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Article

Using Risk Stratification to Optimize Mammography Screening in Chinese Women

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Abstract

Background: The cost-effectiveness of mammography screening among Chinese women remains contentious. Here, we characterized breast cancer (BC) epidemiology in Hong Kong and evaluated the cost-effectiveness of personalized risk-based screening. **Methods:** We used the Hong Kong Breast Cancer Study (a case-control study with 3501 cases and 3610 controls) and Hong Kong Cancer Registry to develop a risk stratification model based on well-documented risk factors. We used the Shanghai Breast Cancer Study to validate the model. We considered risk-based programs with different screening age ranges and risk thresholds under which women were eligible to join if their remaining BC risk at the starting age exceeded the threshold. **Results:** The lifetime risk (15-99 years) of BC ranged from 1.8% to 26.6% with a mean of 6.8%. Biennial screening was most cost-effective when the starting age was 44 years, and screening from age 44 to 69 years would reduce breast cancer mortality by 25.4% (95% credible interval [CrI] = 20.5%-29.4%) for all risk strata. If the risk threshold for this screening program was 8.4% (the average remaining BC risk among US women at their recommended starting age of 50 years), the coverage was 25.8%, and the incremental cost-effectiveness ratio (ICER) was US$18 151 (95% CrI = $10 408-$27 663) per quality-of-life-year (QALY) compared with no screening. The ICER of universal screening was $34 953 (95% CrI = $22 820-$50 268) and $48 303 (95% CrI = $32 210-$68 000) per QALY compared with no screening and risk-based screening with 8.4% threshold, respectively. **Conclusion:** Organized BC screening in Chinese women should commence as risk-based programs. Outcome data (e.g., QALY loss because of false-positive mammograms) should be systemically collected for optimizing the risk threshold.

Globally breast cancer (BC) is the most common malignancy in women, accounting for an estimated one-quarter of all malignancies (1). Although BC is the top female cancer among Chinese populations and the incidence has been increasing (2), the lifetime risk of developing BC in Hong Kong, Shanghai, Singapore, Taiwan, and elsewhere in mainland China remains 32%-82% lower than that in Western populations (2-4). The epidemiology of BC is different between Chinese and Western women: both the age-specific BC incidence and mortality are different (e.g., BC incidence increases earlier in Chinese women and plateaus at the age of menopause before decreasing around age 70 years); the effects of breast density and other risk factors of BC are different (e.g., Chinese women have denser breasts, which would make mammography less sensitive); and most importantly, BC is susceptible to life-course and contemporaneous risks, and major epidemiologic differences are anticipated given the different stage and trajectory over time between China and the West. Therefore, wholesale adoption of inferences drawn from the West that have so far dominated the literature would be inappropriate (5). Secondary prevention by mass screening

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mammography in Chinese women remains controversial with limited direct evidence of benefit supporting its population-based deployment (2,6). Despite such an empirical vacuum, haphazard opportunistic screening in women at average risk has substantially increased in mainland China (7).

Nevertheless, at the individual level, it is important to offer women an informed choice, especially in places where the private sector thrives but with no organized BC screening programs, including the prosperous Chinese coastal cities. Individual variation in risk is substantial within any given population. For example, although the average lifetime risk of developing BC was 4.5% for women in Shanghai, the lifetime risk for women at the 90th risk percentile was 9.5%, which was comparable with the population average in the United Kingdom and United States (8,9). As such, compared with universal screening conventionally adopted in Western populations, risk-based screening that aims to stratify the female population by their remaining lifetime risk and targets only high-risk women for organized screening would be more in keeping with precision preventive care. Indeed, some Western countries have already begun to assess the potential benefits of switching from universal to risk-based screening (10). Recent studies in the United Kingdom and United States suggested that personalized screening tailored to individuals' risks and preferences could improve the efficiency and effectiveness of BC screening (11,12).

Here, we report the development and validation of a risk stratification model for screening Chinese well women in Hong Kong and Shanghai and evaluation of the comparative cost-effectiveness of risk-based and universal screening.

Methods

Data

We characterized the epidemiology of BC in Hong Kong using 1) data from the Hong Kong Breast Cancer Study (HKBCS), which is a hospital-based case-control study (see Supplementary Figure 1, available online) that we conducted in September 2016-August 2019 to elucidate the risk factors of BC cases and effectiveness of mammography screening in reducing BC mortality; and 2) 2014-2016 data on BC incidence and mortality from the Hong Kong Cancer Registry (HKCR) (4). Briefly, HKBCS comprised 400 and 3101 women who were newly diagnosed with ductal carcinomas in situ and invasive breast cancer (IBC), respectively, between September 2016 and June 2019 (response rate = 75%). We recruited 3610 control participants with similar ages who were diagnosed with diseases unrelated to BC in other hospital departments during the same period at the recruitment sites with no history of cancer (response rate = 57%).

All participants gave written informed consent. The HKBCS study was approved by the institutional review board of The University of Hong Kong and hospital clusters of HKW, HKE, KC/KE, KW, NTW, NTE under the hospital authority in the public sector and the relevant institutions in the private sector in Hong Kong.

The Model

We developed a proportional hazard model with parameters θ (see Table 1; Supplementary Tables 1 and 2 and Supplementary Figure 2, available online) to emulate the HKBCS and HKCR data simultaneously and simulated the development of BC in a hypothetical risk-stratified birth cohort over a woman's lifetime. In addition to age, we assumed the risk of developing BC depended on a woman's: 1) family history of BC among first-degree relatives, 2) prior benign breast disease diagnosis, 3) age of menarche, 4) age at first live birth, 5) body mass index, and 6) physical activity level (8). We partitioned the cohort into 288 risk strata, which corresponded to all combinations of risk factor levels. The case-fatality rate (and, hence, survival probability) of IBC depended only on the age and stage at diagnosis, whereas the stage-specific relative 5-year survival probabilities were constant (13). We stratified HKBCS subjects into screenees and nonscreenees based on their screening history and assumed that the average behavior of the screenees corresponded to biennial screening (see Supplementary Figure 3, available online). We assumed that screening had no effect on the inherent biological risk of BC (14-16). However, compared with nonscreenees, screenees would be diagnosed earlier with less advanced stages (ie, higher survival probabilities) if they developed BC (see Supplementary Tables 3 and 4, available online). We estimated the model parameters θ using Markov Chain Monte Carlo methods (see the Supplementary Methods, available online for details) (17).

To test whether our framework was applicable to other populations in China, we ran it with data from the Shanghai Breast Cancer Study (SBCS) and Shanghai Cancer Registry and then compared the inferred BC epidemiology in Shanghai with that reported in the original SBCS publication (8). SBCS is a population-based, case-control study of 3039 patients with invasive breast cancer and 3082 age- and frequency-matched control participants who were randomly selected from the general population through the Shanghai Resident Registry. We also compared the inferred effects of the risk factors on the risk of BC in Hong Kong and Shanghai.

The Effectiveness and Cost-Effectiveness of Screening

We compared no screening with biennial screening starting at age 40-60 years and stopping at age 69 or 74 years. The specificity of mammography is typically less than 90%, thus when applied to whole populations, mass screening would lead to a substantial number of false-positive mammograms and consequently unnecessary breast tissue biopsies (18,19). As such, numerous previous studies have emphasized that the impact of screening on quality-adjusted life years (QALYs) depended strongly on the quality-of-life detriment associated with positive mammograms (e.g., due to anxiety) and invasive diagnostic procedures (20,21). However, a recent study (22) reported that although women with false-positive mammograms suffered from increased short-term anxiety, there was no measurable health utility decrement compared with women with negative mammograms. We assumed that sensitivity and specificity of mammography were constant across all risk strata. To avoid underestimating the cost-effectiveness of screening in the base case, we assumed no QALY loss for all screens including positive screens but accounted for the QALY loss due to confirmatory tissue biopsy arising from positive mammograms (see Supplementary Table 1, available online).

We calculated the differential cost and QALY associated with screening for each of the 288 risk strata and the corresponding incremental cost-effectiveness ratios (ICER) at an annual discount rate of 3%. The ICER of universal screening was calculated from the aggregated differential costs and QALYs for all risk strata. Under a risk-based program with starting age a^* and risk threshold r^*, women would be eligible to join the program if their remaining lifetime risk of BC at age a^* exceeded r^*. All costs were converted to US dollars based on the exchange rate in 2018 (1 US$ = 7.8 HK$).

Table 1. Relative hazards in Hong Kong and Shanghai[a]

Risk factor	Relative hazard (95% CrI)		No. of controls		Overall proportion of women (95% CrI)[b]	
	Hong Kong 2016-2019	Shanghai Early 2000s	Hong Kong 2016-2019	Shanghai Early 2000s	Hong Kong 2016-2019	Shanghai Early 2000s
Age of menarche, y						
≥15	0.66 (0.57-0.75)	0.73 (0.64-0.81)	535	673	0.153 (0.144-0.162)	0.330 (0.314-0.345)
12-14	1	1	1569	1212	0.448 (0.438-0.462)	0.594 (0.577-0.609)
≤11	1.19 (1.11-1.30)	1.23 (1.01-1.49)	1439	159	0.398 (0.386-0.410)	0.076 (0.068-0.087)
Age at first live birth, y						
<25	1	1	974	558	0.277 (0.267-0.288)	0.288 (0.277-0.305)
25-29	1.00 (0.89-1.13)	1.12 (1.01-1.24)	1066	1097	0.300 (0.289-0.309)	0.553 (0.544-0.572)
≥30	1.50 (1.33-1.71)	1.84 (1.73-2.11)	745	349	0.208 (0.197-0.218)	0.159 (0.147-0.167)
Nulliparous[c]	1.64 (1.44-1.79)		794		0.215 (0.203-0.226)	
Family history of breast cancer among first-degree relatives						
No	1	1	3357	1985	0.929 (0.921-0.934)	0.970 (0.965-0.975)
Yes	1.96 (1.68-2.25)	1.55 (1.13-1.91)	253	61	0.071 (0.066-0.079)	0.030 (0.026-0.035)
Prior benign breast disease diagnosis						
No	1	1	3045	1464	0.848 (0.840-0.856)	0.730 (0.719-0.743)
Yes	1.61 (1.43-1.79)	1.77 (1.72-1.81)	557	582	0.152 (0.144-0.161)	0.270 (0.257-0.280)
Body mass index, kg/m^2						
<18.5	0.95 (0.83-1.00)	0.72 (0.58-0.95)	208	110	0.067 (0.060-0.072)	0.055 (0.048-0.064)
18.5-23	1	1	1381	887	0.429 (0.418-0.440)	0.436 (0.421-0.451)
>23	1.36 (1.30-1.45)	1.27 (1.15-1.42)	1777	1047	0.505 (0.492-0.516)	0.509 (0.492-0.519)
Physical activity[d]						
No	1	1	2828	1430	0.784 (0.776-0.793)	0.686 (0.674-0.698)
Yes	0.92 (0.85-0.98)	0.92 (0.86-0.99)	767	615	0.216 (0.208-0.224)	0.314 (0.299-0.325)

[a]The C statistic (which is the same as the Area Under the Receiver Operating Characteristic Curve or AUC) is 0.60 for Hong Kong Breast Cancer Study and 0.62 for Shanghai Breast Cancer Study from our model. CrI = credible interval.
[b]The proportion of females were estimated jointly in the model based on the number of participants in the control group accounting for missing data.
[c]Less than 2% of Shanghai women were nulliparous, and they were grouped with the women whose age at first live birth was 30 years or older.
[d]Physical activity refers to exercising intensively (e.g., lifting heavy objects, cardiovascular exercise, riding fast on bicycle) at least once a week on average in the last 10 years.

Results

The Epidemiology of Breast Cancer

The fitted model was congruent with the data (Figure 1, A-C) with a C statistic of 0.60 (95% credible interval [CrI] = 0.54-0.65) for HKBCS. We estimated that the lifetime risk (i.e., age 15-99 years assuming competing mortality by age in the model) of IBC ranged from 1.8% to 26.6% among all Hong Kong Chinese women with mean 6.8% (Figure 1, D), whereas the lifetime risk of BC mortality ranged from 0.2% to 3.0% with mean of 1.1% (Figure 1, E). Women in the top 30% risk strata accounted for approximately 50% of the BC cases in the general population. Family history of BC, history of benign breast disease, obesity, and lack of physical activity increased the risk by 96% (RR = 1.96, 95% CrI = 1.68-2.25), 61% (RR = 1.61, 95% CrI = 1.43-1.79), 36% (RR = 1.36, 95% CrI = 1.30-1.45), and 8% (for regular physical activity, RR = 0.92, 95% CrI = 0.85-0.98), respectively (Table 1). Compared with women whose age of menarche was 12-14 years, those who began menstruation at younger (≤11) and older ages (≥15) were 1.19 (95% CrI = 1.11-1.30) and 0.66 (95% CrI = 0.57-0.75) times more likely to develop BC, respectively. Compared with women whose age at first live birth was 30 years or younger, those who gave their first live birth at older ages and were nulliparous were 1.50 (95% CrI = 1.33-1.71) and 1.64 (95% CrI = 1.44-1.79) times more likely to develop BC, respectively. The estimated 5-year survival probabilities at diagnosis for stage 1-4 were 99.9% (95% CrI = 99.6%-100%), 94.7% (95% CrI = 93.2%-96.0%), 77.7% (95% CrI = 75.1%-80.2%), and 27.7% (95% CrI = 24.9%-30.4%), respectively; the corresponding 10-year survival probabilities were 99.7% (95% CrI = 99.4%-100%), 89.7% (95% CrI = 87.7%-91.5%), 60.3% (95% CrI = 57.3%-63.4%), and 7.7% (95% CrI = 6.1%-9.4%) (Figure 1, F). Overall, the average 5- and 10-year survival probabilities of IBC were 89% (95% CrI = 88%-91%) and 84% (95% CrI = 81%-88%), respectively (Supplementary Table 2, available online).

Applying our framework to the Shanghai SBCS data yielded relative hazards that were similar to the odds ratios estimated in the original SBCS publication (Supplementary Table 5, available online) with comparable C statistic [0.62 for SBCS from our model vs 0.63 in the original SBCS publication (8)]; the former had slightly lower discrimination power because the model required it to converge with the population-level BC incidence and mortality statistics as well. The inferred relative hazards were similar to that in Hong Kong (Table 1). However, the inferred lifetime risk of BC and survival probability were lower in Shanghai. This was unsurprising because SBCS was conducted during 1998-2005 (ie, 15-20 years earlier than HKBCS) when BC incidence was lower and access, quality, and affordability of BC screening and treatments were substantially inferior compared with the present. These results suggested that our framework for BC risk stratification and disease progression was likely generalizable to other urban populations in China.

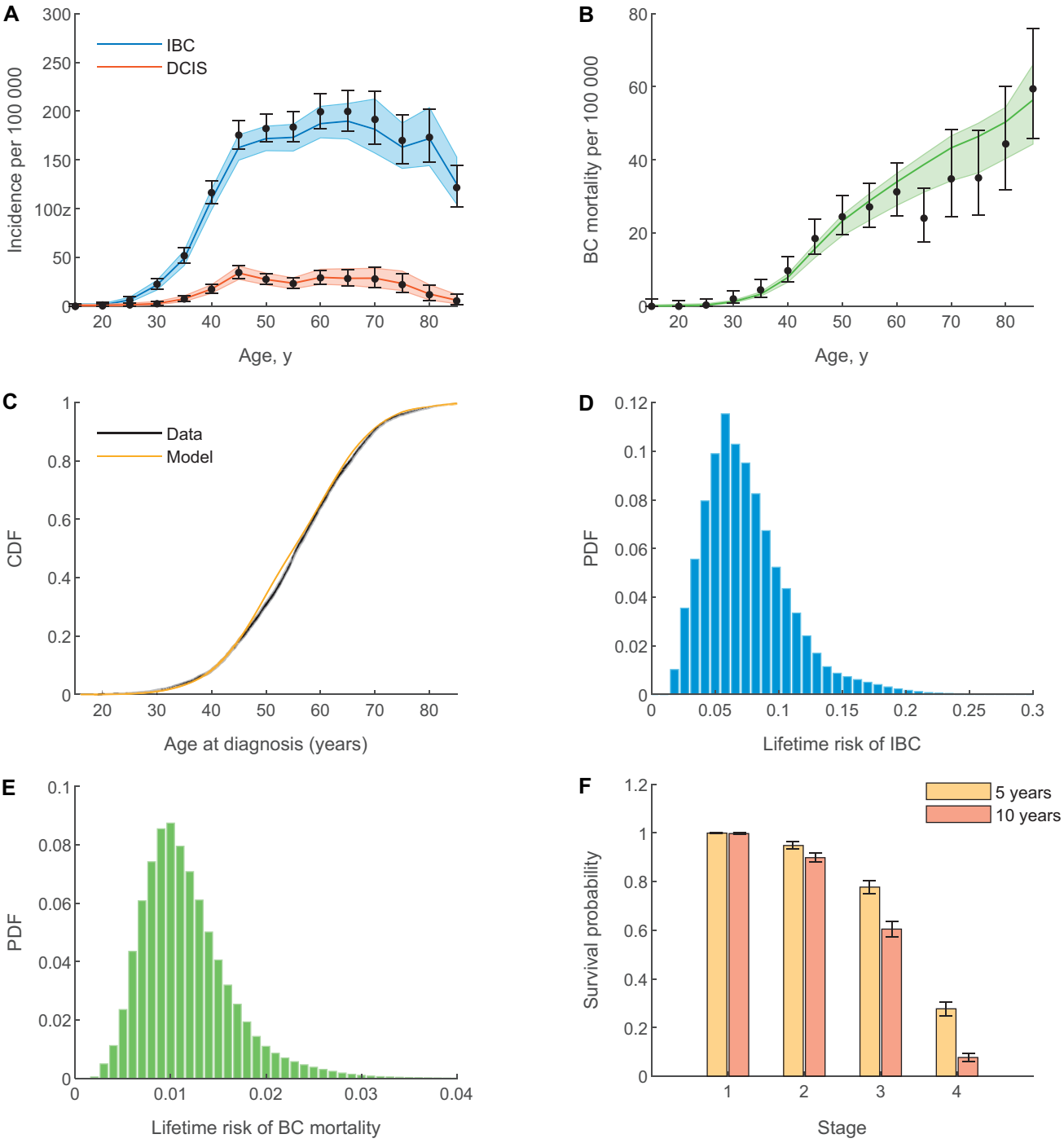

Figure 1. Inferred breast cancer epidemiology. **Black dots** and **vertical bars** indicate point estimates and 95% confidence intervals from the data (**A, B, and F**). **Lines** and **shades** indicate posterior means and 95% credible intervals from the model (**A, B, and C**). **A)** The calibrated model was congruent with the observed incidence of ductal carcinoma in situ (DCIS) and invasive breast cancer (IBC) in the Hong Kong Cancer Registry (HKCR). **B)** The calibrated model was congruent with the observed breast cancer mortality in HKCR. **C)** The calibrated model was congruent with the observed age distribution of the cases in Hong Kong Breast Cancer Study. CDF: cumulative density function. **D-E)** Probability density function (PDF) of lifetime risk of IBC and breast cancer (BC) mortality among women in the hypothetical birth cohort comprising 288 risk strata. (F) Inferred average 5-year and 10-year survival probability by the stage at diagnosis.

The Uptake and Effectiveness of Screening

We estimated that screening uptake was 5.1% (95% CrI = 4.6%-5.5%), 12.0% (95% CrI = 10.2%-13.9%), and 17.2% (95% CrI = 15.6%-18.7%) at age 40, 55, and 70 years, respectively (Supplementary Table 2, available online). We estimated that biennial screening would allow BC to be diagnosed 0.45 (95% CrI = 0.34-0.58) years earlier on average with substantial stage shift to the left or downstaging (see Figure 2, A; Supplementary Table 2, available online). Regardless of risk stratum, the hazard ratio of BC mortality between screenees and nonscreenees was almost constant at 0.76 (95% CrI = 0.60-0.90) between ages

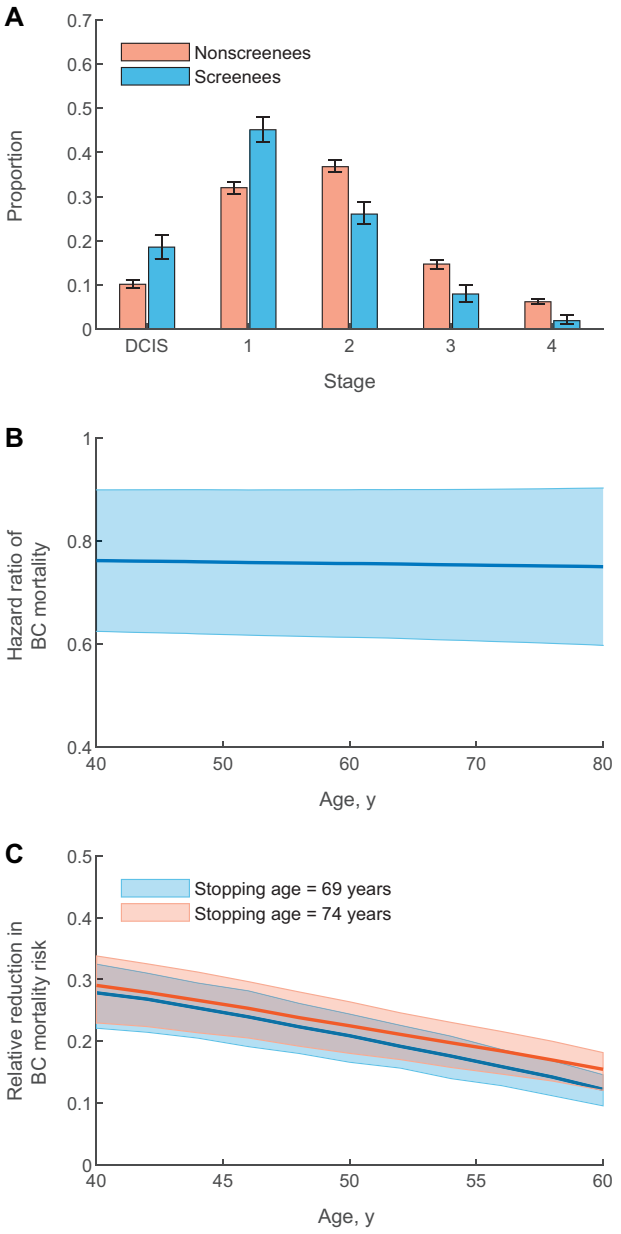

Figure 2. Effectiveness of biennial mammography screening. **A)** Inferred stage distribution of breast cancer (BC) cases among screenees and nonscreenees. **Bars** indicate posterior means. **Vertical lines** indicate 95% credible intervals. **B)** Hazard ratio of BC mortality between screenees and nonscreenees. **Lines** indicate posterior means. **Shades** indicate 95% credible intervals. **C)** Relative reduction in BC mortality risk conferred by biennial screening with different starting and stopping ages. **Lines** indicate posterior means. **Shades** indicate 95% **CrIs**. DCIS = ductal carcinoma in situ.

40 and 80 years (Figure 2, B). Consequently, a woman who screened biennially from age 50 to 69 years would reduce lifetime risk of BC mortality by 21% (95% CrI = 17%-24%) with 0.09 (95% CrI = 0.07-0.11) probability of experiencing 1 or more episodes of unnecessary tissue biopsy because of false-positive mammograms (Figure 2, C). Extending the starting age to 40 years and stopping age to 74 years would increase BC mortality risk reduction to 28% (95% CrI = 22%-32%) and 22% (95% CrI = 18%-26%), respectively.

The Cost-Effectiveness of Screening

Unlike relative reduction in BC mortality risk, the cost, QALY gained, and ICER of screening strongly depended on a woman's risk of BC (Figure 3, A-F). The ICER was minimized for all risk strata if screening started at age 44 years (Figure 3, E and F), though the difference in ICER was marginal compared with starting age of 40 years. As such, we set the default starting age at 44 years in what follows. Compared with no screening, biennial screening from age 44 to 69 years had an ICER of $153 983 (95% CrI = $109 193-$215 108) and $6718 (95% CrI = $2067-$12 631) per QALY for women in the 1st and 99th risk percentile (whose lifetime risk was 0.34 and 3.62 times the population average), respectively. The ICERs would increase by 15% (95% CrI = 11%-18%) under the most pessimistic assumption regarding QALY loss attributed to positive screening mammograms. If status quo opportunistic screening were used as the comparator instead of no screening, the ICERs would increase by 4.2% (95% CrI = 2.3%-6.1%).

Universal Screening

Biennial screening from age 44 to 69 years for all women would provide 0.020 (95% CrI = 0.017-0.024) QALY gain at a net cost of $709 (95% CrI = $505-$908) per woman, which corresponded to an ICER of $34 953 (95% CrI = $22 820-$50 268) per QALY (Figure 3, G). Extending the starting age to 40 years and stopping age to 74 years would increase the ICER by 3.4% (95% CrI = 2.7%-5.8%) and 12.9% (95% CrI = 11.4%-14.7%), respectively (Figure 3, G and H). Therefore, lowering the starting age was a more cost-effective way than extending the stopping age for maximizing the health benefits of screening.

Risk-Based Screening

The proportion of women eligible for screening increased markedly as the risk threshold decreased (Figure 4). If the risk threshold for biennial screening from age 44 to 69 was set at 8.4%, then the average remaining lifetime risk of BC among eligible screenees at the starting age of 44 years was 11.1%, which would be equivalent to the US national average at their recommended screening starting age of 50 years (Figure 4, A). Under this risk-based screening program, 25.8% of the cohort would be eligible for screening (Figure 4, C). Compared with no screening, this risk-based program (with risk threshold at 8.4%) provided a health gain of 0.009 (95% CrI = 0.007-0.011) QALY at a net cost of $159 (95% CrI = $98-$224) per woman, respectively, which corresponded to an ICER of $18 151 (95% CrI = $10 408-$27 663) per QALY (Figure 5, A). Expanding this risk-based program into universal screening from age 44 to 69 years would incur an ICER of $48 303 (95% CrI = $32 210-$68 000) per QALY (Figure 5, A). The ICERs among no screening, risk-based screening, and universal screening increased by 12%-15% if the stopping age was extended to 74 years (Figure 5, B).

Discussion

We have developed a generic and robust inference framework for characterizing the epidemiology of BC and effectiveness of screening in Hong Kong Chinese women, which could serve as a reliable sentinel for the rest of China and the overseas diaspora given its relatively advanced trajectory and stage of

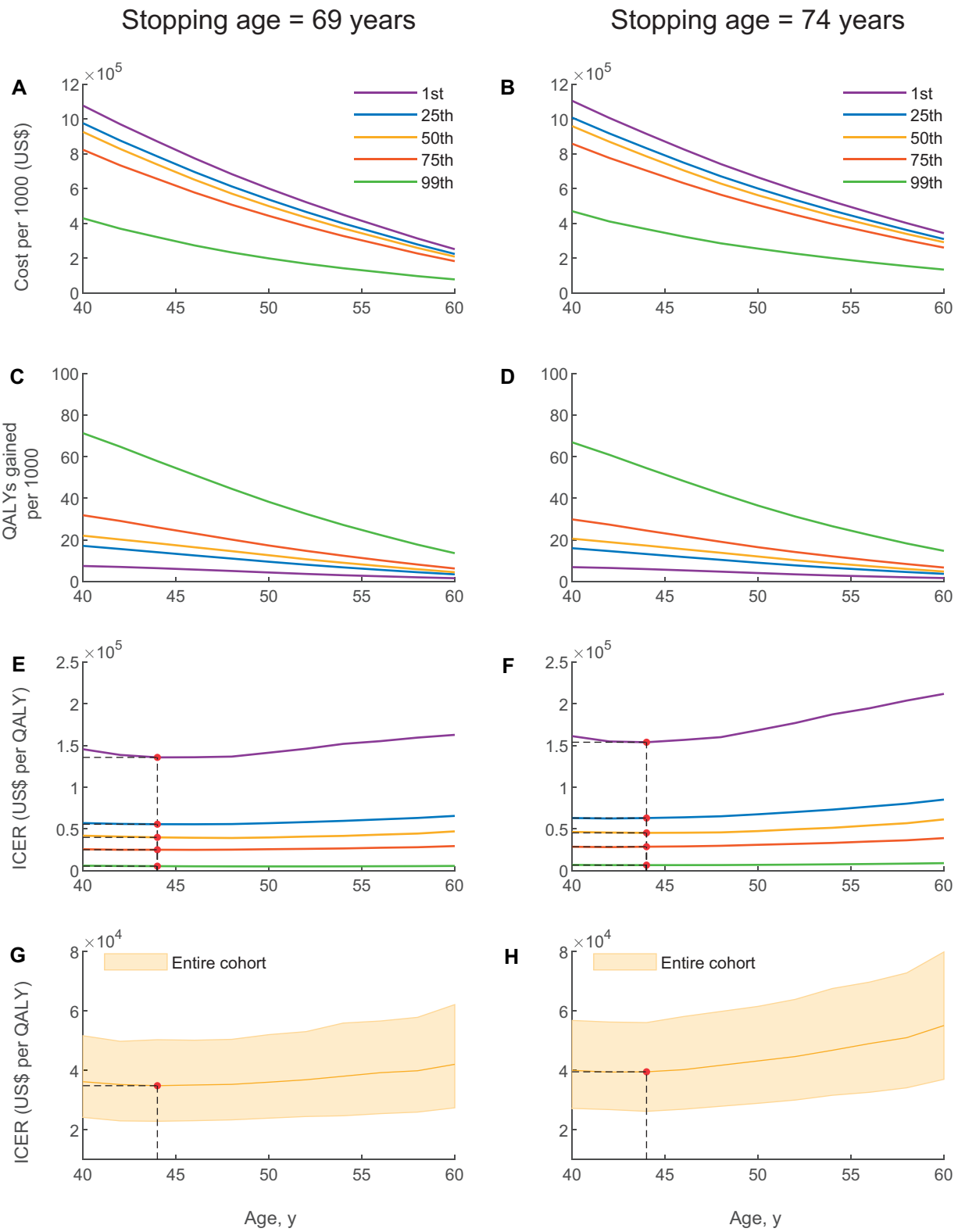

Figure 3. Cost-effectiveness of biennial mammography screening compared with no screening in the hypothetical cohort with stopping age 69 and 74 years. **A-F)** Cost, quality-adjusted life years (QALYs) gained and incremental cost-effectiveness ratio (ICER) as a function of starting age for women at the 1st, 25th, 50th, 75th, and 99th risk percentile. **G-H)** ICER as a function of starting age for the entire cohort. **Lines** and **shades** indicate means and 95% prediction intervals. The **circles** indicate that the ICERs were minimized when the starting age was 44 years.

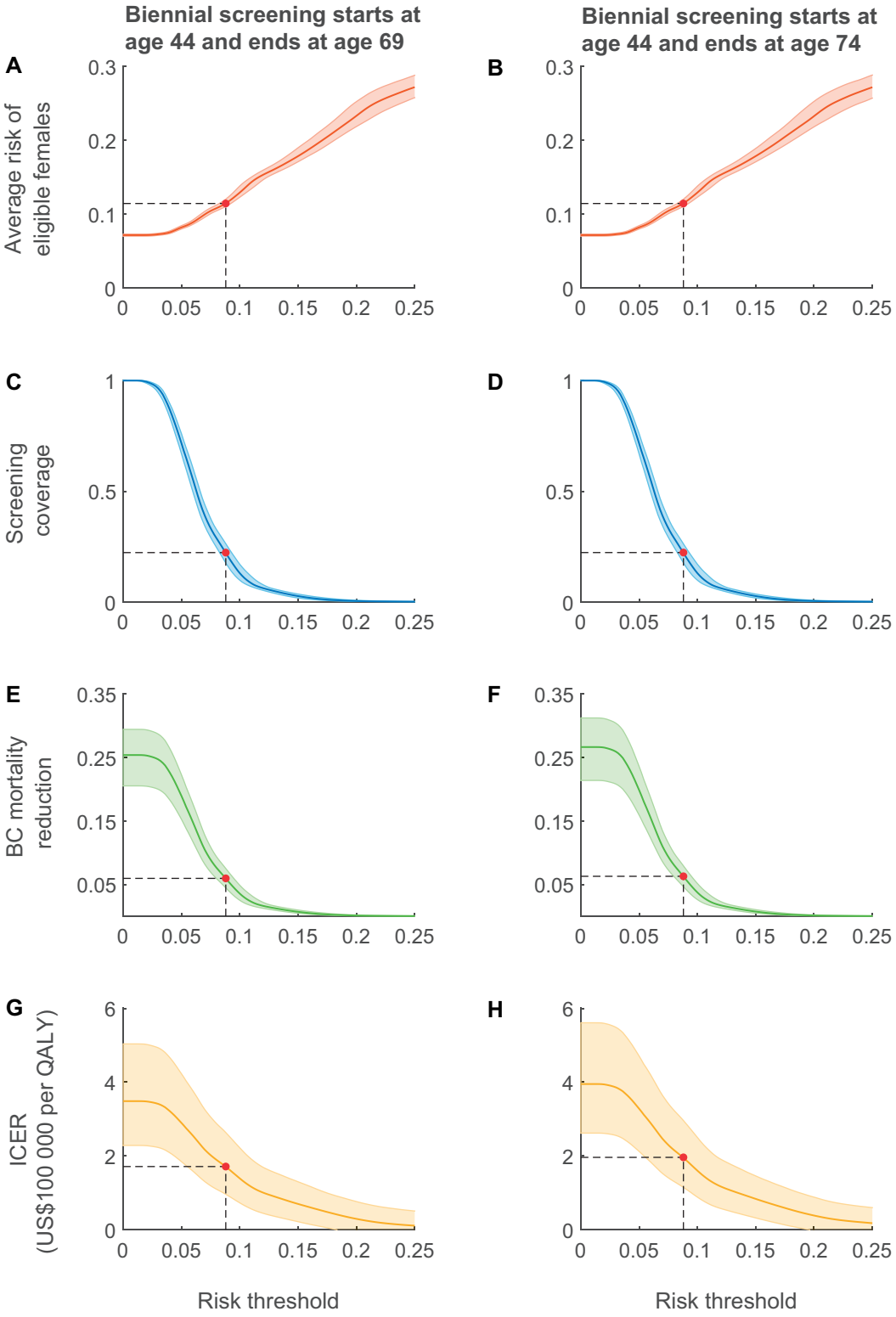

Figure 4. Screening coverage, effectiveness, and cost-effectiveness of risk-based screening as a function of risk threshold. Biennial screening started at age 44 years and stopped at age 69 or 74 years. **A-B)** Average remaining lifetime risk among women eligible for risk-based screening. The **red circles** corresponding to setting the risk threshold such that the remaining lifetime risk of breast cancer (BC) among eligible screenees was the same as the US national average at age 50 years when their screening program starts (i.e., 11.1%). **C-D)** Screening coverage (i.e., proportion of the birth cohort eligible for risk-based screening). **E-H)** Relative reduction in BC mortality for the cohort and the associated incremental cost-effectiveness ratio (ICER) conferred by risk-based screening. QALY = quality-adjusted life years.

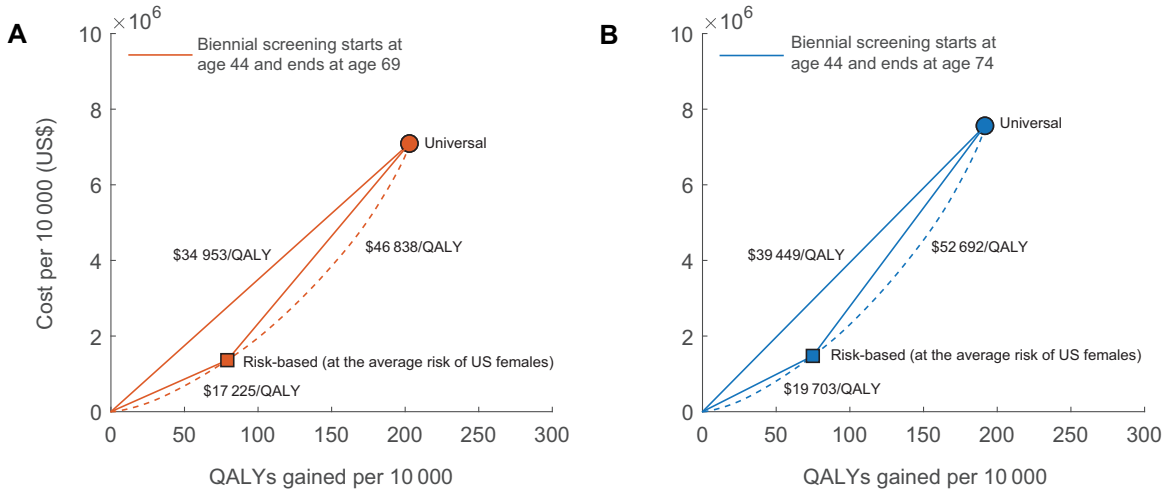

Figure 5. Comparative cost-effectiveness of universal and risk-based screening. **Circles** indicate universal screening. **Squares** indicate risk-based screening under which the average remaining lifetime risk of eligible screenees at the starting age was the same as the US national average at the age of 50 years (see Figure 4). **Dashed lines** indicate the risk-based screening at different risk thresholds. **A)** The cost-effectiveness planes show the increase in cost and quality-adjusted life years (QALYs) compared with no screening per birth cohort when biennial screening started at age 44 years and stopped at age 69 years. **B)** The cost-effectiveness planes show the increase in cost and QALYs compared with no screening per birth cohort when biennial screening started at age 44 years and stopped at age 74 years.

socioeconomic development (as we have illustrated using Shanghai as a comparator). The validity of our framework and results can be further assessed against findings from other local and overseas studies. Our findings concerning risk factors among Chinese women accord with the established literature (8). The inferred BC stage distribution of screenees and non-screenees is very similar to that reported for women in Taiwan, which has implemented organized biennial screening for women aged 45-69 years since 2004 (Supplementary Table 3, available online); this supports our assumption that the average screening behavior of the screenees in HKBCS corresponded to biennial screening. The age-specific 5-year survival probabilities of IBC and the relative reduction in BC mortality inferred in our model are consistent with that reported in the United Kingdom and other high-income countries (23-25). Taken together, these comparisons lend added credence to the reliability of our calibrated model for BC and estimated cost-effectiveness of mammography screening.

We conclude that risk-based and conventional universal BC screening would provide similar relative reduction in BC mortality among screenees, but the former would be far more cost-effective at different screening starting ages. However, a recent cohort study in Taiwan (26) reported that compared with annual clinical breast examination, risk-based biennial mammography screening only provided a modest reduction in BC mortality (hazard ratio [HR] = 0.89, 95% confidence interval [CI] = 0.75 to 1.06) compared with its universal counterpart (HR = 0.62, 95% CI = 0.50 to 0.76). This should be interpreted in the context where 45%-49% of women enrolled in their risk-based screening were assessed as high-risk and referred for mammography, and the proportion adherent to these referrals was 58%-62%. That is, 26% of the women enrolled in their risk-based screening underwent mammography. Because they used the initial number of enrolled women (i.e., before risk assessment was done) as the denominator for calculating hazard ratios, the hazard ratio reduction in risk-based screening (0.11) was approximately 0.26 times that in universal screening (0.38). Of additional note, we recommend caution in understanding their propensity-score–based findings, which concluded a relative risk reduction of 38% for universal biennial screening contrasted with virtually the entire corpus of past work consisting of both randomized control trials (RCTs) and empirical evidence suggesting approximately only half that quantum at around 20% (24). The correct interpretation reconciling the apparent contradiction, however, requires careful teasing out of the underlying data reporting structures. Moreover, we assessed biennial mammography screening strategies following the recommendations in most of the Western populations. The screening interval could be adjusted with more data on the pathology of breast cancer cases detected after the risk-based screening program was implemented.

Risk-based strategies optimize BC screening by reducing unnecessary mammography and tissue biopsy among low-risk women. The probability of a biopsy arising from an initial false-positive screen over 10 years of biennial mammography was 6%-10% in the United States (18), and breast biopsy had a complication rate of 8%-15% (6,19) (i.e., 1.5%-4.5% of low- and average-risk women would experience at least 1 episode of complications due to unnecessary biopsy for biennial screening from age 44 to 69 years). Given that the cost-effectiveness of BC screening strongly depends on QALY loss brought about by false-positive mammograms and consequent tissue biopsy, jurisdictions that consider commencing organized population-wide screening could take the following risk-based approach: 1) select an initial risk threshold that could be accommodated by current screening capacity (e.g., based on the national average in the United States or United Kingdom); 2) measure the QALY loss among screenees with false-positive mammograms and tissue biopsy during a pilot phase of the program; and 3) reevaluate the screening parameters in light of the additional data generated from the pilot phase of the program and adjust the risk threshold (in accordance with other existing cancer prevention programs, e.g., colorectal screening in Hong Kong).

Enhancing the discriminative power of the BC risk prediction model is key to improve the performance of risk-based screening (via more accurate risk stratification). After the risk-based BC screening program is rolled out, our model could be further improved with data on mammographic breast density that has been shown to be an additional useful factor for BC risk

stratification (27). Previous studies have also shown that polygenic risk profiles based on single nucleotide polymorphisms (SNPs) are strong predictors of BC (28). In a recent polygenic risk score model based on 313 SNPs (28), 35% of all BCs would be expected to occur in women in the highest 20% of the risk distribution. Although we did not consider SNPs in our model because no data were available in HKBCS and only limited data on a few SNPs were available in SBCS (8), similarly, we estimated 40% of breast cancer would be expected to occur in women in the highest 25.8% of the risk distribution in the Hong Kong population. Given that sequencing for personalized medicine is becoming more accessible, albeit still struggling to overcome challenges associated with direct application of the hitherto predominantly Caucasian-derived evidence to other racial or ethnic groups, and that the cost will continue to fall in the future, genetic risk profiles should be included as a core predictor for next-generation BC screening. Minimizing unnecessary tissue biopsy is another key to improve the compliance and cost-effectiveness of BC screening. There is a need to develop innovative and effective methods to replace mammography or supplement it with noninvasive and accurate reflex testing to improve the positive predictive value of screening.

Finally, although the ICER for universal screening at $34 953 falls within the acceptable range as one would expect in most Western developed countries, we should highlight that China officially remains a middle-income country with large disparities at the subnational level. The risk-based screening ICER of $18 151, which is almost half that of universal screening, represents much better value-based care. As a first step coming from no organized screening, to expand the opportunity to be screened as fairly and as efficiently as possible, it would be prudent to commence risk-based screening before further considering a universal strategy. Such a decision for the population will of course be controversial and subject to debate at the policy level. In the future, we would also recommend that individual choice be taken into account, based on the ethos of personal preference and tailored preventive care, where our model could further incorporate an additional module that takes into account women's own risk appetite (29,30).

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Data Availability

Requests for data should be made to the corresponding author. Requests of codes should be made to the corresponding author.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359–86.
2. Fan L, Strasser-Weippl K, Li J-J, et al. Breast cancer in China. *Lancet Oncol*. 2014;15(7):e279–89.
3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
4. Hong Kong Hospital Authority. Hong Kong Cancer Registry. http://www3.ha.org.hk/cancereg/. Accessed December 30, 2020.
5. Wong IOL, Schooling CM, Cowling BJ, et al. Breast cancer incidence and mortality in a transitioning Chinese population: current and future trends. *Br J Cancer*. 2015;112(1):167–170.
6. Leung GM, Lam TH, Thach TQ, et al. Will screening mammography in the East do more harm than good? *Am J Public Health*. 2002;92(11):1841–1846.
7. Mei Z, Yijing Z, Heling B, et al.; for the National Center for Chronic and Non-Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China. Breast cancer screening rates among women aged 20 years and above—China, 2015. *China CDC Weekly*. 2021;3(13):267–273.
8. Zheng W, Wen W, Gao Y-T, et al. Genetic and clinical predictors for breast cancer risk assessment and stratification among Chinese women. *J Natl Cancer Inst*. 2010;102(13):972–981.
9. Sun L, Legood R, Sadique Z, et al. Cost-effectiveness of risk-based breast cancer screening programme, China. *Bull World Health Organ*. 2018;96(8):568–577.
10. Onega T, Beaber EF, Sprague BL, et al. Breast cancer screening in an era of personalized regimens: a conceptual model and National Cancer Institute initiative for risk-based and preference-based approaches at a population level. *Cancer*. 2014;120(19):2955–2964.
11. Pashayan N, Morris S, Gilbert FJ, et al. Cost-effectiveness and benefit-to-harm ratio of risk-stratified screening for breast cancer: a life-table model. *JAMA Oncol*. 2018;4(11):1504–1510.
12. Ayer T, Alagoz O, Stout NK. OR forum—a POMDP approach to personalize mammography screening decisions. *Oper Res*. 2012;60(5):1019–1034.
13. US National Cancer Institute. Surveillance, Epidemiology and End Results Program. https://seer.cancer.gov/. Accessed December 30, 2020.
14. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784–1792.
15. Plevritis SK, Munoz D, Kurian AW, et al. Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000-2012. *JAMA*. 2018;319(2):154–164.
16. Huang X, Li Y, Song J, et al. A Bayesian simulation model for breast cancer screening, incidence, treatment, and mortality. *Medical Decision Making*. 2018;38(suppl 1):78S–88S.
17. George EI, McCulloch RE. Variable selection via Gibbs sampling. *J Am Stat Assoc*. 1993;88(423):881–889.
18. Nelson HD, Pappas M, Cantor A, et al. Harms of breast cancer screening: systematic review to update the 2009 US Preventive Services Task Force recommendation. *Ann Intern Med*. 2016;164(4):256–267.
19. Hofvind S, Ponti A, Patnick J, et al. False-positive results in mammographic screening for breast cancer in Europe: a literature review and survey of service screening programmes. *J Med Screen* . 2012;19(suppl 1):57–66.

20. van Ravesteyn NT, Stout NK, Schechter CB, et al. Benefits and harms of mammography screening after age 74 years: model estimates of overdiagnosis. *J Natl Cancer Inst*. 2015;107(7):djv103.
21. Schousboe JT, Kerlikowske K, Loh A, et al. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med*. 2011;155(1):10–20.
22. Tosteson AN, Fryback DG, Hammond CS, et al. Consequences of false-positive screening mammograms. *JAMA Internal Medicine*. 2014;174(6):954–961.
23. Weedon-Fekjær H, Romundstad PR, Vatten LJ. Modern mammography screening and breast cancer mortality: population study. *BMJ: Br Med J*. 2014;348:g3701.
24. Marmot MG, Altman D, Cameron D, et al. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer*. 2013;108(11):2205.
25. Nelson HD, Fu R, Cantor A, et al. Effectiveness of breast cancer screening: systematic review and meta-analysis to update the 2009 US Preventive Services Task Force recommendation. *Ann Intern Med*. 2016;164(4):244–255.
26. Yen AM-F, Tsau H-S, Fann JC-Y, et al. Population-based breast cancer screening with risk-based and universal mammography screening compared with clinical breast examination: a propensity score analysis of 1429890 Taiwanese women risk-based and universal mammography vs clinical breast examination risk-based and universal mammography vs clinical breast examination. *JAMA Oncol*. 2016;2(7):915–921.
27. Carney PA, Miglioretti DL, Yankaskas BC, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med*. 2003;138(3):168–175.
28. Mavaddat N, Michailidou K, Dennis J, et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am J Hum Genet*. 2019;104(1):21–34.
29. Cohen JD, Li L, Wang Y, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science*. 2018;359(6378):926–930.
30. Puzhko S, Gagnon J, Simard J, et al. Health professionals' perspectives on breast cancer risk stratification: understanding evaluation of risk versus screening for disease. *Public Health Rev*. 2019;40(1):2.