Journal of Traditional and Complementary Medicine 10 (2020) 454–459

Contents lists available at ScienceDirect

Journal of Traditional and Complementary Medicine

journal homepage: http://www.elsevier.com/locate/jtcme

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

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ARTICLE INFO

Article history:
Received 12 March 2019
Received in revised form
15 October 2019
Accepted 19 October 2019
Available online 23 October 2019

Keywords:
Angelica sinensis
Traditional Chinese medicine
Phytomedicine
Herbal medicine
Breast cancer

ABSTRACT

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*.

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

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICD-9-CM, International Classification of Disease 9th version Clinical Modification; NHIRD, national health insurance research database; OR, odds ratio; TCM, traditional Chinese medicine.

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Peer review under responsibility of The Center for Food and Biomolecules, National Taiwan University.

https://doi.org/10.1016/j.jtcme.2019.10.003

breast cancer patient have seven compounds contain *Angelica sinensis*.[9] 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.[10] 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 4–6g/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.[7] 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 lipoid 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 ($\leqq$47 years, >47-<55 years, and $\geqq$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-mobility 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.[7] The total prevalence of *Angelica sinensis* use is similar for cases (50.7%) and controls (50.6%), representing a crude OR of 1.02 (95% confidence interval (CI) 0.99–1.04, P value = 0.24). After controlling for potential confounders, the adjusted OR was reduced to 0.93(95% CI 0.90–0.96, P value < 0.0001), revealing that the use of *Angelica sinensis* and breast cancer risk manifested a weak but statistically significant protective effect(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 < 0.01), 0.92 (95% CI 0.88–0.95, P value < 0.0001), and 0.91 (95% CI 0.87–0.96, P value < 0.0001)for the accumulated dose of 0.1–9.9 g, 10–29.9 g, and more than 30 g, respectively, with 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 prei-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	Controls N = 102786	Crude OR (95% CI)	P	Model 1	P	Model 2	
	Mean (SD) or No. (%)	Mean (SD) or No. (%)			Adjusted OR (95% CI)		Adjusted OR (95% CI)	P
Age, years	53.2 (12.2)	53.1 (12.2)	1.00	0.53				
Residential area								
North	18055 (54.6)	49762 (49.5)	1.00 (REF)				1.00 (REF)	
Central	5348 (16.2)	17735 (17.6)	0.83 (0.80–0.86)	<.0001			0.97 (0.94–1.01)	0.19
South	8790 (26.6)	30043 (29.9)	0.81 (0.78–0.83)	<.0001			0.89 (0.86–0.93)	<.0001
East	693 (2.1)	2387 (2.4)	0.80 (0.73–0.87)	<.0001			0.93 (0.84–1.02)	0.13
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$)								
Dependent	8483 (25.5)	24890 (24.8)	1.00 (REF)				1.00 (REF)	
1-19,999	14226 (42.7)	50222 (50.0)	0.83 (0.80–0.86)	<.0001			0.86 (0.83–0.89)	<.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)	<.0001			1.60 (1.51–1.69)	<.0001
Gynecology cancer	711 (2.1)	1376 (1.3)	1.55 (1.41–1.70)	<.0001	1.57 (1.42–1.74)	<.0001	1.57 (1.41–1.74)	<.0001
Benign breast tumor	14896 (43.5)	8399 (8.2)	8.65 (8.39–8.93)	<.0001	8.79 (8.49–9.10)	<.0001	8.65 (8.35–8.96)	<.0001
Benign uterine tumor	6192 (18.0)	15069 (14.7)	1.29 (1.25–1.33)	<.0001	1.05 (1.01–1.09)	0.02	1.04 (1.00–1.09)	0.03
Metabolic disease	14904 (43.5)	42642 (41.5)	1.09 (1.07–1.12)	<.0001	1.02 (0.99–1.05)	0.20	1.06 (1.03–1.10)	<.001
Estrogen exposure	395 (1.2)	1206 (1.2)	0.98 (0.88–1.10)	0.76	0.95 (0.83–1.08)	0.43	0.97 (0.85–1.11)	0.70
Progesterone exposure	1175 (3.4)	3718 (3.6)	0.95 (0.89–1.02)	0.14	0.88 (0.82–0.96)	<0.01	0.88 (0.81–0.95)	<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.

Table 2
Crude and adjusted ORs of breast cancer in association with *Angelica sinensis* exposure.

	Cases N = 34262	Controls N = 102786	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
	No. (%)	No. (%)				
Angelica sinensis exposure						
No	16879 (49.3)	50767 (49.4)	1.00 (REF)		1.00 (REF)	
Yes	17383 (50.7)	52019 (50.6)	1.02 (0.99–1.04)	0.24	0.95 (0.93–0.98)	<0.0001
Exposure dose (grams)						
0.1–9.9	8017 (23.4)	24271 (23.6)	1.01 (0.97–1.04)	0.76	0.97 (0.93–1.00)	<0.06
10–29.9	4917 (14.4)	14827 (14.4)	1.01 (0.97–1.05)	0.69	0.93 (0.89–0.97)	<0.001
≧30	4039 (11.8)	11612 (11.3)	1.06 (1.02–1.10)	<0.01	0.96 (0.91–1.00)	<0.06
					Trend test: β=-0.024	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio.
Adjusted OR: adjusted for residential area, monthly salary, gynecology cancer, benign breast/uterine tumor, metabolic disease and estrogen/progesterone exposure.
Note: the total exposure dose contain *Angelica sinensis* compound dose x0.1 and *Angelica sinensis* single herb dose x1.

Table 3
Crude and adjusted ORs of breast cancer in association with time period between initial use of *Angelica sinensis* and breast cancer diagnosis.

	Cases N = 34262	Controls N = 102786	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
	No. (%)	No. (%)				
Non-exposure	16879 (49.3)	50767 (49.4)	1.00 (REF)		1.00 (REF)	
Time period between initial use and breast cancer diagnosis						
0y< ~ ≦1y	1342 (3.9)	3584 (3.5)	1.12 (1.05–1.20)	<0.01	1.08 (1.00–1.16)	0.06
1y< ~ ≦2y	1535 (4.5)	4575 (4.5)	1.03 (0.96–1.09)	0.43	0.95 (0.89–1.02)	0.16
2y< ~ ≦3y	1744 (5.1)	5281 (5.1)	1.00 (0.95–1.06)	0.98	0.96 (0.90–1.03)	0.22
3y< ~ ≦4y	2085 (6.1)	6342 (6.2)	1.00 (0.95–1.06)	0.99	0.95 (0.90–1.01)	0.10
4y< ~ ≦5y	2670 (7.8)	7833 (7.6)	1.04 (0.99–1.09)	0.14	0.98 (0.92–1.03)	0.37
5y< ~ ≦6y	2956 (8.6)	8816 (8.6)	1.02 (0.97–1.07)	0.41	0.96 (0.91–1.01)	0.14
6y< ~ ≦7y	2410 (7.0)	7383 (7.2)	0.99 (0.94–1.04)	0.71	0.91 (0.86–0.97)	<.01
7y< ~ ≦8y	1761 (5.1)	5573 (5.4)	0.96 (0.91–1.02)	0.16	0.87 (0.82–0.94)	<.0001
8y< ~ ≦9y	880 (2.6)	2631 (2.6)	1.02 (0.94–1.10)	0.62	0.96 (0.87–1.06)	0.41
					Trend test: β=-0.011	<.0001

Abbreviations: CI, confidence interval; OR, odds ratio; y, years.
Adjusted OR: adjusted for residential area, monthly salary, gynecology cancer, benign breast/uterine tumor, metabolic disease and estrogen/progesterone exposure.

Table 4
Crude and adjusted ORs of breast cancer in association with initial use of *Angelica sinensis* at various ages.

Age at initial use of *Agelica sinensis*	Cases N = 34262	Controls N = 102786	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
	No. (%)	No. (%)				
Non-exposure	16879 (49.3)	50767 (49.4)	1.00 (REF)		1.00 (REF)	
Exposure before menopause (age≦47y)	9119 (26.6)	27152 (26.4)	1.02 (0.99–1.05)	0.17	0.96 (0.92–1.00)	0.04
Exposure during menopause (47y < age<55y)	4152 (12.1)	12614 (12.3)	1.00 (0.96–1.04)	0.95	0.93 (0.88–0.98)	<.001
Exposure after menopause (age≧55y)	4112 (12.0)	12253 (11.9)	1.02 (0.98–1.06)	0.40	0.97 (0.92–1.02)	0.25

Abbreviations: CI, confidence interval; OR, odds ratio; y, years old.
Adjusted OR: adjusted for age, residential area, monthly salary, gynecology cancer, benign breast/uterine tumor, metabolic disease and estrogen/progesterone exposure.

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.[11]

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*[12]. 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.[5] 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[13,14]. 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.[15,16] Furthermore, we found in the age-stratified analyses that the protective effect of *Angelica sinensis* was not statistically significant in the sample after menopause, 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.

Beside 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.[6] In addition to the studies of other cancer, N-Butylidenephthalide, 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.[17–19] And the polysaccharide APS-2a, extracted from *Angelica sinensis*, could also inhibit the proliferation of transplanted sarcoma.[20]

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 s 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 99.9% 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 breast-feeding. 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 research in high credibility. Third, in Taiwan, the same item of scientific TCM powder, made in different pharmaceutical companies (i.e, different brands), may follow the different dose reference, which makes it very difficult even not impossible to figure out the exact ratio of *Angelica sinensis* from each drug code. Thus, we deliberately used 10% to determine the *Angelica sinensis* dose for prescribed compounds with 10% or higher percentage of *Angelica sinensis*. A potential underestimation of *Angelica sinensis* exposure in this study would result in exposure misclassification. However, such exposure misclassification is likely to be non-differential, which again would lead to underestimate rather than overestimate the association between *Angelica sinensis* and breast cancer.

5. 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 potentail souces of bias, our study tended to support the potentail 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.

Acknowledgement

The authors are grateful for the financial support by a grant from Ministry of Science and Technology (MOST 106-2629-B-006-002).

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