

Risk-based screening programmes for cancer diagnosis: A systematic review with narrative synthesis

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ABSTRACT

Introduction: Risk-based screening (RBS) has emerged as a promising alternative to age-based cancer screening. However, evidence regarding real-world implementation outcomes remains fragmented. Thus, a systematic review was conducted to evaluate the implementation methodologies and outcomes of RBS programmes across different cancer types.

Methods: MEDLINE, Embase, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials and Scopus were systematically searched from their respective dates of inception up to 8 July 2024. Prospective and randomised controlled trials (RCTs), which implement the RBS of cancer in an asymptomatic population, or studies retrospectively evaluating the outcomes of the same were included. Geographic distribution, population characteristics, RBS methodology, diagnostic accuracy and clinical outcomes were narratively synthesised.

Results: Among the 33 included studies (i.e. 21 prospective cohort, 8 RCTs, 3 retrospective and 1 non-RCT), sample sizes ranged from 102 to 1,429,890 participants. Most RBS trials were conducted in China (n=7, 21.2%), followed by the Netherlands (n=4, 12.1%) then the US, Australia and Sweden (n=3, 9.8%). Studies predominantly examined colorectal (27.3%), breast (21.2%) and prostate cancer (18.2%). Three main stratification approaches emerged: algorithmic (48.5%), validated risk models (39.4%) and physician assessment (9.1%). Implementation outcomes showed higher uptake in moderate-risk (75.4%) compared to high-risk (71.3%) and low-risk groups (67.9%). Five studies demonstrated cost-effectiveness with increased quality-adjusted life years, while 12 studies showed superior or non-inferior cancer detection rates compared to traditional screening.

Conclusion: The RBS of cancer has the potential to optimise healthcare resource allocation while minimising harm and increasing receptiveness for patients. More work is needed to evaluate long-term outcomes prior to the scaling of RBS programmes.

Keywords: early detection of cancer, health services and outcomes, preventive medicine, risk-based screening, systematic review

CLINICAL IMPACT

What is New

- Risk-based screening (RBS), an emerging approach for the early detection of cancer, can lead to superior or non-inferior cancer detection rates compared to traditional screening with better cost-effectiveness and patient acceptability.
- Effective programmes were documented for common cancers, such as breast and cervical cancer, across different geographical regions.

Clinical Implications

- RBS can potentially optimise healthcare resource allocation while minimising harms from unnecessary screening.
- Long-term outcomes from large-scale programmes and participant experiences need to be evaluated before widespread RBS implementation.

INTRODUCTION

Cancer remains one of the most significant public health burdens, with almost 20 million new cases and 9.7 million deaths attributable to cancer in 2022.¹ The detection and diagnosis of cancer remain a challenge for clinicians, as approximately half of recorded cancers are only detected at the advanced stage.^{2,3} Late cancer diagnoses often translate to poor patient prognosis and limited therapeutic options with low curative potential.^{4,5} Thus, there is much interest in methods for the early detection of cancer to achieve better survivorship outcomes.

The objective of early detection is to confirm the presence of cancer or precancerous lesions in an individual at the earliest time to inform management. One approach is screening, where investigations are

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done proactively for an asymptomatic population to identify individuals with high-risk cancers for further evaluation, such as biopsy or prophylactic therapy.⁶ Organised cancer screening programmes at the state or national levels are often age-based, where all asymptomatic individuals are recommended for an investigation for a particular cancer at a specific frequency once they reach a certain age.⁷ However, recent studies have found that cancer incidence is rising among younger age groups,⁸⁻⁹ which precludes this increasingly at-risk population from current early detection strategies. Furthermore, age-based screening is agnostic to inter-individual risk profiles, which potentially reduce its diagnostic accuracy¹⁰ and increase screening harms associated with false positive results or overdiagnosis.^{11,12} Investigations with higher specificity or sensitivity are often associated with higher cost or invasiveness, such as colonoscopy for colorectal cancer and magnetic resonance imaging (MRI) for prostate cancer, which complicates population-wide adoption. Yet, lower-cost and non-invasive modalities, which may be easily implemented at a population level, are associated with lower sensitivity and/or specificity, such as urine prostate-specific antigen, which can lead to false positives and negatives.

One emerging solution is risk-based screening (RBS), where a detailed cancer risk profile of an individual is used to tailor screening recommendations, such as age of screening, screening modalities and frequency. Risk profiles can include indices, such as family history of malignancy, cancer-related biomarker levels, lifestyle, past medical history and socioeconomic status.^{13,14} Recent advances in genomic medicine have also incorporated polygenic risk scores (PRS) or single-nucleotide polymorphisms into these risk profiles. One example is the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), which predicts the chances of a woman carrying breast or ovarian cancer susceptibility genes (e.g. BRCA1, BRCA2) and risk of developing such malignancies.¹⁵ The algorithm computes these probabilities by considering the family history of related cancers, the presence of high-risk gene variants, and associated lifestyle factors such as contraceptive use and mammographic density.¹⁵

Studies have shown that the implementation of BOADICEA and similar breast cancer risk models for RBS is cost-effective¹⁶ and acceptable¹⁷ among females. Although many *in silico* studies have been published on cancer risk prediction models, the evidence on the practical implementation of RBS remains limited. There have been RBS trials exploring the implementation of risk-based cancer screening, such as the Colorectal cancer RiSk Prediction¹⁸ trial in Australia and the Stockholm Model 3 - Magnetic Resonance Imaging trial¹⁹ in Sweden for prostate

cancer. Yet to date, no systematic review has been conducted to evaluate the effectiveness of RBS programmes beyond those for breast cancer²⁰ and lung cancer.²¹ As such, the efficacy of RBS across different cancers and the range of methodologies employed have not been summarised. Thus, a systematic review was conducted to (1) summarise current RBS methodologies for each cancer among pragmatic trials; (2) evaluate the effectiveness in terms of accuracy, cost and patient acceptability of implemented RBS programmes; and (3) highlight potential equity gaps in such programmes.

METHODS

The systematic review was conducted with reference to the Cochrane Handbook for Systematic Reviews of Intervention²² and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²³ The review was prospectively registered in the International Prospective Register of Systematic Reviews (CRD42024542831).

Search strategy

A systematic search was conducted on Embase and MEDLINE on the Ovid platform, PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL from their respective dates of inception to 8 July 2024. The search strategy comprised controlled search terms, such as “early detection of cancer”, “neoplasms” and “diagnostic screening programs.” Text terms relating to risk stratification, screening programmes and cancer were also incorporated. The strategy was piloted on PubMed, and further reviewed and refined by a medical information specialist. The strategy was then translated to other databases as befitting their native search syntax. The full search strategies can be found in Supplementary Table S1. A bibliometric search of the references of included studies was conducted for completeness.

Study selection and data extraction

Studies investigating the uptake and effectiveness of implemented RBS programmes among asymptomatic participants without a current diagnosis of the cancer being screened were included. The exclusion criteria included studies of paediatric patients, studies of *in silico* modelling of RBS outcomes, reviews of any kind, conference abstracts, letters and editorials. Title-abstracts retrieved with the aforementioned search strategies were uploaded to Covidence, a collaborative systematic review management platform. Two investigators (YYT and MFBF) independently screened the title-abstracts against the inclusion and exclusion criteria. Full-text papers were then retrieved and independently screened for inclusion by the investigators.

Data extraction was performed with data entered into a collaborative spreadsheet that was piloted on the first 3 studies. The extraction sheet was further refined after discussions among the investigators and deployed for the rest of the articles. Similar to study selection, data extraction was performed independently by the 2 investigators for each article (YYT and FF). Primary endpoints were the uptake of the initial risk stratification test and subsequent risk-informed procedures, and the diagnostic accuracy of RBS. Secondary endpoints included the participant acceptability of RBS, cost-effectiveness metrics and long-term mortality and morbidity outcomes.

Any disagreements at the study selection, data extraction and quality assessment stages were resolved via discussions between the investigators (YYT and MFBF). A third review author (ST) was consulted if no consensus was reached.

Quality assessment

The risk of bias of included studies was assessed independently by 2 investigators for each study (YYT and MFBF). Specifically, the Cochrane Risk-of-Bias 2 (RoB2) tool²⁴ was used to assess randomised controlled trials (RCTs), while the Cochrane Risk Of Bias In Non-randomised Studies of Intervention (ROBINS-I) tool²⁵ was used for prospective and retrospective cohort studies. Risk of bias was then visualised using the Risk-

of-Bias VISualisation tool²⁶ as traffic-light plots and summary plots.

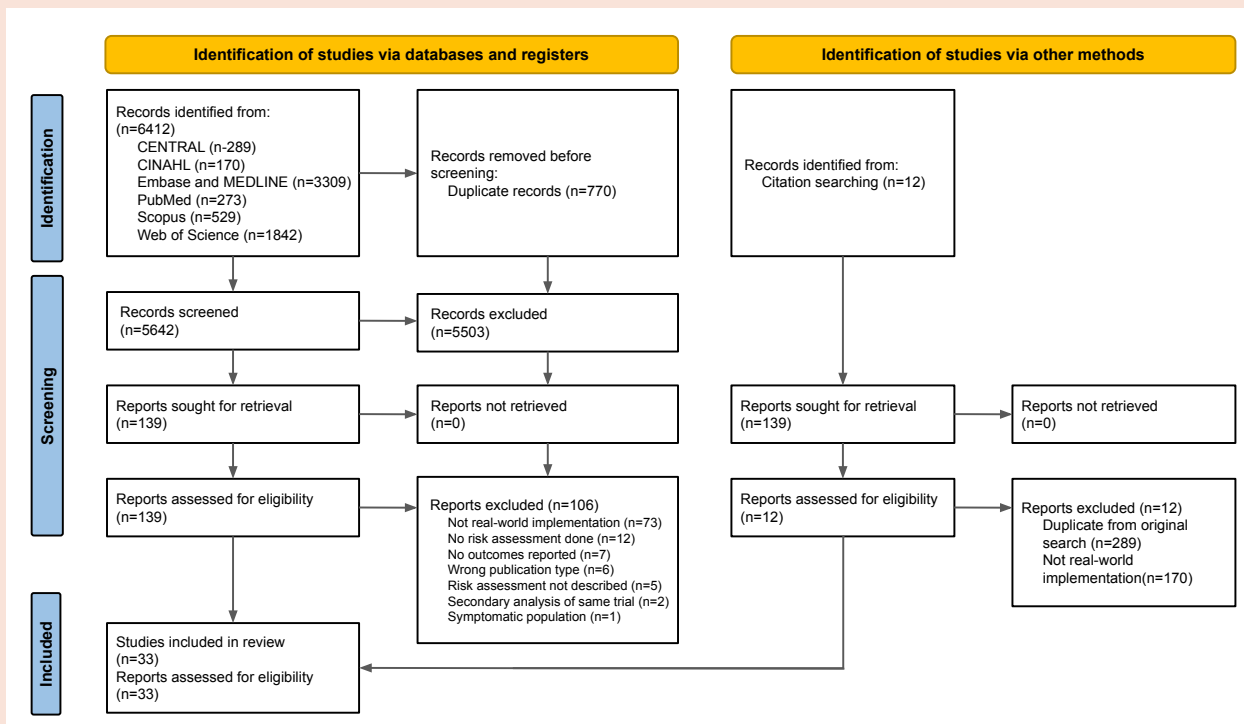
Data synthesis

Due to the heterogeneous methods and outcomes reported as expected of implementation studies, a quantitative meta-analysis was not conducted. Instead, the outcomes were summarised with descriptive statistics, such as median, interquartile range (IQR) and mean proportions where appropriate. Narrative synthesis was conducted to summarise qualitative aspects of the study characteristics, risk stratification methodologies, follow-up interventions and evaluated outcomes.

RESULTS

The systematic database search for primary studies yielded 6412 citations, of which 770 were duplicates. Among the 5503 citations excluded, primary reasons for exclusion include the absence of implementation of real-world RBS programmes, RBS programmes that did not focus on cancer and inappropriate study designs. The full-texts of 139 citations were retrieved following the title-abstract sieve, of which 106 were excluded for reasons such as lacking real-world implementation of risk stratification or not reporting any outcomes. On searching the bibliography of the included articles, the full-text papers of 12 additional

Fig. 1. PRISMA flowchart of study selection.



Source: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int J Surg* 2021;88:105906.

citations were retrieved, of which all were excluded from the review (Fig. 1).

Hence, 33 studies satisfied the inclusion criteria, and their data were extracted for evidence synthesis,^{18,19,27-57} and their characteristics are summarised in Table 1. Of the 33 studies, 21 studies were prospective cohort studies (63.6%),^{19,27,28,30-32,34-37,40,43,45,47,50-52,54-57} 8 were RCTs (24.2%),^{18,33,38,39,41,46,49,53} 3 were retrospective studies of previous or ongoing RBS programmes (9.1%),^{29,42,44} and 1 was a non-RCT (3.0%).⁴⁸ The studies were published within a year range of 2008–2024. Most studies (n=22, 66.7%) were multicentre trials at a national level embedded within primary to tertiary care settings,^{18,19,27-29,31,34,36,41-44,46,48-51,53-56} while the remainder were single-centre screening trials (n=11, 33.3%).^{30,32,35,37-40,45,47,52,57} The sample size ranged from 102 participants in a single-centre trial⁵⁰ to 1,429,890 participants in a nationwide cancer screening trial.²⁹

The most common cancer to be evaluated for RBS was colorectal (n=9, 27.3%),^{18,33,38,43,45-47,51,53} followed by breast (n=7, 21.2%),^{29,31,32,35,36,40,48} then prostate (n=6, 18.2%).^{19,37,41,42,52,56} By region, most studies were conducted in Europe (n=16, 48.5%), followed by the Asia-Pacific (n=12, 36.4%) then North America (n=5, 15.2%). By country, most studies were conducted in China (n=7, 21.2%),^{27,30,45,51-54} followed by the Netherlands (n=4, 12.1%),^{28,37,44,46} Sweden,^{19,41,56} Australia^{18,33,50} and the US^{36,42,47} (both n=3, 9.1%, respectively) (Fig. 2). Of the studies with a comparator arm, 9 compared against standard care protocols,^{18,33,35,38,44,48,49,53,55} 3 studies compared against a universal screening protocol,^{29,41,46} 2 studies compared against no screening^{28,39} and 1 study compared against the population with average cancer risk.³⁶

Risk-of-bias outcomes are presented in Figs. 3A–D. Among the RCTs, 4 were rated as low risk of bias,^{18,46,49,53} 1 with some concerns³⁹ and 3 with high risk of bias.^{33,38,41} The domains with significant methodological issues were mainly that of outcome measurement, due to the implementation of participant self-report of screening as the main measurement method. Among the non-randomised studies of intervention, 5 were rated as low risk of bias,^{31,32,40,44,52} 12 had some concerns^{19,29,30,34,43,45,47,48,50,51,54,57} and 8 were rated as high risk of bias.^{27,28,35-37,42,55,56} Significant methodological issues were raised with regard to deviations from the intended intervention due to the lack of compliance reporting and measures to ensure compliance. There were also issues with confounding due to the insufficient reporting of baseline characteristics and absence of confounder adjustment, as well as the selection of outcomes due to the absence of a protocol existing prior to the study publication.

RBS methods

A summary of risk stratification methods by cancer type is presented in Table 2. Across the 33 studies, 23

utilised some form of imaging or clinical investigation that was specific to the cancer evaluated. These tests include mammogram for breast cancer, prostate serum antigen test for prostate cancer, fecal immunochemistry test for colorectal cancer and high-risk human papillomavirus types testing for cervical cancer. One study conducted Epstein-Barr virus serology testing for the risk stratification of nasopharyngeal carcinoma.⁵⁴ Twenty-three studies assessed the level of genetic risk of the participant, mostly via family history of cancer, while 4 studies conducted genetic testing on recruited participants to assess for high-risk cancer genetic polymorphisms to calculate a polygenic risk score.^{19,31,40,41} Otherwise, cancer risk score was calculated with previously validated risk models incorporating participant characteristics, relevant family and personal history and symptoms, such as the Gail model³² and Tyrer-Cuzick model⁴⁸ for breast cancer. Clinical questionnaires were deployed in 24 studies for risk assessment, of which 20 studies^{18,29,32-35,37,38,41-43,45-48,50,51,53,54,57} assessed the family history of cancer or related pathologies, such as polyps in colorectal cancer.⁴⁵ Eleven studies assessed lifestyle factors that were associated with the cancer risk evaluated in the questionnaire,^{18,31,32,34,38,39,46,49,51,53,57} the most common of which was smoking history. Thirteen studies assessed the previous medical history that was associated with the cancer risk evaluated,^{18,19,31,32,34,38,39,41,43,47,49,51,57} such as a previous diagnosis of inflammatory bowel disease in colorectal cancer⁴³ or a prescription of contraceptives in breast cancer.^{31,32} Seven studies assessed self-reported cancer-specific symptomatology among the participants.^{18,37,38,43,45,49,57}

After collecting information on risk factors, stratification was done primarily via 3 approaches. Most studies stratified interventions by the presence or absence of a singular or combination of risk factors through an algorithmic approach (n=16, 48.5%),^{27-30,32,35,36,39,41,44,45,49,52,53,56} while 13 studies calculated a risk score using a previously validated model to stratify participants.^{18,19,31,34,37,38,40,46-48,51,54,57} Validated models include the Stockholm-3 model for prostate cancer¹⁹ and the PLCO_{m2012} model for lung cancer.³⁴ The remaining 3 studies involved a risk assessment by the physician to personalise a risk-stratified intervention for the participant.^{42,43,50} Across the studies, participants would be stratified between 2 and 3 risk strata, each with a set of strata-specific interventions. One study further personalised these interventions to the individual risk profile of the participants in addition to strata-specific interventions, specifically personalising the initiation age of mammography and MRI of the breast.⁴⁰

A summary of risk-stratified interventions by cancer type is presented in Table 3. Participants within the high-risk strata were often recommended invasive procedures or biopsies, such as colonoscopy in

Table 1. Summary of study characteristics.

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Stojadinovic 2008 ³²	US	NRSI (prospective)	Multicentre, international screening trial in a tertiary care setting	Intervention: 1751 Control: 390	Breast	Point-of-care electrical impedance scan of breast tissue	High: Informed findings and given risk-appropriate follow-up Low: Routine screening
Venturini 2013 ³⁶	Italy	NRSI (prospective)	Single-centre in a primary care setting	Intervention: 1666 Control: NA	Breast	Point-of-care mammogram results Clinical questionnaire calculating Gail model score	High: Referred for both ultrasound and contrasted MRI Moderate: Mammography and ultrasound Low: Mammography only
Budal 2014 ⁵⁵	Norway	NRSI (prospective)	Multicentre, national screening programme	Intervention: 1744 Control: NA	Cervical	Point-of-care high-risk HPV testing	High: Immediate colposcopy Low: Routine screening
Grönberg 2015 ¹⁹	Sweden	NRSI (prospective)	Multicentre, national screening trial in a primary care setting	Intervention: 47,688 Control: NA	Prostate	Utilised STHLM3 model Plasma protein biomarkers related to PCa Genetic testing for high-risk polymorphisms Prostate examination results Clinical questionnaire eliciting age, family history of cancer and recent prostate biopsy findings	High: Prostate biopsy and urologist referral Low: No biopsy
Pedersen 2015 ³⁹	Denmark	RCT	Single-centre screening trial in a primary care setting	Intervention: 2052 Control: 2052	Lung	Low-dose CT scan Self-reported age, smoking history and previous COPD diagnosis	High: Annual screening by low-dose CT scans Low: Return to routine screening
Field 2016 ⁴⁹	UK	RCT	Multicentre, national screening trial in a cancer specialist centre setting	Intervention: 2028 Control: 2027	Lung	Self-reported age, smoking history and previous medical record	High: Immediate referral to multidisciplinary team Moderate: Follow-up CT at 3 and 12 months

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Yen 2016 ²⁹	Taiwan	NRSI (retrospective)	Multicentre, national breast cancer screening programme	Intervention: 1,429,890 Control: NA	Breast	Clinical questionnaire eliciting family history of cancer, menstrual and reproductive history	Average: Follow-up CT at 12 months Low: No follow-up
Yousaf-Khan 2016 ²⁸	Netherlands	NRSI (prospective)	Multicentre, international screening trial in a community setting	Intervention: 5297 Control: NA	Lung	Point-of-care CT imaging	High: Biennial mammography Low: Return to routine screening
Guivathian 2017 ⁴⁷	US	NRSI (prospective)	Single-centre screening trial in a tertiary care setting	Intervention: 700 Control: NA	Colorectal	Clinical questionnaire eliciting past personal history of cancer, polyp history and family history of polyps	High: Genomic evaluation Moderate: Low-dose follow-up CT and VDT Low: Next regular screening
Swenen 2017 ³⁵	Belgium	NRSI (prospective)	Single-centre screening trial in a cancer specialist centre setting	Intervention: 11,123 Control: 2008	Breast	Clinical breast examination Clinical questionnaire eliciting family and personal history of cancer	High: Ultrasound Low: Biennial mammogram
Li 2018 ⁴⁵	China	NRSI (prospective)	Single-centre, community mass screening programme	Intervention: 891,199 Control: NA	Colorectal	FIT test results Clinical questionnaire eliciting biodata, CRC-related symptoms and family history of CRC	High: Colonoscopy Low: FIT
Dwarte 2019 ⁵⁰	Australia	NRSI (prospective)	Multicentre, national in a cancer specialist centre setting	Intervention: 102 Control: NA	Pancreatic	Endoscopic ultrasound results Blood test results Genetic risk assessment using PancPRO, a questionnaire eliciting family history of cancer	High: Close surveillance or treatment Average: Yearly endoscopic ultrasound for 5 years

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Chen 2021 ⁵⁴	China	NRSI (prospective)	Multicentre, national screening programme in a community setting	Intervention: 53,382 Control: NA	Nasopharyngeal	Epstein-Barr virus serology results	High: Endoscopy Moderate: Annual blood testing Low: 5-yearly visit
Loopik 2021 ⁴⁴	Netherlands	NRSI (retrospective)	Multicentre, national screening programme in a primary care setting	Intervention: 619,253 Control: 769,442	Cervical	Point-of-care high-risk HPV test	High: Cytologic assessment on physician-sampled material and colposcopy Low: Return to routine screening
Nordström 2021 ⁴¹	Sweden	RCT	Multicentre, national screening trial in a community setting	Intervention: 1372 Control: 921	Prostate	Utilised STHLM3 model Plasma protein biomarkers related to PCa Genetic testing for high-risk polymorphisms Prostate examination results Clinical questionnaire eliciting age, family history of cancer and recent prostate biopsy findings	High: Sytematic and MRI-guided biopsy Low: Return to routine screening
Reesink 2021 ³⁷	Netherlands	NRSI (prospective)	Single-centre screening trial in a primary care setting	Intervention: 496 Control: NA	Prostate	MRI-imaging of prostate with PI-RADS staging European Randomized Study of Screening for Prostate Cancer risk calculation, utilising age, family history of PCa, related symptoms and PSA levels	High: Targeted and systematic biopsy Moderate: Sytematic biopsy Low: No biopsy
Xu 2021 ³⁰	China	NRSI (prospective)	Single-centre screening trial in a tertiary care setting	Intervention: 2444 Control: NA	Cervical	Cytology with reference to Bethesda grading Point-of-care DH3 HPV test assay	High: Colposcopy and biopsies Moderate: Rescreening by cytology every 12 months

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Adeoye 2022 ⁵⁷	Hong Kong	NRSI (prospective)	Single-centre screening trial in a community setting	Intervention: 100 Control: 881	Oral	Visual oral examination Clinical questionnaire assessing family history, biodata, lifestyle factors, past medical history and related symptoms	High: Screening required Moderate: Screening on availability Low: Routine opportunistic screening
Kortlever 2022 ⁴⁶	Netherlands	RCT	Multicentre, national screening programme in a primary care setting	Intervention: 11,364 Control: 11,384	Colorectal	Clinical questionnaire eliciting smoking history, recent FIT results, family history of cancer and biodata	High: Colonoscopy Low: Return to routine screening
Michael 2022 ⁴²	US	NRSI (retrospective)	Multicentre, national screening trial in a primary care setting	Intervention: 564 Control: NA	Prostate	PSA test results Clinical questionnaire eliciting age, race and family history of cancer	High: Urology referral
Trevena 2022 ³³	Australia	RCT	Multicentre, national in a primary care setting	Intervention: 12,420 Control: 12,880	Colorectal	Clinical questionnaire eliciting family history of cancer	High: Assessment by familial cancer service or colonoscopy Moderate: Colonoscopy every 5 years Low: FOBT every 2 years
Chen 2023 ⁵³	China	RCT	Multicentre, national community screening programme	Intervention: 3937 Control: 7858	Colorectal	Clinical questionnaire to calculate Asia-Pacific Colorectal Screening Score	High: Colonoscopy Low: FIT screening and routine screening
Chiu 2023 ⁵²	China	NRSI (prospective)	Single-centre screening trial in a primary care setting	Intervention: 1536 Control: NA	Prostate	PSA test scores Prostate Health Index scores MRI prostate findings	High: MRI-guided and systematic prostate biopsy Moderate: Systematic prostate biopsy Average: No biopsy
Emery 2023 ¹⁸	Australia	RCT	Multicentre, national screening trial in a primary care setting	Intervention: 369 Control: 365	Colorectal	Clinical questionnaire assessing family history, biodata, lifestyle factors, past medical history and related symptoms	High: Referral to familial cancer centre for formal assessment Moderate: Colonoscopy every 5 years

Table 1. Summary of study characteristics. (Cont'd)

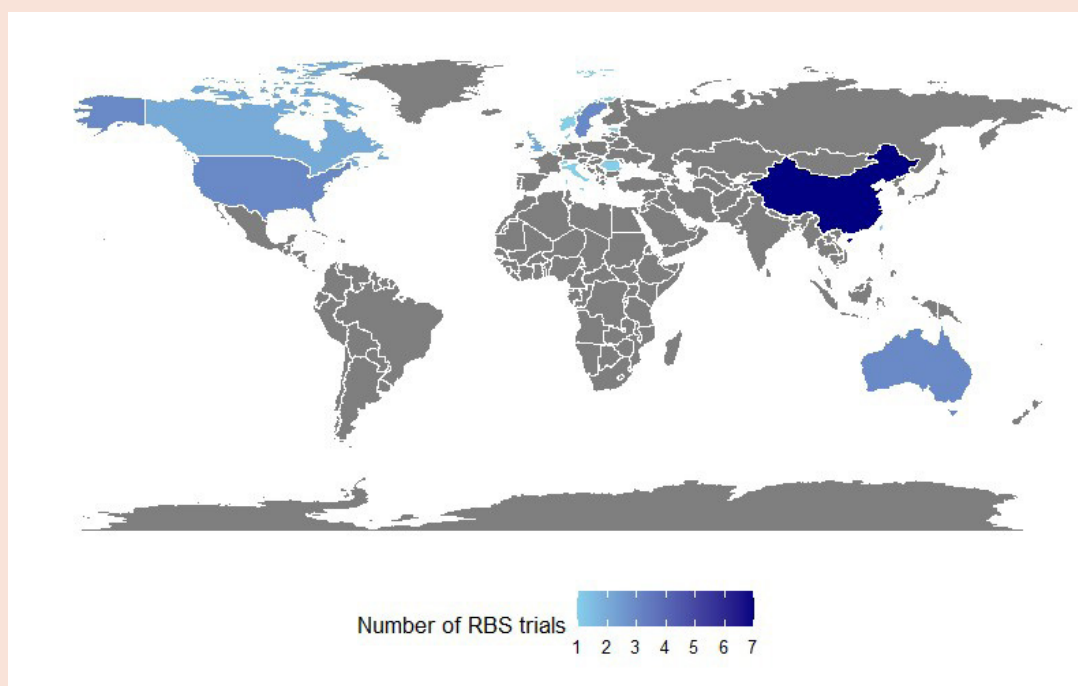
Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Gareth Evans 2023 ⁴⁸	UK	NRCT	Multicentre, national screening programme in a primary care setting	Intervention: 2472 Control: NA	Breast	Breast density scores from mammogram Clinical questionnaire to calculate Tyrer-Cuzick score	Average: iFOBT every 2 years High: Appointment with relevant medication Moderate: Appointment with relevant medication
Padrik 2023 ⁴⁰	Estonia	NRSI (prospective)	Single-centre screening trial in a cancer specialist center setting	Intervention: 2637 Control: NA	Breast	Polygenic risk score of 2803 single-nucleotide polymorphisms derived from gene testing	High: Earlier initiation of mammography and MRI-breast with discussion of chemoprevention therapy Moderate: Earlier initiation of mammography and discussion of chemoprevention therapy Slightly raised: Earlier initiation of mammography Low: Mammography from 50 years old onwards
Alterbeck 2024 ⁵⁶	Sweden	NRSI (prospective)	Multicentre, national screening trial in a primary care setting	Intervention: 999 Control: NA	Prostate	PSA test results	High: Referral to urologist with targeted and systematic biopsies Average: Invitation to screen in 2 years Low: Invitation to screen in 5 years
Dong 2024 ⁵¹	China	NRSI (prospective)	Multicentre, national screening programme in a tertiary care setting	Intervention: 946,706 Control: NA	Colorectal	FIT test results Clinical questionnaire eliciting biodata, family history of cancer, biodata, lifestyle factors, past medical history and CRC-related symptoms	High: Colonoscopy Low: Return to routine screening

Table 1. Summary of study characteristics. (Cont'd)

Study	Country	Study design	Setting	Sample size	Cancer type	Risk assessment methodology	Follow-up
Manuc 2024 ⁴³	Romania	NRSI (prospective)	Multicentre, national screening trial in a primary care setting	Intervention: 170,413 Control: NA	Colorectal	Clinical questionnaire eliciting family history of CRC and cancer syndromes, past medical history and CRC-related symptoms	High: Colonoscopy Average: FIT
Plys 2024 ³⁸	Switzerland	RCT	Single-centre screening trial in a primary care setting	Intervention: 258 Control: 257	Colorectal	Clinical questionnaire eliciting input for QCancer-Colorectal risk calculator, such as family history of cancer, biodata, CRC-related lifestyle factors, past medical history and CRC-related symptoms	High: Colonoscopy Moderate: Choice between FIT or colonoscopy Low: FIT
Tammemagi 2024 ³⁴	Canada	NRSI (prospective)	Multicentre, national screening programme in a community setting	Intervention: 7329 Control: NA	Lung	Utilised PLCO _{n2012} risk model Biodata (e.g. age, ethnicity) Family history of lung cancer Smoking history Past medical history	High: Low-dose CT scan Average: Return to routine screening
Walker 2024 ³¹	Canada	NRSI (prospective)	Multicentre, national screening programme in a primary care setting	Intervention: 4246 Control: NA	Breast	Polygenic risk score calculated from oral saliva samples Clinical questionnaire based on BOADICEA model that factors in family history of cancer, biodata, lifestyle factors and past medical history	High: Mammogram and MRI-breast Moderate: Earlier initiation of mammogram Average: Mammogram every 2 years from age 50 onwards
Yu 2024 ²⁷	China	NRSI (prospective)	Multicentre national screening programme in a primary care setting	Intervention: 9218 Control: NA	Cervical	Cytology with reference to Bethesda grading Point-of-care high-risk HPV test	High: Colposcopy and biopsy as appropriate Low: Follow-up with cytology after 3 years

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; COPD: chronic obstructive pulmonary disease; CRC: colorectal cancer; CT: computed tomography; FIT: fecal immunochemistry test; FOBT: fecal occult blood test; HPV: human papillomavirus; iFOBT: immunochemical fecal occult blood test; MRI: magnetic resonance imaging; NA: not applicable; NRCT: non-randomised controlled trial; NRSI: non-randomised studies of intervention; PCa: prostate cancer; PLCO_{n2012}: Prostate, Lung, Colorectal, and Ovarian Model 2012; PSA: prostate serum antigen; RCT: randomised controlled trial; STHLM3: Stockholm-3 model; VDT: volume doubling time

Fig. 2. Distribution of completed RBS programmes worldwide.



RBS: risk-based screening

Figs. 3. Traffic-light plots describing the risk of bias as assessed by (A, C) Cochrane Risk-of-Bias 2 tool and (B, D) Cochrane Risk Of Bias In Non-randomised Studies of Interventions stratified by studies and risk-of-bias domains, respectively.

(A)

		Risk of bias					
		D1	D2	D3	D4	D5	Overall
Study	Pedersen 2015	⊖	⊕	⊕	⊕	⊕	⊖
	Field 2016	⊕	⊕	⊕	⊕	⊕	⊕
	Nordström 2021	⊕	⊖	⊖	⊖	⊕	⊗
	Kortlever 2022	⊕	⊕	⊕	⊕	⊕	⊕
	Trevena 2022	⊕	⊕	⊗	⊖	⊖	⊗
	Chen 2023	⊕	⊕	⊕	⊕	⊕	⊕
	Emery 2023	⊕	⊕	⊕	⊕	⊕	⊕
	Plys 2024	⊕	⊗	⊕	⊖	⊕	⊗

D1: Randomisation process

D2: Deviations from intended interventions

D3: Missing outcome data

D4: Measurement of the outcome

D5: Selection of the reported result

Judgement

⊗ High

⊖ Unclear

⊕ Low

Figs. 3. Traffic-light plots describing the risk of bias as assessed by (A, C) Cochrane Risk-of-Bias 2 tool and (B, D) Cochrane Risk Of Bias In Non-randomised Studies of Interventions stratified by studies and risk-of-bias domains, respectively. (Cont'd)

(B)

	Risk of bias							Overall
	D1	D2	D3	D4	D5	D6	D7	
Stojadinovic 2008	+	-	+	X	+	+	-	X
Venturini 2013	+	+	+	+	+	+	+	+
Budal 2014	-	+	+	-	+	-	-	X
Gronberg 2015	+	+	+	-	+	+	+	-
Yen 2016	+	+	+	X	+	+	+	-
Yousaf-Khan 2016	-	-	+	-	X	+	+	X
Guivatchian 2017	+	-	+	+	+	+	+	-
Swenen 2017	-	+	+	-	-	+	-	X
Li 2018	+	+	-	-	+	+	-	-
Dwarte 2019	+	-	+	+	+	+	-	-
Chen 2021	+	+	+	-	+	+	-	-
Loopik 2021	+	+	+	+	+	+	+	+
Reesink 2021	-	-	+	-	X	+	-	X
Xu 2021	-	+	+	+	+	+	-	-
Adeoye 2022	+	-	+	+	+	-	-	-
Michael 2022	-	+	+	-	X	+	+	X
Chiu 2023	+	+	+	+	+	+	+	+
Gareth Evans 2023	-	+	+	+	-	+	+	-
Padrik 2023	+	+	+	+	+	+	+	+
Alterbeck 2024	-	-	+	+	X	+	+	X
Dong 2024	+	+	+	-	-	+	+	-
Manuc 2024	+	+	-	-	+	+	-	-
Tammemagi 2024	+	-	+	+	+	+	+	-
Walker 2024	+	+	+	+	+	+	+	+
Yu 2024	-	-	+	-	-	+	-	X

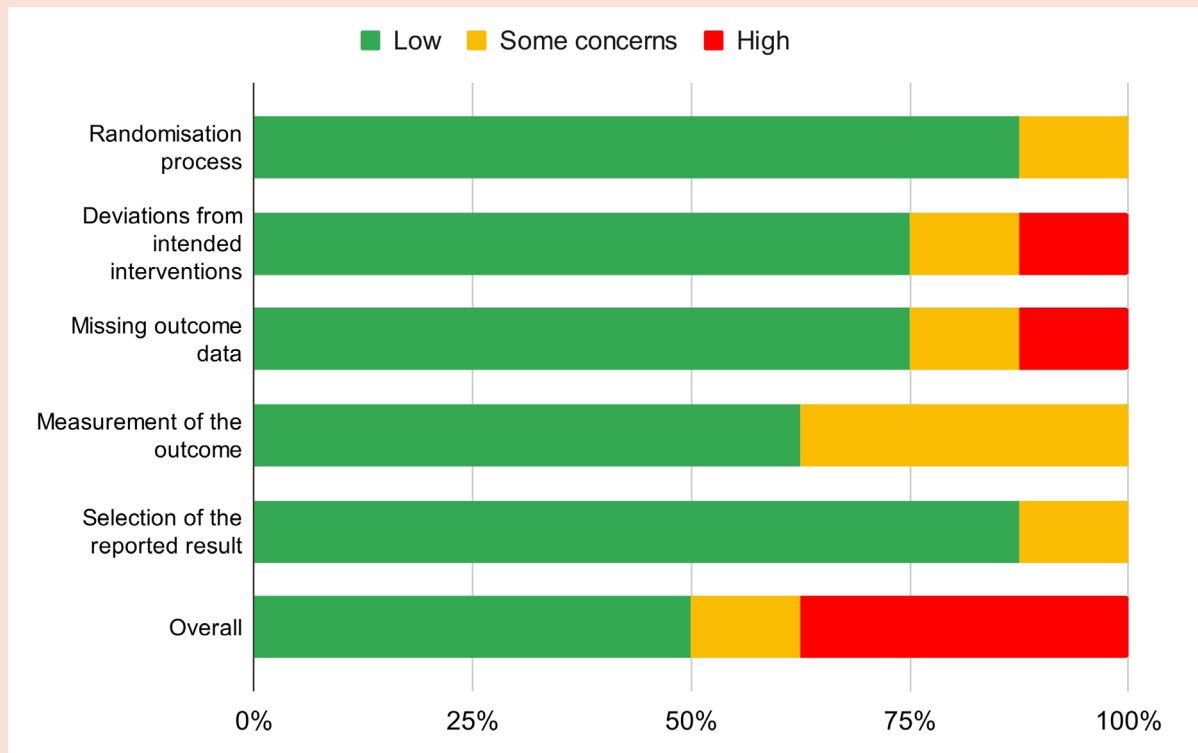
Study

D1: Bias due to confounding
D2: Bias in the selection of participants into the study
D3: Bias in the classification of interventions
D4: Bias due to deviations from intended interventions
D5: Bias due to missing data
D6: Bias in the measurement of outcomes
D7: Bias in the selection of the reported result

Judgement
X High
- Unclear
+ Low

Figs. 3. Traffic-light plots describing the risk of bias as assessed by (A, C) Cochrane Risk-of-Bias 2 tool and (B, D) Cochrane Risk Of Bias In Non-randomised Studies of Interventions stratified by studies and risk-of-bias domains, respectively. (Cont'd)

(C)



(D)

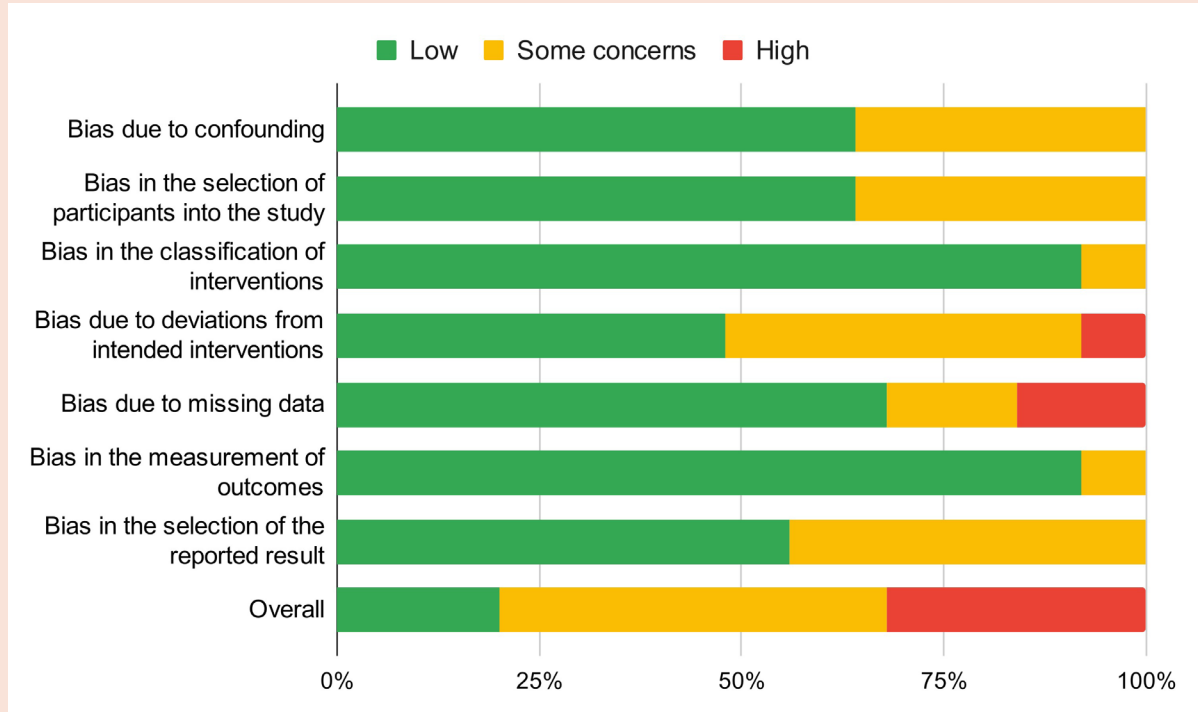


Table 2. Summary of risk stratification methods reported across included studies.

Cancer type	Risk stratification methods	Validated risk models
Breast	- Clinical breast examination - Gene testing for polygenic risk scoring - Point-of-care mammogram - Point-of-care electrical impedance scanning - Self-report or clinic-administered risk questionnaires	BOADICEA Gail model Tyrer-Cuzick model
	- Cervical cytology - Point-of-care human papillomavirus testing	None
Colorectal	- Fecal immunochemical test - Self-report or clinic-administered risk questionnaires	Asia Pacific Colorectal Screening Score
Lung	- Computed tomography imaging - Self-report or clinic-administered risk questionnaires	Liverpool Lung Model PLCO _{m2012}
Nasopharyngeal	Epstein-Barr virus serology	None
Oral	- Visual oral examination - Self-report or clinic-administered risk questionnaires	None
Pancreatic	- Blood test - Endoscopic ultrasound of pancreas - Self-report or clinic-administered risk questionnaires	PancPRO
Prostate	- Blood test - Gene testing for high-risk polymorphisms - Manual prostate examination - Magnetic resonance imaging results - Prostate serum antigen test - Self-report or clinic-administered risk questionnaires	STHLM3 European Randomized Study of Screening for Prostate Cancer

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; PLCO_{m2012}: Prostate, Lung, Colorectal, and Ovarian; STHLM3: Stockholm - Model 3

colorectal cancer screening^{33,38,43,45,46,51,53} and referral to a specialist or an oncology clinic for follow-up.^{18,19,28,33,42,56} One study further recommended discussion with a clinician for the initiation of chemoprevention therapy of breast cancer.⁴⁰ Participants within the moderate-risk strata were recommended non-invasive tests instead or returned to routine screening with a higher frequency than average participants.

RBS outcomes

Cancer risk and survivorship outcomes

Of the 33 studies, 10 studies did not record cancer diagnoses as an outcome measure among the risk-stratified participants.^{18,31,33,38,40,41,43,44,48,50} Seven studies found that higher risk-strata participants had a statistically significant higher rate of cancer diagnosis than lower risk-strata participants,^{28,30,39,42,44,50,54} which concurred with the theoretical risk model findings of the respective studies. In the remaining studies that reported cancer diagnosis endpoints, 4 studies reported a follow-up duration of less than a year,^{35,37,46,47} 14 studies reported a follow-up duration between 1 and 5 years,^{27,30,32,36,42,45,49,52,53,55-57,70,72} while 5 studies

followed up with patients for 5 years or more.^{28,29,39,51,54} In terms of outcomes, 2 studies found that RBS participants had a statistically significant higher rate of cancer diagnosis than control participants,^{36,41} while 3 studies found that RBS was non-inferior to the control paradigm in diagnosing cancer.^{29,46,53} Only one study, the Danish Lung Cancer Screening Trial, reported on the mortality outcomes of participants, specifically that there was no significant differences in lung cancer mortality between the participants that underwent RBS and those that did not undergo screening.³⁹

Only 12 studies reported at least one measure of diagnostic test accuracy of the implemented RBS programme,^{28,30,34,36,40,44-46,54,55,57} such as sensitivity or area under the receiver operating characteristic curve.

Participant uptake and acceptability

Nine studies reported on the extent of uptake of strata-specific interventions.^{18,19,29,30,33,34,37,38,43,44,46-49,51,53,56,57} The median proportion of high-risk participants that received their strata-specific intervention was 71.3% (IQR 38.8%), 75.4% (IQR 38.3%) for moderate-risk participants and 67.9% (IQR 55.0%) for low-risk participants. One study found that risk-stratified

Table 3. Summary of follow-up interventions for each cancer type stratified by risk level.

Cancer type	Risk		
	Low	Moderate	High
Breast	Routine screening	Early initiation of mammogram Higher frequency of mammogram	Referral for mammogram and magnetic resonance imaging Discussion for chemoprevention therapy
Cervical	Routine screening Follow-up cytology	Not applicable	Immediate colposcopy with or without biopsy
Colorectal	Fecal occult blood test/fecal immunochemical test Routine screening	Higher frequency of colonoscopy	Genomic evaluation Immediate colonoscopy Referral to cancer specialist centre
Lung	Routine screening	Follow-up computed tomography	Immediate computed tomography imaging Referral to multidisciplinary oncology team Referral to pulmonologist
Nasopharyngeal	Routine follow-up	Blood test	Nasoendoscopy
Oral	Routine opportunistic screening	Scheduled screening on availability	Screening required
Pancreatic	Not applicable	Regular endoscopic ultrasound for a duration	Close surveillance
Prostate	Routine screening	Systematic prostate biopsy	Magnetic resonance imaging-guided and systematic prostate biopsy Referral to urology

participants who were made aware of their cancer risk assessment were significantly more likely to undergo risk-appropriate screening than those who did not.¹⁸ Three studies reported significant positive changes in patient-reported outcomes, such as decreased anxiety towards cancer, high satisfaction with the screening process or increased perceived risk of cancer.^{18,34,50} One study further reported qualitative findings, following an in-depth interview of the participants, which concluded that participants found genetic counselling useful as they gained knowledge of their own risk factors for cancer and were empowered to proactively self-monitor or act upon their cancer risk profile.⁵⁰

Cost-effectiveness and healthcare utilisation

Seven studies analysed the comprehensive health services and outcomes of RBS programmes, yielding promising results.^{18,19,32,34,49,51,53} The majority of these studies^{18,32,49,51,53} concluded that RBS can lead to potential cost savings and a significant increase in quality-adjusted life years compared to existing screening guidelines. Additionally, one study found that RBS resulted in substantially reduced rates of

unnecessary biopsies,¹⁹ while another study revealed that RBS programmes did not lead to increased waiting times for computed tomography scans, despite the increased scan volume.³⁴

DISCUSSION

Significant developments have facilitated the translation of cancer risk prediction models into the real-world implementation of RBS programmes to stratify asymptomatic individuals for risk-appropriate screening. To the authors' knowledge, this is the first systematic review to consolidate the evidence base for the real-world implementation of RBS programmes. A majority of the studies explored screening for colorectal cancer, followed by breast and prostate cancer with most RBS programmes employing algorithm-driven risk stratification or validated risk scoring equation based on the presence of risk factors. Although few studies have recorded cancer diagnoses among participants, available data indicate RBS programmes either outperform or demonstrate non-inferiority to standard screening guidelines. Furthermore, studies assessing participant acceptability found that those enrolled in RBS viewed such

programmes positively, citing improvements in education towards cancer risk and their options with respect to their individual propensities for cancer.

Although many risk models for various cancer types have been elucidated, the implementation of such models to inform risk-appropriate screening in the real-world setting remains poorly studied. Various *in silico* studies have demonstrated the potential cost-effectiveness of RBS over age-based screening paradigms,⁵⁸⁻⁶⁰ yet such cost-savings may be erroneously high as modelling studies often overestimate the real-world compliance rate to risk-appropriate screening among the participants. Hence, future studies on cancer screening can consider reporting health services outcomes, such as cost-savings incurred or disability-adjusted life-years, so as to quantify the cost-effectiveness of RBS in relation to the upfront costs of risk stratification. Factors impacting the attendance of RBS and subsequent follow-up visits are similar to that of traditional screening,⁶¹ including perceived lack of self-efficacy, fear of cancer diagnosis, cultural beliefs towards cancer and inconvenience.^{17,62,63} Recent work has shown that one way to overcome these barriers is through timely and reassuring communication of results and their implications to patients, as well as centring the discussion of cancer risk management around autonomy and self-efficacy.⁶² Our review found that participants in the higher risk strata had higher adherence to follow-up, which implies that differing sets of facilitators and barriers to RBS and follow-up exist between participants of different risk-strata. Thus, future research should focus on understanding these stratum-specific barriers to RBS attendance and follow-up adherence, thus enabling the development of targeted interventions that can be implemented alongside RBS programmes. Such studies can be part of a broader implementation framework, which can include approaches such as but not limited to (1) stratum-specific barrier assessment studies, (2) development of targeted interventions and (3) research into comparative effectiveness across different implementation strategies.

There may be public and provider resistance against the de-implementation of screening among supposedly low-risk participants if RBS were to be effectuated,⁶⁴ as it contradicts pre-existing age-based screening guidelines as recognised in the public consciousness.^{65,66} RBS may expose high-risk individuals to discrimination by insurers and employers. Furthermore, RBS that implements PRS derived from genomic testing may face even more significant challenges, such as high costs⁶⁷ and the ethico-legal consequences following genomic testing, including data privacy, test result uncertainty and conflict with personal and religious values.^{68,69} Thus, healthcare

system administrators and policymakers may consider consulting public opinion and work closely with private insurers to design fair and reasonable risk-stratification screening programmes. Subsequently, extensive public communication might be required to address the complexity underlying RBS programmes and to reconcile pre-existing sociocultural beliefs and ideas towards cancer screening, so as to enhance the public enthusiasm and uptake of such programmes. There is a role for healthcare professionals (HCPs) in the promotion of RBS as well, especially general practitioners and family medicine specialists, as they are often the first healthcare encounter that most patients have. A recent review reported that HCPs are more likely to accept and promote RBS if presented with robust evidence of its efficacy and cost-effectiveness that outweighs the need for more resources and patient-facing work.⁷⁰ Thus, healthcare administrators and policymakers can also consider providing more support to HCPs on-the-ground in the implementation of such programmes, by having guideline update sessions, providing more administrative support or streamlining care pathways for referrals.

Even if RBS were to be implemented in spite of the aforementioned barriers, consideration must be given to underserved populations and the applicability of models to non-Caucasian populations. In this systematic review and among other studies, most risk-prediction models were derived from the case-control studies of majority-Caucasian cohorts, such as the Stockholm-3 model,⁷¹ BOADICEA model⁷² and PLCO_{m2012}⁷³ model. Thus, the transferability of these models to non-Caucasian populations is limited, which explains the observed lack of RBS studies in the Asia-Pacific, South American and Middle Eastern–North African (MENA) regions. Yet, it is precisely these same countries that may benefit the most from RBS due to the potential cost-savings and patient harm reduction observed in successful programmes, suggesting its suitability for adoption in low-resource regions within those geographies. As such, there exist ethnic disparities in early cancer detection tools, which are further compounded by existing socioeconomic inequalities that already complicate healthcare access among underserved populations.^{74,75} Of note, China is an exception as researchers were able to utilise the China Kadoorie Biobank to derive risk-prediction models representative of their population,⁷⁶⁻⁷⁸ although no real-world implementation of these models has been recorded to our knowledge. One study⁵³ also utilised the Asia-Pacific Colorectal Screening Score⁷⁹ in the implementation of RBS, which is more representative of Asian populations.

Despite the above problems, RBS remains a promising way forward for cancer screening based on the findings of this review. First, RBS was able to

reduce costs and excessive patient harm by reducing the number of unnecessary investigations while maintaining good accuracy in diagnosing true cancers. This was achieved when RBS programmes were able to match the appropriately powered investigation to the risk level of the individual. Furthermore, the participants viewed genomic testing for cancer screening positively, and the newfound knowledge empowered them to manage their cancer risk levels appropriately. Hence, such factors underlying the acceptability or refusal of an individual to RBS must be better studied to inform the real-world implementation of RBS, such that it can achieve high uptake in both screening and follow-up across all demographics.

In terms of quality assessment, study quality was poor among the non-randomised studies of intervention, as only 5 studies were rated with a low overall risk of bias. One significant factor was the absence of measures to account for deviations from the risk-stratified interventions among the participants. Studies either reported a low compliance rate of risk-stratified interventions among the participants or did not consider the capacity of participants to seek care and opinions extraneous to the study paradigm. This bias further translated to the high rates of lost-to-follow-up among some of the studies as well, since participants who did not comply with the risk-stratified intervention may drop out from the study altogether. Study quality was higher but could be improved among the RCTs, especially in terms of outcome measurement. This was so as among trials that assessed the initial compliance of RBS, outcomes were measured via participant self-reporting, which is less accurate than medical record linkage. Otherwise, the RCTs were generally well-designed and likely to report unbiased findings. In addition to risk of bias assessed by RoB2 and ROBINS-I, the authors further identified the potential for both differential verification bias and lead-time bias in these studies. Differential verification biases may arise because low-risk participants often received less rigorous or no follow-up investigations compared to high-risk participants, leading to the inconsistent verification of outcomes between groups. This could impact the assessment of diagnostic accuracy by inflating the detection rates among high-risk participants who received more intensive evaluations. Additionally, lead-time bias may influence survival outcomes, as high-risk participants are likely diagnosed earlier due to expedited diagnostic testing, which may appear to extend survival compared to low-risk individuals. Studies evaluating treatment, morbidity and mortality outcomes among these cohorts should therefore account for both differential verification bias and lead-time bias to provide a more accurate interpretation of RBS effectiveness.

The primary strength of our review was the comprehensiveness of the search done across 7

databases. Furthermore, our review focused on implementation trials to address the translation gap of cancer risk prediction models with a comprehensive synthesis of outcomes beyond that of usual clinical indicators, such as diagnostic test accuracy measures or mortality estimates. However, there are some limitations. The main limitation is that of the significant heterogeneity in study designs and outcomes reported across the included studies. As such, meta-analysis was precluded from our review as well as limiting the comparability of results between trials. However, as RBS is a complex public health intervention, such heterogeneity is expected especially in a real-world implementation setting. Thus, the authors attempted to improve the interpretability of results by using a systematic approach in narrative synthesis and summarising key risk stratification methodologies by cancer types.

CONCLUSION

The RBS of cancer is being implemented worldwide, following the *in silico* development and validation of various cancer risk prediction models. A majority of real-world-implemented RBS programmes screened for colorectal cancer, followed by breast and prostate cancer. Most studies were conducted in either the North American or European region, with most Asian studies conducted in China. More risk prediction models need to be developed primarily from non-Caucasian cohorts to facilitate the translation of RBS to Asian, South American and MENA settings. This review also suggests concerns regarding the uptake of risk-appropriate screening in real-world settings, necessitating qualitative studies to elucidate the facilitators and barriers of RBS among patients and clinicians alike. As RBS becomes increasingly mainstream, subsequent studies must take care in adjusting for potential lead time and verification bias when assessing survivorship outcomes, while also evaluating the cost-effectiveness and ethico-legal considerations of personalised screening strategies.

Supplementary material

Table S1. Complete search strategies used for retrieval of articles in this systematic review in the following databases: (A) CENTRAL, (B) CINAHL, (C) Embase and MEDLINE on OvidSP, (D) PubMed, (E) SCOPUS and (F) Web of Science.

Ethics statement

Not applicable, as no new data were collected from human or animal subjects.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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REFERENCES

- Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229-63.
- Office for National Statistics. Cancer survival by stage at diagnosis for England (experimental statistics): Adults diagnosed 2012, 2013 and 2014 and followed up to 2015. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfollowedupto2015>. Accessed 8 August 2024.
- Li YL, Qin YC, Tang LY, et al. Patient and Care Delays of Breast Cancer in China. *Cancer Res Treat* 2019;51:1098-106.
- Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *Br J Cancer* 2015;112:S92-107.
- Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ* 2020;371:m4087.
- Brawley OW, Kramer BS. Cancer screening in theory and in practice. *J Clin Oncol* 2005;23:293-300.
- Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin* 2017;67:100-21.
- Arnold M, Karim-Kos HE, Coebergh JW, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. *Eur J Cancer* 2015;51:1164-87.
- Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010. *JAMA Surg* 2015;150:17-22.
- Kerlikowske K, O’Kane ME, Esserman LJ. Fifty years of age-based screening: time for a new risk-based screening approach. *Evid Based Med* 2014;19:183.
- Harris RP, Sheridan SL, Lewis CL, et al. The harms of screening: a proposed taxonomy and application to lung cancer screening. *JAMA Intern Med* 2014;174:281-5.
- Heleno B, Thomsen MF, Rodrigues DS, et al. Quantification of harms in cancer screening trials: literature review. *BMJ* 2013;347:f5334.
- Fitzgerald RC, Antoniou AC, Fruk L, et al. The future of early cancer detection. *Nat Med* 2022;28:666-77.
- Crosby D, Bhatia S, Brindle KM, et al. Early detection of cancer. *Science* 2022;375:eaay9040.
- Lee A, Mavaddat N, Wilcox AN, et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet Med* 2019;21:1708-18.
- Khan SA, Hernandez-Villafuerte KV, Muchadeyi MT, et al. Cost-effectiveness of risk-based breast cancer screening: A systematic review. *Int J Cancer* 2021;149:790-810.
- Rainey L, van der Waal D, Wengström Y, et al. Women’s perceptions of the adoption of personalised risk-based breast cancer screening and primary prevention: a systematic review. *Acta Oncol* 2018;57:1275-83.
- Emery JD, Jenkins MA, Saya S, et al. The Colorectal cancer Risk Prediction (CRISP) trial: a randomised controlled trial of a decision support tool for risk-stratified colorectal cancer screening. *Br J Gen Pract* 2023;73:e556-65.
- Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol* 2015;16:1667-76.
- Velentzis LS, Freeman V, Campbell D, et al. Breast Cancer Risk Assessment Tools for Stratifying Women into Risk Groups: A Systematic Review. *Cancers (Basel)* 2023;15:1124.
- Fabbro M, Hahn K, Novaes O, et al. Cost-Effectiveness Analyses of Lung Cancer Screening Using Low-Dose Computed Tomography: A Systematic Review Assessing Strategy Comparison and Risk Stratification. *Pharmacoecon Open* 2022;6:773-86.
- Cumpston M, Flemyng E, Thomas J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). <https://www.cochrane.org/authors/handbooks-and-manuals/handbook/archive/v6.4>. Accessed 10 July 2025.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int J Surg* 2021;88:105906.
- Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:14898.
- Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
- McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods* 2021;12:55-61.
- Yu YQ, Jiang MY, Zhang X, et al. Effectiveness of high-risk human papillomavirus genotyping for cervical cancer screening. A multicentre screening cohort study in rural China. *An Sist Sanit Navar* 2024;47:e1065.
- Yousaf-Khan U, van der Aalst C, de Jong PA, et al. Risk stratification based on screening history: the NELSON lung cancer screening study. *Thorax* 2017;72:819-24.
- Yen AMF, Tsau HS, Fann JCY, et al. Population-Based Breast Cancer Screening With Risk-Based and Universal Mammography Screening Compared With Clinical Breast Examination: A Propensity Score Analysis of 1 429 890 Taiwanese Women. *JAMA Oncol* 2016;2:915-21.
- Xu HF, Liu Y, Luo YL, et al. The Risk Stratification for Cervical Cancer and Precursors of Domestic HPV Testing With HPV 16/18 Genotyping in Women With NILM Cytology in Central China: A Cohort Study. *Front Oncol* 2021;11:716762.
- Walker MJ, Blackmore KM, Chang A, et al. Implementing Multifactorial Risk Assessment with Polygenic Risk Scores for Personalized Breast Cancer Screening in the Population Setting: Challenges and Opportunities. *Cancers (Basel)* 2024;16:2116.
- Venturini E, Losio C, Panizza P, et al. Tailored breast cancer screening program with microdose mammography, US, and MR Imaging: short-term results of a pilot study in 40-49-year-old women. *Radiology* 2013;268:347-55.
- Trevena LJ, Meiser B, Mills L, et al. Which Test Is Best? A Cluster-Randomized Controlled Trial of a Risk Calculator and Recommendations on Colorectal Cancer Screening Behaviour in General Practice. *Public Health Genomics* 2022;1-16.
- Tammemägi MC, Darling GE, Schmidt H, et al. Risk-based lung cancer screening performance in a universal healthcare setting. *Nat Med* 2024;30:1054-64.
- Swenen L, Bleret V, Lifrang E, et al. [A new approach to breast cancer screening]. *Rev Med Liege* 2017;72:87-91.
- Stojadinovic A, Nissan A, Shriver CD, et al. Electrical impedance scanning as a new breast cancer risk stratification tool for young women. *J Surg Oncol* 2008;97:112-20.
- Reesink DJ, Schilham MGM, van der Hoeven EJ, et al. Comparison of risk-calculator and MRI and consecutive pathways

- as upfront stratification for prostate biopsy. *World J Urol* 2021;39:2453-61.
38. Plys E, Bulliard JL, Chaouch A, et al. Colorectal Cancer Screening Decision Based on Predicted Risk: Protocol for a Pilot Randomised Controlled Trial. *JMIR Res Protoc* 2023; 12:e46865.
 39. Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial—overall design and results of the prevalence round. *J Thorac Oncol* 2009;4:608-14.
 40. Padrik P, Puustusmaa M, Tönnison N, et al. Implementation of Risk-Stratified Breast Cancer Prevention With a Polygenic Risk Score Test in Clinical Practice. *Breast Cancer (Auckl)* 2023;17:11782234231205700.
 41. Nordström T, Discacciati A, Bergman M, et al. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. *Lancet Oncol* 2021;22:1240-9.
 42. Michael ZD, Kotamarti S, Arcot R, et al. Initial Longitudinal Outcomes of Risk-Stratified Men in Their Forties Screened for Prostate Cancer Following Implementation of a Baseline Prostate-Specific Antigen. *World J Mens Health* 2023;41:631-9.
 43. Manuc M, Diculescu M, Dumitru E, et al. Introducing Colorectal Cancer Screening in Romania - Preliminary Results from the Regional Pilot Programs (ROCCAS). *J Gastrointest Liver Dis* 2024;33:37-43.
 44. Loopik DL, Koenjer LM, Siebers AG, et al. Benefit and burden in the Dutch cytology-based vs high-risk human papillomavirus-based cervical cancer screening program. *Am J Obstet Gynecol* 2021;224:200.e1-200.e9.
 45. Li W, Zhao LZ, Ma DW, et al. Predicting the risk for colorectal cancer with personal characteristics and fecal immunochemical test. *Medicine (Baltimore)* 2018;97:e0529.
 46. Kortlever TL, van der Vlugt M, Duijkers FAM, et al. Diagnostic yield of a risk model versus faecal immunochemical test only: a randomised controlled trial in a colorectal cancer screening programme. *Br J Cancer* 2023;129:791-6.
 47. Guivatchian T, Koeppe ES, Baker JR, et al. Family history in colonoscopy patients: feasibility and performance of electronic and paper-based surveys for colorectal cancer risk assessment in the outpatient setting. *Gastrointest Endosc* 2017;86:684-91.
 48. Gareth Evans D, McWilliams L, Astley S, et al. Quantifying the effects of risk-stratified breast cancer screening when delivered in real time as routine practice versus usual screening: the BC-Predict non-randomised controlled study (NCT04359420). *Br J Cancer* 2023;128:2063-71.
 49. Field JK, Duffy SW, Baldwin DR, et al. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess* 2016;20:1-146.
 50. Dwarte T, McKay S, Johns A, et al. Genetic counselling and personalised risk assessment in the Australian pancreatic cancer screening program. *Hered Cancer Clin Pract* 2019;17:30.
 51. Dong X, Du L, Luo Z, et al. Combining fecal immunochemical testing and questionnaire-based risk assessment in selecting participants for colonoscopy screening in the Chinese National Colorectal Cancer Screening Programs: A population-based cohort study. *PLoS Med* 2024;21:e1004340.
 52. Chiu PK, Lam TY, Ng CF, et al. The combined role of MRI prostate and prostate health index in improving detection of significant prostate cancer in a screening population of Chinese men. *Asian J Androl* 2023;25:674-9.
 53. Chen H, Shi J, Lu M, et al. Comparison of colonoscopy, fecal immunochemical test, and risk-adapted approach in a colorectal cancer screening trial (TARGET-C). *Clin Gastroenterol Hepatol* 2023;21:808-18.
 54. Chen GH, Liu Z, Ji MF, et al. Prospective assessment of a nasopharyngeal carcinoma risk score in a population undergoing screening. *Int J Cancer* 2021;148:2398-406.
 55. Budal EB, Haugland HK, Skar R, et al. HPV DNA testing improves CIN2+ risk stratification and detection of CIN2+ in delayed triage of ASCUS and LSIL. A population-based follow-up study from Western Norway. *Cancer Med* 2014;3:182-9.
 56. Alterbeck M, Thimansson E, Bengtsson J, et al. A pilot study of an organised population-based testing programme for prostate cancer. *BJU Int* 2024;133:87-95.
 57. Adeoye J, Sakeen Alkandari A, Tan JY, et al. Performance of a simplified scoring system for risk stratification in oral cancer and oral potentially malignant disorders screening. *J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol* 2022; 51:464-73.
 58. Dan YY, Chuah BYS, Koh DCS, et al. Screening based on risk for colorectal cancer is the most cost-effective approach. *Clin Gastroenterol Hepatol* 2012;10:266-71.e1-6.
 59. Vilapriño E, Forné C, Carles M, et al. Cost-effectiveness and harm-benefit analyses of risk-based screening strategies for breast cancer. *PLoS One* 2014;9:e86858.
 60. Kumar V, Cohen JT, van Klaveren D, et al. Risk-Targeted Lung Cancer Screening. *Ann Intern Med* 2018;168:161-9.
 61. Weller DP, Patnick J, McIntosh HM, et al. Uptake in cancer screening programmes. *Lancet Oncol* 2009;10:693-9.
 62. Bas S, Sijben J, Bischoff EWMA, et al. Acceptability of risk-based triage in cervical cancer screening: A focus group study. *PLoS One* 2023;18:e0289647.
 63. Young B, Robb KA. Understanding patient factors to increase uptake of cancer screening: a review. *Future Oncol* 2021;17: 3757-75.
 64. Roberts MC. Implementation Challenges for Risk-Stratified Screening in the Era of Precision Medicine. *JAMA Oncol* 2018;4:1484-5.
 65. Haas JS, Sprague BL, Klabunde CN, et al. Provider Attitudes and Screening Practices Following Changes in Breast and Cervical Cancer Screening Guidelines. *J Gen Intern Med* 2016;31:52-9.
 66. Squiers LB, Holden DJ, Dolina SE, et al. The public's response to the U.S. Preventive Services Task Force's 2009 recommendations on mammography screening. *Am J Prev Med* 2011; 40:497-504.
 67. Aizuddin AN, Ramdhan AR, Syed Omar SA, et al. Genetic Testing for Cancer Risk: Is the Community Willing to Pay for It? *Int J Environ Res Public Health* 2021;18:8752.
 68. Frost CJ, Andrus IL, Buys SS, et al. Assessing patient readiness for personalized genomic medicine. *J Community Genet* 2019;10:109-20.
 69. Zhong A, Darren B, Loiseau B, et al. Ethical, social, and cultural issues related to clinical genetic testing and counseling in low- and middle-income countries: a systematic review. *Genet Med* 2021;23:2270-80.
 70. Taylor LC, Law K, Hutchinson A, et al. Acceptability of risk stratification within population-based cancer screening from the perspective of healthcare professionals: A mixed methods systematic review and recommendations to support implementation. *PLoS One* 2023;18:e0279201.
 71. Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50–69 years (STHLM3): a prospective population-based diagnostic study. *Lancet Oncol* 2015;16:1667-76.
 72. Antoniou AC, Pharoah PPD, Smith P, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer* 2004;91:1580-90.
 73. Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. *N Engl J Med* 2013;368:728-36.

74. O'Connor JM, Sedghi T, Dhodapkar M, et al. Factors Associated With Cancer Disparities Among Low-, Medium-, and High-Income US Counties. *JAMA Netw Open* 2018;1:e183146.
75. El Saghir NS, El Tomb PA, Carlson RW. Breast Cancer Diagnosis and Treatment in Low- and Mid-Resource Settings: the Role of Resource-Stratified Clinical Practice Guidelines. *Curr Breast Cancer Rep* 2018;10:187-95.
76. Zhu X, Lv J, Zhu M, et al. Development, validation, and evaluation of a risk assessment tool for personalized screening of gastric cancer in Chinese populations. *BMC Med* 2023;21:159.
77. Abhari RE, Thomson B, Yang L, et al. External validation of models for predicting risk of colorectal cancer using the China Kadoorie Biobank. *BMC Med* 2022;20:302.
78. Han Y, Lv J, Yu C, et al. Development and external validation of a breast cancer absolute risk prediction model in Chinese population. *Breast Cancer Res* 2021;23:62.
79. Yeoh KG, Ho KY, Chiu HM, et al. The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. *Gut* 2011;60:1236-41.