Benefits and harms of polygenic risk scores in organised cancer screening programmes: a cost-effectiveness analysis

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Summary

Background While polygenic risk scores (PRS) could enable the streamlining of organised cancer screening programmes, its current discriminative ability is limited. We conducted a cost-effectiveness analysis to trade-off the benefits and harms of PRS-stratified cancer screening in China.

Methods The validated National Cancer Center (NCC) modelling framework for six cancers (lung, liver, breast, gastric, colorectum, and oesophagus) was used to simulate cancer incidence, progression, stage-specific cancer detection, and risk of death. We estimated the number of cancer deaths averted, quality-adjusted life-years (QALY) gained, number needed to screen (NNS), overdiagnosis, and incremental cost-effectiveness ratio (ICER) of one-time PRS-stratified screening strategy (screening 25% of PRS-defined high-risk population) for a birth cohort at age 60 in 2025, compared with unstratified screening strategy (screening 25% of general population) and no screening strategy. We applied lifetime horizon, societal perspective, and 3% discount rate. An ICER less than $18,364 per QALY gained is considered cost-effective.

Findings One-time cancer screening for population aged 60 was the most cost-effective strategy compared to screening at other ages. Compared with an unstratified screening strategy, the PRS-stratified screening strategy averted more cancer deaths (61,237 vs. 40,329), had a lower NNS to prevent one death (307 vs. 451), had a slightly higher overdiagnosis (14.1% vs. 13.8%), and associated with an additional 130,045 QALYs at an additional cost of $1942 million, over a lifetime horizon. The ICER for all six cancers combined was $14,930 per QALY gained, with the ICER varying from $7928 in colorectal cancer to $39,068 in liver cancer. ICER estimates were sensitive to changes in risk threshold and cost of PRS tools.

Interpretation PRS-stratified screening strategy modestly improves clinical benefit and cost-effectiveness of organised cancer screening programmes. Reducing the costs of polygenic risk stratification is needed before PRS implementation.

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Keywords: Cancer screening; Polygenic risk score; Cost-effectiveness; China

Introduction

Cancer is the leading cause of death before the age of 70 years in China and worldwide.[1] Organised cancer screening programmes are among the most effective approaches to reduce cancer mortality.[2] One of the targets of the Healthy China 2030 programme is to improve 5-year cancer survival via cancer prevention and cancer screening. Currently, China is carrying out cancer screening programmes based on the six major types of cancer with the highest mortality, including lung, liver, gastric, colorectal, oesophageal, and female breast cancer.[3] The health impact of cancer screening is predicated on multiple factors, including cancer incidence, natural history of cancer progression, performances of

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Research in context

Evidence before this study

We searched PubMed and China National Knowledge Infrastructure databases, with no language restrictions, for studies of cost-effectiveness of polygenetic risk scores (PRS)-stratified cancer screening published up to April 30, 2023, using the terms ("cancer") AND ("screening") AND ("risk-stratified" OR "genetic score" OR "genetic risk" OR "PRS" OR "polygenetic risk scores" OR "polygenetic risk") AND ("cost" OR "cost-effectiveness" OR "health economic"). We found that most studies investigating PRS have explored the potential of utilizing them as risk assessment tools to improve the efficiency of cancer screening. A total of 10 studies in high-income countries investigated the cost-effectiveness of PRS-stratified screening strategy for prostate, colorectal, and breast cancer. Of the 10 studies, 8 concluded that polygenic risk-informed cancer screening was likely to be more cost-effective than alternatives. No analyses were identified that assessed the cost-effectiveness of deploying PRS tools for multi-cancer screening programmes to date.

Added value of this study

We evaluated the costs, benefits, harms and cost-effectiveness of PRS-stratified screening for six cancers (lung, liver, gastric, breast, colorectum, and oesophagus), using a modelling framework that incorporated data from the Chinese cancer screening programmes. The results suggested that adopting PRS tools to cancer screening programmes could improve the efficiency of screening while providing various benefits, such as averted more cancer deaths and a reduced NNS per one death averted. Although the overdiagnosis rate of PRS-stratified screening was slightly elevated, the additional harms it causes was much less than the benefits. However, the cost-effectiveness of PRS-based screening strategies was modest due to the elevated screening costs associated with whole-genome sequencing. Colorectal and female breast cancer were the most cost-effective cancer types for PRS-stratified screening strategy among the six cancers, while liver cancer is less likely to be considered as a feasible utilization case.

Implications of all the available evidence

Our study provided economic evidences for a PRS-stratified screening strategy for cancer screening programmes. Implementing PRS-stratified screening strategy could improve the efficiency and effectiveness of Chinese cancer screening programmes. However, applying PRS tools to population-based cancer screening programme were not likely to be cost-effectiveness currently, because the relatively higher costs of PRS-defined risk assessment. When the cost of whole-genome sequencing reduced sufficiently to enable PRS-stratified cancer screening to be economically feasible, a robust quantification of the benefits vs. harms as well as ethical and social implications of this approach will require a rigorous, randomized, population-level investigation. Incorporating PRS tools into the chronic disease prevention and control policies in China may maximize the health and economic benefits of comprehensive chronic disease prevention, such as expanding PRS tools developed for cancer screening to stroke and coronary heart disease screening.

screening modalities, and screening-related harms.[4] Tailoring screening to an individual's risk level could improve the efficiency of the screening programmes and reduce its harms.[5–8]

Genome-wide association studies (GWAS) have made it possible to identify single nucleotide polymorphisms (SNPs), herein called genetic variants, that are associated with an increased risk of developing different cancer types. Panels of these SNPs have been developed to generate polygenic risk scores (PRSs), which has been widely utilized for personalized risk assessment.[9,10] It is proposed that PRSs might enable more efficient targeting of existing cancer screening programmes in the United Kingdom.[4] However, risk-stratified screening would require assessing the risk of all populations, which would entail additional costs. Whether these incremental costs could be balanced by potential gains in yields like quality-adjusted life-years (QALYs) saved is a crucial issue that determines the feasibility of PRS application in the population. A total of 10 studies have assessed the cost-effectiveness of utilizing PRS in cancer screening, and 8 of these studies concluded that polygenic risk-informed cancer screening was likely to be more cost-effective than alternatives.[11] However, all of these studies predominantly concentrated in high-income countries and targeted a single type of cancer, such as prostate, colorectal, and breast cancer.[11] Whether deploying PRS tools for low- and middle-income countries and for multi-cancer screening programmes is cost-effective remains unknown.

This study aimed to assess the benefits, harms and cost-effectiveness of utilizing PRS-based risk assessment in Chinese cancer screening programmes for six leading cancers (lung, liver, gastric, colorectum, oesophagus, and female breast).

Methods

We used the National Cancer Center (NCC) mathematical modelling framework to simulate the natural histories of six cancers (lung, liver, breast, gastric, colorectum, and oesophagus) in China.[12] Firstly, we compared the cost-effectiveness of strategies for a one-time cancer screening at ages from 40 to 75 to determine the optimal screening age. Secondly, we estimated the investments, benefits, and harms of one-time screening at the optimal age for each cancer type in

three scenarios: PRS-stratified screening, unstratified screening, and no screening. Finally, we calculated the cost-effectiveness of PRS-stratified screening for each cancer type and all evaluated cancers combined, using the unstratified screening and no screening scenarios as the comparators.

Mathematical models

The NCC mathematical modelling framework is a collection of simulation models for six major cancers to support decision-making regarding screening in China.[12] All models were developed using extensively validated structures and calibrated to Chinese national epidemiological cancer data. Each cancer was modelled separately to simulate the natural histories represented by states of normal, precancerous lesion, stage-specific invasive cancer, and death. All models were constructed using the R software version 4.1.3 with base packages and the following additional packages: dplyr, doSNOW and foreach.

The models simulate males and females per single year age cohort, from the age of entry into the model and continue with annual time-steps until death or 85+ years of age (i.e., a combined age group of 85 years and older), whichever occurs first. Competing non-cancer mortality (i.e., risk of death from causes other than the specific cancer) was present in all states. As the simulated population ages, precancerous lesions may arise, and some can subsequently progress to preclinical cancer. Clinical signs and symptoms may occur at any time during the development of the disease, and preclinical cancers may be diagnosed. With screening, cancer may either be prevented at the precancerous stage or detected at an earlier stage with a more favourable prognosis. Thus, the incidence and/or mortality rate of cancer may be reduced. The models assumed that within-stage survival is worse for symptomatically detected cancers vs. screen-detected cancers, which is clinically plausible and consistent with the findings of screening studies.[13,14]

All models were calibrated to the observed empirical data, including sex- and age-specific cancer incidence and mortality from population-based cancer registration, and stage and histology distribution from hospital-based cancer registration.[15–17] We also externally validated the models against the cancer incidence and mortality observed from the China Kadoorie Biobank study,[18,19] a population-based prospective cohort of 0.5 million adults recruited in 2004–08 from 10 geographically defined regions in China.[20] Finally, we compared the model estimated survival rates to the observed net survival rates from population-based cancer registration.[21] Our validation exercise suggested that each NCC model reproduces cancer statistics for cancer registration and cancer cases observed in a large prospective cohort in China.[12] Period effects driven by the identified or unidentified cancer risk factors are considered in the calibrated models. We adjusted the onset of precancerous lesions to match sex-specific secular trends in incidence for each site (i.e., implicitly capturing the underlying effects of changing risk factors).[12]

Screening scenarios

The population within the targeted age ranges for cancer screening in China (i.e., aged 40–75 years) exceeds 630 million.[3] Challenges induced by the huge target population and limited healthcare resources make it almost impossible for China to consider repeat screening strategy in organised screening programmes. Similar to the strategies adopted in current organised cancer screening programmes in China,[3] our evaluation only considered the one-time cancer screening strategy. We assumed that the one-time screening would be provided in 2025 because China would require at least one year to mobilize the necessary healthcare resources. To determine the optimal age for the one-time screening strategy, we conducted separate simulations for residents aged 40–75 (with 5-year increments) who might receive organised screening in 2025. The optimal screening age was then determined using the cost-effectiveness plane (Appendix p 8). An optimal strategy for screening at age 60 was identified, because its incremental cost-effectiveness ratio (ICER) is lower than the cost-effectiveness threshold, when compared to the next-least-expensive strategy situated on the efficiency frontier (the next-best strategy).

We considered three screening scenarios, namely PRS-stratified screening, unstratified screening, and no screening (Fig. 1). We conducted separate simulations of these three scenarios in China from 2025 to 2050, at the optimal age of 60 years old, in order to capture the lifetime outcomes. Number of individuals of the birth cohort at age 60 in 2025 would be 22,519,389 (i.e., 11,242,616 of men and 11,276,773 of women). Cancer screening programmes in China adopted a three-stage procedure that includes risk assessment, clinical screening, and diagnostic work-up (Fig. 1). The eligible population assessed as high-risk will be referred to the corresponding clinical screening process; screen positive participants and false-positive screen results will receive diagnostic work-ups; screen detected patients with confirmed cancers or precancerous lesions will receive treatment or management as appropriate. For PRS-stratified screening scenarios, we assumed that 100% of the targeted population would receive a PRS-based risk assessment, and the risk threshold of PRS in base case analysis was 25% (i.e., top quartile). Individuals above the risk threshold were defined as high-risk population. An individual can be classified as a high-risk person for more than one cancer through PRS-based risk assessment and then go through multiple clinical screenings and possible diagnostic work-ups.

The key parameters for screening are outlined in Table 1. The odds ratio for cancer of PRS-defined 25%

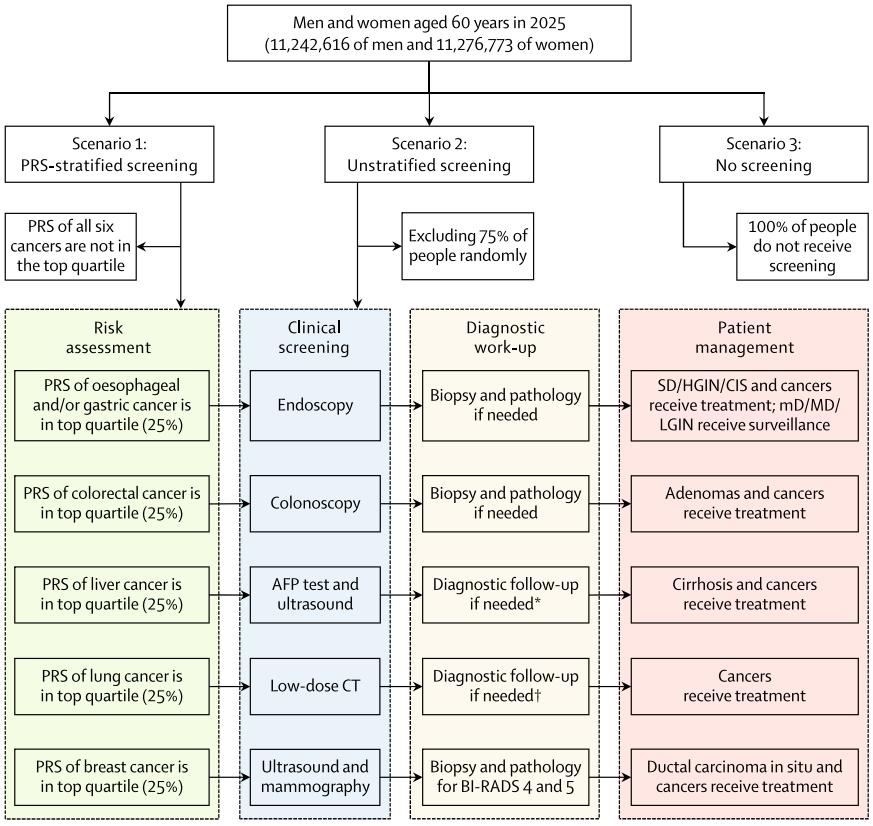

***Fig. 1:* Screening scenarios and procedures** * Only one of AFP test and ultrasound were positive, namely suspicious for liver cancer, but no definitive diagnosis. † Non-calcified solid nodule or part-solid nodule ≥6 mm, or non-solid nodule ≥8 mm, namely suspicious for lung cancer, but no definitive diagnosis. AFP, Alpha-Fetoprotein; BI-RADS, Breast Imaging Reporting and Data System; CIS, Carcinoma in Situ; CT, Computed Tomography; HGIN, High-Grade Intraepithelial Neoplasia; LGIN, Low-Grade Intraepithelial Neoplasia; MD, Moderate Dysplasia; mD, Mild Dysplasia; PRS, Polygenic Risk Score; SD, Severe Dysplasia.

high-risk quantiles were informed from population-based cohort studies in Chinese populations,[9,22–26] and the proportion of high-risk individuals in PRS-based risk assessment was estimated by assuming PRS follow a Gaussian distribution in populations.[4] Uptake rates of clinical screening, and risks of complications associated with screening tests were extracted from the cancer screening programme. The sensitivity and specificity of the screening tests were based on the diagnostic test accuracy studies. Detailed parameters, their ranges and data sources are listed in Appendix (pp 2–7).

Costs and utilities

From a societal perspective, the costs considered included those associated with PRS-stratified risk assessment, screening tests, diagnostic work-up, and treatments for cancer and precancerous lesions (Appendix pp 2–7). For risk assessment and screening tests, overheads related to the administration and promotion of the screening programme and the individuals' travel costs and time lost were also included. For precancerous lesions and invasive cancer treatments, we considered all components of direct medical costs, direct non-medical costs, and indirect costs. Cost data were obtained from the pilot cancer screening programme by employing a micro-costing method, except for the cost of PRS-stratified risk assessment, where we assumed a cost of $100 to sequence a human genome (i.e., for all evaluated cancers combined). Direct medical costs encompass all expenses associated with purchasing healthcare services, including costs from outpatient visits, hospitalizations, surgeries, radiotherapy, medications, diagnostic tests, consultations, nursing care, and bed charges. Direct non-medical costs were the expenses incurred to access healthcare services and support treatment activities, including costs related to transportation, meals, nutrition, accommodation, and expenses for caregivers. Indirect costs were estimated by multiplying the average salary with the time lost for both patients and their family caregivers.[27] All unit costs were adjusted to the year 2022 using the government-reported consumer price index for healthcare and then

Parameters	Colorectal cancer	Oesophageal cancer	Female breast cancer	Gastric cancer	Liver cancer	Lung cancer
Polygenic risk score						
Odds ratio for cancer for PRS-defined 25% high-risk quantile (vs. population average)	1.97	1.86	1.62	1.41	1.55	1.32
Percentage of cancers captured within the PRS-defined 25% high-risk quantile	43.52%	41.82%	37.92%	34.11%	36.69%	32.38%
Screening						
Screening modalities	Colonoscopy	Endoscopy[a]	Ultrasound and mammography	Endoscopy[a]	AFP and ultrasound	Low-dose CT
Uptake rate	0.44	0.49	0.90	0.49	0.70	0.70
Sensitivity for precancerous lesions	0.75, 0.85 and 0.95 for small, medium and large adenomas	0.41, 0.50, and 0.87 for mD, MD, and SD/CIS	0.79 for DCIS	0.79 for intraepithelial neoplasia/CIS	0.69 for cirrhosis	–
Sensitivity for cancer	0.95	0.94	0.93	0.87	0.63 and 0.97 for early- and late-stage	0.88
Specificity	0.94	0.92	0.93	0.91	0.84	0.91

Uncertainty intervals and data sources of all parameters are given in the Appendix Table S1. AFP, Alpha-Fetoprotein; CIS, Carcinoma in Situ; CT, Computed Tomography; DCIS, Ductal Carcinoma in Situ; MD, Moderate Dysplasia; mD, Mild Dysplasia; PRS, Polygenic Risk Score; SD, Severe Dysplasia. [a]One endoscopic screening for both oesophageal cancer and gastric cancer.

Table 1: **Characteristics of PRS tools and screening methods for six cancers.**

converted into US dollars using average exchange rates for 2022 (i.e., $1.00 US dollar = 7.00 Chinese yuan).

Utility losses specific to patients with precancerous lesions and cancers in stages I–IV were obtained from the cancer screening programme or meta-analysis (Appendix pp 2–7). Health-related quality of life was measured using the EQ-5D instruments and mapped to utility values. We assumed that the false-positive screen results had little impact on quality of life in the base-case analysis, whereas the utility weight was 0.98 in sensitivity analysis (i.e., a decrement in quality of life was assumed in sensitivity analysis).

Outcomes

Using unstratified screening strategy (screening 25% of general population) and no screening strategy as the comparators, we assessed the benefits, harms, and cost-effectiveness of PRS-stratified screening from a lifetime horizon. To assess the benefits of screening, we present averted cancer deaths and QALYs saved. To assess screening harms, we present the costs induced by screening related complications, the number needed to screen (NNS) clinically (i.e., clinical screening rather than risk assessment) per cancer death prevented, and the overdiagnosis rate (Appendix p 7). Overdiagnosis rate was defined as the number of overdiagnosed cancers divided by the number of screen-detected cancers. Overdiagnosed cancers were defined as the additional number of cancer cases expected in the screening scenarios (cancers diagnosed and the cancers that would develop from precancerous lesions if they were not removed at screening) compared with the estimated number of cases diagnosed in the no-screening scenarios.[28,29] To assess cost-effectiveness, we present undiscounted and discounted ICER. Both costs and health outcomes were discounted at a rate of 3% annually and presented as 2022 values.[30] The willingness-to-pay threshold of ICER was set at 1.5 times the Chinese gross domestic product per capita in 2022 (US$18,364) for one quality-adjusted life-year (QALY) gained.[31] Combined results for all evaluated cancers were obtained by aggregating the number of cases, deaths, screenings, costs, and QALYs for each cancer type, and then calculating ratios such as NNS, overdiagnosis rate, and ICERs.

Sensitivity analysis

We varied each input value in the model over a plausible range in the one-way deterministic sensitivity analyses to examine the impact of uncertainty in the individual input parameters on the outcomes of PRS-stratified screening. Probabilistic sensitivity analysis was conducted by performing 10,000 Monte Carlo simulations to sample parameter values from their distributions and estimate the outcomes. The results of the probabilistic sensitivity analysis were used to calculate the 95% uncertainty intervals (UIs) of the model results.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

By adopting a PRS-stratified screening strategy for six cancers in a birth cohort at age 60, a total of 61,237 cancer deaths would be averted over a lifetime horizon, which was 20,908 more deaths averted than with an

unstratified screening strategy (Table 2). For six cancers combined, the NNS to prevent one death was 307 in the PRS-stratified screening strategy and 451 in the unstratified screening strategy. The NNS to prevent one death varied from 152 for colorectal cancer to 1473 for liver cancer in the PRS-stratified screening strategy, and from 226 for colorectal cancer to 2140 for liver cancer in the unstratified screening strategy (Table 2). By adopting the PRS-stratified screening strategy, 14,073 (14.1%) of the screen-detected cancers were estimated to be overdiagnosed, compared to that of 9336 (13.8%) by adopting the unstratified screening strategy. For specific cancer types adopting the PRS-stratified screening strategy, female breast cancer had the highest overdiagnosis rate of 21.4%, while lung cancer had the lowest rate of 3.2% (Table 2). Screenings for five cancers among males result in a lower overdiagnosis rate and NNS to prevent one death, and avoid more cancer deaths compared to screenings for six cancers among females (Appendix pp 9 and 10).

Compared with no screening, unstratified screening resulted in an additional 268,077 QALYs at an extra cost of $691 million, with an ICER of $2579 per QALY gained (Table 3). PRS-stratified screening, on the other hand, yielded an additional 398,122 QALYs at an extra cost of $2633 million, with an ICER of $6613 per QALY

Cancer type	Deaths averted	NNS per one death averted	QALYs saved[a]	Costs of screening complications (thousand $)	Overdiagnosed cases[b]	Overdiagnosis rate (%)
All six cancers						
Unstratified screening	40,329 (29,497–55,486)	451 (397–520)	476,032 (338,090–665,770)	3482 (1753–6686)	9336 (7897–10,614)	13.8 (12.5–14.5)
PRS-stratified screening	61,237 (43,818–85,525)	307 (256–383)	710,800 (496,102–1008,116)	3482 (1753–6686)	14,073 (11,332–16,974)	14.1 (12.7–14.4)
Colorectal cancer						
Unstratified screening	10,819 (7820–13,924)	226 (205–253)	103,064 (73,502–134,606)	670 (384–1058)	724 (578–853)	8.6 (7.0–10.4)
PRS-stratified screening	18,834 (13,444–24,716)	152 (136–173)	179,429 (126,083–237,707)	670 (384–1058)	1260 (1005–1490)	8.6 (7.0–10.4)
Oesophageal cancer						
Unstratified screening	4573 (3177–7043)	599 (524–702)	52,194 (35,911–80,053)	14 (10–397)	129 (106–161)	5.2 (4.1–6.3)
PRS-stratified screening	7651 (5308–11,792)	366 (319–432)	87,318 (60,146–134,854)	14 (10–397)	215 (178–269)	5.2 (4.1–6.3)
Female breast cancer						
Unstratified screening	6800 (5679–7754)	366 (333–412)	64,618 (49,877–78,284)	0	6345 (5422–7018)	21.4 (18.3–23.7)
PRS-stratified screening	10,316 (8078–12,579)	244 (206–297)	98,019 (72,253–125,243)	0	9624 (7736–11,519)	21.4 (18.3–23.7)
Gastric cancer						
Unstratified screening	9150 (6326–14,210)	299 (262–343)	105,934 (73,587–161,996)	14 (11–395)	747 (580–999)	10.9 (8.3–13.9)
PRS-stratified screening	12,485 (8490–19,518)	223 (192–264)	144,549 (98,560–223,198)	14 (11–395)	1020 (788–1365)	10.9 (8.3–13.9)
Liver cancer						
Unstratified screening	1817 (1392–2410)	2140 (1667–2668)	39,802 (29,837–50,783)	0	880 (699–1071)	20.7 (17.1–25.1)
PRS-stratified screening	2666 (1926–3682)	1473 (1099–1955)	58,409 (41,667–78,477)	0	1292 (963–1668)	20.7 (17.1–25.1)
Lung cancer						
Unstratified screening	7169 (5103–10,145)	544 (393–730)	110,419 (75,376–160,046)	2783 (1348–4836)	511 (336–736)	3.2 (2.1–4.6)
PRS-stratified screening	9285 (6572–13,238)	421 (303–572)	143,077 (97,393–208,638)	2783 (1348–4836)	661 (434–950)	3.2 (2.1–4.6)

The PRS-stratified screening strategy provided cancer screenings for 25% of the PRS-defined high-risk population (i.e., individuals with a PRS above the risk threshold of the top quartile), while the unstratified screening strategy provided cancer screenings for 25% of the general population. Components may not sum to totals due to rounding. NNS, number needed to screen; PRS=Polygenic risk scores; QALY, quality-adjusted life-years. [a]QALYs are undiscounted (0% discount). [b]Overdiagnosis rate was defined as the number of overdiagnosed cancers divided by the number of screen-detected cancers. Overdiagnosed cases are the additional number of cancer cases expected in the screening scenarios (cancers diagnosed and the cancers that would develop from precancerous lesions if they were not removed at screening) compared with the estimated number of cases diagnosed in the no-screening scenarios.

Table 2: **Benefits vs. harms of PRS-stratified screening and unstratified screening, compared with no screening.**

Cancer type	Compared with no screening				Compared with unstratified screening			
	Incremental cost (million $)[a]	QALYs saved[a]	Discounted ICER ($/QALY)[a]	Undiscounted ICER ($/QALY)[b]	Incremental cost (million $)[a]	QALYs saved[a]	Discounted ICER ($/QALY)[a]	Undiscounted ICER ($/QALY)[b]
All six cancers								
Unstratified screening	691 (497–947)	268,077 (185,302–381,028)	2579 (1972–3342)	1154 (724–1723)	–	–	–	–
PRS-stratified screening	2633 (1773–3711)	398,122 (271,702–573,216)	6613 (3868–10,731)	3591 (1924–6144)	1942 (1111–2979)	130,045 (78,033–203,059)	14,930 (7362–27,722)	8532 (4280–17,140)
Colorectal cancer								
Unstratified screening	53 (22–92)	53,997 (37,284–72,074)	984 (420–1746)	−236 (−582 to 181)	–	–	–	–
PRS-stratified screening	370 (218–564)	94,008 (64,385–126,901)	3939 (2112–7004)	1456 (429–3095)	317 (169–507)	40,012 (25,793–56,788)	7928 (3762–15,482)	3740 (1376–7875)
Oesophageal cancer								
Unstratified screening	49 (31–100)	30,332 (20,777–46,493)	1629 (1067–2845)	699 (342–1471)	–	–	–	–
PRS-stratified screening	384 (242–589)	50,745 (34,822–78,372)	7576 (3995–12,941)	4475 (2202–7869)	335 (184–523)	20,413 (14,030–31,781)	16,413 (7303–29,168)	10,087 (4292–18,118)
Female breast cancer								
Unstratified screening	206 (172–248)	33,942 (24,849–42,309)	6055 (4881–8497)	2669 (2146–3660)	–	–	–	–
PRS-stratified screening	436 (348–552)	51,487 (36,296–67,451)	8468 (6368–12,505)	4053 (2999–5955)	230 (152–330)	17,545 (9008–27,366)	13,135 (7979–25,489)	6732 (3871–13,438)
Gastric cancer								
Unstratified screening	37 (15–71)	61,769 (42,731–94,011)	605 (239–1007)	80 (−173 to 353)	–	–	–	–
PRS-stratified screening	374 (222–570)	84,286 (57,362–129,698)	4440 (2225–7687)	2524 (1098–4585)	337 (187–529)	22,516 (12,860–38,993)	14,960 (6509–30,610)	9227 (3826–19,216)
Liver cancer								
Unstratified screening	180 (136–215)	20,401 (14,329–26,913)	8825 (6265–12,087)	4863 (3554–6181)	–	–	–	–
PRS-stratified screening	553 (387–734)	29,938 (20,352–41,325)	18,459 (11,641–29,238)	10,259 (6580–15,593)	373 (219–557)	9537 (4246–16,321)	39,068 (18,708–91,519)	21,802 (10,583–50,649)
Lung cancer								
Unstratified screening	166 (120–221)	67,636 (45,333–99,228)	2453 (1544–3838)	1474 (915–2309)	–	–	–	–
PRS-stratified screening	515 (357–702)	87,659 (58,484–129,469)	5879 (3463–9628)	3769 (2206–6160)	349 (200–533)	20,023 (12,096–31,810)	17,453 (8510–33,348)	11,526 (5589–21,966)

The PRS-stratified screening strategy provided cancer screenings for 25% of the PRS-defined high-risk population (i.e., individuals with a PRS above the risk threshold of the top quartile), while the unstratified screening strategy provided cancer screenings for 25% of the general population. Components may not sum to totals due to rounding. ICER, incremental cost-effectiveness ratio; PRS, Polygenic risk scores; QALY, quality-adjusted life-years. [a]Discounted at an annual rate of 3% and presented as 2022 values. [b]0% discount.

Table 3: **Cost-effectiveness of PRS-stratified screening and unstratified screening.**

gained (Table 3). When compared with the unstratified screening strategy, the PRS-stratified screening strategy was associated with an additional 130,045 QALYs at an additional cost of $1942 million, giving an ICER of $14,930 per QALY gained. The ICER for colorectal cancer, female breast cancer, gastric cancer, oesophageal cancer, and lung cancer were $7928, $13,135, $14,960, $16,413, and $17,453 per QALY saved, respectively, all falling below the cost-effectiveness threshold of $18,364, but all higher than China's per capita income of $5269. In contrast, the ICER for liver cancer screening ($39,068 per QALY saved) exceeded the cost-effectiveness threshold (Table 3). The ICERs in females were higher than those in males for each cancer type, except for female breast cancer (Appendix pp 10 and 11).

The ICER lies below the cost-effectiveness threshold of $18,364 when the risk threshold ranges from the 18th to 74th percentile, with a minimum value of $12,441 per QALY gained at the 44th percentile (Fig. 2). With the risk-threshold adjustment, PRS-stratified screening for all cancers could be brought below the cost-effectiveness threshold, except for liver cancer (Fig. 2 and Appendix pp 12 and 13). The ICER linearly increased as the cost of sequencing a human genome increased. When the cost of sequencing a human genome was higher than $222, the PRS-stratified screening strategy for each of the six cancers was not likely to be cost-effective (Fig. 2).

In the sensitivity analysis, the ICER was found to be most sensitive to the potential range of the discount rate, cost of PRS-based risk assessment, proportion of high-risk individuals captured by PRS-based risk assessment, and variation of within-stage survival between symptomatically detected cancers vs. screen-detected cancers (Appendix pp 14–19). The parameter ranges explored may cause the ICER to exceed the Chinese willingness-to-pay threshold of $18,364 per QALY, except for colorectal cancer screening in males (Appendix pp 14–19). At a willingness to pay of $18,364 per QALY, the probabilities of cost-effectiveness for the PRS-stratified screening strategy ranged from 2.23% for liver cancer screening to 99.35% for colorectal cancer screening (Appendix pp 20–26).

Discussion

In this modelling study, we synthesized the best available data to simulate the benefits, harms, and cost-effectiveness of PRS in the screening of the six leading cancers in China. Our analysis suggested that PRS-based cancer screening would avoid more cancer deaths, reduce the NNS per death avoided, and save more QALYs compared to the unstratified screening. However, it also represented more overdiagnosed cases and higher screening costs. Trade-off the benefits, harms, and costs, the ICER of the PRS-stratified screening strategy was slightly lower than the cost-effectiveness threshold in China. Except for liver cancer, the ICERs of the other five cancers are below the threshold but higher than China's per capita income.

The PRS stratification may not fully address the numerous significant challenges that frequently impede cancer screening initiatives, including the overdiagnosis of indolent cancers. The PRS-stratified screening group demonstrated a relatively higher overall rate of overdiagnosis at 14.1%, albeit still considered acceptable. The overdiagnosis rates of breast cancer and liver cancer were relatively high. For breast cancer, the high overdiagnosis rate may due to the detection of indolent preclinical cancer and the detection of progressive preclinical cancer in women who would have died of an unrelated cause before clinical diagnosis.[28] For liver cancer, overdiagnosed cases include those that would develop from screen-detected cirrhosis if they were not treated. However, most cases of cirrhosis receive treatment not only because of the risk of developing liver cancer but also due to the competing risks of mortality from other liver diseases.[32] When comparing the benefit-to-harm of two screening strategies, both of which yielded an overdiagnosis to deaths averted ratio of 0.23. The ratio of overdiagnosis to cancer death averted in the PRS-stratified screening group for female breast cancer, as estimated in our modelling, was 0.93, which is comparable to the estimates made by Pashayan and colleagues in their analysis. Specifically, their study found that when 29% of the population above the risk threshold were screened, the ratio of overdiagnosis to cancer death averted was 0.99.[33] This suggests that our model is reasonably robust. In addition, we may overestimate the number of overdiagnoses in the PRS-stratified group, because we assumed that the probability of overdiagnosis does not vary by risk. Overdiagnosis has been shown to vary inversely by polygenic risk.[34,35] That is, if higher risk is associated with increased risk of progression of cancer, i.e., a shorter sojourn time, then overdiagnosis would be lower in the PRS-stratified screening group.

We present colorectal cancer and breast cancer as being the most cost-effective for PRS stratification among the six cancers on account of the combination of stronger PRS predictiveness and higher disease frequency than other cancers, along with the sensitivity and uptake rate of established cancer screening tools. This is consistent with previous studies, which have shown that risk stratification can main the benefits of screening for breast and colorectal cancer.[4,33,36] Besides, our study also first proved that PRS-stratified risk stratification is a cost-effective approach for gastric, oesophageal and lung cancer screening. Despite China's substantial burden of liver cancer, PRS-stratified screening for liver cancer is unlikely to be considered a feasible approach in this country. Screening for early-stage liver cancer using alpha-fetoprotein (AFP) and ultrasound demonstrated a low sensitivity, thereby

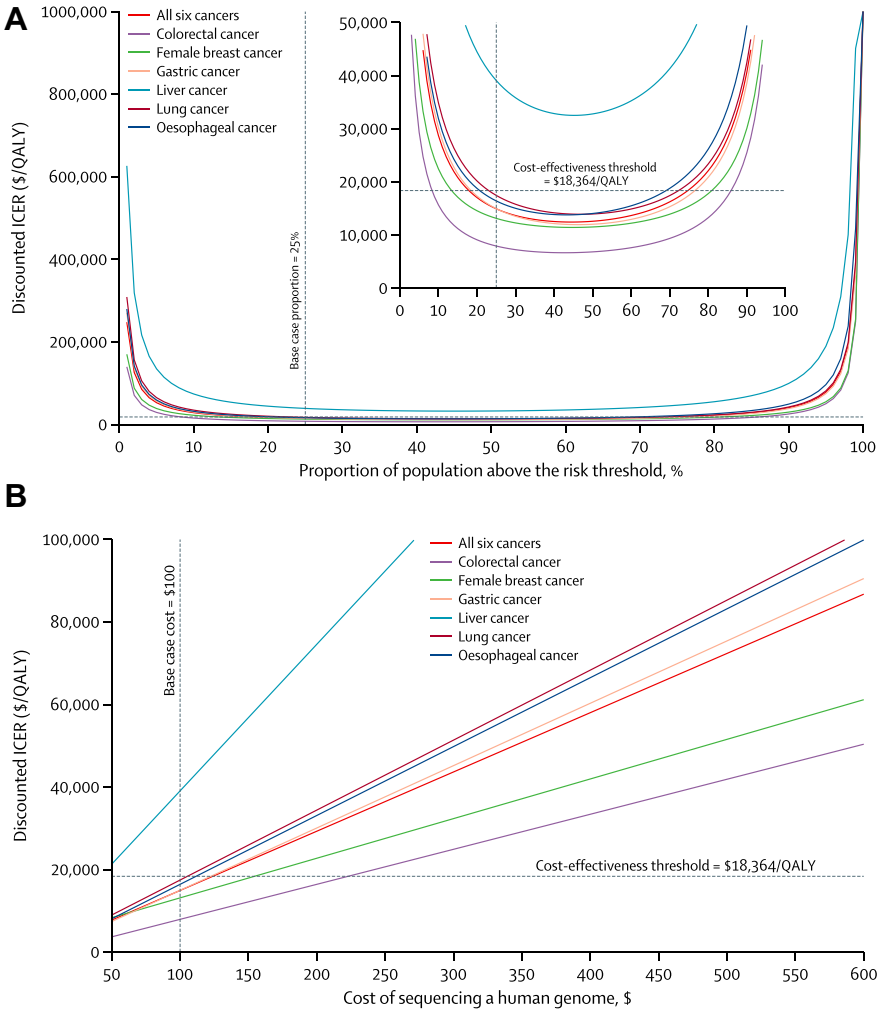

Fig. 2: **Incremental cost effectiveness ratios by (A) risk-threshold of PRS and (B) cost of PRS-based risk assessment**. Results are reported for PRS-stratified screening compared with unstratified screening. Proportion of population above the risk threshold were reported from 0 risk. The base case risk threshold is 25%, indicating that PRS-stratified screening strategy considered 25% of the population above the risk threshold. PRS, Polygenic Risk Score.

contributing to a higher ICER in liver cancer screening. Moreover, in China, more than 70% of liver cancers are attributable to hepatitis B and C virus infections,[37] resulting in diminished efficacy of PRS in identifying high-risk populations and optimizing the preservation of QALYs.

Although our modelling indicates that PRS-stratified screening strategies could improve the effectiveness of cancer screening, promoting PRS tools in Chinese cancer screening may still prove impractical considering the high ICER. Even with adjustments in the risk threshold, the ICER still exceeds $12,000 per QALY gained. The high cost of whole-genome sequencing is identified as the primary factor contributing to this barrier. With continued reductions in the costs associated with whole-genome sequencing, wider promotion and adoption of PRS-stratified screening in populations may become feasible. Another major factor limiting the use of PRS in cancer screening is its modest predictiveness for cancer. With the advancement of GWAS-related technologies and mathematical approaches, improvements in PRS predictiveness would be gained from the addition of newly discovered SNPs. However, the improvements may be marginal, as for most cancers, the aetiology is largely dominated by non-genetic factors and there is an upper limit to the heritability. For breast cancer, for example, the total heritability is estimated to be 31%, and for colorectal cancer is 15%.[38] Numerous studies have shown that lifestyle and epidemiological factors, including family history, smoking status, alcohol consumption, body mass index (BMI) and diet are associated with the development of cancer.

It has been demonstrated that incorporating these factors into models can enhance the predictiveness of PRS tools.[39] Therefore, combining PRS with other factors to stratify the population into several risk strata may be more effective in improving the cost-effectiveness of cancer screening.

Apart from the factors related to cost-effectiveness, the implementation of the PRS-stratified screening programme raises several other challenges. Due to the limited predictiveness of PRS, a significant number of incident cases will always be excluded from PRS-stratified screening programmes, as they are considered low risk. However, the majority of cancer cases may arise from the low-risk population defined by PRS, which is known as the Rose's prevention paradoxthe majority of cancer cases may arise from the low-risk population defined by PRS, which is known as the Rose's prevention paradox'the majority of cancer cases may arise from the low-risk population defined by PRS, which is known as the Rose prevention paradox. Another challenge is the potential for individuals classified as low-risk to neglect health lifestyle advice or relevant symptoms, while those classified as high-risk may experience heightened anxiety because lack of PRS-related health literacy. As such, it is important to engage the public in decisions about screening program modification, to base the decision on robust evidence, and to communicate the benefits and harms of cancer screening.

The Healthy China 2030 programme proposed to implement a comprehensive prevention and control strategy for chronic diseases, which includes strengthening the screening and early detection of other chronic diseases such as stroke and coronary heart disease, in addition to cancer. Since genetic factors play an important role in the occurrence and development of cardiovascular diseases, genetic risk scoring models based on PRS have been developed to predict and evaluate the risk of cardiovascular diseases,[40,41] indicating the potential value of PRS in cardiovascular disease screening. Given this improvment, PRS tools that are primarily based on cancer screening may also aid in the screening of cardiovascular diseases, which can further improve the health-economic benefits of overall chronic disease screening in China. However, further studies are required to assess the feasibility and efficacy of PRS-stratified screening programmes for cardiovascular diseases, and to explore the potential implications of these findings for public health policy in China.

Our study should be interpreted in light of its limitations. Firstly, our modelling assumed no difference in uptake on screen between the unstratified scenario and the PRS-stratified scenario. However, individuals identified as high-risk by risk assessment are more likely to participate in cancer screening.[42] As a result, our study may underestimate the effectiveness of PRS-stratified screening. Secondly, our model only accounted for the scenario of one-time screening, overlooking the implications of repeated screening, which is commonly adopted by the high-income countries.[3] While continuous screening does not incur additional PRS costs, the effectiveness of subsequent screenings is lower compared to the prevalent round screening. Therefore, the cost-effectiveness of utilizing PRS for continuous screening may also be depend upon the strategy of repeat screenings, therefore our results may not be generalizable to other populations. Thirdly, when calculating the combined results for all cancers, we did not consider the interactions between each cancer type. In the real-world screening, individuals may rarely participate in screenings for all six cancers. As such, the summation of all six cancers should not be considered as a realistic scenario but rather as a statistical indicator. Moreover, it is challenging to determine which screenings have higher priority in order to eliminate overlapping effects. Lastly, the parameters of our model were derived from the Chinese population, incorporating data from both prospective and case–control studies. For instance, due to the lack of population-based evaluation data, the odds ratio utilized to assess the performance of PRS in oesophageal cancer screening programme was informed by a large-scale case-control study in China, and there could have potential variability in real-world performance.[26] The generalizability of our findings may be limited, as the genetic heritability of cancer can vary significantly across different ancestries and regions.

In conclusion, our findings indicated that adopting a PRS-stratified screening strategy could bring several benefits and have the potential to improve the effectiveness of organised cancer screening programmes in Chinas .However, the higher ICERs suggested that the benefits may not outweigh the harms and costs associated with the use of PRS tools in a population-based cancer screening programme. The goal of PRS-stratified cancer screening should be to improve health outcomes while minimizing harms. Therefore, more evidence is needed before implementing PRS tools in Chinese cancer screening programmes, and further considering the ethical and social implications of large-scale genetic sequencing.

Contributors

CX, YX, and WC conceived the study. CX and YX acquired the data. CX built the model in R. YX and HL did the model validation. CX and YX drafted and finalised the manuscript. CX and WC had access to the data and verified the data. All authors interpreted the results, provided input to the manuscript, and approved the final manuscript for submission.

Data sharing statement

All the data used for the model in this study are available in the Appendix.

Declaration of interests
We declare no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101012.

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