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Risk prediction models for breast cancer: systematic review and critical appraisal

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055398
Article Type:	Original research
Date Submitted by the Author:	13-Jul-2021
Complete List of Authors:	Zheng, Yadi; Chinese Academy of Medical Sciences & Peking Union Medical College Li, Jiang; Chinese Academy of Medical Sciences & Peking Union Medical College Wu, Zheng; Chinese Academy of Medical Sciences & Peking Union Medical College Li, He; Chinese Academy of Medical Sciences & Peking Union Medical College Cao, Maomao; Chinese Academy of Medical Sciences & Peking Union Medical College Li, Ni; Chinese Academy of Medical Sciences & Peking Union Medical College He, Jie; Chinese Academy of Medical Sciences & Peking Union Medical College
Keywords:	Epidemiology < TROPICAL MEDICINE, Public health < INFECTIOUS DISEASES, Breast tumours < ONCOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Risk prediction models for breast cancer: systematic review and critical appraisal

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Word count: 2880

Figures/Tables: 5

ABSTRACT

Objectives: To systematically review and critically appraise published studies of risk prediction models for breast cancer in the general population without breast cancer, and provide evidence for future research in the field.

Design: Systematic review using the Prediction model study Risk Of Bias Assessment Tool (PROBAST) framework.

Data sources: PubMed, the Cochrane Library and Embase were searched from inception to August 2020.

Eligibility criteria: We included studies reporting multivariable models to estimate the individualized risk of developing breast cancer among women. Search was limited to English language only.

Data extraction and synthesis: Two reviewers independently screened, reviewed, extracted and assessed studies with discrepancies resolved through discussion or a third reviewer. And risk of bias was assessed according to the PROBAST (Prediction model Risk of Bias Assessment Tool) framework.

Results: 72,353 studies were screened and 36 studies with 43 risk prediction models were included in the review. Most of the studies used logistic regression to develop breast cancer risk prediction models for Caucasian women by case-control data. The most

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10 widely used risk factor was family history and the highest area under the curve was 0.943
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12 (95% confidence interval: 0.919~0.967). And all the models included in the review had
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15 high risk of bias.

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17 **Conclusions:** No risk prediction models were recommended and more key variables
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19 should be collected and validated well in the existing models in the future. And high-
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21 quality breast cancer risk prediction models assessed by Prediction model Risk of Bias
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23 Assessment Tool should be developed and validated among Asian women.
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28 **PROSPERO registration number:** CRD42020202570
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30 **Strengths and limitations of this study**

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33 1. Thoroughly conducted systematic review collecting data from major existing databases.
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36 2. Critically appraised published studies of risk prediction models for breast cancer in the
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38 general population and provide evidence for future research in the field.
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41 3. PROBAST was used to assess the quality of prediction models, which was developed
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43 through a consensus process involving a group of methodological experts in the area of
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45 clinical prediction tools and quality assessment.
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48 4. Studies only about the external validation of the present risk models were not included
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50 in the review.
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53 5. Our study highlighted high-quality breast cancer risk prediction models assessed by
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PROBAST should be developed and validated among Asian women.

Keywords: breast cancer; risk prediction model; review; quality assessment; Prediction model Risk of Bias Assessment Tool

INTRODUCTION

Breast cancer is a major public health problem, and one of the most severe burdensome cancer among women worldwide ¹, accounting for 11.7% of new cancer cases and 6.9% of cancer deaths in 2020. And the prevalence of breast cancer is projected to increase over the coming years and ranks first among all cancers in 2020 ². Prevention of breast cancer is associated with a reduction in mortality ³, and the methods of predicting women at elevated risk and prevent the disease have been less successful. Numerous breast cancer risk prediction models have been developed to identify the combined effect of risk factors of breast cancer to advise population healthy life, routine screening, genetic testing, and to direct breast cancer research. Risk-stratified screening can improve cost-effectiveness and maximize benefits and minimize harms like overdiagnosis ⁴. Individualized prediction model for breast cancer could be used in practice to assist decision making about mass screening or opportunistic screening and treatment strategy.

A recent breast cancer screening guideline ⁵ suggests that breast cancer screening increase the early detection rate and reduce the incidence if the screening is applied in

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10 appropriate at-risk populations. However, major gaps exist in our knowledge to determine
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12 the risk of breast cancer accurately in order to apply these approaches to appropriate
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14 populations of women.
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18 A lot of breast cancer risk prediction models have been developed over the past few
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20 decades. Many breast cancer risk models have undergone validation including
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22 discrimination and calibration in study populations other than those used in initial
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24 development, or have been further assessed in comparative studies. Breast cancer related
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26 predictors including hormonal factors, environmental factors, family histories, genetic
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28 factors and radiographic factors have been based on in these risk models, which would
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30 improve the generalizability. For example, the Gail model ⁶, one of the most famous
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32 models, has been widely used and validated worldwide since it was developed in 1989 ⁷⁻
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41 This study is a systematic and critical review of breast cancer risk prediction models
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43 overall by using meta-analysis and the Prediction model Risk of Bias Assessment Tool
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45 (PROBAST) ¹³⁻¹⁴ to assess estimates and the methodological features, in order to find
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47 more methods of accurate predicting breast cancer risk, prepare for the development of
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49 risk prediction models, and prevent the disease successfully for the future research.
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53 **METHODS**

Protocol and registration

The current review was designed according to the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)¹⁵ and was recorded in the PROSPERO database (registration number: CRD42020202570).

Literature search and eligibility criteria

We systematically searched PubMed, the Cochrane Library and Embase from inception to August 2020. The detailed search strategies were reported in Appendix Table 1. Articles identified from the search were loaded into EndNote X7 and duplicates were removed.

Inclusion criteria: 1) a model used data from cross-sectional studies cohort studies, case-control studies, and randomized controlled trials; 2) a model estimating the individualized risk of breast cancer; 3) a model developed for the general population without breast cancer; 4) reported a multivariable (i.e., at least 2 variables or predictors) model; 5) published in English.

Exclusion criteria: 1) external validation studies that only validated previous models in a different population without adding any additional information such as modifications on the risk factors; 2) models developed by machine learning.

Data extraction

One reviewer screened the search results based on title and abstract, a second reviewer reviewed a random sub-set (10%) of these studies independently. Full text reports were then assessed for eligibility with discrepancies resolved through discussion or a third reviewer.

We extracted information in two categories: 1) For all studies included in the review, we extracted the following information: author, publication year, study design, research method, targeted population, number of risk factors, risk factors, model performance and sample size of development. 2) For studies included validation part, we also extracted the following information: type of validation, study design, targeted population, model performance and sample size of validation. The information was extracted by one reviewer and checked by a second reviewer.

Risk of bias assessment

We used PROBAST to assess the reported prediction models, a new tool designed by a group of experts all over the world to assess the risk of bias and applicability of diagnostic and prognostic prediction models, which can be used in critical appraisal of studies that develop, validate, or update prediction models for individualized predictions¹³⁻¹⁴. In brief, it contains 20 signaling questions in four domains: participants, predictors,

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10 outcome, and statistical analysis. Signaling questions can be answered as yes, probably
11 yes, no, probably no, or no information. A domain where at least one signaling question
12 is answered as no or probably no should be judged as high risk of bias. And only if all
13 domains are judged as low risk of bias, the total bias is judged as low risk as well.
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20 Before putting PROBAST into use, we formed a ten-people study group including
21 prediction model researchers, statisticians, evidence-based medicine specialists etc. to
22 learn and practice the appropriate use of this new tool systematically. Only after everyone
23 understood all these twenty questions totally, we would move to the peer quality
24 assessment part. Risk of bias of every prediction model was assessed by two reviewers
25 independently with discrepancies resolved through discussion or a third reviewer.
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36 If there were more than one models developed in one study, we only assessed the
37 risk of bias once due to their similarity. And we also assessed the risk of external
38 validation of prediction model when it was conducted in the same article that included
39 model development.
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46 **Data synthesis and analysis**

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48 We calculated and reported descriptive statistics to summarize the characteristics of
49 the models. And we calculated 12 the most frequently used risk factors and classified all
50 risk factors into eight categories: Age, reproductive factors, family history of cancer,
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10 hormone, gene-related factors, lifestyle, medical history and test, and basic information.
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12 Classification details can be seen in Appendix Table 2. Then we used network diagram
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14 to see the connections of categorized risk factors. And we used forest plot to describe the
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16 model performance. The expected observed (E/O) ratio was not included in the forest plot
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18 because it was only reported in 6 out of 36 studies. All analyses were performed using
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20 Sata 16.0 and NetDraw.
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25 **Patient and public involvement**

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28 There was no patient or public involvement in this study.
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30 **RESULTS**

31 **Study selection**

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36 A total of 97,964 indexed records (51,193 in PubMed, 3,163 in Cochrane Library
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38 and 43,608 in Embase), 25,611 were eliminated as duplicates found in all databases,
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40 leaving a total of 72,353 publications. 38 articles were included primarily after screening
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42 by title and abstract. 1 brief communication and 1 model that was developed based on the
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44 meta-analysis were excluded while full text screening, resulting in 36 studies with 43
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46 models were included in the review eventually. (Figure 1).
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50 **Study characteristics**

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54 A brief summary of the 36^{6,16-50} included studies is presented in Appendix Table 3.
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10 The included studies were published from 1989 to 2020. And 22 of the studies were
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12 conducted over the past ten years with 5 studies published in 2017 especially. Sixteen out
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14 of the thirty-six studies used data from case-control studies to develop prediction models
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16 6,17,19,23-26,29-31,39, 40,42,45,48,50, twelve from prospective cohorts 16,18,20-22,27,32-37, seven from
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18 nested case-control studies 28,38, 41,43,46,47,49 and one from cross-sectional study 44. Twenty-
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20 eight studies used logistic regression to fit prediction models 6,17-19,22-26,28-32,34,38-50, six
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22 used cox proportional hazards regression 20,21,27,33,35,36, one used Poisson regression 16 and
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24 one used competing risk regression 37. Of all forty-three models in thirty-six studies,
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26 fourteen models were developed in Caucasian women 6,16,18,23,26,28,29,34,41,44,46,49, thirteen
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28 in multiple ethnicities women 20-22,24,27,30,35-38,43,47, eleven in Asian women
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30 17,19,31,32,39,42,48,50, two for African-American women 25,33, two in Hispanic women 40 and
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32 one in Nigerian women 45.

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41 The number of risk factors included in the models ranged from three to eighteen.
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43 Figure 2 showed the association between different kinds of risk factors after classifying
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45 risk factors into eight categories. Figure 2 showed that reproductive factors and family
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47 history of cancer were used most frequently and these two kinds of risk factors were used
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49 in 37 models together. And reproductive factors together with age, medical history and
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51 test together with family history of cancer, reproductive factors together with medical
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10 history and test, family history of cancer together with age, reproductive factors together
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12 with basic information and family history of cancer together with basic information were
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14 used in more than 20 models, 29, 28, 27, 25, 24, 21, respectively.

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17 Twenty-five studies reported c-statistics ^{18-22,26-28,30-32,34-39,41,42,44-47,49,50}, ranged from
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19 0.59(95% confidence interval: 0.57~0.61) to 0.943(95% confidence interval:
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21 0.919~0.967). Qiu, et al ⁵⁰ had the highest c-statistics (0.943, 95% confidence interval:
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23 0.919~0.967), and Lee et al ¹⁹ and Salih et al ⁴⁴ reported area under the curve (AUC) over
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25 0.8, 0.867 and 0.864(95% confidence interval: 0.81~0.92), respectively. E/O ratios can
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27 be obtained from seven studies ^{22,27,29,32,35,36,45}. Figure 3 showed that the overall AUC was
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29 0.66(95% confidence interval: 0.66~0.67) for fourteen studies ^{21, 26, 27, 30, 32, 34, 37, 38, 41, 44,}
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31 ^{45, 47, 49, 50} that reported the AUC and 95% confidence interval. And the AUCs of the
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33 subgroups in five studies ^{18, 22, 31, 39, 46} were between 0.6 to 0.7.

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36 In all these thirty-six studies, nine studies assessed prediction models with internal
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38 validation ^{22,26,27,33,39,43-46}, eight with external validation ^{23,25,29,31,37,40,48,50}, and one with
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40 both ³². Thirteen studies reported the discriminatory accuracy as the AUC ^{23,25,27,29,31-}
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42 ^{33,37,39,40,45,48,50}, and ten studies used the expected/observed event ratio (or
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44 observed/expected event ratio) to measure the calibration accuracy of the model
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46 ^{23,25,27,29,31,33,37,40,44,48}.

Quality assessment

A summary of the quality assessment is shown in Table 1. Overall, all models assessed by PROBAST in the review had high risk of bias, low risk and high risk in outcome domain and analysis domain, respectively. Almost 60% models had low risk in participants domain and more than a half had low risk in predictors domain, 27 models and 30 models respectively. (As shown in Figure 4).

The main reasons for the high risk in analysis domain were model performance measures evaluated inappropriately, categorization of continuous predictors, no reporting of overfitting and optimism in model performance and missing data handled inappropriately (Appendix Table 4).

Table 1. Summary of risk of bias assessment.

Study	Participants	Predictors	Outcome	Analysis	Overall
Gail et al ⁶	H	L	L	H	H
Rosner et al ¹⁶	L	L	L	H	H
Ueda et al ¹⁷	H	L	L	H	H
Colditz et al ¹⁸	L	L	L	H	H
Lee et al ¹⁹	H	H	L	H	H

Tice et al ²⁰	L	L	L	H	H
Tice et al ²¹	L	L	L	H	H
Barlow et al ²²	L	L	L	H	H
Decarli et al ²³	H	H	L	H	H
Decarli et al ^{23*}	L	L	L	H	H
Novotny et al ²⁴	H	H	L	H	H
Gail et al ²⁵	H	H	L	H	H
Gail et al ^{25*}	L	L	L	H	H
Anna et al ²⁶	H	H	L	H	H
Tice et al ²⁷	L	L	L	H	H
Tamimi,et al ²⁸	L	L	L	H	H
Petracci et al ²⁹	H	H	L	H	H
Petracci et al ^{29*}	L	L	L	H	H
Dite et al ³⁰	H	H	L	H	H
Park et al ³¹	H	H	L	H	H
Park et al ^{31*}	L	L	L	H	H
Anothaisintawee et al ³²	H	L	L	H	H

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10	Anothaisintawee et al ^{32*}	L	L	L	H	H
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12	Boggs et al ³³	L	L	L	H	H
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14	Brentnall et al ³⁴	L	L	L	H	H
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17	Kerlikowske et al ³⁵	L	L	L	H	H
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20	Tice et al ³⁶	L	L	L	H	H
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22						
23	Schonberg et al ³⁷	L	L	L	H	H
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25	Schonberg et al ^{37*}	L	L	L	H	H
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27						
28	Shieh et al ³⁸	L	L	L	H	H
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30	Wang et al ³⁹	H	H	L	H	H
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33	Banegas, et al ⁴⁰	H	L	L	H	H
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36	Banegas et al ^{40*}	L	L	L	H	H
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39	Eriksson et al ⁴¹	L	L	L	H	H
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41	Hsieh, et al ⁴²	H	H	L	H	H
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44	Husing et al ⁴³	L	L	L	H	H
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46	Salih et al ⁴⁴	L	L	L	H	H
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49	Wang et al ⁴⁵	H	H	L	H	H
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52	Zhang et al ⁴⁶	L	L	L	H	H
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Clendenen et al ⁴⁷	L	H	L	H	H
Wang et al ⁴⁸	H	H	L	H	H
Wang et al ^{48*}	L	L	L	H	H
Abdolell et al ⁴⁹	L	L	L	H	H
Qiu et al ⁵⁰	H	H	L	H	H
Qiu et al ^{50*}	H	H	L	H	H

* The external validation was performed in the same study.

L indicates low risk of bias; H indicates high risk of bias.

DISCUSSION

Summary of main results

This systematic review identified 36 studies with 43 risk prediction models developed and/or validated for breast cancer in general population. Most of the studies used logistic regression to develop breast cancer risk prediction models for Caucasian women by case-control data. The most widely used risk factor was family history. And reproductive factors together with family history factor were used in most models. The highest AUC was 0.943 (95% confidence interval: 0.919~0.967) from Qiu, et al ⁵⁰. And the overall AUC was 0.66(95% confidence interval: 0.66~0.67) for fourteen studies ^{21, 26, 27, 30, 32, 34, 37, 38, 41, 44, 45, 47, 49, 50} that reported the AUC and 95% confidence interval. All the

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10 studies presented a high risk of bias due to the high risk in analysis domain, which were
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12 mainly because of model performance measures evaluated inappropriately, categorization
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14 of continuous predictors, no reporting of overfitting and optimism in model performance
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16 and missing data handled inappropriately.
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19 20 **Agreements and disagreements with other reviews** 21

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23 As we can learn from the review, there were more and more risk prediction models
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25 of breast cancer over the past thirty years, and most of the models were developed in the
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27 Caucasian women, which agreed with the systematic review published by Louro et al in
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29 2019 ⁵¹. Compared with this review, we identified more prediction models and used a
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31 newly published tool to assess the quality of included models.
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35 Over the past ten years, some new variables (such as oral contraceptives, diabetes
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37 and alcohol consumption) have been included in prediction models. Increased use of the
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39 inclusion of common genetic variation in the prediction models was in accord with Louro
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41 et al in 2019 ⁵¹ and Anothaisintawee et al in 2012 ⁵². However, neither of them included
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43 models developed with potential biomarkers like tumor-associated antigens. By contrast,
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45 we included one model developed by Qiu, et al ⁵⁰ in 2019 included five tumor-associated
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47 antigens. And the model performed well with a high AUC 0.943(95% confidence interval:
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49 0.919,0.967).
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Strengths and limitations of the study

We used PROBAST to assess the quality of prediction models, which was developed through a consensus process involving a group of methodological experts in the area of clinical prediction tools and quality assessment and has been used widely in many fields⁵³⁻⁵⁶ since it came out.

Despite the strength, there are three main limitations. Firstly, because of the large number of references retrieved, only one reviewer screened the references by title and abstract. But we checked reference of relevant reviews and primary studies, finding no missed studies. Secondly, quality assessment could be thought to be subjective, which is an inherent bias of systematic review. However, two independent reviewers extracted and assessed the risk prediction models using PROBAST whose authors have indicated essentially objective guidelines and explanations. Moreover, studies only about the external validation of the present risk models were not included in the review. But during the screening of indexed records, we can learn that some models have been validated in many different populations. Take Gail for example, it has been modified and validated in many different ethnicities⁵⁷⁻⁶⁰.

Implication to research and clinical practice

Ten models^{19,30-32,37-39,42,44,49} selected predictors based on univariable analysis,

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10 causing a high risk in analysis domain, which should be avoided. Risk prediction models
11 should include predictors those are well-established and with clinical credibility
12 regardless of any statistical significance ^{61,62}. Because sometimes predictors only have
13 important relationship with the outcome after adjustment for confounding covariates, and
14 covariates hold no independent predictive power when other covariates are included ^{13,63}.

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23 Some models were high risk in analysis domain because of missing data handled
24 inappropriately, which may lead to biased associations between risk factors and breast
25 cancer as well as biased model performance because of the selectivity of participants ⁶⁴.
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32 So imputation techniques are supposed to apply when data are missing ^{65,66}.

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When developing the risk prediction models, there were only nine studies included
internal validation ^{22,26,27,33,39,43-46}, leaving most models without internal validation. Lack
of performing internal validation may increase the risk of overfitting ⁶⁷. Thus, we suggest
that internal validation should be performed before external validation.

PROBAST was created by many international experts, providing a series of
guidelines about model development and validation, which can be easily applied and
improve clinical practice of prediction models. So, the new and most recommended
methodology should be used when a new model is developed or the exiting models are
updated.

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10 In the light of the results of our review, it is still hard to recommend any of the
11 models to be applied in the breast cancer screening due to the high risk of bias. And cost-
12 effectiveness should be considered when a model is going to be applied in clinical practice.
13 Because even though the model with some risk factors that cost more to get (e.g., high
14 risk gene) has better model performance, it is still hard to be applied in poor area ⁶⁸.
15 What's more, an existing model should be modified or updated before used in another
16 group of people with different characteristics, which may improve the performance of
17 prediction models.
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30 Breast cancer incidence has risen to the first place by 2020 all over the world, which
31 makes it more crucial to develop breast cancer prediction models for different ethnic
32 groups. And in China, we have launched many breast cancer screening programs. For
33 example, Rural Women "two cancers" Check Project Management Solutions have
34 covered 31 provinces and 1437 counties since 2009. And Cancer Screening Program in
35 Urban China conducted by the National Cancer Center has covered 28 provinces and 67
36 cities with more than 4 million people involved and 2 million people screened by
37 ultrasound and Mammography since 2012, which will provide large data for us to develop
38 a high-quality breast cancer risk prediction model in Chinese and will have great
39 significance for breast cancer prevention of Asian women.
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CONCLUSIONS

All 43 models assessed in our review using PROBAST performed the high risk of bias, leaving no model is recommended in the routine screening program. Some new variables, like oral contraceptives, diabetes, and alcohol consumption, have been widely used in prediction models over the past ten years. More key variables should be collected and validated well in the exiting models to improve the model performance. And it is necessary to develop and validate high-quality breast cancer risk predication models among Asian women.

Contributors: YZ and JL conceptualized the study and created the first version of the review protocol. ZW, HL, MC, NL and JH critically reviewed the review protocol and approved it. YZ and HL screened eligible articles. YZ extracted the data, supported by ZW, MC. YZ and JL drafted the first version of the manuscript, supported by NL and JH. All authors contributed to data interpretation and critically assessed it. All authors approved the final version of the manuscript.

Funding: This work was supported by the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences grant number 2019PT320027.

Competing interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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10 **Patient consent for publication:** Not required.

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12 **Data availability statement:** All data of the current study is present in the main
13 manuscript, figures, tables and online supplemental material.
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17 **Ethics statement:** This study does not involve human participants.
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10 **Figure legends:**

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12 Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses)
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14 flowchart.

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17 Figure 2. Network diagram of categorized risk factors.

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20 Figure 3. Area under the curve (AUC) and confidence intervals reported by the included
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25 Figure 4. Risk of bias assessment (using PROBAST) of all assessed models based on
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Records identified through database searching
(PubMed 51,193; Cochrane Library 3,163; Embase 43,608)

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Records after duplicated removed

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Records excluded by title&abstract screening

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Articles assessed for eligibility

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N=2
Records excluded by full test screening:
Brief communication(1);
Development based on the meta-analysis(1)

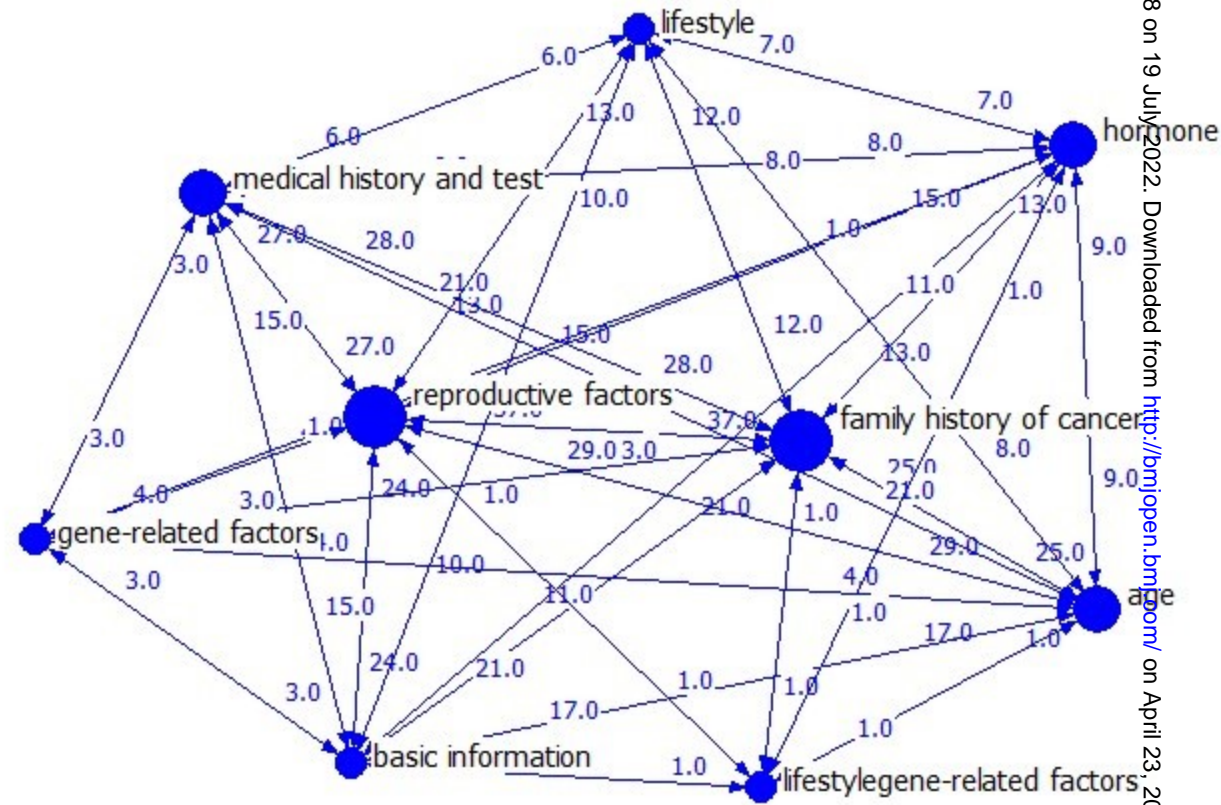
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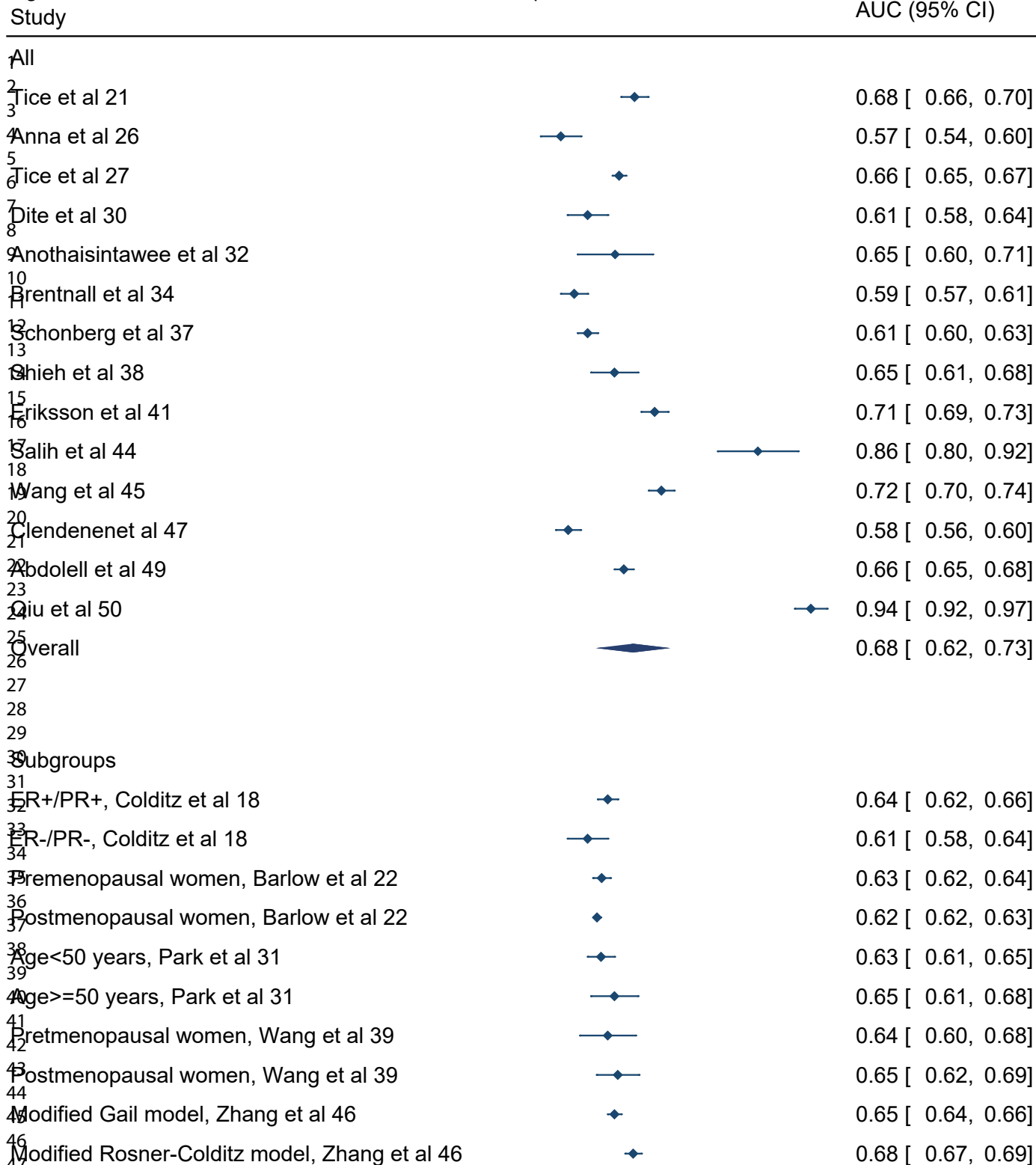
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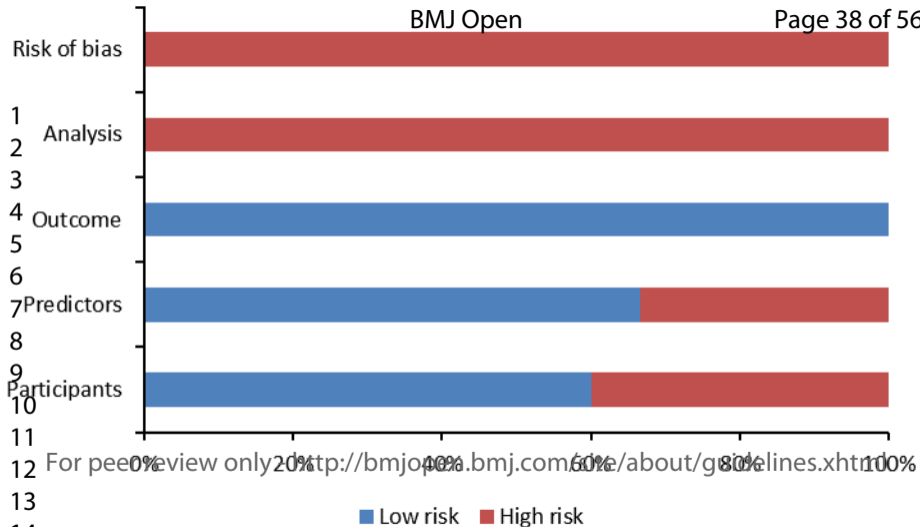
For peer review only: <http://bmjopen.bmj.com/site/about/guidelines.xhtml>
N=36
Studies included in the review



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Appendix

Appendix Table 1. Searching strategy.

Searching strategy
Take PubMed for example:
<p>#1 "Breast Neoplasms"[Mesh] OR "Breast Carcinoma In Situ"[Mesh] OR "Breast Neoplasms, Male"[Mesh] OR "Carcinoma, Ductal, Breast"[Mesh] OR "Carcinoma, Lobular"[Mesh] OR "Hereditary Breast and Ovarian Cancer Syndrome"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh] OR "Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR phyllodes tumor[Title/Abstract] OR breast sarcoma[Title/Abstract] OR mamma cancer*[Title/Abstract] OR mammary cancer*[Title/Abstract] OR mammary gland cancer*[Title/Abstract] OR Mammary Ductal Carcinoma*[Title/Abstract] OR breast gland cancer*[Title/Abstract] OR breast gland neoplasm*[Title/Abstract] OR Breast Neoplasm*[Title/Abstract] OR Breast Tumor*[Title/Abstract] OR Breast Cancer*[Title/Abstract] OR Mammary Cancer*[Title/Abstract] OR Breast Malignant Neoplasm*[Title/Abstract] OR Breast Malignant Tumor*[Title/Abstract] OR Human Mammary Carcinoma*[Title/Abstract] OR Human Mammary Neoplasm*[Title/Abstract] OR Breast Carcinoma*[Title/Abstract] OR Lobular Carcinoma*[Title/Abstract] 383,395</p> <p>#2 ("Machine Learning"[Mesh] OR "Regression Analysis"[Mesh] OR "Multivariate Analysis"[Mesh] OR "Models, Biological"[Mesh] OR "Models, Statistical"[Mesh] OR "Neural Networks, Computer"[Mesh] OR "Algorithms"[Mesh] OR "Artificial Intelligence"[Mesh]) AND "Risk Assessment" [Mesh] 49,055</p> <p>#3 predict*[Title/Abstract] AND (outcome*[Title/Abstract] OR mortality[Title/Abstract] OR index[Title/Abstract] OR rule*[Title/Abstract] OR decision*[Title/Abstract] OR scor*[Title/Abstract]) 576,113</p> <p>#4 risk*[Title/Abstract] AND (predict*[Title/Abstract] OR calculate*[Title/Abstract]) OR</p>

assess*[Title/Abstract] OR scor*[Title/Abstract] OR algorithm[Title/Abstract]) 945,708
 #5 model*[Title/Abstract] AND (logistic[Title/Abstract] OR statistic*[Title/Abstract] OR
 risk*[Title/Abstract] OR predict*[Title/Abstract]) 877,551
 #6 “area under the curve”[Title/Abstract] OR “area under the receiver operator characteristic
 curve”[Title/Abstract] OR AUC[Title/Abstract] OR scor* system[Title/Abstract] OR “summary
 receiver operating characteristic”[Title/Abstract] OR SROC[Title/Abstract] 197,599
 #7 OR/1-5 2,031,685
 #8 #6 AND #7 51,193

Appendix Table 2. Classification of risk factors.

age	
reproductive factors	age at menarche, age at first birth, menopause, age at subsequent births, menstrual regularity, total menstrual duration, breastfeeding, breast density, parity, reproductive characteristics, microcalcifications and masses, abortions, breast volume
family history of cancer	family history of breast cancer, family history of any cancer
hormone	hormone therapy, oral contraceptives, estrogen plus progestin use, testosterone, estradiol, sex hormone binding globulin, Insulin-like growth factor-I, estrone sulphate, prolactin, anti-Müllerian hormone
gene-related factors	polygenic risk score, rs2981582 (FGFR2), rs3803662(TOX3), rs889312(MAP3K1), rs13387042(2q35), rs13281615(8q24), rs4415084 (FGF10), rs3817198 (LSP1), rs981782(HCN1), rs10822013(ZNF365), rs3784099(RAD51B)
lifestyle	alcohol consumption, smoking status, exercise, light at night, sleep quality, vegetables and fruits, cereals, life satisfaction score

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<p>1</p> <p>2</p> <p>3</p> <p>4</p> <p>5 medical history and test</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p>	<p>previous biopsies, benign breast disease, nipple aspirate fluid cytology, prior breast procedure, prior false-positive mammogram, breast inflammatory, benign breast category, benign breast disease, atypical hyperplasia, mammogram in past 2 years, diabetes, myocardial infarction, stroke, emphysema, congestive heart failure, p53, CyclinB1, p16, p62,14-3-3ξ</p>
<p>13 basic information</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p> <p>26</p> <p>27</p> <p>28</p> <p>29</p> <p>30</p> <p>31</p> <p>32</p> <p>33</p> <p>34</p> <p>35</p> <p>36</p> <p>37</p> <p>38</p> <p>39</p> <p>40</p> <p>41</p> <p>42</p> <p>43</p> <p>44</p> <p>45</p> <p>46</p>	<p>body mass index, weight, education, ethnicity, occupational activity, height</p>

Appendix Table 3. Summary of the 36 included studies.

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Author	Year	develop							validate				
		Study design	Research method	Targeted population	No of risk factors	Risk factors	Model development (AUC (95%CI); E/O ratio (95%))	Sample size of development	Type of validation	Study design	Targeted population	Model validation (AUC (95%CI); E/O ratio (95%))	Sample size of validation
Gail et al ⁶	1989	Case-control study	Logistic regression	Caucasian; 20–79 years	5	Age, age at menarche, age at first birth, number of previous biopsies, number of first degree relatives with breast cancer	AUC: none; E/O ratio: none	2,852cases/ 3,146 controls	None	None	None	None	None
Rosner et al ¹⁶	1996	Prospective cohort study	Poisson regression	Caucasian; 30–64 years	5	Age, age at menarche, age at first birth, menopause, age at subsequent births	AUC: none; E/O ratio: none	2,249 cases/ 89,132 total	None	None	None	None	None
Ueda et al ¹⁷	2003	Case-control study	Logistic regression	Asian women; age was not specified.	4	Age at menarche, age at first birth, family history of breast cancer, body mass index	AUC: none; E/O ratio: none	376 cases/ 430 controls	None	None	None	None	None
Colditz et al ¹⁸	2004	Prospective cohort study	Logistic regression	Caucasian; 30-64 years	11	Age, age at menarche, age at first birth, menopause, age at subsequent births, benign breast disease, postmenopausal hormone use, family history of breast cancer in a first-degree relative, weight, body mass index, alcohol consumption	AUC: ER+/PR+: 0.64 (0.63,0.66); ER-/PR-: 0.61 (0.58, 0.64); E/O ratio: none	2,846 cases/ 66,145 total	None	None	None	None	None
Lee et al ¹⁹	2004	Case-control study	Logistic regression	Asian women; age was not specified.	1) Hospitalized controls: 5 2) Nurse/teacher controls: 5	1) Hospitalized controls: family history, menstrual regularity, total menstrual duration, age at first full-term pregnancy, duration of breastfeeding 2) Nurse/teacher controls: age, education level, menstrual regularity, drinking status, smoking status	AUC: 1) Hospitalized controls: 0.714; 2) Nurse/teacher controls: 0.867; E/O ratio: none	1) Hospitalized controls: 384 cases/ 166 controls; 2) Nurse/teacher controls: 384 cases/	None	None	None	None	None

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Tice et al ²⁰	2005	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 18 years and older	6	Age, age at menarche, previous biopsy, age at first birth, first degree breast cancer, nipple aspirate fluid cytology	AUC: 0.64; E/O ratio: none	400 cases/6,904 total	None	None	None	None	None
Tice et al ²¹	2005	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35 years and older	6	Age, age at menarche, previous biopsy, age at first birth, first degree breast cancer, breast density	AUC: 0.68 (0.66,0.70); E/O ratio: none	955 cases/81,777 total	None	None	None	None	None
Barlow et al ²²	2006	Prospective cohort study	Logistic regression	Multiple ethnicities, 35-84 years	1) Pre menopausal women: n: 4 2) Postmenopausal women: n: 10	1) Premenopausal women: age, breast density, family history of breast cancer, a prior breast procedure 2) Postmenopausal women: age, breast density, race, ethnicity, family history of breast cancer, a prior breast procedure, body mass index, natural menopause, hormone therapy, a prior false-positive mammogram	AUC: Premenopausal women: 0.631 (0.618, 0.644); postmenopausal women: 0.624 (0.619, 0.630) E/O ratio *: Premenopausal women: 1.000 postmenopausal women: 1.001	1) Premenopausal women: 1,726 cases/568,215 total; 2) postmenopausal women: 9,300 cases/1,642,824 total	Internal validation	None	None	None	None
Decarli et al ²³	2006	Case-control study	Logistic regression	Caucasian; 20-74 years	5	Age, age of menarche, number of breast biopsies, age at first live birth, first degree breast cancer	AUC: none; E/O ratio: none	2569 cases/2588 controls	External validation	Prospective cohort study	Caucasian; 35-64 years	AUC: 0.59; E/O ratio: 0.96(0.84, 1.11)	194 cases /10,031 total

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Novotny et al ²⁴	2006	Case-control study	Logistic regression	Multiple ethnicities; 23-84 years	8	Age of menarche, number of biopsies, age at first childbirth, number of breast cancer cases in first-degree relatives, number of any cancer cases in first-degree relatives, breast inflammatory, body mass index, number of conceptions	AUC: none; E/O ratio: none	2299 cases/ controls	None	None	None	None	
Gail et al ²⁵	2007	Case-control study	Logistic regression	African-American Women; 35-64 years	5	Age, age at menarche, number of affected mother or sisters, age at first live birth, number of previous benign biopsy examinations	AUC: none; E/O ratio: none	1607 cases/ 1647 controls	External validation	Prospective cohort study	African American women; 50-79 years	AUC: 0.555 (0.535,0.575); E/O ratio: 0.93b	350 cases/ /14,059 total
Anna et al ²⁶	2008	Case-control study	Logistic regression	Caucasian; age was not specified	5	Age, age at menarche, number of biopsies, age at first live birth, family history	AUC: 0.57 (0.54, 0.60); E/O ratio: none	558 cases/ 1207 controls	Internal validation	None	None	None	None
Tice et al ²⁷	2008	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35 years or older	5	Age, ethnicity, first degree breast cancer, previous biopsies, breast density	AUC: 0.657 (0.65,0.67); E/O ratio: 1.00 (0.98,1.03)	14,766 cases/ 1095484 total	Internal validation	Prospective cohort study	Multiple ethnicities; 35 years or older	AUC: 0.660(0.65,0.66); E/O ratio: 1.03(0.99,1.06)	3,465 cases/ 251,789 total
Tamimi et al ²⁸	2010	Nested case-control study	Logistic regression	Caucasian; 40-79 years	11	The type of benign breast disease, age, age at menarche, age at first birth and at each subsequent birth, age at menopause and type of menopause, history of benign breast diseases, family history of breast cancer in mother or sister, height, weight at age 18 years, current use of postmenopausal hormones (including type and duration of use), alcohol intake	AUC: 0.635; E/O ratio: none	240 cases/ 1036 controls	None	None	None	None	None

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5	Petracci et al ²⁹	2011	Case-control study	Logistic regression	Caucasian; 20-74 years	8	Reproductive characteristics, education, occupational activity, family history, biopsy history, alcohol consumption, leisure physical activity, body mass index.	AUC: none; E/O ratio: 1.10 (0.96,1.26)	2569 cases/ 2588 controls	External validation	Prospective cohort study	Caucasian; 35-64 years	AUC: Age<50: 0.62(0.555,0.689) ; age>=50: 0.57 (0.519,0.614); E/O ratio: 1.10(0.96,1.26)	206 cases/ 8,426 total
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10	Dite et al ³⁰	2013	Case-control study	Logistic regression	Multiple ethnicities; 35-59 years	13	Age, ethnicity, age at menarche, age at birth of first child, number of first-degree relatives with breast cancer, number of biopsies, presence of atypical hyperplasia, rs2981582(FGFR2), rs3803662(TOX3), rs889312(MAP3K1), rs13387042(2q35), rs13281615(8q24), rs4415084 (FGF10), rs3817198 (LSP1)	AUC: 0.61 (0.58,0.64); E/O ratio: none	962 cases/ 463 controls	None	None	None	None	
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19	Park et al ³¹	2013	Case-control study	Logistic regression	Asian women; age was not specified.	1) Age <50 years: 7 2) Age >=50 years: 7	1)Age<50 years: a family history of breast cancer in first-degree relatives, age at menarche, menopausal status, age at first full-term pregnancy, duration of breast feeding, oral contraceptive usage, exercise. 2)Age>=50 years: a family history of breast cancer in first degree relatives, age at menarche, age at menopause, experience of pregnancy, body mass index, oral contraceptive usage, exercise	AUC: Age<50 years: 0.63 (0.61-0.65); Age>=50 years: 0.65 (0.61- 0.68); E/O ratio: none	3,789 cases/ 3,789 controls	External validation	Prospective cohort study	None	1)Korean Multi-Center Cohort (KMCC): AUC: 0.61(0.49,0.72); E/O ratio: 0.97(0.67,1.40) 2)National Cancer Center (NCC) cohort: AUC: 0.89(0.85,0.93) E/O ratio: 0.96(0.70,1.37)	1) KMCC: 29cases/ 6148 total; 2)NCC: 36 cases/ 7546 total
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34	Anothaisi et al ³²	2014	Cross-sectional study	Logistic regression	Asian women; age was not specified	4	Age, menopausal status, body mass index, use of oral contraceptives	AUC: 0.651 (0.595, 0.707); O/E ratio: 1.00 (0.82, 1.21) ^b	107cases/ 15,718total	Internal and external validation	Cross-sectional study	Asian women; 18 years or older	Internal validation: AUC: 0.646(0.642,0.650); E/O ratio: none; External validation:	35 cases/ 4,978 total
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												AUC: 0.609(0.511,0.706); O/E ratio: 0.97 (0.68, 1.35) ^b	
Boggs et al ³³	2015	Prospective cohort study	Cox proportional hazards regression	African-American Women; 30-69 years	9	Family history, previous biopsy, body mass index at age 18 years, age at menarche, age at first birth, oral contraceptive use, bilateral oophorectomy, estrogen plus progestin use, height	AUC: none; E/O ratio: none	896 cases/ 55,093 total	Internal validation	Prospective cohort study	African American Women; 30-69 years	AUC: 0.59 (0.56, 0.61); E/O ratio: 0.96(0.88,1.05)	506 cases/ 48,193 total
Brentnall et al ³⁴	2015	Prospective cohort study	Logistic regression	Caucasian; 47-73 years	1) Gail model +Density residual 2) Tyrer-Cuzick model +density residual 11	1) Gail model+ Density residual: Age, Ethnicity, age at menarche, age at first birth, number of previous biopsies, benign disease, number of first degree relatives with breast cancer, density residual 2) Tyrer-Cuzick+ density residual: Age, gen phenotype, family history, age at menarche, age at first birth, menopause, atypical Hyperplasia, lobular carcinoma in situ, height, body mass index, density residual	(1) Primary (invasive+ DCIS): 1)Gail model+ Density residual: AUC: 0.59(0.57,0.61); E/O ratio: none; 2)Tyrer- Cuzick+ density residual: AUC: 0.61(0.59,0.63); E/O ratio: none; (2) Secondary(invasive): 1)Gail model+ Density residual: AUC: 0.59(0.57,0.61); E/O ratio: none; 2)Tyrer-Cuzick+ density residual: AUC: 0.61(0.58–0.63); E/O ratio: none	697 cases/ 50,628 total	None	None	None	None	

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5	Kerlikows ke et al ³⁵	2015	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35-74 years	5	Age, ethnicity, first degree breast cancer, previous biopsies, changes in breast density	AUC: 5-year risk model: 0.640; 10-year risk model: 0.628; E/O ratio: 5-year risk model: 0.98(0.96,1.00); 10-year risk model: 0.95(0.94,0.96)	13,715 cases/ 722,654 total	None	None	None	None	
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13	Tice et al ³⁶	2015	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35-74 years	6	Age, race/ethnicity, family history of breast cancer, history of breast biopsy, benign breast disease diagnoses, breast density	AUC: 0.665; E/O ratio: 5 Years: 1.04(1.02 ,1.06); 10 years: 1.05 (1.03,1.06)	17908 cases/ 1,135,977 total	None	None	None	None	
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18	Schonberg et al ³⁷	2016	Prospective cohort study	Competing risk regression	Multiple ethnicities; 57-85 years	16	Age at study entry, postmenopausal hormone use, number of first-degree relatives with history of breast cancer and age at diagnosis, history of breast biopsy, highest body mass index in past 10 years, age at menopause, age at first birth and parity, average alcohol use per day (highest average use in past 10 years), cigarette use, mammogram in past 2 years, limited in moderate daily activity, diabetes, myocardial infarction, stroke, emphysema, congestive heart failure	AUC: 0.61 (0.60,0.63); E/O ratio: none	73,066 total	External validation	Prospective cohort study	Multiple ethnicities; 55-91 years	AUC: 0.57 (0.55,0.58); E/O ratio: 0.92(0.88,0.97)	74,887 total
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32	Shieh et al ³⁸	2016	Nested case- control study	Logistic regression	Multiple ethnicities; 36-86 years	7	Age, ethnicity, first degree breast cancer, previous biopsies, breast density, polygenic risk score, body mass index	AUC:0.65(0.61,0.68); E/O ratio: none	486 cases/ 495 controls	None	None	None	None	
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Wang et al	2016	Case-control study	Logistic regression	Asian women; 20-84 years	1)Pre menopausal; 5; 2)Post menopausal; 11	1) Premenopausal: age, number of parity, case number of breast cancer in first-degree relatives, light at night, sleep quality; 2) Postmenopausal: age, number of parity, case number of breast cancer in first-degree relatives, light at night, body mass index, age at menarche, age at first give birth, ever breast feeding, ever using of oral contraceptive, hormone replacement treatment, history of benign breast diseases.	1) Pretmenopausal women: AUC: 0.640(0.598,0.681); E/O ratio: none; 2) Postmenopausal women: 0.655(0.621,0.653); E/O ratio: none	923 cases / 918 controls	Internal validation	Case-control study	Asian women; 20-84 years	1) Premenopausal: average AUC: 0.621; 3) Postmenopausal: Average AUC: 0.632	None																																

5	Banegas et al ⁴⁰	2017	Case-control study	Logistic regression	Hispanic Women; 35-79 years	1) The US-born Hispanic risk model: age at first full-term pregnancy, biopsy for benign breast disease, family history of breast cancer; 3) The foreign-born the Hispanic risk model: age at first full-term pregnancy, biopsy for benign breast disease, family history of breast cancer, age at menarche	None	1086 cases/ 411 controls	External validation	Prospective cohort study	Hispanic Women; 50-79 years	1)US-born Hispanics: AUC: 0.564 (0.485, 0.644); O/E:1.07 (0.81 ,1.40) ^b ; 2)Foreign-born Hispanics: AUC: 0.625 (0.487 ,0.764); O/E: 0.66 (0.41,1.07) ^b 4) Hispanics of unknown nativity: AUC: 0.582(0.509,0.656); O/E: 0.89(0.69,1.14) ^b	130 cases/ 6,220 total
26	Eriksson et al ⁴¹	2017	Nested case-control study	Logistic regression	Caucasian; 40-74 years	7 MD, computer-aided detection of microcalcifications and masses, use of hormone replacement therapy, family history of breast cancer, menopausal status, age, body mass index	AUC: 0.71(0.69,0.73); E/O ratio: none	433cases / 1732 controls	None	None	None	None	None
31	Hsieh et al ⁴²	2017	Case-control study	Logistic regression	Asian women; 20-90 years	11 FGFR2 (rs2981582), HCN1 (rs981782), MAP3K1 (rs889312), TOX3(rs3803662), ZNF365(rs10822013), RAD51B(rs3784099), age, body mass index, age at menarche, parity, menopausal status	AUC: 0.6652; E/O ratio: none	446 cases/ 514 controls	None	None	None	None	None

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5	Husing et al ⁴³	2017	Nested case-control study	Logistic regression	Multiple ethnicities; 26-77 years	13	Menopausal status, age at menarche, age at menopause, duration of postmenopausal hormones use, parity, number of children and age at first full term pregnancy, family history of breast cancer, alcohol consumption at recruitment, body mass index, measurements of testosterone, estradiol, sex hormone binding globulin, Insulin-like growth factor-I	AUC: none; E/O ratio: none	1,217 cases/ 1,976 controls	Internal validation	None	None	None	None
15	Salih et al ⁴⁴	2017	Cross-sectional study	Logistic regression	Caucasian; 32-74 years	5	Age, age at menarche, family history, vegetables and fruits weekly servings, type of cereals used	AUC: 0.864(0.81,0.92)	63 cases/ 90 controls	Internal validation	None	None	O/E ratio: 0.78 ^b	None
19	Wang et al ⁴⁵	2018	Case-control study	Logistic regression	Nigerian women; age was not specified	9	Age, age at menarche, parity, duration of breastfeeding, family history of breast cancer, height, body mass index, benign breast diseases, alcohol consumption	AUC: 0.720(0.701,0.739); E/O ratio: 1.01 (0.93,1.09)	1,208 cases/ 1,484 controls	Internal validation	None	Nigerian women; 20-79 years	AUC: 0.694 (0.666,0.721); E/O ratio: none	603 cases/ 741 controls

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Zhang et al ⁴⁶	2018	Nested case-control study	Logistic regression	Caucasian; 34-70 years	1) Gail model 1 model + PRS + MD + T + EIS +PRL: 10; 2) Rosner-Colditz model ner-Colditz z model + PRS + MD + T + EIS + PRL: 16	1) Gail model+ PRS + MD + T + EIS +PRL: Age, age at menarche, previous biopsies, age at first birth, first degree breast cancer, PRS, MD, EIS, T, PRL 2) Rosner-Colditz model+ PRS + MD + T + EIS + PRL: age, age at menarche, age at first birth, menopause, age at subsequent births, benign breast disease, hormone replacement therapy, first degree breast cancer, weight, body mass index, alcohol, PRS, MD, EIS, T, PRL	AUC: Gail model+ PRS + MD + T + EIS +PRL: 0.65(0.64,0.66); Rosner-Colditz model+ PRS + MD + T + EIS + PRL: 0.678 (0.666,0.690); E/O ratio: none	4,006 cases / 7,874 controls	Internal validation	None	None	None	None
Clendenen et al ⁴⁷	2019	Nested case-control study	Logistic regression	Multiple ethnicities; 35-50 years	6	Age at menarche, age at first live birth, number of benign breast biopsies, number of first-degree family members with breast cancer, AMH, tT	AUC: 0.581(0.562,0.599); E/O ratio: none	1,762 cases/ 1,890 controls	None	None	None	None	None
Wang et al ⁴⁸	2019	Case-control study	Logistic regression	Asian women; 25-70 years	6	Number of abortions, age at first live birth, benign breast disease history, body mass index,	None	328 cases / 656 controls	External validation	Respective cohort study	Asian women	AUC: 0.64 (0.55,0.72); E/O ratio: 1.03 (0.74,1.49)	34 cases/ 13,176 total

						breast cancer family history, life satisfaction score							
Abdolell et al ⁴⁹	2020	Nested case-control study	Logistic regression	Caucasian; 40-75 years	5	Age at screen, percent mammographic density, breast volume, core biopsy history, family history	AUC: 0.664(0.650,0.678); E/O ratio: none	1,882 cases/ 5,888 controls	None	None	None	None	None
Qiu et al ⁵⁰	2020	Case-control study	Logistic regression	Asian women; 29-81 years	5	p53, CyclinB1, p16, p62,14-3-3ξ	AUC:0.943(0.919,0.967); E/O ratio: none	184 cases/ 184 controls	External validation	Case-control study	Asian women; 24-78 years	AUC: 0.916(0.886,0.947); E/O ratio: none	197 cases/ 109 controls

^aE/O ratios were calculated based on the original information. ^bThe original publication reported the Observed/Expected ratio.
 ER: estrogen receptor; PR: progesterone receptor; PRS: polygenic risk score; MD: mammographic density;
 EIS: estrone sulphate; T: testosterone; PRL: prolactin; AMH: anti-Müllerian hormone.

Appendix Table 4. Risk of bias assessment of included based on PROBAST.

Study	Participants		Predictors					Outcome						Analysis					Overall						
	1.1	1.2	2.1	2.2	2.3	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5	4.6	4.7		4.8	4.9				
Gail et al ⁶	N	Y	H	Y	PY	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	H	H				
Rosner et al ¹⁶	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	NI	N	N	Y	H	H
Ueda et al ¹⁷	N	NI	H	Y	PY	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	Y	Y	PY	N	N	Y	H	H
Colditz et al ¹⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	PY	L	Y	N	Y	N	Y	N	Y	Y	H	H
Lee et al ¹⁹	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	Y	N	PY	N	N	Y	H	H
Tice et al ²⁰	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	Y	N	N	N	Y	H	H
Tice et al ²¹	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	Y	N	N	N	Y	H	H

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5	Barlow et al ²²	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	PY	NI	Y	N	N	Y	Y	H	H	
6	Decarli et al ²³	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	N	Y	N	Y	H	H	
7	Decarli et al ^{23*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	N	NI	-	NI	Y	-	-	H	H	
8																											
9	Novotny et al ²⁴	N	PY	H	Y	PN	Y	H	PY	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	PY	N	N	Y	H	H	
10	Gail et al ²⁵	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	PY	N	N	Y	H	H	
11	Gail et al ^{25*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	-	Y	Y	-	-	H	H	
12																											
13	Anna et al ²⁶	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	PY	N	N	Y	H	H	
14	Tice et al ²⁷	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	N	N	Y	Y	Y	Y	Y	Y	H	H
15	Tamimi,et al ²⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	NI	N	N	Y	H	H	
16	Petracci et al ²⁹	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	N	N	Y	H	H	
17	Petracci et al ^{29*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	-	Y	PN	-	-	H	H	
18																											
19	Dite et al ³⁰	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	N	PY	N	N	Y	H	H	
20	Park et al ³¹	N	Y	H	Y	PY	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	N	PY	N	N	Y	H	H	
21	Park et al ^{31*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	NI	-	PY	Y	-	-	H	H	
22																											
23	Anothaisintawee et al ³²	Y	Y	H	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	Y	N	PY	PN	N	Y	H	H	
24	Anothaisintawee et al ^{32*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	Y	-	PY	PN	-	-	H	H	
25																											
26	Boggs et al ³³	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	NI	Y	N	Y	Y	H	H	
27	Brentnall et al ³⁴	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	Y	N	N	N	Y	H	H	
28	Kerlikowske et al ³⁵	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	Y	Y	N	PN	Y	Y	H	H	
29	Tice et al ³⁶	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	Y	PN	Y	Y	H	H	
30	Schonberg et al ³⁷	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	N	Y	N	N	Y	H	H	
31	Schonberg et al ^{37*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	-	Y	PN	-	-	H	H	
32																											
33	Shieh et al ³⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	N	N	N	Y	Y	H	H	
34	Wang et al ³⁹	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	N	PY	N	Y	Y	H	H	
35	Banegas, et al ⁴⁰	N	Y	H	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	PY	N	NI	Y	H	H	
36	Banegas et al ^{40*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	-	PY	Y	-	-	H	H	
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Eriksson et al ⁴¹	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	NI	PY	N	Y	Y	H	H
Hsieh, et al ⁴²	N	NI	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	N	PY	N	Y	Y	H	H
Husing et al ⁴³	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	PY	N	Y	Y	H	H
Salih et al ⁴⁴	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	N	PY	N	Y	Y	H	H
Wang et al ⁴⁵	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	PN	Y	Y	H	H
Zhang et al ⁴⁶	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	Y	Y	PY	N	Y	Y	H	H
Clendenen et al ⁴⁷	Y	Y	L	PN	Y	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	Y	Y	PY	N	N	Y	H	H
Wang et al ⁴⁸	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	Y	N	N	Y	H	H
Wang et al ^{48*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	N	-	Y	PN	-	-	H	H
Abdolell et al ⁴⁹	Y	PY	L	Y	Y	Y	L	PY	Y	Y	Y	Y	Y	L	Y	Y	Y	N	N	PY	N	N	Y	H	H
Qiu et al ⁵⁰	N	NI	H	Y	N	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	PY	N	N	Y	H	H
Qiu et al ^{50*}	N	NI	H	Y	N	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	-	PY	N	-	-	H	H

* The external validation was performed in the same study.

L: low risk of bias; H: high risk of bias; Y: yes; N: no; PY: probably yes; PN: probably no; NI: no information; -: not applicable.



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 and Appendix Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8,9 and Appendix Table 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8,9 and Appendix Table 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7,8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8,9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8,9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8,9 and Appendix Table 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8,9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not performed
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not performed



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not performed
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not performed
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9 and figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9
Study characteristics	17	Cite each included study and present its characteristics.	9,10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	12,13,14,15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9,10,11 and Appendix Table 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix Table 3, table 1, figure 2, figure 3 and figure 4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9, 10,11,12, 13,14,15 and Appendix Table 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not performed
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not performed
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not performed
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not performed
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	15, 16
	23b	Discuss any limitations of the evidence included in the review.	17
	23c	Discuss any limitations of the review processes used.	17
	23d	Discuss implications of the results for practice, policy, and future research.	17, 18, 19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3,6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not performed



PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Reported on page #
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not performed
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	20
Competing interests	26	Declare any competing interests of review authors.	20
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendix Table 1,2,3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
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Risk prediction models for breast cancer: a systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055398.R1
Article Type:	Original research
Date Submitted by the Author:	21-Jan-2022
Complete List of Authors:	Zheng, Yadi; Chinese Academy of Medical Sciences & Peking Union Medical College Li, Jiang; Chinese Academy of Medical Sciences & Peking Union Medical College Wu, Zheng; Chinese Academy of Medical Sciences & Peking Union Medical College Li, He; Chinese Academy of Medical Sciences & Peking Union Medical College Cao, Maomao; Chinese Academy of Medical Sciences & Peking Union Medical College Li, Ni; Chinese Academy of Medical Sciences & Peking Union Medical College He, Jie; Chinese Academy of Medical Sciences & Peking Union Medical College
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Oncology, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, Public health < INFECTIOUS DISEASES, Breast tumours < ONCOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Risk prediction models for breast cancer: a systematic review

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Word count: 2896

Figures/Tables: 5

ABSTRACT

Objectives: To systematically review and critically appraise published studies of risk prediction models for breast cancer in the general population without breast cancer, and provide evidence for future research in the field.

Design: Systematic review using the Prediction model study Risk Of Bias Assessment Tool (PROBAST) framework.

Data sources: PubMed, the Cochrane Library and Embase were searched from inception to 16 December, 2021.

Eligibility criteria: We included studies reporting multivariable models to estimate the individualized risk of developing female breast cancer among different ethnic groups. Search was limited to English language only.

Data extraction and synthesis: Two reviewers independently screened, reviewed, extracted and assessed studies with discrepancies resolved through discussion or a third reviewer. Risk of bias was assessed according to the PROBAST (Prediction model Risk of Bias Assessment Tool) framework.

Results: 63,894 studies were screened and 40 studies with 47 risk prediction models were included in the review. Most of the studies used logistic regression to develop breast cancer risk prediction models for Caucasian women by case-control data. The most

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10 widely used risk factor was reproductive factors and the highest area under the curve was
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12 0.943 (95% confidence interval: 0.919~0.967). All the models included in the review had
13
14 high risk of bias.
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17 **Conclusions:** No breast cancer risk prediction models were recommended for different
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19 ethnic groups and more key variables like breast density and single-nucleotide
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21 polymorphisms (SNPs) should be collected and well validated in the existing models in
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23 the future. High-quality breast cancer risk prediction models assessed by PROBAST
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25 should be developed and validated, especially among Asian women.
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30 **PROSPERO registration number:** CRD42020202570
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33 **Strengths and limitations of this study**

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- 35 1. Thoroughly conducted systematic review collecting data from major existing databases.
- 36 2. Critically appraised published studies of risk prediction models for breast cancer in the
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38 general population and provide evidence for future research in the field.
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- 41 3. PROBAST was used to assess the quality of prediction models, which was developed
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43 through a consensus process involving a group of methodological experts in the area of
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45 clinical prediction tools and quality assessment.
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- 49 4. Studies only about the external validation of the present risk models were not included
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51 in the review.
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10 5. Our study highlighted high-quality breast cancer risk prediction models assessed by
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12 PROBAST should be developed and validated among different ethnic groups, especially
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14 among Asian women.
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17 **Keywords:** breast cancer; risk prediction model; review; quality assessment; Prediction
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19 model Risk of Bias Assessment Tool
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22 INTRODUCTION

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24
25 Breast cancer is a major public health problem, and one of the most severe
26
27 burdensome cancer among women worldwide ¹, accounting for 11.7% of new cancer
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29 cases and 6.9% of cancer deaths in 2020. The prevalence of breast cancer is projected to
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31 increase over the coming years and is the most common cancer in women in 2020 ². Breast
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33 cancer prevention is associated with a reduction in mortality ³, and more researches are
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35 needed to improve the methods of identifying women at elevated risk and preventing the
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37 disease. Numerous breast cancer risk prediction models have been developed to identify
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39 the combined effect of risk factors for breast cancer, guide routine screening and genetic
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41 testing, and reduce the burden of breast cancer. Risk-stratified screening can improve
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43 cost-effectiveness and maximize benefits and minimize harms like overdiagnosis ⁴.
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45 Individualized prediction model for breast cancer could be used in practice to assist
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47 decision making about mass screening or opportunistic screening and treatment strategy.
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10 A recent breast cancer screening guideline ⁵ suggests that breast cancer screening
11 increase the early detection rate and reduce the incidence if the screening is applied in
12 appropriate at-risk populations. However, major gaps exist in our knowledge to determine
13 the risk of breast cancer accurately in order to apply these approaches to appropriate
14 populations of women.
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23 A lot of breast cancer risk prediction models have been developed over the past few
24 decades. Many breast cancer risk models have undergone validation including
25 discrimination and calibration in study populations other than those used in initial
26 development, or have been further assessed in comparative studies. Breast cancer related
27 predictors including hormonal factors, environmental factors, family histories, genetic
28 factors and radiographic factors have been based on in these risk models, which would
29 improve the generalizability. For example, the Gail model ⁶, one of the most famous
30 models, has been widely used and validated worldwide since it was developed in 1989 <sup>7-
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51 This study is a systematic review of breast cancer risk prediction models by using
52 meta-analysis and the Prediction model Risk of Bias Assessment Tool (PROBAST) ¹³⁻¹⁴.
53 The aim of our study is to systematically review published studies of risk prediction
54 models for breast cancer in the general population, find more methods of predicting
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10 female breast cancer risk among one or more ethnic groups, prepare for the development
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12 of risk prediction models, and provide evidence for future research in the field.
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15 **METHODS**

16 17 **Protocol and registration**

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20 The current review was designed according to the Checklist for critical Appraisal
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22 and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)
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24¹⁵ and was recorded in the PROSPERO database (registration number:
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26 CRD42020202570).
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30 **Literature search and eligibility criteria**

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33 We systematically searched PubMed, the Cochrane Library and Embase from
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35 inception to 16 December, 2021. The detailed search strategies were reported in Appendix
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37 Table 1. Articles identified from the search were loaded into EndNote X7 and duplicates
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39 were removed.
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44 Inclusion criteria: 1) a model used data from cross-sectional studies, cohort studies,
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46 case-control studies, and randomized controlled trials; 2) a model estimating the
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48 individualized risk of female breast cancer among one or more ethnic groups; 3) a model
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50 developed for the general population without breast cancer; 4) reported a multivariable
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52 (i.e., at least 2 variables or predictors) model; 5) published in English.
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10 Exclusion criteria: 1) external validation studies that only validated previous models
11 in a different population without adding any additional information such as modifications
12 on the risk factors; 2) models developed by machine learning.
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17 **Data extraction**

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20 Two reviewers screened the search results independently. Full text reports were then
21 assessed for eligibility with discrepancies resolved through discussion or a third reviewer.
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25 We extracted information in two categories: 1) For all studies included in the review,
26 we extracted the following information: author, publication year, study design, research
27 method, targeted population, number of risk factors, risk factors, model performance and
28 sample size of development. 2) For studies included validation part, we also extracted the
29 following information: type of validation, study design, targeted population, model
30 performance and sample size of validation. The information was extracted by one
31 reviewer and checked by a second reviewer.
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43 **Risk of bias assessment**

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46 We used PROBAST to assess the reported prediction models, which is a new tool
47 designed by a group of experts all over the world to assess the risk of bias and applicability
48 of diagnostic and prognostic prediction models. It can be used in critical appraisal of
49 studies that develop, validate, or update prediction models for individualized predictions
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10 13-14. In brief, it contains 20 signaling questions in four domains: participants, predictors,
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12 outcome, and statistical analysis. Signaling questions can be answered as yes, probably
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14 yes, no, probably no, or no information. A domain where at least one signaling question
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16 is answered as no or probably no should be judged as high risk of bias. Only if all domains
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18 are judged as low risk of bias, the total bias is judged as low risk as well.
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23 Before putting PROBAST into use, we formed a ten-people study group including
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25 prediction model researchers, statisticians, evidence-based medicine specialists etc. to
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27 learn and practice the appropriate use of this new tool systematically. Only after everyone
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29 understood all these twenty questions totally, we would move to the peer quality
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31 assessment part. Risk of bias of every prediction model was assessed by two reviewers
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33 independently with discrepancies resolved through discussion or a third reviewer.
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39 If there were more than one models developed in one study, we only assessed the
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41 risk of bias once due to their similarity. We also assessed the risk of external validation
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43 of prediction model when it was conducted in the same article that included model
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45 development.
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48 **Data synthesis and analysis**

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51 We calculated and reported descriptive statistics to summarize the characteristics of
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53 the models. We calculated the most frequently used risk factors and classified all risk
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10 factors into eight categories: Age, reproductive factors, family history of cancer, hormone,
11 gene-related factors, lifestyle, medical history and test, and basic information.
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13 Classification details can be seen in Appendix Table 2. Then we used network diagram
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15 to see the connections of categorized risk factors. We used forest plot to describe the
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17 model performance. The expected observed (E/O) ratio was not included in the forest plot
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19 because it was only reported in 7 out of 40 studies. All analyses were performed using
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21 Stata 16.0 and NetDraw.
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27 **Patient and public involvement**

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30 There was no patient or public involvement in this study.
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32 **RESULTS**

33 **Study selection**

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36 A total of 92,519 indexed records (54,653 in PubMed, 30,374 in Cochrane Library
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38 and 7,492 in Embase), 28,625 were eliminated as duplicates found in all databases,
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40 leaving a total of 63,894 publications. 43 articles were included primarily after screening
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42 by title and abstract. 3 studies which were only about the external validation of previous
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44 models were excluded while full test screening, resulting in 40 studies with 47 models
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51 were included in the review eventually. (Figure 1).
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53 **Study characteristics**

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10 A brief summary of the 40^{6,16-54} included studies is presented in Appendix Table 3.
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12 The included studies were published from 1989 to 2021. 25 of the studies were conducted
13 over the past ten years with 5 studies published in 2017 especially. Seventeen out of the
14 forty studies used data from case-control studies to develop prediction models<sup>6,17,19,23-
15 26,29-31,39, 41,43,46,49,51,54</sup>, thirteen from prospective cohorts^{16,18,20-22,27,33-37,40,52}, eight from
16 nested case-control studies^{28,38, 42,44,47,48,50,53} and two from cross-sectional study^{32,45}.
17 Thirty-one studies used logistic regression to fit prediction models<sup>6,17-19,22-26,28-32,34,38-
18 51,53,54</sup>, seven used cox proportional hazards regression^{20,21,27,33,35,36,52}, one used Poisson
19 regression¹⁶ and one used competing risk regression³⁷. Of all forty-seven models in forty
20 studies, sixteen models were developed in Caucasian women^{6,16,18,23,26,28,29,34,40,42,45,47,50,53},
21 thirteen in multiple ethnicities women^{20-22,24,27,30,35-38,44,48}, twelve in Asian women
22 17,19,31,32,39,43,49,51,52, two in African-American women^{25,33}, two in Hispanic women⁴¹, one
23 in Nigerian women⁴⁶ and one in Cypriot Women⁵⁴.
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43 The association between eight categories of risk factors was shown in Figure 2.
44 Reproductive factors had the biggest node size, which meant that this factor was most
45 frequently connected with other factors among prediction models. The number between
46 two factors meant the times these two factors were included in the same models, some of
47 which were over thirty. For instance, reproductive factors and family history of cancer
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10 were included in the same models for forty times, and reproductive factors and age were
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12 included in the same models for thirty-one times.

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15 Twenty-nine studies reported c-statistics ^{18-22,26-28,30-32,34-40,42,43,45-48,50-54}, ranged from
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17 0.59(95% confidence interval: 0.57~0.61) to 0.943(95% confidence interval:
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19 0.919~0.967). Qiu, et al ⁵¹ had the highest c-statistics (0.943, 95% confidence interval:
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21 0.919~0.967), and Lee et al ¹⁹ and Salih et al ⁴⁵ reported area under the curve (AUC) over
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23 0.8, 0.867 and 0.864(95% confidence interval: 0.81~0.92), respectively. E/O ratios can
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25 be obtained from eight studies ^{22,27,29,32,35,36,46,52}. Figure 3 showed that the overall AUC
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27 was 0.68(95% confidence interval: 0.63~0.73) for sixteen studies ^{21,26,27,30,32,34,37,38,42,}
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29 ^{45,46,48,50,51,52,54} that reported the AUC and 95% confidence interval. The AUCs of the
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31 subgroups in five studies ^{18,22,31,39,47} were between 0.6 to 0.7.

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38 In all these forty studies, nine studies assessed prediction models with internal
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40 validation ^{22,26,27,33,39,44-47}, ten with external validation ^{23,25,29,31,37,41,49,51-53}, and one with
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42 both ³². Fifteen studies reported the discriminatory accuracy as the AUC ^{23,25,27,29,31-}
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44 ^{33,37,39,41,46,49,51-53}, and eleven studies used the expected/observed event ratio (or
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46 observed/expected event ratio) to measure the calibration accuracy of the model
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51 ^{23,25,27,29,31,33,37,41,45,49,52}.

52 53 54 **Quality assessment**

A summary of the quality assessment is shown in Table 1. Overall, all models assessed by PROBAST in the review had high risk of bias. There was a low and high risk of bias in the outcome and analysis domains respectively. Over 60% models had low risk in participants domain and about 70% models had low risk in predictors domain, 32 models and 36 models respectively. (As shown in Figure 4).

The main reasons for the high risk in analysis domain were model performance measures evaluated inappropriately, categorization of continuous predictors, no reporting of overfitting and optimism in model performance and missing data handled inappropriately (Appendix Table 4).

Table 1. Summary of risk of bias assessment.

Study	Participants	Predictors	Outcome	Analysis	Overall
Gail et al ⁶	H	L	L	H	H
Rosner et al ¹⁶	L	L	L	H	H
Ueda et al ¹⁷	H	L	L	H	H
Colditz et al ¹⁸	L	L	L	H	H
Lee et al ¹⁹	H	H	L	H	H
Tice et al ²⁰	L	L	L	H	H
Tice et al ²¹	L	L	L	H	H
Barlow et al ²²	L	L	L	H	H
Decarli et al ²³	H	H	L	H	H
Decarli et al ^{23*}	L	L	L	H	H
Novotny et al ²⁴	H	H	L	H	H
Gail et al ²⁵	H	H	L	H	H
Gail et al ^{25*}	L	L	L	H	H
Anna et al ²⁶	H	H	L	H	H

Tice et al ²⁷	L	L	L	H	H
Tamimi,et al ²⁸	L	L	L	H	H
Petracci et al ²⁹	H	H	L	H	H
Petracci et al ^{29*}	L	L	L	H	H
Dite et al ³⁰	H	H	L	H	H
Park et al ³¹	H	H	L	H	H
Park et al ^{31*}	L	L	L	H	H
Anothaisintawee et al ³²	H	L	L	H	H
Anothaisintawee et al ^{32*}	L	L	L	H	H
Boggs et al ³³	L	L	L	H	H
Brentnall et al ³⁴	L	L	L	H	H
Kerlikowske et al ³⁵	L	L	L	H	H
Tice et al ³⁶	L	L	L	H	H
Schonberg et al ³⁷	L	L	L	H	H
Schonberg et al ^{37*}	L	L	L	H	H
Shieh et al ³⁸	L	L	L	H	H
Wang et al ³⁹	H	H	L	H	H
Mass et al ⁴⁰	L	L	L	H	H
Banegas, et al ⁴¹	H	L	L	H	H
Banegas et al ^{41*}	L	L	L	H	H
Eriksson et al ⁴²	L	L	L	H	H
Hsieh, et al ⁴³	H	H	L	H	H
Husing et al ⁴⁴	L	L	L	H	H
Salih et al ⁴⁵	L	L	L	H	H
Wang et al ⁴⁶	H	H	L	H	H
Zhang et al ⁴⁷	L	L	L	H	H
Clendenen et al ⁴⁸	L	H	L	H	H
Wang et al ⁴⁹	H	H	L	H	H
Wang et al ^{49*}	L	L	L	H	H
Abdoell et al ⁵⁰	L	L	L	H	H
Qiu et al ⁵¹	H	H	L	H	H
Qiu et al ^{51*}	H	H	L	H	H
Han et al ⁵²	L	L	L	H	H
Han et al ^{52*}	L	L	L	H	H

Rosner et al ⁵³	L	L	L	H	H
Rosner et al ^{53*}	L	L	L	H	H
Yiangou et al ⁵⁴	H	L	L	H	H

* The external validation was performed in the same study.

L indicates low risk of bias; H indicates high risk of bias.

DISCUSSION

Summary of main results

This systematic review identified 40 studies with 47 risk prediction models developed and/or validated for breast cancer among different ethnic groups. Most of the studies used logistic regression to develop breast cancer risk prediction models for Caucasian women by case-control data. The most widely used risk factor was reproductive factors. Reproductive factors together with family history factor were used in most models. The highest AUC was 0.943 (95% confidence interval: 0.919~0.967) from Qiu, et al ⁵¹. The overall AUC was 0.68(95% confidence interval: 0.63~0.73) for sixteen studies ^{21,26,27,30,32,34,37,38,42,45,46,48,50,51,52,54} that reported the AUC and 95% confidence interval. All the studies presented a high risk of bias due to the high risk in analysis domain, which were mainly because of model performance measures evaluated inappropriately, categorization of continuous predictors, no reporting of overfitting and optimism in model performance and missing data handled inappropriately.

Agreements and disagreements with other reviews

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10 As we can learn from the review, there were more and more risk prediction models
11 of breast cancer over the past thirty years. Most of the models were developed in the
12 Caucasian women, which agreed with the systematic review published by Louro et al in
13 2019 ⁵⁵. Compared with this review, we identified more prediction models and used a
14 newly published tool to assess the quality of included models.
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23 Over the past ten years, some new variables (such as oral contraceptives, diabetes,
24 and alcohol consumption) have been included in prediction models. Increased use of the
25 inclusion of common genetic variation in the prediction models was in accord with Louro
26 et al in 2019 ⁵⁵ and Anothaisintawee et al in 2012 ⁵⁶. However, neither of them included
27 models developed with potential biomarkers like tumor-associated antigens. By contrast,
28 we included one model developed by Qiu, et al ⁵¹ in 2019 included five tumor-associated
29 antigens. The model performed well with a high AUC 0.943(95% confidence interval:
30 0.919,0.967).
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43 **Strengths and limitations of the study**

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46 PROBAST was developed through a consensus process involving a group of
47 methodological experts in the area of clinical prediction tools and quality assessment. We
48 used it to assess the quality of prediction models, which has been used widely in many
49 fields ⁵⁷⁻⁶⁰ since it came out.
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10 Despite the strength, there are three main limitations. Firstly, we didn't
11 systematically search gray literature. Therefore, some models may not be identified.
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13 Secondly, quality assessment could be thought to be subjective, which is an inherent bias
14 of systematic review. However, two independent reviewers extracted and assessed the
15 risk prediction models using PROBAST whose authors have indicated essentially
16 objective guidelines and explanations. Moreover, studies only about the external
17 validation of the present risk models were not included in the review, but the original
18 developments of these risk models were covered. For instance, the study describes the
19 original developments of Gail model ⁶ was included in our research, while the studies
20 only about the external validation of Gail model ⁶¹⁻⁶⁴ were not included.
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36 **Implication to research and clinical practice**

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38 Eleven models ^{19,30-32,37-39,43,45,50,54} selected predictors based on univariable analysis,
39 causing a high risk in analysis domain, which should be avoided. Risk prediction models
40 should include predictors those are well-established and with clinical credibility
41 regardless of any statistical significance ^{65,66}. Because sometimes predictors only have
42 important relationship with the outcome after adjustment for confounding covariates, and
43 covariates hold no independent predictive power when other covariates are included ^{13,67}.
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54 Some models were high risk in analysis domain because of missing data handled
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10 inappropriately, which may lead to biased associations between risk factors and breast
11 cancer as well as biased model performance because of the selectivity of participants ⁶⁸.
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15 So imputation techniques are supposed to apply when data are missing ^{69,70}.

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18 When developing the risk prediction models, there were only nine studies included
19 internal validation ^{22,26,27,33,39,44-47}, leaving most models without internal validation. Lack
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22 of performing internal validation may increase the risk of overfitting ⁷¹. Thus, we suggest
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25 that internal validation should be performed before external validation.
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30 PROBAST was created by many international experts, providing a series of
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33 guidelines about model development and validation, which can be easily applied and
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36 improve clinical practice of prediction models. So, the new and most recommended
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39 methodology should be used when a new model is developed or the existing models are
40 updated.

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43 In the light of the results of our review, it is still hard to recommend any of the
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46 models to be applied in the breast cancer screening due to the high risk of bias. More key
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49 variables like mammographic density and single-nucleotide polymorphisms (SNPs)
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52 should be well collected and validated in the existing models to improve the model
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55 performance. High mammographic density is a strong risk factor for breast cancer ^{72,73},
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58 and several studies have found that mammographic density improves the accuracy of risk-
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10 prediction models ^{74,75}. Studies have shown that adding SNPs into risk-prediction models
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12 can improve model performance with promising results ⁷⁶⁻⁷⁸. Cost-effectiveness should
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14 be considered when a model is going to be applied in clinical practice. Because even
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16 though the model with some risk factors that cost more to get (e.g., high risk gene) has
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18 better model performance, it is still hard to be applied in poor area ⁷⁹. What's more, an
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20 existing model should be modified or updated before used in another group of people
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22 with different characteristics, which may improve the performance of prediction models.
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28 Breast cancer incidence has risen to the first place by 2020 all over the world, which
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30 makes it more crucial to develop breast cancer prediction models for different ethnic
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32 groups. In China, we have launched many breast cancer screening programs. For example,
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34 Rural Women "two cancers" Check Project Management Solutions have covered 31
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36 provinces and 1437 counties since 2009. Cancer Screening Program in Urban China
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38 conducted by the National Cancer Center has covered 28 provinces and 67 cities with
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40 more than 4 million people involved and 2 million people screened by ultrasound and
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42 Mammography since 2012. The program will provide large data for us to develop a high-
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44 quality breast cancer risk prediction model in Chinese and will have great significance
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46 for breast cancer prevention of Asian women.
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53 CONCLUSIONS

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10 All 47 models assessed in our review using PROBAST performed the high risk of
11 bias, leaving no model is recommended in the routine screening program. Some new
12 variables, like oral contraceptives, diabetes, and alcohol consumption, have been widely
13 used in prediction models over the past ten years. More key variables like breast density
14 and SNPs should be collected and well validated in the existing models to improve the
15 model performance. It is necessary to develop and validate high-quality breast cancer risk
16 predication models among different ethnic groups, especially among Asian women.

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28 **Contributors:** YZ and JL conceptualized the study and created the first version of the
29 review protocol. ZW, HL, MC, NL, and JH critically reviewed the review protocol and
30 approved it. YZ and HL screened eligible articles. YZ extracted the data, supported by
31 ZW, MC. YZ drafted the first version of the manuscript, supported by JL, NL, and JH.
32 All authors contributed to data interpretation and critically assessed it. All authors
33 approved the final version of the manuscript.

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44 **Funding:** This work was supported by the Non-profit Central Research Institute Fund of
45 Chinese Academy of Medical Sciences (grant number: 2019PT320027).

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47
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49 **Competing interest:** The author(s) declared no potential conflicts of interest with respect
50 to the research, authorship, and/or publication of this article.

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54 **Patient consent for publication:** Not required.

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10 **Data availability statement:** All data of the current study is present in the main
11 manuscript, figures, tables, and online supplemental material.
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15 **Ethics statement:** This study does not involve human participants.
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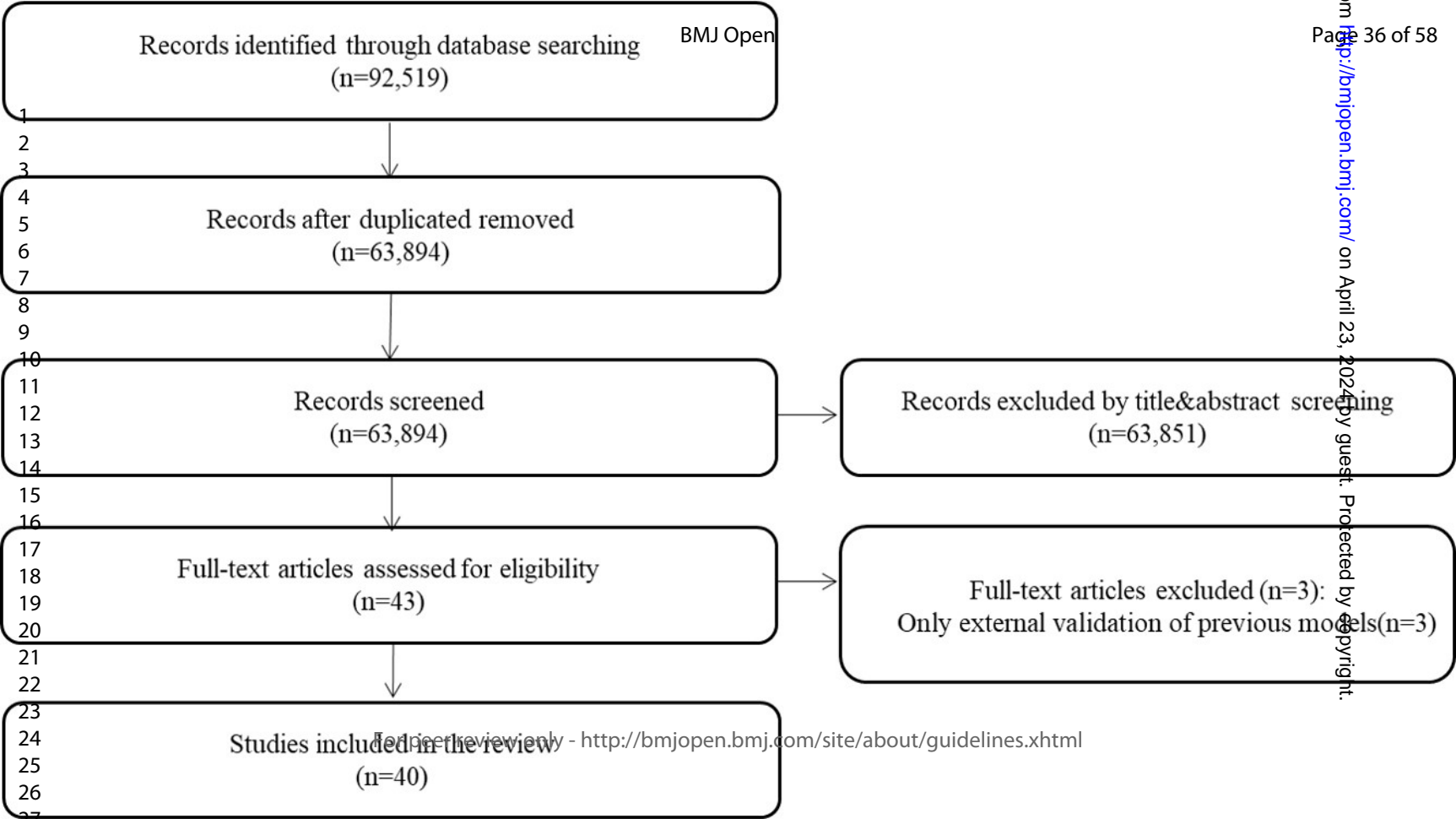
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15 Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses)
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17 flowchart.
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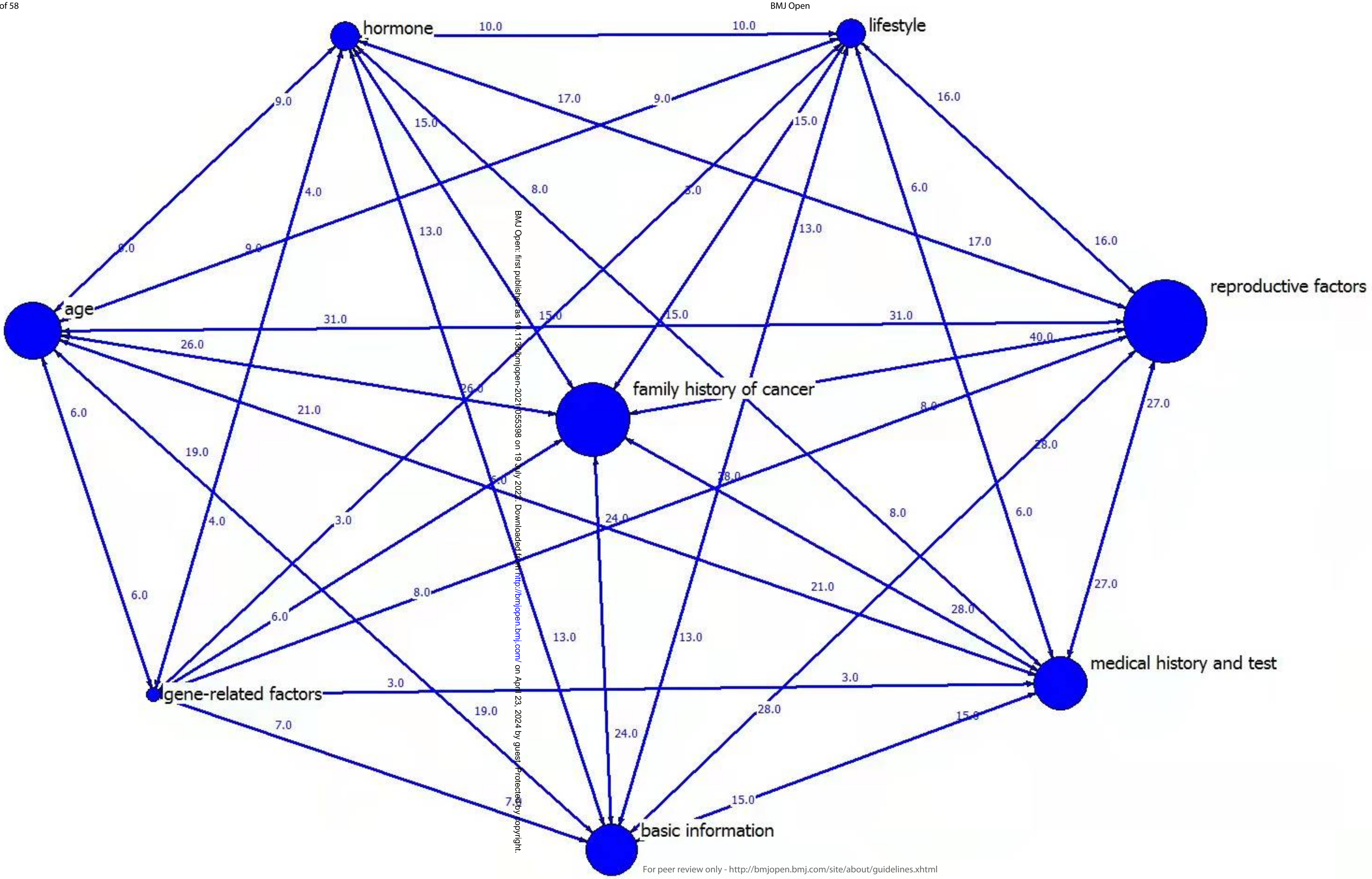
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20 Figure 2. Network diagram of eight categorized risk factors (age, basic information,
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22 family history of cancer, gene-related factors, hormone, lifestyle, medical history and
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24 test, and reproductive factors).
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28 Figure 3. Area under the curve (AUC) and confidence intervals reported by the included
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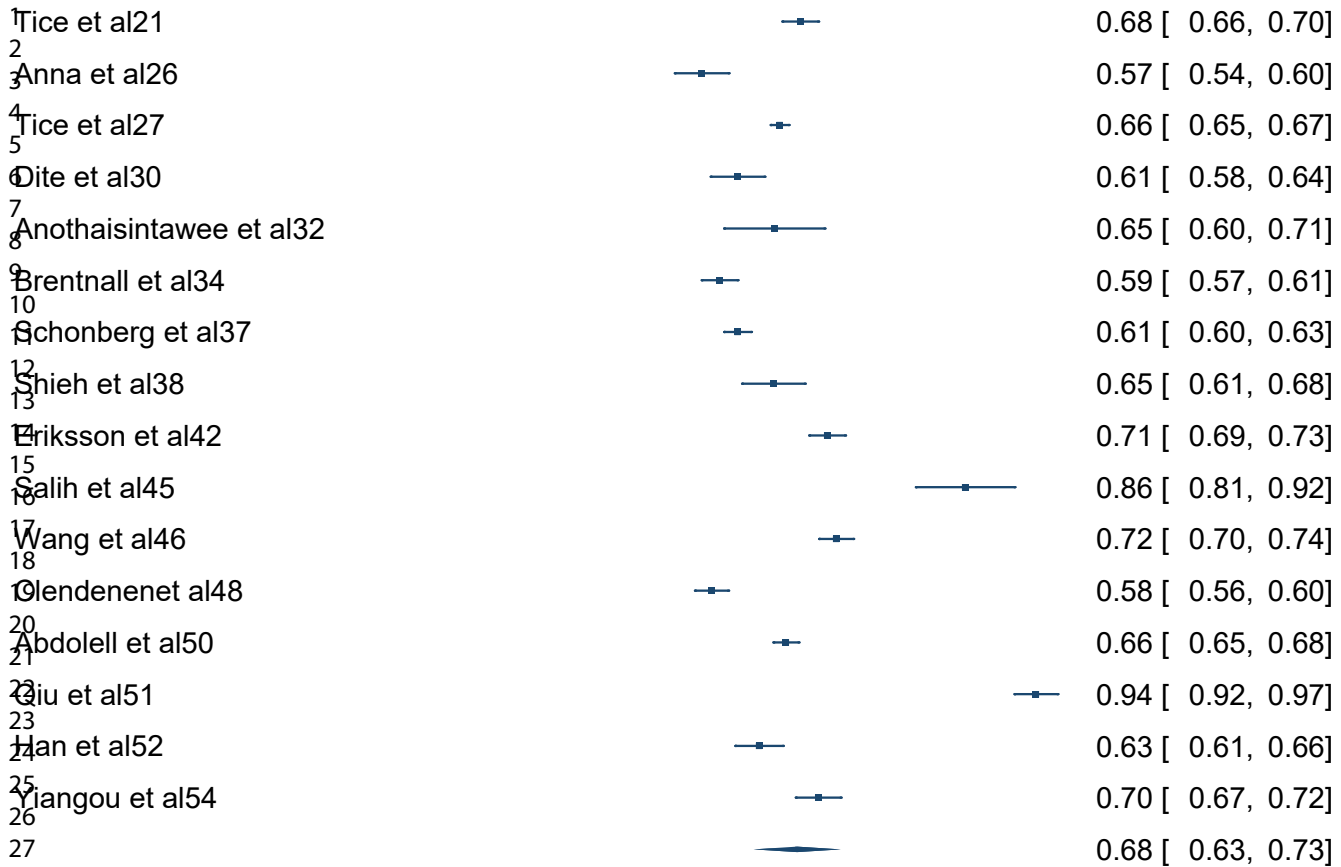
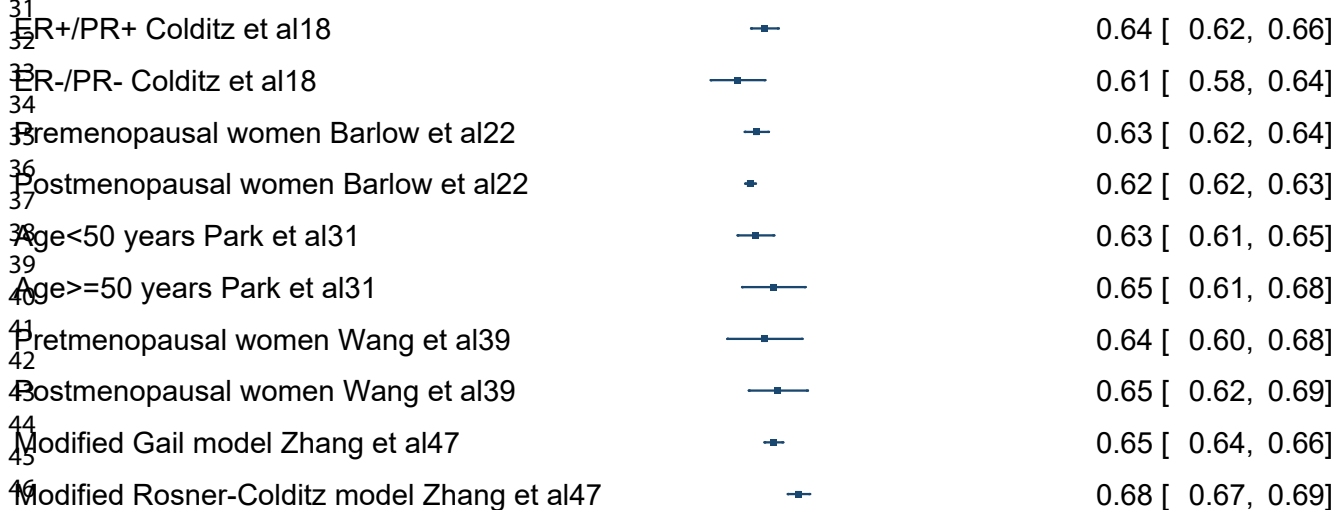
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33 Figure 4. Risk of bias assessment (using PROBAST) of all assessed models based on
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35 four domains.
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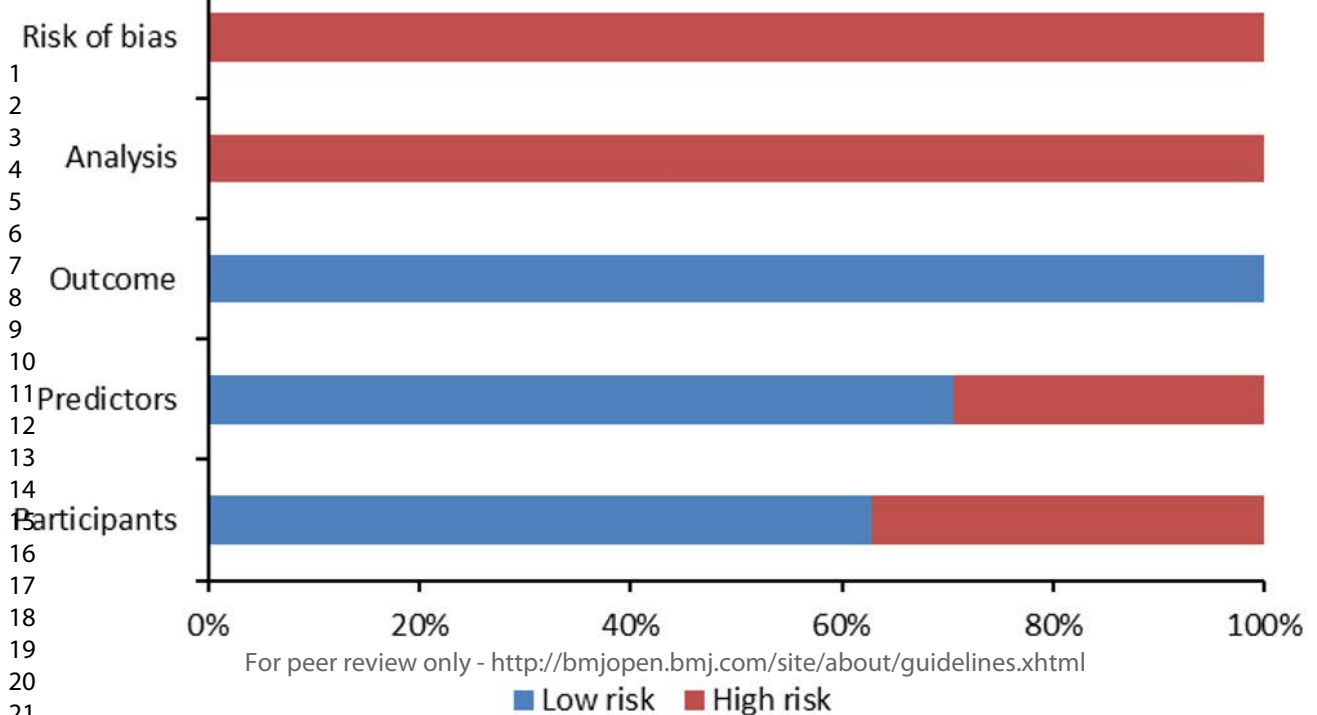


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All**Subgroups**

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■ Low risk ■ High risk

Appendix

Appendix Table 1. Searching strategy.

Searching strategy
Take PubMed for example:
#1 "Breast Neoplasms"[Mesh] OR "Breast Carcinoma In Situ"[Mesh] OR "Breast Neoplasms, Male"[Mesh] OR "Carcinoma, Ductal, Breast"[Mesh] OR "Carcinoma, Lobular"[Mesh] OR "Hereditary Breast and Ovarian Cancer Syndrome"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh] OR "Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR phyllodes tumor[Title/Abstract] OR breast sarcoma[Title/Abstract] OR mamma cancer*[Title/Abstract] OR mammary cancer*[Title/Abstract] OR mammary gland cancer*[Title/Abstract] OR Mammary Ductal Carcinoma*[Title/Abstract] OR breast gland cancer*[Title/Abstract] OR breast gland neoplasm*[Title/Abstract] OR Breast Neoplasm*[Title/Abstract] OR Breast Tumor*[Title/Abstract] OR Breast Cancer*[Title/Abstract] OR Mammary Cancer*[Title/Abstract] OR Breast Malignant Neoplasm*[Title/Abstract] OR Breast Malignant Tumor*[Title/Abstract] OR Human Mammary Carcinoma*[Title/Abstract] OR Human Mammary Neoplasm*[Title/Abstract] OR Breast Carcinoma*[Title/Abstract] OR Lobular Carcinoma*[Title/Abstract] 418,670
#2 ("Regression Analysis"[Mesh] OR "Multivariate Analysis"[Mesh] OR "Models, Biological"[Mesh] OR "Models, Statistical"[Mesh] OR "Algorithms"[Mesh]) AND "Risk Assessment" [Mesh] 52,269
#3 predict*[Title/Abstract] AND (outcome*[Title/Abstract] OR index[Title/Abstract] OR rule*[Title/Abstract] OR decision*[Title/Abstract] OR scor*[Title/Abstract]) 624,639
#4 risk*[Title/Abstract] AND (predict*[Title/Abstract] OR calculate*[Title/Abstract] OR assess*[Title/Abstract] OR scor*[Title/Abstract] OR algorithm[Title/Abstract]) 1,109,068
#5 model*[Title/Abstract] AND (logistic[Title/Abstract] OR statistic*[Title/Abstract] OR risk*[Title/Abstract] OR predict*[Title/Abstract]) 1,1035,123
#6 OR/2-5 2,195,108
#7 #1 AND #6 54,653

Appendix Table 2. Classification of risk factors.

age	
reproductive factors	age at menarche, age at first birth, menopause, age at subsequent births, menstrual regularity, total menstrual duration, breastfeeding, breast density, parity, reproductive characteristics, microcalcifications and masses, abortions, breast volume
family history of cancer	family history of breast cancer, family history of any cancer
hormone	hormone therapy, oral contraceptives, estrogen plus progestin use, testosterone, estradiol, sex hormone binding globulin, Insulin-like growth factor-I, estrone sulphate, prolactin, anti-Müllerian hormone
gene-related factors	polygenic risk score, rs2981582 (FCFR2), rs3803662(TOX3), rs889312(MAP3K1), rs13387042(2q35), rs13281615(8q24), rs4415084 (FGF10), rs3817198 (LSP1), rs981782(HCN1), rs10822013(ZNF365), rs3784099(PAD51B)
lifestyle	alcohol consumption, smoking status, exercise, light at night, sleep quality, vegetables and fruits, cereals, life satisfaction score
medical history and test	previous biopsies, benign breast disease, nipple aspirate fluid cytology, prior breast procedure, prior false-positive mammogram, breast inflammatory, benign breast category, benign breast disease, atypical hyperplasia, mammogram in past 2 years, diabetes, myocardial infarction, stroke, emphysema, congestive heart failure, p53, CyclinB1, p16, p62,14-3-3ξ
basic information	body mass index, weight, education, ethnicity, occupational activity, height, residence area

Appendix Table 3. Summary of the 40 included studies.

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Author	Year	develop							validate				
		Study design	Research method	Targeted population	No of risk factors	Risk factors	Model development (AUC (95%CI); E/O ratio (95%))	Sample size of development	Type of validation	Study design	Targeted population	Model validation (AUC (95%CI); E/O ratio (95%))	Sample size of validation
Gil et al ⁶	1989	Case-control study	Logistic regression	Caucasian; 20–79 years	5	Age, age at menarche, age at first birth, number of previous biopsies, number of first degree relatives with breast cancer	AUC: none; E/O ratio: none	2,852cases/ 3,146 controls	None	None	None	None	None
Donner et al ¹⁶	1996	Prospective cohort study	Poisson regression	Caucasian; 30–64 years	5	Age, age at menarche, age at first birth, menopause, age at subsequent births	AUC: none; E/O ratio: none	2,249 cases/ 89,132 total	None	None	None	None	None
Yoda et al ¹⁷	2003	Case-control study	Logistic regression	Asian women; age was not specified.	4	Age at menarche, age at first birth, family history of breast cancer, body mass index	AUC: none; E/O ratio: none	376 cases/ 430 controls	None	None	None	None	None
Colditz et al ¹⁸	2004	Prospective cohort study	Logistic regression	Caucasian; 30-64 years	11	Age, age at menarche, age at first birth, menopause, age at subsequent births, benign breast disease, postmenopausal hormone use, family history of breast cancer in a first-degree relative, weight, body mass index, alcohol consumption	AUC: ER+/PR+: 0.64 (0.63,0.66); ER-/PR-: 0.61 (0.58, 0.64); E/O ratio: none	2,846 cases/ 66,145 total	None	None	None	None	None
Lee et al ¹⁹	2004	Case-control study	Logistic regression	Asian women; age was not specified.	1) Hospitalized controls: 5 2) Nurse/teacher controls: 5	1) Hospitalized controls: family history, menstrual regularity, total menstrual duration, age at first full-term pregnancy, duration of breastfeeding 2) Nurse/teacher controls: age, education level, menstrual regularity, drinking status, smoking status	AUC: 1) Hospitalized controls: 0.714; 2) Nurse/teacher controls: 0.867; E/O ratio: none	1) Hospitalized controls: 384 cases/ 166 controls; 2) Nurse/teacher controls: 384 cases/	None	None	None	None	None

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					se/teac her contro ls: 5			104 controls					
Tice et al ²⁰	2005	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 18 years and older	6	Age, age at menarche, previous biopsy, age at first birth, first degree breast cancer, nipple aspirate fluid cytology	AUC: 0.64; E/O ratio: none	400 cases/6,904 total	None	None	None	None	
Tice et al ²¹	2005	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35 years and older	6	Age, age at menarche, previous biopsy, age at first birth, first degree breast cancer, breast density	AUC: 0.68 (0.66,0.70); E/O ratio: none	955 cases/81,777 total	None	None	None	None	
Barlow et al ²²	2006	Prospective cohort study	Logistic regression	Multiple ethnicities, 35-84 years	1) Premenopausal women: n: 4 2) Postmenopausal women: n: 10	1) Premenopausal women: age, breast density, family history of breast cancer, a prior breast procedure 2) Postmenopausal women: age, breast density, race, ethnicity, family history of breast cancer, a prior breast procedure, body mass index, natural menopause, hormone therapy, a prior false-positive mammogram	AUC: Premenopausal women: 0.631 (0.618, 0.644); postmenopausal women: 0.624 (0.619, 0.630) E/O ratio *: Premenopausal women: 1.000 postmenopausal women: 1.001	1) Premenopausal women: 1,726 cases/568,215 total; 2) postmenopausal women: 9,300 cases/1,642,824 total	Internal validation	None	None	None	
DeCarli et al ²³	2006	Case-control study	Logistic regression	Caucasian; 20-74 years	5	Age, age of menarche, number of breast biopsies, age at first live birth, first degree breast cancer	AUC: none; E/O ratio: none	2569 cases/2588 controls	External validation	Prospective cohort study	Caucasian; 35-64 years	AUC: 0.59; E/O ratio: 0.96(0.84, 1.11)	194 cases /10,031 total

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11 12 13 14 15 16 17	Gail et al ²⁵	2007	Case-control study	Logistic regression	African-American Women; 35-64 years	5	Age, age at menarche, number of affected mother or sisters, age at first live birth, number of previous benign biopsy examinations	AUC: none; E/O ratio: none	1607 cases/ 1647 controls	External validation	Prospective cohort study	African American women; 50-79 years	AUC: 0.555 (0.535,0.575); E/O ratio: 0.93b	350 cases /14,059 total
18	Anna et al ²⁶	2008	Case-control study	Logistic regression	Caucasian; age was not specified	5	Age, age at menarche, number of biopsies, age at first live birth, family history	AUC: 0.57 (0.54, 0.60); E/O ratio: none	558 cases/ 1207 controls	Internal validation	None	None	None	None
19 20 21 22	Rice et al ²⁷	2008	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35 years or older	5	Age, ethnicity, first degree breast cancer, previous biopsies, breast density	AUC: 0.657 (0.65,0.67); E/O ratio: 1.00 (0.98,1.03)	14,766 cases/ 1095484 total	Internal validation	Prospective cohort study	Multiple ethnicities; 35 years or older	AUC: 0.660(0.65,0.66); E/O ratio: 1.03(0.99,1.06)	3,465 cases/ 251,789 total
23 24 25 26 27 28 29 30 31 32 33 34	Mammi et al ²⁸	2010	Nested case-control study	Logistic regression	Caucasian; 40-79 years	11	The type of benign breast disease, age, age at menarche, age at first birth and at each subsequent birth, age at menopause and type of menopause, history of benign breast diseases, family history of breast cancer in mother or sister, height, weight at age 18 years, current use of postmenopausal hormones (including type and duration of use), alcohol intake	AUC: 0.635; E/O ratio: none	240 cases/ 1036 controls	None	None	None	None	None

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5	Tracci et al ²⁹	2011	Case-control study	Logistic regression	Caucasian; 20-74 years	8	Reproductive characteristics, education, occupational activity, family history, biopsy history, alcohol consumption, leisure physical activity, body mass index.	AUC: none; E/O ratio: 1.10 (0.96,1.26)	2569 cases/ 2588 controls	External validation	Prospective cohort study	Caucasian; 35-64 years	AUC: Age<50: 0.62(0.555,0.689) ; age>=50: 0.57 (0.519,0.614); E/O ratio: 1.10(0.96,1.26)	206 cases/ 8,426 total
10	De et al ³⁰	2013	Case-control study	Logistic regression	Multiple ethnicities; 35-59 years	13	Age, ethnicity, age at menarche, age at birth of first child, number of first-degree relatives with breast cancer, number of biopsies, presence of atypical hyperplasia, rs2981582(FGFR2), rs3803662(TOX3), rs889312(MAP3K1), rs13387042(2q35), rs13281615(8q24), rs4415084 (FGF10), rs3817198 (LSP1)	AUC: 0.61 (0.58,0.64); E/O ratio: none	962 cases/ 463 controls	None	None	None	None	None
19	Park et al ³¹	2013	Case-control study	Logistic regression	Asian women; age was not specified.	1) Age <50 years: 7 2) Age >=50 years: 7	1)Age<50 years: a family history of breast cancer in first-degree relatives, age at menarche, menopausal status, age at first full-term pregnancy, duration of breast feeding, oral contraceptive usage, exercise. 2)Age>=50 years: a family history of breast cancer in first degree relatives, age at menarche, age at menopause, experience of pregnancy, body mass index, oral contraceptive usage, exercise	AUC: Age<50 years: 0.63 (0.61-0.65); Age>=50 years: 0.65 (0.61- 0.68); E/O ratio: none	3,789 cases/ 3,789 controls	External validation	Prospective cohort study	None	1)Korean Multi-Center Cohort (KMCC): AUC: 0.61(0.49,0.72); E/O ratio: 0.97(0.67,1.40) 2)National Cancer Center (NCC) cohort: AUC: 0.89(0.85,0.93) E/O ratio: 0.96(0.70,1.37)	1) KMCC: 29cases/ 6148 total; 2)NCC: 36 cases/ 7546 total
34	Thaisintawee et al ³²	2014	Cross-sectional study	Logistic regression	Asian women; age was not specified	4	Age, menopausal status, body mass index, use of oral contraceptives	AUC: 0.651 (0.595, 0.707); O/E ratio: 1.00 (0.82, 1.21) ^b	107cases/ 15,718total	Internal and external validation	Cross-sectional study	Asian women; 18 years or older	Internal validation: AUC: 0.646(0.642,0.650); E/O ratio: none; External validation:	35 cases/ 4,978 total

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												AUC: 0.609(0.511,0.706); O/E ratio: 0.97 (0.68, 1.35) ^b	
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10 11 12 13 14 15 16	2015	Prospective cohort study	Cox proportional hazards regression	African-American Women; 30-69 years	9	Family history, previous biopsy, body mass index at age 18 years, age at menarche, age at first birth, oral contraceptive use, bilateral oophorectomy, estrogen plus progestin use, height	AUC: none; E/O ratio: none	896 cases/ 55,093 total	Internal validation	Prospective cohort study	African American Women; 30-69 years	AUC: 0.59 (0.56, 0.61); E/O ratio: 0.96(0.88,1.05)	506 cases/ 48,193 total
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36	2015	Prospective cohort study	Logistic regression	Caucasian; 47-73 years	1) Gail model 2) Tyrer-Cuzick+ density residual: 3) Tyrer-Cuzick+ density residual: 4) Tyrer-Cuzick+ density residual: 5) Tyrer-Cuzick+ density residual: 6) Tyrer-Cuzick+ density residual: 7) Tyrer-Cuzick+ density residual: 8) Tyrer-Cuzick+ density residual: 9) Tyrer-Cuzick+ density residual: 10) Tyrer-Cuzick+ density residual: 11) Tyrer-Cuzick+ density residual:	1) Gail model+ Density residual: Age, Ethnicity, age at menarche, age at first birth, number of previous biopsies, benign disease, number of first degree relatives with breast cancer, density residual 2) Tyrer-Cuzick+ density residual: Age, gen phenotype, family history, age at menarche, age at first birth, menopause, atypical Hyperplasia, lobular carcinoma in situ, height, body mass index, density residual	(1) Primary (invasive+ DCIS): 1)Gail model+ Density residual: AUC: 0.59(0.57,0.61); E/O ratio: none; 2)Tyrer- Cuzick+ density residual: AUC: 0.61(0.59,0.63); E/O ratio: none; (2) Secondary(invasive): 1)Gail model+ Density residual: AUC: 0.59(0.57,0.61); E/O ratio: none; 2)Tyrer-Cuzick+ density residual: AUC: 0.61(0.58-0.63); E/O ratio: none	697 cases/ 50,628 total	None	None	None	None	None

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5	erlikowske et al	2015	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35-74 years	5	Age, ethnicity, first degree breast cancer, previous biopsies, changes in breast density	AUC: 5-year risk model: 0.640; 10-year risk model: 0.628; E/O ratio: 5-year risk model: 0.98(0.96,1.00); 10-year risk model: 0.95(0.94,0.96)	13,715 cases/ 722,654 total	None	None	None	None	
13	Lee et al ³⁶	2015	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35-74 years	6	Age, race/ethnicity, family history of breast cancer, history of breast biopsy, benign breast disease diagnoses, breast density	AUC: 0.665; E/O ratio: 5 Years: 1.04(1.02 ,1.06); 10 years: 1.05 (1.03,1.06)	17908 cases/ 1,135,977 total	None	None	None	None	
18	Jonberg et al	2016	Prospective cohort study	Competing risk regression	Multiple ethnicities; 57-85 years	16	Age at study entry, postmenopausal hormone use, number of first-degree relatives with history of breast cancer and age at diagnosis, history of breast biopsy, highest body mass index in past 10 years, age at menopause, age at first birth and parity, average alcohol use per day (highest average use in past 10 years), cigarette use, mammogram in past 2 years, limited in moderate daily activity, diabetes, myocardial infarction, stroke, emphysema, congestive heart failure	AUC: 0.61 (0.60,0.63); E/O ratio: none	73,066 total	External validation	Prospective cohort study	Multiple ethnicities; 55-91 years	AUC: 0.57 (0.55,0.58); E/O ratio: 0.92(0.88,0.97)	74,887 total
32	Leech et al ³⁸	2016	Nested case-control study	Logistic regression	Multiple ethnicities; 36-86 years	7	Age, ethnicity, first degree breast cancer, previous biopsies, breast density, polygenic risk score, body mass index	AUC:0.65(0.61,0.68); E/O ratio: none	486 cases/ 495 controls	None	None	None	None	

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5	Vang et al ³⁹	2016	Case-control study	Logistic regression	Asian women; 20-84 years	1)Pre menopausal: 5; 2)Post menopausal: 11	1) Premenopausal: age, number of parity, case number of breast cancer in first-degree relatives, light at night, sleep quality; 2) Postmenopausal: age, number of parity, case number of breast cancer in first-degree relatives, light at night, body mass index, age at menarche, age at first give birth, ever breast feeding, ever using of oral contraceptive, hormone replacement treatment, history of benign breast diseases.	1) Pretmenopausal women: AUC: 0.640(0.598,0.681); E/O ratio: none; 2) Postmenopausal women: 0.655(0.621,0.686); E/O ratio: none	923 cases / 918 controls	Internal validation	Case-control study	Asian women; 20-84 years	1) Premenopausal: average AUC: 0.621; 3) Postmenopausal: Average AUC: 0.632	None
19	Mdas et al ⁴⁰	2016	Prospective cohort study	Logistic regression	Caucasian	11	Age at menarche, menopause, age at first birth, parity, alcohol consumption, height, smoking status, BMI, family history, hormone therapy, PRS	AUC: 0.640; E/O ratio: none	17,171 cases / 19,862 controls	None	None	None	None	None

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26 27 28 29 30	Eksson et al ⁴²	2017	Nested case-control study	Logistic regression	Caucasian; 40-74 years	7 MD, computer-aided detection of microcalcifications and masses, use of hormone replacement therapy, family history of breast cancer, menopausal status, age, body mass index	AUC: 0.71(0.69,0.73); E/O ratio: none	433cases / 1732 controls	None	None	None	None	None
31 32 33 34 35 36 37 38	Hsieh et al ⁴³	2017	Case-control study	Logistic regression	Asian women; 20-90 years	11 FGFR2 (rs2981582), HCN1 (rs981782), MAP3K1 (rs889312), TOX3(rs3803662), ZNF365(rs10822013), RAD51B(rs3784099), age, body mass index, age at menarche, parity, menopausal status	AUC: 0.6652; E/O ratio: none	446 cases/ 514 controls	None	None	None	None	None

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Using et al ⁴⁴	2017	Nested case-control study	Logistic regression	Multiple ethnicities; 26-77 years	13	Menopausal status, age at menarche, age at menopause, duration of postmenopausal hormones use, parity, number of children and age at first full term pregnancy, family history of breast cancer, alcohol consumption at recruitment, body mass index, measurements of testosterone, estradiol, sex hormone binding globulin, Insulin-like growth factor-I	AUC: none; E/O ratio: none	1,217 cases/ 1,976 controls	Internal validation	None	None	None	None
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Salih et al ⁴⁵	2017	Cross-sectional study	Logistic regression	Caucasian; 32-74 years	5	Age, age at menarche, family history, vegetables and fruits weekly servings, type of cereals used	AUC: 0.864(0.81,0.92)	63 cases/ 90 controls	Internal validation	None	None	O/E ratio: 0.78 ^b	None
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Wang et al ⁴⁶	2018	Case-control study	Logistic regression	Nigerian women; age was not specified	9	Age, age at menarche, parity, duration of breastfeeding, family history of breast cancer, height, body mass index, benign breast diseases, alcohol consumption	AUC: 0.720(0.701,0.739); E/O ratio: 1.01 (0.93,1.09)	1,208 cases/ 1,484 controls	Internal validation	None	Nigerian women; 20-79 years	AUC: 0.694 (0.666,0.721); E/O ratio: none	603 cases/ 741 controls

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5	Chang et al ⁴⁷	2018	Nested case-control study	Logistic regression	Caucasian; 34-70 years	1) Gail model 1 Age, age at menarche, previous biopsies, age at first birth, first degree breast cancer, PRS, MD, EIS, T, PRL + PRS + MD + T + EIS + PRL: 10; 2) Rosner-Colditz model ner-Colditz model z + PRS + MD + T + EIS + PRL: 16	1) Gail model+ PRS + MD + T + EIS +PRL: Age, age at menarche, previous biopsies, age at first birth, first degree breast cancer, PRS, MD, EIS, T, PRL 2) Rosner-Colditz model+ PRS + MD + T + EIS + PRL: age, age at menarche, age at first birth, menopause, age at subsequent births, benign breast disease, hormone replacement therapy, first degree breast cancer, weight, body mass index, alcohol, PRS, MD, EIS, T, PRL	AUC: Gail model+ PRS + MD + T + EIS +PRL: 0.65(0.64,0.66); Rosner-Colditz model+ PRS + MD + T + EIS + PRL: 0.678 (0.666,0.690); E/O ratio: none	4,006 cases / 7,874 controls	Internal validation	None	None	None	None
31	Endeneten al ⁴⁸	2019	Nested case-control study	Logistic regression	Multiple ethnicities; 35-50 years	6 Age at menarche, age at first live birth, number of benign breast biopsies, number of first-degree family members with breast cancer, AMH, tT	Age at menarche, age at first live birth, number of benign breast biopsies, number of first-degree family members with breast cancer, AMH, tT	AUC: 0.581(0.562,0.599); E/O ratio: none	1,762 cases/ 1,890 controls	None	None	None	None	None
36	Wong et al ⁴⁹	2019	Case-control study	Logistic regression	Asian women; 25-70 years	6 Number of abortions, age at first live birth, benign breast disease history, body mass index,	Number of abortions, age at first live birth, benign breast disease history, body mass index,	None	328 cases / 656 controls	External validation	Respective cohort study	Asian women	AUC: 0.64 (0.55,0.72); E/O ratio: 1.03 (0.74,1.49)	34 cases/ 13,176 total

						breast cancer family history, life satisfaction score							
Abdoell et al ⁵⁰	2020	Nested case-control study	Logistic regression	Caucasian; 40-75 years	5	Age at screen, percent mammographic density, breast volume, core biopsy history, family history	AUC: 0.664(0.650,0.678); E/O ratio: none	1,882 cases/ 5,888 controls	None	None	None	None	
Qiu et al ⁵¹	2020	Case-control study	Logistic regression	Asian women; 29-81 years	5	p53, CyclinB1, p16, p62,14-3-3ξ	AUC: 0.943(0.919,0.967); E/O ratio: none	184 cases/ 184 controls	External validation	Case-control study	Asian women; 24-78 years	AUC: 0.916(0.886,0.947); E/O ratio: none	197 cases/ 109 controls
Lin et al ⁵²	2021	Prospective cohort study	Cox regression	Asian women; 30-79 years	8	age, residence area, education, BMI, height, family history of cancer, parity, age at menarche	AUC: 0.634(0.608,0.661); E/O ratio: 1.01(0.94,1.09)	2,287 cases/ 300,824 total	External validation	Prospective cohort study	Asian women;	AUC: 0.585(0.564,0.605) E/O ratio: 0.94(0.89,0.99)	73,203 total
Koener et al ⁵³	2021	Nested case-control study	Logistic regression	Caucasian; 40-75 years	4	Age, breast density, questionnaire score, PRS	AUC: 0.658 E/O ratio: none	2,799 cases/ 75,557 controls	External validation	Nested case-control study	Caucasian; 40-75 years	AUC: 0.687	438 cases/ 898 controls
Yangou et al ⁵⁴	2021	Case-control study	Logistic regression	Cypriot Women	11	menopause, age at menarche, parity, age at first birth, breastfeeding, height, BMI, hormone therapy, smoking status, family history, PRS	AUC: 0.70 (0.67,0.72) E/O ratio: none	1,109 cases/ 1,177 controls	None	None	None	None	None

^aE/O ratios were calculated based on the original information. ^bThe original publication reported the Observed/Expected ratio.

ER: estrogen receptor; PR: progesterone receptor; PRS: polygenic risk score; MD: mammographic density;

E1S: estrone sulphate; T: testosterone; PRL: prolactin; AMH: anti-Müllerian hormone; NI: no information.

Appendix Table 4. Risk of bias assessment of included models based on PROBAST.

Study	Participants		Predictors			Outcome						Analysis					Overall								
	1.1	1.2	2.1	2.2	2.3	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5		4.6	4.7	4.8	4.9				
Gail et al ⁶	N	Y	H	Y	PY	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	PY	N	N	Y	H	H
Rosner et al ¹⁶	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	NI	N	N	Y	H	H
Ueda et al ¹⁷	N	NI	H	Y	PY	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	Y	Y	PY	N	N	Y	H	H
Colditz et al ¹⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	PY	L	Y	N	Y	N	Y	N	N	Y	Y	H	H
Lee et al ¹⁹	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	Y	N	PY	N	N	Y	H	H
Tice et al ²⁰	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	Y	N	N	N	Y	H	H
Tice et al ²¹	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	Y	N	N	N	Y	H	H
Barlow et al ²²	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	PY	NI	Y	N	N	Y	Y	H	H
Decarli et al ²³	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	N	Y	N	Y	H	H
Decarli et al ^{23*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	N	NI	-	NI	Y	-	-	H	H
Novotny et al ²⁴	N	PY	H	Y	PN	Y	H	PY	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	PY	N	N	Y	H	H
Gail et al ²⁵	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	PY	N	N	Y	H	H
Gail et al ^{25*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	-	Y	Y	-	-	H	H
Anna et al ²⁶	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	PY	N	N	Y	H	H
Tice et al ²⁷	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	N	N	Y	Y	Y	Y	Y	H	H
Tamimi,et al ²⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	NI	N	N	Y	H	H
Petracci et al ²⁹	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	N	N	Y	H	H
Petracci et al ^{29*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	-	Y	PN	-	-	H	H
Dite et al ³⁰	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	N	PY	N	N	Y	H	H
Park et al ³¹	N	Y	H	Y	PY	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	N	PY	N	N	Y	H	H
Park et al ^{31*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	NI	-	PY	Y	-	-	H	H
Anothaisintawee et al ³²	Y	Y	H	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	Y	N	PY	PN	N	Y	H	H

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5	Anothaisintawee et al ^{32*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	Y	-	PY	PN	-	-	H	H	
6	Boggs et al ³³	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	NI	Y	N	Y	Y	H	H	
7	Brentnall et al ³⁴	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	Y	N	N	N	Y	H	H	
8	Kerlikowske et al ³⁵	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	N	PN	Y	Y	H	H
9	Tice et al ³⁶	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	Y	PN	Y	Y	H	H	
10	Schonberg et al ³⁷	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	N	Y	N	N	Y	H	H	
11	Schonberg et al ^{37*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	N	-	Y	PN	-	-	H	H
12	Shieh et al ³⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	N	N	N	Y	Y	H	H	
13	Wang et al ³⁹	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	N	PY	N	Y	Y	H	H	
14	Maas et al ⁴⁰	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	PY	PN	PN	Y	H	H
15	Banegas, et al ⁴¹	N	Y	H	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	PY	N	NI	Y	H	H	
16	Banegas et al ^{41*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	-	PY	Y	-	-	H	H	
17	Eriksson et al ⁴²	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	NI	PY	N	Y	Y	H	H	
18	Hsieh, et al ⁴³	N	NI	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	N	PY	N	Y	Y	H	H	
19	Husing et al ⁴⁴	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	PY	N	Y	Y	H	H	
20	Salih et al ⁴⁵	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	N	PY	N	Y	Y	H	H	
21	Wang et al ⁴⁶	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	PN	Y	Y	H	H	
22	Zhang et al ⁴⁷	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	PY	N	Y	Y	H	H
23	Clendenen et al ⁴⁸	Y	Y	L	PN	Y	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	PY	N	N	Y	H	H
24	Wang et al ⁴⁹	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	Y	N	N	Y	H	H	
25	Wang et al ^{49*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	N	-	Y	PN	-	-	H	H	
26	Abdolell et al ⁵⁰	Y	PY	L	Y	Y	Y	L	PY	Y	Y	Y	Y	Y	L	Y	Y	Y	N	N	PY	N	N	Y	H	H	
27	Qiu et al ⁵¹	N	NI	H	Y	N	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	PY	N	N	Y	H	H	
28	Qiu et al ^{51*}	N	NI	H	Y	N	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	-	PY	N	-	-	H	H	
29	Han et al ⁵²	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	Y	Y	Y	H	H	
30	Han et al ^{52*}	Y	Y	L	Y	Y	Y	L	PY	Y	Y	Y	Y	Y	L	Y	Y	Y	N	-	NI	Y	-	-	H	H	

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Rosner et al ⁵³	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	N	N	Y	H	H
Rosner et al ^{53*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	-	PY	N	-	-	H	H
Yiangou et al ⁵⁴	N	Y	H	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	PN	N	PY	N	PN	Y	H	H

* The external validation was performed in the same study.

L: low risk of bias; H: high risk of bias; Y: yes; N: no; PY: probably yes; PN: probably no; NI: no information; -: not applicable.

- 1.1. Were appropriate data sources used, e.g., cohort, RCT, or nested case-control study data?
- 1.2. Were all inclusions and exclusions of participants appropriate?
- 2.1. Were predictors defined and assessed in a similar way for all participants?
- 2.2. Were predictor assessments made without knowledge of outcome data?
- 2.3. Are all predictors available at the time the model is intended to be used?
- 3.1. Was the outcome determined appropriately?
- 3.2. Was a prespecified or standard outcome definition used?
- 3.3. Were predictors excluded from the outcome definition?
- 3.4. Was the outcome defined and determined in a similar way for all participants?
- 3.5. Was the outcome determined without knowledge of predictor information?
- 3.6. Was the time interval between predictor assessment and outcome determination appropriate?
- 4.1. Were there a reasonable number of participants with the outcome?
- 4.2. Were continuous and categorical predictors handled appropriately?
- 4.3. Were all enrolled participants included in the analysis?
- 4.4. Were participants with missing data handled appropriately?
- 4.5. Was selection of predictors based on univariable analysis avoided? (Development studies only)
- 4.6. Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately?
- 4.7. Were relevant model performance measures evaluated appropriately?
- 4.8. Were model overfitting, underfitting, and optimism in model performance accounted for? (Development studies only)
- 4.9. Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? (Development studies only)



PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5,6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6,7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 and Appendix Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8,9 and Appendix Table 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8,9 and Appendix Table 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7,8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8,9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8,9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8,9 and Appendix Table 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8,9

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not performed
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not performed
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not performed
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not performed
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9 and figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9
Study characteristics	17	Cite each included study and present its characteristics.	9,10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	12,13,14,15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9,10,11 and Appendix Table 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix Table 3, table 1, figure 2, figure 3 and figure 4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9, 10,11,12, 13,14 and Appendix Table 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not performed
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not performed
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not performed
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not performed
DISCUSSION			

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14,15
	23b	Discuss any limitations of the evidence included in the review.	15,16
	23c	Discuss any limitations of the review processes used.	15,16
	23d	Discuss implications of the results for practice, policy, and future research.	16,17,18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3,6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not performed
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not performed
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Competing interests	26	Declare any competing interests of review authors.	19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendix Table 1,2,3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
 For more information, visit: <http://www.prisma-statement.org/>

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BMJ Open

Risk prediction models for breast cancer: a systematic review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055398.R2
Article Type:	Original research
Date Submitted by the Author:	14-Apr-2022
Complete List of Authors:	Zheng, Yadi; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Office of Cancer Screening Li, Jiang; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Office of Cancer Screening Wu, Zheng; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Office of Cancer Screening Li, He; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Office of Cancer Screening Cao, Maomao; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Office of Cancer Screening Li, Ni; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Office of Cancer Screening He, Jie; National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Department of Thoracic Surgery
Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Oncology, Public health
Keywords:	Epidemiology < TROPICAL MEDICINE, Public health < INFECTIOUS DISEASES, Breast tumours < ONCOLOGY, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Risk prediction models for breast cancer: a systematic review

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Word count: 2772

Figures/Tables: 5

ABSTRACT

Objectives: To systematically review and critically appraise published studies of risk prediction models for breast cancer in the general population without breast cancer, and provide evidence for future research in the field.

Design: Systematic review using the Prediction model study Risk Of Bias Assessment Tool (PROBAST) framework.

Data sources: PubMed, the Cochrane Library and Embase were searched from inception to 16 December, 2021.

Eligibility criteria: We included studies reporting multivariable models to estimate the individualized risk of developing female breast cancer among different ethnic groups. Search was limited to English language only.

Data extraction and synthesis: Two reviewers independently screened, reviewed, extracted, and assessed studies with discrepancies resolved through discussion or a third reviewer. Risk of bias was assessed according to the PROBAST (Prediction model Risk of Bias Assessment Tool) framework.

Results: 63,894 studies were screened and 40 studies with 47 risk prediction models were included in the review. Most of the studies used logistic regression to develop breast cancer risk prediction models for Caucasian women by case-control data. The most

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10 widely used risk factor was reproductive factors and the highest area under the curve was
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12 0.943 (95% confidence interval: 0.919~0.967). All the models included in the review had
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14 high risk of bias.
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17 **Conclusions:** No risk prediction models for breast cancer were recommended for
18
19 different ethnic groups and models incorporating mammographic density or single-
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21 nucleotide polymorphisms (SNPs) among Asian women are few and poorly needed.
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23 High-quality breast cancer risk prediction models assessed by PROBAST should be
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25 developed and validated, especially among Asian women.
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30 **PROSPERO registration number:** CRD42020202570
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33 **Strengths and limitations of this study**

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35

- 36 1. Thoroughly conducted systematic review collecting data from major existing databases.
- 37
38 2. Critically appraised published studies of risk prediction models for breast cancer in the
39
40 general population and provide evidence for future research in the field.
- 41
42 3. PROBAST was used to assess the quality of prediction models, which was developed
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44 through a consensus process involving a group of methodological experts in the area of
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46 clinical prediction tools and quality assessment.
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49 4. Studies only about the external validation of the present risk models were not included
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51 in the review.
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10 5. Our study highlighted high-quality breast cancer risk prediction models assessed by
11
12 PROBAST should be developed and validated among different ethnic groups, especially
13
14 among Asian women.
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17 **Keywords:** breast cancer; risk prediction model; review; quality assessment; Prediction
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19 model Risk of Bias Assessment Tool
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22 23 INTRODUCTION

24
25 Breast cancer is a major public health problem, and one of the most severe
26
27 burdensome cancer among women worldwide ¹, accounting for 11.7% of new cancer
28
29 cases and 6.9% of cancer deaths in 2020. The prevalence of breast cancer is projected to
30
31 increase over the coming years and is the most common cancer in women in 2020 ². Breast
32
33 cancer prevention is associated with a reduction in mortality ³, and more researches are
34
35 needed to improve the methods of identifying women at elevated risk and preventing the
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37 disease. Numerous breast cancer risk prediction models have been developed to identify
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39 the combined effect of risk factors for breast cancer, guide routine screening and genetic
40
41 testing, and reduce the burden of breast cancer. Risk-stratified screening can improve
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43 cost-effectiveness and maximize benefits and minimize harms like overdiagnosis ⁴.
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45 Individualized prediction model for breast cancer could be used in practice to assist
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47 decision making about mass screening or opportunistic screening and treatment strategy.
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10 A recent breast cancer screening guideline ⁵ suggests that breast cancer screening
11 increase the early detection rate and reduce the incidence if the screening is applied in
12 appropriate at-risk populations. However, major gaps exist in our knowledge to determine
13 the risk of breast cancer accurately in order to apply these approaches to appropriate
14 populations of women.
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23 A lot of breast cancer risk prediction models have been developed over the past few
24 decades. Many breast cancer risk models have undergone validation including
25 discrimination and calibration in study populations other than those used in initial
26 development, or have been further assessed in comparative studies. Breast cancer related
27 predictors including hormonal factors, environmental factors, family histories, genetic
28 factors and radiographic factors have been based on in these risk models, which would
29 improve the generalizability. For example, the Gail model ⁶, one of the most famous
30 models, has been widely used and validated worldwide since it was developed in 1989 <sup>7-
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10 female breast cancer risk among one or more ethnic groups, prepare for the development
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12 of risk prediction models, and provide evidence for future research in the field.
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15 **METHODS**

16 17 **Protocol and registration**

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20 The current review was designed according to the Checklist for critical Appraisal
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22 and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)
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24¹⁵ and was recorded in the PROSPERO database (registration number:
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26 CRD42020202570).
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30 **Literature search and eligibility criteria**

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33 We systematically searched PubMed, the Cochrane Library and Embase from
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35 inception to 16 December, 2021. The detailed search strategies were reported in Appendix
36
37 Table 1. Articles identified from the search were loaded into EndNote X7 and duplicates
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39 were removed.
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44 Inclusion criteria: 1) a model used data from cross-sectional studies, cohort studies,
45
46 case-control studies, and randomized controlled trials; 2) a model estimating the
47
48 individualized risk of female breast cancer among one or more ethnic groups; 3) a model
49
50 developed for the general population without breast cancer; 4) reported a multivariable
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52 (i.e., at least 2 variables or predictors) model; 5) published in English.
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10 Exclusion criteria: 1) external validation studies that only validated previous models
11 in a different population without adding any additional information such as modifications
12 on the risk factors; 2) models developed by machine learning.
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17 **Data extraction**

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20 Two reviewers screened the search results independently. Full text reports were then
21 assessed for eligibility with discrepancies resolved through discussion or a third reviewer.
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25 We extracted information in two categories: 1) For all studies included in the review,
26 we extracted the following information: author, publication year, study design, research
27 method, targeted population, number of risk factors, risk factors, model performance and
28 sample size of development. 2) For studies included validation part, we also extracted the
29 following information: type of validation, study design, targeted population, model
30 performance and sample size of validation. The information was extracted by one
31 reviewer and checked by a second reviewer.
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43 **Risk of bias assessment**

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46 We used PROBAST to assess the reported prediction models, which is a new tool
47 designed by a group of experts all over the world to assess the risk of bias and applicability
48 of diagnostic and prognostic prediction models. It can be used in critical appraisal of
49 studies that develop, validate, or update prediction models for individualized predictions
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10 13-14. In brief, it contains 20 signaling questions in four domains: participants, predictors,
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12 outcome, and statistical analysis. Signaling questions can be answered as yes, probably
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14 yes, no, probably no, or no information. A domain where at least one signaling question
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16 is answered as no or probably no should be judged as high risk of bias. Only if all domains
17
18 are judged as low risk of bias, the total bias is judged as low risk as well.
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22
23 Before putting PROBAST into use, we formed a ten-people study group including
24
25 prediction model researchers, statisticians, evidence-based medicine specialists etc. to
26
27 learn and practice the appropriate use of this new tool systematically. Only after everyone
28
29 understood all these twenty questions totally, we would move to the peer quality
30
31 assessment part. Risk of bias of every prediction model was assessed by two reviewers
32
33 independently with discrepancies resolved through discussion or a third reviewer.
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39 If there were more than one models developed in one study, we only assessed the
40
41 risk of bias once due to their similarity. We also assessed the risk of external validation
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43 of prediction model when it was conducted in the same article that included model
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45 development.
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48 **Data synthesis and analysis**

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51 We calculated and reported descriptive statistics to summarize the characteristics of
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53 the models. We calculated the most frequently used risk factors and classified all risk
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10 factors into eight categories: Age, reproductive factors, family history of cancer, hormone,
11 gene-related factors, lifestyle, medical history and test, and basic information.
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13 Classification details can be seen in Appendix Table 2. Then we used network diagram
14
15 to see the connections of categorized risk factors. We used forest plot to describe the
16
17 model performance. The expected observed (E/O) ratio was not included in the forest plot
18
19 because it was only reported in 7 out of 40 studies. All analyses were performed using
20
21 Stata 16.0 and NetDraw.
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27 **Patient and public involvement**

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30 There was no patient or public involvement in this study.
31

32 **RESULTS**

33 **Study selection**

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36 A total of 92,519 indexed records (54,653 in PubMed, 30,374 in Cochrane Library
37
38 and 7,492 in Embase), 28,625 were eliminated as duplicates found in all databases,
39
40 leaving a total of 63,894 publications. 43 articles were included primarily after screening
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42 by title and abstract. 3 studies which were only about the external validation of previous
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44 models were excluded while full test screening, resulting in 40 studies with 47 models
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51 were included in the review eventually. (Figure 1).
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53 **Study characteristics**

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10 A brief summary of the 40^{6,16-54} included studies is presented in Appendix Table 3.
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12 The included studies were published from 1989 to 2021. 25 of the studies were conducted
13 over the past ten years with 5 studies published in 2017 especially. Seventeen out of the
14 forty studies used data from case-control studies to develop prediction models<sup>6,17,19,23-
15 26,29-31,39, 41,43,46,49,51,54</sup>, thirteen from prospective cohorts^{16,18,20-22,27,33-37,40,52}, eight from
16 nested case-control studies^{28,38, 42,44,47,48,50,53} and two from cross-sectional study^{32,45}.
17 Thirty-one studies used logistic regression to fit prediction models<sup>6,17-19,22-26,28-32,34,38-
18 51,53,54</sup>, seven used cox proportional hazards regression^{20,21,27,33,35,36,52}, one used Poisson
19 regression¹⁶ and one used competing risk regression³⁷. Of all forty-seven models in forty
20 studies, sixteen models were developed in Caucasian women^{6,16,18,23,26,28,29,34,40,42,45,47,50,53},
21 thirteen in multiple ethnicities women^{20-22,24,27,30,35-38,44,48}, twelve in Asian women
22 17,19,31,32,39,43,49,51,52, two in African-American women^{25,33}, two in Hispanic women⁴¹, one
23 in Nigerian women⁴⁶ and one in Cypriot Women⁵⁴.

24
25 The association between eight categories of risk factors was shown in Figure 2.
26
27 Reproductive factors had the biggest node size, which meant that this factor was most
28 frequently connected with other factors among prediction models. The number between
29 two factors meant the times these two factors were included in the same models, some of
30 which were over thirty. For instance, reproductive factors and family history of cancer
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10 were included in the same models for forty times, and reproductive factors and age were
11 included in the same models for thirty-one times.
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15 Twenty-nine studies reported c-statistics ^{18-22,26-28,30-32,34-40,42,43,45-48,50-54}, ranged from
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17 0.59(95% confidence interval: 0.57~0.61) to 0.943(95% confidence interval:
18 0.919~0.967). Qiu, et al ⁵¹ had the highest c-statistics (0.943, 95% confidence interval:
19 0.919~0.967), and Lee et al ¹⁹ and Salih et al ⁴⁵ reported area under the curve (AUC) over
20 0.8, 0.867 and 0.864(95% confidence interval: 0.81~0.92), respectively. E/O ratios can
21 be obtained from eight studies ^{22,27,29,32,35,36,46,52}. Figure 3 showed that the overall AUC
22 was 0.68(95% confidence interval: 0.63~0.73) for sixteen studies ^{21,26,27,30,32,34,37,38,42,}
23 45,46,48,50,51,52,54 that reported the AUC and 95% confidence interval. The AUCs of the
24 subgroups in five studies ^{18,22,31,39,47} were between 0.6 to 0.7.
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38 In all these forty studies, nine studies assessed prediction models with internal
39 validation ^{22,26,27,33,39,44-47}, ten with external validation ^{23,25,29,31,37,41,49,51-53}, and one with
40 both ³². Fifteen studies reported the discriminatory accuracy as the AUC ^{23,25,27,29,31-}
41 33,37,39,41,46,49,51-53, and eleven studies used the expected/observed event ratio (or
42 observed/expected event ratio) to measure the calibration accuracy of the model
43 ^{23,25,27,29,31,33,37,41,45,49,52}.
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53 **Quality assessment**

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A summary of the quality assessment is shown in Table 1. Overall, all models assessed by PROBAST in the review had high risk of bias. There was a low and high risk of bias in the outcome and analysis domains respectively. Over 60% models had low risk in participants domain and about 70% models had low risk in predictors domain, 32 models and 36 models respectively. (As shown in Figure 4).

The main reasons for the high risk in analysis domain were model performance measures evaluated inappropriately, categorization of continuous predictors, no reporting of overfitting and optimism in model performance and missing data handled inappropriately (Appendix Table 4).

Table 1. Summary of risk of bias assessment.

Study	Participants	Predictors	Outcome	Analysis	Overall
Gail et al ⁶	H	L	L	H	H
Rosner et al ¹⁶	L	L	L	H	H
Ueda et al ¹⁷	H	L	L	H	H
Colditz et al ¹⁸	L	L	L	H	H
Lee et al ¹⁹	H	H	L	H	H
Tice et al ²⁰	L	L	L	H	H
Tice et al ²¹	L	L	L	H	H
Barlow et al ²²	L	L	L	H	H
Decarli et al ²³	H	H	L	H	H
Decarli et al ^{23*}	L	L	L	H	H
Novotny et al ²⁴	H	H	L	H	H
Gail et al ²⁵	H	H	L	H	H
Gail et al ^{25*}	L	L	L	H	H
Anna et al ²⁶	H	H	L	H	H

Tice et al ²⁷	L	L	L	H	H
Tamimi,et al ²⁸	L	L	L	H	H
Petracci et al ²⁹	H	H	L	H	H
Petracci et al ^{29*}	L	L	L	H	H
Dite et al ³⁰	H	H	L	H	H
Park et al ³¹	H	H	L	H	H
Park et al ^{31*}	L	L	L	H	H
Anothaisintawee et al ³²	H	L	L	H	H
Anothaisintawee et al ^{32*}	L	L	L	H	H
Boggs et al ³³	L	L	L	H	H
Brentnall et al ³⁴	L	L	L	H	H
Kerlikowske et al ³⁵	L	L	L	H	H
Tice et al ³⁶	L	L	L	H	H
Schonberg et al ³⁷	L	L	L	H	H
Schonberg et al ^{37*}	L	L	L	H	H
Shieh et al ³⁸	L	L	L	H	H
Wang et al ³⁹	H	H	L	H	H
Mass et al ⁴⁰	L	L	L	H	H
Banegas, et al ⁴¹	H	L	L	H	H
Banegas et al ^{41*}	L	L	L	H	H
Eriksson et al ⁴²	L	L	L	H	H
Hsieh, et al ⁴³	H	H	L	H	H
Husing et al ⁴⁴	L	L	L	H	H
Salih et al ⁴⁵	L	L	L	H	H
Wang et al ⁴⁶	H	H	L	H	H
Zhang et al ⁴⁷	L	L	L	H	H
Clendenen et al ⁴⁸	L	H	L	H	H
Wang et al ⁴⁹	H	H	L	H	H
Wang et al ^{49*}	L	L	L	H	H
Abdoell et al ⁵⁰	L	L	L	H	H
Qiu et al ⁵¹	H	H	L	H	H
Qiu et al ^{51*}	H	H	L	H	H
Han et al ⁵²	L	L	L	H	H
Han et al ^{52*}	L	L	L	H	H

Rosner et al ⁵³	L	L	L	H	H
Rosner et al ^{53*}	L	L	L	H	H
Yiangou et al ⁵⁴	H	L	L	H	H

* The external validation was performed in the same study.

L indicates low risk of bias; H indicates high risk of bias.

DISCUSSION

Summary of main results

This systematic review identified 40 studies with 47 risk prediction models developed and/or validated for breast cancer among different ethnic groups. Most of the studies used logistic regression to develop breast cancer risk prediction models for Caucasian women by case-control data. The most widely used risk factor was reproductive factors. Reproductive factors together with family history factor were used in most models. The highest AUC was 0.943 (95% confidence interval: 0.919~0.967) from Qiu, et al ⁵¹. The overall AUC was 0.68(95% confidence interval: 0.63~0.73) for sixteen studies ^{21,26,27,30,32,34,37,38,42,45,46,48,50,51,52,54} that reported the AUC and 95% confidence interval. All the studies presented a high risk of bias due to the high risk in analysis domain, which were mainly because of model performance measures evaluated inappropriately, categorization of continuous predictors, no reporting of overfitting and optimism in model performance and missing data handled inappropriately.

Agreements and disagreements with other reviews

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10 As we can learn from the review, there were more and more risk prediction models
11 of breast cancer over the past thirty years. Most of the models were developed in the
12 Caucasian women, which agreed with the systematic review published by Louro et al in
13 2019 ⁵⁵. Compared with this review, we identified more prediction models and used a
14 newly published tool to assess the quality of included models.
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23 Over the past ten years, some new variables (such as oral contraceptives, diabetes,
24 and alcohol consumption) have been included in prediction models. Increased use of the
25 inclusion of common genetic variation in the prediction models was in accord with Louro
26 et al in 2019 ⁵⁵ and Anothaisintawee et al in 2012 ⁵⁶. However, neither of them included
27 models developed with potential biomarkers like tumor-associated antigens. By contrast,
28 we included one model developed by Qiu, et al ⁵¹ in 2019 included five tumor-associated
29 antigens. The model performed well with a high AUC 0.943(95% confidence interval:
30 0.919,0.967).
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43 **Strengths and limitations of the study**

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46 PROBAST was developed through a consensus process involving a group of
47 methodological experts in the field of clinical prediction tools and quality assessment.
48 We used it to assess the quality of prediction models, which has been used widely in many
49 fields ⁵⁷⁻⁶⁰ since it came out.
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Despite the strength, there are four main limitations. Firstly, we didn't systematically search gray literature. Therefore, some models may not be identified. Secondly, quality assessment could be thought to be subjective, which is an inherent bias of systematic review. However, two independent reviewers extracted and assessed the risk prediction models using PROBAST whose authors have indicated essentially objective guidelines and explanations. Moreover, studies only about the external validation of the present risk models were not included in the review, but the original developments of these risk models were covered. For instance, the study describes the original developments of Gail model⁶ was included in our research, while the studies only about the external validation of Gail model⁶¹⁻⁶⁴ were not included. What's more, papers about genetically oriented models like BOADICEA^{65,66} and BRACAPRO⁶⁷ were not included in our study because some rare truncating/pathogenic variants like BRCA1 and BRCA2 are needed to be tested, which might be too expensive to use for general population in the mass screening⁵⁵.

Implication to research and clinical practice

Eleven models^{19,30-32,37-39,43,45,50,54} selected predictors based on univariable analysis, causing a high risk in analysis domain, which should be avoided. Risk prediction models should include predictors those are well-established and with clinical credibility regardless of any statistical significance^{68,69}. Because sometimes predictors only have

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10 important relationship with the outcome after adjustment for confounding covariates, and
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12 covariates hold no independent predictive power when other covariates are included ^{13,70}.

15 Some models were high risk in analysis domain because of missing data handled
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17 inappropriately, which may lead to biased associations between risk factors and breast
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19 cancer as well as biased model performance because of the selectivity of participants ⁷¹.
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21 So imputation techniques are supposed to apply when data are missing ^{72,73}.

25 When developing the risk prediction models, there were only nine studies included
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27 internal validation ^{22,26,27,33,39,44-47}, leaving most models without internal validation. Lack
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29 of performing internal validation may increase the risk of overfitting ⁷⁴. Thus, we suggest
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31 that internal validation should be performed before external validation.

35 PROBAST was created by many international experts, providing a series of
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37 guidelines about model development and validation, which can be easily applied and
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39 improve clinical practice of prediction models. So, the new and most recommended
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41 methodology should be used when a new model is developed or the existing models are
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43 updated.
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48 In the light of the results of our review, it is still hard to recommend any of the
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50 models to be applied in the breast cancer screening due to the high risk of bias. Adding
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52 variables like mammographic density or single-nucleotide polymorphisms (SNPs) to risk-
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10 prediction models can improve the model performance and has been well validated in the
11 general population of European-ancestry women^{40,75-80}. But the model incorporating
12 breast density or SNPs among Asian women is few and poorly needed. Cost-effectiveness
13 should be considered when a model is going to be applied in clinical practice. Because
14 even though the model with some risk factors that cost more to get (e.g., high risk gene)
15 has better model performance, it is still hard to be applied in poor area ⁸¹. What's more,
16 an existing model should be modified or updated before used in another group of people
17 with different characteristics, which may improve the performance of prediction models.
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30 Breast cancer incidence has risen to the first place by 2020 all over the world, which
31 makes it more crucial to develop breast cancer prediction models for different ethnic
32 groups. In China, we have launched many breast cancer screening programs. For example,
33 Rural Women "two cancers" Check Project Management Solutions have covered 31
34 provinces and 1437 counties since 2009. Cancer Screening Program in Urban China
35 conducted by the National Cancer Center has covered 28 provinces and 67 cities with
36 more than 4 million people involved and 2 million people screened by ultrasound and
37 Mammography since 2012. The program will provide large data for us to develop a high-
38 quality breast cancer risk prediction model in Chinese and will have great significance
39 for breast cancer prevention of Asian women.
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CONCLUSIONS

All 47 models assessed in our review using PROBAST performed the high risk of bias, leaving no model is recommended in the routine screening program. Some new variables, like oral contraceptives, diabetes, and alcohol consumption, have been widely used in prediction models over the past ten years. Models incorporating mammographic density or SNPs among Asian women are few and poorly needed. It is necessary to develop and validate high-quality breast cancer risk predication models among different ethnic groups, especially among Asian women.

Contributors: YZ and JL conceptualized the study and created the first version of the review protocol. ZW, HL, MC, NL, and JH critically reviewed the review protocol and approved it. YZ and HL screened eligible articles. YZ extracted the data, supported by ZW, MC. YZ drafted the first version of the manuscript, supported by JL, NL, and JH. All authors contributed to data interpretation and critically assessed it. All authors approved the final version of the manuscript.

Funding: This work was supported by the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (grant number: 2019PT320027).

Competing interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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10 **Patient consent for publication:** Not required.

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12 **Data availability statement:** All data of the current study is present in the main
13 manuscript, figures, tables, and online supplemental material.
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17 **Ethics statement:** This study does not involve human participants.
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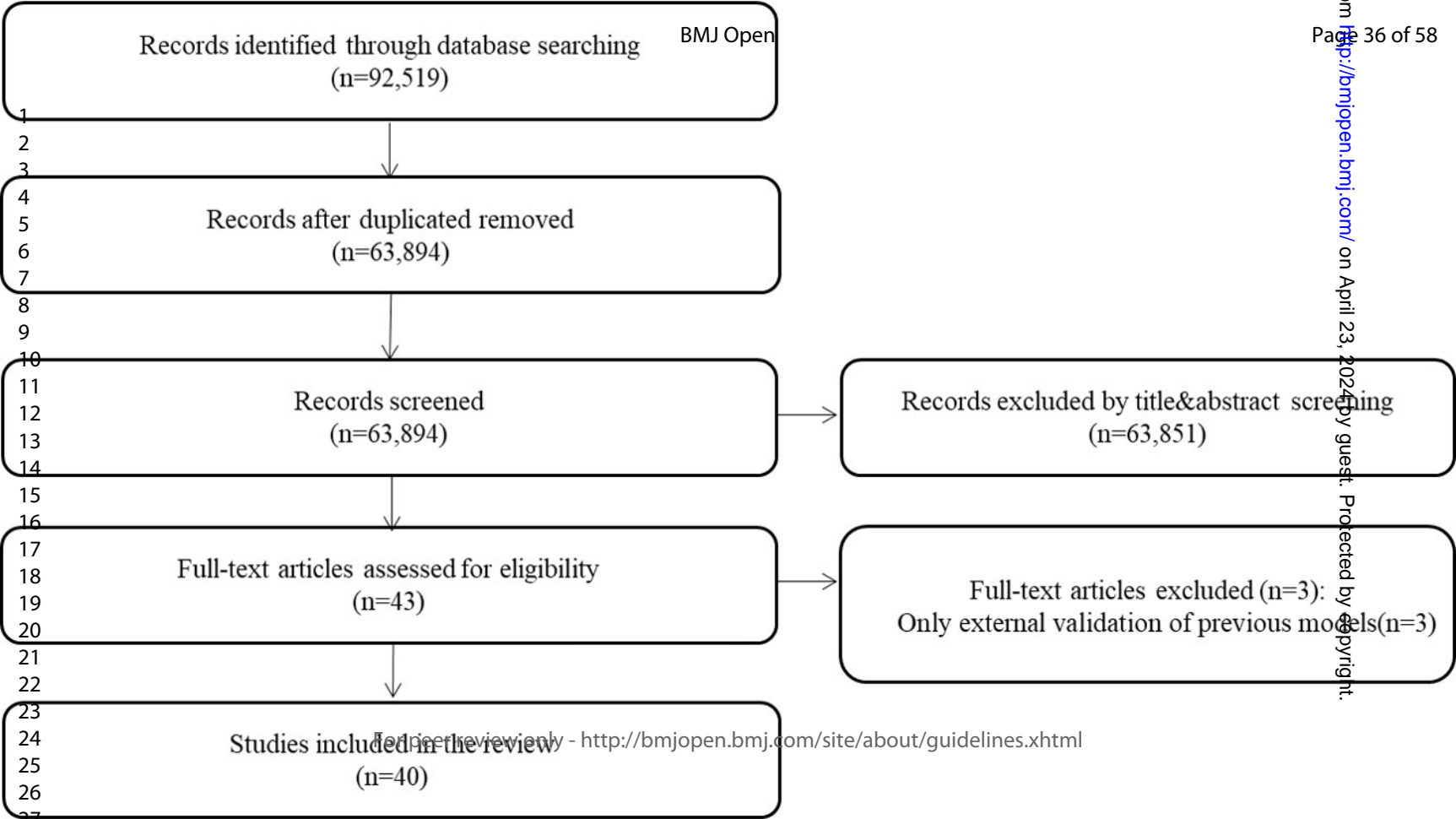
23 **Figure legends:**

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25 Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses)
26 flowchart.
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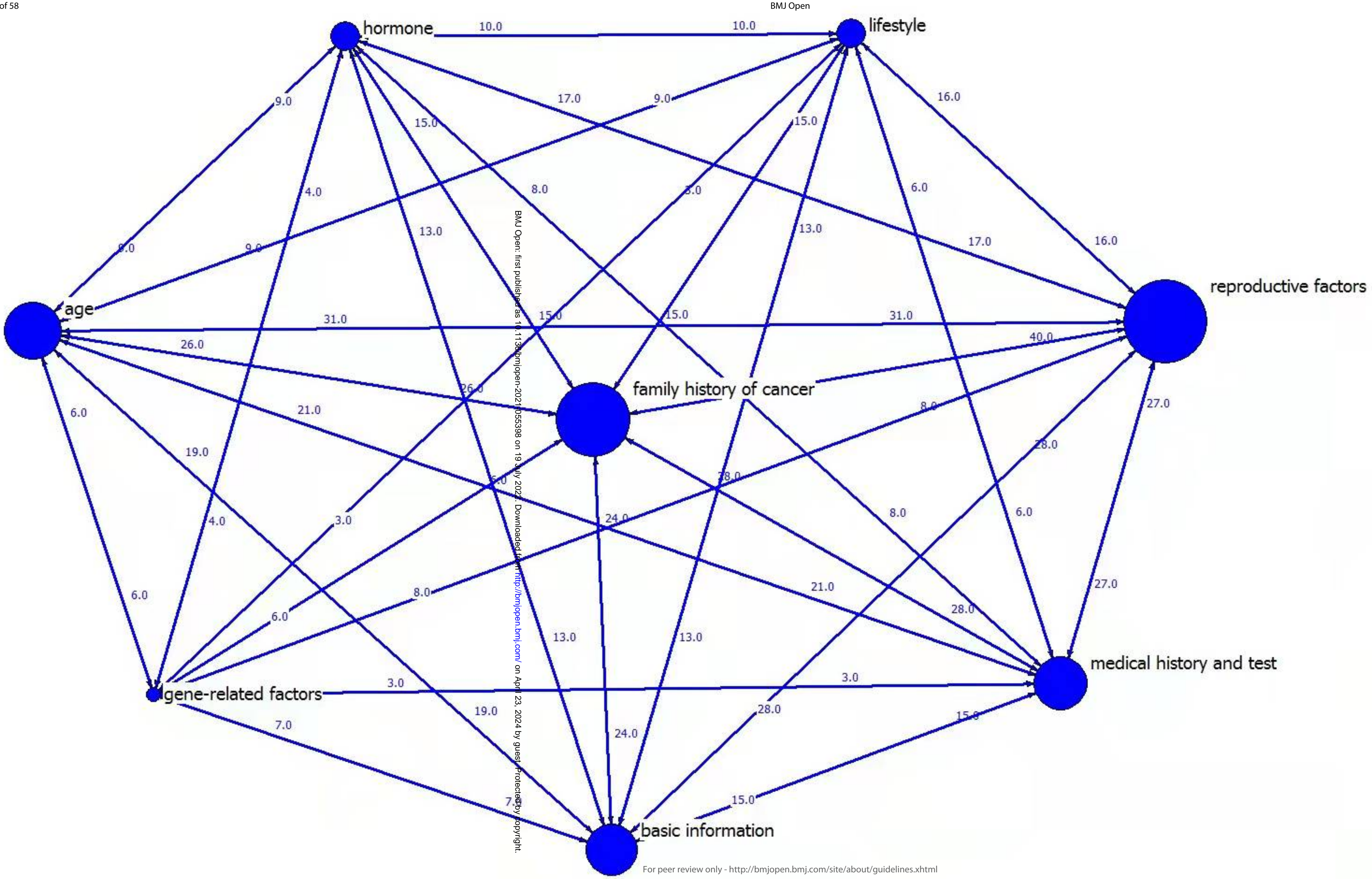
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30 Figure 2. Network diagram of eight categorized risk factors (age, basic information,
31 family history of cancer, gene-related factors, hormone, lifestyle, medical history and
32 test, and reproductive factors).
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38 Figure 3. Area under the curve (AUC) and confidence intervals reported by the included
39 studies.
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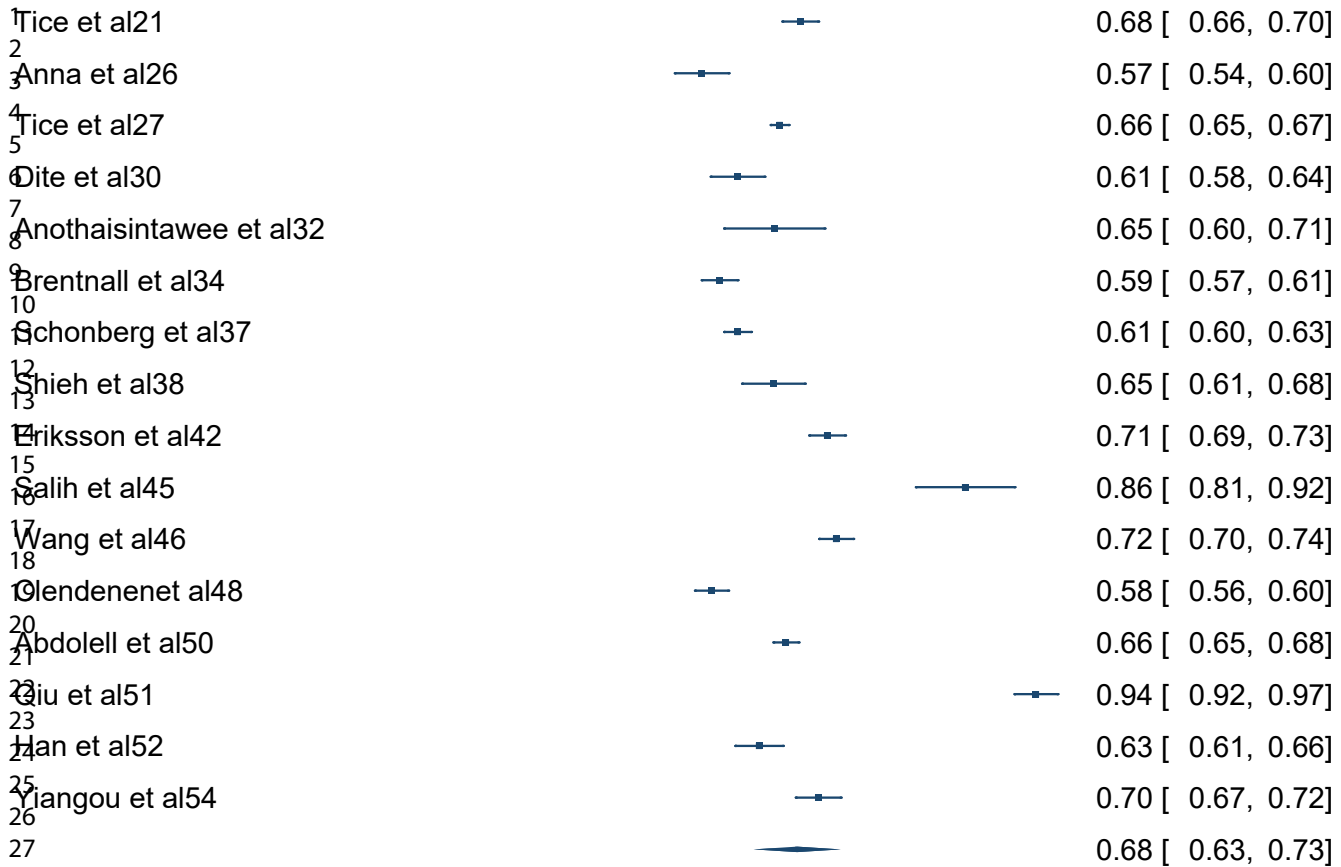
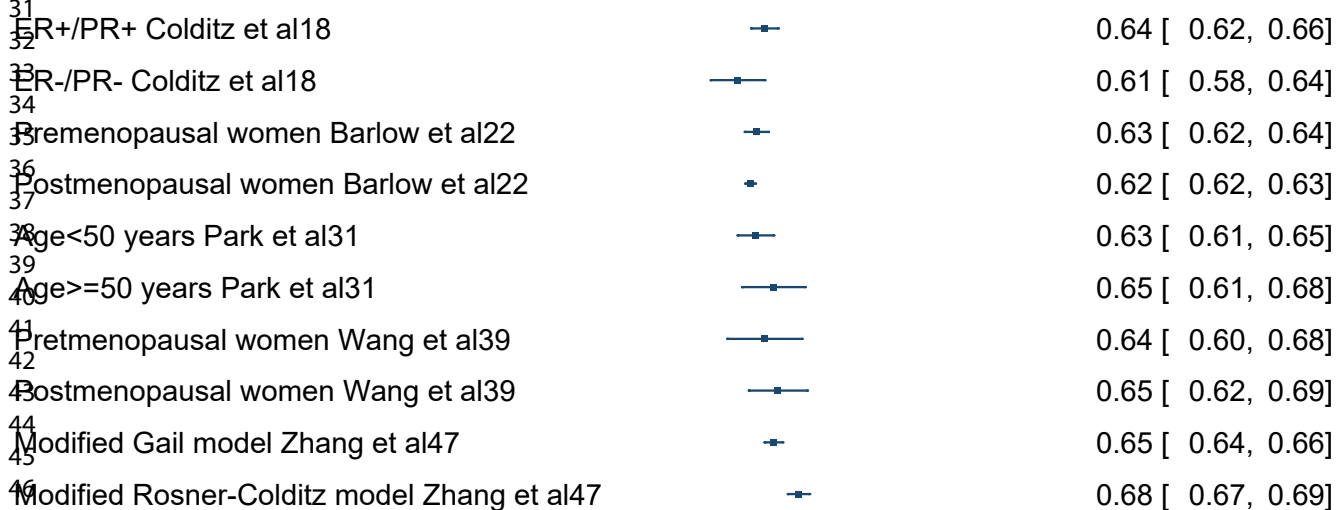
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43 Figure 4. Risk of bias assessment (using PROBAST) of all assessed models based on
44 four domains.
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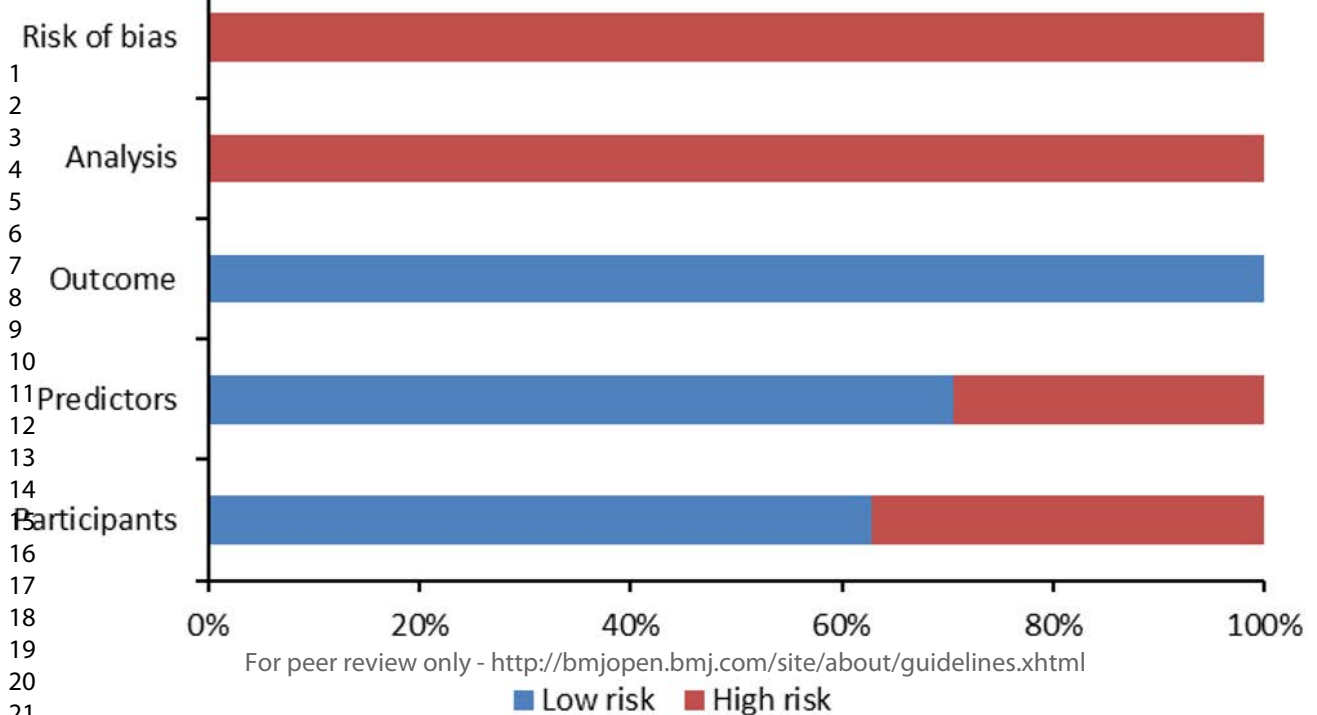


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All**Subgroups**

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■ Low risk ■ High risk

Appendix

Appendix Table 1. Searching strategy.

Searching strategy
Take PubMed for example:
#1 "Breast Neoplasms"[Mesh] OR "Breast Carcinoma In Situ"[Mesh] OR "Breast Neoplasms, Male"[Mesh] OR "Carcinoma, Ductal, Breast"[Mesh] OR "Carcinoma, Lobular"[Mesh] OR "Hereditary Breast and Ovarian Cancer Syndrome"[Mesh] OR "Inflammatory Breast Neoplasms"[Mesh] OR "Triple Negative Breast Neoplasms"[Mesh] OR "Unilateral Breast Neoplasms"[Mesh] OR phyllodes tumor[Title/Abstract] OR breast sarcoma[Title/Abstract] OR mamma cancer*[Title/Abstract] OR mammary cancer*[Title/Abstract] OR mammary gland cancer*[Title/Abstract] OR Mammary Ductal Carcinoma*[Title/Abstract] OR breast gland cancer*[Title/Abstract] OR breast gland neoplasm*[Title/Abstract] OR Breast Neoplasm*[Title/Abstract] OR Breast Tumor*[Title/Abstract] OR Breast Cancer*[Title/Abstract] OR Mammary Cancer*[Title/Abstract] OR Breast Malignant Neoplasm*[Title/Abstract] OR Breast Malignant Tumor*[Title/Abstract] OR Human Mammary Carcinoma*[Title/Abstract] OR Human Mammary Neoplasm*[Title/Abstract] OR Breast Carcinoma*[Title/Abstract] OR Lobular Carcinoma*[Title/Abstract] 418,670
#2 ("Regression Analysis"[Mesh] OR "Multivariate Analysis"[Mesh] OR "Models, Biological"[Mesh] OR "Models, Statistical"[Mesh] OR "Algorithms"[Mesh]) AND "Risk Assessment" [Mesh] 52,269
#3 predict*[Title/Abstract] AND (outcome*[Title/Abstract] OR index[Title/Abstract] OR rule*[Title/Abstract] OR decision*[Title/Abstract] OR scor*[Title/Abstract]) 624,639
#4 risk*[Title/Abstract] AND (predict*[Title/Abstract] OR calculate*[Title/Abstract] OR assess*[Title/Abstract] OR scor*[Title/Abstract] OR algorithm[Title/Abstract]) 1,109,068
#5 model*[Title/Abstract] AND (logistic[Title/Abstract] OR statistic*[Title/Abstract] OR risk*[Title/Abstract] OR predict*[Title/Abstract]) 1,1035,123
#6 OR/2-5 2,195,108
#7 #1 AND #6 54,653

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Appendix Table 2. Classification of risk factors.

age	
reproductive factors	age at menarche, age at first birth, menopause, age at subsequent births, menstrual regularity, total menstrual duration, breastfeeding, breast density, parity, reproductive characteristics, microcalcifications and masses, abortions, breast volume
family history of cancer	family history of breast cancer, family history of any cancer
hormone	hormone therapy, oral contraceptives, estrogen plus progestin use, testosterone, estradiol, sex hormone binding globulin, Insulin-like growth factor-I, estrone sulphate, prolactin, anti-Müllerian hormone
gene-related factors	polygenic risk score, rs2981582 (FCFR2), rs3803662(TOX3), rs889312(MAP3K1), rs13387042(2q35), rs13281615(8q24), rs4415084 (FGF10), rs3817198 (LSP1), rs981782(HCN1), rs10822013(ZNF365), rs3784099(PAD51B)
lifestyle	alcohol consumption, smoking status, exercise, light at night, sleep quality, vegetables and fruits, cereals, life satisfaction score
medical history and test	previous biopsies, benign breast disease, nipple aspirate fluid cytology, prior breast procedure, prior false-positive mammogram, breast inflammatory, benign breast category, benign breast disease, atypical hyperplasia, mammogram in past 2 years, diabetes, myocardial infarction, stroke, emphysema, congestive heart failure, p53, CyclinB1, p16, p62,14-3-3ξ
basic information	body mass index, weight, education, ethnicity, occupational activity, height, residence area

Appendix Table 3. Summary of the 40 included studies.

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Author	Year	develop							validate				
		Study design	Research method	Targeted population	No of risk factors	Risk factors	Model development (AUC (95%CI); E/O ratio (95%))	Sample size of development	Type of validation	Study design	Targeted population	Model validation (AUC (95%CI); E/O ratio (95%))	Sample size of validation
Gil et al ⁶	1989	Case-control study	Logistic regression	Caucasian; 20–79 years	5	Age, age at menarche, age at first birth, number of previous biopsies, number of first degree relatives with breast cancer	AUC: none; E/O ratio: none	2,852cases/ 3,146 controls	None	None	None	None	None
Donner et al ¹⁶	1996	Prospective cohort study	Poisson regression	Caucasian; 30–64 years	5	Age, age at menarche, age at first birth, menopause, age at subsequent births	AUC: none; E/O ratio: none	2,249 cases/ 89,132 total	None	None	None	None	None
Yoda et al ¹⁷	2003	Case-control study	Logistic regression	Asian women; age was not specified.	4	Age at menarche, age at first birth, family history of breast cancer, body mass index	AUC: none; E/O ratio: none	376 cases/ 430 controls	None	None	None	None	None
Colditz et al ¹⁸	2004	Prospective cohort study	Logistic regression	Caucasian; 30-64 years	11	Age, age at menarche, age at first birth, menopause, age at subsequent births, benign breast disease, postmenopausal hormone use, family history of breast cancer in a first-degree relative, weight, body mass index, alcohol consumption	AUC: ER+/PR+: 0.64 (0.63,0.66); ER-/PR-: 0.61 (0.58, 0.64); E/O ratio: none	2,846 cases/ 66,145 total	None	None	None	None	None
Lee et al ¹⁹	2004	Case-control study	Logistic regression	Asian women; age was not specified.	1) Hospitalized controls: 5 2) Nurse/teacher controls: 5	1) Hospitalized controls: family history, menstrual regularity, total menstrual duration, age at first full-term pregnancy, duration of breastfeeding 2) Nurse/teacher controls: age, education level, menstrual regularity, drinking status, smoking status	AUC: 1) Hospitalized controls: 0.714; 2) Nurse/teacher controls: 0.867; E/O ratio: none	1) Hospitalized controls: 384 cases/ 166 controls; 2) Nurse/teacher controls: 384 cases/	None	None	None	None	None

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					se/teac her contro ls: 5			104 controls					
Tice et al ²⁰	2005	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 18 years and older	6	Age, age at menarche, previous biopsy, age at first birth, first degree breast cancer, nipple aspirate fluid cytology	AUC: 0.64; E/O ratio: none	400 cases/6,904 total	None	None	None	None	
Tice et al ²¹	2005	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35 years and older	6	Age, age at menarche, previous biopsy, age at first birth, first degree breast cancer, breast density	AUC: 0.68 (0.66,0.70); E/O ratio: none	955 cases/81,777 total	None	None	None	None	
Barlow et al ²²	2006	Prospective cohort study	Logistic regression	Multiple ethnicities, 35-84 years	1) Premenopausal women: n: 4 2) Postmenopausal women: n: 10	1) Premenopausal women: age, breast density, family history of breast cancer, a prior breast procedure 2) Postmenopausal women: age, breast density, race, ethnicity, family history of breast cancer, a prior breast procedure, body mass index, natural menopause, hormone therapy, a prior false-positive mammogram	AUC: Premenopausal women: 0.631 (0.618, 0.644); postmenopausal women: 0.624 (0.619, 0.630) E/O ratio *: Premenopausal women: 1.000 postmenopausal women: 1.001	1) Premenopausal women: 1,726 cases/568,215 total; 2) postmenopausal women: 9,300 cases/1,642,824 total	Internal validation	None	None	None	
DeCarli et al ²³	2006	Case-control study	Logistic regression	Caucasian; 20-74 years	5	Age, age of menarche, number of breast biopsies, age at first live birth, first degree breast cancer	AUC: none; E/O ratio: none	2569 cases/2588 controls	External validation	Prospective cohort study	Caucasian; 35-64 years	AUC: 0.59; E/O ratio: 0.96(0.84, 1.11)	194 cases /10,031 total

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5 6 7 8 9 10	Novotny et al ²⁴	2006	Case-control study	Logistic regression	Multiple ethnicities; 23-84 years	8	Age of menarche, number of biopsies, age at first childbirth, number of breast cancer cases in first-degree relatives, number of any cancer cases in first-degree relatives, breast inflammatory, body mass index, number of conceptions	AUC: none; E/O ratio: none	2299 cases/ controls	None	None	None	None	
11 12 13 14 15 16 17	Gail et al ²⁵	2007	Case-control study	Logistic regression	African-American Women; 35-64 years	5	Age, age at menarche, number of affected mother or sisters, age at first live birth, number of previous benign biopsy examinations	AUC: none; E/O ratio: none	1607 cases/ 1647 controls	External validation	Prospective cohort study	African American women; 50-79 years	AUC: 0.555 (0.535,0.575); E/O ratio: 0.93b	350 cases /14,059 total
18	Anna et al ²⁶	2008	Case-control study	Logistic regression	Caucasian; age was not specified	5	Age, age at menarche, number of biopsies, age at first live birth, family history	AUC: 0.57 (0.54, 0.60); E/O ratio: none	558 cases/ 1207 controls	Internal validation	None	None	None	None
19 20 21 22	Rice et al ²⁷	2008	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35 years or older	5	Age, ethnicity, first degree breast cancer, previous biopsies, breast density	AUC: 0.657 (0.65,0.67); E/O ratio: 1.00 (0.98,1.03)	14,766 cases/ 1095484 total	Internal validation	Prospective cohort study	Multiple ethnicities; 35 years or older	AUC: 0.660(0.65,0.66); E/O ratio: 1.03(0.99,1.06)	3,465 cases/ 251,789 total
23 24 25 26 27 28 29 30 31 32 33 34	Mammi et al ²⁸	2010	Nested case-control study	Logistic regression	Caucasian; 40-79 years	11	The type of benign breast disease, age, age at menarche, age at first birth and at each subsequent birth, age at menopause and type of menopause, history of benign breast diseases, family history of breast cancer in mother or sister, height, weight at age 18 years, current use of postmenopausal hormones (including type and duration of use), alcohol intake	AUC: 0.635; E/O ratio: none	240 cases/ 1036 controls	None	None	None	None	None

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5	Tracci et al ²⁹	2011	Case-control study	Logistic regression	Caucasian; 20-74 years	8	Reproductive characteristics, education, occupational activity, family history, biopsy history, alcohol consumption, leisure physical activity, body mass index.	AUC: none; E/O ratio: 1.10 (0.96,1.26)	2569 cases/ 2588 controls	External validation	Prospective cohort study	Caucasian; 35-64 years	AUC: Age<50: 0.62(0.555,0.689) ; age>=50: 0.57 (0.519,0.614); E/O ratio: 1.10(0.96,1.26)	206 cases/ 8,426 total
10	De et al ³⁰	2013	Case-control study	Logistic regression	Multiple ethnicities; 35-59 years	13	Age, ethnicity, age at menarche, age at birth of first child, number of first-degree relatives with breast cancer, number of biopsies, presence of atypical hyperplasia, rs2981582(FGFR2), rs3803662(TOX3), rs889312(MAP3K1), rs13387042(2q35), rs13281615(8q24), rs4415084 (FGF10), rs3817198 (LSP1)	AUC: 0.61 (0.58,0.64); E/O ratio: none	962 cases/ 463 controls	None	None	None	None	None
19	Park et al ³¹	2013	Case-control study	Logistic regression	Asian women; age was not specified.	1) Age <50 years: 7 2) Age >=50 years: 7	1)Age<50 years: a family history of breast cancer in first-degree relatives, age at menarche, menopausal status, age at first full-term pregnancy, duration of breast feeding, oral contraceptive usage, exercise. 2)Age>=50 years: a family history of breast cancer in first degree relatives, age at menarche, age at menopause, experience of pregnancy, body mass index, oral contraceptive usage, exercise	AUC: Age<50 years: 0.63 (0.61-0.65); Age>=50 years: 0.65 (0.61- 0.68); E/O ratio: none	3,789 cases/ 3,789 controls	External validation	Prospective cohort study	None	1)Korean Multi-Center Cohort (KMCC): AUC: 0.61(0.49,0.72); E/O ratio: 0.97(0.67,1.40) 2)National Cancer Center (NCC) cohort: AUC: 0.89(0.85,0.93) E/O ratio: 0.96(0.70,1.37)	1) KMCC: 29cases/ 6148 total; 2)NCC: 36 cases/ 7546 total
34	Thaisintawee et al ³²	2014	Cross-sectional study	Logistic regression	Asian women; age was not specified	4	Age, menopausal status, body mass index, use of oral contraceptives	AUC: 0.651 (0.595, 0.707); O/E ratio: 1.00 (0.82, 1.21) ^b	107cases/ 15,718total	Internal and external validation	Cross-sectional study	Asian women; 18 years or older	Internal validation: AUC: 0.646(0.642,0.650); E/O ratio: none; External validation:	35 cases/ 4,978 total

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5	erlikowske et al	2015	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35-74 years	5	Age, ethnicity, first degree breast cancer, previous biopsies, changes in breast density	AUC: 5-year risk model: 0.640; 10-year risk model: 0.628; E/O ratio: 5-year risk model: 0.98(0.96,1.00); 10-year risk model: 0.95(0.94,0.96)	13,715 cases/ 722,654 total	None	None	None	None	
13	Lee et al ³⁶	2015	Prospective cohort study	Cox proportional hazards regression	Multiple ethnicities; 35-74 years	6	Age, race/ethnicity, family history of breast cancer, history of breast biopsy, benign breast disease diagnoses, breast density	AUC: 0.665; E/O ratio: 5 Years: 1.04(1.02 ,1.06); 10 years: 1.05 (1.03,1.06)	17908 cases/ 1,135,977 total	None	None	None	None	
18	Jonberg et al	2016	Prospective cohort study	Competing risk regression	Multiple ethnicities; 57-85 years	16	Age at study entry, postmenopausal hormone use, number of first-degree relatives with history of breast cancer and age at diagnosis, history of breast biopsy, highest body mass index in past 10 years, age at menopause, age at first birth and parity, average alcohol use per day (highest average use in past 10 years), cigarette use, mammogram in past 2 years, limited in moderate daily activity, diabetes, myocardial infarction, stroke, emphysema, congestive heart failure	AUC: 0.61 (0.60,0.63); E/O ratio: none	73,066 total	External validation	Prospective cohort study	Multiple ethnicities; 55-91 years	AUC: 0.57 (0.55,0.58); E/O ratio: 0.92(0.88,0.97)	74,887 total
32	Leech et al ³⁸	2016	Nested case-control study	Logistic regression	Multiple ethnicities; 36-86 years	7	Age, ethnicity, first degree breast cancer, previous biopsies, breast density, polygenic risk score, body mass index	AUC:0.65(0.61,0.68); E/O ratio: none	486 cases/ 495 controls	None	None	None	None	

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5	Wang et al ³⁹	2016	Case-control study	Logistic regression	Asian women; 20-84 years	1)Pre menopausal: 5; 2)Post menopausal: 11	1) Premenopausal: age, number of parity, case number of breast cancer in first-degree relatives, light at night, sleep quality; 2) Postmenopausal: age, number of parity, case number of breast cancer in first-degree relatives, light at night, body mass index, age at menarche, age at first give birth, ever breast feeding, ever using of oral contraceptive, hormone replacement treatment, history of benign breast diseases.	1) Pretmenopausal women: AUC: 0.640(0.598,0.681); E/O ratio: none; 2) Postmenopausal women: 0.655(0.621,0.686); E/O ratio: none	923 cases / 918 controls	Internal validation	Case-control study	Asian women; 20-84 years	1) Premenopausal: average AUC: 0.621; 3) Postmenopausal: Average AUC: 0.632	None
19	Mdas et al ⁴⁰	2016	Prospective cohort study	Logistic regression	Caucasian	11	Age at menarche, menopause, age at first birth, parity, alcohol consumption, height, smoking status, BMI, family history, hormone therapy, PRS	AUC: 0.640; E/O ratio: none	17,171 cases / 19,862 controls	None	None	None	None	None

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26 27 28 29 30	Eksson et al ⁴²	2017	Nested case-control study	Logistic regression	Caucasian; 40-74 years	7 MD, computer-aided detection of microcalcifications and masses, use of hormone replacement therapy, family history of breast cancer, menopausal status, age, body mass index	AUC: 0.71(0.69,0.73); E/O ratio: none	433cases / 1732 controls	None	None	None	None	None
31 32 33 34 35 36 37 38	Hsieh et al ⁴³	2017	Case-control study	Logistic regression	Asian women; 20-90 years	11 FGFR2 (rs2981582), HCN1 (rs981782), MAP3K1 (rs889312), TOX3(rs3803662), ZNF365(rs10822013), RAD51B(rs3784099), age, body mass index, age at menarche, parity, menopausal status	AUC: 0.6652; E/O ratio: none	446 cases/ 514 controls	None	None	None	None	None

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Using et al ⁴⁴	2017	Nested case-control study	Logistic regression	Multiple ethnicities; 26-77 years	13	Menopausal status, age at menarche, age at menopause, duration of postmenopausal hormones use, parity, number of children and age at first full term pregnancy, family history of breast cancer, alcohol consumption at recruitment, body mass index, measurements of testosterone, estradiol, sex hormone binding globulin, Insulin-like growth factor-I	AUC: none; E/O ratio: none	1,217 cases/ 1,976 controls	Internal validation	None	None	None	None
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Salih et al ⁴⁵	2017	Cross-sectional study	Logistic regression	Caucasian; 32-74 years	5	Age, age at menarche, family history, vegetables and fruits weekly servings, type of cereals used	AUC: 0.864(0.81,0.92)	63 cases/ 90 controls	Internal validation	None	None	O/E ratio: 0.78 ^b	None
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Wang et al ⁴⁶	2018	Case-control study	Logistic regression	Nigerian women; age was not specified	9	Age, age at menarche, parity, duration of breastfeeding, family history of breast cancer, height, body mass index, benign breast diseases, alcohol consumption	AUC: 0.720(0.701,0.739); E/O ratio: 1.01 (0.93,1.09)	1,208 cases/ 1,484 controls	Internal validation	None	Nigerian women; 20-79 years	AUC: 0.694 (0.666,0.721); E/O ratio: none	603 cases/ 741 controls

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5	Chang et al ⁴⁷	2018	Nested case-control study	Logistic regression	Caucasian; 34-70 years	1) Gail 1 model + PRS + MD + T + EIS +PRL: 10; 2) Ros ner- Coldit z model + PRS + MD + T + EIS + PRL: 16	1) Gail model+ PRS + MD + T + EIS +PRL: Age, age at menarche, previous biopsies, age at first birth, first degree breast cancer, PRS, MD, EIS, T, PRL 2) Rosner-Colditz model+ PRS + MD + T + EIS + PRL: age, age at menarche, age at first birth, menopause, age at subsequent births, benign breast disease, hormone replacement therapy, first degree breast cancer, weight, body mass index, alcohol, PRS, MD, EIS, T, PRL	AUC: Gail model+ PRS + MD + T + EIS +PRL: 0.65(0.64,0.66); Rosner-Colditz model+ PRS + MD + T + EIS + PRL: 0.678 (0.666,0.690); E/O ratio: none	4,006 cases / 7,874 controls	Internal validation	None	None	None	None
31	Andersen et al ⁴⁸	2019	Nested case-control study	Logistic regression	Multiple ethnicities; 35-50 years	6 Age at menarche, age at first live birth, number of benign breast biopsies, number of first-degree family members with breast cancer, AMH, tT	AUC: 0.581(0.562,0.599); E/O ratio: none	1,762 cases/ 1,890 controls	None	None	None	None	None	
36	Wong et al ⁴⁹	2019	Case-control study	Logistic regression	Asian women; 25-70 years	6 Number of abortions, age at first live birth, benign breast disease history, body mass index,	None	328 cases / 656 controls	External validation	Respective cohort study	Asian women	AUC: 0.64 (0.55,0.72); E/O ratio: 1.03 (0.74,1.49)	34 cases/ 13,176 total	

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						breast cancer family history, life satisfaction score							
Abdoell et al ⁵⁰	2020	Nested case-control study	Logistic regression	Caucasian; 40-75 years	5	Age at screen, percent mammographic density, breast volume, core biopsy history, family history	AUC: 0.664(0.650,0.678); E/O ratio: none	1,882 cases/ 5,888 controls	None	None	None	None	
Qiu et al ⁵¹	2020	Case-control study	Logistic regression	Asian women; 29-81 years	5	p53, CyclinB1, p16, p62,14-3-3ξ	AUC: 0.943(0.919,0.967); E/O ratio: none	184 cases/ 184 controls	External validation	Case-control study	Asian women; 24-78 years	AUC: 0.916(0.886,0.947); E/O ratio: none	197 cases/ 109 controls
Lin et al ⁵²	2021	Prospective cohort study	Cox regression	Asian women; 30-79 years	8	age, residence area, education, BMI, height, family history of cancer, parity, age at menarche	AUC: 0.634(0.608,0.661); E/O ratio: 1.01(0.94,1.09)	2,287 cases/ 300,824 total	External validation	Prospective cohort study	Asian women;	AUC: 0.585(0.564,0.605) E/O ratio: 0.94(0.89,0.99)	73,203 total
Koener et al ⁵³	2021	Nested case-control study	Logistic regression	Caucasian; 40-75 years	4	Age, breast density, questionnaire score, PRS	AUC: 0.658 E/O ratio: none	2,799 cases/ 75,557 controls	External validation	Nested case-control study	Caucasian; 40-75 years	AUC: 0.687	438 cases/ 898 controls
Yanagou et al ⁵⁴	2021	Case-control study	Logistic regression	Cypriot Women	11	menopause, age at menarche, parity, age at first birth, breastfeeding, height, BMI, hormone therapy, smoking status, family history, PRS	AUC: 0.70 (0.67,0.72) E/O ratio: none	1,109 cases/ 1,177 controls	None	None	None	None	None

^aE/O ratios were calculated based on the original information. ^bThe original publication reported the Observed/Expected ratio.

ER: estrogen receptor; PR: progesterone receptor; PRS: polygenic risk score; MD: mammographic density;

E1S: estrone sulphate; T: testosterone; PRL: prolactin; AMH: anti-Müllerian hormone; NI: no information.

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Appendix Table 4. Risk of bias assessment of included models based on PROBAST.

Study	Participants		Predictors			Outcome						Analysis					Overall								
	1.1	1.2	2.1	2.2	2.3	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5		4.6	4.7	4.8	4.9				
Gail et al ⁶	N	Y	H	Y	PY	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	PY	N	N	Y	H	H
Rosner et al ¹⁶	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	NI	N	N	Y	H	H
Ueda et al ¹⁷	N	NI	H	Y	PY	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	Y	Y	PY	N	N	Y	H	H
Colditz et al ¹⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	PY	L	Y	N	Y	N	Y	N	N	Y	Y	H	H
Lee et al ¹⁹	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	Y	N	PY	N	N	Y	H	H
Tice et al ²⁰	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	Y	N	N	N	Y	H	H
Tice et al ²¹	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	PY	Y	N	N	N	Y	H	H
Barlow et al ²²	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	PY	NI	Y	N	N	Y	Y	H	H
Decarli et al ²³	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	N	Y	N	Y	H	H
Decarli et al ^{23*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	N	NI	-	NI	Y	-	-	H	H
Novotny et al ²⁴	N	PY	H	Y	PN	Y	H	PY	Y	Y	Y	Y	Y	L	Y	N	N	N	Y	PY	N	N	Y	H	H
Gail et al ²⁵	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	Y	PY	N	N	Y	H	H
Gail et al ^{25*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	-	Y	Y	-	-	H	H
Anna et al ²⁶	NY	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	PY	N	N	Y	H	H
Tice et al ²⁷	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	N	N	Y	Y	Y	Y	Y	H	H
Tamimi,et al ²⁸	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	NI	Y	NI	N	N	Y	H	H
Petracci et al ²⁹	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	N	N	Y	H	H
Petracci et al ^{29*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	-	Y	PN	-	-	H	H
Dite et al ³⁰	N	Y	H	Y	PN	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	NI	N	PY	N	N	Y	H	H
Park et al ³¹	N	Y	H	Y	PY	Y	H	Y	Y	Y	Y	Y	Y	L	Y	N	Y	N	N	PY	N	N	Y	H	H
Park et al ^{31*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	NI	-	PY	Y	-	-	H	H
Anothaisintawee et al ³²	Y	Y	H	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	N	N	Y	Y	N	PY	PN	N	Y	H	H

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Rosner et al ⁵³	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	Y	PY	N	N	Y	H	H
Rosner et al ^{53*}	Y	Y	L	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	N	-	PY	N	-	-	H	H
Yiangou et al ⁵⁴	N	Y	H	Y	Y	Y	L	Y	Y	Y	Y	Y	Y	L	Y	Y	Y	PN	N	PY	N	PN	Y	H	H

* The external validation was performed in the same study.

L: low risk of bias; H: high risk of bias; Y: yes; N: no; PY: probably yes; PN: probably no; NI: no information; -: not applicable.

- 1.1. Were appropriate data sources used, e.g., cohort, RCT, or nested case-control study data?
- 1.2. Were all inclusions and exclusions of participants appropriate?
- 2.1. Were predictors defined and assessed in a similar way for all participants?
- 2.2. Were predictor assessments made without knowledge of outcome data?
- 2.3. Are all predictors available at the time the model is intended to be used?
- 3.1. Was the outcome determined appropriately?
- 3.2. Was a prespecified or standard outcome definition used?
- 3.3. Were predictors excluded from the outcome definition?
- 3.4. Was the outcome defined and determined in a similar way for all participants?
- 3.5. Was the outcome determined without knowledge of predictor information?
- 3.6. Was the time interval between predictor assessment and outcome determination appropriate?
- 4.1. Were there a reasonable number of participants with the outcome?
- 4.2. Were continuous and categorical predictors handled appropriately?
- 4.3. Were all enrolled participants included in the analysis?
- 4.4. Were participants with missing data handled appropriately?
- 4.5. Was selection of predictors based on univariable analysis avoided? (Development studies only)
- 4.6. Were complexities in the data (e.g., censoring, competing risks, sampling of control participants) accounted for appropriately?
- 4.7. Were relevant model performance measures evaluated appropriately?
- 4.8. Were model overfitting, underfitting, and optimism in model performance accounted for? (Development studies only)
- 4.9. Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? (Development studies only)



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4,5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5,6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	6,7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	6 and Appendix Table 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	8,9 and Appendix Table 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8,9 and Appendix Table 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	7,8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	8,9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	8,9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	8,9 and Appendix Table 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	8,9



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not performed
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not performed
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not performed
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not performed
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	9 and figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	9
Study characteristics	17	Cite each included study and present its characteristics.	9,10
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	12,13,14,15
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	9,10,11 and Appendix Table 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix Table 3, table 1, figure 2, figure 3 and figure 4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	9, 10,11,12, 13,14 and Appendix Table 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not performed
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not performed
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not performed
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not performed
DISCUSSION			

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Reported on page #
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	14,15
	23b	Discuss any limitations of the evidence included in the review.	15,16
	23c	Discuss any limitations of the review processes used.	15,16
	23d	Discuss implications of the results for practice, policy, and future research.	16,17,18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3,6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not performed
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not performed
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	19
Competing interests	26	Declare any competing interests of review authors.	19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendix Table 1,2,3

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
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