Effects of Reproductive and Demographic Changes on Breast Cancer Incidence in China: A Modeling Analysis

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Background Breast cancer incidence is currently low in China. However, the distribution of reproductive and lifestyle risk factors for breast cancer among Chinese women is changing rapidly. We quantified the expected effect of changes in breast cancer risk factors on future rates of breast cancer in China.

Methods We first validated and calibrated the Rosner–Colditz log-incidence breast cancer model in Chinese women who participated in the Shanghai Women's Health Study cohort (N = 74942). We then applied the calibrated model to a representative sample of Chinese women who were aged 35–49 years in 2001 using data from the Chinese National Family Planning and Reproductive Health Survey (NFPRHS, N = 17078) to predict the age-specific and cumulative breast cancer incidence among all Chinese women of this age group. We evaluated the relative impact of changes in modifiable risk factors, including alcohol intake, parity, postmenopausal hormone use, and adult weight gain, on cumulative incidence of breast cancer.

Results Breast cancer incidence in China is expected to increase substantially from current rates, estimated at 10–60 cases per 100000 women, to more than 100 new cases per 100000 women aged 55–69 years by 2021. We predicted 2.5 million cases of breast cancer by 2021 among Chinese women who were 35–49 years old in 2001. Modest reductions in hormone and alcohol use, and weight maintenance could prevent 270000 of these cases.

Conclusions China is on the cusp of a breast cancer epidemic. Although some risk factors associated with economic development are largely unavoidable, the substantial predicted increase in new cases of breast cancer calls for urgent incorporation of this disease in future health care infrastructure planning.

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One-fifth of the world's women live in China. Incidence rates of breast cancer in most of China are currently low compared with those in Western countries. For example, the age-standardized incidence rate of breast cancer in the rural county of Qidong is 12.8 per 100000 women, which is approximately one-tenth that of white women in the United States (1). However, Shanghai (2), Hong Kong (3), Japan (4), and Singapore (5) have recently experienced rapid increases in breast cancer incidence rates, and breast cancer is now the most common cancer among women in these regions. Furthermore, breast cancer incidence among Asian-American women is increasing (6): Rates in Japanese-American women have surpassed the age-specific incidence rates in white US women (2). These trends have been attributed to strong cohort effects that have arisen because of shifts in risk factor profiles of younger women (3–5,7).

Established risk factors for breast cancer in women include older age, a family history of breast cancer, greater height, adult weight gain, high birth weight, alcohol intake, high mammographic density, postmenopausal hormone use, and certain reproductive factors, including earlier menarche, later age at first pregnancy, less breastfeeding, lower parity, and longer interval between births (8). Higher body mass index (BMI) is associated with a reduced risk of breast cancer in premenopausal women and an increased risk of breast cancer in postmenopausal women (8). The hypothesis that all of these risk factors are likely to be

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common to women of all ethnicities, including Chinese women, is supported by data from an international case–control study (9) and a multiethnic cohort (10), which demonstrated that, despite variations in the overall absolute rates of breast cancer, the associations between these factors and the risk of breast cancer were similar across different ethnic groups. For example, the beneficial effects of earlier first birth, higher parity, and later age at menarche and the detrimental effects of family history, adult weight gain, greater height, and use of hormone replacement therapy have been confirmed for Chinese women living in Singapore (11) and Shanghai (12,13). Furthermore, breast tumors of Asian women have molecular and genetic characteristics that are similar to those of white women (14).

The distribution of risk factors for breast cancer among Chinese women has changed substantially in parallel with China's economic and social development. Secular trends in physical growth among Chinese girls have been reported, including increases in height (15) and in the prevalence of overweight and obesity (16). Furthermore, increases in the number of Chinese women in the workforce as well as decreases in fertility have drastically changed the underlying distributions of reproductive factors associated with the risk of breast cancer. For example, the average birth rate among Chinese women dropped from 5.9 births per woman in 1970 to 2.9 births per woman in 1979 and then to 1.7 births per woman in 2004 (17). Meanwhile, the average age at menarche decreased from 16.5 years in the 1940s to 13.9 years in the 1980s (18).

In this study, we evaluated the distribution of demographic and reproductive factors associated with breast cancer risk in China and quantified the impact of changes in these factors on future breast cancer incidence rates. Specifically, we validated the Rosner–Colditz log-incidence breast cancer model (8,19) in Chinese women who participated in the Shanghai Women's Health Study (SWHS) (20). We then applied the model to Chinese national survey data to predict future trends in the incidence of breast cancer in China. We conducted a sensitivity analysis to assess the relative impact of population-level changes in adult weight gain, postmenopausal hormone therapy use, alcohol use, and parity on breast cancer incidence to identify possible strategies for prevention.

CONTEXT AND CAVEATS

Prior knowledge

Although the incidence of breast cancer is currently low in most of China compared with Western countries, it has increased dramatically over the last several decades in several cities in China and in other Asian populations, making breast cancer the most common cancer among women in these regions.

Study design

The Rosner–Colditz log-incidence breast cancer model was validated in Chinese women who participated in the Shanghai Women's Health Study and then applied to Chinese national survey data to predict future trends in the incidence of breast cancer in China associated with changes in demographic and reproductive factors.

Contribution

Breast cancer incidence in China is expected to increase substantially from the current estimated rate of 10–60 cases per 100 000 women to more than 100 cases per 100 000 women aged 55–69 years by 2021. Modeling predicts 2.5 million cases of breast cancer by 2021 among Chinese women who were 35–49 years old in 2001. Modest reductions in hormone and alcohol use, and weight maintenance are predicted to prevent approximately 10% of these cases.

Implications

The substantial predicted increase in breast cancer cases in China focuses attention on the adequacy of national infrastructure for breast cancer therapy, the possible benefits of population-based screening for breast cancer, and possible prevention strategies.

Limitations

Underreporting of the number of children a woman had given birth to in the national survey was possible. The limited availability of individual-level data for many of the demographic variables necessitated the use of various assumptions and imputations in the model, which may have resulted in uncertainty in some projected estimates. The model may slightly overestimate breast cancer incidence at older ages because it does not account for competing risks.

From the Editors

Study Population and Methods

Study Population

Our study population consisted of women who participated in the Chinese National Family Planning and Reproductive Health Survey in 2001 (NFPRHS 2001). The Chinese National Family Planning Commission surveyed a representative and random sample of premenopausal women aged 15–49 years living in 31 provinces in China. Data were collected on 39 585 women from 346 cities and counties and from 1041 villages. A total of 74% of the women who were surveyed lived in rural areas, and the overall response rate was 98.3%. Participants in the NFPRHS 2001 were assured of the anonymity and confidentiality of their responses to increase the reliability of the information collected. The dataset for this study population has been described previously (21); for this study, we analyzed relevant reproductive data. Because only a small proportion of women in China give birth after age 35, the number of children born to a woman by age 35 approximates her lifetime parity. To ensure that we would have complete information on reproductive history, we restricted our analysis to women who were aged 35 years or older before the survey was administered in 2001 (N = 17 078).

Breast Cancer Model and Validation

We used the Rosner–Colditz log-incidence breast cancer model, which was developed in 1996 and updated in 2000 using data from the Nurses' Health Study cohort (22). The model is presented in the Appendix and has previously been described in detail (8,19). Briefly, it incorporates the effects of various risk factors, including history of benign breast disease, family history of breast cancer, parity, age at first birth, age at and type of menopause (surgical vs natural), use of postmenopausal hormones, alcohol use, height, and weight, to estimate the incidence of breast cancer during a woman's lifetime. The Rosner–Colditz model has been validated in white

Table 1. Expected number of breast cancers and ratios of expected to observed numbers of breast cancer cases (E/O ratios) by age group, Shanghai Women's Health Study cohort*

				Before model calibration		After model calibration‡	
Age group, y	No. of person-years	Observed no. of cases	E_{SEER}†	E_{model}	E_{model}/O (95% CI)	E_{model}‡	E_{model}‡/O (95% CI)
40–44	59891	45	72	58	1.29 (0.96 to 1.72)	41	0.91 (0.68 to 1.22)
45–49	116490	107	233	149	1.39 (1.15 to 1.68)	104	0.97 (0.80 to 1.17)
50–54	81767	92	213	126	1.37 (1.12 to 1.68)	88	0.96 (0.78 to 1.18)
55–59	56089	63	185	91	1.44 (1.12 to 1.84)	64	1.02 (0.80 to 1.31)
60–64	52699	63	206	87	1.38 (1.08 to 1.77)	61	0.97 (0.76 to 1.24)
65–69	65673	72	292	116	1.61 (1.27 to 2.03)	81	1.13 (0.89 to 1.42)
70–74	32474	42	156	65	1.55 (1.15 to 2.10)	45	1.07 (0.79 to 1.45)
75–79	1237	3	6	4	1.33 (0.43 to 4.12)	3	1.00 (0.32 to 3.10)

* SEER = Surveillance, Epidemiology, and End Results (Program) database; CI = confidence interval.

† Expected number of cases of breast cancer in each age group after standardization to US SEER rates over the same time period.

‡ Calibration was used to address model overprediction. Model intercept reduced by the natural logarithm of 1.43 (ie, 0.357).

American women (23), for whom the observed incidence of breast cancer was comparable to the expected incidence based on rates for US women obtained from the Surveillance, Epidemiology, and End Results (SEER) database [expected-to-observed ratio (E/O) = 1.0; 95% confidence interval (CI) = 0.98 to 1.03 (24)]. To our knowledge, this model has not yet been validated in an Asian population.

We examined the validity of this model in Chinese women by using data from the SWHS. The SWHS is a cohort of 74942 adult Chinese women from urban communities who were recruited between 1997 and 2000 and are interviewed in person every 2 years to collect personal and health-related information (20). We applied the Rosner–Colditz model to the Shanghai cohort to predict the expected annual incidence of breast cancer for each cohort member. We calculated the cumulative incidence rates and expected number of cases of breast cancer in the entire cohort for each year from the year of recruitment up to 2004.

To assess the goodness of fit of our model within this group of Chinese women, we compared the expected and observed number of breast cancer cases in the overall cohort and within 5-year age groups. Based on the age-specific incidence rates from the SEER database, the expected number of cases (E_{SEER}) was 2.79 times higher (95% CI = 2.55 to 3.04 times higher) than the observed number of cases, whereas after adjusting for risk factors using the Rosner–Colditz model, the expected number of cases (E_{model}) approached the observed number of cases. Specifically, after applying US incidence rates to the number of Shanghai women in each age group, we expected 1357 cases of breast cancer in the Shanghai cohort. The observed number of cases was 487. After adjusting for all the risk factors using the Rosner–Colditz model, the expected number of cases was 696. Therefore, the model accounted for 76% of the discrepancy between United States and Chinese incidence rates (ie, difference between the model and the observed Chinese rates [1357 − 696 = 661] divided by the difference between the United States and the observed Chinese rates [1357 − 487 = 870], or 661/870 = 0.759).

The overall E/O using the Rosner–Colditz model was 1.43 (95% CI = 1.31 to 1.56), which suggests that such a model developed in white American women overestimates breast cancer incidence in Chinese women in Shanghai by approximately 40%. This overestimate could be due to several differences between the predominantly white American women in whom the model was developed, and the Asian women to whom it was applied, including the lower average height and BMI of the Asian women. Differences in physical activity, dietary factors (25), breastfeeding, or variations in the underlying genetic predisposition and endogenous hormone levels may also explain the discrepancy (26,27). Furthermore, the fact that mammographic screening rates are very low in China and relatively high in the United States makes the difference in the numbers of detected cancers even more pronounced.

To correct for this overestimation, we calibrated the log-incidence model by adjusting the intercept by 0.357 (the natural logarithm of 1.43). After adjustment, the E/O was 1.00 (95% CI = 0.91 to 1.09) and showed adequate validity given that the 95% CIs included 1 in all age groups (Table 1). The goal of this calibration was to obtain a model that would provide conservative, lower limit predictions of breast cancer incidence.

Prediction

We applied the adjusted Rosner–Colditz model to the NFPRHS dataset to predict annual breast cancer incidence for each woman surveyed. For our primary modeling analysis, we used individual-level data from the NFPRHS dataset as well as data from population-representative health surveys, the published literature, and the SWHS cohort. Individual-level data included each woman's age from 2001 to 2021, age at first birth, parity, and the interval between births. Age at menarche, in 10-year age groups, according to year of birth was imputed from aggregate data in the 1997 NFPRHS (J. D. Qu MD, personal communication). The aggregate-level estimates from other representative sources were imputed into the prediction model and randomly assigned to the 17078 women in the NFPRHS dataset.

BMI and height were assigned according to distributions in the SWHS cohort and the China Health and Nutrition Survey. In addition, on the basis of mean values from the SWHS, we assumed that 17% of women would ever develop benign breast disease, 2% would have had a positive family history of breast cancer, 3% would have used postmenopausal hormone therapy for 2 years after menopause, and 1% would have had an oopherectomy at age

45. We estimated the average weekly alcohol intake to be 14 g (about one glass of wine or beer) and randomly applied this value to 10% of the population based on data from other studies in China and Hong Kong that showed that approximately 10% of women in this age group drink alcohol (T. Hesketh MD, PhD and G. Leung MD, personal communication). Because all of the women surveyed were premenopausal, we assumed that menopause would occur at age 49 years, which has been well documented as the mean age at menopause for women of many ethnicities, including Chinese women (18). We examined the robustness of our estimates to the choice of these imputed values in a sensitivity analysis (see below).

Time- and age-specific incidence rates, cumulative incidence rates, and the expected number of cases were calculated for 17 078 NFPRHS participants who were aged 35–49 years at baseline in 2001. Our predictions of breast cancer risk extend 20 years forward in time, up to 2021, when the NFRPHS participants would be 55–69 years old. We used information from the China 2000 Census (27) to approximate the population distribution of Chinese women in 2001. Our estimates of cumulative incidence of breast cancer derived from the representative sample of Chinese women (ie, the NFPRHS participants) were applied to the total number of Chinese women aged 35–49 years [N = 130 304 574 (28)] to obtain overall predictions for this age group across China.

Sensitivity Analysis

To assess the range of our predictions according to different assumptions about demographic changes in China, we recalculated the predicted age-specific and cumulative incidence rates, as well as the expected numbers of cases, according to different assumptions about patterns of weight gain, hormone replacement therapy use, alcohol use, age at menopause, and parity (see Appendix).

Results

Our projection analysis included 17 078 women aged 35–49 years who participated in the NFPRHS. The mean age of these women at the NFPRHS interview was 41 years (SD = 4.6 years). The mean birth rate in the overall NFPRHS was 1.94 (SD = 0.6; 2.11 in rural areas and 1.43 in urban areas); among women 35–49 years old, it was 2.10 (SD = 0.6). The mean age at first birth was 24 years (SD = 2.9 years; median age at first birth = 26 years, range = 14–39 years).

Projected age- and birth cohort–specific breast cancer incidence rates up to the year 2021 are shown in Table 2 and Figure 1. These breast cancer incidence rates ranged from 39.0 per 100 000 women for women who were born between 1962 and 1966 and were 35–39 years old in 2001 to 132.3 per 100 000 women for women who were born between 1952 and 1956 and would be 65–69 years old in 2021. The age-specific incidence rates were higher among more recent birth cohorts; for example, the incidence of breast cancer in women aged 55–59 years is higher in women born between 1962 and 1966 (109.8 per 100 000) than in women born between 1952 and 1956 (102.6 per 100 000). On the basis of the cumulative incidence rates, the model predicted that 146 cases of breast cancer would occur within this sample of 17 078 women by 2011 and that 326 cases would occur by 2021. When we applied the model to the entire Chinese population of women of the same age distribution in 2000 as our sample population (N = 130 304 574) (28), the predicted number of cases of breast cancer by 2011 was approximately 1.1 million. The predicted number of breast cancer cases increased to nearly 2.5 million by 2021 (Table 2).

Sensitivity Analysis

We examined the dependence of these breast cancer incidence predictions on variations in modifiable risk factors by changing our

Table 2. Predicted breast cancer incidence among NFPRHS participants by year of birth*

	Year of birth			
	1952–1956	1957–1961	1962–1966	All (1952–1966)
Age-specific incidence per 100 000 women in 2001–2021				
Age group in 2001–2021, y				
35–39	—	—	39.0	39.0
40–44	—	63.8	64.7	64.3
45–49	83.3	86.6	90.0	86.9
50–54	88.1	92.6	95.5	92.3
55–59	102.6	107.0	109.8	106.7
60–64	115.7	120.9	—	118.2
65–69	132.3	—	—	132.3
Cumulative incidence per 100 000 women				
By 2011	994.6	894.0	711.2	855.3
By 2021	2152.0	1963.3	1677.2	1912.7
Population size and number of cases				
NFPRHS population (2001)	N = 5495	N = 4940	N = 6643	N = 17 078
By 2011	55	44	47	146
By 2021	118	97	111	326
Chinese population†	N = 40 838 382	N = 39 465 761	N = 50 000 431	N = 130 304 574
By 2011	406 180	352 807	355 604	1 114 591
By 2021	878 829	774 822	838 599	2 492 250

* — = not applicable; NFPRHS = National Family Planning and Reproductive Health Survey.

† Chinese population data from the 2000 census were used to approximate the number of women in each age group in 2001.

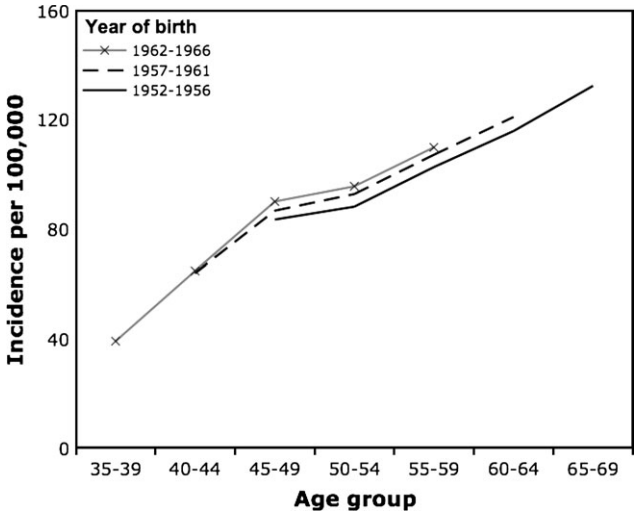

Figure 1. Predicted age-specific breast cancer incidence according to year of birth.

assumptions about the frequency of postmenopausal hormone use, alcohol use, and weight gain (Figure 2). These estimates reflect theoretical changes in risk factors that we applied to the general Chinese population. Compared with an estimated cumulative incidence of 1912.7 cases per 100 000 women from the base case model, a model that incorporated concurrent increases in the extent of postmenopausal hormone use, alcohol consumption, and weight gain predicted an additional 76 cases of breast cancer per 100 000 women by 2021. This increase corresponds to approximately 100 000 additional cases of breast cancer in Chinese women who will be aged 55–69 years in 2021. A reduction in parity, from the national average of 2.1 births per woman to 1.1 births per woman (which is similar to birth rates in several developed Asian and European countries), would account for an additional 200 000 cases in this subgroup of Chinese women. Conversely, a model that incorporated a stable weight in adulthood resulted in 140 fewer cases per 100 000 women, or a total of 190 000 fewer cases. A model that included low alcohol consumption, stable weight and infrequent use of postmenopausal hormones indicated possible prevention of 270 000 new cases of breast cancer overall in this subset of women across China by 2021. Under these conservative assumptions, the cumulative incidence of breast cancer was predicted to be 1704 cases per 100 000 women by 2021, corresponding to a total of 2.2 million incident cases across China by 2021.

Discussion

Breast cancer incidence has increased dramatically over the past 30 years in several cities in China and in other Asian populations. Our modeling results show that this trend is likely to continue across China. On the basis of our modeling results, we predict that the nationwide incidence of breast cancer among women who will be 55–69 years in 2021 will increase from the current rate, which has been estimated at 10–60 cases per 100 000 women (2,29). Applying these rates to the 130 million Chinese women in this age group, we estimate nearly 2.5 million cases of breast cancer from 2001 to 2021 among women who were 35–49 years old in 2000. Even under very conservative assumptions of low alcohol use, no postmenopausal hormone use, and no adult weight gain, we predict that the cumulative incidence of breast cancer will increase to at least 2.2 million new cases of breast cancer among this subgroup of women across China over the 20-year period from 2001 to 2021. These results point to an emerging epidemic of breast cancer in China, where breast cancer incidence rates are approaching those in Western nations, in which breast cancer is the most commonly diagnosed female cancer. Our findings raise important issues regarding future health care infrastructure needs, the role of breast cancer screening programs, and possible prevention strategies.

The strengths of this study include our use of a validated and calibrated model of breast cancer and a representative population that included both rural and urban Chinese women. The validation used regional data from Shanghai (SWHS), and the prediction modeling was performed using representative national survey data (NFPRHS). To our knowledge, this is the first quantitative

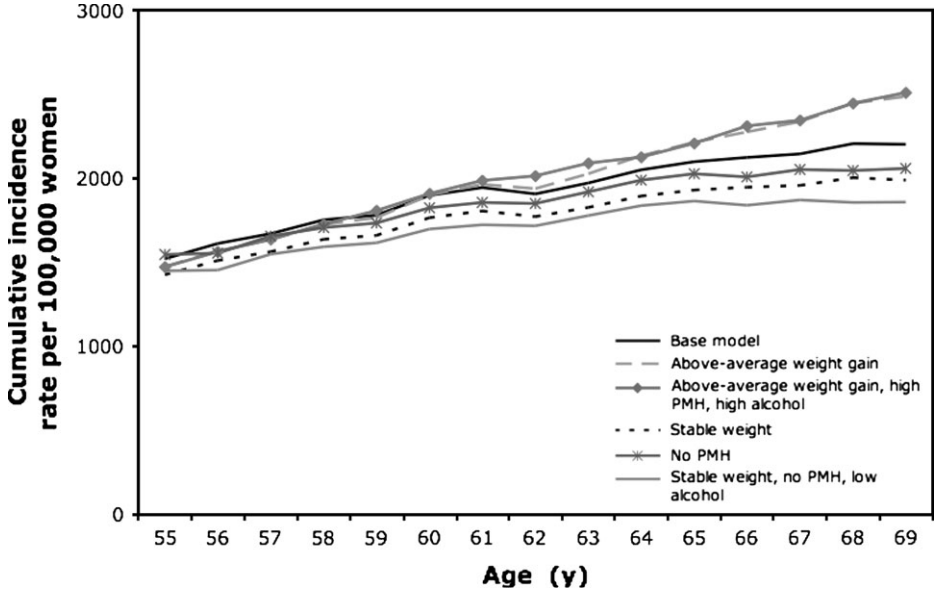

Figure 2. Sensitivity analysis of age-specific cumulative incidence of breast cancer per 100 000 women by 2021 according to different population assumptions. PMH = postmenopausal hormone use.

analysis of the impact of demographic change on breast cancer trends in a developing country.

Nonetheless, our analysis has several limitations. First, although the NFPRHS dataset we used is based on a representative sample of all Chinese women of reproductive age, some women who responded to the survey may have deliberately underreported the number of children they had given birth to in order to avoid the consequences of violating China's one-child family policy. An underestimate in a protective factor such as parity would result in an overestimation of the number of projected cases of breast cancer. However, NFPRHS participants were ensured anonymity and confidentiality in an attempt to reduce such underreporting. Second, the limited availability of individual-level data for many of the demographic variables necessitated the use of various assumptions and imputations in the model, which may have resulted in uncertainty in the projected estimates, especially when predicting breast cancer after menopause. In particular, we assumed that the distributions of BMI, height, hormone therapy use, age at menopause, and benign breast disease in Chinese women living in China were similar to those of Chinese women living in Shanghai. We also assumed that these imputed variables were not correlated with each other. Third, our model does not account for competing risks and may, therefore, slightly overestimate breast cancer incidence at older ages. However, as the population of China ages, chronic diseases, including breast cancer, are likely to become more prevalent. Despite these limitations, we believe that our results reflect the best possible estimates given the available data and our results send an important public health message that warrants immediate action regarding health care planning in China. Additional studies that include representative individual-level data on breast cancer risk factors and breast cancer incidence are needed to provide more comprehensive and accurate estimates of breast cancer burden.

One important consideration in the interpretation of our findings is whether a model that was developed in white American women is valid when used to predict breast cancer in Chinese women. By using information on risk factors that are common to women of all ethnicities, we found that the Rosner–Colditz model was able to explain as much as 76% of the difference in rates between American and Chinese women. Nonetheless, the model overestimated Chinese breast cancer incidence rates by approximately 40%. This overestimate may be due to differences between white American women and Chinese women in diet, genetics, body shape, or other breast cancer risk factors or may reflect systematic differences in how breast cancer screening is recorded on cancer records. Regardless of whether the model itself or quality of the data used to validate it account for this discrepancy, our estimates, after calibrating down by 40%, are conservative.

There are several reasons that the true burden of breast cancer may be even higher than our estimates. Our predictions apply to a small fraction of the Chinese female population (those aged 35–49 years in 2001, 21% of the female population); thus, the overall number of breast cancer cases that will develop by 2021 is likely to be far more than what we have estimated. Younger women (ie, those born after 1967) were not included in this analysis because we wanted to ensure that the reproductive information was accurate. However, because breast cancer risk factors are more prevalent in this younger group, our calculations may underestimate the true breast cancer incidence rates across all Chinese women. In addition, the predictions from the sensitivity analyses could be substantially higher if concurrent changes were to occur in multiple risk factors that interact with each other. Nonetheless, our findings are consistent with trends of increasing breast cancer incidence rates predicted in an earlier study (29) and observed in other, more developed Asian regions (3,4,30,31) that have undergone temporal shifts in reproductive and lifestyle risk factors (toward lower fertility, increased weight, more frequent use of postmenopausal hormones, and higher alcohol consumption).

Our sensitivity analyses allowed us to model the effects of changes in modifiable risk factors on predicted breast cancer incidence rates. Modest increases in the use of postmenopausal hormones and alcohol and in weight were predicted to cause an additional 100 000 new cases of breast cancer by 2021. Although increases in the prevalence of these behavioral risk factors may contribute to the future burden of disease, these risk factors also provide targets for public health interventions: Moderation in these three factors could prevent 270 000 new cases of breast cancer in among women aged 35–49 years in 2001. In addition to preventing premenopausal breast cancer, avoidance of weight gain through physical activity and good nutrition is likely to benefit overall health by preventing diabetes and cardiovascular disease, which are established health care priorities in China (32,33). Moreover, among Western women who drink alcohol, sufficient dietary folate has been shown to mitigate the excess risk of breast cancer associated with alcohol consumption and, hence, a potential prevention effort could lie in emphasizing increasing folic acid intake. The recent declines in US breast cancer rates that have been attributed to decreases in use of hormone therapy (34,35) have also been noted in Asian women (36), making reductions in hormone use a realistic health care goal for breast cancer prevention in China.

Given the parallel shifts in the underlying breast cancer risk factors that have been noted across the developing world, our findings may have implications for many other developing countries worldwide. For example, our results raise questions about the adequacy of national infrastructure for breast cancer therapy and the possible benefits of population-based screening for breast cancer. Although mammography has been beneficial in reducing the health burden of malignant breast cancers in Western countries (37), cost-effectiveness analyses in Hong Kong suggest that mammography may not be cost-effective for Asian populations (38,39). Further research on the regional patterns of breast cancer incidence, including possible differences between urban and rural areas, is needed to guide screening policy.

Our findings highlight the likely consequences of recent changes in reproductive and other lifestyle patterns on breast cancer incidence in China and, perhaps, other developing countries. The decline in fertility in China is part of a worldwide trend toward having fewer children that is associated with economic and social development and is not thought to be attributable to any single policy measure (21). Breast cancer prevention is only one of many considerations that should influence population planning; economic development, environmental sustainability, and cultural priorities are also critical considerations. However, not all proposals to achieve economic and demographic goals have equivalent

health effects. To prevent breast cancer, fertility policies should emphasize early, rather than late, childbearing and shorter, rather than longer, spacing between births and breast-feeding.

In summary, we predict a substantial increase in breast cancer incidence in China over the next two decades. The underlying causes of this emerging epidemic, namely shifting reproductive trends and growth and lifestyle changes that are associated with economic development, are applicable to many developing nations worldwide. Our findings may have implications for both health care planning within China and across the developing world. Weight maintenance and avoidance of alcohol and postmenopausal hormones may form targets for public health interventions and be used to mitigate the future burden of this disease.

Appendix

Description of the Log-Incidence Model of Breast Cancer

We fit our log-incidence model of breast cancer to incident cases of invasive breast cancer identified during follow-up of the Nurses' Health Study cohort. The approach to model fitting was to assume that incidence at time $t(I_t)$ is proportional to the number of cell divisions (C_t) accumulated throughout life up to age t, that is

$$I_t = kC_t. \quad [1]$$

The cumulative number of breast cell divisions is calculated as follows:

$$C_t = C_o \prod_{i=0}^{t-1} (C_{i+1}/C_i) = C_o \prod_{i=0}^{t-1} \lambda_i. \quad [2]$$

Thus, $\lambda_i = C_{i+1}/C_i$ represents the rate of increase of breast cell divisions from age i to age $i + 1$. Log (λ_i) is assumed to be a linear function of risk factors that are relevant at age i. The set of relevant risk factors and their magnitude may vary according to the stage of reproductive life. The overall model is given by

$$\begin{aligned}\log I = {} & \alpha + \beta_o(t^* - t_o) + \beta_1 b + \beta_2(t_1 - t_o)b_{1,t-1} + \gamma_1(t - t_m)m_A + \gamma_2(t - t_m)m_B \\ & + \delta_1 \,\mathrm{pmh}_A + \delta_2 \,\mathrm{pmh}_B + \delta_3 \,\mathrm{pmh}_C + \delta_4 \,\mathrm{pmh}_{\mathrm{cur},t} + (\delta_4 + \delta_5)\mathrm{pmh}_{\mathrm{past},t} \\ & + \beta_3 \mathrm{BMI}_1 + \beta_3^* \mathrm{BMI}_2 + \dagger_4 h_1 + \beta_4^* h_2 + \alpha_1 \,\mathrm{bbd} + \alpha_2 \,\mathrm{bbd}\, t_o + \alpha_3 \,\mathrm{bbd}(t^* - t_o) \\ & + \alpha_4 \,\mathrm{bbd}(t - t_m)\boldsymbol{m}_t + \phi \,\mathrm{fhx} + \beta_5 \,\mathrm{alc}_1 + \beta_5^* \,\mathrm{alc}_2 + \beta_5^{**} \,\mathrm{alc}_3,\end{aligned} \quad [3]$$

where t = age; t_o = age at menarche; t_m = age at menopause; t^* = min (age, age at menopause); m_t = 1 if postmenopausal at age t, 0 otherwise; s_t = parity at age t; t_i = age at ith birth, i = 1, …, s; b = birth index = $\sum_{i=1}^{St} (t^* - t_i)b_{it}$; b_{it} = 1 if parity is greater than or equal to i at age t, = 0 otherwise; m_A = 1 if natural menopause, = 0 otherwise; m_B = 1 if bilateral oophorectomy, = 0 otherwise; bbd = 1 if benign breast disease = yes, = 0 otherwise; fhx = 1 if family history of breast cancer in mother or sister = yes, = 0 otherwise; pmh_A = number of years on oral estrogen; pmh_B = number of years on oral estrogen and progesterone; pmh_C = number of years on other types of postmenopausal hormones; $\mathrm{pmh}_{\mathrm{cur},t}$ = 1 if current user of postmenopausal hormones at age t, = 0 otherwise; $\mathrm{pmh}_{\mathrm{past},t}$ = 1 if past user of postmenopausal hormones at age t, = 0 otherwise; BMI_j = body mass index at age j (kg/m^2); alc_j = alcohol consumption (grams) at age j; h = height (inches).

The terms for BMI, height, and alcohol in relation to menopause and use of hormones are summarized below:

$$\mathrm{BMI}_1 = \sum_{j=t_o}^{t^*-1} (\mathrm{BMI}_j - 21.8) + \sum_{j=t_m}^{t-1} (\mathrm{BMI}_j - 24.4)\mathrm{pmh}_{\mathrm{cur},j} m_j,$$

$$\mathrm{BMI}_2 = \sum_{j=t_m}^{t-1} (\mathrm{BMI}_j - 24.4)(1 - \mathrm{pmh}_{\mathrm{cur},j}) m_j,$$

$$h_1 = (h - 64.5)(t^* - t_o) \quad h_2 = (h - 64.4) \sum_{j=t_m}^{t-1} (1 - \mathrm{pmh}_{\mathrm{cur},j}) m_j,$$

$$\mathrm{alc}_1 = \sum_{j=18}^{t^*-1} \mathrm{alc}_j,$$

$$\mathrm{alc}_2 = \sum_{j=t_m}^{t-1} \mathrm{alc}_j \mathrm{pmh}_{\mathrm{cur},j} m_j,$$

$$\mathrm{alc}_3 = \sum_{j=t_m}^{t-1} \mathrm{alc}_j (1 - \mathrm{pmh}_{\mathrm{cur},j}) m_j,$$

where β_0 represents the rate of increase in incidence prior to menopause among nulliparous women with no benign breast disease and no family history; β_1 and β_2 represent modification to the rate of increase in incidence for parous women according to the number and precise spacing of births; γ_1 and γ_2 represent rates of increase in incidence after menopause according to type of menopause among women without benign breast disease not currently using postmenopausal hormones; δ_1, δ_2 and δ_3 represent modifications to the rate of increase in incidence after menopause among women currently using postmenopausal hormones according to the duration of the specific types of postmenopausal hormones used; δ_4 and δ_5 represent the immediate effect of starting and stopping postmenopausal hormone use on rates of increase in incidence after menopause; and ϕ represents the effect of family history of breast cancer on the number of breast cell divisions at birth (ie, C_o).

β_3 represents the effect of BMI either before menopause or after menopause on breast cancer incidence for a woman who is currently on postmenopausal hormones. β^*_3 represents the effect of BMI after menopause on breast cancer incidence while not on postmenopausal hormones. β_4 and β_3 are the effects of height defined similarly to β_3 and β^*_3 and β_5 β^*_5 and β^{**}_5 represent effects of alcohol before menopause, after menopause on postmenopausal hormones, and after menopause not on postmenopausal hormones, respectively. The rationale for the separate terms is the finding in exploratory analyses and from the literature (40) that effects of BMI and possibly height and alcohol on breast cancer incidence are different before and after menopause and that the effect of BMI on breast cancer incidence after menopause differs according to whether a woman is or is not currently on postmenopausal hormones (41). α_1, α_2, α_3, and α_4 represent modifications to 1) the number of breast cell divisions at birth, 2) the rates of increase in the number of cell divisions after birth, but before menarche, 3) the rates of increase in the number of cell divisions after menarche, but before menopause, and 4) the rates of increase in the number of cell divisions after menopause among women with benign breast disease, respectively. The rationale for these extra terms involving benign breast disease is that the relative risk for benign breast disease varies according to age, with the relative risk being strongest among younger women and diminishing over time.

The general rationale for a log-incidence model of a specific cancer is that the number of precancerous cells increases multiplicatively with time, whereas the risk factor profile from birth to current age (eg, 35 years) differentially affects the rate of increase in incidence. Specifically, for the breast cancer incidence model described above, the number of precancerous cells is assumed to increase annually at the rate of (β_0) prior to menopause for nulliparous women; at the rate of exp(β_0+ $\beta_1 s$) prior to menopause for parous women with parity = s, and so forth. Finally, the number of precancerous cells increases immediately after the first birth by exp[$\beta_2(t_1$-$t_0)$] The incidence rate of breast cancer is, therefore, assumed to be approximately proportional to the number of precancerous cells.

Incidence Calculations

Cumulative incidence was calculated according to the following formula:

$$\mathrm{CI} = 1 - e^{-\sum(r_i)},$$

where r_i is the incidence rate for each year. Because of the lag in recruitment from 1997 to 2000 and loss to follow-up, individual women were followed for different lengths of time. We therefore calculated each woman's expected cumulative incidence for the length of time she was actually followed in the cohort. By summing over the predicted cumulative incidences for each woman, we obtained the expected number of cases in the entire cohort. We further subdivided the follow-up time into 5-year age groups and calculated the average incidence rates within each age group, thus estimating the age-specific incidence rates predicted in this population. The sum of the cumulative incidences for each 5-year age group yielded the expected number of cases within each age group. Confidence

intervals for E/O ratio described in validation section were calculated according to the following formula:

$$E/O \exp^{\pm 1.96\sqrt{1/O}}.$$

Sensitivity Analysis Assumptions

1. Stable weight: no changes in weight from age 18 years onward; mean BMI = 23 kg/m^2.
2. Average weight gain: 0.1 annual increase in BMI from BMI 20 kg/m^2 at age 18 (42).
3. Above-average weight gain: 0.2 annual increase in BMI from BMI of 20 kg/m^2 at age 18.
4. Low alcohol use: 2% of women drinking an average of 2 g of alcohol per day.
5. High alcohol use: 40% of women drinking an average of 2 g of alcohol per day.
6. No postmenopausal hormone use: 0% of women using hormones.
7. High postmenopausal hormone use: 6% of women using hormone therapy (2% estrogen and progesterone, 2% estrogen only, 2% other hormone therapy) for 2 years following menopause.
8. Fertility rate: 1.1 births per woman.
9. High alcohol use, above-average weight gain, and high postmenopausal hormone use (ie, assumptions 3, 5, and 7).
10. Stable weight, low alcohol use, and no postmenopausal hormone uses (ie, assumptions 1, 4, and 6).

References

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). *SEER*Stat Database: Incidence - SEER 9 Regs Limited-Use*, Nov 2007 Sub (1973–2005), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2008, based on the November 2007 submission. http://seer.cancer.gov/registries/characteristics.html.
2. Parkin DM, Whelan SL, Ferlay J, Storm H. *Cancer Incidence in Five Continents, Vol. I to VIII.* Lyon: IARC Cancer Base 2005;7.
3. Leung GM, Thach TQ, Lam TH, et al. Trends in breast cancer incidence in Hong Kong between 1973 and 1999: an age-period-cohort analysis. *Br J Cancer.* 2002;87(9):982–988.
4. Minami Y, Tsubono Y, Nishino Y, Ohuchi N, Shibuya D, Hisamichi S. The increase of female breast cancer incidence in Japan: emergence of birth cohort effect. *Int J Cancer.* 2004;108(6):901–906.
5. Seow A, Duffy SW, McGee MA, Lee J, Lee HP. Breast cancer in Singapore: trends in incidence 1968–1992. *Int J Epidemiol.* 1996;25(1):40–45.
6. Deapen D, Liu L, Perkins C, Bernstein L, Ross RK. Rapidly rising breast cancer incidence rates among Asian-American women. *Int J Cancer.* 2002;99(5):747–750.
7. Chia KS, Reilly M, Tan CS, et al. Profound changes in breast cancer incidence may reflect changes into a Westernized lifestyle: a comparative population-based study in Singapore and Sweden. *Int J Cancer.* 2005;113(2):302–306.
8. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol.* 2000;152(10):950–964.
9. Pathak DR, Whittemore AS. Combined effects of body size, parity, and menstrual events on breast cancer incidence in seven countries. *Am J Epidemiol.* 1992;135(2):153–168.
10. Pike MC, Kolonel LN, Henderson BE, et al. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. *Cancer Epidemiol Biomarkers Prev.* 2002;11(9):795–800.
11. Ng EH, Gao F, Ji CY, Ho GH, Soo KC. Risk factors for breast carcinoma in Singaporean Chinese women: the role of central obesity. *Cancer.* 1997;80(4):725–731.
12. Gao YT, Shu XO, Dai Q, et al. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. *Int J Cancer.* 2000;87(2):295–300.
13. Shu XO, Jin F, Dai Q, et al. Association of body size and fat distribution with risk of breast cancer among Chinese women. *Int J Cancer.* 2001;94(3):449–455.
14. Yu K, Lee CH, Tan PH, Tan P. Conservation of breast cancer molecular subtypes and transcriptional patterns of tumor progression across distinct ethnic populations. *Clin Cancer Res.* 2004;10(16):5508–5517.
15. Ji CY, Ohsawa S, Kasai N. Secular changes in the stature, weight and age at maximum growth increments of urban Chinese girls from the 1950s to 1985. *Am J Hum Biol.* 1995;7:473–484.
16. Wu Y. Overweight and obesity in China. *BMJ.* 2006;333(7564):362–363.
17. Hesketh T, Lu L, Xing ZW. The effect of China's one-child family policy after 25 years. *N Engl J Med.* 2005;353(11):1171–1176.
18. Chen J, Campbell C, Li J, Peto R. *Diet, Life-style, and Mortality in China: A Study of the Characteristics of 65 Chinese Counties.* Oxford, UK: Oxford University Press; 1991.
19. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. *J Natl Cancer Inst.* 1996;88(6):359–364.
20. Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. *Am J Epidemiol.* 2005;162(11):1123–1131.
21. Ding QJ, Hesketh T. Family size, fertility preferences, and sex ratio in China in the era of the one child family policy: results from national family planning and reproductive health survey. *BMJ.* 2006;333(7564):371–373.
22. Colditz GA. The nurses' health study: a cohort of US women followed since 1976. *J Am Med Womens Assoc.* 1995;50(2):40–44.
23. Rockhill B, Byrne C, Rosner B, Louie MM, Colditz G. Breast cancer risk prediction with a log-incidence model: evaluation of accuracy. *J Clin Epidemiol.* 2003;56(9):856–861.
24. Rosner B, Colditz GA, Iglehart JD, Hankinson SE. Risk prediction models with incomplete data with application to prediction of estrogen receptor-positive breast cancer: prospective data from the Nurses' Health Study. *Breast Cancer Res.* 2008;10(4):R55.
25. Cui X, Dai Q, Tseng M, Shu XO, Gao YT, Zheng W. Dietary patterns and breast cancer risk in the shanghai breast cancer study. *Cancer Epidemiol Biomarkers Prev.* 2007;16(7):1443–1448.
26. Bernstein L, Yuan JM, Ross RK, et al. Serum hormone levels in premenopausal Chinese women in Shanghai and white women in Los Angeles: results from two breast cancer case-control studies. *Cancer Causes Control.* 1990;1(1):51–58.
27. Setiawan VW, Haiman CA, Stanczyk FZ, Le Marchand L, Henderson BE. Racial/ethnic differences in postmenopausal endogenous hormones: the multiethnic cohort study. *Cancer Epidemiol Biomarkers Prev.* 2006;15(10):1849–1855.
28. International Data Base, U.S. Census Bureau. *China 2000 Census.* www.census.gov/ipc/www/idbnew.html. Accessed September 31, 2007.
29. Yang L, Parkin DM, Ferlay J, Li L, Chen Y. Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer Epidemiol Biomarkers Prev.* 2005;14(1):243–250.
30. Wong IO, Cowling BJ, Schooling CM, Leung GM. Age-period-cohort projections of breast cancer incidence in a rapidly transitioning Chinese population. *Int J Cancer.* 2007;121(7):1556–1563.
31. Shen YC, Chang CJ, Hsu C, Cheng CC, Chiu CF, Cheng AL. Significant difference in the trends of female breast cancer incidence between Taiwanese and Caucasian Americans: implications from age-period-cohort analysis. *Cancer Epidemiol Biomarkers Prev.* 2005;14(8):1986–1990.
32. He J, Gu D, Wu X, et al. Major causes of death among men and women in China. *N Engl J Med.* 2005;353(11):1124–1134.
33. Wang L, Kong L, Wu F, Bai Y, Burton R. Preventing chronic diseases in China. *Lancet.* 2005;366(9499):1821–1824.
34. Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. *J Clin Oncol.* 2006;24(33):e49–e50.
35. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med.* 2007;356(16):1670–1674.

36. Leung KY, Ling M, Tang GW. Use of hormone replacement therapy in the Hong Kong public health sector after the Women's Health Initiative trial. *Maturitas.* 2005;52(3–4):277–285.
37. Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet.* 2002;359(9310):909–919.
38. Woo PP, Kim JJ, Leung GM. What is the most cost-effective population-based cancer screening program for Chinese women? *J Clin Oncol.* 2007; 25(6):617–624.
39. Wong IO, Kuntz KM, Cowling BJ, Lam CL, Leung GM. Cost effectiveness of mammography screening for Chinese women. *Cancer.* 2007;110(4): 885–895.
40. Hunter DJ, Willett WC. Diet, body size and breast cancer. *Epidemiol Rev.* 1993;15(1):110–132.
41. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. *J Am Med Assoc.* 1997;278:1407–1411.
42. Wang H, Du S, Zhai F, Popkin BM. Trends in the distribution of body mass index among Chinese adults, aged 20–45 years (1989–2000). *Int J Obes (Lond).* 2007;31(2):272–278.

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