

The potential interaction of hereditary and reproductive factors in the etiology of mammary gland hyperplasia: a case-control study

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Abstract

Background: Family history of breast cancer and female reproductive factors may work together to influence hyperplasia of mammary gland (HMG) risk. However, the association with HMG risk is poorly characterized and might be important to understand the causation of HMG.

Methods: A total of 1881 newly diagnosed HMG cases and 1900 controls were recruited between 2012 and 2017. We collected each participant's demographic characteristics, female reproductive factors and family history of breast cancer. A multi-analytic strategy combining unconditional logistic regression, multifactor dimensionality reduction (MDR) and crossover approaches were applied to systematically identify the interactions of family history of breast cancer and reproductive factors on HMG susceptibility.

Results: In MDR analysis, high-order interactions among education level, breastfeeding duration and family history of breast cancer were identified among women (OR=7.069, 95%CI: 6.080-8.219). Similarly, in crossover analysis, compared with individuals having low education level and no family history of breast cancer, HMG risk increased significantly for those having high education level and family history of breast cancer (OR=36.389, 95%CI: 11.469-115.451), similar additive interaction effect was observed among short breastfeeding duration women (OR=27.699, 95%CI: 3.730-205.699).

Conclusion: This study suggests high-order interactions of high education level, short breastfeeding duration and family history of breast cancer may synergistically increased HMG risk.

Introduction

Hyperplasia of mammary gland (HMG), a multi-factorial complicated disease, accounts for more than 70% of all breast disease that occurs frequently among middle-aged women and is highly associated with breast cancer¹. Perhaps due to the quickening pace of life, with increasing work-related pressure, the prevalence of HMG is high in China². Understanding indicators of HMG in middle-aged women play an important part in public health and clinical implications. Researches have identified multiple risk factors for HMG³, such as late age at menopause^{4, 5}, nulliparity^{4, 5}, lacking breastfeeding⁶, high-level education⁷ and family history of breast cancer⁸. Nevertheless, etiology of HMG remains largely unknown. Family history of breast cancer is an important indicator for a woman's future risk of developing breast cancer⁹. Part of the genetic information can be explained by hereditary history^{3, 10}. There is growing recognition that large sample sizes are needed in order to identify heredity variants that have effects modified by the environment as well¹¹. Hereditary-environment interactions have the potential to illustrate the biological causes of disease, distinguish individuals for whom risk factors are most related¹² and develop precision medicine essentially¹³. However, few researches have considered interactions between family history of breast cancer and potentially modifiable risk factors for HMG. Besides, existing studies only take single statistical method to study the interactions between family history of breast cancer and potential modifiable risk factors which are lack of internal validation and decreased statistical power to identify underlying hereditary-environment interactions efficiently¹⁴.

Using data collected in a large community-based case-control study, we assessed the correlation of HMG with reproductive factors in women self-reporting first and second-degree relatives. We hypothesize that interactions between female reproductive factors and family history of breast cancer will confer an even greater risk of HMG. In this research, we adopted multi-analytic strategies to scientifically examine the interactions between hereditary and female reproductive factors. We used several statistical approaches, including traditional multiple logistic regression, multifactor dimensionality reduction (MDR) in addition to crossover analysis to explore high-order hereditary-environment interactions in HMG susceptibility.

Methods

1. Study subjects

This study is based on the National Basic Public Health Service Project which provided free of charge for urban and rural residents by Chinese government. From October 2012 to December 2017, 1966 patients that newly diagnosed by color doppler ultrasonography confirmed hyperplasia of mammary glands (HMG) were selected as cases. Contemporaneously, 1993 HMG-free controls (imaging showed no abnormality) were chosen as controls from the community health service center of Harbin. Inclusion criteria was female subjects newly diagnosed, aged above 35 years, living in Harbin for at least 6 months, agreed with color doppler ultrasonography examination. Patients with mastitis, angiosarcoma, tumor of mammary glands, breast cancer or other cancers were excluded. 85 cases (4.4%) and 93 controls (4.7%) were excluded because data of female reproductive information or family history of breast cancer appeared abnormal value or missing. Finally, a total of 1881 cases and 1900 controls were enrolled (Fig. 1). All pertinent clinical results were reviewed by two general practitioners to ensure the diagnosis. All participants provided informed consents and the study was approved by the Ethical Committee of Harbin Center for Disease Control and Prevention.

2. Data collection

Basic characteristics of demographic information (age, ethnicity, education level, marriage, occupation, and so on), female reproductive factors including menopausal status, age at menopause, parturition and age at first delivery, age at menarche, breastfeeding and its duration, family history of breast cancer were obtained using a structured questionnaire administered by trained interviewers face-to-face. In this research, history of breast cancer was defined as breast malignancy in first-degree or second-degree relatives (such as mother, sister, grandmothers or aunts). Regular menstruation was considered as menstrual time with 2–7 days and menstrual cycle with 24–35 days. Menopause referred to the specific period from the appearance of endocrine, biological and clinical characteristics related to menopause to the postmenopausal period. Gland fibrous or cystic or single type of HMG was included in our study. According to the fifth editions of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) guidelines, the cases classified into stages I–V were involved in our study. The details as follows: BI-RADS 2-Benign found, BI-RADS 3-Benign lesions, BI-RADS 4-Suspicion for

malignancy and BI-RADS 5-Highly suggestive of malignancy. The higher grade of lesion site (left breast, right or bilateral site of breast) was taken as BI-RADS grade.

3. Statistical analyses

The Odds Ratios (ORs) and corresponding 95% Confidence Intervals (95% CI) were summarized to estimate the associations between reproductive factors and HMG risk by univariate and manual stepwise multivariate logistic regression. All reference values for exposure were the lower level of the variables. Interactions between family history of breast cancer and female reproductive factors were evaluated by the methods of multivariate logistic regression and Multifactor Dimensionality Reduction (MDR). MDR approach includes a cross-validation procedure that minimizes the possibility of a false positive results by dividing the data into a testing set and a training set. The cross-validation consistency (CVC) provided a summary for the number of cross-validation intervals for discovering a particular model. Higher numbers meant more stable results. The joint effects between female reproductive factors and family history of breast cancer on the risk of HMG were analyzed by the crossover method. Additive interactions were calculated by Relative Excess Risk of Interaction (RERI), Attributable Proportions of Interaction (API) and Synergy Index (SI) as described by Andersson¹⁵. The potential confounding variables were controlled in the process of analyzing the interactions. $P < 0.05$ was considered statistically significant and all P-values were two-tailed. All statistical analyses were performed with SPSS (version 21.0, IBM SPSS Statistics), SAS (version 9.2, SAS Institute, Cary, NC, USA) and MDR software (version 2.0, Unix, USA).

Results

1. Basic characteristics of HMG patients and controls

The female reproductive factors and ORs for HMG are presented in Table 1. Of the 1881 cases, 1627 were Han ethnicity and 1203 Han ethnicity accounted for the 1900 controls. The difference of mean (SD) ages between cases (51.27 ± 6.62) and controls (51.21 ± 6.62) were not significant ($t = 0.27$, $P = 0.89$). Among the study population, distributions of BMI, education, marriage and occupation type were significantly different between cases and controls ($P < 0.05$). Cases tended to be higher educated; more married people, mental worker and familial tendency; older age at first delivery, shorter breastfeeding duration; less breastfeeding, regular menstruation and parturition than controls. Age at menopause was also significantly different between cases and controls in the 50–54 groups. According to Breast Imaging Reporting and Data System (BI-RADS), 1646 cases were classified as stage II, 192 as stage III, 38 as stage IV, 5 as stage V HMG. BMI and occupation were treated as potential confounders and adjusted in crossover, multiplier interaction and additive interaction analyses.

Table 1
Univariate logistic regression analysis of influencing factors of HMG

Effect factors	Number of Cases (%)	Number of Controls (%)	OR (95%CI)	P value
Age (year)				
35–44	324(17.2)	331(17.4)	1	
45–54	1002(53.3)	1015(53.4)	1.009(0.846–1.203)	0.925
55–64	488(25.9)	487(25.6)	1.024(0.840–1.248)	0.817
≥ 65	67(3.6)	67(3.5)	1.022(0.704–1.481)	0.910
BMI (kg/m ²)				
≤18.5	31(1.7)	18(1.0)	1	
18.5–23.9	1073(57.4)	1120(59.3)	0.556(0.309-1.000)	0.050
24-27.9	646(34.5)	658(34.8)	0.570(0.316–1.029)	0.062
≥ 28	120(6.4)	93(4.9)	0.749(0.395–1.422)	0.377
Nation				
Han people	1627(97.8)	1203(97.6)	1	
Other	37(2.2)	29(2.4)	0.943(0.577–1.543)	0.816
Education level				
Senior school or below	1452(77.2)	1745(91.8)	1	
College or above	429(22.8)	155(8.2)	3.326(2.733–4.048)	0.000
Marriage				
Unmarried	19(1.0)	5(0.30)	1	
Married	1862(99.0)	1895(99.7)	0.259(0.096–0.694)	0.067
Occupation				
White collar	892(47.4)	372(19.6)	1	

Effect factors	Number of Cases (%)	Number of Controls (%)	OR (95%CI)	P value
Blue collar	989(52.6)	1528(80.4)	0.270(0.233–0.312)	0.000
Regular menstruation				
No	633(33.7)	231(12.2)	1	
Yes	1248(66.3)	1669(87.8)	0.273(0.231–0.323)	0.000
Age at menarche (year)				
0–11	49(2.6)	37(1.9)	1	
≥ 12	1832(97.4)	1863(98.1)	0.743(0.482–1.143)	0.177
Breastfeeding				
No	346(19.1)	104(5.5)	1	
Yes	1461(80.9)	1792(94.5)	0.245(0.195–0.308)	0.000
Breastfeeding duration(month)				
0–6	187(12.8)	69(3.9)	1	
≥ 7	1274(87.2)	1723(96.1)	0.273(0.205–0.363)	0.000
Menopause				
premenopausal	1003(53.3)	973(51.2)	1	
postmenopausal	878(46.7)	927(48.8)	0.919(0.809–1.044)	0.194
Age at menopause(year)				
35–49	317(36.1)	272(29.3)	1	
50–54	520(59.2)	630(68.0)	0.708(0.580–0.864)	0.001
≥ 55	41(4.7)	25(2.7)	1.407(0.834–2.374)	0.201
Parturition				
No	109(5.8)	2(0.10)	1	

Effect factors	Number of Cases (%)	Number of Controls (%)	OR (95%CI)	P value
Yes	1769(94.2)	1897(99.9)	0.017(0.004–0.069)	0.000
Age at first delivery(year)				
20–24	439(24.8)	619(32.6)	1	
≥ 25	1330(75.2)	1278(67.4)	1.467(1.270–1.695)	0.000
Family history of breast cancer				
No	1414(75.2)	1885(99.2)	1	
Yes	467(24.8)	15(0.8)	41.504(24.706–69.922)	0.000

2. Associations between sociodemographic factors, BMI, female reproductive factors and risk of HMG

Individuals who got married, manual worker, regular menstruation, breastfeeding history, longer breastfeeding duration, early age at menopause, parturition had 0.26, 0.27, 0.27, 0.25, 0.27, 0.71 and 0.02-fold reduction risk of HMG when compared with controls. A significant increasing of HMG risk, associated with later age at first delivery and family history of breast cancer were observed in case-control (OR = 1.47, 95%CI: 1.27–1.70 and OR = 41.50, 95%CI: 24.71–69.92, respectively).

After multifactor unconditional logistic regression model, we found that education level, BMI, age at first delivery and family history of breast cancer were statistically positively associated with HMG (OR = 1.62, 95%CI: 1.27–2.07; OR = 1.15, 95%CI: 1.01–1.30; OR = 1.33, 95%CI: 1.11–1.59; OR = 37.87, 95%CI: 22.33–64.20, respectively), whereas occupation type and breastfeeding duration were statistically negatively associated with HMG (OR = 0.30, 95%CI: 0.25–0.36; OR = 0.34, 95%CI: 0.25–0.46, respectively).

3. Female reproduction and family history of breast cancer interactions and the risk of HMG

Table 2 displays the Cross-Validation Consistency (CVC) for the 1-factor and 4-factor model for each situation. The three factors model including the education level, breastfeeding duration and family history of breast cancer had a maximum testing accuracy of 71.11% and a maximum CVC of 100%. Therefore, this model was regarded as the best among all the interaction models calculated by MDR. Compared with

the "low-risk" combinations, participants classified as "high-risk" combinations significantly increasing HMG risk by 7.07-folds (95%CI: 6.08–8.22).

Table 2
Multiple logistic regression analysis of influencing factors of HMG

Explore factors	OR (95%CI)	P value
Education level	1.619(1.265–2.071)	0.000
Occupation Type	0.303(0.254–0.363)	0.000
BMI	1.146(1.007–1.304)	0.039
Breastfeeding duration	0.336(0.245–0.461)	0.000
Age at first delivery	1.328(1.112–1.586)	0.002
Family history of breast cancer	37.865(22.334–64.197)	0.000

4. The multiplier interactions between female reproductive factors and family history of breast cancer on the risk of HMG

We did not find statistically significant multiplier interactions between education level (OR = 0.43, 95%CI: 0.11–1.59, P = 0.20), breastfeeding duration (OR = 1.42, 95%CI: 0.18–11.38, P = 0.74), education level&breastfeeding duration (OR = 0.67, 95%CI: 0.35–1.30, P = 0.24) and family history of breast cancer.

5. The combination effect between female reproduction and family history of breast cancer on the risk of HMG

A significant individual and joint effects between education level, breastfeeding duration and family history of breast cancer were detected (Table 3). The co-existence of family history of breast cancer and high-level education particularly increased the risk of HMG to 36.39 (95%CI: 11.47-115.45), higher than the individual risks associated with high-level education alone (OR = 1.96, 95%CI: 1.57–2.46) but lower than the individual risks associated with family history of cancer (OR = 46.52, 95%CI: 25.97–83.32). The combination of family history of breast cancer and breastfeeding duration were associated with a markedly increased risk for HMG (OR = 12.74, 95%CI: 6.85–23.71).

Table 3
Analysis of Multifactor Dimensionality Reduction (MDR) results

Model	Training Bal. ACC.	Testing Bal. ACC.	CVC
Family history of breast cancer	0.620	0.620	10/10
Breastfeeding duration/ Family history of breast cancer	0.693	0.693	10/10
Education level/ Breastfeeding duration/ Family history of breast cancer	0.711	0.711	10/10
Education level/ Age at first delivery/ Breastfeeding duration/ Family history of breast cancer	0.711	0.709	10/10

Table 4
Details of the optimal model based on MDR

Indicators	Training Dataset Statistics	Testing Dataset Statistics	Whole Dataset Statistics
Balanced Accuracy	0.711	0.711	0.711
Accuracy	0.712	0.712	0.712
Sensitivity	0.593	0.593	0.593
Specificity	0.829	0.829	0.829
Odds Ratio	7.069(6.031–8.287)	7.069(4.389–11.387)	7.069(6.080–8.219)
χ^2	643.056	71.451	714.506
p	< 0.001	< 0.001	< 0.001
Precision	0.775	0.775	0.775
Kappa	0.423	0.423	0.423
F-Measure	0.672	0.672	0.672
Cross-validation Consistency	10/10		

Table 5

The multiplier interaction between family history of breast cancer and environmental factors

Effect factors	Family history of breast cancer	
	OR (95%CI)	P value
Education level	0.425(0.114–1.587)	0.203
Breastfeeding duration	1.417(0.176–11.382)	0.743
Education level&Breastfeeding duration	0.673(0.347–1.303)	0.240
ORs adjusted for body mass index (BMI) and occupation type		

Table 6

Crossover analysis in assessing the association between family history of breast cancer and environmental factors for HMG

Effect Factors	Number of Cases (%)	Number of Controls (%)	Total	Prevalence of breast hyperplasia (%)	OR (95%CI)
Family history of breast cancer/Education level					
No/Low-level	1103(58.6)	1733(91.2)	2836(75.0)	38.89	1
No/High-level	311(16.5)	152(8)	463(12.2)	67.17	1.962(1.565–2.459)
Yes/Low-level	349(18.6)	12(0.6)	361(9.5)	96.68	46.519(25.974–83.316)
Yes/High-level	118(6.3)	3(0.2)	121(3.2)	97.52	36.389(11.469–115.451)
Family history of breast cancer/Breastfeeding duration					
No/Low-level	130(8.9)	68(3.7)	198(6.09)	65.66	1
No/High-level	966(66.12)	1709(95.37)	2675(82.23)	36.11	0.327(0.238–0.450)
Yes/Low-level	57(3.9)	1(0.06)	58(1.78)	98.28	27.699(3.730–205.699)
Yes/High-level	308(21.08)	14(0.78)	322(9.90)	95.65	12.742(6.848–23.708)
ORs adjusted for body mass index (BMI) and occupation type					

Table 7

Additive interaction between family history of breast cancer and environmental factors

Effect factors	RERI (OR, 95%CI)	API (OR, 95%CI)	SI (OR, 95%CI)
Family history of breast cancer/Education level	-11.093(-60.922-38.736)	-0.305(-1.980-1.371)	0.761(0.204-2.846)
Family history of breast cancer/Breastfeeding duration	-14.285(-69.794-41.225)	-1.121(-5.578-3.336)	0.451(0.051-4.025)
ORs adjusted for body mass index (BMI) and occupation type; RERI: Relative Excess Risk of Interaction; API: Attributable Proportions of Interaction; SI: Synergy Index			

6. The additive effect between female reproduction and family history of breast cancer on the risk of HMG

Because the combination of family history of breast cancer and breastfeeding duration, family history of breast cancer and education level were found in joint effects, their additive effects were analyzed subsequently. The ORs and 95%CI of Relative Excess Risk of Interaction (RERI), Attributable Proportions of Interaction (API) and Synergy Index (SI) are indicators for additive interactions. There were no statistically significant additive interactions between education level, breastfeeding duration and family history of breast cancer on risk of HMG.

Discussion

Hyperplasia of mammary glands (HMG) is one of a common disease in women. Breast pain and lump are the main clinical manifestations of HMG¹⁶. Endocrine disorders¹⁷, mental factors¹⁸ and genetic factors¹⁹ have a certain impact on the disease. There are many treatment methods for HMG, such as hormone replacement drugs²⁰, traditional Chinese medicine¹⁶ and lifestyle intervention²¹. However, the pathogenesis of HMG is still unclear.

Our study is the largest case-control study up to now on HMG and provides ample evidence that the risk of HMG does not only apply to family history of breast cancer alone, but may also extend to breastfeeding duration and education level in Harbin, China. Possible interactions between hereditary and reproductive factors of HMG were noted.

We applied a variety of algorithms to explore the interactions between family history of breast cancer and female reproductive factors for which an interaction might be possible. Firstly, MDR was used to analyse the interactions between six environmental factors that were statistically significant in multiple logistic regression. High-dimensional interactions including education level, breastfeeding duration and family history of breast cancer were detected. Secondly, our results seemed biologically plausible. We found a

strong synergistic effect between family history of breast cancer and high education level after adjusted for BMI and occupation. Therefore, more attention should be paid to enhance the awareness and health education among HMG women with high education level and family history of breast cancer²². Additionally, antagonistic effect between family history of breast cancer and breastfeeding duration was also observed which was consistent with the published literature²³. Based on these results, women with a family history of breast cancer may reduce their excess risk of HMG through adjustments in reproductive choices²³. Thirdly, because the additive model might be better able to explain the biologic interaction, we also estimated the RERI, API and SI by additive model, whereas we did not find statistical difference. There maybe sample sizes decreased after strata that lead to the reducing statistical power²⁴. Although we did not find effect of education level or breastfeeding duration combined with family history of breast cancer, several lines of evidence suggest that our findings are biologically plausible. In consist with other studies, our research also find HMG individuals with a family history of breast cancer are easier to develop neoplasia^{25, 26}. The activation of Akt 1 peaked in lactation by hormone- and anchorage-mediated pathways which regulates survival of epithelial cells. Shorter time breastfeeding duration decreased Akt 1 significantly that contributes to HMG²⁷. High education often accompanies with high stress is thought to be connected with increasing risk of breast disease²⁸. Normal growth of the mammary gland involves endocrine signals from the Hypothalamic-Pituitary-Gonadal (HPG) axis²⁹. Stress has been shown to disrupt the function of endocrine system and increase susceptibility to HMG³⁰. Additionally, increasing level of inflammatory burden and Hypothalamic-Pituitary-Adrenocortical (HPA) axis dysregulation subsequent to stress may also impair HMG³¹. These observations indicated that hereditary-environment interactions might be especially important for HMG because their effects on disease susceptibility were strongly decided by exposure to education and other female reproductive factors. Therefore, it is suitable to consider that HMG prevention strategies should be individualized according to individual's exposure to risk factor profiles³².

A dominating superiority of our research is that hereditary-environment interactions are consistently distinguished by both nonparametric and parametric statistical models. Logistic regression has the advantage of analysing for main effect. When high-order interactions involving multidimensional elements are taken into account, they may be limited to deal with simultaneous factors³³. MDR can identify putative high-order interactions but limit in analyzing main effects in many diseases³⁴. Crossover analysis can evaluate the independent and joint roles of genetic and exposure on disease hazard²⁴. However, it can only analyze the interactions between binary variables³⁵. Recent studies have manifested that multiple complementary analytical strategies, including logistic regression and MDR, could improve statistical power to identify underlying hereditary-environment interactions efficiently^{36, 37}. Although each strategy used different algorithms to define these interactions, results from MDR and crossover analysis consistently showed that family history of breast cancer was the most significant single risk for HMG, and HMG risk was substantially associated with education level and breastfeeding duration interactions. In this research, the two analytic methods (MDR, crossover analysis) validated each other and emphasized the repeatability of our results.

This study has few limitations. First, due to the limitation of data acquisition, we only analyzed the association between family history of breast cancer and female reproductive factors. Further studies are imperative to understand whether the interactions are related to some factors, such as dietary habits, lifestyles, Hormone Replacement Therapy (HRT) or genetic background and so on. Second, the results acquired in this research could be affected by recall bias which frequently appears in case-control study and replication in another independent samples of observed interaction is needed to be verified in a single study. Third, the number of cases in the strata were relatively small and therefore, these variables may not have been adequately powered to assess interactions. Expanding the sample size or finding other more applicable statistical analysis methods to analyze interactions is needed in further study. Fourth, due to the financial restrictions, all patients with HMG did not perform tissue biopsies, so the related mechanism of patients with different types of HMG is needed in further research. However, this provides further support for a different etiology of HMG and suggests that models used to predict HMG risk should take interactions into account.

To the best of our knowledge, our research is the first study to estimate the interaction of family history of breast cancer and female reproductive factors on HMG risk, and we believe that it provides some clues for research into the related mechanisms.

Conclusion

High-order interactions of higher education level, shorter breastfeeding duration and family history of breast cancer might synergistically increased HMG risk. HMG prevention strategies should be individualized according to individual's exposure to risk factor profiles.

Abbreviations

HMG:Hyperplasia of Mammary Gland; MDR:Multifactor Dimensionality Reduction; BMI:Body Mass Index; RERI:Relative Excess Risk of Interaction; API:Attributable Proportions of Interaction; SI:Synergy Index; CVC:Cross-Validation Consistency; ORs:Odds Ratios; 95%CI:Corresponding 95% Confidence Intervals; HPG:Hypothalamic-Pituitary-Gonadal; HPA:Hypothalamic-Pituitary-Adrenocortical; HRT:Hormone Replacement Therapy

Declarations

Consent for publication

Not applicable.

Availability of data and material

The analyzed data can be accessed from the corresponding author on reasonable request.

Author's contributions

HG constructed statistical analysis strategy and drafted the manuscript. CY organized and coordinated epidemiological investigations. JF supervised the analysis. LL performed the statistical analysis. DP conceived of the study, and participated in its design and helped to review the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the ethic committee of Harbin Center for Disease Control and Prevention (No.01-2012). All the participants provided written informed consent before they were interviewed for this study.

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Competing interests

The authors declare that they have no conflict of interest.

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Figures

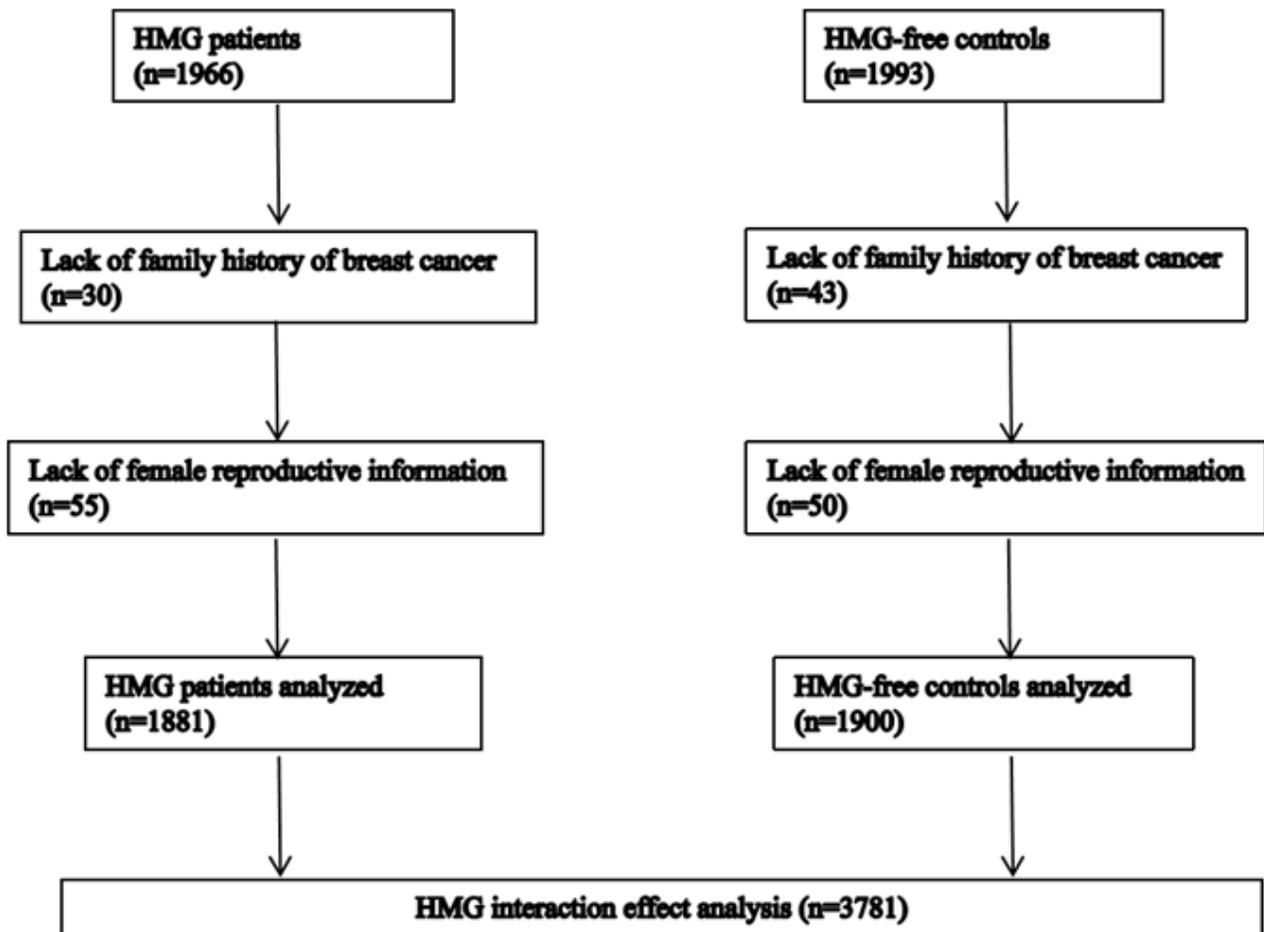


Figure 1

Flowchart of participant inclusion in the case-control study