Preplanned Studies

Pregnancy Loss in Relation to the Risks of Female-Specific Cancers in a Population-Based Cohort and Mendelian Randomization Study — China, 2004–2017

Yongle Zhan[1,2,&]; Yawen Wang[3,&]; Yimin Qu[1,&]; Lin Zhang[1,4,5]; Xuan Liu[1]; Ruiyi Liu[1]; Peng Xue[1]; Jiaxu Wang[1]; Dongxu Qin[1]; Hexin Yue[1]; Canqing Yu[6]; Jun Lyu[6]; Yu Guo[7]; Zhengming Chen[8]; Yu Jiang[1,#]; Liming Li[6,#]; China Kadoorie Biobank Collaborative Group

Summary

What is already known about this topic?

Limited evidence exists regarding the relationship between pregnancy loss and female-specific cancers within the Chinese population from prospective cohort studies.

What is added by this report?

Terminations were associated with a 13% lower risk of endometrial cancer, whereas stillbirths were related to an 18% higher risk of cervical cancer. Rural residents with a history of pregnancy loss experienced a 19% and 38% increased risk of breast and cervical cancers, respectively, compared to their urban counterparts. Moreover, a positive graded relationship between live births and pregnancy loss on cervical cancer was observed.

What are the implications for public health practice?

This study has significant implications for identifying women at an increased risk for breast and genital cancers and contributes to the development of effective public health strategies for female cancer prevention. Future research on reproductive history, particularly in rural areas, should be given priority in efforts to improve female cancer screening and early detection.

Breast cancer (BC) is the most common cancer and the leading cause of cancer-related deaths among females globally (*1*). Cervical and ovarian cancer also contribute to significant burdens of cancer-related disability and mortality (*2*). Consequently, identifying at-risk groups is crucial for the early detection of breast and gynecological malignancies. Pregnancy loss (PL) is a prevalent occurrence worldwide, with approximately 2.6 million stillbirths and over 20% of pregnancies ending in spontaneous abortions in 2015 (*3*–*4*). Termination has reached a global prevalence of 3.5% among women of reproductive age between 2010–2014 (*5*). Reproductive factors, including pregnancy and PL, have been repeatedly associated with breast and gynecologic cancers, yielding inconclusive results. Earlier studies demonstrated that compared to nulliparous women, parous women exhibited lower long-term risks of breast cancer and endometrial cancer (*6*–*7*). However, a recent individual-level meta-analysis indicated that the risk of breast cancer increased for women with higher parity (*8*). Regarding PL, previous observational studies proposed its association with female-specific cancer (*9*–*10*), while a recent nationwide cohort study in Denmark contradicted any correlation between pregnancy loss and subsequent cancer development (*11*). Additionally, there is limited evidence addressing this topic within the Chinese population. Considering that the reproductive patterns of Chinese women have changed significantly over the past few decades, a proper understanding of the link between PL and female cancer risk is pivotal in China. Thus, this large cohort study, consisting of 298,008 participants, provides the most comprehensive assessment of the associations between PL and long-term female-specific cancer risk among Chinese women between 2004 and 2017.

In this study, we utilized a large female sample from the China Kadoorie Biobank (CKB) study, which is an ongoing nationwide cohort study involving 512,891 individuals (59% women) recruited at baseline between 2004 and 2008 and followed up for morbidity and mortality at ten regional study sites (Licang, Nangang, Meilan, Wuzhong, Liubei, Pengzhou, Maijixiang, Huixian, Tongxiang, and Liuyang) across China. After excluding participants with a cancer history (n=1,160), insufficient information on reproductive history (n=47), and nullipara (n=2,857), a total of 298,008 women were included in the final

analyses. Reproductive history, encompassing the number of pregnancies, parities, spontaneous miscarriages, terminations, and stillbirths, was assessed using a structured questionnaire. Time to first onset of breast cancer (C50), cervical cancer (C53), endometrial cancer (C54.1), and ovarian cancer (C56) was recorded through linkage to local disease and death registers, health insurance databases, residential records, and the registries of the China's Disease Surveillance Points system based on ICD-10 codes (International Classification of Diseases, 10th Revision). Follow-up person-years were calculated from the date of baseline enrollment to either the date of cancer, death, loss to follow-up, or December 31, 2017, whichever occurred first.

Cox proportional hazards (PH) models were conducted to estimate hazard ratios (*HR*s) and 95% confidence intervals (*CI*s) for cancer in relation to PL. Cox models were stratified by age-at-risk (five-year intervals) and regions, and HRs were adjusted for body mass index (BMI), socioeconomic status, alcohol consumption, smoking, physical activity, sleep quality, comorbidity, age at menarche, oral contraceptive use, and gynecological operation history. A two-sample Mendelian randomization (MR) analysis, adhering to the three assumptions (independence, relevance, and exclusion restriction), was further executed to estimate potential causal relationships. Instrumental variables [i.e., single nucleotide polymorphism (SNPs)] of three exposure traits (miscarriages, terminations, and stillbirths) were obtained from the genome-wide association studies (GWAS) catalog (https://www.ebi.ac.uk/gwas/). Summary GWAS data on cancer traits (i.e., breast, cervical, endometrial, and ovarian cancers) were acquired from the BioBank Japan.

The random-effects inverse-variance weighted (IVW) method and a series of sensitivity analyses, including MR-Egger regression, weighted-median, simple-mode, and weighted-mode, were employed for MR analyses. Horizontal pleiotropy was assessed by the MR-Egger intercept. All *P* values were two-sided, and statistical significance was set at the <0.05 level. The aforementioned analyses were performed using R4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). The study's flow chart is presented in Figure 1.

In the sample of 298,008 women, 9.1% reported a history of miscarriage, 52.5% reported termination, and 5.7% reported stillbirth. Participant characteristics across the number of PLs are shown in Table 1. After a median follow-up of 9.2 years, 1,997 new cases of female breast cancer (incidence rate: 0.7‰), 950 cervical cancer cases (incidence rate: 0.3‰), 338 endometrial cancer cases (incidence rate: 0.1‰), and 377 ovarian cancer cases (incidence rate: 0.1‰) were observed. A 13% decreased risk of endometrial cancer per additional termination (*HR*=0.87, 95% *CI*: 0.78–0.98, *P*=0.019) and an 18% increased risk of

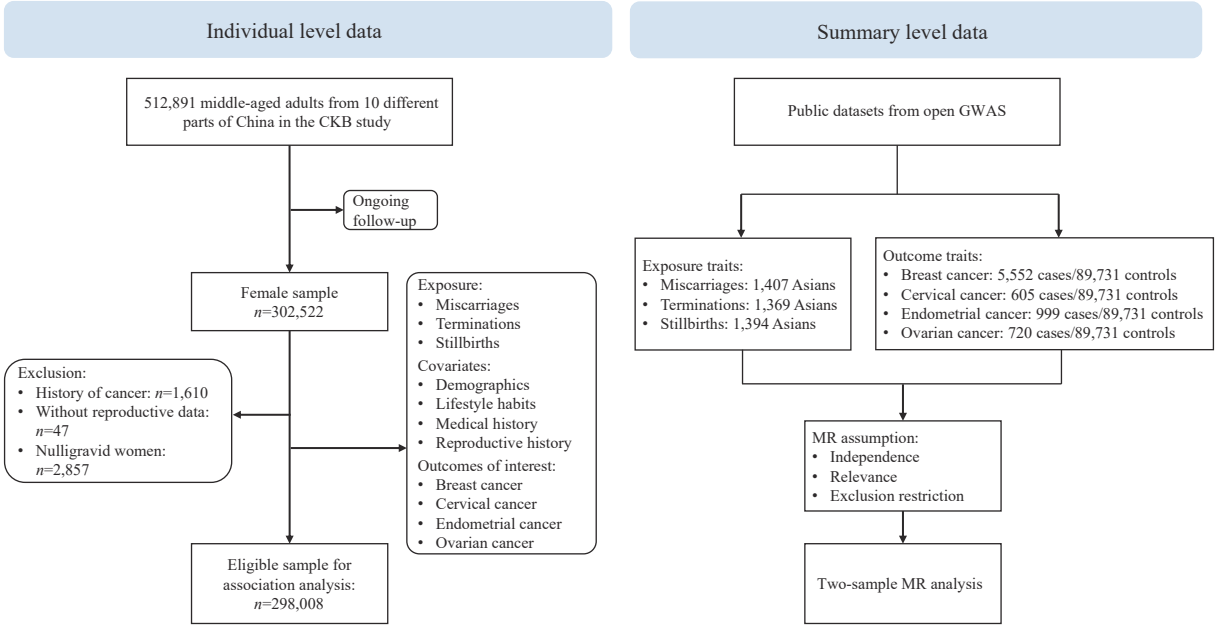


FIGURE 1. Flow chart of the present study.
Abbreviation: CKB=China Kadoorie Biobank; GWAS=genome-wide association studies; MR=Mendelian randomization.

TABLE 1. Baseline characteristics of participants by number of miscarriages, terminations, and stillbirths (*n*=298,008).

Characteristic	Total	Miscarriages			Terminations			Stillbirths		
		0	1	≥2	0	1	≥2	0	1	≥2
Sample, %		90.9	7.2	1.9	47.5	27.8	24.7	94.3	4.4	1.3
Rural residents, %	55.7	54.3	68.5	72.8	70.0	44.8	40.3	54.8	67.5	77.9
Age, years	51.4±10.5	51.2±10.4	53.7±11.0	55.1±11.6	52.4±10.9	50.9±10.2	50.1±9.7	51.0±10.3	56.7±10.5	62.3±9.5
BMI, kg/m^2	23.8±3.5	23.8±3.4	23.7±3.5	23.6±3.6	23.6±3.5	23.9±3.3	24.1±3.4	23.9±3.4	23.4±3.5	22.8±3.6
High school and above, %	17.8	18.4	11.3	10.4	11.4	21.9	25.3	18.4	7.9	2.8
Manual worker, %	57.7	57.8	57.5	55.5	62.9	54.9	51.1	58.4	48.8	37.2
Income ≥20,000 CNY/year, %	40.7	41.7	32.4	27.3	33.1	49.4	45.7	41.0	37.9	30.8
High SES, %	32.4	33.6	21.8	18.9	21.5	40.8	44.2	33.5	17.3	7.5
Ever drinker, %	36.4	36.5	34.9	35.2	30.7	38.5	44.9	37.2	23.9	17.6
Ever smoker, %	5.1	5.0	5.8	6.5	4.7	4.7	6.1	5.0	6.2	5.8
Physical activity, MET-hour/day	20.5±12.8	20.6±12.8	19.6±12.5	18.6±11.9	20.9±12.8	20.5±13.0	19.6±12.4	20.7±12.8	17.6±11.5	14.3±9.8
Sleep disturbance, %	18.8	18.5	22.2	22.7	18.8	18.3	19.5	18.5	22.5	27.1
NCD history, %	33.7	33.4	37.0	38.5	32.6	34.1	35.4	33.3	40.1	43.4
Age at menarche, years	15.4±2.0	15.6±2.0	15.6±2.0	15.6±2.0	15.6±2.0	15.3±1.9	15.2±1.9	15.4±2.0	15.9±2.0	15.9±2.0
Oral contraceptive use, %	9.9	10.1	8.0	7.2	4.6	12.0	17.8	10.1	6.7	5.5
Gynecological operation history, %	5.4	5.4	4.9	4.8	4.5	5.8	6.6	5.5	4.6	3.7
Number of live births	2.2±1.3	2.2±1.3	2.7±1.5	2.9±1.7	2.6±1.4	2.0±1.2	1.8±1.1	2.2±1.3	2.8±1.4	3.3±1.5

Abbreviation: BMI=body mass index; CNY=Chinese Yuan; SES=socioeconomic status; MET=metabolic equivalent; NCD=noncommunicable disease.

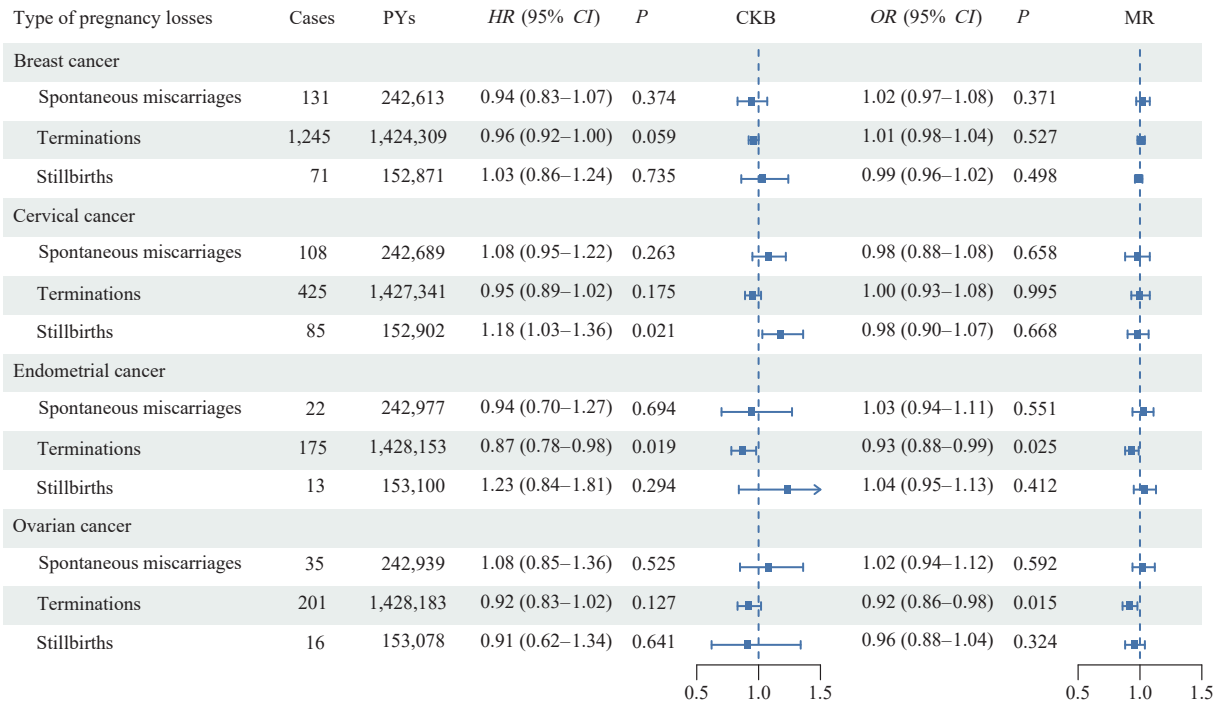


FIGURE 2. Associations between pregnancy losses and female-specific cancers by CKB and MR in Asian population.
Abbreviation: PYs=person-years; *HR*=hazard ratio; *CI*=confidence interval; CKB=China Kadoorie Biobank; MR=Mendelian randomization.

cervical cancer per additional stillbirth (*HR*=1.18, 95% *CI*: 1.03–1.36, *P*=0.021) were identified (Figure 2).

When stratified by living region, rural residents with a termination history had a 19% higher risk of breast cancer (*HR*=1.19, 95% *CI*: 1.02–1.40, $P_{heterogeneity}$<0.001) compared to urban residents. Furthermore, rural residents with a miscarriage history faced a 38% increased risk of cervical cancer (*HR*=1.38, 95% *CI*: 1.11–1.73, $P_{heterogeneity}$<0.001). In the joint-relationship analysis, a significant graded relationship between live birth and pregnancy loss on cervical cancer was observed. Among women having 3 or more live births, adjusted *HR*s were 4.93 (95% *CI*: 3.76–6.45) for those without miscarriage, 5.32 (3.63–7.79) for those with one miscarriage, and 6.99 (4.06–12.03) for those with more than two miscarriages.

Details on exposure-associated SNPs for MR analyses are shown in Table 2. The numbers of included SNPs ranged from 23 to 41, and the proportions of variance explained by SNPs (R^2) varied from 6.28% to 9.82%. Most traits displayed a considerable weak instrument bias (F-stat <10). The power to detect a significant effect size [odds ratio (*OR*)=0.8/1.2] in our MR analyses was highest for termination on breast cancer (power=99%), and lowest for stillbirth on cervical cancer (power=28%). In the MR analysis, terminations were found to be causally associated with a 7% lower risk of endometrial cancer (*OR*=0.93, 95% *CI*: 0.88–0.99, *P*=0.025) and an 8% lower risk of ovarian cancer (*OR*=0.92, 95% *CI*: 0.86–0.98, *P*=0.015) (Figure 2). MR-Egger intercepts indicated low levels of horizontal pleiotropy among all selected SNPs (*P*>0.05) (Supplementary Table S1, available in http://weekly.chinacdc.cn). Sensitivity analysis results are presented in Supplementary Figure S1 (available in http://weekly.chinacdc.cn).

DISCUSSION

This extensive cohort study, consisting of 298,008 participants, offers a comprehensive evaluation of the associations between pregnancy loss and long-term female-specific cancer risks in Chinese women. Termination was found to be linked with a reduced risk of endometrial cancer, whereas stillbirth was correlated with an increased risk of cervical cancer. A Mendelian randomization analysis in individuals of Asian ancestry was conducted to further assess the causal relationships between these factors.

The findings of this study align closely with previous research conducted in other countries. For example, a cross-national study demonstrated that pregnancies ending in either spontaneous or induced abortion did not increase the risk of female breast cancer [relative risk (*RR*)=0.98, 95% *CI*: 0.92–1.04] (*12*).

TABLE 2. Details of the instruments used as proxy pregnancy loss on female-specific cancer risk.

Phenotypes	Total population	SNPs (*n*)	F-stat	R^2 (%)	Power (%)
Breast cancer					
Spontaneous miscarriages		23	4.03	6.28	94
Terminations	95,283	32	4.18	9.11	99
Stillbirths		34	2.71	6.34	95
Cervical cancer					
Spontaneous miscarriages		29	4.29	8.29	29
Terminations	90,336	35	4.15	9.82	35
Stillbirths		41	2.71	7.60	28
Endometrial cancer					
Spontaneous miscarriages		29	4.29	8.29	42
Terminations	90,730	35	4.15	9.82	50
Stillbirths		41	2.71	7.60	41
Ovarian cancer					
Spontaneous miscarriages		29	4.29	8.29	33
Terminations	90,451	35	4.15	9.82	39
Stillbirths		41	2.71	7.60	31

Abbreviation: SNP=single nucleotide polymorphism.

Additionally, a nationwide register-based study with 57,347,622 person-years of follow-up revealed that pregnancy termination was associated with a significantly decreased risk of endometrial cancer (*RR*=0.53, 95% *CI*: 0.45–0.64) (*9*).

A potential explanation for the reduced risk of endometrial cancer associated with pregnancy termination may be that the termination process contributes to the removal of endometrial cells, particularly those in the early stages of malignant transformation (*13*). Another conceivable mechanism involves the early gestational effect occurring in the initial weeks post-conception, wherein the rapid increase of the progesterone-to-estrogen ratio enhances the endometrial system (*9*). In terms of the increased risk of cervical cancer linked to stillbirth, the underlying mechanism remains uncertain. Nonetheless, evidence has demonstrated that recurrent pregnancy loss is associated with aberrant progesterone receptors, which may subsequently contribute to the dysfunction of tumor suppressors in uterine cancer cells and further induce uterine tumors (*14*).

Our study revealed an intriguing dose-response relationship between the number of PLs and live births in relation to female cancer risk. As the number of live births increased, a higher risk of female cancer was observed in women with multiple PLs. Although parity, serving as a proxy for women's fecundity, may indicate a healthy endocrine and endometrial system, completed pregnancies could still stimulate the growth of cells that are in the early stages of malignant transformation (*15*).

Previous research has demonstrated that social determinants, such as geographical location, socioeconomic status, and education level, significantly influence the incidence and progression of female cancers. Particularly in rural areas, female residents may face financial constraints, poor sanitation, and inadequate medical care due to their relatively low socioeconomic status. As a result, they may be less aware of the importance of regular medical check-ups and treatments for cancer prevention and management (*16*). Furthermore, rural Chinese women often begin childbearing at a younger age and continue to be sexually active for an extended duration (*17*). Consequently, they may experience increased exposure to unidentified risk factors associated with the development of gynecological malignancies.

The primary strength of this study lies in its comprehensive examination of the associations between three types of pregnancy loss and the long-term risk of female malignancy in a large-scale prospective cohort in China. Additionally, a two-sample Mendelian randomization analysis was utilized to further confirm these causal relationships. Nevertheless, our study faces several limitations. First, reproductive history data were self-reported, which may be subject to recall and reporting bias. Second, some residual confounders (e.g., environmental factors and pregnancy-induced conditions) related to pregnancy loss and female oncology were not adjusted for. Third, data regarding the number, consecutiveness, and intervals of pregnancy losses were unavailable, limiting our ability to gain an in-depth understanding of the underlying mechanisms linking incomplete pregnancy and female malignancy. Finally, the current study was unable to perform an MR interaction analysis due to the unavailability of individual-level genotype data.

In conclusion, this study is the first large-scale nationwide cohort investigation in China to uncover the relationship between pregnancy loss and female-specific cancers among Chinese women. The utilization of Mendelian randomization analysis further strengthens the causal evidence supporting these findings. The results offer valuable insights into the link between reproductive history and the development of cancer, as well as guidance for identifying high-risk groups for female-specific cancers. This research contributes significantly to public health practices aimed at preventing and detecting these cancers early. Further examination of reproductive history, particularly in rural regions, is essential in determining accurate risk stratification, which will prove beneficial for developing screening and prevention strategies regarding female-specific cancers.

Conflicts of interest: No conflicts of interest.

Acknowledgements: Chinese Center for Disease Control and Prevention, Chinese Ministry of Health, National Health and Family Planning Commission of China, and ten regional health administrative departments; study participants and project staff in each of the ten regional centers, as well as the project development and management teams based in Beijing, Oxford, and the ten regional centers.

Funding: Supported by the National Key Research and Development Program of China (2016YFC0900500, 2016YFC0900501, and 2016YFC0900504), the Kadoorie Charitable Foundation in Hong Kong SAR, and Wellcome Trust in the UK (088158/Z/09/Z and 104085/Z/14/Z).

doi: 10.46234/ccdcw2023.078

[#] Corresponding authors: Yu Jiang, jiangyu@pumc.edu.cn; Liming Li, lmlee@vip.163.com.

[1] Department of Epidemiology and Biostatistics, School of Population Medicine and Public Health, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [2] Division of Urology, Department of Surgery, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China; [3] Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; [4] Melbourne School of Population and Global Health, The University of Melbourne, Victoria, Australia; [5] Centre of Cancer Research, Victorian Comprehensive Cancer Centre, Melbourne, Victoria, Australia; [6] Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China; [7] Fuwai Hospital Xishan Branch Court, Chinese Academy of Medical Sciences, Beijing, China; [8] Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford, UK.
[&] Joint first authors.

Submitted: March 25, 2023; Accepted: May 08, 2023

REFERENCES

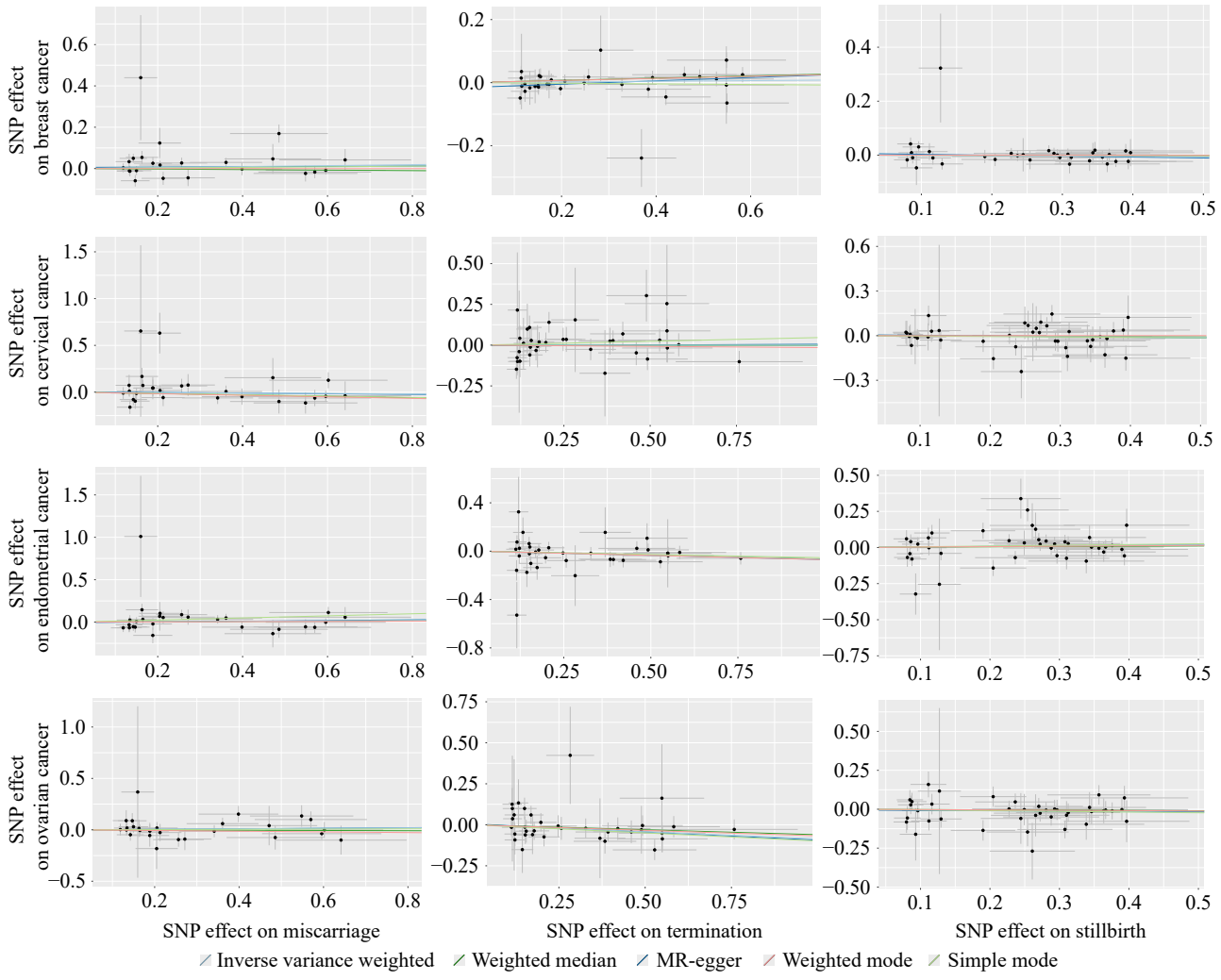
1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209 – 49. http://dx.doi.org/10.3322/caac.21660.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394 – 424. http://dx.doi.org/10.3322/caac.21492.
3. The American College of Obstetricians and Gynecologists. Practice bulletin no. 150: early pregnancy loss. Obstet Gynecol 2015;125 (5):1258 – 67. http://dx.doi.org/10.1097/01.AOG.0000465191.27155.25..
4. Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet 2016;387(10018):587 – 603. http://dx.doi.org/10.1016/S0140-6736(15)00837-5.
5. Sedgh G, Bearak J, Singh S, Bankole A, Popinchalk A, Ganatra B, et al. Abortion incidence between 1990 and 2014: global, regional, and subregional levels and trends. Lancet 2016;388(10041):258 – 67. http://dx.doi.org/10.1016/S0140-6736(16)30380-4.
6. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50 302 women with breast cancer and 96 973 women without the disease. Lancet 2002;360(9328):187 – 95. http://dx.doi.org/10.1016/s0140-6736(02)09454-0.
7. Pocobelli G, Doherty JA, Voigt LF, Beresford SA, Hill DA, Chen C, et al. Pregnancy history and risk of endometrial cancer. Epidemiology 2011;22(5):638 – 45. http://dx.doi.org/10.1097/EDE.0b013e3182263018.
8. Nichols HB, Schoemaker MJ, Cai JW, Xu JW, Wright LB, Brook MN, et al. Breast cancer risk after recent childbirth: a pooled analysis of 15 prospective studies. Ann Intern Med 2019;170(1):22 – 30. http://dx.doi.org/10.7326/m18-1323.
9. Husby A, Wohlfahrt J, Melbye M. Pregnancy duration and endometrial cancer risk: nationwide cohort study. BMJ 2019;366:l4693. http://dx.doi.org/10.1136/bmj.l4693.
10. Dick MLB, Siskind V, Purdie DM, Green AC, et al. Incomplete pregnancy and risk of ovarian cancer: results from two Australian case-control studies and systematic review. Cancer Causes Control 2009;20(9):1571 – 85. http://dx.doi.org/10.1007/s10552-009-9402-3.
11. Mikkelsen AP, Egerup P, Ebert JFM, Kolte AM, Nielsen HS, Lidegaard Ø. Pregnancy loss and cancer risk: a nationwide observational study. eClinicalMedicine 2019;15:80 – 8. http://dx.doi.org/10.1016/j.eclinm.2019.08.017.
12. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83 000 women with breast cancer from 16 countries. Lancet 2004;363(9414):1007 – 16. http://dx.doi.org/10.1016/S0140-6736(04)15835-2.
13. Xu WH, Xiang YB, Ruan ZX, Zheng W, Cheng JR, Dai Q, et al. Menstrual and reproductive factors and endometrial cancer risk: results from a population-based case-control study in urban Shanghai. Int J Cancer 2004;108(4):613 – 9. http://dx.doi.org/10.1002/ijc.11598.
14. Patel B, Elguero S, Thakore S, Dahoud W, Bedaiwy M, Mesiano S. Role of nuclear progesterone receptor isoforms in uterine pathophysiology. Hum Reprod Update 2015;21(2):155 – 73. http://dx.doi.org/10.1093/humupd/dmu056.
15. Lambe M, Hsieh CC, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. N Engl J Med 1994;331(1):5 – 9. http://dx.doi.org/10.1056/nejm199407073310102.
16. Chen MZ, Luo Y, Fu JX, Wang T, Meng YT, Xu C, et al. Reproductive health status and related knowledge among women aged 20-39 years in rural China: a cross-sectional study. Reprod Health 2020;17(1):90. http://dx.doi.org/10.1186/s12978-020-00939-2.
17. Janis JA, Ahrens KA, Ziller EC. Female age at first sexual intercourse by rural-urban residence and birth cohort. Women's Health Issues 2019;29(6):489 – 98. http://dx.doi.org/10.1016/j.whi.2019.07.004.

SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Results of MR using the inverse-variance weighted method.

Phenotypes	Effect size		Heterogeneity			Pleiotropy		
	OR (95% *CI*)	*P*	Q-stat	*P*	I^2 (%)	MR-egger intercept	MR-egger *P*	MR-PRESSO global test-*P*
Breast cancer								
Spontaneous miscarriages	1.02 (0.97–1.08)	0.371	42.24	0.006	47.92	0.01	0.731	0.175
Terminations	1.01 (0.98–1.04)	0.527	38.16	0.176	18.75	−0.02	0.150	0.152
Stillbirths	0.99 (0.96–1.02)	0.498	18.67	0.971	0.00	0.01	0.561	0.982
Cervical cancer								
Spontaneous miscarriages	0.98 (0.88–1.08)	0.658	30.57	0.245	14.94	<0.01	0.896	0.323
Terminations	1.00 (0.93–1.08)	0.995	31.97	0.567	0.00	<0.00	0.878	0.538
Stillbirths	0.98 (0.90–1.07)	0.668	36.66	0.577	0.00	0.01	0.827	0.534
Endometrial cancer								
Spontaneous miscarriages	1.03 (0.94–1.11)	0.551	31.49	0.210	17.44	−0.01	0.814	0.227
Terminations	0.93 (0.88–0.99)	0.025	31.26	0.602	0.00	0.00	0.948	0.656
Stillbirths	1.04 (0.95–1.13)	0.412	60.27	0.016	35.29	<0.00	0.989	0.388
Ovarian cancer								
Spontaneous miscarriages	1.02 (0.94–1.12)	0.592	16.57	0.922	0.00	<0.00	0.974	0.893
Terminations	0.92 (0.86–0.98)	0.015	20.80	0.963	0.00	0.01	0.822	0.962
Stillbirths	0.96 (0.88–1.04)	0.324	33.23	0.730	0.00	−0.01	0.846	0.732

Abbreviation: *OR*=odds ratio; *CI*=confidence interval; MR=Mendelian randomization; PRESSO=pleiotropy residual sum and outlier.



SUPPLEMENTARY FIGURE S1. Scatter plot displaying the impact of each SNP on various female cancer types for each phenotype.
Abbreviation: MR=Mendelian randomization; SNP=single nucleotide polymorphism.