

Chinese herbal products and the reduction of risk of breast cancer among females with type 2 diabetes in Taiwan

A case–control study

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Abstract

Women with type 2 diabetes have a higher risk of developing breast cancer. In Taiwan, traditional Chinese medicine is widely used to treat diabetes; however, its precise influence has not been empirically tested.

The objective of the case–control study is to estimate the effect on the risk of breast cancer of using traditional Chinese medicine for women with type 2 diabetes.

More than 80% of women with type 2 diabetes have used traditional Chinese medicine. The most commonly prescribed drug was metformin and the herbal formulas were the *Di Huang Wan* series, including *Liu Wei Di Huang Wan*, *Qi Ju Di Huang Wan*, and *Zhi Bai Di Huang Wan*, followed by *Bai Hu Jia Ren Shen Tang* and *Yu Quan Wan*. For the effect of metformin, women who used traditional Chinese medicine including *Di Huang* series have a lower risk of breast cancer HR: 0.35 (95%CI: 0.23–0.51) in women younger than 55 and HR: 0.54 (95%CI: 0.37–0.79) in women older than 55.

The protective effect of the *Di Huang Wan* series may be due to the synergetic effect of reducing blood glucose or increasing insulin sensitivity and delaying the insulin resistance of cells. The relationship between the *Di Huang Wan* series and breast cancer of women with type 2 diabetes requires further investigation.

Abbreviations: aDCSI = adapted Diabetes Complications Severity Index, BNHI = Bureau of National Health Insurance, CHP = Chinese herbal products, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, TCM = traditional Chinese medicine.

Keywords: breast cancer, Chinese herbal medicine, Liu Wei Di Huang Wan, metformin, National Health Insurance Research Database, Taiwan, type 2 diabetes

1. Introduction

Diabetes mellitus has been reported to be related to an increased risk of several types of cancer, due to various mechanisms such as the insulin/IGF-I-signaling pathway and the effect of hyperinsulinemia on other hormones.^[1] Women with type 2 diabetes

are at greater risk of developing breast cancer than women without diabetes, because high glucose levels in the blood may promote cancer genesis of breast cells.^[2]

Metformin reduces blood sugar levels by suppressing glucose production in the liver and increasing insulin sensitivity in other tissue. Although the mechanism is unclear, medicine for diabetes like metformin is considered to prevent the development of breast cancer^[3] and has been undergoing clinical trials to evaluate its efficacy.^[4] The mechanism is supposed to be related to the insulin system,^[5] insulin-like growth hormone system,^[6] or female hormone system.^[7] Therefore, the breast cancer risk of diabetes among women with diabetes might differ between the reproductive age and postmenopausal age.

Type 2 diabetes is common in Taiwan and the prevalence is still growing,^[8] with metformin being widely used in Taiwan. In Taiwan, patients with diabetes are free to choose between Western medicine and traditional Chinese medicine (TCM) to treat diabetes-related symptoms or the side effects of antidiabetic drugs. TCM has been used for hundreds of years in Taiwan and our previous study proved women with diabetes were more likely to use TCM, resulting in a high proportion of concurrent use antidiabetic drugs and TCM. Although TCM practitioners prescribe TCM according to syndrome differentiation rather than the serum glucose level, previous study showed TCM has a protective effect against subsequent renal failure in a dose-response manner, suggesting the hypoglycemic effect of Chinese herbal medicine. Further analysis indicated *Liu Wei Di Huang*

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Wan is one of the most common formulas prescribed for treating diabetes in Taiwan,^[9] and taking Chinese herbal formulae containing *Liu Wei Di Huang Wan* showed a one-year delay in the development of kidney failure.^[10]

Another research work confirmed TCM consumption decreased the subsequent risk of endometrial cancer in estrogen receptor-positive breast cancer patients, suggesting the antiproliferative effect via a mechanism involving inhibiting MGMT protein expression.^[11–13] With this in mind, the aims of the study were to determine whether TCM therapy could decrease breast cancer risk in women with diabetes and to identify Chinese herbal formulae which might give early relief to diabetes-related and hormone-related symptoms as well as protect the women's breast against cancer.

2. Method

2.1. Data collection

We conducted a case–control study based on 12-year of follow up drawn from the National Health Insurance Research Database (NHIRD), which was a medical record of people in Taiwan and established in 1996 by the Bureau of National Health Insurance (BNHI). Since citizens in Taiwan were forced to join the National Health Insurance program, the database recruited approximated 96% of people in the nation. The database was collected from all medical records reimbursed by BNHI and the identification information of patients and the medical institute was encrypted. However, demographic data such as sex, birthday, insurance salary, and living area were still included. The medical information including the dosage and duration of each prescription was recorded; the information of operation and diagnosis was recorded in the form of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

The special feature of NHIRD in Taiwan is that it includes TCM. Thus, we can estimate the effect of TCM on the human body or the interaction when combining it with modern medicine. Herbal remedies, acupuncture, and manipulation are all recorded in NHIRD; however, herbal remedies are the major treatment for internal diseases. There are more than 10,000 of licenses for herbs and herbal formulas, with this information being accessible on the website of the BNHI.

We chose adult women as our study object, aged from 20 to 79, and then excluded women with breast cancer or have been prescribed tamoxifen in the first year to ensure the breast cancer was newly developed. We also excluded women with type 1 diabetes and women not suffering from diabetes.

There were a total of 504,162 women extracted from the 1million randomly sampled database, as shown in Figure 1. After excluding women younger than 20 and older than 80 ($n=169,059$), or women diagnosed with any cancer ($n=3250$) or prescribed tamoxifen before the end of 2000 ($n=83$), 331,770 women remained. We also excluded women without diabetes ($n=296,902$) or with type 1 diabetes ($n=1040$) to ensure the final 33,828 subjects recruited into our study were women with type 2 diabetes.

2.2. Cases and controls

The cases who had breast cancer were defined as women coded with the diagnosis of breast cancer (ICD-9: 174) in the database. In order to confirm the diagnosis, the patients must be registered in the registry for catastrophic illness patients in the database. The controls matched to the cases were selected from other women with type 2 diabetes but did not have breast cancer in the database.

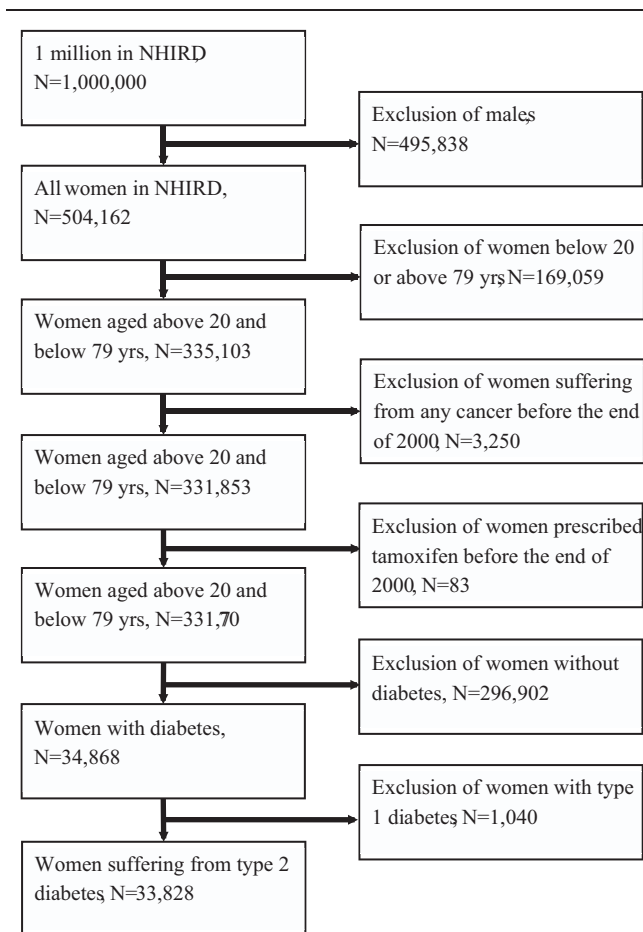


Figure 1. Algorithm explaining the recruitment of subjects from the National Health Insurance Research Database of Taiwan from 2001 to 2012. NHIRD = National Health Insurance Research Database.

A 1:10 case–control match on the propensity score was performed to adjust variables including the age of women, insured region and the severity of diabetic complications of patients, the severity of diabetic complications was calculated with the adapted Diabetes Complications Severity Index (aDCSI), which is composed of 7 categories, including retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease, and metabolic condition. We matched these factors to avoid their effects and focused on the effects of metformin and herbal products.

2.3. Exposure variables

The herbs and drug treatment for diabetes is the major topic of our study; the use of metformin is categorized by the cumulative dosage to estimate the dose-response relationship, which was categorized into 5 groups: patients did not use metformin, patients used metformin below 250 grams, 250 to 1000 grams, 1000 to 2500 grams, and over 2500 grams. The usage of Chinese herbal product is categorized into 3 groups: patients did not use Chinese herbal products (CHP) including patients used less than 500 grams, patients used CHP more than 500 grams but excluding the *Di Huang Wan* series, and patients used CHP more than 500 grams and including *Di Huang Wan* series. There are several formulae include *Liu Wei Di Huang Wan*, such as *Ba Wei Di Huang Wan*, *Zhi Bai Di Huang Wan*, *Qi Ju Di Huang Wan*, *Ji*

Sheng Shen Qi Wan, *Mai Wei Di Huang Wan*, all of these formulas were concluded as *Di Huang Wan* series.

Female hormone usage is an important factor in breast cancer, thus it should be a confounder in the study. Current hormone user as known as women take hormone in the year before the development of breast cancer have a higher risk than women stopped taking hormone more than one year.^[11] Thus we defined the usage of the hormone as the prescription in the last year before the diagnosis of breast cancer for cases or before December 31, 2012, for controls and classified into 4 groups: women who had not been prescribed hormone, current usage of estrogen, current usage of progesterone, and both of them.

Cox proportional hazard regression models were performed to calculate the adjusted hazard ratio and 95% confidence intervals to estimate the effect of CHP, metformin, and female hormone, and the analysis of the study was managed with SAS version 9.4 (SAS Institute, Cary, NC).

2.4. Ethics statement

The protocol had been approved by the research ethics committee of China Medical University Hospital, Taichung, Taiwan (protocol no. CMUH105-REC3-015).

3. Results

The demographics data were shown in Table 1. There were 593 women who had breast cancer and 33,235 were not, women developed breast cancer if they were younger, lived in a higher urbanized city, and with lower severity of diabetic complications. In order to control these variables, the cases and controls were matched on the propensity score to avoid their effects. As shown in Table 2, 428 cases and 4280 controls remained and the 3 variables were matched. After matching, the average years of using metformin or CHP were 5.4 ± 3.6 and 3.4 ± 3.3 years in the cases, 5.7 ± 4.3 and 3.8 ± 3.8 years in the controls.

Table 3 shows the main result in our study, which is the use of metformin or herbal medicine will not increase the risk of breast cancer. The risk decreases significantly when patients take metformin and 2 other types of antidiabetic drugs, with a hazard ratio of 0.50 (95%CI: 0.36–0.67). The same effect is noted in patients who used TCM. The hazard ratio is 0.57 (95% CI: 0.45–0.73) in patients using TCM excluding *Di Huang Wan* series and the hazard ratio is 0.23 (95%CI: 0.34–0.59) in patients using TCM including *Di Huang Wan* series. Like our previous study, women who received female hormone had an increased risk of breast cancer, in particular combining estrogen and progesterone. If patients had taken metformin with the other 2 types of antidiabetic treatments, and they were also older than 55 years old, the hazard ratio decreased to 0.52 (95%CI: 0.32–0.85), the effect is also significant in women younger than 55 years old with hazard ratio 0.48 (95%CI: 0.32–0.72). The effect comes up when using herbal products. If patients used the herbal product excluding the *Di Huang Wan* series, the risk will reduce to 0.57 (95%CI: 0.45–0.73). When they used formulas including the *Di Huang Wan* series, they will have a lower risk with a hazard ratio of 0.35 (95%CI: 0.23–0.51) in women younger than 55. For patients older than 55 years old, the hazard ratio will be 0.54 (95%CI: 0.37–0.79).

The usage of metformin and the risk of breast cancer have demonstrated a dose response. As shown in Table 4, the hazard ratio decreased from 0.63 (95%CI: 0.44–0.91) for women used

Table 1

Demographic characteristics of unmatched population from the National Health Insurance Research Database of Taiwan from 2001 to 2012.

	Case (%)	Control (%)	P-value [†]
Total patients	593	33,235	
Duration of metformin use	5.0 ± 3.6	6.1 ± 4.4	
Duration of TCM use	3.3 ± 3.2	4.1 ± 3.9	
Age at recruitment, years			<.0001
Average	54.5 ± 10.8	54.6 ± 12.5	
20–29	2 (0.3)	1015 (3.1)	
30–39	49 (8.3)	2967 (8.9)	
40–49	151 (25.5)	7823 (23.5)	
50–59	191 (32.2)	8782 (26.4)	
60–69	142 (23.9)	8364 (25.2)	
70–79	58 (9.8)	4284 (12.9)	
Insured region			.0008
Highly urbanized	211 (35.6)	9475 (28.5)	
Moderate urbanized	179 (30.2)	9914 (29.8)	
Boomtown	87 (14.7)	5012 (15.1)	
General town	65 (11.0)	4864 (14.6)	
Aging population	13 (2.2)	807 (2.4)	
Farm town	18 (3.0)	1845 (5.6)	
Remote town	20 (3.4)	1318 (4.0)	
aDCSI [‡]			<.0001
0	332 (56.0)	10,133 (30.5)	
1	95 (16.0)	6350 (19.1)	
2	82 (13.8)	5624 (16.9)	
3	28 (4.7)	3674 (11.1)	
4	27 (4.6)	2759 (8.3)	
≥ 5	29 (4.9)	4695 (14.1)	
Metformin, g			.0438
0	83 (14.0)	5654 (17.0)	
1–250	95 (16.0)	5907 (17.8)	
250–1000	131 (22.1)	7033 (21.2)	
1000–2500	121 (20.4)	7024 (21.1)	
≥ 2500	163 (27.5)	7617 (22.9)	
Hormone usage			<.0001
No	526 (88.7)	32,038 (96.4)	
Estrogen only	39 (6.6)	696 (2.1)	
Progesterone only	8 (1.3)	321 (1.0)	
Estrogen plus progesterone	20 (3.4)	180 (0.5)	
Propensity score	0.0252 ± 0.0123	0.0173 ± 0.0114	

* aDCSI: adapted Diabetes Complications Severity Index.

† Chi-squared test.

metformin < 250 grams to 0.39 (95%CI: 0.29–0.54) for women used metformin >2500 grams, the effects were similar in women younger than 55 and older than 55.

4. Discussion

Multiple studies have shown type 2 diabetics are at an increased risk of developing invasive breast cancer.^[2,12] In the present population-based study, female patients with type 2 diabetes who consumed CHPs were compared with those who had never consumed CHPs during a 12-year follow-up. A lower annual breast cancer incidence was observed in the TCM user group than in the nonuser group from 2001 to 2012. A greater than 28% reduction in the risk of developing breast cancer was detected in the TCM user group. Subgroup analyses found the *Liu Wei Di Huang Wan* user group had a 48% reduction in the risk of developing breast cancer in a dose-response manner. The major risk factors for breast cancer, namely age, metformin dose, and

Table 2
Demographic characteristics of 1:10 matched population from the National Health Insurance Research Database of Taiwan between 2001 and 2012.

	Case (%)	Control (%)	P-value [†]
Patients matched	428	4280	
Duration of metformin use	5.4±3.6	5.7±4.3	
Duration of TCM use	3.4±3.3	3.8±3.8	
Age at recruitment, years			.7467
Average	53.8±10.6	53.2±11.1	
20–29	2 (0.5)	20 (0.5)	
30–39	34 (7.9)	422 (9.9)	
40–49	118 (27.6)	1222 (28.6)	
50–59	154 (36.0)	1433 (33.5)	
60–69	83 (19.4)	787 (18.4)	
70–79	37 (8.6)	396 (9.3)	
Insured region			.0151
Highly urbanized	157 (36.7)	1286 (30.0)	
Moderate urbanized	127 (29.7)	1272 (29.7)	
Boomtown	63 (14.7)	625 (14.6)	
General town	39 (9.1)	607 (14.2)	
Aging population	11 (2.6)	89 (2.1)	
Farm town	15 (3.5)	224 (5.2)	
Remote town	16 (3.7)	177 (4.1)	
aDCSI [*]			.9550
0	179 (41.8)	1721 (40.2)	
1	83 (19.4)	886 (20.7)	
2	82 (19.2)	794 (18.6)	
3	28 (6.5)	319 (7.5)	
4	27 (6.3)	270 (6.3)	
5	29 (6.8)	290 (6.8)	
Metformin, g			<.0001
0	156 (36.4)	808 (18.9)	
1–250	46 (10.7)	826 (19.3)	
250–1000	71 (16.6)	910 (21.3)	
1000–2500	80 (18.7)	880 (20.6)	
≥ 2500	75 (17.5)	856 (20.0)	
Hormone usage			<.0001
No	375 (87.6)	4132 (96.5)	
Estrogen only	34 (7.9)	90 (2.1)	
Progesterone only	7 (1.6)	38 (0.9)	
Estrogen plus progesterone	12 (2.8)	20 (0.5)	
Propensity score	0.6244±0.0671	0.6276±0.0660	

* aDCSI: adapted Diabetes Complications Severity Index.

† Chi-squared test.

hormone therapies were controlled through multivariate modeling and thus cannot act as confounders, as shown in Table 2. Our results suggest *Liu Wei Di Huang Wan* seems to act as a complementary medicine when considered as part of a treatment paradigm shift when a female diabetic woman is at high risk of breast cancer.

Several clinical studies revealed a significantly higher risk of breast cancer in association with hyperinsulinemia and insulin resistance.^[7] Metformin is known to correct hyperinsulinemia and insulin resistance, resulting in an association with diminished breast cancer development^[13] or reduced cellular proliferation^[4] and induced apoptosis.^[14] The protective effect of metformin on developing invasive breast cancer among reproductive age and older women was observed in the present study, corroborating the result obtained in the previous studies.^[15] Note, the current study indicated not all antidiabetic medications which might correct hyperglycemia offer similar tumor-suppressing effects as metformin. In accordance with previous results, metformin

medication has been negatively associated with breast cancer risk, but the combination of other types of antidiabetic medications was not considered in most studies. The current study sheds some light on the phenomenon of prescription in diabetes care that 91.9% (28,386/30,879) of type 2 diabetes women took metformin in Taiwan and above 90% of them took at least 2 types of antidiabetic medications concurrently in real practice. The synergistic effects of 2 or 3 types of antidiabetic drugs in treating hyperinsulinemia and insulin resistance should not be ignored^[16] and may reasonably result in a reduced breast cancer risk. The present results furthered our knowledge of diabetes health care in that the use of combinations of oral blood glucose lowering drugs in treating hyperinsulinemia and insulin resistance is better not only in obtaining long-term control of blood sugar but also in reducing breast cancer risk by more than monotherapy.

Although most women with diabetes receive at least 2 types of diabetes drugs, >80% of them sought medical help from TCM practitioners simultaneously with the intention of either treating diabetic-association symptoms or relieving the uncomfortable side effects of diabetes drugs. Our previous study indicated TCM practitioners in Taiwan added CHP to antidiabetic treatment, resulting in a significantly decreased risk of kidney failure.^[8] The previous report suggested integrating TCM healthcare into diabetes care is a potentially efficacious therapy for reducing hyperglycemia and therefore relieving the nephropathic complications in diabetes mellitus. The current findings demonstrated integrating TCM healthcare into diabetes care is a complementary therapy for reducing breast cancer risk among women of reproductive age which might be through a similar mechanism. Further, comparing the clinical features of non-TCM users, women with diabetes receiving CHP showed a nearly 2-year delay in the development of breast cancer. Whether TCM healthcare alone or CHP merely enhance the effects of metformin in blocking tumor cell proliferation or induce the apoptosis of breast cancer cell warrants further investigation.

According to various common symptoms of diabetes, namely, unusual thirst, blurred vision, frequent urination, and a cold feeling in the limbs, TCM doctors frequently prescribe *Liu Wei Di Huang Wan* or add 2 or 4 Chinese herbs to tailor *Liu Wei Di Huang Wan* to become *Zhi Bo Di Huang Wan*, *Qi Ju Di Huang Wan*, *Ji Sheng Shen Qi Wan*, or *Ba Wei Di Huang Wan* for relieving the aforementioned symptoms,^[9] respectively. In an additional analysis, we assessed the effect of a prescription-containing *Liu Wei Di Huang Wan* on the hazard ratio of developing breast cancer. The adjusted hazard ratio for *Liu Wei Di Huang Wan* users compared with non-TCM users was 0.45 (95% CI 0.34–0.59), whereas it remained unaltered for users of other Chinese herbal drugs among women of reproductive age. Previous studies suggested activation of the insulin pathway, activation of the insulin-like-growth-factor pathway, and regulation of endogenous sex hormones might be the major 3 possible mechanisms associating diabetes with breast cancer.^[15,17,18] The current result infers the preventive effect of developing breast cancer after receiving prescription containing a quantity of *Liu Wei Di Huang Wan* might be via inactivation of either the insulin pathway or the insulin-like-growth-factor pathway rather than the regulation of endogenous sex hormones.^[11] Finally, because of the anonymization of patients' identification numbers in the NHIRD database, we were unable to rule out the presence of a family history of breast cancer and to consider body mass index during model construction. No prior knowledge shows the aforementioned personal risk factors or

Table 3

Number of cases, controls, adjusted hazard ratios and 95% confidence intervals for breast cancer estimated using the multivariate Cox regression model based on the data from the National Health Insurance Research Database of women with type 2 diabetes in Taiwan from 2001 to 2012.

	Aged 20–79		Aged 20–54		Aged 55–79	
	Case/control	HR (95%CI)	Case/control	HR (95%CI)	Case/control	HR (95%CI)
Antidiabetics						
None	124/509	1	88/330	1	36/179	1
Metformin users						
Metformin alone	20/363	0.79 (0.47–1.32)	14/242	0.93 (0.49–1.74)	6/121	0.40 (0.15–1.09)
Metformin+1	81/903	0.82 (0.58–1.16)	39/549	0.79 (0.49–1.26)	42/354	0.89 (0.52–1.51)
Metformin+2 above	171/2206	0.50 (0.36–0.67)	80/1,148	0.48 (0.32–0.72)	91/1058	0.52 (0.32–0.85)
Metformin nonusers						
1 drug	26/206	1.42 (0.89–2.28)	12/104	1.62 (0.83–3.14)	14/102	1.41 (0.71–2.79)
2 drugs	5/59	0.88 (0.35–2.20)	2/32	0.76 (0.18–3.18)	3/27	1.03 (0.31–3.50)
3 above	1/34	0.23 (0.03–1.65)	0/11	–	1/23	0.33 (0.05–2.50)
TCM						
TCM < 500 g	317/2766	1	173/1,510	1	144/1256	1
TCM exclude DHWS*	44/587	0.57 (0.45–0.73)	29/366	0.54 (0.39–0.76)	15/221	0.57 (0.40–0.82)
DHWS user	67/927	0.45 (0.34–0.59)	33/540	0.35 (0.23–0.51)	34/387	0.54 (0.37–0.79)
Hormone usage						
No	375/4132	1	204/2,294	1	171/1838	1
Estrogen only	34/90	4.04 (2.65–6.14)	18/67	2.29 (1.24–4.24)	16/23	8.49 (4.77–15.11)
Progesterone only	7/38	1.52 (0.56–4.10)	6/36	0.98 (0.31–3.11)	1/2	12.65 (1.71–93.78)
Estrogen plus progesterone	12/20	5.04 (2.37–10.71)	7/19	2.20 (0.70–6.90)	5/1	42.77 (13.42–136.31)

* DHWS refers to *Di Huang Wan* series.

Table 4

Number of cases, controls, adjusted hazard ratios and 95% confidence intervals of breast cancer estimated with the cox proportional hazards model based on the data from the National Health Insurance Research Database of patients with diabetes mellitus in Taiwan from 2001 to 2012.

	Age 20–79		Aged 20–54		Aged 55–79	
	Case/control	AHR* (95%CI)	Case/control	AHR* (95%CI)	Case/control	AHR* (95%CI)
Metformin usage (g)						
None	156/808	1	102/477	1	54/331	1
< 250	46/826	0.63 (0.44–0.91)	24/510	0.66 (0.40–1.08)	22/316	0.57 (0.33–0.97)
250~1,000	71/910	0.77 (0.56–1.05)	37/542	0.77 (0.50–1.19)	34/368	0.69 (0.43–1.09)
1,000~2,500	80/880	0.59 (0.44–0.81)	41/488	0.60 (0.39–0.91)	39/392	0.60 (0.39–0.94)
>= 2,500	75/856	0.39 (0.29–0.54)	31/399	0.34 (0.21–0.53)	44/457	0.45 (0.29–0.70)

* Adjusted hazard ratio: adjusted for usage of TCM and female hormone.

family history is related to the usage of TCM. This tendency is assumed to be similar among TCM users and non-TCM users. We studied a population of type 2 diabetic women; therefore, the relevance of our findings in nondiabetic women is unknown. By using the retrospective review of claim reimbursement data as our source for exposure information, we assumed either prescribed antidiabetic medication or herbal products are equivalent to the actually consumed medications. Even if the women did not take all of the prescribed medications, our findings would only underestimate the effect of CHP or *Liu Wei Di Huang Wan* on breast cancer.

Integrating TCM healthcare into diabetes care would seem to help decrease the risk of developing breast cancer. Prescriptions containing *Di Huang Wan* series are recommended for their potential effects in reducing progressive diabetic nephropathy or in decreasing breast cancer risk. We suggest an integration of both healthcare technologies might be the optimal healthcare, especially for those women with the renal disease and moderate renal insufficiency.

Author contributions

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