid directly into a testing strip, offering a fast and accurate diagnosis to allow a quick and adequate therapeutic intervention[21]. These tests would allow the patient to be selected for auxiliary imaging based on the presence of specific biomarkers which would specifically indicate the presence of occult cancer in patients with a normal SM.

Data and software availability

All data underlying the results is available as part of the article.

Competing interests

Biomarkers, Ltd, a split -off Roma Laboratories, Ltd is a company dedicated to the development of biomarkers for cancer.

Grant information

The authors declare no grants were involved in supporting this work.

Acknowledments

To University of Hull, University of York and Robert Gordon University libraries for use of their resources

Supplementary Material

	Database	Ref. (doi Article/Project)	Authors	Year	A. Study design	
					Q1	Q2
	Pubmed	10.3390/ijms18040878	Coy JF	2017	?	no
	Pubmed	10.18632/oncotarget.9561	Moon et al.	2016	ER+, TN, HER2+	no
	Pubmed	10.1016/j.cca.2016.08.003	Parisi et al.	2016	?	no
	Pubmed	10.1111/cas.12880	Shimomura et al.	2016	?	no
	Pubmed	10.1371/journal.pone.0122106	Garczyk et al.	2015	?	yes
	Pubmed	10.1186/1471-2407-14-176	Khan et al.	2014	?	no

Table 1

Supplementary Material
SM1: PRISMA flow diagram
SM2: STANDARD TOOL
A- Study design
1. Breast cancer subtypes analysed?
2. Distinguishes lymph node (LN) negative (-) and LN positive (+) breast cancer or precancerous lesions?
3. Control samples include healthy volunteers and patients with other conditions rather than breast cancer and advanced breast cancer patients?

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