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Impact of known risk factors on endometrial cancer burden in Chinese women

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Abstract

Objective—This study aimed to provide data on the impact of known risk factors on endometrial cancer burden.

Methods—Using data of 1 199 endometrial cancer cases and 1 212 frequency matched controls from a population-based case-control study carried out in urban Shanghai, China from 1997 to 2003, multivariable adjusted odds ratios were obtained from unconditional logistic regression analyses. Partial population attributable risks were calculated and corresponding 95% confidence intervals (95% CIs) were estimated using a bootstrap method.

Results—An estimated 16.94% of endometrial cancer cases were attributed to overweight or obesity; 8.39% to meat intake; 5.45% to non-regular tea drinking; 5.23% to physical inactivity; and 1.77% to family history of endometrial, breast, or colorectal cancers. Overall, these risk factors accounted for 36.01% (95% CI: 28.55%–43.11%) of total endometrial cancer cases. Similar results were observed when analysis was restricted to post-menopausal women.

Conclusion—Among modifiable lifestyle factors, overweight and obesity accounted for the largest proportion of endometrial cancer in the study population. Lifestyle alterations, such as maintenance of healthy weight, regular exercise, consumption of less meat, and tea drinking, could potentially prevent endometrial cancer by more than one third.

Keywords

endometrial cancer; partial population attributable risk; risk factors; prevention; case-control study

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Introduction

Endometrial cancer (EC) is the sixth most common cancer in women worldwide and has a large geographic variation in incidence and mortality rates (Ferlay et al., 2013). EC is one of the most common gynecological malignancies in Chinese women. Due to industrialization and urbanization, the age adjusted incidence rate has risen over the past several decades to 4.7 per 100 000 person years in 2009 (Wei et al., 2012; Wei et al., 2013). In more developed areas of China, EC has supplanted cervical cancer and ranks the first in gynecological malignancies (Ferlay et al., 2013; Wei et al., 2013). With increasing obesity, physical inactivity, and life expectancy, it is estimated that EC incidence may rise further. Although EC was not previously a major health concern in China, the increasing trends have led to more studies on EC prevention from the public health perspective.

Most ECs are estrogen related (Amant et al., 2005; Sorosky 2012). Established risk factors include obesity, diabetes, nulliparity, infertility, early menarche, late age of menopause, as well as unopposed estrogen replacement therapy and tamoxifen treatment (Amant et al., 2005; Sorosky 2012). Regular physical activity, smoking, oral contraceptive, and intra-uterine device use may protect against EC, and women with a family history of colorectal, breast, or endometrial cancer are at an increased risk (Amant et al., 2005; Sorosky 2012; World Cancer Research Fund, 2013). Among dietary factors, higher intake of animal food and glycaemic load were found to be associated with an increased risk of EC, whereas increasing phytoestrogen consumption was suggested to be protective (Amant et al., 2005; Sorosky 2012; World Cancer Research Fund, 2013). Despite the fact that the risk factors of EC have been extensively studied, their impact at population level has not been well-addressed.

Population attributable risk (PAR) is the most commonly used measure of a risk factor's impact at a population level. It is useful for policymakers in planning public health intervention strategies (Ahrens and Pigeot, 2014; Rockhill et al., 1998). As some risk factors are highly correlated and might have combined impacts on EC, PAR calculated for a single risk factor tends to be overestimated. Partial PAR, also known as average PAR, taking into consideration of the sequential removal of multiple risk factors, thus enables us to evaluate multiple exposure factors simultaneously and has the advantage of not adding up to more than 100%, which is more practical in epidemiological studies (Eide and Gefeller, 1995; Rückinger et al., 2009). To the best of our knowledge, no study examining the partial PAR of EC in Asian people has been published to date.

In this report, we estimated the adjusted PARs and partial PARs of major risk factors for EC using data collected from a large population-based, case-control study.

Material and methods

Study population—The study population included participants of the Shanghai Endometrial Cancer Study (SECS), a population-based, case-control study conducted in urban Shanghai, China. Details of the study design have been described elsewhere (Xu et al., 2007). Briefly, a total of 1 199 incident EC cases aged 30-69 were identified between January 1997 and December 2003 using the Shanghai Cancer Registry. The diagnosis of

cancer was confirmed by an expert panel through careful review of medical records and/or available pathological information. Cases were defined with ICD-9 codes of 182. A total of 96.68% of the cases were type I EC. Control subjects were randomly selected from the general population using the Shanghai Resident Registry and were frequency matched to the corresponding cases based on age (within 5-yr intervals). Of the 1 629 eligible controls, 1 212 (74.4%) participated in the study. The study was approved by the institutional review boards of Vanderbilt University, Nashville, TN, and the Shanghai Cancer Institute, Shanghai, China, and written informed consent was obtained from all participants of the study.

Data collection—In-person interviews were completed by trained medical professionals for each participant at enrollment. A structured questionnaire was used to obtain information from cases and controls covering demographic factors, prior disease history, menstrual and reproductive history, hormone and other medication use, dietary habits, physical activity, tobacco and alcohol use, and family history of cancer. In addition, a standard protocol was followed to measure anthropometrics including weight, height, and waist and hip circumferences during the interview (Xu et al., 2005).

Model development—Variables considered for the model were based on literature review and their significance in our data. The risk of EC was estimated by odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using unconditional logistic regression. The reference group for each variable was defined as the group with the lowest risk. We first carried out a univariate analysis with all well-established risk or protective factors for EC and other possible risk factors identified in our study. Variables with P values up to 0.20 in the univariate analysis were included in the multivariate analysis. Variables that lost significance ($P > 0.05$) were excluded from the model. In the third step, factors excluded from the first and second steps were re-fitted subsequently to the multivariate model to avoid omission of important factors (Hosmer et al., 2013). Moreover, we also fit the multivariate model with other procedures including backward regression, forward regression, full model, and full stepwise sequence (Shtatland et al., 2004). The model with minimal Akaike information criterion (AIC) was selected as the final model. Collinearities were evaluated by variance inflation factor (VIF). Potential pairwise interactions were estimated using likelihood ratio tests by comparing the log likelihoods between models with or without the interaction terms. In addition, when we compared the model additionally adjusted for age and education with the final model, the estimated parameters changed little and the model fitness did not improve. Therefore, we presented the model without these variables.

Variables that remained in the final model were: BMI (kg/m^2 , <23 , 23-27.4, 27.5); regular tea drinking (yes, no); regular physical activity (yes, no); total meat intake (g/day , <75 , 75-124.9, 125); oral contraceptive use (ever, never); intra-uterine device use (ever, never); parity (1, never); menopausal status (pre-menopausal, post-menopausal); age at menopause (year, 50, <50); menstruation span (year, <30 , 30-34.9, 35); history of diabetes (yes, no); history of endometrial hyperplasia (yes, no); family history of colorectal, breast or endometrial cancers (yes, no).

Estimation of PARs—Multivariate adjusted PARs were estimated using Bruzzi's method with parameters derived from an unconditional logistic regression model (Bruzzi et al.,

1985). The 95% CI was estimated using a bootstrap method with 1000 repeats, and the 2.5th and 97.5th quantiles of the 1 000 resulting PARs were reported as 95% CIs (Efron and Tibshirani, 1993; Kooperberg and Petitti, 1991). Partial PARs and their 95% CIs were evaluated with Eide's method (Eide and Gefeller, 1995) using an adopted SAS macro (Rückinger et al., 2009). PARs were estimated for the factors that remained in the final model on the assumptions that all populations were moved to the group with lowest risk and their risk of developing EC could be avoided (Ahrens and Pigeot, 2014). As some risk factors were highly correlated and might have combined impacts on EC, PAR calculated for single risk factor tends to be overestimated (Walter 1998). We also estimated the PARs for combinations of these factors. Additional analyses were performed for post-menopausal women. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 1 199 EC cases and 1 212 healthy controls were included in our study. Cases and controls were well matched on the basis of age, with means of 54.98 years and 55.08 years respectively. Compared to the control group, EC cases had a slightly higher education level, although the ORs were insignificant, and they were more likely to be professional workers. Cases and controls were comparable with respect to family income and marital status (data not shown).

Major risk factors of EC in this population are presented in Table 1. The associations observed in this study were consistent with the literature. Compared with controls, EC cases were more likely to be overweight or obese, physically inactive, have higher intake of meat, and less likely to drink tea. Pre-menopause and longer menstruation span were associated with increased EC risk, whereas oral contraceptive, intra-uterine device use, and having given live birth were associated with decreased EC risk. EC cases had a higher prevalence of diabetes and endometrial hyperplasia. The risk of EC was also increased among subjects with a first-degree relative affected by colorectal, breast, or endometrial cancer. The prevalence of hormone replacement therapy (HRT) use in this population was very low (4.42% for cases and 4.04% for controls) and was not associated with EC. Smoking, alcohol drinking, and history of hypertension also failed to enter the final model (data not shown).

The multivariate adjusted and partial PARs as percentages are shown in Table 1. The strongest attributable risk factor for EC was overweight/obesity with a partial PAR of 16.94% (95%CI: 12.61%-21.23%). Among other lifestyle factors, about 8.39% (95%CI: 4.26%-12.69%) of EC cases could be attributed to meat intake, followed by non-regular tea drinking (5.45%, 95%CI: 1.55%-9.48%), and physical inactivity (5.23%, 95%CI: 1.18%-9.25%). Among menstrual and reproductive factors analyzed, never use oral contraceptives or intra-uterine device, later age at menopause, and long menstruation span all contributed to a considerable proportion of EC, with partial PARs ranging from 5.61% to 14.55%. Although highly related to EC, nulliparity and family history of certain types of cancer only accounted for 0.86% and 1.77% of EC, largely because of the low prevalence in this population.

Table 2 shows the PARs of lifestyle related factors in different combinations. The partial PAR for overweight/obesity and physical inactivity combined was 22.17% (95%CI: 16.19%-27.25%). The summary PAR for all four lifestyle related factors together was 36.01% (95%CI: 28.55%-43.11%). The summary PAR for other factors, including oral contraceptive use, intra-uterine device use, parity, menopause status, menstruation span, history of diabetes, history of endometrial hyperplasia, and family history of colorectal, breast, or EC, was 50.09% (95%CI: 43.17%-56.50%).

Similar results were observed in separate analyses in post-menopausal women. Overweight or obesity accounted for 15.66% (95%CI: 9.94%-21.17%) of EC, followed by meat intake (9.93%), physical inactivity (5.16%), and non-regular tea drinking (4.25%), but the PAR for non-regular tea drinking was insignificant (95%CI: -1.2%-9.8%) (Supplemental Table 1). The PAR for total meat intake was a little higher than in all women. The overall PAR for lifestyle related factors added up to 35.00% (95%CI: 25.63%-43.73%), which was similar to that observed in the entire study (Supplemental Table 2).

Discussion

On the basis of a large population-based, case-control study, we estimated the PARs of established risk factors for EC in Chinese women. We found that overweight or obesity had a major impact on EC in this population. Alterations in lifestyle factors, including weight, physical activity, meat intake, and tea drinking, could potentially prevent EC by more than one third. To our knowledge, this is the first study to investigate the partial PAR and combined impact of lifestyle factors for EC in an Asian population.

The partial PAR was originally introduced by Eide et al. as average PAR in the 1990s (Eide and Gefeller, 1995). It covered all possible orders of sequential removal of risk factors and partitioned the disease risk in complex multifactorial situations. Compared to traditional approaches, partial PAR has the advantage of additivity which makes it more reasonable in public health practice (Gefeller et al., 1998). Moreover, it might be useful as an important epidemiologic indicator for policy makers in developing potential intervention and prevention strategies.

In our study population, overweight or obesity accounted for the largest part of EC, which was consistent with researches in other populations, but the effect size was less comparable due to the difference in the definition of “overweight” and statistical methods. Two studies in Asian populations reported the PAR for excess body weight (Wang et al., 2012; Park et al., 2014). Excess body weight was responsible for 32.7% of EC cases in Korea (BMI 23) and 18.91% in China (BMI 25). Both of them used Levin’s formula (Levin 1953) irrespective of other risk factors, and neither of them provided CIs for their PARs. Results obtained from western countries showed considerable variations. Overweight or obesity accounted for about 40% of EC cases worldwide (BMI 25) (IARC 2002), 30% in European countries (BMI 25) (Renhehen et al., 2010), 40% in the United States (BMI 30) (Polednak 2008), 51% in the UK (BMI 25) (Reeves et al., 2007), 22% in Canada (BMI 30) (Luo et al., 2007), 32.2% in Italy (BMI 25) (Parazzini et al., 1989), and 61% in South Africa (BMI 21) (Joubert et al., 2000). Differences in age ranges, definition of overweight/obesity, and

statistical methods used in these studies may explain, in part, the discrepancy of the effect size of obesity on EC.

Reports on attributable risk for EC were limited with respect to other risk factors. A pooled analysis of 15 European countries showed that 8% to 26% of EC was attributable to insufficient physical activity (sufficient: accumulated 3 000 metabolic equivalents (METs)-minutes over 7 days, or 1 500 METs-minutes of vigorous-intensity physical activity over 3 days or more) (Friedenreich et al., 2010). A UK study reported that 3.8% of EC cases were attributable to exercising less than 15 METs-hours per week (Parkin 2010) ³¹. In our study, over 71.23% of cases and 66.50% of controls never performed regular exercise during adulthood, with only 8.75% of women exercising up to the World Health Organization's (WHO) recommendation on physical activity.

The contribution of family history of cancers toward EC was relatively small. In our population, the partial PAR for EC was only 1.77%. In a multicenter case-control study in the US, 4.7 % of incident EC among women aged 20 to 54 years might be attributable to a family history of EC and 1.8% to colorectal cancer (Gruber and Thompson, 1996). A Swedish study found a PAR of 2.09% (1.88%-2.27%) for family history of cancer (Hemminki et al, 2005). The study also reported that parity and age at last birth accounted for the largest proportion of EC with a PAR of 45.51% (43.05%-47.70%), assuming that all women would have had a parity of at least 3 and the last childbirth after 34 years. However, such an assumption was unrealistic, and the PAR was likely to be overestimated because only a small portion of subjects fell into this category. A study from New Zealand evaluated the combined impact of diabetes, physical inactivity, and overweight/obesity on the age standardized rates of EC, showing a PAR of 50.5% (38.6%–64.3%) for Pacific, 18.7% (14.6%–23.1%) for Maori, and 10.3% (8.7%–12.1%) for European/other ethnic groups (Meredith et al., 2012).

Several issues should be taken into account in the interpretation of PAR. In the first place, the calculation of PAR was performed on the basis of a causal assumption of specific exposure with disease. Results should be interpreted with caution if the evidence of a causal relationship was not very convincing and the underlying biologic mechanism was not fully understood. Secondly, when estimating PAR using case-control data, we assume that the ORs approximate the relative risk in prospective studies. Moreover, the magnitude of PAR for each risk factor was highly dependent on the method applied. In our study, there was a marked difference in PARs obtained by two approaches. For example, the adjusted PAR was almost 40% for overweight or obesity, whereas the partial PAR was only 16.63%. The overall adjusted PAR of four lifestyle factors was 53.76% and the approach of partial PAR yielded a result of 36.01%. Meanwhile, the magnitude of PAR was also closely related to the cut-off points in categorization of a risk factor because it may alter the estimation of risk as well as the prevalence of exposure. In the analysis of overweight or obesity, if we define overweight as BMI of at least 25, the WHO criteria for obesity, the partial PAR would decrease to 10.61%.

The strengths and limitations of this study should be mentioned. Our study is the largest population-based, case-control study on EC in China. Anthropometric data were based on

measurement instead of self-reporting. Most of the major risk factors of EC were covered and their associations with EC were consistent with published literature. In addition to using the commonly used method to calculate PAR in case-control studies, we presented partial PARs and 95% CIs for individual factors as well as for different combinations, which could provide further public health implications. The limitations of the study should also be considered for interpretation of results. As mentioned, when estimating PAR with case-control data, we assume that the odds ratios approximate the relative risk in prospective studies. The ORs in our study could be considered as the approximation of RRs, as EC is relatively rare (Rothman et al., 2012). Second, like other case-control studies, possible recall bias, selection bias, and misclassification cannot be completely eliminated. Physical activity in our study was acquired by a self-report questionnaire rather than objective measurements. However, the physical activity questionnaire used in the Shanghai Women's Health Study, which was identical to our study, has been proved to be reproducible and valid (Matthews et al., 2003).

In summary, in this large population-based case-control study, we quantified the potential impact of established risk factors of EC in a Chinese population. We found overweight/obesity was responsible for most of the EC cases in this population. More than one third of EC cases could be prevented through changes in lifestyle factors. As the prevalence of obesity in China has continued to increase in the past decades (Stern et al., 2014), more efforts should be made at both individual and governmental level to reduce its health consequences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Major risk factors and population attributable risks for endometrial cancer in the Shanghai Endometrial Cancer Study

Table 1

Factor	Cases (%)	Controls (%)	OR (95%CI) ^a	Adjusted PAR (95%CI) ^b	Partial PAR (95%CI) ^c
BMI					
<23	309 (25.79)	526 (43.44)	1.00	39.88 (31.50-47.37)	16.94 (12.61-21.23)
23-27.4	533 (44.49)	512 (42.28)	1.74 (1.42-2.14)		
27.5	356 (29.72)	173 (14.29)	3.37 (2.61-4.35)		
Regular tea drinking					
Yes	357 (29.77)	378 (31.19)	1.00	15.90 (4.88-26.74)	5.45 (1.55-9.48)
No	842 (70.23)	834 (68.81)	1.29 (1.06-1.57)		
Regular physical activity					
Yes	345 (28.77)	406 (33.50)	1.00	15.70 (3.73-26.40)	5.23 (1.18-9.25)
No	854 (71.23)	806 (66.50)	1.28 (1.05-1.56)		
Total meat intake(g/day)					
<75	298 (24.85)	413 (34.08)	1.00	23.39 (12.27-33.75)	8.39 (4.26-12.69)
<125	363 (30.28)	394 (32.51)	1.18 (0.94-1.49)		
125	538 (44.87)	405 (33.42)	1.71 (1.37-2.14)		
Oral contraceptive use					
Ever	219 (18.27)	302 (24.92)	1.00	23.28 (8.31-35.77)	8.15 (2.77-13.33)
Never	980 (81.73)	910 (75.08)	1.40 (1.12-1.75)		
Intra-uterine device use					
Ever	497 (41.45)	658 (54.29)	1.00	26.01 (17.95-33.15)	9.91 (6.49-13.28)
Never	702 (58.55)	554 (45.71)	1.80 (1.47-2.20)		
Parity					
1	1089 (90.83)	1161 (95.79)	1.00	3.05 (0.15-5.94)	0.86 (0.03-1.91)
0	110 (9.17)	51 (4.21)	1.50 (1.01-2.23)		
Menopause status					
Post-menopausal	701 (58.47)	765 (63.12)	1.00	15.35 (9.17-21.33)	5.61 (3.14-8.31)
Pre-menopausal	498 (41.53)	447 (36.88)	1.59 (1.29-1.95)		
Menstruation span(year)					
<30	289 (24.16)	459 (37.97)	1.00	36.27 (27.25-44.54)	14.55 (10.23-19.08)

Factor	Cases (%)	Controls (%)	OR (95%CI) ^a	Adjusted PAR (95%CI) ^b	Partial PAR (95%CI) ^c
<35	495 (41.39)	513 (42.43)	1.60 (1.30-1.99)		
35	412 (34.45)	237 (19.60)	2.50 (1.96-3.20)		
History of diabetes					
No	1005 (84.74)	1121 (93.11)	1.00	8.00 (5.10-10.82)	2.81 (1.61-4.13)
Yes	181 (15.26)	83 (6.89)	2.10 (1.55-2.85)		
History of endometrial hyperplasia					
No	1021 (86.38)	1184 (98.50)	1.00	12.23 (10.31-14.33)	6.44 (4.89-8.26)
Yes	161 (13.62)	18 (1.50)	9.82 (5.80-16.62)		
Family history of colorectal, breast or endometrial cancers					
No	1092 (91.46)	1151 (95.60)	1.00	4.74 (2.70-6.74)	1.77 (0.89-2.82)
Yes	102 (8.54)	53 (4.40)	2.24 (1.54-3.28)		

CI, confidence interval; PAR, population-attributable risk.

^aORs were adjusted for all the other variables listed in the table.

^bWith Bruzzi's method.

^cWith Edge's method.

Combined population attributable risks for endometrial cancer in the Shanghai Endometrial Cancer Study

Table 2

Factors	PAR% (95%CI) ^a	Partial PAR(95%CI) ^b
BMI+ physical inactivity	43.50 (27.78-57.96)	22.17 (16.19-27.25)
BMI+ physical inactivity +non-regular tea drinking	31.80 (-12.14-61.02)	27.61 (21.13-33.64)
BMI+ physical inactivity +total meat intake	56.41 (1.93-86.90)	30.56 (24.2-36.95)
BMI+ physical inactivity +total meat intake+non-regular tea drinking	53.76 (23.40-74.52)	36.01 (28.55-43.11)
all the other factors	74.82 (53.41-89.94)	50.09 (43.17-56.5)

CI, confidence interval; PAR, population-attributable risk.

^a with Bruzzi's method

^b with Edge's method