A population-based case-control study on the association of Angelica sinensis exposure with risk of breast cancer

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A B S T R A C T

Background: Due to a lack of evidence from large-scale epidemiological studies by far on this issue, whether there is a link between Angelica sinensis exposure and breast cancer risk remained inconclusive.

Methods: We conducted a population-based case-control study using Taiwan’s National Health Insurance claim data, in which all breast cancer patients newly diagnosed between 2005 and 2008 were employed as the case group (n = 34,262) and a random sample of non-breast cancer individuals selected from 1-million beneficiaries registered in 2005 was served as the control group. For fair comparability, we employed the time density sampling method to select controls who were matched to case on date of breast cancer diagnosis and age with a case/control ratio of 1/3 (n = 102,786).

Results: We found that the use of Angelica sinensis presents a weakly but significantly protective effect on breast cancer (adjusted odds ratio (aOR) 0.95, 95% confidence interval (CI) 0.93–0.98), with a significant dose-gradient relationship. We also noted a stronger association with breast cancer with initial use of Angelica sinensis at a longer time before breast cancer diagnosis, and found that the seemingly protective effect of Angelica sinensis was more obvious among women who had initial use at 47–55 years (aOR 0.93, 95% CI 0.88–0.98).

Conclusion: This population-based case-control study revealed that exposure to Angelica sinensis showed a weakly but significantly protective effect on breast cancer risk, which could ease people’s concern over the potential carcinogenic effect from exposure to Angelica sinensis.

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1. Introduction

Since hormone replacement therapy had been found to increase the risk of breast cancer,1,2 the scientists also had concerns about the breast cancer carcinogenic effect of phytohormone contained in herbs of traditional Chinese medicines (TCM), especially Angelica sinensis (Dang-guai), which is commonly used to improve gynecological disease even as flavoring in many Asia countries as well as countries outside of Asia where Angelica sinensis is also commonly used. In the related research of Angelica sinensis, some researchers found that Angelica sinensis extract could stimulate the proliferation of breast cancer cells.3,4 However, the results observed in the subsequent experiments were not consistent. It was even observed that some Angelica sinensis extract had anti-cancer effects such as inhibiting estrogen activity or promoting apoptosis of breast cancer cells.5,6 By far, there is no consensus on the issue of Angelica sinensis and breast cancer risk relationship.

Among the top ten common used TCM herbs in Taiwan, two compound contain Angelica sinensis.7 In addition, there were about 30% of patients in Taiwan use Chinese medicine after been diagnosed with breast cancer,8 and the top ten compound drugs used in...
breast cancer patient have seven compounds contain *Angelica sinensis*. To sum up, *Angelica sinensis* was very common prescribed in general public and breast cancer patients in Taiwan, but there was still no evidence of large epidemiological literature on the exact relationship between exposure of *Angelica sinensis* and breast cancer.

We conducted this population-based epidemiological study to investigate whether intake of *Angelica sinensis* preparations by women was associated with breast cancer incidence.

2. **Method**

2.1. **Research database and study design**

In Taiwan, national health insurance coverage rate is over 99.9%, and its health insurance information known as national health insurance research database (NHIRD) is a representative empirical dataset in the field of health care related research. We conducted a population-based case-control study design based on Taiwan’s National Health Insurance claim data (medical claims of all cancer patients and of a random sample of 1-million people registered in 2005) released by the National Health Research Institutes.

2.2. **Selection of cases and controls**

The case series was all newly diagnosed breast cancer patients with the International Classification of Disease 9th version Clinical Modification (ICD-9-CM) codes 174.X and catastrophic illness registration in Taiwan between 2005-2008; the control group was randomly selected from the 1-million beneficiaries who registered with the National Health Insurance program in 2005 and had no breast cancer diagnosis between 2000 and 2008. To improve the comparability, we employed the time density sampling method to select controls which were matched to case on date of breast cancer diagnosis and age in year, with a case/control ratio of 1/3.

2.3. **Exposure to Angelica sinensis**

The prescriptions of the *Angelica sinensis* in Taiwan are carried out by the TCM doctors, qualified by the national examination, with the supervision of the Health Insurance Bureau. Both *Angelica sinensis* individual and compound drugs used are scientific Chinese medicine powders produced by GMP pharmaceutical factories, and often applied to the syndromes of blood deficiency and blood stasis determined by TCM doctors, with mean dosage generally single herb 1.5 g/day, compounds are 4–6 g/day.

Exposure to *Angelica sinensis* was defined by the use of single prescription of *Angelica sinensis* or compounds in which the formula proportion of *Angelica sinensis* was greater than or close to 10% during the observation period. In addition, the commonly-used formulas containing *Angelica sinensis* surveyed by previous studies were also included. Exposure of *Angelica sinensis* and other potential confounders was retrospectively retrieved between 2000/1-1 and date of breast cancer diagnosis.

2.4. **Exposure to potential confounding factors**

Both exogenous hormone and selected co-morbidity were considered as potential confounders in this study. Exposure to exogenous hormone was defined as ever using medication containing estrogen and progesterone before the diagnosis of breast cancer. The diagnosis of malignant neoplasm of female genital organs (include malignant neoplasm of ovaries, uterus, and cervix uteri) was according to ICD-9-CM codes 180.X, 182.X, 183.X, 184.X; benign neoplasm of breast, benign uterine tumor (include endometriosis, leiomyoma of uterus) and metabolic disease (include obesity, hypertension, disorders of lipid metabolism) were determined based on ICD-9-CM codes 217, 617.X, 218.X, 278.X, 401.X, and 272.X, respectively. The age of case group was set at the time being diagnosed with breast cancer and control group was set at the time being matched. The insurance payment and areas were captured according to the registry for beneficiaries in 2000 as baseline of claim data. Information of the above-mentioned potential confounders were identified from both inpatient and outpatient between 1997/1/1 and the diagnosis of breast cancer.

2.5. **Statistical analysis**

We analyzed all data with SAS (version 9.4; SAS Institute, Cary, NC). Descriptive statistics and analytical statistics were employed conforming to the study purpose and the variable property. The α level was set at 0.05.

2.6. **Descriptive statistics**

It was used to describe and compare between case and control group with respect to various socio-demographic variables, medications, and co-morbidity, including age, insurance premium based salary, residential areas, diagnosis of gynecologic cancer, benign cyst of breast, benign neoplasm of uterus, disorder of metabolism, exposure history of estrogen and progesterone. We calculated means and standard deviations for continuous variables, as well as number and percentage for categorical variables.

2.7. **Inferential statistics**

We used simple conditional logistic regression model was used to estimate the crude odds ratio (OR) of breast cancer in association with exposure to both single and compound prescriptions of *Angelica sinensis*. The adjusted OR of breast cancer was further estimated from multiple conditional logistic regression by taking into account the potential confounders. The trend test was used to observe whether the dose-response relationship exist between exposure to *Angelica sinensis* and breast cancer. We also assessed the time period between initial use of *Angelica sinensis* and breast cancer diagnosis in association with breast cancer risk; and explored whether age (≤ 47 years, >47–<55 years, and ≥ 55 years) at first exposure to *Angelica sinensis* may pose differential influences on breast cancer risk. The later analysis was set to investigate the potential influence of menopause on the relation between *Angelica sinensis* and breast.

2.8. **Sensitivity analysis**

We performed two sensitivity analyses to assess the potential confounding bias that could be involved in this study. First, there has been concern since 2005 over the potential breast cancer risk associated with *Angelica sinensis* use. We therefore performed separate analyses based on the data before and after 2005 to assess the potential confounding by indication, in which TCM doctors might tend to not prescribe *Angelica sinensis* to women at potentially higher risk of breast cancer (e.g., abnormal mammography report or family history of breast cancer) after 2005. Second, we also used acupuncture habit as a negative exposure, which is believed to have no effect on breast cancer incidence, to assess the potential influence of unmeasured confounders (mainly socioeconomic status and reproductive factors).
3. Result

3.1. Study population

The present study included total number of 34,262 cases and 102,786 controls. The average age of both groups was similar at around 53 years old. More cases than controls were living in Northern areas (more urbanized) and having higher salary. The prevalence of phytohormone exposure and selected co-morbidity was also higher in cases than in controls (Table 1).

3.2. Exposure to Angelica sinensis and breast cancer

The single herb prescription of Angelica sinensis was accounted for 6.2% and 6.3% in case and control group respectively, which was much less than the compound prescription accounting for 49.9% and 49.8%. This has shown the usage of Angelica sinensis in Taiwan was compound prescription in large degree, corresponding to the literature review previously mentioned. The total prevalence of was compound prescription in large degree, corresponding to the literature review previously mentioned. The total prevalence of the compound prescription among cases was 49.9%, representing a crude OR of 1.02 (95% CI 0.94-0.99), and 49.7% in the control group (OR = 0.95, 95% CI 0.93-0.97) (Table 2). Analysis of the dose-response relationship between use of single and compound prescription of Angelica sinensis and breast cancer risk showed an adjusted OR of 0.95 (95% CI 0.92-0.98), P value < 0.001). This has also shown a significant downward trend (beta = -0.024, P value < 0.001) (Table 2).

3.3. Breast cancer risk in association with initial exposure

Table 3 shows the ORs of breast cancer in relation to the time period between initial use of Angelica sinensis and breast cancer diagnosis. The risk of breast cancer was not significantly associated with a time period less than 6 years. However, when the initial use of Angelica sinensis was more than 6 years before breast cancer diagnosis, the significantly protective effect appeared. In addition, there is a tendency that the earlier the initial use of Angelica sinensis happened, the stronger the seemingly protective effect of Angelica sinensis was observed. The regression coefficient of trend test was -0.011 (P value < 0.0001) (Table 3).

3.4. The influence of menopause

This study stratified women according to age at exposure to Angelica sinensis. The most obvious protective effect was in women whose initial Angelica sinensis exposure was at pre-menopausal ages (47–55 years) (aOR: 0.93, 95% CI 0.88–0.98). The adjusted OR was marginally significant for exposure at premenopausal ages, but was insignificant for exposure to Angelica sinensis after menopausal ages (Table 4).

3.5. Sensitivity analysis

In the first sensitivity analysis, we noted that Angelica sinensis exposure before 2005 was associated with a significantly reduced risk of breast cancer with an aOR of 0.94 (95% CI 0.92-0.97). The aOR associated with after Angelica sinensis exposure after 2005, on the other hand, showed no significantly lower aOR (1.02, 95% CI 0.96-1.08). The above results showed no obvious confounding by indication for our data. The second sensitivity analysis revealed that exposure to acupuncture was not significantly associated with breast cancer with an aOR of 1.05 (95% CI 1.01–1.09). In addition, the aOR associated with 1–4, 5–9, and ≥10 times of acupuncture use was estimated at 1.03 (95% CI 0.98–1.08), 1.06 (95% CI 0.96–1.17), and 1.12 (95% CI 1.01–1.23), respectively. A significantly positive association between frequent use of acupuncture and breast cancer risk implied certain unadjusted confounders that could exaggerate the risk of breast cancer among TCM users.

4. Discussion

4.1. Main findings

This study found that the use of Angelica sinensis manifested a weak and protective effect to breast cancer risk after we adjusted for potential confounders. Furthermore, the dose-response

Table 1

Demographics and clinical characteristics of cases and controls.

| Demographics and clinical characteristics | Cases N = 34262 (Mean (SD) or No. (%)) | Controls N = 102786 (Mean (SD) or No. (%)) | Crude OR (95% CI) | P | Model 1 | P | Model 2 | P |
|-----------------------------------------|----------------------------------------|----------------------------------------|------------------|---|---------|---|---------|---|
| Age, years                              | 51.2 (12.2)                            | 53.1 (12.2)                            | 1.00             | 0.53 | 1.00 (REF) |     | 0.97 (0.94–1.01) | 0.19 |
| Residential area                        |                                        |                                        |                  |     | 0.89 (0.86–0.93) | <0.0001 | 0.89 (0.86–0.93) | <0.0001 |
| North                                   | 18055 (54.6)                           | 49762 (49.5)                           | 1.00 (REF)       |     | 1.00 (REF) |     | 1.00 (REF) |     |
| Central                                  | 5348 (16.2)                            | 17735 (17.6)                           | 0.83 (0.80–0.86) | <0.0001 |            |     |            |     |
| East                                     | 693 (2.1)                              | 2387 (2.4)                             | 0.80 (0.73–0.87) | <0.0001 |            |     |            |     |
| Islands                                  | 194 (0.6)                              | 596 (0.6)                              | 0.90 (0.76–1.06) | 0.19 |            |     | 1.02 (0.85–1.22) | 0.84 |
| Insurance premium based monthly salary (NT$) |                                        |                                        |                  |     | 1.00 (REF) |     | 0.97 (0.94–1.01) | 0.19 |
| Dependent                                | 8483 (25.5)                            | 24890 (24.8)                           | 1.00 (REF)       |     | 1.00 (REF) |     | 0.86 (0.83–0.89) | <0.0001 |
| 1-19,999                                | 14226 (42.7)                           | 50222 (50.0)                           | 0.83 (0.80–0.86) | <0.0001 |            |     | 0.86 (0.83–0.89) | <0.0001 |
| 20,000–39,999                           | 6686 (20.0)                            | 18844 (18.8)                           | 1.04 (1.01–1.08) | 0.02 |            |     | 1.01 (0.97–1.06) | 0.59 |
| >39,999                                  | 3932 (11.8)                            | 6570 (6.5)                             | 1.76 (1.67–1.84) | <0.0001 |            |     | 1.60 (1.51–1.69) | <0.0001 |
| Gynecology cancer                       | 711 (21.1)                             | 1376 (1.3)                             | 1.55 (1.41–1.70) | <0.0001 |            |     | 1.57 (1.42–1.74) | <0.0001 |
| Benign breast tumor                      | 14896 (41.5)                           | 8399 (8.2)                             | 8.65 (8.39–8.93) | <0.0001 |            |     | 8.79 (8.49–9.10) | <0.0001 |
| Benign uterine tumor                     | 6192 (18.0)                            | 15069 (14.7)                           | 1.29 (1.25–1.33) | <0.0001 |            |     | 1.05 (1.01–1.09) | 0.02 |
| Metabolic disease                       | 14904 (43.5)                           | 42642 (41.5)                           | 1.09 (1.07–1.12) | <0.0001 |            |     | 1.02 (0.99–1.05) | 0.20 |
| Estrogen exposure                        | 395 (1.2)                              | 1206 (1.2)                             | 0.98 (0.88–1.10) | 0.76 |            |     | 0.95 (0.83–1.08) | 0.43 |
| Progesterone exposure                    | 1175 (3.4)                             | 3718 (3.6)                             | 0.95 (0.89–1.02) | 0.14 |            |     | 0.88 (0.82–0.96) | <0.01 |

Abbreviations: SD, standard deviation; CI, confidence interval; OR, odds ratio; NT$, New Taiwan dollar.
Model 1 adjusted only co-morbidity and estrogen/progesterone exposures.
Model 2 further adjusted demographic characteristics in addition to the factors adjusted in Model 1.
relationship displayed the increasing protective effect in association with an increase in the doses of single and compound prescription of Angelica sinensis. We also observed a tendency that the earlier the initial use of Angelica sinensis happened, the stronger the seemingly protective effect of Angelica sinensis was observed. The findings mentioned above revealed that there was no evidence suggesting an increased breast cancer risk, but instead a small protective effect from the use of Angelica sinensis. Furthermore, the study findings also conformed to the current literature which revealed that TCM could provide a protection effect in breast cancer patients.

4.2. Interpretation of study findings

A recent literature review revealed that Angelica sinensis did not pose stimulatory effect on breast cancer in both in vitro and in vivo studies, which largely removes people’s fear of Angelica sinensis.

The previous study had observed that the extracts of Angelica sinensis, on contrary with previous cell culture, possessed the potential of anti-estrogen effect under the condition of the estradiol existing in cells. In Taiwan, recent studies based on the NHIRD also provided support for the protection role of Angelica sinensis. For example, Siwutang (contain 25% Angelica sinensis) and single Angelica sinensis were both associated with lower risk of and better outcome for breast cancer patients. Epigenetic research also found that extraction of Angelica sinensis Z-ligustilide could restore the inhibitory effect of anti-hormone drug tamoxiphen on breast cancer cells, and suggested that it may be used as an adjuvant in the hormone therapy. Furthermore, we found in the age-stratified analyses that the protective effect of Angelica sinensis was not statistically significant in the sample after menoopause, which also suggested that the protective effect was correlated with the existence of estrogen. Future studies may be carried out to examine whether our study findings can be reproduced.
Besides phytohormone mechanisms, other research revealed that the polysaccharide of Angelica sinensis could activate caspase-3 protease by cyclic AMP response element binding protein to facilitate the apoptosis of breast cancer cells. In addition to the studies of other cancer, N-Butyldienephthalide, which extracted from Angelica sinensis, could induce p53 pathways contributing to the apoptosis and anti-proliferative effect in glioblastoma multiforme, liver and colon cancer cells. And the polysaccharide APS-2a, extracted from Angelica sinensis, could also inhibit the proliferation of transplanted sarcoma.

4.3. Study strengths and limitations

Our study has a number of strengths. First, the current evidence on whether using Angelica sinensis could enhance the risk of breast cancer mostly comes from cell experiments. To the best of our knowledge, our study is the first population-based cohort study that analyzed the risk of breast cancer in association with exposure to Angelica sinensis. Second, this study used a random sample of Taiwan’s NHIRD, which covers medical claims of more than 99.5% of Taiwanese residents. With such population-based medical claim data, the potential for selection bias was considered small. Both cases and controls were sampled from the same population, and such nested case-control design further provides reassurance that the potential for selection bias is minimal. Most importantly, the time density sampling method was used in this study, which increased the comparability between cases and controls with respect to the potential time-related confounding.

There were several limitations involved in this study that should be addressed. First, self-paid medications were not included in the NHIRD, which could result in erroneous ascertainment of Angelica sinensis exposure. However, the potential bias resulting from such exposure misclassification is likely to be non-differential, which would tend to attenuate rather than overestimate the association of Angelica sinensis with breast cancer. Secondly, we can only control the potential confounders available from the NHIRD, and were unable to manage the potential confounding by some other known risk factors for breast cancer, especially those reproductive and genetic risk factors for breast cancer. Despite that, there were no apparent associations of prescription of Angelica sinensis with reproductive and genetic risk factors for breast cancer. In addition, we managed to control for the residential area and insurance premium based monthly salary, which may help reduce the potential confounding by several socioeconomic related risk factors for breast cancer, such as education, times of pregnancy and breastfeeding. Furthermore, we used acupuncture habit to verify the correction in the socioeconomic status of TCM users as falsification analysis, the results of which still supported the outcome of this study.

4.4. Conclusion

This population-based case-control study suggested that exposure to Angelica sinensis showed a weakly but significantly protective effect on breast cancer risk. The results remained intact after various falsification approaches and sensitivity analyses. Although limited by potential sources of bias, our study tended to support the potential protective effect from exposure to Angelica sinensis, which could ease people’s concern over the potential carcinogenic effect from exposure to Angelica sinensis.

Ethical approval

Access to the research data was approved by the National Health Research Institutes Review Committee (Approval number NHIRD # 100206).

Informed consent

Informed consent of the study participants was not required because the dataset used in this study consists of de-identified secondary data released for research purposes.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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References

1. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1997;350(9084):1047–1059.
2. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. J Am Med Assoc. 2002;288(3):321–333.
3. Amato P, Christophe S, Mellon PL. Estrogenic activity of herbs commonly used as remedies for menopausal symptoms. Menopause. 2002;9(2):145–150.
4. Lau CB, Ho TC, Chan TW, Kim SC. Use of dong quai (Angelica sinensis) to treat peri- or postmenopausal symptoms in women with breast cancer: is it appropriate? Menopause. 2005;12(6):734–740.
5. Godecke T, Yao P, Napolitano JG, et al. Integrated standardization concept for Angelica botanicals using quantitative NMR. Fitoterapia. 2012;83(1):1–3.
6. Zhou WJ, Wang S, Hu Z, Zhou ZY, Song CJ. Angelica sinensis polysaccharides promotes apoptosis in human breast cancer cells via CREB-regulated caspase-3 activation. Biochem Biophys Res Commun. 2015;467(1):562–569.
7. Hsieh SC, Lai JN, Lee CF, Hu FC, Tseng WL, Wang JD. The prescribing of Chinese herbal products in Taiwan: a cross-sectional analysis of the national health insurance reimbursement database. Pharmacoeconomie Drug Saf. 2008;17(6):609–619.
8. Lin YH, Chiu JH. Use of Chinese medicine by women with breast cancer: a nationwide cross-sectional study in Taiwan. Complement Ther Med. 2011;19(3):137–143.
9. Lai JN, Wu CT, Wang JD. Prescription pattern of Chinese herbal products for breast cancer in taiwan: a population-based study. Evid Based Compl Altern Med. 2012;2012:891893.
10. National Health Insurance Administration MoHaW. Taiwan, R.O.C. . National Health Insurance Annual Report 2014-2015, 2014.
11. Lee YW, Chen TL, Shih YR, et al. Adjunctive traditional Chinese medicine therapy improves survival in patients with advanced breast cancer: a population-based study. Cancer. 2014;120(9):1338–1344.
12. Yue GG, Wong LS, Leung HW, et al. Is Danggui safe to be taken by breast cancer patients?—a skepticism finally answered by comprehensive preclinical evidences. Front Pharmacol. 2019;10:706.
13. Tsai YT, Lai JN, Lo PC, Chen CN, LinJG. Prescription of Chinese herbal products is associated with a decreased risk of invasive breast cancer. Medicine. 2017;96(35), e7918.
14. Wu CT, Lai JN, Tsai YT. The prescription pattern of Chinese herbal products that contain Dang-Qui and risk of endometrial cancer among tamoxifen- treated female breast cancer survivors in taiwan: a population-based study. PloS One. 2014;9(12), e113887.
15. Ma H, Li L, Dou G, et al. Z-ligustilide restores tamoxifen sensitivity of ERα
negative breast cancer cells by reversing MTA1/IFI16/HDACs complex medi-
ated epigenetic repression of ERα. Oncotarget. 2017;8(17):29328–29345.
16. Qi H, Jiang Z, Wang C, et al. Sensitization of tamoxifen-resistant breast cancer
cells by Z-ligustilide through inhibiting autophagy and accumulating DNA
damages. Oncotarget. 2017;8(17):29300–29317.
17. Tsai NM, Chen YL, Lee CC, et al. The natural compound n-butylenephthalide
derived from Angelica sinensis inhibits malignant brain tumor growth in vitro
and in vivo. J Neurochem. 2006;99(4):1251–1262.
18. Chen YL, Jian MH, Lin CC, et al. The induction of orphan nuclear receptor Nur77
expression by n-butylenephthalide as pharmaceuticals on hepatocellular car-
cinoma cell therapy. Mol Pharmacol. 2008;74(4):1046–1058.
19. Kan WL, Cho CH, Rudd JA, Lin G. Study of the anti-proliferative effects and
synergy of phthalides from Angelica sinensis on colon cancer cells.
J Ethnopharmacol. 2008;120(1):36–43.
20. Cao W, Li XQ, Hou Y, Fan HT, Zhang XN, Mei QB. [Structural analysis and anti-
tumor activity in vivo of polysaccharide APS-2a from Angelica sinensis]. Zhong
Yao Cai. 2008;31(2):261–266.