Original Article

Attributable Causes of Breast Cancer and Ovarian Cancer in China: Reproductive Factors, Oral Contraceptives and Hormone Replacement Therapy

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ABSTRACT

Objective: To provide an evidence-based, consistent assessment of the burden of breast cancer attributable to reproductive factors (RFs, including nulliparity, mean number of children, age at first birth and breastfeeding), use of oral contraceptives (OCs, restricted to the age group of 15–49 years), and hormone replacement therapy (HRT), as well as of the burden of ovarian cancer attributable to the mean number of children in China in 2005.

Methods: We derived the prevalence of these risk factors and the relative risk of breast and ovarian cancer from national surveys or large-scale studies conducted in China. In the case of RFs, we compared the exposure distributions in 2001 and counterfactual exposure.

Results: Exposure of RFs in 2001 was found to account for 6.74% of breast cancer, corresponding to 9,617 cases and 2,769 deaths, and for 2.78% of ovarian cancer (711 cases, 294 deaths). The decrease in mean number of children alone was responsible for 1.47% of breast cancer and 2.78% of ovarian cancer. The prevalence of OC use was 1.74% and the population attributable fraction (PAF) of breast cancer was 0.71%, corresponding to 310 cases and 90 deaths. The PAF of breast cancer due to HRT was 0.31%, resulting in 297 cases and 85 deaths.

Conclusion: RFs changes in China contributed to a sizable fraction of breast and ovarian cancer incidence and mortality, whereas HRT and OCs accounted for relatively low incidence of breast cancer in China.

Key words: Reproductive factors; Oral contraceptives; Hormone replacement therapy; Cancer; Population attributable fraction

INTRODUCTION

Breast cancer is the most frequent cancer of women with an estimated 1.4 million new cases in 2008 worldwide, according to GLOBOCAN 2008[1]. There are generally increasing rates of breast cancer in the world, and incidence rates are high in most of the developed areas and low in most of Asia including China[2]. However, cancer registries in China are recording annual increases in incidence of 3% to 4%, which is much higher than average increasing rates (about 0.5%) in other countries[2]. Ovarian cancer ranks the seventh most common cancer in women worldwide. Incidence rates are highest in developed countries. There are relative low age-standardized incidence and mortality rates in China (3.8 and 1.5 per 100,000)[1].

Reproductive factors (RFs), and exogenous

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hormones, majorly oral contraceptive (OC) and hormone replacement therapy (HRT), are known risk factors to breast cancer and ovarian cancer. The RFS for which the evidence of a causal link with breast cancer is established include parity, age at first birth, total number of children, and duration of breast-feeding[3-6]. In addition, total number of children is also causally associated with ovarian cancer[7, 8]. Current or recent OC use contributes to the increased risk of breast cancer, particularly in young women and a history of OC use has clearly been shown to reduce the risk of ovarian cancer. Prolonged HRT use is found to be one of the important risk factors of breast cancer[9]. There is also evidence that HRT is associated with ovarian cancer occurrence[7].

As major risk factors, the unfavorable trend of RF change and prevalent OC and HRT use can lead to increasing incidence rates of breast cancer and/or ovarian cancer. The weight of these three risk factors to the burden of cancer in a given population is critical for better understanding of the relative importance of risk factors and for prioritization of public health efforts. Since one-fifth of new cancer cases worldwide occurs in China every year[8], attributable causes of cancers in China is in need of investigation to guide efforts in cancer control and prevention.

Attributable risks of these risk factors to breast cancer and ovarian cancer have been studied systematically in developed countries such as the United States and France[10, 11]. In contrast, the distribution of these factors in China is different from European and North American countries: HRT use in China is restricted to menopausal women who have peri-menopause symptoms. OC use is only one of the contraception methods used among women. The family planning policy implemented three decades ago and the lifestyle changes from economic improvement during this period in China have led to changes in RFs. No systematic assessment of the use of HRT and OC and the impact of RF on breast and ovarian cancer is available for China. Based on the rising incidence of breast and ovarian cancer and the different exposure situation regarding risk factors in China, we aimed to evaluate the proportion of breast and ovarian cancer risk attributable to these three factors in China.

MATERIALS AND METHODS

Overview

This study was to estimate the contribution of reproductive and hormonal factors to the burden of cancer through the calculation of proportion of specific cancers occurring in China in 2005 attributable to these risk factors (population attributable fraction, PAF). Our estimate of PAF was calculated based on the counterfactual scenario of total avoidance of exposure, except evaluation for RFs. We obtained estimates of relative risk (RR) and prevalence of each risk factor in Chinese women to derive estimate of PAF.

For three risk factors in this study, there is no lag time considered between at which time prevalence of specific factor was drawn and at which time cancer statistics was obtained. The latency period in PAF study does not apply to RFs, for which recent exposure is more important to determine cancer risk. Because current OC use is associated with breast cancer and such risk would disappear after cessation of OC use[12]. No lag time was considered for OC use in PAF analysis. Similarly, past HRT, defined as use of HRT ceased at least one year previously, has been associated rarely with a significant small increase in breast cancer risk[13].

To evaluate RR of breast cancer or ovarian cancer associated with RF, OC and HRT or their prevalence in China, we conducted a systematic publication search on PubMed, Medical Database of China Online Journals, Database for Chinese Technical Periodicals, China National Knowledge Infrastructure, On-line Visual Display Unit Interrogation of Databases, Excerpta Medical Database, the Cochrane Library, and cited references. Language was limited to English and Chinese. Search terms included risk factor, RF, OCs, HRT, menopause, perimenopausal women, China, Asia, breast cancer, ovarian cancer, social science, investigation, attitude, and health. Criteria for priority selection of data sources are: studies on national population or a representative sample preferred over studies of selected populations; meta-analyses over single studies; and Chinese data over data from other Asian countries or regions.

RFs

To collect population-based data on the prevalence of RFs, we browsed yearbooks[14-20] of health, population, family planning, fertility and reproductive health in China from 1980 to 2008. Additionally, we searched publications or data analysis books[21-30] from related national surveys or investigations of representative samples conducted during this period. Department of Health or National Population and Family Planning Commission performed these surveys or investigations in 1985, 1987, 1988, 1992, 1995, 1997, 2001, and 2004. Two dataset books[31, 32] were also used to include data from national population and fertility surveys conducted in 1982 and 1990. We also examined a few studies[33, 34] presenting prevalence of RFs, although they were conducted in local populations.

Five factors were considered in our study: nulliparity, expressed as a percentage of nulliparous women; parity, expressed as the mean number of children per parous woman (breast cancer attributable fraction) or mean number of children per woman (ovarian cancer attributable fraction); age at first birth, expressed as a percentage of women with age at first birth ≥30 years; and duration of breastfeeding, expressed as the average number of months of total breastfeeding. In total, we were able to extract prevalence data of all five factors in 1982, 1987, 1988, 1990, 1992, 1995, 1997 and 2001. Sporadic data in other years were found for one or more factors. Thereafter, we presented data in 1982 and 2001 to obtain the maximized time interval for sensitivity analysis, and used the latter time point to approximate prevalence in 2005 for PAF derivation.

For the prevalence of nulliparous women, the 2001 survey[30] only provided the data for women aged 15–49 years. Accordingly, prevalence in 1982[32] was calculated in the same age group. For parity, we divided the total number of children ever born by women aged 15–49 years in 1982 by the total number of parous women or women of this age group[32]. In the 2001 data[30], the total number of children was calculated by summing up the number of women in categories of increasing number of children ever born, weighted by the number of children in each category. This was then divided by the total number of parous women or women aged 15–49 years. For the percentage of women with age at first birth equal to or greater than 30 years, the overall distribution of married women aged 15–49 years by age at first birth in 2000 was given[30] and used as a surrogate for the 2001 data. In 1982[32], such distribution was given by age at survey and age at birth of first child, instead of an overall distribution. Thus, we summed up all numbers of women giving first birth at age ≥30 years by age at survey from 15 year to 49 years and all numbers of women ever giving birth and aged 15–49 years at time of survey, respectively, and then calculated the percentage. For the number of breastfeeding months, we used the distribution of live births by months of pure breastfeeding from 1980 to 1984[24] to estimate the distribution in 1982. The total number of breastfeeding months is a weighted sum of months of pure breastfeeding by the number of live births who were breastfed for this (specific) number of months. This was then divided by the total number of live births. We assigned duration of 15 months to the open-ended highest category (8 or more months). The prevalence in 2001 was calculated using the same method, with a smaller sample size and using 2000 data[30] as surrogates.

Five meta-analyses, including studies from various regions of China, were available. However, these analyses either used controls which were not applicable to our prevalence data or had unclear definition on RFs. Gao, et al. reported association between RFs and breast cancer from a Shanghai breast cancer study and provided clearly defined RR estimates[34]. We derived RR estimates for breast cancer from this study. The RR estimate for ovarian cancer was derived from a case-control ovarian cancer study in Beijing[35]. The RR of breast cancer for nulliparity was 1.31, which for parity was 0.79 per child, that for age at first birth equal or above 30 years was 1.45, and that for breastfeeding was 0.98 per month. The RR of ovarian cancer for parity was 0.79 per child. The RR for number of children and duration of breastfeeding were obtained using a formula for continuous variables.

$Log\ RR = log\ (RRu) \times d$

(RRu: RR for unit exposure; d: average exposure level)

OCs

Only current OC use was considered in our analysis. We can not distinguish continuous or intermittent use. Age-specific prevalence of OC usage was derived from a 2001 national survey of 32,464 women[30]. We presume such prevalence unchanged in 2005. Four meta- analyses[36-39] were found to estimate RR for current OC use. We used the RR of 1.41 from the meta-analysis of the best quality[38].

HRT

HRT exposure refers to past or current use of HRT, because no distinction was made between them in the available studies. Similarly, continuous and intermittent use could not be separated. HRT includes estrogen-alone therapy (ERT) and estrogen plus progesterone therapy (EPRT). The majority of perimenopausal women in China take ERT. Because no ratio of ERT and EPRT use in Chinese women was found, we presume all women to have ERT. Eleven studies provided data on prevalence of HRT use in specific areas of China from 1990 to 2007; however, none of these studies focused on the entire country. We used these data to estimate the situation in 2005. Five out of eleven studies met selection criteria and were used for calculating the prevalence of HRT use in China[40-44]. The total sample size was 14,759. Most studies reported that the duration of HRT use was less than 5 years in China. Only one study documented the prevalence of HRT use as being longer than 5 years. PAF of HRT use was thus too small to be considered when evaluating its attribution to ovarian cancer because of rare data about prevalence of long-term HRT use in China.

For our study, no appropriate meta-analysis was available to estimate the RR of breast cancer to HRT use in China or Asia. Thus, we used the RR from the Million Women study[45]. For breast cancer, the RR of HRT use is 1 for 1 year, 1.25 for 1–4 years, and 1.32 for 5–9 years. We approximated these two risks to that for 1–5 years and 6–10 years in our calculation, respectively. For ovarian cancer, there was no related study to estimate the RR of ovarian cancer to HRT use in China or Asia.

Cancer Incidence and Mortality in China

Data from the Third National Death Cause Survey in China in 2004–2005 were used to derive the number of deaths from breast and ovarian cancer (Table 1). This retrospective survey was conducted in 160 randomized counties and 53 high-risk areas between 2004 and 2005. Cancer incidence data were estimated using the Mortality to Incidence (M/I) ratio and cancer deaths. Details on mortality and incidence data have been provided elsewhere[46].

PAF Calculation

PAF is defined as the proportion of cancers in the total population that can be attributed to a risk factor. PAF was calculated by the following formula, which was described by Levin[47], where RR is the relative risk, and P is the prevalence of exposure in a population.

$$PAF = \frac{P \times (RR-1)}{[P \times (RR-1)] + 1}$$

For continuous variables in risk factors such as number of children and duration of breastfeeding, PAF was obtained by multiplying the RR for unit exposure (RRu, e.g., RR for 1 child) and the average exposure level (d), shown in the following formula.

$$Log\ RR = log\ (RRu) \times d$$
$$PAF = (RR-1)/RR$$

For RFs, we compared the exposure distribution in 2001 to a counterfactual exposure distribution which assumed zero nulliparity, none of women giving first birth after 30 years old, 2 children per woman, and 12 months of breastfeeding. We further conducted a sensitivity analysis using 1982 exposure prevalence data as a counterfactual scenario. In other words, we estimated the effect of the changes in RFs between 1982 and 2001 on the burden of breast and ovarian cancer. In the case of OC and HRT, the counterfactual scenario was that of no exposure. We calculated the number of cancer cases and deaths attributable to the different risk factors by applying the respective PAF to cancer incidence and mortality data.

Table 1. Number of deaths and cases of breast cancer and ovarian cancer in women by age group in 2005 in China

Site (age group, years)	Deaths	Cases
Breast (15–19)	9	26
Breast (20–24)	69	211
Breast (25–29)	262	917
Breast (30–34)	845	2,945
Breast (35–39)	2,964	10,097
Breast (40–44)	4,370	15,348
Breast (45–49)	4,591	15,977
Breast (15–49)	13,110	45,529
Breast (40–65)	27,153	94,289
Breast (all age groups*)	40,134	142,732
Ovary (15–49)	2,377	5,751
Ovary (40–65)	5,907	14,310
Ovary (all age groups*)	10,482	25,616

*All age groups: groups with age over 15 years. Data on incidence and mortality of breast and ovarian cancers were obtained from the Third National Death Cause Survey in China[46].

RESULTS

Exposure data to RF in 1982 and 2001 are given in Table 2. The percentage of nulliparous women was 37.91% in 1982 and 20.39% in 2001. The mean number of children per parous woman in 1982 was 3.28, and per woman was 2.04 to ovarian cancer; corresponding data in 2001 were 1.80 and 1.44. The proportion of women with age at first birth above or equal to 30 years old was 1.35% in 1982 and 4.86% in 2001. Number of months of breastfeeding was 9.39 in 1982 and 6.54 in 2001.

The total PAF due to RF in 2001 for breast cancer was 21.12% using the hypothetical counterfactual exposure distribution (Table 3). The sensitivity analysis showed the total PAF for breast cancer was 29.75%, based on the comparison of 2001 and 1982 RF exposure prevalence data (Table 4). The total PAF of ovarian cancer to RF in 2001 was 12.37%. The sensitivity analysis demonstrated that the comparison between 2001 and 1982 resulted in PAF to ovarian cancer equal to 13.19%.

Table 5 reports the number of breast and ovarian cancer cases and deaths attributable to RF in 2001, compared with the hypothetical counterfactual exposure distribution. There were 9,617 breast cancer cases and 2,769 breast cancer deaths attributable to RF, which accounted for 6.74% of breast cancer incidence and 6.90% of mortality, and was equal to or less than 1% in all cancers.

Table 2. Exposure prevalence of RFs in 1982 and 2001 in China

RFs	Age group (years)	1982			2001		
		n	Exposure	Reference	*n*	Exposure	Reference
Nulliparous %	15–49	248,036,697	37.91	Yao XW, 1995[32]	39,586	20.39	Pan GY, 2004[30]
Mean number of children per parous woman (for breast cancer)	15–49	248,036,697	3.28	Yao XW, 1995[32]	39,586	1.80	Pan GY, 2004[30]
Mean number of children per woman (for ovarian cancer)	15–49	248,036,697	2.04	Yao XW, 1995[32]	39,586	1.44	Pan GY, 2004[30]
With age at first birth ≥30 years (%)	15–49	191,629	1.35	Yao XW, 1995[32]	1,008	4.86*	Pan GY, 2004[30]
Number of breastfeeding months	n/a	4,702	9.39†	Jiang ZH, 2000[24]	1,569	6.54‡	Pan GY, 2004[30]

*Exposure in 2001 on % with age at first birth ≥30 years used data in 2000. †Number of breastfeeding months in 1982 was average data estimated from 1980 to 1984. ‡Number of breastfeeding months in 2001 used data in 2000.

Table 3. Comparison of RFs exposure in 2001 and counterfactual exposure and corresponding PAF to breast cancer and ovarian cancer

RFS	Exposure difference*	RR	Notation for RR	PAF† (%)
Mean number of children per woman (for ovarian cancer)	–0.56	0.79	Risk reduction per child	12.37
Nulliparous (%)	20.39	1.31		5.95
Mean number of children per parous woman (for breast cancer)	–0.20	0.79	Risk reduction per child	4.61
With age at first birth ≥30 years (%)	4.86	1.45		2.14
Number of breastfeeding months	–5.46	0.98	Risk reduction per 12 months of breastfeeding	8.43

*Counterfactual exposure distribution of RFs assumes: % Nulliparous = 0, mean number of children per woman (or parous woman) = 2, % with age at first birth ≥30 years = 0, number of breastfeeding months = 12. †PAF calculation for nulliparity and % with age at first birth ≥30 years was based on ordered RRs. PAF calculation for number of children and number of breastfeeding months was based on continuous RRs.

Table 4. Changes in RFs between 1982 and 2001 in China and corresponding changes in PAF to breast cancer and ovarian cancer (sensitivity analysis)

RFs	Exposure difference	RR	Notation for RR	PAF* (%)
Mean number of children per woman (for ovarian cancer)	–0.60	0.79	Risk reduction per child	13.19
Nulliparous (%)	17.52	1.31		–5.74
Mean number of children per parous woman (for breast cancer)	–1.48	0.79	Risk reduction per child	29.45
With age at first birth ≥30 years (%)	3.51	1.45		1.56
Number of breastfeeding months	–2.84	0.98	Risk reduction per 12 months of breastfeeding	4.48
Total change in PAF for breast cancer				29.75

*PAF calculation for nulliparity and % with age at first birth ≥30 years was based on ordered RRs. PAF calculation for number of children and number of breastfeeding months was based on continuous RRs.

We presented the total prevalence of current OC use, the resulting PAF, and cancer deaths and incidence attributable to OC use in age group of 15–49 years in Table 6. The overall prevalence of OC use in women aged 15–49 years was 1.74%. The total PAF in breast cancer attributable to OC use was 0.71%. Considering the lower number of breast cancer cases and deaths in the 15–49 age groups, the total number of breast cancer cases and deaths attributable to OC use in parous women was 310 and 90, respectively.

The overall prevalence of HRT use was 6.72% (992/14,759), as presented in Table 7. The prevalence of HRT use for one year and five years was 3.72% (549/14,759) and 1.61% (237/14,759), respectively. The total PAF of HRT accounted for breast cancer was 0.31%, corresponding to 85 deaths and 297 cases. It was only responsible for 0.08% of ovarian cancer, resulting from the small PAF due to lack of data.

Table 5. Estimation of the number of breast cancer and ovarian cancer cases and deaths in China in 2005 attributable to RFs in 2001

RFs	Attributable to cancer type	PAF (%)	Cases		Deaths	
			Number	No. attributable	Number	No. attributable
Mean number of children per woman	Ovarian cancer among parous women	12.37	5,751	711	2,377	294
Nulliparous (%)	Breast cancer among parous women	5.95	45,529	2,707	13,110	779
Mean number of children per parous woman	Breast cancer among parous women	4.61	45,529	2,097	13,110	604
With age at first birth (%) ≥30 years	Breast cancer among parous women	2.14	45,529	975	13,110	281
Number of breastfeeding months	Breast cancer among parous women	8.43	45,529	3,838	13,110	1,105
Total	Breast cancer			9,617 (6.74%)		2,769 (6.90%)
	All cancers			10,328 (1.05%)		3,063 (0.48%)

Table 6. Prevalence of current OC use in Chinese women and attributable numbers of breast cancer cases and deaths

	Current OC use (%)	PAF* (%)	Breast cancer cases	Breast cancer deaths	No. of breast cancer cases attributable to OC use	No. of breast cancer deaths attributable to OC use
Age of 15–49 years	1.74	0.71	45,529	13,110	310 (0.68%)	90 (0.69%)
All age groups			142,732	40,134	0.22%	0.22%
All cancers					0.03%	0.01%

*PAF calculation takes RR value of 1.41.

Table 7. Incidence and mortality of breast cancer in China attributable to HRT use

Duration of HRT use	Prevalence (%)	RR	PAF (%)	Deaths		Cases	
				No. attributable	All age groups (%)	No. attributable	All age groups (%)
1 year	3.72	1.00	0	0	0	0	0
1–5 years	1.61	1.25	0.29	78	0.19	273	0.19
6–10 years	0.08	1.32	0.02	7	0.02	24	0.02
Total*	6.72		0.31	85	0.21	297	0.21

*The total prevalence of HRT in China is 6.72%, which includes women without specified time of HRT use.

DISCUSSION

Our study provides an evidence-based, consistent assessment of numbers of cancer deaths and cases in China in the year 2005, which could be attributable to reproductive factors and exogenous hormone (OCs and HRT). Compared with counterfactual exposure distribution, there was 8.4% attributable to reduced duration of breastfeeding, 6% to nulliparity and 4.6% to decreased number of children for breast cancer, and 12.4% for ovarian cancer in 2001. Greatly influenced by government policy and economic development, reproduction behavior in China has significantly changed in recent decades. Therefore, RF changes over 20 years contribute to approximately 7% of breast cancer occurrence and mortality. The estimated overall prevalence of HRT and OC use in 2005 was 6.72% and 1.74%, respectively, with about 0.2% of breast cancer cases and deaths attributable to each agent usage. OC and HRT use account for a very small fraction of the burden of breast cancer due to the unpopularity of their use.

For sensitivity analysis, we used PAF change due to RF change estimated between 1982 and 2001 to calculate changes in cancer incidence and mortality. There is a considerable difference between sample sizes of the prevalence data of RFs collected in 1982 and 2001. In 1982, a large survey regarding fertility and reproduction was conducted involving 60% of the Chinese female population at that time. About 297 million women were surveyed in order to determine the prevalence of several important RFs including parity data in China. However, despite a growing population in 2001, the national survey on family planning and reproduction health in 2001 only sampled 39,586 women, a number which is ten thousand times less than the number surveyed in 1982. Since both studies were based on representative samples of the population and response rates were high, incomparability between datasets due to sample size difference can be minimized. It is worth noting that current prevalence data for PAF calculation was limited to women aged 15–49 years, but most breast cancer cases occur after 40 years old and among women not at parous age. The same concern applies to ovarian cancer. Since there is lack of reproductive data among women in wider age ranges, the overall percentage of breast cancer cases or deaths attributable to RF change might be underestimated. Thus, there is a significant need for large surveys structured to include older women to represent reproduction status for the entire population.

Family planning policy began to be implemented in China in late 1970s. As a result of this policy, though the percentage of parous women has been increasing over the years, there has been a decreasing trend in the number of children averaged per woman or parous woman, as seen by our collected data from 1982 to 2004 (data not shown). Consequently, this significant decrease contributes the greatest change in PAF (29.5%) for breast cancer in the sensitivity analysis. Correspondingly, PAF change due to the decreasing mean number of children per woman for ovarian cancer also accounted for 13.2%. Furthermore, recent data has shown an even lower mean number of children per parous woman or woman, which might contribute to greater PAF change and more cancer cases or deaths attributable after 2001. On the other hand, when comparing the 2001 data with ideal exposure, the exposure difference shrank, and the PAF to breast cancer was only 4.6%. PAF to ovarian cancer, however, remained close to the result of the sensitivity analysis.

The effect of family planning policy on reproduction in China was also seen in regard to age at first birth. Recommendations by the government on late marriage and birth have allowed more women to choose to have their first child at a time of their own choice. Taking into account the strides in education and career development, more and more women, especially from urban areas, have decided to delay having children to a later time in their lives. The percentage of age at first birth greater than or equal to 30 years old has, as expected, been on the increase over the past several years. PAF change for breast cancer due to this factor is, however, not as significant as due to parity for breast cancer. However, a comparison of the 2001 data, with its small sample size (1,008 women), against the 1982 data, which surveyed 191,629 women, might yield conservative estimates, since other source data from around 2005 suggest a bigger proportion of women having their first birth after 30 years old. In accordance with delayed age at first birth among Chinese women, the number of breastfeeding months was also reduced. Further- more, as we used 15 months to roughly estimate the mean number of months of pure breastfeeding longer than 8 months (see method section), it is possible that the duration of breastfeeding is conservatively estimated at each time point. More studies should be conducted to provide more accurate estimates on duration of breastfeeding.

Several studies[48-50] found that OC use is associated with different levels of risk for breast cancer in younger and older women. However, most studies use 40- or 45-year old women as a parameter to separate younger and older age groups, while our data surveyed women from 15 to 49 years old in China. PAF calculation in our study assumes the same risk for different age groups. We found more women aged 15–19 years use OC for contraception, whereas only about 2% of women 20 years old or older rely on OC for birth control. It is logical that younger women, especially when they have not yet had a child, would choose to use OC, while older women most commonly tend to undergo tubal ligation or use an intrauterine device (IUD) for birth control. Overall, PAF increase in breast cancer due to OC use is very low, as are cancer cases and deaths attributable to OC use. This is largely because of the very low prevalence of OC use in China.

Our study showed that HRT prevalence is lower than in Europe and North America. The prevalence of HRT use in China is 6.7% (excluding women for whom there was no information on the duration of using HRT), compared with 20.7% in the USA in 1995[51], 18.4% in Denmark in 1997[52] and 19% in the UK in 1990[53]. The major reason might be that the majority of Chinese perimenopausal women did not have enough knowledge about the perimenopause syndrome. Less than 20% of perimenopausal women seek advice on perimenopause syndrome from their gynecologist[43]. The percentage of perimenopausal women aware of HRT was as low as 7.9%[42]. The data makes clear that not all Chinese women select HRT, regardless of the presence of symptoms, while only a small number of women take HRT because of serious symptoms. Also, most perimenopausal women in China often discontinue HRT after their symptoms have been effectively brought under control[43]. That explained the reason that the prevalence of HRT use for over 5 years is very low in China. This led to the total PAF of breast cancer attributable to HRT in China of 0.31%, clearly lower than that reported in developed countries such as France (0.4% for ERT users and 18.8% for ERT and EPRT users)[11].

Bernstein reviewed that many other RFs, such as early age at menarche or late age at menopause, are identified as risk factors for breast cancer[54] and that tubal ligation protects against ovarian cancer[7]. These RFs were not studied in this paper, but they might have effect on cancer incidence and mortality as well. Other risk factors of breast cancer and ovarian cancer include family history, obesity, dietary factor, cigarette smoking, alcohol drinking and genetics[7, 10, 55]. Also, the time interval we chose in the sensitivity analysis is relatively short since long-term change in cancer incidence and mortality due to RF change is more obvious. The shortage of data, especially before 1980, can not allow for a longer-term interval. Nevertheless, prevalence data of RFs and OC use are from national surveys and based on relatively big sample size, which guaranteed good data quality. Prevalence data of HRT use and RR estimates for RFs and OC use were from either meta-analyses results or literature based on a representative sample in China. This ensured good data used and robust conclusions made in this study. The value of our study is that we used national data instead of local data in PAF calculation, which could be applied to general population.

As the study on PAF of breast and ovarian cancer to RFs, OCs and HRT in China, our report provides an estimation of the number and percentage of cancer cases and deaths attributable to these factors, which may serve as a basis for future research in cancer prevention and control. It suggests that in the process of implementing family planning policy, health considerations should be taken into account and related health programs might be offered for disease prevention and control.

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