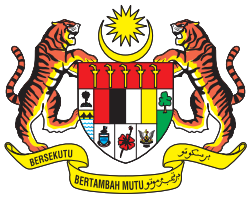

Health Technology Assessment Report

Breast Cancer Risk Prediction Model For Health Risk Assessment (HRA) Module

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organizations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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EXECUTIVE SUMMARY

Background

Breast cancer is the commonest cancer among women and the commonest cause of cancer death worldwide. Similarly in Malaysia, it was reported to be the commonest cancer in women with overall age standardized incidence rate (ASR) of 29.1 per 100,000 population (National Cancer Registry 2007), higher than incidence in other developing countries (ASR of 20 per 100,000 population). About 30 to 40% of Malaysian women presented at a later stage of breast cancer (stage III and IV). Hence, affordable and effective approaches in cancer control are needed for early detection, diagnosis and treatment of breast cancer particularly in the less developed countries. The growing public awareness of breast cancer and its risk factors, with availability of medical and surgical risk reduction options has led consultation of many women on their breast cancer risk. Considerable effort has been directed at identifying risk factors and developing risk prediction models for breast cancer. Prediction model is a mathematical equation designed to quantify the risk an individual woman would develop a particular cancer in a defined period. It provides an estimation of disease risk that can be used to guide management for women at all level of risks. Multiple prediction models have been developed to assist with breast cancer risk prediction efforts. Reliable accurate prediction models can inform future disease burdens, health policies, individual decisions on future screening behaviour and adoption of risk reduction strategies, counsel those at risk, design prevention strategies for at risk populations and plan intervention trials. Subsequently, the adoption of such models should guide decision-making, improve patient outcomes and the cost-effectiveness of care. Given the variance in breast cancer risk, surveillance and primary prevention adapted to individual risk level may be the most effective use of resources for preventing, detecting and improving breast cancer survival.

In Malaysia, currently there is no breast cancer risk assessment/prediction model in the prediction of individual risks of developing breast cancer in existing health risk assessment (HRA) module of Ministry of Health. An opportunistic screening policy is currently being practiced for breast cancer in Malaysia by means of both primary and secondary prevention approach as part of cancer control strategy. Therefore, there is a need to assess the feasibility of having a risk assessment/prediction model as a HRA module in enhancing early detection of breast cancer by capturing wider coverage of general population. Introduction of a risk assessment/risk prediction model for breast cancer is timely in addressing unmet needs of identifying high risk individuals in the Malaysian community, towards enhancing early detection of breast cancer in facilitating more effective cancer control strategies. This assessment was requested by a Senior Principal Assistant Director, Health Education Division, Ministry of Health.

Technical features

A risk prediction model is a statistical tool for estimating the probability that a currently healthy individual with specific risk factors will develop a future condition, such as breast cancer, within a certain time. It uses multiple predictors (covariates) to estimate the probability or risk that a certain outcome is present. The goal of risk prediction is to provide individualised risk (absolute risk) with associated measures of uncertainty thus stratifying individuals by these risks. It is accomplished by combining the baseline risk of developing the condition with an individual's risk score. The baseline risk of the condition represents the underlying population risk for patients whose risk factor values are not present, which is usually estimated from a prospective population-based cohort study. The risk-score component shows how much the baseline risk is multiplied for increasing values of the risk factors, which may also be estimated using a cohort study or for rare conditions, a case-control study. The variables in the model can be any combination of environmental, behavioural, genetic or psychological attributes of the person. Developed models need to provide accurate and validated (internally and externally; temporal, geographical and domain/setting) estimates of disease probabilities. Performance of predictive tests is commonly measured by means of calibration (the ability to predict the number of events in subgroups of the population) and discrimination (the ability to distinguish at the individual level between those who will develop the disease and those who will not). Calibration performance is commonly reported by E/O statistics comparing expected (E) and observed (O) number of events, and discrimination performance by concordance (c)-statistics. Performance of the model may also vary according to the population they are applied to. Cancer risk prediction model is classified into absolute risk prediction model aimed at assessing probability that an individual with given risk factors and a given age will develop cancer over a defined period of time (such as Gail model); and gene carrier status risk prediction models aimed at assessing mutation probability of an individual or carrying a gene mutation that predisposes to a particular cancer (such as BOADICEA, BRCAPRO, Cuzick-Tyrer (IBIS models) and Manchaster Scoring System). Each model has unique attributes stemming from the methodology, sample size and population characteristics used to create the model.

Policy question

i. In Ministry of Health, should a breast cancer risk prediction model for health risk assessment (HRA) module be introduced as one of the strategies in the prevention of breast cancer under the Malaysia National Cancer Control Programme?

ii. If breast cancer risk prediction model for HRA module is to be introduced, which risk prediction model should be adopted in Malaysia?

Objectives

i. To assess the effectiveness in term of predictive accuracy of breast cancer risk assessment/prediction models among women

ii. To assess the safety, organizational, ethical issues and economic implications related to risk assessment/prediction models for breast cancer among women

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to May 2015), EBM Reviews-Cochrane Central Register of Controlled Trials (May 2014), EBM Reviews – Database of Abstracts of Review of Effects (2nd Quarter 2015), EBM Reviews-Health Technology Assessment (2nd Quarter 2015), EBM Reviews-NHS Economic Evaluation Database (2nd Quarter 2015). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 20 March 2015. From cross referencing

of retrieved articles, additional articles were identified. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

Results

A total of 830 titles were identified through Ovid interface, Pubmed and references of retrieved articles. A total of 123 abstracts were screened using the inclusion and exclusion criteria resulting in 58 potentially relevant articles. After the critical appraisal, only 14 full texts out of the above were finally included in this review comprising of two systematic reviews, one randomised controlled trial and eleven observational studies (eight cohorts and three cross sectional). No evidence on cost-effectiveness or cost-utility analysis was retrieved.

Of these, eleven articles were related to the effectiveness (predictive accuracy) of risk assessment/ risk prediction/ health risk assessment models for breast cancer, which were two systematic reviews and nine observational studies (eight cohort and two cross sectional). The other two articles were related to safety of risk prediction models for breast cancer. The articles were published between 2009 and 2015. The included systematic reviews were both published in 2012. Most of the observational studies were conducted in the U.S.A., with one each from Italy, Singapore, Thailand and Korea.The total pooled sample size of included studies was 437,049 subjects. Sample sizes for each of the observational studies ranged from 690 to 135,329 subjects. The length of follow-up ranged from five years to ten years.

Effectiveness (predictive accuracy)

Models being assessed were Gail model (also known as Breast Cancer Risk Assessment Tool) including Gail 1 and Gail 2 (updated) model, Contraceptive and Reproductive Experience (CARE) model, model by Petracci, model by Pfeiffer, Vermont model, model by Anothaisintawee and BWHS model.

Performance of prediction model is commonly measured by means of calibration and discrimination. A well-fitted model has Expected/Observed (E/O) ratio close to 1, a number lower underestimates the condition's incidence and a number higher overestimates the incidence. The concordance (c)-statistics measure model discrimination performance which is similar to area under the receiver operating characteristic curve (ROC). A c-statistics of 1.0 indicates perfect discrimination and 0.5 equivalents to no discrimination between people who develop the condition and those who do not.

Performance of Gail model (also known as Breast Cancer Risk Assessment Tool, BCRAT)

Gail 1 model estimates the absolute risk for both invasive and insitu breast cancer (ductal and lobular), derived from data of the Breast Cancer Detection Demonstration project. Gail 2 model is a modification of Gail 1, used to estimate the risk of invasive breast cancer using data from Surveillance, Epidemiology and End Result (SEER) Programme of the US National Cancer Institute.

i. Calibration performance

- Validation cross-population showed underestimation of breast cancer cases in two studies, overestimation of breast cancer cases was observed in one study37 and pool result showed it has good calibration
- Pool E/O ratio was 1.13(95% CI 0.80 to 1.60) for Gail 1 model (I-squared: 95.0%) and 0.95 (95% CI 0.92 to 1.02) for Gail 2 model (I-squared: 92.5%)
- E/O ratio ranges from 0.86(95% CI 0.82 to 0.90), 0.87(95% CI 0.85 to 0.89) in white post-menopausal women aged 50 to 74 years, to E/O ratio of 0.85(95% CI 0.83 to 0.88) in Hispanic and non-Hispanic post-menopausal women aged 50 to 79 years; both in US for Gail 2 model
- E/O ratio was 1.85(95% CI 1.68 to 2.04) among women aged 50 to 64 in Singapore for Gail 2 model

Updating the Gail 2 model improved models calibration

- E/O ratio of 1.03 (95% CI 1.00 to 1.05)
  [using Surveillance Epidemiology End Result (SEER) breast cancer incidence and mortality 1995 to 2003)]
- E/O ratio of 1.00 (95% CI 0.94 to 1.08) (using SEER 2003 to 2006)

ii. Discriminative ability

- Pool concordance (c)-statistics was 0.63 for Gail 2 model (I-squared: 94.5%)

- Overall area under curve (AUC) and c-statistics ranges from 0.54 to 0.63 for Gail 2 model in the three validation studies in the US
  - [0.58 in the US white post-menopausal women aged 50 to 74 years, between 0.58 (95% CI 0.56 to 0.58) for non-Hispanic white and 0.63 (95% CI 0.58 to 0.67) for Hispanic US postmenopausal women aged 50 to 79and 0.54 (95% CI 0.52 to 0.56) among Vermont women aged 70 years and older]

Performance of Contraceptive and Reproductive Experience (CARE) model

i. Calibration performance
- Validation in a single study showed underestimation of breast cancer cases with E/O ratio of 0.88 (95% CI 0.82 to 0.94) among black women aged 30 to 69 years

ii. Discriminative ability
- Age-specific c-statistics for total invasive breast cancer was 0.57 (95% CI 0.55 to 0.59)
- Age-adjusted c-statistics for specific breast cancer subtypes:
  0.59 (95% CI 0.57 to 0.61)(Estrogen receptor positive (ER+) breast cancer)
  0.54 (95% CI 0.50 to 0.57)(Estrogen receptor negative (ER-) breast cancer)

Performance of model by Petracci

i. Calibration performance
- Validation in a single study showed the model was well calibrated with E/O ratio of 1.10 (95% CI 0.96 to 1.26) among Italian women aged 35 to 64 years

ii. Discriminative ability
- c-statistics was 0.62 (95% CI 0.55 to 0.69)(women younger than 50 years)
- c-statistics was 0.57(95% CI 0.52 to 0.61)(women more than 50 years)

Performance of model by Pfeiffer

i. Calibration performance
- Validation in a single study showed the model was well calibrated with E/O ratio of 1.00 (95% CI: 0. 96 to1.04) among white women aged 30 to 55 years

ii. Discriminative ability
- Overall AUC was 0.58 (95% CI 0.57 to 0.59) in the above validated population

Performance of Vermont model

i. Discriminative ability
   Validation in a single study showed the model discriminative power was modest with c-statistics of 0.55 (95% CI 0.53 to 0.58) among Vermont women aged 70 years and older

Performance of model by Anothaisintawee

i. Calibration performance
- Validation in a single study showed the derived model was well calibrated with O/E ratio of 1.00 (95% CI 0.82 to 1.21)

ii. Discriminative ability
- C-statistics (overall) was 0.65 (95% CI 0.59 to 0.70) for prediction of breast cancer cases

Performance of BWHS model

i. Calibration performance
- Validation in a single study showed the BWHS model was well calibrated with E/O ratio of 0.96 (95% CI 0.88 to 1.05)

ii. Discriminative ability
- AUC (overall) was 0.59 (95% CI 0.56 to 0.61)

Safety

- The only reported adverse event was anxiety Women who had higher risk status had an odd of having increased anxiety about 5 times greater than women who had lower risk status (OR 5.03; 95% CI 1.54 to 16.43)
- About 18.9% of subjects disagree with tailored risk associated with BCRAT (Gail model)

Cost implication

- No evidence retrieved on breast cancer risk assessment/prediction model

- Potential direct cost implicated on the designing, developing, testing and commissioning of available one breast cancer risk prediction model into a health risk assessment module was given at approximately RM75,000

Organizational

Computerized risk estimate using any model requires computer literate user/patient and internet access.

Cancer risk prediction model needs to be continually calibrated and revalidated. The complexity of prediction modelling research from developing and internally validating a prediction model, testing, adjusting or updating the model for other individuals (external validation); and assessing its impact on therapeutic management and patient outcomes need a dedicated research expertise. Uncertainties associated with risk estimates should be addressed and informed particularly when clinical decision has serious consequences.

Among ethical issues that arose following cancer risk assessment was psychological harms resulting from being labelled 'at risk', and additional diagnostic procedures that can artificially increase sense of risk. The 'at risk' label also has implication for future health care cost. Theoretically increased psychological distress from risk labelling may contribute to other healthcare demands and raising the health care cost.

Conclusion

There was sufficient good level of retrievable evidence for breast cancer risk prediction model. There were six models identified for predicting breast cancer risk with Gail model is the most widely studied and validated model in various population. The Gail model appeared to have good calibration in validation studies done cross-population; however there is considerable heterogeneity across studies. This model showed moderate performance in terms of discriminatory ability.

For other risk prediction models, there was insufficient good level of retrievable evidence with only one study each of those other models (CARE model, model by Petracci, model by Pfeiffer, Vermont model, model by Anothaisintawee and BWHS model). The models were well calibrated in the validated population however appeared modest in discriminating woman who will be having breast cancer, than for those who will not in the study population.

There was insufficient evidence on the safety related to cancer risk prediction models for the detection of women who will develop breast cancer. Although there was minor adverse psychological sequale reported among high risk women who demonstrated to be five times more likely to have increased anxiety, it may be considered relatively safe.

There was no retrievable evidence on economic evaluation of health risk assessment or risk prediction model for breast cancer, or cost implication involved in developing a new risk prediction model without genetic component for breast cancer retrieved. The cost involved in validating a model by a prospective cohort validation study could be very costly depending on the number of study participants and years of follow up. However potential direct cost implicated to the designing, developing, testing and commissioning of available one breast cancer prediction model was given approximately at RM75,000.

Cancer risk prediction models need continual validation to give meaningful risk estimate and to ensure its applicability in the setting it will be used. The complexity to develop and subsequently validate any breast cancer risk prediction model specifically models without genetic component is reflected in the necessary local data required and availability of dedicated research expertise to create a robust model with consistent performance.

Recommendation

Although the above review showed that the Gail model had good calibration and moderate discriminative ability, it is not suitable to be introduced as one of the strategy in the prevention of breast cancer under the Malaysian National Cancer Control Programme yet as it needs further validation to develop a well-fitted model that would have better predictive ability tailored to Malaysian population. In addition, this model needs continual validation to determine the consistency of its performance.

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ABBREVIATIONS

ACS	American Cancer Society
AUC	Area under curve
ASR	Age Standardized Incidence Rate
c-statistic	concordance statistic
BCDPP	Breast Cancer Detection Demonstration Project
BCRAT	Breast Cancer Risk Assessment Tool
BWHS	Black Women Health Study
BOADICEA	Breast and Ovarian analysis of disease incidence and carrier estimation algorithm
CARE	Contraceptive and Reproductive Experience
CEA	Cost-effectiveness analysis
CUA	Cost-utility analysis
CI	Confidence interval
E/O	expected over observed ratio
EBM	Evidence Based Medicine
GM	Gail model
HBOC	Hereditary breast and ovarian cancer syndrome
HRA	Health Risk Assessment
IBIS	International Breast Cancer Intervention Study
LPPKN	Lembaga Pembangunan Penduduk dan Keluarga Negara
MSS	Manchester Scoring System
NCR	National Cancer Registry
NHMS	National Health Morbidy Survey
NHW	non Hispanic white
NIH-AARP	NIH Diet and Health Study
NPV	negative predictive value
OCP	Oral ContraceptivePill
OR	Odds ratio
PLCO	Prostate, Lung, Colorectal and Ovarian cancer screening trial
RCT	Randomised controlled trial
ROC	Receiver operating curve
RR	relative risk
PPV	positive predictive value
RCT	randomised controlled trial
SBCSP	Singapore Breast Cancer Screening Project
SD	Standard deviation
SEER	Surveillance Epidemiology End Result
US	United States
U.S.A.	United States of America
WHI	Woman Health Initiative

BREAST CANCER RISK PREDICTION MODEL FOR HEALTH RISK ASSESSMENT MODULE

1 BACKGROUND

Breast cancer is the most commonly diagnosed cancer among women worldwide which represents 1 in 4 of all cancers and the most common cause of cancer death (522,000 deaths in 2012). Worldwide, it is also the second most commonly diagnosed cancer. Globally, the incidence is rising with 1.7 million women were diagnosed with breast cancer in 2012 and mortality has increased by 14% since the 2008 estimates.[1] Incidence rates is higher in more developed region, however mortality is much higher in less developed countries due to lack of early detection and access to treatment facilities.[1] In Malaysia, the National Cancer Registry (NCR) 2007 reported that breast cancer was the most commonly diagnosed cancer in women with overall age standardized incidence rate (ASR) of 29.1 per 100,000 population.[2] Though ASR was dropped from 39.3 per 100,000 population in 2006,[3] it was higher than incidence in other developing countries with ASR of 20 per 100,000 population.[4] The rising incidence is worsened by the fact that about 30 to 40% of Malaysian women presented at a later stage of breast cancer (stage III and IV) compared to other counterparts in the developing countries.[5] The increase has been said related to changes in dietary and reproductive pattern, urbanization and ageing population.[6,7] Hence, affordable and effective approaches in cancer control are needed for early detection, diagnosis and treatment of breast cancer particularly in the less developed countries.[1]

The growing public awareness of breast cancer and its risk factors with availability of medical and surgical risk reduction options has led consultation of many women on their breast cancer risk.[8] The widely quoted general population lifetime risk of having breast cancer is one in eight to one in 12, and the risk in any given decade was never greater than one in 30. The proportion of all female deaths due to breast cancer per decade is never greater than 20% with the greatest proportion from the middle age group (35 to 55 years).[9] For familial breast cancer, approximately five to ten percent of cases occur in women with Hereditary Breast Ovarian Cancer Syndrome (HBOC), which has mutation in BRCA1 and BRCA2 genes.[10] Women with BRCA1 and BRCA2 mutation have a 50% to 80% lifetime risk of breast cancer. These women also have a 40% to 60% lifetime risk of having contralateral breast cancer.[10,11] Specific BRCA mutation is clustered among certain ethnic groups such as Ashkenazi Jews, in the Netherlands, Iceland and Sweden. A woman's breast cancer risk is an important consideration when making recommendation about screening mammography as screening is more beneficial for those at higher risk of developing the disease.[12] The organized breast cancer screening programmes using mammography has been well established in Europe and Northern America resulting in improved five year survival rate, as high as 89%.[13] Providing breast cancer screening programme using mammography to every woman in most developing countries is not feasible, thus identifying women with relatively higher risk of developing breast cancer is a promising alternative.[14]

Considerable effort has been directed at identifying risk factors and developing risk prediction models for breast cancer. Multiple prediction models have been developed to assist with breast cancer risk prediction efforts.[10] Prediction model of breast cancer is a mathematical equation designed to quantify the risk an individual woman would develop breast cancer in a defined period.[14] Accurate breast cancer risk assessment is vital to personalize screening and risk reduction strategies.[8]Reliably accurate prediction models can inform future disease burdens, health policies and individual decisions, as well as to counsel those at risk and determine eligibility for prospective prevention trial.[15,16] These empirically derived models are used in clinical setting to guide decision making about future screening behaviour or adoption of risk reduction strategies.[17] These models

have been used to estimate the costs of population burden of cancer, plan intervention trials, create benefit-risk indices and design prevention strategies for at risk populations.[18] It is also meant to personalize management strategies for all women with the aim of increasing survival in high-risk women while decreasing cost and complications in low-risk women.[19] Given the variance in breast cancer risk, surveillance and primary prevention adapted to individual risk level may be the most effective use of resource for preventing, detecting and improving breast cancer survival.[17]

Risk factors are often required as input variables in the prediction model.[14] These risk factors need to be assessed to evaluate its risk over time including family history, hormonal and reproductive risk factors such as the use of exogenous hormones (estrogen and progesterone), endogenous hormonal factors (ages at menarche, menopause and first childbirth), and environmental risks such as alcohol intake, diet, exercise, obesity, as well as increase breast density.[20] The Malaysian CPG on Management of breast cancer stratify risk factor as low (relative risk RR 1.0 to 1.4), moderate (RR 1.5 to 2.0) and high (RR of more than 2.0).[21] Models containing modifiable risk factors are of particular interest to patients and those involved in reducing population incidence rates[15] as 21% of all breast cancer deaths worldwide are attributable to alcohol use, overweight and obesity, and physical inactivity.[22]

Breast cancer risk assessment provides an estimation of disease risk that can be used to guide management for women at all level of risks. Risk may be assessed as likelihood of developing breast cancer or as likelihood of detecting a BRCA1 or BRCA2 mutation.[19] Types of cancer risk assessment models are; model aimed at assessing breast cancer risk over time or to predict probability of being diagnosed with a cancer; and the other aimed at assessing mutation probability of an individual or carrying a gene mutation that predisposes to a particular cancer.[6] The most commonly used models for the former type were the Gail and Claus model.19 Some of the latter models are the Breast and Ovarian Analysis Of Disease Incidence And Carrier Estimation Algorithm (BOADICEA), BRCAPRO, Couch, Shattuck Eiden, Frank, Tyrer-Cuzick (IBIS models) and Manchaster scoring.[6, 19] Each model has unique attributes stemming from the methodology, sample size and population characteristics used to create the model. Understanding the strength and weaknesses of each model facilitates accurate breast cancer risk assessment.[19] The Gail model provides five-year and lifetime risk estimate of having breast cancer and is accessible on the internet. The Claus model is useful for assessing breast cancer risk with a family history, similarly with BRCAPRO, BOADICEA and IBIS models which can produce both mutation probabilities and breast and ovarian cancer estimates.[16]

Identification of individual with a suspected heritable cancer syndrome (HBOC) has implications for evaluation and application of risk reducing options such as chemoprevention and prophylactic surgery.[23] These underline the need for risk prediction model for breast cancer, not only to predict which women will develop the disease, but also to apply appropriate intervention and lifestyle measures in order to prevent the disease.[6] Developed models first and foremost need to provide accurate and (internally and externally) validated estimates of probabilities of specific health conditions or outcomes in the targeted individuals. Subsequently, the adoption of such models by professionals must guide their decision-making, improve patient outcomes and the cost-effectiveness of care.[24] Better understanding of these model performances, including the strengths and limitations is needed before applying them in clinical practice.

In Malaysia, currently there is no breast cancer risk assessment/prediction model in the prediction of individual risks of developing breast cancer in existing health risk assessment (HRA) module of Ministry of Health. An opportunistic screening policy is currently being practiced for breast cancer in Malaysia by means of both primary and secondary prevention approach as part of cancer control strategy.[7] Therefore, there is a need to assess the feasibility of having a risk assessment/prediction model as a HRA module in enhancing early detection of breast cancer by cap-

turing wider coverage of general population, in facilitating effective cancer control strategies in the country. This HTA was requested by a Senior Principal Assistant Director, Health Education Division, Ministry of Health.

TECHNICAL FEATURES

2.1 BREAST CANCER RISK PREDICTION MODEL

A risk prediction model is a statistical tool for estimating the probability that a currently healthy individual with specific risk factors (e.g. age, menopausal status) will develop a future condition, such as breast cancer, within a certain time period (such as within five years or lifetime).[15] It uses multiple predictors (covariates) to estimate the probability or risk that a certain outcome is present.[24] The goal of risk prediction is to provide individualized risk (absolute risk) with associated measures of uncertainty thus stratify individuals by these risks.[24,25]Other risk parameters of interest in clinical oncology are relative risk and survival probability.The absolute risk is an important estimate in clinical setting that assist in individual decision making. [24,25]

These models are used/applied in planning cancer intervention and screening trials, assisting in creating benefit-risk indices, estimating the population burden, cost of cancer and impact of specific intervention, identifying individuals at high risk who may benefit from targeted screening or chemoprevention, designing population prevention strategies and improving clinical decision making.[18]

Developed models first and foremost need to provide accurate and (internally and externally) validated estimates of probabilities of specific health conditions or outcomes in the targeted individuals. Subsequently, the adoption of such models by professionals must guide their decision-making, and improve patient outcomes and the cost-effectiveness of care.[24]

2.2 DEVELOPING AND VALIDATING BREAST CANCER RISK PREDICTION MODEL

Risk prediction is accomplished by identifying characteristics that are associated with high or low risk of developing a disease and then combining those characteristics in a statistical model to produce probability estimate of developing the disease over a given period. [26]

Risk models combine the baseline risk of developing the condition with an individual's risk score, i.e. a score derived from their set of risk factor values multiplied by the 'beta' weights (e.g. log odds ratios) associated with these factors, as estimated from a statistical equation. The baseline risk of the condition represents the underlying population risk for patients whose risk factor values are all zero (or 'not present'), and this is usually estimated from a prospective population-based cohort study. The risk-score component shows how much the baseline risk is multiplied for increasing values of the risk factors, and may also be estimated using a cohort study or, for rare conditions, a case-control study. [15]

The two main statistical models used to identify important risk factors and to estimate their associated beta weights are logistic regression and Cox proportional hazards regression. [15]

The variables in the model can be any combination of environmental, behavioural, genetic or psychological attributes of the person. As well as estimating risk estimates for specific individuals, risk predictions model can also make a population-based estimate of risk by using average risk factor values from the population. [15]

Initial effort at defining breast cancer risk were primarily empirical.Later estimates of breast cancer or probability of being BRCA1/2 carrier were derived using statistical techniques such as logistic regression, Bayesian analyses, genetic modelling using the method of maximum likelihood and log-incidence models.[25]

After a risk prediction model has been developed in a sample from a population, it then needs to be validated in further independent samples from the same population, and indeed within samples from different populations to ensure that it is reliable and generalisable. Frequently the predictive accuracy of the model is not as good in the validation sample as the original sample, and so adjustments are made leading to new or modified models being gradually developed over time. Even if the same risk factor variables are included, their beta weights may be changed which would then constitute a different model, as the risk score would then change. The performance of prediction models may also vary according to the population they are applied to, so that a model may have good accuracy in a high risk population and not in a low risk population and vice versa.[15]

Model validation is taking the original model or simplified score with its predictors and assigned weights (eg regression coefficient) as estimated from the development study, measuring the predictor and outcome values in the new individuals, applying the original model into these data and quantifying the model's predictive performance. Developed models need to provide accurate and validated (internally and externally; temporal, geographical and domain/setting) estimates of disease probabilities. [24]

2.3 PERFORMANCE OF CANCER RISK PREDICTION MODEL

Variety of ways is available to describe the performance of predictive tests. Many of the statistical measures used are well-known from diagnostic test studies, such as sensitivity, specificity and the AUC (area under the receiver operating characteristic curve (ROC)). In practice, only some of these statistics are reported in modelling and validation articles for risk prediction models. The two most common are the expected over observed ratio (E/O) statistic and the concordance (c) statistic, interpreted as follows:

- The E/O statistic measures the calibration performance of the model. Calibration or reliability assesses the ability of a model to predict the number of events in subgroups of the population.18 Calibration is most commonly evaluated by use of goodness of fit or chi-square statistic which compares the observed number (O) and expected numbers of events (E), so a well fitting model should have the number close to 1. A number lower underestimates the incidence of the condition whereas a number higher overestimates the incidence. Often E/O statistics are presented for deciles of the population defined by predicted risk, to see whether E/O is close to 1 in all deciles or not.[15] Good calibration is important in all models, particularly in those used to estimate population disease burden and to plan population level intervention. Recalibration of a model can be performed when risk is systematically over or underestimated. [18]

- The concordance (c) statistic which corresponds to the area under the receiver operating characteristic curve measures the discrimination performance of the model. [15,18] Discrimination measures a model's ability to distinguish at the individual level between those who will develop the disease and those who will not. It gives the proportion of randomly chosen pairs from the sample (i.e. a person with the condition paired with one without it), where the person with the condition has a higher predicted risk than the one without. AUC statistic of 0.5 is equivalent to no discrimination between people who develop the condition and those who do not, whereas 1.0 indicates perfect discrimination.[15] Each point on the ROC curve shows the effect of a rule for turning of a risk estimate into a prediction of the development of breast cancer in woman. Good discrimination in a model is important for decisions made at individual level (clinical decision making and screening).[18]

Performance assessment of the models is commonly assessed in two ways; at the population level and at the level of individual woman. Model performance at population level is assessed by comparing the number of women in their study who the model estimated (E) would develop breast

cancer with the number of women who actually were diagnosed with breast cancer (O) resulting in the overall E/O ratio. [26] Performance of the model could also be assessed at the individual level. At this level, a model that discriminates well should consistently predict a higher risk of breast cancer for woman who will be diagnosed with the disease, than for women who will not. Concordance statistic value ranges from 0.50 (equivalent to coin toss) to 1.0 (perfect discrimination).[26]

Accuracy scores including positive and negative predictive values can be used to evaluate how well a model categorizes specific individuals. This measure is especially helpful in evaluating models used for clinical decision making. However, even with good sensitivity and specificity, the positive predictive value may be low especially for rare disease.[18]

2.4 TYPES OF MODEL RELATED TO BREAST CANCER PREDICTION

2.4.1 Model to define the risk of developing breast cancer

Many risk prediction models have been developed that have looked at a variety of different risk factors for developing breast cancer.The number of models has grown steadily, with the most well-known is the Gail model and other available models are such as the Claus model, the Tyrer-Cuzick model and the Jonker model. [15]

Among the published breast cancer risk prediction models (absolute risk prediction) are Ottman et al (1983), Anderson et al (1985), Gail et al (1989), Taplin et al (1993), Claus et al (1993), Rosner et al (1996), Colditz et al (2000), Ueda et al (2003) and Tyrer et al (2004).[18]

2.4.1.1 Gail model

Gail and colleagues (1989) described a risk assessment model that focuses primarily on nongenetic risk factors with limited information on family history.
This model is used to estimate a woman's risk of developing invasive breast cancer over specific periods of time. Health care providers may use this model to assess breast cancer risk, inform decision-making about chemoprevention strategies, or to help determine eligibility for clinical trials.[27]

The model was originally designed to determine eligibility for the Breast Cancer Prevention Trial and has been made available in the National Cancer Institute website. Individualised breast cancer probabilities from information on relative risk and baseline hazard rate are generated.[6]

The Gail model considers the following factors to assess breast cancer risk:
- Personal medical history, including the number of previous breast biopsies and the presence of atypical hyperplasia (a precancerous condition) in a previous biopsy
- Reproductive history (age at the start of menstruation and age at the first live birth of a child)
- Family history of breast cancer among first-degree relatives

Limitation:
- The model considers limited information about family breast cancer history, which could underestimate risk
- It does not include several breast cancer-specific risk factors, such as personal history of breast cancer, use of hormone replacement therapy, breast density, breast feeding, or age at menopause
- It does not include lifestyle factors that may increase risk, such as smoking, alcohol consumption, diet or physical inactivity

2.4.1.2 Breast Cancer Risk Assessment Tool (BCRAT)

The Gail model 1 is publicly available in a slightly modified version as the Breast Cancer Risk Assessment Tool (*http://www.cancer.gov/bcrisktool)*[27]. The Breast Cancer Risk Assessment Tool is based on the Gail model. This tool has been tested (validated) using data from large studies of women and been shown to provide accurate estimates of breast cancer risks in white women as well as African American and Asian and Pacific Islander women in the United States.

This online tool estimates a woman's risk of developing invasive breast cancer over a 5-year time period and over her lifetime.

The tool estimates breast cancer risk based on the following risk factors:
- Age
- Age at first period
- Age at first live birth of a child
- Family history of breast cancer
- Personal history of breast cancer
- Number of past breast biopsies, including number of breast biopsies that showed atypical hyperplasia (a precancerous condition that increases breast cancer risk)
- Race/ethnicity

Its score provides an estimate of the average risk for a group of women with similar risk factors. For example, if the tool gives a score of 1.7 per cent, this means that an estimated 1.7 per cent of women with similar risk factors will develop breast cancer in the next 5 years.
Limitations of this model are similar to those of Gail model.

2.4.2 Model to define the risk of being a carrier of mutation in breast cancer susceptibility gene

Among the published breast cancer risk prediction models (for gene carrier status) or genetic risk models are Couch et al (1997),Shattuck-eidens et al (1997), Parmigiani et al (1998), Berry et al (1998), Frank et al (1998), Antoniou et al (2002), de la Hoya et al (2002), Vahteristo et al (2001), Apicella et al (2003), Jonker et al (2003) and others.[18]

Some of the widely used mutation carrier prediction algorithms are Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), BRCAPRO, IBIS and eCLAUS model. These models assume an underlying genetic model for breast cancer susceptibility.[28]

2.4.2.1 Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA)

The BOADICEA is a computer program (risk prediction model) used to calculate the risks of breast and ovarian cancer in women based on their family history. It is also used to compute BRCA1 and BRCA2 mutation carrier probabilities and age specific risk of breast and ovarian cancer. It also estimates the likelihood of a woman developing breast cancer in five years, and over the course of her lifetime. The tool is used to help inform a woman's decision-making about genetic counselling and testing. The programme is free for anyone to use and risk can be calculated using the BOADICEA Web application. It was developed using complex segregation analysis of breast and ovarian cancer based on a combination of families identified through population based studies of breast cancer and families with multiple affected individuals who had been screened for BRCA1/2 mutations.[27]

The tool estimates breast cancer risk based on:
- Family cancer history
- Genetic mutation status

Results: A decision to go for genetic counselling is usually made when the model predicts a 10% or greater chance that the patient has a mutation of the BRCA1, BRCA2, or both genes.
Limitation:

- The major limitation of this tool is that it only considers genetic mutation status and family history. It does not take any other breast cancer risk factors into account.
- The tool was developed using data for the United Kingdom. It may be applicable to populations in other high-income countries; however estimations of risk in other populations may be unreliable.

2.4.2.2 IBIS Breast Cancer Risk Evaluation Tool

The IBIS tool (also called the Tyrer-Cuzick model) is used to calculate a person's likelihood of carrying the BRCA 1 or 2 mutations, which are associated with increased breast cancer risk. It estimates the likelihood of a woman developing breast cancer in 10 years and over the course of her lifetime. The tool is used to help inform a person's decision-making about genetic counselling and testing.[29]

The tool estimates breast cancer risk based on the following risk factors:

- Age
- Age at first live birth of a child
- Age at menopause
- Height and weight
- Use of hormone replacement therapy
- Comprehensive family history

Result: Genetic counselling is advised when the model predicts a 10% or greater chance that the person has a mutation of the BRCA1, BRCA2, or both genes. The tool does not include risk factors associated with lifestyle or breast density as its limitation.[29] Major advantage over BRCAPRO is that this model allows for the presence of multiple genes of differing penetrance. It does produce a readout of BRCA1/2, but also allows for a lower penetrance of BRCAX.[6]

2.4.2.3 BRCAPRO model

This is a Bayesian model developed by Parmigani and colleagues that incorporated published BRCA1 and BRCA2 mutation frequencies, cancer penetrance in mutation carriers, cancer status (affected, unaffected or unknown) and age of consultees' first degree and second degree relatives. An advantage of this model is that it includes information on both affected and unaffected relatives. It also provides estimates for the likdlihood of findingeither BRCA1 or BRCA2 mutation in the family. An output that calculates breast cancer risk using the likelihood of BRCA1/2 can be utilised. Major drawback from breast cancer risk assessment aspect is that no other 'genetic' element is allowed for. As such, this model will underestimate risk in breast-cancer-only families.[6]

3 POLICY QUESTION

i. In Ministry of Health, should a breast cancer risk prediction model for health risk assessment (HRA) module be introduced as one of the strategies in the prevention of breast cancer under the Malaysia National Cancer Control Programme?
ii. If breast cancer risk prediction model for HRA module is to be introduced, which risk prediction model should be adopted in Malaysia?

4 OBJECTIVES

i. To assess the effectiveness in term of predictive accuracy of breast cancer risk assessment/ prediction models among women
ii. To assess the safety, organizational, ethical issues and economic implications related to risk assessment/prediction models for breast cancer among women

4.1 RESEARCH QUESTIONS

i. What are the effectiveness in term of predictive accuracy of breast cancer risk assessment/ prediction models among women
ii. What are the safety, organizational, ethical issues and economic implications related to the use of breast cancer risk assessment/prediction models among women

5 METHODS

5.1 LITERATURE SEARCH STRATEGY

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to May 2015), EBM Reviews-Cochrane Central Register of Controlled Trials (May 2014), EBM Reviews – Database of Abstracts of Review of Effects (2nd Quarter 2015), EBM Reviews-Health Technology Assessment (2nd Quarter 2015), EBM Reviews-NHS Economic Evaluation Database (2nd Quarter 2015). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 20 March 2015. Additional articles were identified from reviewing the references of retrieved articles.

5.2. STUDY SELECTION

Based on the policy question the following inclusion and exclusion criteria were used:-

5.3. INCLUSION CRITERIA

- Population : Adult woman more than 18 years old
- Intervention : Breast cancer risk assessment/ risk prediction model/ Health Risk Assessment models involving single or multiple risk factors
- Comparators : -
- Outcome :

  i. Performance of available breast cancer risk prediction models in terms of its predictive accuracy - sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), calibration as measured by expected/observed ratio, discrimination as measured by AUC or c-statistic

  ii. Strengths and weaknesses of retrieved risk prediction model (qualitative)

  iii. Effectiveness/benefit of the breast cancer risk assessment/predictive model related to patient outcome as measured by detection rate, acceptance, awareness, receptiveness

  iv. Organizational (operational, training, resources), ethical, legal and economic implication

- Study design : No restriction of study type. HTA report, Systematic Review, Randomised Controlled Trial (RCT), Non Randomised Controlled Trial, diagnostic accuracy studies, Observational Studies (Cohort study, Case Control study, Cross Sectional study with gold standard), and economic evaluation studies such as cost-effectiveness / cost-utility analysis.
- Full text articles published in English.

5.4 EXCLUSION CRITERIA:-

- Study design: Animal study, laboratory study, narrative review, case reports.
- Studies on risk assessment/ risk prediction/ health risk assessment models for breast cancer with any genetic component as risk factor
- Studies in women who already had breast cancer when recruited or studies involving male subjects
- Non English full text article.

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. All identified citations (titles and abstracts) were assessed for the above eligibility criteria. If it was absolutely clear from the title and / or abstract that the study was not relevant, it was excluded. If it was unclear from the title and / or the abstract, the full text article was retrieved. Full text articles were ordered for all included and possibly included citations. Two reviewers assessed the content of the full text articles and did data extraction. Disagreements were resolved by discussion.

5.5. QUALITY ASSESSMENT STRATEGY

The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool by two reviewers.[30] For SR the criteria assessed include selection of studies, assessment of quality of included studies, heterogeneity of included studies. For cohort study, the criteria assessed were selection of the cohort, accurate measurement of exposure and outcome, confounding factors, follow-up adequacy and length. The CASP checklist is as in Appendix 4. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1).[31]

5.6 DATA EXTRACTION STRATEGY

Data were extracted from the included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 6) and checked by another reviewer. Disagreements were resolved by discussion. Details on : (1) methods including study design, (2) study population (3) type of intervention, (4) comparators, (5) outcome measures including economic evaluation and organizational issues were extracted. Other information on author, journal and publication year, and study objectives were also extracted. The method to assess the model performance (predictive ability) which included calibration using a ratio of expected over observed value (O/E) with 95% confidence interval or goodness of fit test and discrimination using ROC analysis or concordance statistic were recorded. If studies had validated the prediction models, the type of validations, method used, and result of validation were also recorded. Modification of the previous prediction model by the author was recorded, either by removing or modifying standard variable or adding new variable. The extracted data were presented and discussed with the expert committee.

5.7 METHODS OF DATA SYNTHESIS

Data on the effectiveness (predictive accuracy), related safety issues, organizational issues and cost implication of risk assessment/ risk prediction/ health risk assessment models for breast cancer were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6 RESULTS

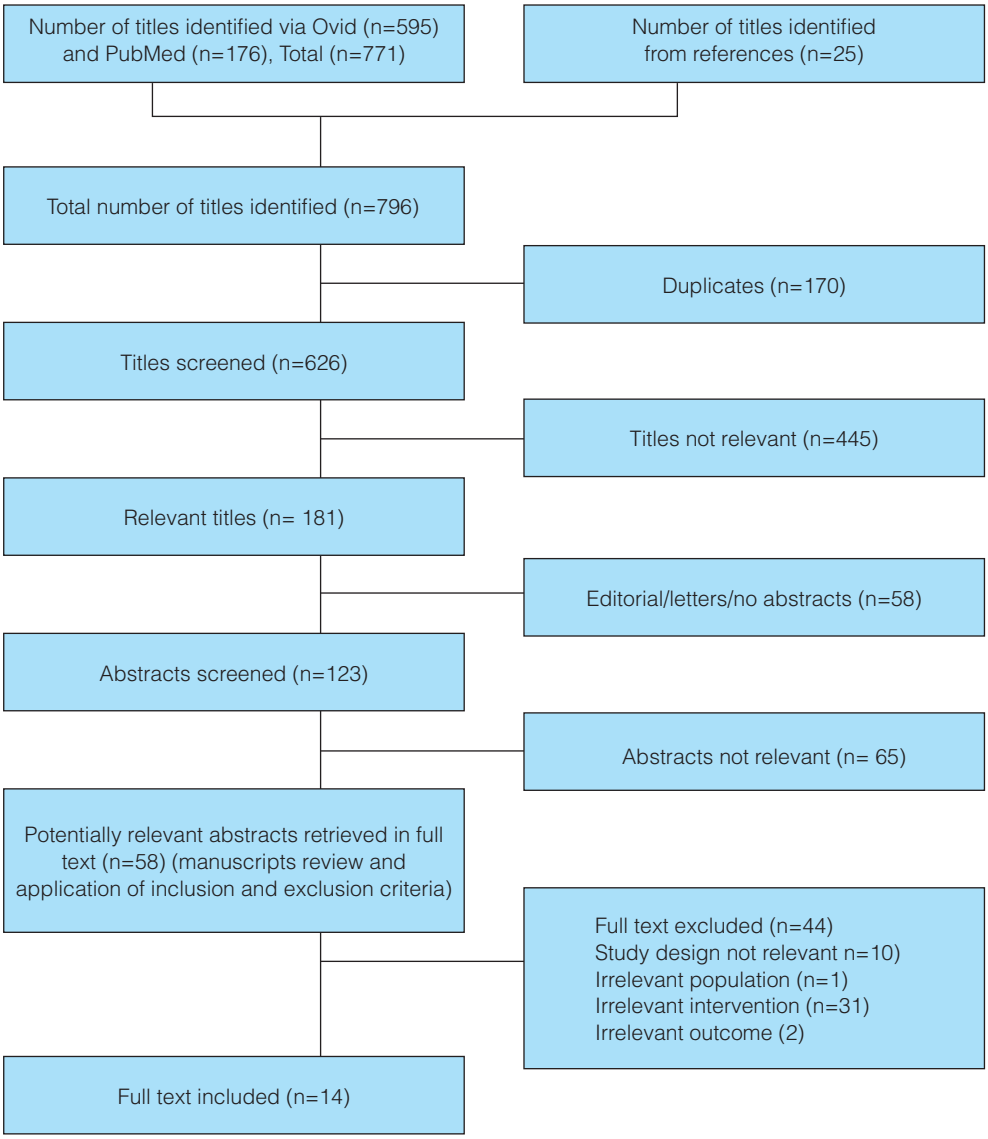
A total of 805 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2015), EBM Reviews-Cochrane Central Register of Controlled Trials (July 2014), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2015), EBM Reviews-Health Technology Assessment (1st Quarter 2015), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2015), and PubMed. Twenty-five were identified from references of retrieved articles.

After removal of 170 duplicates, 626 titles were screened. A total of 181 titles were found to be potentially relevant and 123 abstracts were screened using the inclusion and exclusion criteria. Of these, 65 abstracts were found to be irrelevant. Fifty-eight potentially relevant abstracts were retrieved in full text.

After applying the inclusion and exclusion criteria and critical appraisal to the 65 full text articles, 14 full text articles were included and 55 full text articles were excluded. Twelve (12) out of the fourteen included articles were related to effectiveness in terms of predictive accuracy of breast cancer risk prediction models whereas the other two (2) were related to safety aspect of the models. The fourteen (14) full text articles finally selected for this review were comprised of two systematic reviews, one randomised trial and eleven observational studies (eight cohorts and three cross sectional). No evidence on cost-effectiveness / cost-utility analysis was retrieved.

Forty-five articles were excluded due to irrelevant study design and including those primary studies already included in the systematic review (n = 10), irrelevant population (n = 1) irrelevant intervention (n = 32), irrelevant outcome (n = 2) and). The excluded articles were listed as in Appendix 7. There was no HTA report on risk assessment/risk prediction/ health risk assessment models for breast cancer.

Figure 1: Flow chart of study selection



6.1 STUDY DESCRIPTION

Fourteen (14) full text articles were finally selected for this review which comprised of two systematic reviews, one randomised controlled trial and eleven observational studies (eight cohorts and three cross sectional).

Of the 14 articles, twelve studies were eligible and met the inclusion criteria thus included in the effectiveness (predictive accuracy) of breast cancer risk prediction models in this review. They were two systematic reviews and ten observational studies (eight cohort studies and two cross sectional studies). The other two (2) articles were studies related to safety aspect of the models.

The included articles were published between 2009 and 2015. Both the included systematic reviews were published in 2012, in which their search were done up to June and October 2010. Most of the observational studies were conducted in the U.S.A., with one each from Italy, Singapore, Thailand and Korea. The total pooled sample size of all included studies was 437,049 subjects. Samples sizes for each of the observational studies ranged from 690 to 135,329 subjects. The length of follow-up ranged from five years to ten years.

Most of the study participants were general women without history of breast cancer at premenopausal and postmenopausal ages from white, African-American and Hispanic ethnicity. One study assessed the model performance in Asian women and one specific for Thai women. Most of the studied population were from various large cohort studies such as Black Women's Health Study, NIH Diet & Health Study (NIH-AARP), US Prostate, Lung, Colorectal and Ovarian Screening Trial (PLCO) study; cohort of women in Vermont Breast Cancer Surveillance System underwent breast cancer screening programme, Woman Health Initiative (WHI) study, Italian Florence-EPIC cohort and Singapore Breast Cancer Screening Project.

6.1.1 Risk of bias

Risk of bias in the included cohort studies are summarised as in Table 1.

Table 1: Assessment of risk of bias in included cohort studies

Criteria/Studies	Selection (cohort) recruited in acceptable way	Exposure accurately measured	Outcome accurately measured	Confounding factors taken into account	Follow-up complete and long enough
Schonfeld 2010 [33]	Yes	Yes	Yes	Can't tell	Yes
Chay 2012 [37]	Yes	Yes	Yes	Can't tell	Yes
Banegas 2012 [36]	Yes	Yes	Yes	Can't tell	Yes
Boggs 2013 [38]	Yes	Yes	Yes	Can't tell	Yes
Petracci 2010 [40]	Yes	Yes	Yes	Can't tell	Yes
Pfeiffer 2013 [41]	Yes	Yes	Yes	Yes	Yes
Boggs 2015 [42]	Yes	Yes	Yes	Can't tell	Yes
Vacek 2011 [12]	Yes	Can't tell	Yes	Can't tell	Yes

Cross sectional study have potentially higher risk of bias.

6.1.2 Review of Gail Model

Gail model was one of the earliest model, developed in 1989 and described here as Gail.[32] It was developed through a case - control study of women participated in the American Cancer Society's mammography feasibility study, the Breast Cancer Detection and Demonstration Project. It estimates the risk an American woman would develop invasive breast cancer over specified time interval e.g., five or ten years given age and risk factors. According to Schonfeld,[33] the probability of developing breast cancer in the Gail 1 model is computed by combining relative risks (RRs) estimated from the Breast Cancer Detection Demonstration Project (BCDDP) with attributable risks, age-specific breast cancer incidence rates, and competing mortality rates from all other causes from the Surveillance, Epidemiology and End Results (SEER) program for the years 1983 to 1987.[33]

The six risk factors included in the model were age, age at first live birth, age at menarche, history of breast cancer in first-degree relatives, number of previous breast biopsies and history of atypical

hyperplasia.[34] The Gail model components of age at menarche, first degree family history of breast cancer, biopsy history, and reproductive history, emerged as having the strongest collective risk assessment "fit" after being screened alongside several other candidate risk factors.

Expression of these four risk factors yields a combined relative risk for the individual patient, and this relative risk is in turn converted into an "absolute" risk by a "baseline" risk multiplier. The baseline risk is computed by using Surveillance, Epidemiology, and End Results (SEER) program data on age-specific breast cancer incidence rates in White American women. [35]

In 1992, Anderson published Gail 2 model in a technical report which is described by Constantino et al in 2010. [34] This model is for predicting invasive breast cancer only, and the baseline risk is estimated using SEER database available from the placebo arm of a RCT on adjuvant tamoxifen treatment. The Gail 2 model was used to establish eligibility for tamoxifen treatment by estimating baseline risk of breast cancer.[34] The major limitation of Gail model is inclusion of only first degree relative, which result in underestimating risk in the 50% of families with cancer in the paternal lineage and also takes no account of the age of onset of breast cancer.[6]

6.2 EFFECTIVENESS (PREDICTIVE ACCURACY)

6.2.1 Gail model

Three studies reported validation of Gail (also known as BCRAT) model (Table 1). The validation population was mostly from United States (US) post-menopausal white women aged 50 to 79 years Hispanics and non-Hispanic [33,36] with one study from Asia also in women aged 50 to 64 years.[37]

Two studies recalibrated/updated the Gail model with SEER incidence and mortality of 1995-2003 [33] and RR from SEER 1993-1997 breast cancer incidence.[36]

Performance statistics were reported by the three studies. Two studies found underestimation of breast cancer cases by 13 to 18% using the Gail model, however upgrading of the model demonstrated it was improved to E/O of 1.03 and O/E of 1.08 respectively[33,36]. Another study found the Gail model overestimated breast cancer risk among Singaporean women aged 50 to 64.[37] Overall discriminative accuracy of the studies was modest with c-statistic ranges between 0.58 to 0.67.

The three articles conducting validation and recalibration of the Gail model is described here with summary of its finding is illustrated as in Table 2.

Schonfeld SJ et al conducted a prospective cohort study in the United States in 2010 to evaluate the Gail model calibration in two cohorts (National Institutes of Health AARP Diet and Health Study (NIH-AARP, 1995 to 2003), and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO, 1993 to 2006), following changes in US breast cancer incidence during the 1990s. The Gail model uses breast cancer incidence rates and competing mortality rates from the Surveillance, Epidemiology and End Results (SEER) program (1983 to 1987), while this updated model used SEER incidence and mortality rates from the period corresponding to the cohorts, 1995 to 2003. In this study, cancer ascertainment was done through linkage with state cancer registries (NIH-AARP), through annual mailed questionnaires to participants and medical records confirmation (PLCO). Reports from physicians, Death Index and cancer registries were periodically searched when available. Risk factors included in the Gail model were obtained from baseline questionnaires. Calibration of updated model was evaluated using combined Gail model RR with SEER breast cancer incidence rates 1995 to 2003. This study involved Women from NIH-AARP (a large prospective study of 200,000 women age 50 to 71 years, from 1995 to 1996) and PLCO (a multicenter screening trial involving 77,500 women, between 1993 and 2001; aged 55 to 74 years at baseline included white, post-menopausal women with known parity, no history of in-situ or invasive breast cancer, and age younger than 90 years at the start of follow-up. This study has validated the Gail model (SEER 1983 to 1987) in two cohorts. They found the Gail model significantly underpredicted the number of invasive breast cancers in both cohorts; with E/O ratio of 0.87 (95% CI, 0.85 to 0.89) in NIH-AARP (underprediction by 13%) and E/O ratio of 0.86 (95% CI, 0.82 to 0.90) in PLCO (underprediction by 14%). Updating the Gail model (using SEER 1995 to 2003), has improved its calibration in both cohorts, E/O ratio of 1.03 (95% CI, 1.00 to 1.05) in NIH-AARP and E/O ratio of 1.01 (95% CI: 0.97 to

1.06) in PLCO. Further updating of the Gail model (using SEER 2003 to 2006) demonstrated it was well calibrated in PLCO cohort (E/O ratio of 1.00; 95%CI, 0.94 to 1.08). The discriminatory ability was unchanged by the recalibration; with the overall AUCs for the updated model were 0.58 in NIH-AARP and 0.59 in PLCO.[33]

Chay WY et al had conducted a prospective cohort validation study in 2012 to evaluate the performance of the Gail Model (GM) as an appropriate breast cancer risk assessment tool in the Asian population. The study population consisted of 28,104 women aged 50 to 64 years who participated in the Singapore Breast Cancer Screening Project (SBSCP), a population-based mammography screening project among female Singaporeans conducted between October 1994 and February 1997 and did not have breast cancer during screening. Women with breast cancer or other cancers, pregnant or had mammography or breast biopsy 12 months prior study were excluded. Cancer ascertainment was done through the Singapore Cancer Registry and the National Death Register. To evaluate the performance of the GM, the expected number of invasive breast cancer cases were compared to number of actual cases observed within 5-year and 10-year follow-up. They found 144 and 409 incidence of invasive breast cancers within 5 years and 10 years from screening, respectively. In term of model calibration, The GM over-estimated the overall breast cancer risk at 5 year from screening with E/O ratio of 2.51 (95%CI 2.14 to 2.96); predicted invasive breast cancer cases were 362 cases and observed invasive breast cancer cases were 144 cases.The model was also over-estimated breast cancer risk across all age groups, with the highest discrepancy demonstrated among older women aged 60 to 64 years with E/O ratio of 3.53 (95%CI 2.57 to 4.85). Similarly at 10 year from screening the model also over-estimated overall breast cancer risk with E/O ratio of 1.85 (95%CI 1.68 to 2.04). The corresponding predicted and observed invasive breast cancer cases were 758 and 409 cases respectively. Over-prediction of the number of breast cancers by GM was higher for women who were 60 to 64 years old (E/O ratio of 2.54, 95% CI 2.57 to 4.85). Trends of E/O ratio by age group and predicted risk quintile group which were based on 10-year prediction were broadly similar to those based on 5-year prediction. The author concluded that this study validates the Gail model risk factors individually but it over-predicts the risk of invasive breast cancer in the setting of a developed Asian country, with the largest difference seen in older women aged between 60 and 64 years old. Consequently, it has become imperative to evaluate local breast cancer epidemiology in order to validate existing models of breast cancer risk. Future work should focus on the development of appropriately calibrated models for better prediction of risk, which would benefit individual counselling and cancer prevention research.[37]

Banegas et al in 2012 similarly carried out a cohort validation study to examine the performance of Breast Cancer Risk Assessment Tool (BCRAT) and updated BRCAT in Hispanic women in the United States. BCRAT combines 1990 to 1996 breast cancer incidences for Hispanic women with relative risk of risk factors from non Hispanic white (NHW). In this study, the relative risks, calibration and discriminatory accuracy of BCRAT risk projections for 6,353 Hispanic were compared to 128,976 NHW postmenopausal participants aged 50 to 79 in the Women's Health Initiative study, a large longitudinal study involving Hispanic and NHW. BCRAT risk factors were obtained from the enrollment questionnaire. All reported invasive breast cancers were adjudicated locally and centrally. Calibration for an 'updated BCRAT' that combined BCRAT relative risks with 1993 to 2007 SEER breast cancer incidences that are simultaneous with the WHI was re-evaluated. [36]

Calibration of BCRAT found that the model underestimated the number of breast cancer diagnoses by 18% among Hispanics (O/E of 1.18, 95%CI 0.99 to 1.40; p= 0.06) and by 18% as well for NHW women (O/E of 1.18, 95%CI 1.14 to 1.21; p< 0.001). The discriminatory ability of BRCAT was modest with c-statistic (AUC) of 0.63 (95%CI 0.58 to 0.67) for Hispanic women and 0.58 (95%CI: 0.56 to 0.58) for NHW women in the WHI. Validation of updated model however demonstrated an improved calibration for both Hispanic women (O/E of 1.08, p= 0.4) and NHW women (O/E of 0.98, p= 0.2). [36]

6.2.2 Contraceptive and Reproductive Experience (CARE) model

We identified two studies reported on Contraceptive and Reproductive Experience (CARE) model in which one study did validation[38] and another study did comparison of CARE model.[39] (Table 3) The validation population was African-American women aged range from 30 to 69 years.

Table 2: Description summary of risk prediction study characteristics related to performance of Gail model

Study author	Design	Model	Risk factors	Validated population	Validation statistic	
					Calibration	Discriminatory ability
Schonfeld 2010 [33]	Cohort	Gail model (SEER incidence and mortality 1983 to 1987) & updated Gail model (SEER incidence and mortality 1995- 2003)	• Age at menarche • No. of first degree relative with breast ca • Age at first birth • No. of breast biopsy	White, post-menopausal women aged 50 to 74 years at baseline with known parity, no history of in-situ or invasive breast cancer, and age younger than 90 years at the start of follow-up From two cohorts; NIH-AARP (a large prospective study of 200,000 women from 1995 to 1996) and PLCO (a multicenter screening trial involving 77,500 women, between 1993 and 2001)	i. The Gail model: - E/O ratio = 0.87 (95% CI 0.85 to 0.89) in NIH-AARP (underprediction by 13%), - E/O ratio = 0.86 (95% CI 0.82 to 0.90) in PLCO (underprediction by 14%), ii. Updated model (SEER 1995-2003): ➢ E/O ratio = 1.03 (95% CI 1.00 to 1.05) in NIH-AARP ➢ E/O ratio = 1.01 (95% CI: 0.97 to 1.06) in PLCO. i. Updated Gail model in PLCO (SEER 2003 to 2006): E/O ratio = 1.00; (95%CI 0.94 to 1.08).	- • Updated model: ➢ Overall AUCs were 0.58 in NIH-AARP and 0.59 in PLCO.
Chay 2012 [37]	Cohort	Gail model	• Age at menarche • Age at first livebirth • Previous breast biopsy • No. of first degree relative with breast ca	28,104 women aged 50 to 64 years from Singapore Breast Cancer Screening Project (SBCSP), a population-based mammography screening project among female Singaporeans conducted between October 1994 and February 1997. Excluded: women with breast cancer or other cancers, pregnant or had mammography or breast biopsy 12 months prior study	Gail Model i. 5 year from screening - Overall: E/O ratio = 2.51 (95% CI = 2.14 to 2.96) ➢ The GM over-estimated breast cancer risk across all age groups, with the highest discrepancy among older women aged 60 - 64 years (E/O = 3.53, 95% CI = 2.57-4.85) ii.10 year from screening E/O ratio = 1.85 (95% CI = 1.68 to 2.04) Over-prediction of the number of breast cancers by GM was higher for women who were 60 to 64 years old (E/O ratio = 2.54, 95% CI = 2.57 to 4.85	-
Banegas 2012 [36]	Cohort	Breast Cancer Risk Assessment Tool (BCRAT) combines 1990-1996 breast cancer incidence for Hispanic women with relative risk of risk factors from NHW & Updated BCRAT (RR from SEER 1993-1997 breast cancer incidence)	age, age at first live birth, age at menarche, number of first-degree relatives with breast cancer, number of breast biopsies and presence of atypical hyperplasia on a previous breast biopsy	6,353 Hispanic and 128,976 NHW postmenopausal participants aged 50–79 without a history of breast cancer or mastectomy in WHI	• BCRAT ➢ Hispanics women O/E = 1.18, 95% CI = 0.99 to 1.40; p = 0.06) ➢ NHW women O/E = 1.18, 95% CI = 1.14 to 1.21; p< 0.001). ➢ (both underestimation by 18%) • Updated BCRAT ➢ Hispanic women O/E = 1.08, p= 0.4 ➢ NHW women O/E = 0.98, p= 0.2	- Concordance statistic (AUC) : 0.63 (95%CI:0.58 to 0.67) for Hispanic women = 0.58 (95%CI:0.56 to 0.58) for NHW women in the WHI (p= 0.03)

Performance statistics were reported by one study (Boggs 2013)[38] and they found underestimation of breast cancer cases by 12% using the CARE model with modest discriminative accuracy with c-statistic of 0.57 (overall), 0.59 for Estrogen Receptor positive (ER+) breast cancer and 0.54 for Estrogen Receptor negative (ER-breast cancer). Summary of these studies are illustrated in Table 3. Boggs et al in 2013 conducted a prospective cohort validation study to assess the calibration and discriminatory accuracy of the CARE model among both younger and older black women and to assess the model's predictive ability for specific breast cancer subtypes (estrogen receptor positive (ER+) and estrogen receptor negative (ER–) breast cancer) in US. The study involved 45,942 Black women (from Black Women's Health Study) aged 30 to 69 years at baseline, with majority (41.6%) were between 30 to 39 years at baseline. The Black Women's Health Study (BWHS) was an ongoing follow-up study of black women (1995) involving women aged 21 to 69. Women who had a history of cancer (n = 1859) or died (n = 64) before start of follow-up or with missing information on any risk factors in the model (n = 215) were excluded in the analysis of this study. CARE model factors were obtained from the BWHS baseline questionnaire. Self-administered baseline questionnaire were collected. Biennial follow-up questionnaires ascertain incident breast cancer (self report) from 1997 to 2005, which was confirmed by medical record or by cancer registry. Median age at diagnosis was 52 years. The mean length of follow up was 9.5 years (end of follow up was 31 December 2005). They found The CARE model underestimated the number of invasive breast cancers overall by 12% in this BWHS cohort with overall E/O ratio of 0.88 (95%CI=0.82 to 0.94), predicted and observed breast cancer cases were 749.6 and 852 cases respectively. CARE model showed underprediction of breast cancer risks among all categories of age, age at menarche, number of biopsies and number of affected relatives (E/O of 0.78-0.96, 0.84-0.91, 0.76-0.91 and 0.85-1.00), underprediction was greatest among women with previous biopsy, however the differences were not statistically significant. The discriminatory power of the CARE model in black women was modest with average age-specific concordance (c) statistics for total invasive breast cancer was 0.57 (95%CI 0.55 to 0.59). The result demonstrated that discrimination was worse for ER– breast cancer with average age-adjusted c statistics of 0.59 (95%CI 0.57 to 0.61) for ER+ breast cancer and 0.54 (95%CI 0.50 to 0.57) for ER– breast cancer.[38]

Adams-Campbell et al in 2009 conducted a cross sectional study to compare breast cancer risk estimates using the Gail model and the CARE model. The Gail model has been used to predict invasive breast cancer risk in women, however it underestimates risk in African-American women. The Contraceptive and Reproductive Experience (CARE) model has been developed to replace the Gail model in predicting breast cancer risk in African-American women. The study population completed risk assessment forms based on age at menarche, age at first live birth, number of affected relatives and number of previous benign biopsy examinations, between 2002 and 2005 to determine risk estimates. 5-year breast cancer risk was calculated for both the Gail and CARE models in the study subjects. The proportion of women with elevated breast cancer risk (risk ≥ 1.67%) was also compared. The sudy involved 883 African-American women undergone mammography in the breast cancer screening program at Howard University Cancer Center, Washington with mean age of 53.8±10.8 years (minimum 35 years). They found the mean 5-year breast cancer risk was higher in CARE model, 1.29% (range: 0.20 to 4.50%) compared to Gail model, 0.88% (range: 0.18 to 6.60%). Similarly, the proportion of women with elevated breast cancer risk (risk ≥ 1.67%) was higher using the CARE model (21%) compared to Gail model (7%) ($p < 0.0001$). A large difference of proportion of elevated breast cancer risk was observed for women ≥60 years of age between CARE model (51.7%) and Gail model (14.2%). The CARE model risk predictions were higher than those from the Gail model in all risk factor categories namely age at menarche, breast biopsy, age at first live birth; and in women 40 years and older, and those with at least one or no relatives with breast cancer.[39]

6.2.3 Other breast cancer risk prediction model

In this section, four studies reported development of new risk prediction model and subsequent validation which has been conducted in Italy[40], US[41,42] and Thailand.[43]

The validation population varies from Italian women aged 20 to 74 years [40], non Hispanic white women with median age of 52 years [41], African American women aged between 30 and 69 years (mean age 39.9)[42] and Thailand women median aged 54 years.[43]

Table 3: Description summary of risk prediction study characteristics related to performance of CARE model

Study author	Design	Model	Risk factors	Outcome	Study/ validated population	Validation statistic	
						Calibration	Discriminatory ability
Adams-Campbell 2009 [39]	Cross sectional	Contraceptive and Reproductive Experience (CARE) Model	• age at menarche, • age at first live birth, • number of affected relatives • number of previous benign biopsy examinations	•5 year breast cancer risk ➢ 0.88% (Range: 0.2-6.6%) (Gail model) -1.29% (Range:0.2–4.5%) (CARE model) • Proportion of women with elevated breast cancer risk (risk ≥ 1.67%) - 7% (Gail model) 21% (CARE model) (p< 0.0001). - For women ≥60 years of age, large differences of proportion observed; Gail model (14.2%) and CARE model (51.7%)	883 African-American women who participated in the breast cancer screening program at Howard University Cancer Center, Washington Mean age: 53.8±10.8 years	-	-
Boggs 2013 [38]	Cohort	Care MODEL	Age Age at menarche No. of biopsies No of affected relatives	Validation	45,942 Black women (from Black Women's Health Study) aged 30 to 69 years at baseline Excluded: Women who had a history of cancer (n = 1859) or died (n = 64) before start of follow-up or with missing information on any risk factors in the model (n = 215), this analysis included 45 942. Age at baseline = 30 to 39 years (41.6%; majority) Median age at diagnosis = 52 years	CARE model: E/O ratio = 0.88 (95% CI=0.82 to 0.94)	Age-specific concordance statistic for total invasive breast cancer - 0.57 (95% CI = 0.55 to 0.59) Age-adjusted concordance statistics - 0.59 (95% CI = 0.57 to 0.61) (ER+ breast cancer) - 0.54 (95% CI = 0.50 to 0.57) (ER–breast cancer)

Three studies used different cohort from different study for model development and subsequent validation [40,41,43] whereas Boggs in 2015 used different cohort from a similar study for model development and validation.

Petracci included non-modifiable and modifiable risk factors (eight factors) in the new model, Pfeiffer developed model that share many hormonal and epidemiological risk factors; breast, endometrial and ovarian cancer in the US (nine factors), Boggs included nine risk factors in the BWHS model and Anothaisintawee included four variables/risk factors in the final model.

Performance statistics were reported by the four studies and they found the models were well calibrated with overall E/O ratio of 1.10,[40] 1.00[41] and 0.96[42] and O/E of 1.00[43] for prediction of breast cancer cases with modest discriminative accuracy c-statistic of 0.65,[43] 0.62,[40] 0.58,[41] and 0.59[42]. Summary of these studies are illustrated as in Table 4.

Petracci et al in 2010 conducted a prospective cohort study to estimate the effects of changes in modifiable risk factors on the absolute risk of breast cancer. In this study, a model was developed to predict the absolute risk of breast cancer using data from a multicentre case–control study of women in Italy (2569 case patients and 2588 control subjects studied from June 1, 1991, to April 1, 1994 involving six regions) and incidence and mortality data from the Florence Registries. Data from the case control study were used to select the non-modifiable and modifiable risk factors and to estimate the relative risks. The model included five non-modifiable risk factors (reproductive

Table 4: Description summary of risk prediction study characteristics related to performances of other models

Study author	Design	Model	Risk factors	Outcome	Study/ validated population	Validation statistic	
						Calibration	Discriminatory ability
Petracci 2010 [40]	Cohort validation study	Petracci	• Non-modifiable (five) and modifiable risk factors (three) • Age at menarche • Age at first live birth • No. of affected first degree relative • No. of biopsies • Occupational physical activity level • Education • Leisure-time physical activity level • Alcohol intake • BMI	• New model (multicentre case–control study 1991 to 1994) • Validation (Florence-EPIC cohort 1998 to 2004) • Impact of reducing modifiable exposures on absolute breast cancer risk ➢ For 45-year-old Mean ARR = 0.6% (95% CI = 0.3 to 1.0%) and 1.4% (95% CI = 0.7 to 2.0%) (for 10 and 20 years projection) ➢ For 65-year-old ARR=0.9% (95% CI = 0.5 to 1.3%) and 1.6% (95% CI = 0.9 to 2.3%) (for 10 and 20 years projection) (absolute risk reduction from exposure modifications was nearly proportional to the risk before modifying the risk factors and increased with age and risk projection time span) ➢ Mean 20-year reductions in absolute risk - Women aged 65 years : 1.6% (95% CI: 0.9 to 2.3%), - Women with positive family history: 3.2% (95% CI: 1.8 to 4.8%), - Women in the highest 10% of the total population risk 4.1% (95% CI: 2.5 to 6.8%)	• Model development : Multicentre case–control study: 2569 cases (female patients with breast cancer, aged 23 to 74 years, median age: 55 years); control subjects (n = 2588) were women aged 20 to 74 years (median age: 56 years) without breast cancer • Model validation: The Florence-EPIC cohort included 10, 083 women aged 35–64 years	➢ Overall: E/O ratio = 1.10 (95% CI = 0.96 to 1.26, p=0.19) ➢ Other variables: The model showed over-prediction of breast cancer risks for these subgroups; • Women aged 60 years or more, E/O ratio = 1.47 (95% CI = 1.03 to 2.09) • Women aged 30 or more at first live birth, E/O ratio = 1.72 (95% CI = 1.24 to 2.38) • Women with 12 years or more of education. E/O ratio = 1.34 (95% CI = 1.09 to 1.65)	➢ c-statistic = 0.62 (95% CI: 0.55 to 0.69) (women younger than 50 years) ➢ c-statistic = 0.57 (95% CI: 0.52 to 0.61) (women aged 50 years and older)

Study author	Design	Model	Risk factors	Outcome	Study/ validated population	Validation statistic	
						Calibration	Discriminatory ability
Pfeiffer 2013 [41]	Cohort validation study	Pfeiffer	• menopause hormone therapy (MHT) use • other MHT use • age at first live birth • menopausal status • age at menopause • family history • benign breast disease/biopsy • alcohol • BMI	• New model (NIH-AARP & PCLO study) • Validation (NHS study) • Breast cancer risk projection - Absolute risk estimates = 1.57% to 21.78% (10 year projection) - Absolute risk estimates = 3.64% to 35.11% (20 year projection)	Final study population included 191,604 (NIH-AARP) and 64,440 (PLCO) women for breast cancer analysis For model validation: Final validation included 57,906 women from the Nurses Health Study, aged 30–55 (for the breast cancer model) Restriction: Non-Hispanic, white women who completed baseline questionnaire, had follow-up information, and had no personal history of the cancer of interest at baseline, Age at baseline = 30 to 39 years (41.6%; majority) Median age at diagnosis = 52 years	New model: ➢ Overall E/O ratio = 1.00 (95% CI:0.96 to1.04) ➢ Significant underestimation in premenopausal women (30-55 years); E/O ratio = 0.73 (95% CI: 0.65 to 0.83) BCRAT model ➢ Overall E/O ratio = 1.0 (95%CI 0.97 to 1.04 ➢ Women above 55 years; E/O ratio= 0.80 (95%CI 0.70 to 0.92) ➢ Premenopausal women (aged 30 to 55), E/O ratio= 0.81 (95%CI 0.72 to 0.92).	➢ Overall AUC in the NHS cohort = 0.58 (95% CI: 0.57 to 0.59).
Boggs 2015 [42]	Cohort	BWHS model	• 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	• New model development (BWHS 1995 to 2005) • Validation (BWHS 2006 to 2010) ➢ Proportion of women with elevated risk of breast cancer (5-year predicted risk of 1.66% or greater) & comparison ➢ Women younger than 50 years - 2.8% (BWHS model) vs 0.1% (CARE model) ➢ Women more than 50 years old - 32.2% (BWHS model) vs 7.3% (CARE model) ➢ Overall (women age 30 to 69 years) - 14.6% (BWHS model) vs 3.0% (CARE model)	55,879 African American women from the BWHS cohort aged 30 to 69 years at baseline or who reached age 30 years during follow-up, had no history of cancer at baseline, and had no missing data on variables in the final model Mean age: 39.9 (1996 cohort) and 47.2 (2006)	BWHS model: Overall E/O ratio = 0.96 (95% CI 0.88 to 1.05) Significant underestimation: ➢ Women without a family history of breast cancer (E/O ratio = 0.90; 95% CI,0.81 to 0.99), ➢ Nulliparous women (E/O ratio = 0.83; 95% CI 0.70 to 0.99), ➢ Women with recent (10years) use of OCP (E/O ratio=0.75; 95% CI 0.63 to 0.89) ➢ In the second lowest age-adjusted quintile of risk (E/O ratio = 0.75; 95%CI 0.61 to 0.91)	➢ AUC (overall) = 0.59 (95% CI 0.56 to 0.61) ➢ AUC = 0.62; (95% CI 0.58 to 0.65) (women younger than 50 years) ➢ AUC = 0.56; (95% CI 0.53 to 0.59) (women more than 50 years) ➢ AUC = 0.58; (95% CI 0.55 to 0.61) (women with ER+) ➢ AUC = 0.62; (95% CI 0.58 to 0.66) (women with ER-)
Anothaisintawee et al in 2014	Cross sectional	Thai model	• age, • menopausal status, • body mass index and • use of oral contraceptives	• Model derivation • Model validation (internal) : used bootstrap with 200 repetitions • Model validation (external) used data from Srinagarind and Songklanagarind Hospitals • Risk score & risk stratification: low, low-intermediate, intermediate-high, and high-risk	17,506 women whom undertook mammographic screening in Ramathibodi Hospital (model derivation) Women undergoing mammographic screening aged 18 years and above were eligible. Those with history of invasive breast cancer, ductal carcinoma in situ or other cancers were excluded	O/E ratio = 1.0 (95%CI 0.82 to 1.21) External validation ; O/E ratio 0.97 (95% CI 0.68 to 1.35)	Overall c-statistic = 0.65 (95%CI 0.59 to 0.70 Internal validation C-statistic = 0.64(95% CI 0.642 to 0.650) External validation C-statistic = 0.61 (95% CI 0.51 to 0.71)

characteristics, education, occupational activity, family history, and biopsy history) and three modifiable risk factors (alcohol consumption, leisure physical activity, and body mass index). The developed model was validated using independent data from the Italian cohort, Florence-EPIC cohort study from 1998 to 2004. This study involved 2569 cases (female patients with breast cancer, aged 23 to 74 years, median age: 55 years); and 2588 control subjects aged 20 to 74 years without breast cancer (median age: 56 years) from a case control study to develop the model and subsequently involved the Florence-EPIC cohort of 10, 083 women aged 35 to 64 years for model validation. The study found that the model was reasonably well calibrated with overall E/O ratio of 1.10 (95%CI 0.96 to 1.26, p=0.19). The model also showed over-prediction of breast cancer risks for other variables, women aged 60 years or more, women aged 30 or more at first live birth, and women with 12 years or more of education. The discriminatory accuracy was modest. It was demonstrated that the absolute risk reduction from exposure modifications was nearly proportional to the risk before modifying the risk factors and increased with age and risk projection time span. Mean 20-year reductions in absolute risk among women aged 65 years were 1.6% (95%CI 0.9 to 2.3%) in the entire population, 3.2% (95%CI 1.8 to 4.8%) among women with a positive family history of breast cancer, and 4.1% (95%CI 2.5 to 6.8%) among women who accounted for the highest 10% of the total population risk, as determined from the Lorenz curve. The author concluded that the new absolute risk prediction model for invasive breast cancer was reasonably well calibrated overall but overestimated the absolute risk of breast cancer in some subgroups such as women aged 60 years or older, and women whose first live birth occurred at age 30 years or later with modest discriminatory accuracy. These data give perspective on the potential reductions in absolute breast cancer risk from preventative strategies based on lifestyle changes. The methods are also useful for calculating sample sizes required for trials to test lifestyle interventions.[40]

Pfeiffer et al in 2013 conducted a prospective cohort study to develop a model in predicting risk of cancers that share many hormonal and epidemiological risk factors; breast, endometrial and ovarian cancer. This study involved different cohorts for model development and validation. The absolute risk prediction model was developed for breast, endometrial, and ovarian cancer by combining data from two large prospective cohorts; the National Cancer Institute (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the National Institutes of Health–AARP Diet and Health Study (NIH-AARP)); and age-specific US population incidence and competing mortality rates from the NCI's Surveillance, Epidemiology, and End Results Program (SEER). Study population for breast cancer analysis included 191,604 (NIH-AARP) aged 50 to 71 and 64,440 (PLCO) women aged 55 to 74. Model validation study population included 57,906 women from the Nurses Health Study, aged 30 to 55 (for the breast cancer model). Cancers were ascertained via annual study updates and death certificates, and verified via review of medical records (PLCO), through linkage with state cancer registries (NIH-AARP). Average follow up was 7.1years (starting one year after the entry mammogram, yielded 141,034 person years of follow-up). The final relative risk model for breast cancer included these risk factors; BMI, estrogen and progestin Menopause Hormone Therapy use, other MHT use, parity, age at first birth, premenopausal, age at menopause, benign breast diseases, family history of breast or ovarian cancer and alcohol consumption.[41]

The study found the new model is well calibrated with overall E/O ratio of 1.00 (95%CI 0.96 to1.04), however it significantly underestimated the number of breast cancers in premenopausal women (aged 30 to 55) with E/O ratio of 0.73 (95%CI 0.65 to 0.83). Peformance of BCRAT model showed it was well calibrated with E/O ratio of 1.0 (95%CI 0.97 to 1.04) and it significantly underestimated number of breast cancers in women above 55 years (E/O ratio of 0.80 (95%CI 0.70 to 0.92) and premenopausal women (aged 30 to 55) with E/O ratio of 0.81 (95%CI 0.72 to 0.92). Discriminatory power were modest for both new model and BCRAT in the NHS validation data with overall AUC of 0.58 (95%CI 0.57 to 0.59) and 0.56 (95% CI 0.55 to 0.58) respectively. Absolute risk estimates were 1.57% to 21.78% (for 10 year breast cancer projection) and 3.64% to 35.11% (20 year projection). The author concluded that these models predict absolute risks for breast, endometrial, and ovarian cancers from easily obtainable risk factors among white, non-Hispanic women aged 50+ years. The models may assist in clinical decision-making related to the risks of these cancers and might improve the ability to identify potential participants for research studies. Limitations are the modest discriminatory ability of the breast and ovarian models, and that these models may not generalize to women of other races.[41]

Boggs et al recently in 2015 conducted a prospective validation study to develop a breast cancer risk prediction model for African American women using prospective data from the BWHS in follow-up from 1995 to 2005 and to validate the model in subsequent follow-up from 2006 to 2010, overall and by age and ER status. The BWHS is an ongoing follow-up study of African American women established in 1995 involving 59,000 African American women from across the US. A breast cancer risk model for the women was developed using relative risks (RR) of invasive breast cancer derived from 10 years of follow-up (1995 to 2005) of BWHS participants age 30 to 69 years at baseline by Cox proportional hazards models. In this study, an absolute risk was estimated using RRs and attributable risks from the BWHS model, age-specific SEER breast cancer rates for African American women (1994 to1998), and age specific competing mortality rates for African American women (1996 to 2000). Using the subsequent five years of follow-up data (2006 to 2010), calibration as the ratio of expected to observed number of breast cancers and discriminatory accuracy using the concordance statistic were evaluated.

Baseline questionnaire on BWHS risk factor were collected (age at menarche, height, weight at age 18 years, waist and hip circumference, educational attainment, family history of breast cancer, parity, age at first birth, duration of breastfeeding, oral contraceptive use, age at menopause, type of menopause, menopausal hormone use, previous diagnosis of benign breast disease). Incident diagnoses of breast cancer were ascertained through self-report on biennial follow-up questionnaires and, for non-respondents, through linkage with state cancer registries. Breast cancer deaths were identified through linkage with the National Death Index. They found t*he BWHS model was well calibrated overall* with E/O ratio of 0.96 (95%CI 0.88 to 1.05), *across a wide age range and across strata of risk factors. It* significantly underestimated risk of breast cancer in these subgroups; women without a family history of breast cancer (E/O ratio of 0.90; 95% CI 0.81 to 0.99), nulliparous women (E/O ratio of 0.83; 95%CI 0.70 to 0.99), women who used oral contraceptives within the previous 10 years (E/O ratio of 0.75; 95% CI 0.63 to 0.89) and women in the second lowest age-adjusted quintile of risk (E/O ratio of 0.75; 95%CI 0.61 to 0.91). *The discriminatory accuracy of the model remains modest but was higher for breast cancer overall and for ER-negative breast cancer than the discriminatory accuracy of a previous model with fewer risk factors. The predictive ability was best for younger women.* The author concluded that the model was well calibrated overall with best predictive ability for younger women. The model may be a useful tool to identify women who may benefit from screening before age 50 years. The proportion of women predicted to meet the 1.66% cut point commonly used to determine eligibility for breast cancer prevention trials was greatly increased relative to previous models. It is unclear how well the model will perform in study populations with different distributions of risk factors; the calibration and discrimination of the BWHS model should be evaluated in independent studies.[42]

Anothaisintawee *et al* in 2014 conducted a cross sectional study to derive and validate breast cancer risk prediction model for Thai women. This study used data from Ramathibodi Hospital which involved 17,506 women whom undertook mammographic screening in the model derivation phase. Another data from Srinagarind and Songklanagarind Hospitals were used to externally validate the derived model. A bootstrap with 200 repetitions was applied for internal validation. Women undergoing mammographic screening aged 18 years and above were eligible and those with history of invasive breast cancer, ductal carcinoma in situ or other cancers were excluded. The study found four risk factors; age, menopausal status, body mass index and use of oral contraceptives were included in the model. C-statistic and O/E ratio were 0.65 (95%CI 0.59 to 0.70) and 1.0 (95%CI 0.82 to 1.21). Internal validation showed C-statistic of 0.64(95% CI 0.642 to 0.650) while external validation demonstrated O/E ratio and C-statistic of 0.97 (95% CI 0.68 to 1.35) and 0.61 (95% CI 0.51 to 0.71), respectively. The author also created risk scores which was stratified as low (0-0.86), low-intermediate (0.87-1.14), intermediate-high (1.15-1.52), and high-risk (1.53-3.40) groups. They concluded that the study had created a Thai breast cancer risk prediction model with good calibration and fair discrimination performance. The additional risk stratification should aid to prioritize high risk women to receive an organized breast cancer screening program in Thailand and other limited-resource countries.[43]

6.2.4 Comparison of breast cancer risk prediction models

Three studies reported comparison of risk prediction models in which two were systematic review[14,15] and another one a prospective cohort study validating several models among white women above 70 years old in Vermont, US. [12]

Performance statistics were reported by the three studies and they found the models were well calibrated with E/O ratio ranging from 0.87 to 1.12 from Anothaisintawee 2012); 1.13 (Gail 1 model), 0.95 (Gail 2 model) and 0.96 (Rosner & Colditz model) in the meta analysis performed by Meads 2012 for prediction of breast cancer cases. Modest discriminative accuracy was demonstrated with c-statistic of 0.54 to 0.55,[2] 0.63[15] and 0.59 to 0.62. [14] Summary of these studies are illustrated as in Table 5.

Meads *et al* in 2012 conducted a systematic review without restriction on study type to identify and evaluate the performance of prediction models for breast cancer that contain **modifiable factors.** This review included 17 studies proposing or validating a breast cancer prediction model in a general female population using multiple variables, at least one of which was a modifiable risk factor. Studies with breast cancer in men, or women who already had breast cancer or benign breast pathology when recruited, studies in high risk groups of women, such as with specific genetic mutations or who have close family relatives with breast cancer, models investigating single risk factor results such as mammography, assessing genetic risk factors only, assessing invasive techniques such as biopsies only, assessing family history of breast or ovarian cancer only and predicting genetic mutations rather than cancer, screening and early detection studies and Models published more than before 1985 were excluded. Evidence searched was conducted between November 2009 and June 2010. No specific quality assessment checklist used. Results were summarised qualitatively, and meta-analysis of model performance statistics was undertaken. The review summarised qualitatively studies describing a new risk prediction model containing at least one modifiable risk factor, that aimed to predict breast cancer in populations and in individual women. Modifiable risk factors that were included in one or more models were alcohol consumption, breast biopsy number, BMI or weight, condom use, exogenous hormone use (HRT, contraceptive pill), and physical activity. Risk factors only included in one model were condom use, family history of any cancer, physical activity and reproductive age period. The most commonly included risk

Table 5: Selected summary characteristics of studies with risk prediction model comparing several model performances

Study author	Design	Model compared	Risk factors	Included studies/ validated population	Outcome	Meta analysis of validation measures	
						Calibration	Discriminatory ability
Meads 2012 [15]	Systematic review (no restriction on study type) Evidence searched between November 2009 and June 2010 No specific quality assessment	17 Models: • Arne 2009 • Barlow 2006 • Boyle 2004 • Chen 2006 • Colditz & Rosner 2000 • Cook 2009 • Decarli 2006 • Gail 1989 • Constantino 2010 • Gail 2007 • Novotny 2006 • Rosner 1994 • Rosner & Colditz 1996 • Rosner 1994 • Tice 2008 • Tyrer & Cuzick 2005 • Wacholder 2010	• Modifiable risk factors included • Commonest risk factors included (age, age at first live birth and/or age at subsequent births and family history of breast cancer)	• Any articles proposing or validating a breast cancer prediction model in a general female population using multiple variables, at least one of which was a modifiable risk factor • Included studies : 26 ➢ Development of a new risk prediction model only = 6 ➢ Both development of a new model and validation of one or more models = 11 ➢ Independent validation of one or more models = 9	- Qualitative summary: • Studies describing a new risk prediction model (17 models) • Modifiable risk factors included • Commonest risk factors included • Studies validating prediction models (Colditz 2000, Gail 1 & Gail 2, Rosner and Colditz 1994, Tyrer and Cuzick 2004) - Performance statistics (meta analysis of E/O ratio and c-statistic)	• Gail 1 Model : ➢ E/O ratio = 1.13 (95% CI: 0.80 to 1.60) • Gail 2 Model : ➢ E/O ratio = 0.95 (95% CI:0.88 to 1.01) • Rosner & Colditz model ➢ Average E/O ratio = 0.96 (95% CI: 0.92 to 1.02)	• Gail 2 Model: ➢ average C statistic = 0.63 (95% CI: 0.59 to 0.67) • Colditz & Rosner Model : ➢ average C statistic = 0.63 (95% CI: 0.63 to 0.64)

Study author	Design	Model compared	Risk factors	Included studies/ validated population	Outcome	Meta analysis of validation measures	
						Calibration	Discriminatory ability
Anothaisintawee 2012 [14]	Systematic review (observational studies) Evidence searched between 1949 (MEDLINE), 1974 (EMBASE) and Oct 2010 No specific quality assessment		• Variables/ risk factors included : - From 5 to 13 variables (age, age at menarche, age at first live birth, family history of breast cancer, numbers of previous breast biopsy, history of atypical hyperplasia, breast density, nipple aspirate fluid cytology, race, family history of any cancer, history of breast inflammation, body mass index, parity, age at subsequent birth, age at menopause, benign breast disease, hormone replacement therapy, alcohol, serum estradiol)	Included studies : 25 • Development/ Modification of previous prediction model = 18 • Validation of existing prediction models = 7	- Qualitative summary - Study description; Among the 18 studies developing/modifying models; • Study sample: from 550 to 2,404,636 • Outcome - Predicting overall invasive breast cancer (13 studies) - Both non-invasive (carcinoma in situ) and invasive breast cancer (five studies) - Estimating the risk of developing estrogen-type specific breast cancer (two studies) • Data used - from general women (i.e., pre- and post-menopausal (most) - based on postmenopausal data only (two studies) • Validations performed : - Internal validation - 4 studies (Boyle P 2004,Chlebowski RT 2007,Barlow WE 2006, Tice JA 2004) - External validation – 5 models (Gail, CARE, modified Gail, Rosner & Colditz, and modified Rosner & Colditz)	- calibration (most of the models) were between 0.87 to 1.12	- Discrimination: - Median c-statistic = 0.63(0.53-0.66) in settings where models were developed; - Median c-statistic = 0.59(0.56-0.63) in settings where models adopted
Vacek PM 2011 [12]	Prospective cohort study	- Gail model, - Tice modification of the Gail model, - Barlow Model - Vermont model		Cohort of 19,779 Vermont women aged 70 and older who had a mammogram in the Vermont Breast Cancer Surveillance System between 1996 and 2001 Inclusion - Not previously diagnosed with breast cancer, did not decline ti use their data Excluded - Prevalent cancers, women diagnosed with cancer Majority (97.7%) were white, (54.6%) aged between 70-74	➢ Incidence of breast cancer ➢ 821 developed breast cancer (5.0%) ➢ Risk score and breast cancer risk ➢ The risk scores computed from each of the models were significantly associated with breast cancer risk in the Cox regression analyses ($p<0.001$). ➢ However, the regression coefficients (ß's) were all significantly lower than one (ß = 0.31 for the Gail model, ß = 0.26 for the Tice model, ß = 0.50 for the Barlow model and ß= 0.54 for the Vermont model) indicating that the observed increases in relative risk per unit of the risk score were much lower than predicted by the models.	-	➢ Discrimination ➢ C-statistics = 0.54 (95% CI = 0.52–0.56) for the Gail model, ➢ C-statistics = 0.54 (95% CI = 0.51–0.56) for the Tice modification of the Gail model, ➢ C-statistics = 0.55 (95% CI = 0.53–0.58) for a model developed by Barlow ➢ C-statistics = 0.55 (95% CI = 0.53–0.58) for a Vermont model

factors in the models were age, age at first live birth and/or age at subsequent births and family history of breast cancer. Of these, models with independent validations were Colditz 2000, Gail 1 (4 studies) and Gail 2 (12 studies), Rosner and Colditz 1994 and Tyrer and Cuzick 2004. Performance statistics performed demonstrated modest discriminatory ability of Gail 2 Model with average c-statistic of 0.63 (95%CI 0.59 to 0.67) and Colditz & Rosner model with average c-statistic of 0.63 (95%CI 0.63 to 0.64). [15]

Meta analysis of these models showed none of the models were significantly well calibrated with E/O ratio of 1.13 (95%CI 0.80 to 1.60) for Gail 1 Model, 0.95 (95% CI 0.88 to 1.01) for Gail 2 Model and 0.96 (95%CI 0.92 to 1.02) for Rosner & Colditz model. The author concluded there is insufficient information to distinguish the most accurate model or models consistently accurate enough for clinical practice due to variable reporting and few validation studies. Further studies are needed; in particular primary studies that conduct a comparative valuation of all of the models on the same dataset. Further validation studies of existing prediction models, research to identify new risk factors, and to develop model with better predictive ability is needed, alongside clearer reporting and continual validation of new models as they develop. [15]

Anothaisintawee *et al* in 2012 also conducted a systematic review to systematically review the development and performance of existing prediction models to identify the most reliable model and indicate their strength and weakness for guiding future model development.

The review included observational studies (cohort, case control or cross sectional study) with these criteria; considered more than one risk factor in the prediction model simultaneously, had the outcome as breast cancer vs non breast cancer, applied any regression equation (Logistic, Poisson or Cox) to build up prediction model and reported each model 's performance (E/O ratio or c-statistic). Evidence searched was conducted between 1949 from MEDLINE (PubMed) and 1974 from EMBASE (Ovid) until October 2010. No specific quality assessment used. Results were summarised qualitatively and meta-analysis was not undertaken. The review summarised qualitatively 25 studies in which 18 were studies on development/modification of previous prediction model and 7 studies on validation of existing prediction models. The review summarized qualitatively and majority of the studies were predicting overall invasive breast cancer (13 studies) and most of the studies used data from general women (pre- and post-menopausal). Up to 13 risk factors were included in the models. The Gail and Rosner and Colditz were two models that were modified by many scholars. They found calibration of most of the models were between 0.87 to 1.12, with reported poor to fair discrimination (c-statistic ranges between 0.53 to 0.66 in internal validation and 0.56 to 0.63 in external validation). The author concluded that most models yielded relatively poor discrimination in both internal and external validation with fair calibration performance of most models. The author stated a need to develop a reliable risk prediction model for breast cancer in future. [14]

Vacek *et al* in 2011 conducted a cohort study to determine the models usefulness as risk assessment tools for women aged 70 and older, (the original Gail model, the Tice modification of the Gail model, the Barlow Model & the Vermont model), to examine their prediction ability to diagnose breast cancer and to compare model performances. This study involved a cohort of 19,779 Vermont women aged 70 and older who had a mammogram in the Vermont Breast Cancer Surveillance System between 1996 and 2001, who were not previously diagnosed with breast cancer. Majority of subjects were white (97.7%) between 70 to 74 years old (54.6%). This study utilized data from the Vermont Breast Cancer Surveillance System (VBCSS) to assemble a cohort, obtain risk factor information and identify subsequent cases of breast cancer. Invasive and in situ breast cancers diagnosed before January 1, 2010 were identified using both the pathology information in the VBCSS and the diagnosis codes in the Medicare & Medicaid Services claims data. Risk score then computed based on each of the four risk models. They found a 5.0% incidence of breast cancer (821 developed breast cancer). The risk scores computed from each of the models were significantly associated with breast cancer risk in the Cox regression analyses ($p<0.001$). The regression coefficients (ß's) were all significantly lower than one (ß = 0.31 for the Gail model, ß = 0.26 for the Tice model, ß = 0.50 for the Barlow model and ß= 0.54 for the Vermont model) indicating that the observed increases in relative risk per unit of the risk score were much lower than predicted by the models. Comparison of model performances showed the discriminative ability were modest among the four models with c-statistics of 0.54 (95%CI 0.52 to 0.56) for the Gail model, 0.54 (95%CI 0.51 to 0.56) for the Tice

modification of the Gail model, 0.55 (95%CI 0.53 to 0.58) for a model developed by Barlow and 0.55 (95%CI 0.53 to 0.58) for the Vermont model. The author concluded that the models are not useful for assessing risk in women aged 70 and older. The study stated that age-related attenuation of the effects of some risk factors makes the prediction of breast cancer in older women particularly difficult. New risk factors and biomarkers for breast cancer are needed as well as statistical models that allow their effects to vary with age. [12]

6.3 SAFETY RELATED TO BREAST CANCER RISK PREDICTION MODELS

Only one study reported on safety or adverse event or unpleasant consequences related to breast cancer risk prediction model in term of its psychological effect namely anxiety. The other study reported subjective perception of belief in breast cancer risk prediction model. Summary is as illustrated in Table 6.

A randomized controlled trial conducted in Korea by Kye *et al* in 2012 aimed at exploring the psychological effect of health risk appraisal using epidemiological risk factor profile. In this study, participants were recruited through advertisements in the websites between October and November 2009. This study involved 60 eligible women aged between 30 to 48 years old without prior cancer diagnosis (median age were 38 years) who were randomized to either a numerical HRA or the HRA using personal risk factor list after completed a baseline interview. The HRA was done through telephone interview and the participants attended intervention sessions which consist of provision of HRA results, pre- and post-HRA assessment for psychological status, and counselling at one month after the interview. The variables measured in this study related to personal risk factor were height, weight, alcohol, vegetable consumption, past history of benign breast disease, menstruation and oral contraceptive pill (OCP). Risk factors for numerical HRA used the Gail model factors. Anxiety level was measured using Spielberger State Trait Anxiety Inventory YZ (Korean version). The study demonstrated that the mean anxiety level was slightly higher for trait (long term) anxiety with mean (SD) of 44.7(9.2) compared to state (temporary) anxiety with mean(SD) of 42.6(9.2). They also found women who had higher risk status, had an odd of having increased anxiety about five times greater than women who had lower risk status (OR 5.03, 95% CI 1.54 to 16.43, p=0.01). The author concluded that communicating the risk status by individual health risk appraisal service can induce psychological sequelae, especially in women having higher risk status. Hospitals, institutes, or medical schools that are operating or planning to operate the online health risk appraisal service should take side effects such as psychological sequelae into consideration. Further research on cancer risk communication strategies for HRA service are required to explore long term outcome and to evaluate more psychological outcome. [44]

Subjective perception of belief in breast cancer risk prediction model was studied by Scherer *et al* in 2012. They conducted a cross sectional study to determine when and why women chose to disbelieve the personalized breast cancer risk numbers.In this study, women whose medical records indicated that they might be at above average risk of developing breast cancer were recruited from the Henry Ford Health System in Detroit and Group Health in Seattle. The subjects participated in an online program which presented tailored information about individual breast cancer risk after completing BCRAT questions and viewing decision aid on chemoprevention. They were presented with tailored absolute risk (BCRAT score) and estimate of risk reduction with chemoprevention. This study involved 690 women at or above average risk of developing breast cancer as estimated by the BCRAT(score range 1.7-19.1) age range 46 to 74 years with majority of the subjects were white (97.6%). The subjects were asked whether they believe the program was personalized and whether they believe the numbers. The BCRAT score was calculated using these factors: age, ethnicity, personal risk of breast cancer, age at first menses, age at first live birth, number of first degree relatives who have had breast cancer, history of breast biopsies. The study found 18.9% of study subjects were disagree with tailored risk (131 participants disagreed with both risk numbers). Among the documented reasons for disagreement (qualitative assessment) were their family history made them either more or less likely to develop breast cancer than their tailored risk number suggested *(I have aunts that have had cancer)*; the risk number seemed too high or too low (*It just seemed low, the percentage was low compared to my concern*); health habits and lifestyle (*I am in excellent health and I live an active healthy lifestyle) and o*thers such as they thought the calculation failed to account for relevant personal information such as family history, medical history, lifestyle,

Table 6: Evidences concerning with safety/undesirable consequence of breast cancer risk prediction models

Study author	Design	Study population	Outcome
Kye SY 2012	Randomized trial	n= 60 women aged between 30 to 48 years old without prior cancer diagnosis median age : 38 years	• Average anxiety level • Mean(SD) of 44.7(9.2) for trait (long term) anxiety, 42.6(9.2) for state (temporary) anxiety • Predictor for increase in anxiety - Anxiety score increased among women who had higher risk status in 'risk score' group at follow up compared to baseline, with mean(SD) at baseline and follow up were 42.8(8.5) and 47.0(9.6) respectively, however it was not significant - Risk status was the independent predictor of increase of state anxiety after health risk appraisal intervention, after adjusted for age, education, HRA type, numeracy, pre-HRA state anxiety and HRA type. - Women who had higher risk status had an odd of having increased anxiety about 5 times greater than women who had lower risk status (OR 5.03, 95% CI 1.54 to 16.43, p=0.01)
Scherer 2013	Cross sectional	n=690 women - at or above average risk of developing breast cancer as estimated by the Breast Cancer Risk Assessment Tool (BCRAT) (score range 1.7-19.1) - age range 46 to 74 years - 97.6% were white	• Influence of intervention on beliefs that the program was personalized - Women who received "detailed information" were more likely to feel that the program was personalized compared to those receiving "standard information"; with mean(SD) of 4.85(1.39) vs 4.64(1.41), p=0.05 respectively • Disagreement with tailored risk ➢ 131 participants disagreed with both risk numbers (18.9%) ➢ Reasons for disagreement (qualitative assessment) - Their family history made them either more or less likely to develop breast cancer than their tailored risk number suggested (I have aunts that have had cancer) - The risk number seemed too high or too low (It just seemed low, the percentage was low compared to my concern) - Health habits and lifestyle (I am in excellent health and I live an active healthy lifestyle). - Others: They thought the calculation failed to account for relevant personal information such as family history, medical history, lifestyle, hormone replacement therapy or unspecified. Authors' conclusion: The benefits of tailored risk statistics may be attenuated by a tendency for people to be skeptical that these risk estimates apply to them personally. Decision aids may provide risk information that is not accepted by patients, but addressing the patients' personal circumstances may lead to greater acceptance

hormone replacement therapy or unspecified. The author concluded that the benefits of tailored risk statistics may be attenuated by a tendency for people to be skeptical that these risk estimates apply to them personally. Decision aids may provide risk information that is not accepted by patients, but addressing the patients' personal circumstances may lead to greater acceptance.[45]

6.4 COST IMPLICATION

There were no retrievable evidences related to the cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) of health risk assessment or risk prediction model for breast cancer.

In this review, we documented cost implication related to the development of health risk assessment or risk prediction model for breast cancer in Malaysia.

If the cancer risk prediction model used is the Gail model or BCRAT, then no cost shall be involved as the access is free. The BCRAT is available to all who have access to the internet at the URL *http://www.cancer.gov/bcrisktool/*. The source code for the BCRAT is available at *http://www.cancer.gov/bcrisktool/download-source-code.aspx*. However, some programming knowledge is required to implement the tool on a local computer or network. There is no application of the tool that can be downloaded in a "ready to use" state. Additionally, there are no restrictions or fees for using or redistributing the Breast Cancer Risk Assessment source code. However, NCI as the originator of the tool should be acknowledged and if the tool is changed in any way, it should be indicated that the new implementation is adapted from NCI's BCRAT.[46]

However no information is retrieavable if a new model for breast cancer risk prediction tailored to our local population is to be developed. No information available on cost implication involved in validating the newly developed model in our setting.

Validation of the prediction models in the population could use the BRCAPRO and BOADICEA as the main tools specifically for models identifying mutation probability. The most appropriate validation for these tools will be a population-based cohort of patients who have been tested for germ line mutations in BRCA1, BRCA2 and other genes. Estimated potential direct cost of a genetic test is approximately RM4,000 to RM12, 000 per patient with the lowest could be at RM500 per patient. To re-validate this in another cohort would be expensive and it would depend on where (and how much) genetic testing would be provided. At the minimum cost of RM500 per patient, with assumption that 1,000 patients will be in the cohort, the minimal direct cost for validation of this tool would be around RM500, 000. (Communication with cancer researcher)

The cost involved in conducting a prospective cohort validation study which involved setting up cohorts to collect prospective occurrence of cancer can be very costly and the actual cost will depend on number of participants and years of follow up. Estimated potential direct cost implicated in designing, developing, testing and commissioning an available risk prediction model into a health risk assessment module is given approximately at RM75,000. (Communication with Programme Officer, Health Education Division). This amount encompasses sum of the relevant activities, in which the details are as listed below:

Services:

- System development (1 lot) RM50,000
- Installation and configuration (1 lot) RM5,000
- Training and Training of Trainer (1 lot) RM15,000
- Documentation (1 lot) RM1,000

Software:

- Portal Management Application and Content Management System (CMS) (1 lot) RM4,000

6.5 ORGANIZATIONAL

The goal of of breast cancer risk assessment is to personalize management strategies for all women with the aim to increase survival in high risk women and to decrease cost and complication in low risk women. Estimated risk yielded by prediction models enables the stratification of individuals or groups of individuals by these risks. High risk women according to Gail is women with five year risk of at least 1.67% and use of tamoxifen is associated with 49% reduction in invasive breast cancer. Women at low risk may be best served with standard mammography and health maintenance recommendations.[19] Intervention according to risk group has been addressed by several guidelines. The American Cancer Society (ACS)[47] recommends mammography screening for average risk women before the age of 40, and the US Preventive Service Task Force[48] recommended screening to be initiated at the age of 50 for average risk women. In 2006, ACS recommended annual MRI screening be used as an adjunct to mammography screening among women with known BRCA mutation, first degree relatives of BRCA carriers who have not been tested and women with lifetime risk of breast cancer of 20 to 25% or greater as defined by models that are largely dependent on complete multigenerational family histories on the maternal and paternal side such as BRCAPRO, Claus and Tyrer-Cuzick models. The Gail model was not recommended for risk assessment for MRI screening in the ACS Guideline because it does not incorporate family history of breast or ovarian cancer in second degree relatives.[49]

NICE in its guideline on Familial Breast Cancer (2013) stated that when available in secondary care, use of a carrier probability calculation method with demonstrated acceptable performance (calibration and discrimination) such as BOADICEA and the Manchester Scoring System as well as family history is recommended to determine who should be offered referral to specialist genetic clinic. Meanwhile in a specialist genetic clinic setting, NICE guideline recommended similarly the use of a carrier probability calculation method with demonstrated acceptable performance (calibration and discrimination) such as BOADICEA and the Manchaster Scoring System to assess probability of a BRCA1 or 2 mutation. Cancer risk communication should be offered as a personal risk estimate and uncertainties about the estimate should also be informed.[50]

Computerized risk estimate using Gail model are available on the National Cancer Institute (NCI) website. The NCI website on Gail model is accessed 20,000 to 30,000 times per month.[26] Other computerized risk estimates such as Claus and BRCAPRO models are available via the CancerGene program which needs internet access.[25] Computerized risk estimate using any model requires computer literate patient and other computerized risk estimates available in the website needs internet access.

Prediction modelling research may distinguish three major phases namely developing and internally validating a prediction model; testing, adjusting or updating the model for other individuals (external validation); and assessing its impact on therapeutic management and patient outcomes.[24] The conduct of this specialized research needs a dedicated team and expertise.

The goal of screening is to detect pre-symptomatic cancer early enough for effective treatment. Cancer risk assessment aims to characterize individuals' chance of developing cancer over a specified period to guide decision making about future screening behaviour and adoption of risk reduction strategies. Among ethical issues arised was psychological harms resulted from being labelled 'at risk', and additional diagnostic procedure can artificially increase sense of risk.The 'at risk' label also has implication for future health care cost. Theoretically increase psychological distress from risk labelling may contribute to future non-adherence to screening and risk reduction recommendations. Uncertainty about risk and benefit of prevention option affect decision making in that depending upon their risk category patient may face difficult decision about managing or reducing risk. In some cases, the result may present women with information that contrast with previously held belief, requiring a period of acceptance and adjustment prior to consideration of preventive options.[17]

Breast cancer risk assessment and available intervention for prevention and early detection among women at increased risk seem to be underutilized in the US population. Only 48% had ordered or referred a patient for BRCA1/2 testing and only 18% had software programs to calculate breast cancer risk. [51] Breast cancer risk assessment, genetic testing and other interventions are utilized even less by racial and ethnic minority women, low income and uninsured women, likely contributing to higher rates of late stage diagnosis. [52] The lack of a single, simple and accessible data collection tool that can produce risk estimates used in various guidelines might hinder the widespread adoption of breast cancer risk assessment in primary care settings. As scientific knowledge improves on how to identifity women at increased risk of breast cancer, tools for risk assessment need to be updated, adapted and used to benefit largest number of women.[50]

Each of the models is derived using different data, study design and risk factors. Steps that may be used in future design and validation of new breast cancer risk prediction model were utilizing material available from either placebo arms of cohort or prior randomized, controlled trial or ongoing prospective observational studies where patients had been followed for a period up to 15 years after data collection to allow both univariate and multivariate analysis of risk factors. Nested case control study would provide the most efficient study design. Subsequent step will involve retrospective validation study and prospective validation study. Analysis of existing data offer possibility to identify risk factors that could be used to develop better risk prediction model.[53] Improvements in the models require revalidation processes. Assessment of individual risk can be undertaken using a variety of models. Models are imperfect even within the fairly developed field of breast cancer risk assessment. Uncertainties associated with risk estimates should be addressed and informed particularly when clinical decision has serious consequences.[25]

There are a number of models available to predict breast cancer risks. The most appropriate validation for it will be a longitudinal study that is following a population attending screening and determining the sensitivity and specificity of the tool in predicting the individuals who develop breast cancer. This is quite difficult to be carried out in Malaysia at the moment since there is no population-based screening programme and there are few (if any) large enough longitudinal cohorts examining breast cancer. (Communication with breast cancer researcher)

Additional practical concern is the issue of insurability of women found to be at high risk of breast cancer. This matter has risen for the measurement of BRCA1 and BRCA2 genes in women. Future legislation may be developed to protect those found to be at high risk.[54]

The lack of a single, simple and accessible data collection tool that can produce risk estimatesmight hinder the adoption of breast cancer risk assessment in healthcare setting. As scientific knowledge of how to identify premalignant and malignant disease earlier in the disease improves, tool for risk assessment need to be updated, adapted and used to benefit the largest number of women. In addition to creating tools that will allow clinicians to generate risk estimates for multiple purposes efforts are needed to ensure all women have access to those potentially life saving interventions.[49]

7 DISCUSSION

There was neither HTA report nor guidelines on health risk assessment or risk prediction model for the detection of breast cancer.

The systematic review found a total of seven breast cancer risk prediction models containing risk factors without genetic component. Some have been independently validated, most notably the Gail model with four validations (by Schonfeld 2010,[33] Chay 2012,[37] Banegas 2012[36] and Vacek 2011[12]).

We have attempted to compare the model performances qualitatively according to the encountered model.

For Gail model, there were limited fair level of evidence from the four studies (Schonfeld 2010, Chay 2012, Banegas 2012 and Vacek 2011). Two studies found underestimation of breast cancer cases by 13 to 18% using the Gail model, however upgrading/recalibration of the model demonstrated it was well calibrated as the E/O improved to 1.03[33] and underestimated breast cancer cases with O/E of 1.08.[36] Another study found the Gail model overestimated breast cancer risk among Singaporean women aged 50 to 64.[37] The studies overall discriminative accuracy was modest with c-statistic ranges between 0.54 to 0.67.[33,6,37,12] The validation population was mostly from US post-menopausal white women aged 50 to 79 years Hispanics and non-hispanic [33,36] and post menopausal Vermont women more than 70 years.[12]

For CARE model, performance statistics were reported by one study [13] and they found underestimation of breast cancer cases by 12% using the CARE model with modest discriminative accuracy with c-statistic of 0.57 (overall), 0.59 (ER+breast cancer) and 0.54 (ER-breast cancer).The validation population was African-American women aged range from 30 to 69 years.

For other models, four studies reported development of new risk prediction model and subsequent validation which has been conducted in Italy[40] the US[41,42] and Thailand.[43] The validated population varies from Italian women aged 20 to 74 years,[40] non-Hispanic white women with median age of 52 years [41] and African American women aged between 30 and 69 years (mean age 39.9).[42] Two studies used different study cohort for model development and subsequent validation [40,41] whereas Boggs[42] used different cohort from similar study for model development and validation. Petracci[40] included non-modifiable and modifiable risk factors (eight factors) in the new model, Pfeiffer[41] developed model that share many hormonal and epidemiological risk factors; breast, endometrial and ovarian cancer in the US (nine factors), and Boggs[42] includes nine risk factors in the BWHS model. Performance statistics reported by the three studies and they found their model were well calibrated with overall E/O ratio of 1.10, [40] 1.00 [41] and 0.96[42] for prediction of breast cancer cases with modest discriminative accuracy (c-statistic of 0.62,[40] 0.58[41] and 0.59[42])

For the three studies studies reporting comparison of few risk prediction models, performance statistics demonstrated the models were well calibrated with E/O ratio ranging from 0.87 to 1.12 from Anothaisintawee 2012); 1.13 (Gail 1 model), 0.95 (Gail 2 model) and 0.96 (Rosner & Colditz model) in the meta analysis performed by Meads 2012 for prediction of breast cancer cases. Modest discriminative accuracy were demonstrated with c-statistic of 0.54-0.55, [12] 0.63 [15] and 0.59 to 0.62.[14]

With regard to safety, only one study with small study subjects reported on safety related to breast cancer risk prediction model in term of its psychological effect namely anxiety. They found women who had higher risk status had an odd of having increased anxiety about five times greater than women who had lower risk status (OR 5.03).[44] The other study reported subjective perception of belief in breast cancer risk prediction model.[45]

There were two local studies published on validation of breast cancer prediction model; however these studies evaluate models predicting mutation probability using BOADICEA and Manchaster Scoring System conducted in Malaysia.[54,55] These two studies demonstrated that the two models performed less well in our population in that it will underestimate the probability of mutation carriers. Therefore the use a lower cut-off may be considered in circumstances where decision to apply on our population been made.

A local study by Thirtagiri *et al* in 2007 evaluated BRCA1 and BRCA2 mutation and compared the accuracy of the BOADICEA and MSS. The study involved 187 breast cancer patients with either early onset breast cancer (age less than 40 years) or a personal and/or family history of breast or ovarian cancer recruited between 2003 and 2007 in University Malaya Medical Centre, Kuala Lumpur where full sequencing of BRCA1 and BRCA2 were carried out. The two prediction algorithms were evaluated. Mean age of diagnosis of all women was 43.8 years (range 22 to 78 years). The overall performance in discriminating between those with and without mutation were moderate as demonstrated by AUC of 0.74 (95%CI 0.67 to 0.81) and 0.82 (95%CI 0.75 to 0.88) for BRCA1, and 0.82 (95%CI 0.75 to 0.88) and 0.56 (95%CI 0.48 to 0.64) for BRCA2, for MSS and BOADICEA respectively.
The AUC for combined BRCA1/2 was better for MSS compared to BOADICEA with AUC of 0.80 (95%CI 0.72 to 0.86) and 0.73 (95%CI 0.65 to 0.80) respectively. They found both models underestimated the number of mutation carriers in the cohort. They also found the score of greater than 15 for combined BRCA1/2 in MSS as an optimal threshold with sensitivity of 72%, specificity of 74%, PPV of 37% and NPV of 93%. They stated that testing could be offered to individuals with personal or family history of cancer if they have MSS score of 15 or above. Lower threshold could be used when resource is available.[54]

Another local study by Hassan N in 2014 also evaluated these two model performances among 1692 incident and prevalent breast cancer cases recruited to the Malaysian Breast Cancer Genetic Study between 2003 and 2012, of whom 665 with early age of onset and/or family history of breast cancer were screened for BRCA1/2 mutation. For 577 subjects where pathologic data were available the added values of ER negativity on the models were evaluated. They found at 10% threshold, AUC was similar for both models and higher for BRCA1 compared to BRCA2 (0.73 and 0.73 for BRCA1, and 066 and 0.64 for BRCA2 in BOADICEA and MMS respectively).The addition of ER status improved the AUC for BRCA1 from 0.73 to 0.81 in BOADICEA and to 0.79 in MMS. The addition of other pathologic features, pr and HER2 did not improve BRCA1 accuracy.[55]

Among the use of breast cancer risk prediction model is its use in stratifying risk among women hence subsequent intervention could be targeted for. Currently several risk stratification exist in our setting aiming at early detection of breast cancer. The Malaysia National Population and Family Development Board or better known as Lembaga Penduduk dan Pembangunan Keluarga Negara (LPPKN) categorise women as high risk if she has any one of these factors; family history of breast cancer, previous history of atypia on breast biopsy or previous history of breast or ovarian cancer or currently on hormone replacement therapy (criteria A), or any two of these factors; family history of breast cancer, nulliparous or women with first childbirth after 30 years, menarche before 12 years old, menopause after 55 years old or body mass index more than 30 (criteria B).[56] This is in tandem with the recent Malaysian Guideline on National Breast Cancer Early Detection Programme indicating mammogram for high risk women (as criteria above) and those above 40 years old.[57] The Malaysian CPG on Management of Breast Cancer on the other hand stratifies risk factor as low (RR between 1.0 and 1.4), moderate (RR between 1.5 and 2.0) and high (RR of more than 2.0).[21] Currently, Malaysia is practicing opportunistic screening for breast cancer as its screening policy, targeting those women attending the wellness clinic, maternal and child health clinics and women attending outpatient clinic in MOH facilities. This involve three main activities for breast cancer screening namely breast self awareness, clinical breast examination and mammography

screening.[7]The prevalence of overall breast examination in Malaysia was 70.3% in the third National Health Morbidity Survey;[57] with highest for Breast Self Examination (57.1%), Clinical Breast Examination (51.7%) and mammogram (7.5%). To further promote greater awareness among women to do mammogram screening for early detection of breast cancer, the Ministry of Women, Family and Community Development provided a RM50 subsidy for every mammogram done in private clinics and hospitals registered with LPPKN for those who meet the eligible criteria which includes high risk women with household income below RM5, 000.[7] None of the available guidelines did document on risk assessment or strafication using any of the existing breast cancer risk prediction model.

Though risk assessment tools can place breast cancer risk in context for women at all risk levels and allow for more focused management recommendations on the basis of the risk, ultimately risk assessment is only an estimate.[19] Nevertheless, people should be offered a personal risk estimate for their cancer risk and carrier probability as well as uncertainties of the information.[51] Risk assessment tools can place breast cancer risk in context for women at all risk levels and allow focused management on the basis of this risk.[19] It is important to note that the risk factors and breast cancer rates in Malaysia are different than the risks and rates used in the existing model such as Gail, which are not comparable. Therefore, any model would have to be recalibrated to Malaysian facts of breast cancer to make it applicable. Cancer risk prediction model needs continual validation to give meaningful risk estimate and ensure its applicability in the setting it will be used. The complexity to develop and subsequently validate any breast cancer risk prediction model specifically models without genetic component is reflected in the data required and availability of dedicated research expertise that is required to come out with a model with consistently outstanding performance.

7.1 LIMITATIONS

The systematic review of literature has several limitations. There were limited validation studies on non-caucasian study population specifically from Asian region on breast cancer risk prediction models without genetic risk factor. A sizable study in Singapore showed gross overestimation of risk. Generalizability of the retrieved evidence is certainly restricted. There is currently no quality assessment tool or standard assessment of risk of bias for risk prediction modelling and validation studies. Altman has recently published a list of criteria nevertheless it was for prognostic modelling study though some factors relevant to prediction models described include components of study design, study population, sample size, completeness of data, variables and presentation.[58] Systematic review of risk prediction studies is rare and difficult. There is also currently no standard reporting for risk prediction studies such as CONSORT guidelines for RCT. Therefore, there are variable reporting style by authors and single study reporting multiple model performances simultaneously are rare. No studies on economic evaluations of risk prediction models retrieved. Although there was no restriction in language during the search but only English full text articles were included in the report.

8 CONCLUSION

There was sufficient good level of retrievable evidence for breast cancer risk prediction model. There were six models identified for predicting breast cancer risk with Gail model is the most widely studied and validated model in various population. The Gail model appeared to have good calibration in validation studies done cross-population, however there is considerable heterogeneity across studies. This model showed moderate performance in terms of discriminatory ability.

For other risk prediction models, there was insufficient good level of retrievable evidence with only one study each of those other models (CARE model, model by Petracci, model by Pfeiffer, Vermont model, model by Anothaisintawee and BWHS model). The models were well calibrated in the validated population however appeared modest in discriminating woman who will be having breast cancer, than for those who will not in the study population.

There was insufficient evidence on the safety related to cancer risk prediction models for the detection of women who will develop breast cancer. Although there was minor adverse psychological sequale reported among high risk women who demonstrated to be five times more likely to have increased anxiety, it may be considered relatively safe.

There was no retrievable evidence on economic evaluation of health risk assessment or risk prediction model for breast cancer, or cost implication involved in developing a new risk prediction model without genetic component for breast cancer retrieved. The cost involved in validating a model by a prospective cohort validation study could be very costly depending on the number of study participants and years of follow up. However potential direct cost implicated to the designing, developing, testing and commissioning of available one breast cancer prediction model was given approximately at RM75,000.

Cancer risk prediction models need continual validation to give meaningful risk estimate and to ensure its applicability in the setting it will be used. The complexity to develop and subsequently validate any breast cancer risk prediction model specifically models without genetic component is reflected in the necessary local data required and availability of dedicated research expertise to create a robust model with consistent performance.

9 RECOMMENDATION

Although the above review showed that the Gail model had good calibration and moderate discriminative ability, it is not suitable to be introduced as one of the strategy in the prevention of breast cancer under the Malaysian National Cancer Control Programme yet as it needs further validation to develop a well-fitted model that would have better predictive ability tailored to Malaysian population. In addition, this model needs continual validation to determine the consistency of its performance.

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Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2

PTK – FM – 02

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
HEALTH RISK ASSESSMENT (HRA) MODULE FOR BREAST CANCER

1. BACKGROUND INFORMATION

Breast cancer is the second most commonly diagnosed cancer worldwide. Among women worldwide, it is the most commonly diagnosed cancer which represents 1 in 4 of all cancers and the most common cause of cancer death (522,000 deaths in 2012). The incidence is rising with 1.7 million women were diagnosed with breast cancer in 2012 and mortality has increased by 14% since the 2008 estimates.[1] Incidence rates is higher in more developed region, however mortality is much higher in less developed countries due to lack of early detection and access to treatment facilities.[1] In Malaysia, the National Cancer Registry (NCR) 2007 reported that breast cancer was the most commonly diagnosed cancer in women with overall age standardized incidence rate (ASR) of 29.1 per 100,000 population.[2] It was however higher than incidence in other developing countries with ASR of 20 per 100,000 population.[3] About 30 to 40% of Malaysian women presented at a later stage of breast cancer (stage III and IV) compared to other counterparts in the developing countries.[4] The increase has been said related to changes in dietary and reproductive pattern, urbanization and ageing population.[5,6] Hence, affordable and effective approaches in cancer control are needed for early detection, diagnosis and treatment of breast cancer particularly in the less developed countries.[1]

The widely quoted general population lifetime risk of having breast cancer is one in eight to one in 12, and the risk in any given decade was never greater than one in 30. The proportion of all female deaths due to breast cancer per decade is never greater than 20% with the greatest proportion from the middle age group (35 to 55 years).[7] For familial breast cancer, approximately five to ten percent of cases occur in women with Hereditary Breast Ovarian Cancer Syndrome (HBOC), which has mutation in BRCA1 and BRCA2 genes.[8] Women with BRCA1 and BRCA2 mutation have a 50% to 80% lifetime risk of breast cancer. These women also have a 40% to 60% lifetime risk of having contralateral breast cancer.[8] The organized breast cancer screening programmes using mammography has been well established in Europe and Northern America resulting in improved five year survival rate, as high as 89%.[9] Providing breast cancer screening programme using mammography to every woman in most developing countries is not feasible, thus identifying women with relatively higher risk of developing breast cancer is a promising alternative.[10]

Prediction model of breast cancer is a mathematical equation designed to quantify the risk an individual woman would develop breast cancer in a defined period.[10] Reliably accurate prediction models can inform future disease burdens, health policies and individual decisions, as well as to counsel those at risk and determine eligibility for prospective prevention trial.[11,12] All known breast cancer risk factors need to be assessed to evaluate its risk over time as accurately as possible including family history, hormonal and reproductive risk factors such as the use of exogenous hormones (estrogen and progesterone), endogenous hormonal factors (ages at menarche, menopause and first childbirth), and environmental risks such as alcohol intake, diet, exercise, obesity, as well as increase breast density.[13] 21% of all breast cancer deaths worldwide are attributable to alcohol use, overweight and obesity, and physical inactivity.[14] Models containing modifiable risk factors are of particular interest to patients and those involved in reducing population incidence rates.[11]

Two main types of cancer risk assessment models are; model aimed at assessing breast cancer risk over time or to predict probability of being diagnosed with a cancer; and the other aimed at assessing mutation probability of an individual or carrying a gene mutation that predisposes to a particular cancer.[5] Some available models are the Gail model, Claus model, Cuzick-Tyrer model, Breast and ovarian analysis of disease incidence and carrier estimation algorithm (BOADICEA), BRCAPRO, Couch, Shattuck Eiden, IBIS models and Manchaster scoring.[5] The Gail model provides 5-year and lifetime risk estimate of having breast cancer and is accessible on the internet. The Claus model is useful for assessing breast cancer risk with a family history, similarly with BRCAPRO, BOADICEA and IBIS models which can produce both mutation probabilities and breast and ovarian cancer estimates.[12]

Identification of individual with a suspected heritable cancer syndrome (HBOC) has implications for evaluation and application of risk reducing options such as chemoprevention and prophylactic surgery.[15] These underline the need for risk prediction model for breast cancer, not only to predict which women will develop the disease, but also to apply appropriate intervention and lifestyle measures in order to prevent the disease.[5] Better understanding of these model performances, including the strengths and limitations is needed before applying them in clinical practice.

In Malaysia, currently there is no risk assessment model/health risk assessment (HRA) for breast cancer in predicting probability of being diagnosed with a cancer and probability of carrying a gene mutation that predisposes individual to a particular cancer in existing cancer control approaches. Hence, this review was requested by a Senior Principal Assistant Director, Health Education Division, Ministry of Health to review the evidence on breast cancer risk assessment model as a tool in enhancing early detection and diagnosis of breast cancer, towards facilitating the implementation of affordable and effective cancer control approach in the country.

2 POLICY QUESTION

i. In Ministry of Health, should a health risk assessment (HRA) model for breast cancer be introduced as one of the strategies in the prevention of breast cancer under the Malaysia National Cancer Control Programme?
ii. If HRA model for breast cancer be introduced, which HRA for model breast cancer should be adopted in Malaysia?

2.1 OBJECTIVES

i. To assess the effectiveness, predictive accuracy, strengths and weaknesses of retrieved breast cancer risk assessment/prediction models among women
ii. To assess the safety, organizational and ethical issues, and economic implications related to risk assessment/prediction models for breast cancer among women

2.2 RESEARCH QUESTIONS

i. What are the effectiveness, predictive accuracy, strengths and weaknesses of retrieved breast cancer risk assessment/prediction models among women
ii. What are the safety, organizational and ethical issues and economic implications related to the use of breast cancer risk assessment/prediction models among women

3 METHODS

Systematic reviews following the principles used by Cochrane Collaboration will be conducted to achieve the objectives of this review

3.1 SEARCH STRATEGY

i. Electronic database will be searched for published literatures pertaining to breast cancer risk assessment/prediction models among women, its performance, accuracy, benefits, strengths and weaknesses, implications
ii. The following databases will be used to carry out the search of evidence:- MEDLINE, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), PubMed, Horizon Scanning, INAHTA Database, HTA database and FDA database.
iii. Additional literatures will be identified from the references of the relevant articles.
iv. Expert in this area will be contacted when necessary to get further information.
v. Handsearching of evidence will be conducted if necessary to find unpublished evidence
vi. General search engine might be used to get additional web-based information if there is no retrievable evidence from the scientific databases.
vii. There will be no limitation applied in the search such as year and language.
viii. The detail of the search strategy will be presented in the appendix.

3.2 INCLUSION AND EXCLUSION CRITERIA

3.2.1 INCLUSION CRITERIA

- Population : Adult woman more than 18 years old
- Intervention : Breast cancer risk assessment/ risk prediction model/ Health Risk Assessment models involving single or multiple risk factors
- Comparators : -
- Outcome :

  i. Performance of available breast cancer risk prediction models in terms of its predictive accuracy - sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), calibration as measured by expected/observed ratio, discrimination as measured by AUC or c-statistic

  ii. Strengths and weaknesses of retrieved risk prediction model (qualitative)

  iii. Effectiveness/benefit of the breast cancer risk assessment/predictive model related to patient outcome as measured by detection rate, acceptance, awareness, receptiveness

  iv. Organizational (operational, training, resources), ethical, legal and economic implication

- Study design : No restriction of study type. HTA report, Systematic Review, Randomised Controlled Trial (RCT), Non Randomised Controlled Trial, diagnostic accuracy studies, Observational Studies (Cohort study, Case Control study, Cross Sectional study with gold standard), and economic evaluation studies such as cost-effectiveness / cost-utility analysis.
- Full text articles published in English.

3.2.2 EXCLUSION CRITERIA

- Breast cancer prognostic models will not be included in this review
- Studies with these design will be excluded:
  i. Animal study
  ii. Narrative review
  iii. Laboratory study

- Studies on risk assessment/ risk prediction/ health risk assessment models for breast cancer with any genetic component as risk factor
- Studies in women who already had breast cancer when recruited or studies involving male subjects
- Non English full text article.

3.3 DATA EXTRACTION STRATEGY

Data will be extracted by a reviewer and checked by a second reviewer using a pre-tested data extraction form. Disagreements will be resolved through discussion. A third person, whose decision is final will be consulted when disagreements persists after discussion.

3.4 QUALITY ASSESSMENT STRATEGY/ASSESMENT OF RISK OF BIAS

The validity of the eligible studies will be assessed by two reviewers independently using Critical Appraisal Skill Programs checklists criteria according to the study designs.
The quality of the evidence will be graded according to US/Canadian Preventive Services Task Force Grading System.

3.5 METHODS OF ANALYSIS/SYNTHESIS

Data will be summarized in evidence table. If the data is suitable for statistical pooling, meta-analyses of the main outcomes will be performed. Otherwise data for the outcomes will be reported narratively.

4. REPORT WRITING

Appendix 3

Search strategy

MEDLINE ® In progress and other Non-Indexed Citations and Ovid Medline® 1946 to present.

1	human mammary neoplasm*.tw.
2	neoplasm* human mammary.tw.
3	breast adj1 neoplasm*.tw.
4	cancer of the breast.tw.
5	cancer of breast.tw
6	mammary carcinoma* human.tw.
7	mammary neoplasm* human.tw.
8	carcinoma* human mammary.tw.
9	human mammary carcinoma*.tw.
10	breast adj1 tumor*.tw.
11	malignant neoplasm of breast.tw.
12	breast adj1 neoplasm*.tw.
13	mammary cancer.tw.
14	malignant tumor of breast.tw.
15	breast adj1 cancer.tw.
16	breast carcinoma.tw.
17	or/1-16
18	assessment* risk.tw.
19	benefit-risk adj1 assessment*.tw.
20	benefit risk assessment.tw.
21	benefit-risk assessment.tw.
22	risk benefit assessment.tw.
23	risk-benefit adj1 assessment*.tw.
24	risks and benefits.tw.
25	risk assessment*.tw.
26	benefits and risks.tw.
27	health risk assessment model.tw.
28	risk prediction.tw.
29	prediction model.tw
30	or/18-29
31	Female.tw.
32	wom*n.tw.
33	wom* group*.tw.
34	group wom*.tw.
35	Adult*.tw.
36	or/31-35
37	17 and 30 and 36

EBM Reviews - Cochrane Database of Systematic Reviews

1	human mammary neoplasm*.tw.
2	neoplasm* human mammary.tw.
3	breast adj1 neoplasm*.tw.
4	cancer of the breast.tw.
5	cancer of breast.tw
6	mammary carcinoma* human.tw.
7	mammary neoplasm* human.tw.
8	carcinoma* human mammary.tw.
9	human mammary carcinoma*.tw.
10	breast adj1 tumor*.tw.
11	malignant neoplasm of breast.tw.
12	breast adj1 neoplasm*.tw.
13	mammary cancer.tw.
14	malignant tumor of breast.tw.
15	breast adj1 cancer.tw.
16	breast carcinoma.tw.
17	or/1-16
18	assessment* risk.tw.
19	benefit-risk adj1 assessment*.tw.
20	benefit risk assessment.tw.
21	benefit-risk assessment.tw.
22	risk benefit assessment.tw.
23	risk-benefit adj1 assessment*.tw.
24	risks and benefits.tw.
25	risk assessment*.tw.
26	benefits and risks.tw.
27	health risk assessment model.tw.
28	risk prediction.tw.
29	prediction model.tw
30	or/18-29
31	Female.tw.
32	wom*n.tw.
33	wom* group*.tw.
34	group wom*.tw.
35	Adult*.tw.
36	or/31-35
37	17 and 30 and 36

Pubmed

("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("human"[All Fields] AND "mammary"[All Fields] AND "neoplasm"[All Fields])) AND ("humans"[MeSH Terms] OR "humans"[All Fields] OR "human"[All Fields]) AND ("mammary glands, human"[MeSH Terms] OR ("mammary"[All Fields] AND "glands"[All Fields] AND "human"[All Fields]) OR "human mammary glands"[All Fields] OR "mammary"[All Fields] OR "breast"[MeSH Terms] OR "breast"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "neoplasm"[All Fields]) OR "breast neoplasm"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("cancer"[All Fields] AND "breast"[All Fields]) OR "cancer of breast"[All Fields]) AND ("mammary glands, human"[MeSH Terms] OR ("mammary"[All Fields] AND 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AND "assessment"[All Fields]) OR "risk assessment"[All Fields]) AND model[All Fields] AND ("risk"[MeSH Terms] OR "risk"[All Fields]) AND prediction[All Fields] AND prediction[All Fields] AND model.[All Fields]

Appendix 4

CRITICAL APPRAISAL SKILLED PROGRAMME CHECKLIST

SYSTEMATIC REVIEW

CRITERIA ASSESSED			
Selection of studies (relevant studies included?)	Yes	No	Can't tell
Assessment of quality of included studies?	Yes	No	Can't tell
If the results of the review have been combined, is it reasonable to do so? (heterogeneity)	Yes	No	Can't tell

RCT

CRITERIA ASSESSED			
Assignment of patients randomised?	Yes	No	Can't tell
Allocation concealment?	Yes	No	Can't tell
Patients, health workers, study personnel blind to treatment?	Yes	No	Can't tell
Intention to treat analysis?	Yes	No	Can't tell
Explanation of loss to follow-up?	Yes	No	Can't tell

Appendix 5

EVIDENCE TABLE : **EFFECTIVENESS (ACCURACY)**

QUESTION : **IS HEALTH RISK ASSESSMENT (HRA)/CANCER RISK ASSESSMENT/RISK PREDICTION MODELS FOR BREAST CANCER EFFECTIVE (ACCURATE) FOR THE DETECTION OF BREAST CANCER PATIENTS?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Meads C, Ahmed I, Riley RD. A systematic review of breast cancer incidence risk prediction models with meta analysis of their performance. Breast Cancer Res Treat 2012.132;365-377.	Systematic review (no restriction on study type) Objective: To identify and evaluate the performance of prediction models for breast cancer that contain modifiable factors Included : Any articles proposing or validating a breast cancer prediction model in a general female population using multiple variables, at least one of which was a modifiable risk factor, no restriction on study type. Exclusion: ➢ Breast cancer in men, ➢ Women who already had breast cancer or benign breast pathology when recruited ➢ Studies in high risk groups of women, such as with specific genetic mutations or who have close family relatives with breast cancer ➢ Models investigating single risk factor results such as mammography, assessing genetic risk factors only, assessing invasive techniques such as biopsies only, assessing family history of breast or ovarian cancer only and predicting genetic mutations rather than cancer ➢ Screening and early detection studies ➢ Models published more than 25 years previously (i.e. before 1985) Sensitive search in databases including MEDLINE and EMBASE was conducted between November 2009 and June 2010. No specific quality assessment checklist used. Results were summarised qualitatively, and where possible meta-analysis of model performance statistics was undertaken.	II-2	Articles included in this systematic review = 26 • Development of a new risk prediction model only = 6 • Both development of a new model and validation of one or more models = 11 • Independent validation of one or more models = 9	-	-	-	**Description of studies:** ➢ Studies describing a new risk prediction model ➢ 17 studies developing a new risk prediction model were found containing at least one modifiable risk factor, that aimed to predict breast cancer in populations and in individual women ➢ The modifiable risk factors that were included in one or more models - alcohol consumption, breast biopsy number, BMI or weight, condom use, exogenous hormone use (HRT, contraceptive pill), and physical activity. ➢ The most commonly included risk factors in the models -age, age at first live birth and/or age at subsequent births and family history of breast cancer ➢ The risk factors only included in one model - condom use, family history of any cancer, physical activity and reproductive age period ➢ Validations of prediction models ➢ Models listed with independent validations - Colditz 2000, Gail 1 (4 articles) and Gail 2 (12 articles), Rosner and Colditz 1994 and Tyrer and Cuzick 2004 ➢ Performance statistics: ➢ Meta analysis of c-statistic - Gail 2 Model: - average C statistic = 0.63 (95% CI: 0.59 to 0.67) - Colditz & Rosner Model : - average C statistic = 0.63 (95% CI: 0.63 to 0.64) • Meta analysis of expected/observed (E/O) ratio: - Gail 1 Model : - average E/O ratio was 1.13 (95% CI: 0.80 to 1.60) - Gail 2 Model : - average E/O ratio was 0.95 (95% CI:0.88 to 1.01) - Rosner & Colditz : average E/O ratio was 0.96 (95% CI:0.92 to 1.02) **The author concluded:** There is insufficient information to distinguish the most accurate model or models consistently accurate enough for clinical practice due to variable reporting and few validation studies. Further studies are needed; in particular primary studies that conduct a comparative valuation of all of the models on the same dataset. Further validation studies of existing prediction models, research to identify new risk factors, and to develop model with better predictive ability is needed, alongside clearer reporting and continual validation of new models as they develop.	Meta analysis done, no sample size and quality assessment

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Anothaisintawee T,Teerawattananon Y, Wiratkapun C et al. Risk prediction models of breast cancer: a systematic review of model performances. Breast Cancer ResTreat.2012;133; 1-10	Systematic review (observational studies) Objective: To systematically review the development and performance of existing prediction models to identify the most reliable model and indicate their strength and weakness for guiding future model development Method Included : Observational studies (cohort, case control or cross sectional study) published in English meet these criteria; - Considered more than one risk factor in the prediction model simultaneously, - had the outcome as breast cancer vs non breast cancer, - applied any regression equation(Logistic, Poisson or Cox)to build up prediction model, - reported each model 's performance (E/O ratio or c-statistic). The method predictive ability, calibration and discrimination were extracted, using E/O ratio and ROC analysis or the concordance statistic respectively. MEDLINE (PubMed) from 1949 and EMBASE (Ovid) were searched from 1974 until October 2010.	II-2	Papers included in this systematic review = 25 • Development/Modification of previous prediction model = 18 • Validation of existing prediction models = 7	-	-	-	**Study description;** Among the 18 studies developing/modifying models; • Study sample: from 550 to 2,404,636 • Outcome - Predicting overall invasive breast cancer (13 studies) - Both non-invasive (carcinoma in situ) and invasive breast cancer (five studies) - Estimating the risk of developing estrogen- type specific breast cancer (two studies) • Data used - from general women (i.e., pre- and post-menopausal (most) - based on postmenopausal data only (two studies) • Validations performed : - Internal validation - 4 studies (Boyle P 2004,Chlebowski RT 2007,Barlow WE 2006, Tice JA 2004) - External validation – 5 models (Gail, CARE, modified Gail, Rosner & Colditz, and modified Rosner & Colditz) • Variables/risk factors included : - From 5 to 13 variables (age, age at menarche, age at first live birth, family history of breast cancer, numbers of previous breast biopsy, history of atypical hyperplasia, breast density, nipple aspirate fluid cytology, race, family history of any cancer, history of breast inflammation, body mass index, parity, age at subsequent birth, age at menopause, benign breast disease, hormone replacement therapy, alcohol, serum estradiol) **Model performance:** ➢ Discrimination: - Median c-statistic = 0.63(0.53-0.66) in settings where models were developed; - Median c-statistic = 0.59(0.56-0.63) in settings where models adopted. Author conclusion: Most models yielded relatively poor discrimination in both internal and external validation. There is still a need to develop a reliable risk prediction model for breast cancer in future.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Adams-Campbell LL Makambi KH, Frederick WWI et al. Breast Cancer Risk Assessments Comparing Gail and CARE Models in African-American Women. Breast J. 2009; 15(0 1): S72–S75. doi:10.1111/ 5244741.2009.00824.x WASHINGTON	Cross sectional Objective: To compare breast cancer risk estimates from the Gail model and the CARE model (to determine if the CARE model generates higher 5-year breast cancer risk estimates for African-American women than the Gail model) Method Gail model has been used to predict invasive breast cancer risk in women, however it underestimates risk in African-American women. The Contraceptive and Reproductive Experience (CARE) model has been developed to replace the Gail model in predicting breast cancer risk in African-American women. A sample of African-American women undergone mammography completed risk assessment forms based on age at menarche, age at first live birth, number of affected relatives and number of previous benign biopsy examinations, between 2002 and 2005 to determine risk estimates. 5-year breast cancer risk was calculated for both the Gail and CARE models in the study subjects. The proportion of women with elevated breast cancer risk (risk ≥ 1.67%) in the models was also compared.	III	883 African-American women who participated in the breast cancer screening program at Howard University Cancer Center, Washington • Mean age : 53.8±10.8 years (minimum 35 years)	CARE model			• Breast cancer risk ➢ Mean 5-year breast cancer risk; = 0.88% (Range: 0.18–6.60%)(Gail model) =1.29% (Range: 0.20–4.50%) (CARE model) • Proportion of women with elevated breast cancer risk (risk ≥ 1.67%) - 7% using the Gail model compared to 21% using the CARE model (p< 0.0001). - For women ≥60 years of age, large differences of proportion observed; Gail model (14.2%) and CARE model (51.7%) • Risk prediction by category • The CARE model risk predictions were higher than those from the Gail model in all categories : (age at menarche, breast biopsy, age at first live birth; and in women 40 years and older, and those with at least one or no relatives with breast cancer). Author conclusion: The CARE model risk predictions were higher than those from the Gail model for African-American women. Use of CARE model has significant implication regarding counselling in African-American women at increased risk for developing breast cancer, and indicates more African-American women would be eligible for breast cancer chemoprevention study and they could be considered for pharmaceuticals with FDA approved indication for breast cancer reduction.	

<table>
<tr><th>Bibliographic citation</th><th>Study
Type / Methods</th><th>LE</th><th>Number of patients and patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow up (if applicable)</th><th>Outcome measures/
Effect size</th><th>General comments</th></tr>
<tr><td>4. Boggs DA, Rosenberg L, Pencina MJ et al.
Validation of a Breast Cancer Risk Prediction Model Developed for Black Women.
J Natl Cancer Inst;2013;105:361–367

US</td><td>Validation study (Prospective cohort)

Objective:
To assess the calibration and discriminatory accuracy of the CARE model among both younger and older black women and to assess the model's predictive ability for specific breast cancer subtypes (estrogen receptor–positive (ER+) and estrogen receptor–negative (ER–) breast cancer)

Method
The Black Women's Health Study (BWHS) was an ongoing follow-up study of black women (1995) involving women aged 21 to 69. Self-administered baseline questionnaire were collected.
CARE model factors were obtained from the BWHS baseline questionnaire.
Biennial follow-up questionnaires ascertain incident breast cancer (self report) from 1997 to 2005, which was confirmed by medical record or by cancer registry. Analysis restricted to women 30 years or older at the start of follow-up on January 1996.</td><td>II-2</td><td>45,942 Black women (from Black Women's Health Study) aged 30 to 69 years at baseline

Excluded:
Women who had a history of cancer (n = 1859) or died (n = 64) before start of follow-up or with missing information on any risk factors in the model (n = 215), this analysis included 45 942.

Age at baseline = 30 to 39 years (41.6%; majority)

Median age at diagnosis = 52 years</td><td></td><td></td><td></td><td>Validation of CARE model;
• Calibration:
- Predicted breast cancer cases (CARE model) = 749.6
- Observed invasive breast cancer cases = 852 cases
- E/O ratio = 0.88 (95%CI=0.82 to 0.94)

➢ CARE model factors
<table><tr><th>Risk factor</th><th>No.predicted</th><th>No.observed</th><th>E/O (95%CI)</th></tr><tr><td colspan="4">Age</td></tr><tr><td>30-39</td><td>156.6.</td><td>183</td><td>0.86(0.74-0.99)</td></tr><tr><td>40-49</td><td>308.4</td><td>322</td><td>0.96(0.86-1.07)</td></tr><tr><td>50-59</td><td>190.2</td><td>245</td><td>0.78(0.69-0.88)</td></tr><tr><td>60-69</td><td>94.3</td><td>102</td><td>0.93(0.76-1.12)</td></tr><tr><td colspan="4">Age at menarche</td></tr><tr><td><12</td><td>213.8</td><td>255</td><td>0.84(0.74-0.95)</td></tr><tr><td>12-13</td><td>409.3</td><td>452</td><td>0.91(0.83-0.99)</td></tr><tr><td>>14</td><td>126.6</td><td>145</td><td>0.87(0.74-1.03)</td></tr><tr><td colspan="4">No. of biopsies</td></tr><tr><td>0</td><td>622.9</td><td>685</td><td>0.91(0.84-0.98)</td></tr><tr><td>>1</td><td>126.7</td><td>167</td><td>0.76(0.65-0.88)</td></tr><tr><td colspan="4">No of affected relatives</td></tr><tr><td>0</td><td>625.2</td><td>707</td><td>0.88(0.82-0.95)</td></tr><tr><td>1</td><td>115.5</td><td>136</td><td>0.85(0.72-1.00)</td></tr><tr><td>2</td><td>9.0</td><td>9</td><td>1.00(0.52-1.92)</td></tr></table>CARE model showed underprediction of breast cancer risks among all categories however were not statistically significant (underprediction greatest among women with previous biopsy).

➢ Factors not in CARE model
- Greatest underprediction of breast cancer risk among women at 25 years or older at birth of first child (E/O=0.79, 95%CI=63 to 0.81, p=0.002).
➢ Breast cancer incidence rates
- Age specific breast cancer incidence rates used in the CARE model (SEER program) were lower than those in BWHS; standardized incidence ratio (SIR) was 0.88 (95% CI = 0.82 to 0.94)

• Discriminatory accuracy
➢ Average age-specific concordance (c) statistic for total invasive breast cancer was 0.57 (95% CI = 0.55 to 0.59).
➢ The average age-adjusted concordance statistics were 0.59 (95% CI = 0.57 to 0.61) for ER+ breast cancer and 0.54 (95% CI = 0.50 to 0.57) for ER– breast cancer.

Author conclusion:
The CARE model underestimated the number of invasive breast cancers overall by 12% in this BWHS cohort. Age at first child's birth may be an important factor to include in a prediction model for black women, as in the Gail model for white women. The discriminatory power of the CARE model in black women was modest. Discrimination was worse for ER– breast cancer, indicating a need to develop a better risk model for women with this breast cancer subtype.</td><td></td></tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Petracci E, Decarli A, Schairer C, et al. Risk Factor Modification and Projections of Absolute Breast Cancer Risk. J Natl Cancer Inst 2011;103:1–12 ITALY	Cohort Objective: To estimate the effects of changes in modifiable risk factors on the absolute risk of breast cancer. Method A model was developed to predict the absolute risk of breast cancer using data from a multicentre case–control study of women in Italy (2569 case patients and 2588 control subjects studied from June 1, 1991, to April 1, 1994 involving six regions) and incidence and mortality data from the Florence Registries. Data from the case control study were used to select the non-modifiable and modifiable risk factors and to estimate the relative risks. The model included five **non-modifiable risk factors** (reproductive characteristics, education, occupational activity, family history, and biopsy history) and three modifiable risk factors (alcohol consumption, leisure physical activity, and body mass index). The model was validated using independent data from the Italian cohort, Florence-EPIC cohort study from 1998 to 2004.	II-2	Model development : Case–control study included 2569 cases (female patients with breast cancer, aged 23 to 74 years, median age: 55 years); control subjects (n = 2588) were women aged 20 to 74 years (median age: 56 years) without breast cancer Model validation: The Florence-EPIC cohort included 10, 083 women aged 35–64 years.	-	-	-	**Final relative risk model:** $\log(\text{odds}) = -5.3437 + 0.0411 \times \text{AgeMen} + 0.8531 \times \text{NumRel} + 0.2627 \times \text{Age1st} + 0.2759 \times \text{NBiops} + 0.2360 \times \text{CurrnDrnk} + 0.2041 \times \text{ExDrnk} + 0.3157 \times \text{Educat} + 0.0783 \times \text{LeiAct} + 0.0946 \times \text{OccAct} + 0.2350 \times \text{InvBmi} \times \text{AgeLT50} + 0.1247 \times \text{Bmi} \times \text{AgeGE50} + 0.1525 \times \text{age} - 0.0013 \times \text{age}^2$ **Validation** • Calibration: ➢ Overall: Predicted breast cancer cases = 225.7 Observed invasive breast cancer cases = 206 E/O ratio = 1.10 (95% CI = 0.96 to 1.26, p=0. .19) ➢ Other variables: The model showed over-prediction of breast cancer risks for women aged 60 years or more, women aged 30 or more at first live birth, and women with 12 years or more of education. • Discrimination ➢ Concordance (c)-statistic = 0.62 (95% CI = 0.55 to 0.69) for women younger than 50 years ➢ (c)-statistic = 0.57 (95% CI = 0.52 to 0.61) for women aged 50 years and older **Absolute risk reduction** ➢ Mean absolute risk reductions (ARR) = 0.6% (95% CI = 0.3 to 1.0%) and 1.4% (95% CI = 0.7 to 2.0%) for 45-year-old women (for 10 and 20 years projection) ➢ ARR=0.9% (95% CI = 0.5% to 1.3%) and 1.6% (95% CI = 0.9% to 2.3%) for 65-year-old women (for 10 and 20 years projection) ➢ Estimated mean absolute risks and mean absolute risk reductions **were larger in women with a family history of breast cancer** ➢ ARR = 1.3% (95% CI = 0.7 to 2.1%) and 2.7% (95% CI = 1.4 to 4.2%) for 45-year-old women (10 and 20 years projection) ➢ ARR=1.9% (95% CI = 1.1% to 2.9%) and 3.2% (95% CI = 1.8% to 4.8%) for 65-year-old women (10 and 20 years projection) Author conclusion: The new absolute risk prediction model for invasive breast cancer was well calibrated overall but overestimated the absolute risk of breast cancer in some subgroups such as women aged 60 years or older, and women whose first live birth occurred at age 30 years or later. The discriminatory accuracy was modest. The absolute risk reduction including exposure modifications was nearly proportional to the risk without including these factors and increased with age and risk projection time. These data give perspective on the potential reductions in absolute breast cancer risk from preventative strategies based on lifestyle changes. The methods are also useful for calculating sample sizes required for trials to test lifestyle interventions.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Vacek PM, Skelly JM, Gelle BM. Breast cancer risk assessment in women aged 70 and older. Breast Cancer Res Treat 2011. 130:291–299. VERMONT & NEW HAMPSHIRE	Prospective cohort study Objective: To determine the models usefulness as risk assessment tools for women aged 70 and older, (the original Gail model, the Tice modification of the Gail model, the Barlow Model & the Vermont model), to examine their prediction ability to diagnose breast cancer and to compare model performances Method This study utilized data from the Vermont Breast Cancer Surveillance System (VBCSS) to assemble a cohort, obtain risk factor information and identify subsequent cases of breast cancer. Invasive and in situ breast cancers diagnosed before January 1, 2010 were identified using both the pathology information in the VBCSS and the diagnosis codes in the Medicare & Medicaid Services claims data. Risk score then computed based on each of the four risk models.	II-2	Cohort of 19,779 Vermont women aged 70 and older who had a mammogram in the Vermont Breast Cancer Surveillance System between 1996 and 2001 Inclusion - Not previously diagnosed with breast cancer, did not decline ti use their data Excluded - Prevalent cancers, women diagnosed with cancer Majority (97.7%) were white, (54.6%) aged between 70-74	-	-	-	➢ Incidence of breast cancer ➢ 821 developed breast cancer (5.0%) ➢ Risk score and breast cancer risk ➢ The risk scores computed from each of the models were significantly associated with breast cancer risk in the Cox regression analyses (p<0.001). ➢ However, the regression coefficients (ß's) were all significantly lower than one (ß = 0.31 for the Gail model, ß = 0.26 for the Tice model, ß = 0.50 for the Barlow model and ß= 0.54 for the Vermont model) indicating that the observed increases in relative risk per unit of the risk score were **much lower** than predicted by the models. ➢ Discrimination ➢ C-statistics = 0.54 (95% CI = 0.52–0.56) for the Gail model, ➢ C-statistics = 0.54 (95% CI = 0.51–0.56) for the Tice modification of the Gail model, ➢ C-statistics = 0.55 (95% CI = 0.53–0.58) for a model developed by Barlow ➢ C-statistics = 0.55 (95% CI = 0.53–0.58) for a Vermont model Author conclusion: The models are not useful for assessing risk in women aged 70 and older. Age-related attenuation of the effects of some risk factors makes the prediction of breast cancer in older women particularly difficult. New risk factors and biomarkers for breast cancer are needed as well as statistical models that allow their effects to vary with age.	
7. Schonfeld SJ, Pee D, Greenlee RT, et al. Effect of Changing Breast Cancer Incidence Rates on the Calibration of the Gail Model. J Clin Oncol 2010. 28:2411-2417. US	Prospective cohort Objective: To evaluate the Gail model calibration in two recent cohorts (National Institutes of Health AARP Diet and Health Study (NIH-AARP, 1995 to 2003), and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO, 1993 to 2006), following changes in US breast cancer incidence during the 1990s Method Gail model uses breast cancer incidence rates and competing mortality rates from the Surveillance, Epidemiology and End Results (SEER) program (1983 to 1987), while this updated model used SEER incidence and mortality rates from period corresponding to the cohorts, 1995-2003. Cancer ascertainment done through linkage with state cancer registries (NIH-AARP), annual mailed questionnaires to participants and medical records confirmation (PLCO), reports from physicians, Death Index and cancer registries. Risk factors included in the Gail modelobtained from baseline questionnaires. Calibration of updated model evaluated using combined Gail model RR with SEER breast cancer incidence rates1995 to 2003.	II-2	Women from NIH-AARP (a large prospective study of 200,000 women age 50 to 71 years, from 1995 to 1996) and PLCO (a multicenter screening trial involving 77,500 women, between 1993 and 2001; Age 55 to 74 years at baseline included white, post-menopausal women with known parity, no history of in situ or invasive breast cancer, and age younger than 90 years at the start of follow-up	-	-	-	➢ Incidence of breast cancer ➢ 5,665 developed breast cancer from 181,979 women (NIH-AARP) ➢ 2,223 developed breast cancer from 64,868 women (PLCO) ➢ Overall age adjusted invasive breast cancer incidence rates (SEER 1995 to 2003) = 389.99 per 100,000 person years; (343.0 per 100,000 person years in SEER 1983 to 1987) ➢ Calibration The Gail model significantly underpredicted the number of invasive breast cancers: - E/O ratio = 0.87 (95% CI, 0.85 to 0.89) in NIH-AARP (underprediction by 13%), - E/O ratio = 0.86 (95% CI, 0.82 to 0.90) in PLCO (underprediction by 14%), Overall, the updated model (SEER 1995 to 2003) was well calibrated: ➢ E/O ratio = 1.03 (95% CI, 1.00 to 1.05) in NIH-AARP and ➢ E/O ratio of 1.01 (95% CI: 0.97 to 1.06) in PLCO. ➢ The Gail model was well calibrated in PLCO when the prediction period was restricted to 2003 to 2006 (E/O ratio =1.00; 95%CI, 0.94 to 1.08). ➢ Discrimination ➢ Discriminatory accuracy was unchanged by the recalibration; the overall AUCs for the updated model were 0.58 in NIH-AARP and 0.59 in PLCO. Author conclusion: The calibration of risk prediction models is sensitive to trends in underlying population rates. This study highlights the importance of using appropriate baseline rates in absolute risk models and the importance of prediction models calibration to ensure their usefulness for clinical decision making.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
8. Chay WY, Ong WS, Tan PH, et al.Validation of the Gail model for predicting individual breast cancer risk in a prospective nationwide study of 28,104 Singapore women. Breast Cancer Research 2012, 14:R19	Validation study (prospective cohort) Objective: to evaluate the performance of the Gail Model(GM) as an appropriate breast cancer risk assessment tool in the Asian population. Method The study population consisted of 28,104 women aged 50 to 64 years who participated in the Singapore Breast Cancer Screening Project (SBSCP) and did not have breast cancer detected during screening. Cancer ascertainment was through the Singapore Cancer Registry and the National Death Register. To evaluate the performance of the GM, the expected number of invasive breast cancer cases were compared to number of actual cases observed within 5-year and 10-year follow-up.	II-2	n= 28,104 women aged 50 to 64 years from Singapore Breast Cancer Screening Project (SBCSP), a population-based mammography screening project among female Singaporeans conducted between October 1994 and February 1997. Excluded: women with breast cancer or other cancers, pregnant or had mammography or breast biopsy 12 months prior study	-	-	-	➢ Incidence of breast cancer 144 and 409 invasive breast cancers were diagnosed within 5 years and 10 years from screening, respectively ➢ Calibration - 5 year from screening - Overall: Predicted invasive breast cancer cases = 362 cases Observed invasive breast cancer cases = 144 cases E/O ratio = 2.51 (95% CI = 2.14 to 2.96) ➢ The GM over-estimated breast cancer risk across all age groups, with the highest discrepancy among older women aged 60 - 64 years (E/O = 3.53, 95% CI = 2.57-4.85) ➢ 10 year from screening ➢ Overall: Predicted invasive breast cancer cases = 758 cases Observed invasive breast cancer cases = 409 cases E/O ratio = 1.85 (95% CI = 1.68 to 2.04) ➢ Over-prediction of the number of breast cancers by GM was higher for women who were 60 to 64 years old (E/O ratio = 2.54, 95% CI = 2.57 to 4.85) ➢ Trends of E/O ratio by age group and predicted risk quintile group which were based on 10-year prediction were broadly similar to those based on 5-year prediction. Author conclusion: This study validates the Gail model risk factors individually but it over-predicts the risk of invasive breast cancer in the setting of a developed Asian country, with the largest difference seen in older women aged between 60 and 64 years old. Consequently, it has become imperative to evaluate local breast cancer epidemiology in order to validate existing models of breast cancer risk. Future work should focus on the development of appropriately calibrated models for better prediction of risk, which would benefit individual counselling and cancer prevention research.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
9. Pfeiffer RM, Park Y, Kreimer AR, et al. Risk Prediction for Breast, Endometrial, and Ovarian Cancer in White Women Aged 50 y or Older: Derivation and Validation from Population-Based Cohort Studies. PLoS Med 2013. 10(7): e1001492. doi:10.1371/journal.pmed.1001492 US	Cohort study Objective: To develop a model in predicting risk of cancers that share many hormonal and epidemiological risk factors; breast, endometrial and ovarian cancer Method Absolute risk prediction model was developed for breast, endometrial, and ovarian cancer by combining data from two large prospective cohorts; the National Cancer Institute (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the National Institutes of Health–AARP Diet and Health Study (NIH-AARP)); and from age-specific US population incidence and competing mortality rates in the NCI's Surveillance, Epidemiology, and End Results Program (SEER). (http://seer.cancer.gov/about/overview.html). Participants completed self administered questionnaire at entry. Breast cancer model includes MHT use,other MHT use,age at first live birth, menopausal status, age at menopause,family history, benign breast disas/biopsy, alcohol, BMI Cancers were ascertained via annual study updates and death certificates, and verified via review of medical records (PLCO), through linkage with state cancer registries (NIH-AARP). All models were validated using independent data from the Nurses' Health Study (NHS).	II-2	PLCO enrolled 78,232 women, aged 55 to 74 y at baseline (between November 1993 and June 2001) NIH-AARP included 567,169 men and women aged 50 to 71 years (1995–1996) Restriction: Non-Hispanic, white women who completed baseline questionnaire, had follow-up information, and had no personal history of the cancer of interest at baseline, **Final study population** included 191,604 (NIH-AARP) and 64,440 (PLCO) women for breast cancer analysis For model validation: Final validation included 57,906 women from the NHS, aged 30–55 (for the breast cancer model)				➢ Final relative risk model (breast cancer) ➢ Variables included in the final RR model: BMI, estrogen and progestin Menopause Hormone Therapy use, other MHT use, parity, age at first birth, premenopausal, age at menopause, benign breast diseases, family history of breast or ovarian cancer, and alcohol consumption ➢ Breast cancer risk projection - Absolute risk estimates = 1.57% to 21.78% (10 year projection) - Absolute risk estimates = 3.64% to 35.11% (20 year projection) ➢ Validation ➢ Calibration • Overall - Incidence of breast cancer observed =2,934 - Incidence of breast cancer predicted =2,930 - E/O ratio = 1.00 (95% CI: 0.96 to1.04). - The model significantly underestimated the number of breast cancers in premenopausal women; E/O ratio = 0.73 (95% CI: 0.65 to 0.83). - E/O ratios were not statistically significantly for other variables ➢ Discrimination ➢ Overall AUC (discriminatory power) in the NHS cohort = 0.58 (95% CI: 0.57 to 0.59). ➢ Compared to BCRAT; BCRAT predicted 2,947 cases resulting in E/O 1.0(95%CI 0.97 to 1.04) Author conclusion: These models predict absolute risks for breast, endometrial, and ovarian cancers from easily obtainable risk factors among white, non-Hispanic women aged 50+ years. The models may assist in clinical decision-making related to the risks of these cancers and might improve the ability to identify potential participants for research studies. Limitations are the modest discriminatory ability of the breast and ovarian models, and that these models may not generalize to women of other races.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
10. Banegas MP, Gail MH, LaCroix A, et al. Evaluating breast cancer risk projections for Hispanic women. Breast Cancer Res Treat. 2012 February ; 132(1): . doi:10.1007/s10549-011-1900-9. US	Validation study (cohort) Objective: To examine the performance of Breast Cancer Risk Assessment Tool (BCRAT) in Hispanic women Method BCRAT combines 1990-1996 breast cancer incidence for Hispanic women with relative risk of risk factors from NHW. In this study, the relative risks, calibration and discriminatory accuracy of BCRAT risk projections for 6,353 Hispanic were compared to 128,976 Non-Hispanic White (NHW) postmenopausal participants aged 50–79 in the Women's Health Initiative (WHI), a large longitudinal study involving Hispanic and NHW. BCRAT risk factors (age, age at first live birth, age at menarche, number of first-degree relatives with breast cancer, number of breast biopsies and presence of atypical hyperplasia on a previous breast biopsy) were obtained from the enrollment questionnaire. All reported invasive breast cancers were adjudicated locally and centrally.Calibration for an 'updated BCRAT' was re-evaluated that combined BCRAT RR with 1993–2007 SEER breast cancer incidences simultaneous with the WHI.	II-2	6,353 Hispanic and 128,976 NHW postmenopausal participants aged 50–79 without a history of breast cancer or mastectomy in WHI	-	-	-	➢ **Validation of BCRAT** • Calibration ➢ The model underestimated the number of breast cancer diagnoses among Hispanics by18% (O/E = 1.18, 95% CI = 0.99 to 1.40; p= 0.06) ➢ The model also underestimated the number of breast cancer diagnoses by 18% for NHW women (O/E = 1.18, 95% CI = 1.14 to 1.21; p< 0.001). • Concordance statistic (AUC) of BCRAT = 0.63 [95%CI:0.58 to 0.67] for Hispanic = 0.58 [95%CI:0.56 to 0.58] for NHW women in the WHI (p= 0.03) ➢ **Validation of updated model** Updating the BCRAT improved calibration for Hispanic women (O/E = 1.08, p= 0.4) and NHW women (O/E = 0.98, p= 0.2). ➢ **Comparison of RR (BCRAT vs WHI)** • For Hispanic women, relative risks for number of breast biopsies (RR= 1.71 vs. 1.27, p= 0.03) and age at first birth (RR = 0.97 vs. 1.24, p= 0.02) were significantly different between the WHI and BCRAT. • The only RR estimate that significantly different between NHW and Hispanic women in the WHI was number of breast biopsies (RR = 1.27 vs 1.71, p= 0.03). Author conclusion: Updating the BCRAT with contemporaneous breast cancer incidence rates improved calibration in the WHI. The modest discriminatory accuracy of the BCRAT for Hispanic women might be improved by using relative risks of risk factor specific to Hispanic women. Further development of a more comprehensive model for Hispanic women, that considers breast cancer risk factors distinct to Hispanic women and is validated in a large cohort of US Hispanic women, is warranted.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
11. Boggs DA, Rosenberg L, Adams-Campbell LL, and Palmer JR. Prospective Approach to Breast Cancer Risk Prediction in African American Women: The Black Women's Health Study Model. J Clin Oncol 2015.33; p1-7. DOI: 10.1200/ JCO.2014.57.2750 United States	Validation study (prospective cohort) Objective: To develop a breast cancer risk prediction model for African American women using prospective data from the BWHS in follow-up from 1995 to 2005 and to validate the model in subsequent follow-up from 2006 to 2010, overall and by age and ER status Method: The BWHS is an ongoing follow-up study of African American women established in 1995 involving 59,000 African American women from across the US. A breast cancer risk model for the women was developed using relative risks (RR) of invasive breast cancer derived from 10 years of follow-up (1995 to 2005) of BWHS participants age 30 to 69 years at baseline by Cox proportional hazards models. Absolute risk was estimated using RRs and attributable risks from the BWHS model, age-specific SEER breast cancer rates for African American women (1994 to1998), and age specific competing mortality rates for African American women (1996 to 2000). Using the subsequent 5 years of follow-up data (2006 to 2010), calibration as the ratio of expected to observed number of breast cancers and discriminatory accuracy using the concordance statistic were evaluated. Baseline questionnaire on BWHS risk factor were collected (age at menarche, height, weight at age 18 years, waist and hip circumference, educational attainment, family history of breast cancer, parity, age at first birth, duration of breastfeeding, oral contraceptive use, age at menopause, type of menopause, menopausal hormone use, previous diagnosis of benign breast disease Incident diagnoses of breast cancer were ascertained through self-report on biennial follow-up questionnaires and, for non-respondents, through linkage with state cancer registries. Breast cancer deaths were identified through linkage with the National Death Index.	II-2	55,879 African American women from the BWHS cohort aged 30 to 69 years at baseline or who reached age 30 years during follow-up, had no history of cancer at baseline, and had no missing data on variables in the final model Mean age: 39.9 (1996 cohort) and 47.2 (2006)				➢ The BWHS model included these factors; 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, and height (factor associated with the largest RR = family history of breast cancer in a first-degree relative diagnosed before age 50 years (RR= 2.24; 95% CI 1.76 to 2.84)) ➢ Incidence of breast cancer: 896 incident invasive breast cancers (1995 to 2005) Median age at diagnosis : 50 years ➢ Validation: ➢ Calibration ➢ Overall E/O ratio = 0.96 (95% CI 0.88 to 1.05) ➢ significant underestimation of risk: ➢ Women without a family history of breast cancer (E/O ratio, 0.90;95% CI,0.81 to 0.99), ➢ nulliparous women (E/O ratio= 0.83; 95% CI 0.70 to 0.99), ➢ women who used oral contraceptives within the previous 10 years (E/O ratio= 0.75; 95% CI 0.63 to 0.89) ➢ In the second lowest age-adjusted quintile of risk (E/O ratio = 0.75; 95% CI 0.61 to 0.91) ➢ Good agreement between the predicted and observed number of breast cancers across categories of other risk factors. ➢ Discriminatory accuracy ➢ Age adjusted AUC (overall) = 0.59 (95% CI 0.56 to 0.61) ➢ AUC = 0.62; 95% CI, 0.58 to 0.65 (women younger than age 50 years) ➢ AUC = 0.56; 95% CI, 0.53 to 0.59 (women age more than 50 years) ➢ AUC = 0.62 (ER-negative breast cancer) ➢ AUC = 0.58 (ER-positive breast cancer) (p=0.1) ➢ Proportion of women with elevated risk of breast cancer (5-year predicted risk of 1.66% or greater) ➢ 2.8% of women younger than 50 years old ➢ 32.2% of women more than 50 years old were classified as being at elevated risk of invasive breast cancer Author conclusion: The BWHS model was well calibrated overall, and the predictive ability was best for younger women. The proportion of women predicted to meet the 1.66% cut point commonly used to determine eligibility for breast cancer prevention trials was greatly increased relative to previous models	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
12. Anothaisintawee, Teerawattananon Y, Wiratkapun c, et al. Development and Validation of a Breast Cancer Risk Prediction Model for Thai Women: A Cross-Sectional Study. Asian Pac J Cancer Prev. 2014. 15 (16), 6811-6817	Cross sectional Objective: to develop and validate a breast cancer risk prediction model for Thai women. Method: • Model derivation (using data collected at Ramathibodi hospital) • Multiple logistic regression was applied to construct the model • Model validation (internal) : used bootstrap with 200 repetitions • Model validation (external) used data from Srinagarind and Songklanagarind Hospitals • Performance were assessed which were calibration and discrimination performances using the observed/ expected ratio and concordance statistic (C-statistic), respectively.	III	17,506 women whom undertook mammographic screening in Ramathibodi Hospital (model derivation) Women undergoing mammographic screening aged 18 years and above were eligible. Those with history of invasive breast cancer, ductal carcinoma in situ or other cancers were excluded				• Model derivation included these risk factors; - age, - menopausal status, - body mass index and - use of oral contraceptives • Model performance: - O/E ratio = 1.0 (95%CI 0.82 to 1.21) (overall) - O/E ratio 0.97 (95% CI 0.68 to 1.35) (External validation) - Overall c-statistic = 0.65 (95%CI 0.59 to 0.70 - C-statistic = 0.64(95% CI 0.64 to 0.65) Internal validation - C-statistic = 0.61(95% CI 0.51 to 0.71) External validation • Risk score & risk stratification: low, low-intermediate, intermediate-high, and high-risk	

EVIDENCE TABLE : **SAFETY**

QUESTION : **IS HEALTH RISK ASSESSMENT MODULE FOR BREAST CANCER OR CANCER RISK PREDICTION MODEL SAFE TO DETECT WOMEN WHO DEVELOP BREAST CANCER?**

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Kye SY, Park K, Park HG et al. Psychological impact of health risk appraisal of Korean women at different levels of breast cancer risk: neglected aspect of the web-based cancer risk assessment tool. Asian Pacific J Cancer Prev. 2012;13:437-441 KOREA	Randomized trial Objective: To explore the psychological effect of health risk appraisal using epidemiological risk factor profile Method: Participants were recruited through advertisements in the websites between October and November 2009.60 eligible women completed a baseline interview, then randomized to either a numerical HRA or the HRA using personal risk factor list. HRA was done through telephone interview. After one month, the participants attended intervention sessions which consist of provision of HRA results, pre- and post-HRA assessment for psychological status, and counselling. Variables measured in personal risk factor; height, weight, alcohol, vegetable consumption, past history of benign breast disease, menstruation and OCP. Risk factors for numerical HRA used Gail model factors. Anxiety level was measured using Spielberger State Trait Anxiety Inventory YZ (Korean version).		n= 60 women aged between 30 to 48 years old without prior cancer diagnosis median age : 38 years	Information on individualized risk for breast cancer	No information	1 month	• Average anxiety level • Mean(SD) 44.7(9.2) for trait (long term) anxiety (42.6(9.2) for state (temporary) anxiety • Predictor for increase in anxiety - Anxiety score increased among women who had higher risk status in 'risk score' group at follow up compared to baseline, with mean(SD) at baseline and follow up were 42.8(8.5) and 47.0(9.6) respectively, however it was not significant - Risk status was the independent predictor of increase of state anxiety after health risk appraisal intervention, after adjusted for age, education, HRA type, numeracy,pre-HRA state anxiety and HRA type. - Women who had higher risk status had an odd of having increased anxiety about 5 times greater than women who had lower risk status (OR 5.03, 95% CI 1.54 to 16.43, p=0.01) Authors' conclusion: Communicating the risk status by individual health risk appraisal service can induce psychological sequelae, especially in women having higher risk status. Hospitals, institutes, or medical schools that are operating or planning to operate the online health risk appraisal service should take side effects such as psychological sequelae into consideration. Further research on cancer risk communication strategies for HRA service are required to explore long term outcome and to evaluate more psychological outcome.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Scherer LD, Ubel PA, McClure J et al. Belief in numbers: when and why women disbelieve tailored breast cancer risk statistics. Patient education and counseling. 2013;92:253-259 DETROIT & SEATTLE, US	Cross sectional Objective: To determine when and why women chose to disbelieve the personalized breast cancer risk numbers. Method: Women whose medical records indicated that they might be at above average risk of developing breast cancer were recruited from the Henry Ford Health System in Detroit and Group Health in Seattle. The subjects participated in an online program which presented tailored information about individual breast cancer risk after completing BCRAT questions and viewing decision aid on chemoprevention. They were presented with tailored absolute risk (BCRAT score) and estimate of risk reduction with chemoprevention. The subjects were asked whether they believe the program was personalized and whether they believe the numbers. The BCRAT score was calculated using these factors: age, ethnicity, personal risk of breast cancer, age at first menses, age at first live birth, number of first degree relatives who have had breast cancer, history of breast biopsies. Intervention: Personalized risk estimate in one of two different ways:- 1. “detailed explanation” of the factors that were used to calculate their tailored risk numbers 2. “standard tailoring”, participants were given no information about how their risk number was generated		n=690 women - at or above average risk of developing breast cancer as estimated by the Breast Cancer Risk Assessment Tool (BCRAT)(score range 1.7-19.1) - age range 46 to 74 years - 97.6% were white				• Influence of intervention on beliefs that the program was personalized: - Women who received “detailed information” were more likely to feel that the program was personalized compared to those receiving “standard information”; with mean(SD) of 4.85(1.39) vs 4.64(1.41), p=0.05 respectively • Disagreement with tailored risk : ➢ 131 participants disagreed with both risk numbers (18.9%) ➢ Reasons for disagreement (qualitative assessment) - Their family history made them either more or less likely to develop breast cancer than their tailored risk number suggested *(I have aunts that have had cancer)* - The risk number seemed too high or too low *(It just seemed low, the percentage was low compared to my concern)* - Health habits and lifestyle *(I am in excellent health and I live an active healthy lifestyle).* - Others: They thought the calculation failed to account for relevant personal information such as family history, medical history, lifestyle, hormone replacement therapy or unspecified. Authors’ conclusion: The benefits of tailored risk statistics may be attenuated by a tendency for people to be skeptical that these risk estimates apply to them personally. Decision aids may provide risk information that is not accepted by patients, but addressing the patients’ personal circumstances may lead to greater acceptance	

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