EFFECT OF SOYBEANS ISOFLAVONESON MENOPAUSAL SYMPTOMS AND ENDOMETRIAL CANCER RISK IN POSTMENOPAUSAL WOMEN: A RANDOMIZED CONTROLLED STUDY.

AshrafM. Kansouh[1] and Abd ELatif M. Elbalshy[2]

Obstetrics and Gynecology Department, Shibeen Elkom Teaching Hospital[1]

Pathology Department, Faculty of Medicine, Benha University[2]

ABSTRACT

***Background**: Isoflavones from soy beans modulate hormonal effects onclimacteric symptoms (number of hot flashes and night sweats) in post-menopausalwomen, and the hormone disorder might result in different cancers including endometrial cancer (EC). However, its effect on the risk of EC is still inconclusive. We aimed to assess the effects of isoflavones on, a risk factor of EC in post-menopausal women. **Objective:** This study aimsat evaluation of the impact of soybeans isoflavones on menopausal symptoms (such as hot flashes and night sweats), evaluate the effect of isoflavones supplementation on endometrial thickness and rate of EC in postmenopausal women in Minofya Governorate. **Methods:** A meta-analysis of randomized controlled study were assessed between July2013 to June2014 and were involved 200 post-menopausal women divided into two groups(Treatment group and Control group) with climacteric symptoms (number of hot flashes and night sweats per day).Hot flashes were measured with a five-point scale (0: absent to 4: very intense) and daily night sweats. This criterion was selected before and after taking half cup (8 large spoons) soya beans boiled (contains 47 mg isoflavones). Transvaginal ultrasonography was used for all women before the study and after 3,6,12 months of taking soya beans as diagnostic procedure to detect endometrial thickness. Endometrial sampling were taken for all women after 12 months from eating soya beans (isoflavones) with a very thin tube inserted into the uterus through the cervix, and the tissue was removed with suction and this process was taken about 1 minute and sent to histopathology. **Results:**The patients were followed up over a 4-month period and data were analyzed using t- test. The outcome measure was fewer hot flashes and night sweats.There was -5.3 (45%),-2.2(42%), -7.5 (45%), reduction in the Day, Night and the 24 -hour hot flashes score with soybeans group, while it was -3.4 (29%), -2.1(33) and -5.5 (30%) reduction with control group. Also there was-3(29%) reduction in night sweats with soya beansgroup and -1(9%) reduction in night sweats with control group. to the final 16 weeks. The percentage of patients who adhered to soybeans isoflavones was 100% during the 16 weeks follow-up period. These results confirm the effectiveness of soybeans isoflavonessupplement (47 mg /day) on vasomotor symptoms in post-menopausal women. Treatment group did not significantly differ on the mean baseline or on trial change in endometrial thickness of the control group, also no significant effect on EC risk in Post-menopausal women. **Conclusion**: One year Soybeans supplementation has a significant decrease in the number of hot flashes and night sweats while displaying very good long-term tolerance,and has no significant effect on EC risk in Post-menopausal women.*

***Keywords**: SoybeansIsoflavones,equal,Climacteric symptoms, Hot Flashes, Night Sweats, endometrial thickness, ECrisk,Post-menopausal*

INTRODUCTION

Menopause is the permanent end of a woman's menstrual periods when symptoms such as hot flashes and night sweats appear in menopause, many women look to the natural world for help. Of the many options available to women in perimenopause and menopause, we classify soy as a menopause "super food." Because it is not only have effective in reducing frequency and severity of hot flashes in thousands of cases at our clinic, butalso it is safe and easy to use for nearly everyone (1).The main sources of phytoestrogens are isoflavonoids, coumestans, and lignans. While the main food source of isoflavones is the soya beans (2).Several studies have shown that women who consume large amounts of soy-based phytoestrogens have fewer menopausal complaints.Twelve studies using soy or soy extracts were done. Soy appeared to have a 'modest' benefit in reducing hot flashes. As with all natural approaches, you should also allow sufficient time for the treatment, generally in the range of 4 to 12 weeks (3) EC is the most common female gynecological cancer in the United States, ranking fourth among all cancers in women in age-adjusted incidence (4). To our knowledge, only three case-control studies had been reported on the role of phytoestrogens on EC risk, with conflicting results. (5)(6).Isoflavones from soy food intake have been found to decrease endogenous estrogen

levels and stimulate the production of sex hormonebinding globulin in the liver, resulting in less freeestradiol. They are also suggested to act as anti-estrogens by competing with the more potent endogenous estrogen. A full list of contributors appears under Acknowledgements for estrogen receptors (7).Few additional studies examining the impact of soy foods, the main source of isoflavones, tended to suggest an inverse association(8).There are studies evaluated the effect of oral isoflavones supplementation on endometrial thickness, a risk factor of EC (9,10) as measured by transvaginal ultrasound (TVU), endometrial thickness can be a biomarker for the proliferative effects of estrogens, and opposing different influences of progesterone .The increase of endometrial thickness may be associated with increased risk of endometrial carcinoma(11,12).However our study was to evaluatethe impact of soybeans isoflavoneson menopausal symptoms (such as hot flashes and night sweats), evaluate the effect of isoflavones supplementation on endometrial thickness and rate of EC in postmenopausal women in Monofya and Qaliubiya Governorate.

PATIENTS & METHODS

The patients subjected to this study were selected from women attending the Department of Obstetrics and Gynecology in Shibeen ElkomTeaching Hospitalby randomized controlled study(Minofya Governorate,Egypt) between July2013 to June 2014.Detailed medical and gynecological history taken from each woman.Women wereexcluded from analysis if they had <12 months amenorrhea or surgical absent uterus or organic pelvic lesion (such as uterine myoma, pelvic cancer, rectal or vaginal bleeding) or they were smokers, orwere using antibiotics, or had inflammatory bowel disease,orliver impairment, or an allergy to soy foodsand all participants were instructed to avoid soy-based foods and soy supplements during the study.An informed consent form wasassigned from each patient before starting the study.Two hundreds (200)postmenopausal women divided into two groups:**Treatmentgroup**:One hundred (100) women complaining from menopausal symptom (such as hot flushes and night sweating).Hot flashes were measured with use of a daily menopause diary,which included the self-reported number and average estimated intensity during the day and night, measured with a five-point scale (0: to 4: very intense) and daily night sweats .This criterion was selected before and after taking half cup (8 large spoon) soya beans boiled (contain 47 mgisoflavones) according to USDA nutrient data laboratory**(**13**).**Transvaginalultrasonography was used for all women before the study and after 3,6 and12 months oftaking soya beans as diagnostic procedure to detect endometrial thickness. The measurement of the endometrium is made at its maximal thickness on a midline sagittal image of the uterus obtained by transvaginal ultrasound. It is a bilayer measurement combining the width of both the anterior and the posterior layers of the endometrium, Endometrial sampling weretaken for all women after 12 months from eating soya beans (isoflavones)with a very thin tube inserted into the uterus through the cervix , and the tissue was removed with suctionand this process was takenabout 1 minute and sent to histopathology.

Controlgroup: one hundred (100) women complaining from menopausal symptom (such as hot flushes and night sweating) , recordedfrequency and severity of symptom daily in questionnaire. Transvaginal ultrasonography were used 3,6,12 months for all women as diagnostic procedure to detect endometrial thickness, endometrial hyperplasia, and follow up along time of study. Endometrial sampling were taken for all women after 12 months, and sent to histopathologyThese women were advised to keep their usual dietEthical approval was obtained from Board of General Health Organization of Teaching Hospitals and Institutes (GOTHI).

Statistical Analysis:

a- The collected data in this study wastabulated and computerized or analysis to obtain the following parameters: Arithmetic mean, standard deviation (SD) and percentage.

b- Comparison of means: comparisons of measured parameters between the two groups were carried out by student‘s t-test, comparisons of value before and after soya beans isoflavonesgroup was done by using a paired T-test.

P value< 0.05 was considered statistically significant results.

P value > 0.05 indicated insignificant results.

RESULTS

Table (1) : Baseline characteristics of postmenopausal women.

Variable	Treatment group	Control group	T- test	P value
Age(years)	56.5±6.3	55.9±5.5	0.32	> 0.5
BMI(Kg/m2)	26.8 ± 4.5	26.6 ±4.2	0.36	> 0.5
Age of menarche(years)	12.6 ± (1.9)	12.6± (1.8)	0.31	> 0.5
Nulliparous(%)	5.4	5.6	0.49	> 0.5
No. of years since menopause	9.8 ± 8.7	8.6 ± 8	0.42	> 0.5
Age at menopause(.>55 year)(%)	4.2	3.9	0.2	> 0.5
Coffee(> 1 cup/day)(%)	23.2	25.5	0.49	> 0.5
No of hot flashes in 24 hours	7.2 ±4.2	7.3± 5.2	0.39	> 0.5
Hot flash score in24 hours	18.3 ±14.1	18.8 ±17.8	0.21	> 0.5

Data are mean ± SD or number (%).

Hot flash score =Intensity X frequency of hot flash

Hot flash score for 24 hours.=[hot flash frequency X intensity for day] + [hot flashfrequency X intensity for night]

No significant modification effect was observed for baseline median age, BMI, Age of menarche(years), Nulliparous(%), menopausal state , coffee drinking on hot flashes and hot flash score in 24 hours

The mean number of episodes of hot flashes in 24 hours was 7.2±4.2, 7.3 ± 5.2 at baseline in treatment and control group.The mean of hot flashes score in 24 hours was 18.3 ±14.1, 18.8 ±17.8at baseline in treatment and control group

Table (2): Difference in mean (%) hot flashes and night sweatsfrom baseline to the final 16weeks of postmenopausal women.

Variable		Treatment group		control group		T- test	P value
		Difference in mean	%	Difference in mean	%		
hot flashes	**Day**					0.42	< 0.5
	No. of hot flashes	-2.1	40	-1.3	27		
	Hot flash score	-5.3	45	-3.4	29		
	Night						
	No. of hot flashes	-1.5	35	-.6	22	0.68	< 0.5
	Hot flash score	-2.2	42	-2.1	33		
	24 Hours						
	No. of hot flashes	-3.6	39	-1.7	26	0.51	< 0.5
	Hot flash score.	-7.5	45	-5.5	30		
night sweats		-3	29	-1	9	0.78	< 0.5

Both groups had significant reductions(< 0.5) in the number of hotflashes during the day, night, and 24 hours and in theirrespective hot flash scores from baseline to the final 16 weeks of treatment and also both groups had significant reductions in night sweats Overall, there was5.3(45%),2.2(42%), 7.5 (45%), reduction in the Day, Night and24-hour hot flash score with soybeangroupand 3.4 (29%), 2.1(33) and 5.5 (30%) reduction with control group. Also there was3(29%) reduction in night sweats with soybeangroup and 1(9%) reduction in night sweats with control groupto the final 16 weeks.

Table(3). Frequency of adverse effects (%) reported by women who consumed Soy bean

Adverse effect	Treatment group(Soy bean) No. of women	%
Weight gain >5% UBW	1	1
GastrointestinalUpset		
Abdominal bloating	3	3
Diarrhea	2	2
Vaginal spotting	2	2

UBW= usual body weight.

More than one adverse effect may be reported for each participant.

List of the most common adverse effect on treatmentsoy group was: one case weight gain >5% UBW, 3 cases abdominal bloating, 2 cases diarrhea and 2 cases vaginal spotting. Nocasedropped out of the study for these reasons. All of these participants were referred for investigation and completed the trial.

Table (4) Baseline 3,6 and 12 months endometrial thickness by vaginal ultrasonography inpostmenopausal women

Variable	Treatment group	control group	T- test	P value
Baseline endometrial thickness.	1.8 ± 2.5mm	1.3 ± 2.7 mm	0.4	> 0.5
Endometrial thickness after 3 months	1.7 ± 2.6mm	1.2 ±2.8 mm	0.46	> 0.5
Endometrial thickness after 6 months	1.8 ± 2.4mm	1.3± 2.9 mm	0.48	> 0.5
Endometrial thickness after 12 months	1.5± 2.3mm	1.2 ± 2.8 mm	0.40	> 0.5

There is no significant change in baseline, after 3, 6,and 12 months endometrial thicknessin either treatment and control groupThe baseline endometrial thickness in treatment group varied from 1.8±2.5mm to 1.5±2.3mm and the baseline endometrial thickness varied from 1.3±2.7mm to 1.2±2.8 mm in control group after 12months.

Table(5): Findings in TVS and Histopathology in treatment and control group after one year in postmenopausal women

Variable	TVS		Histopathology	
	Treatment group (n=95)	control group (n=92)	Treatment group (n=95)	control group (n=92)
Normal endometrium	(n=89)	(n=82)	(n=89)	(n=81)
Atrophy	(n=2)	(n=4)	(n=4)	(n=6)
Hyperplasia	(n=3)	(n=4)	(n=1)	(n=3)
Polyp	(n=1)	(n=2)	(n=1)	(n=2)
Adenocarcinoma	(n=0)	(n=0)	(n=0)	(n=0)

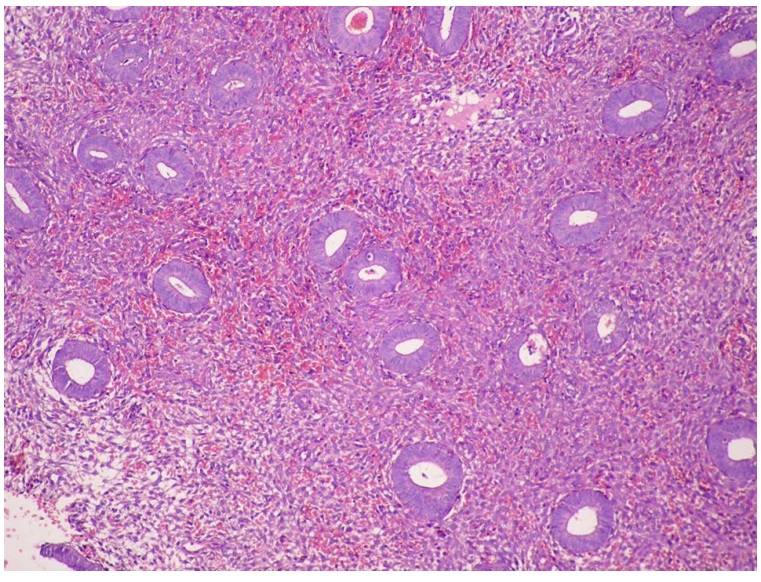
TVS is Trans vaginal ultrasound
Normal endometrium thickness (=5mm)
endometrium thickness < 4 mm meanendometrium Atrophy

asymptomatic endometrial thickness of 8 to 11 mm in a postmenopausal women is not abnormal .if exceeds the normal thickness is referred to as endometrium hyperplasia

TVS among(n=95)cases in treatment group(5 cases were missed)were shown 89cases normal endometrium 2cases atrophy3 cases hyperplasia and one case polyp and in control group (n=92) cases (8 cases were missed) are shown 82cases normal endometrium.4cases atrophy 4 cases hyperplasia and2 cases polyp.

Histopathology results among treatment group (n=95)reveals 89cases normal endometrium, 4cases atrophy,one case hyperplasia,and one case polyp5 cases were sampling failure in treatment group. (Inadequate sample or inability to perform the biopsy).Control group (n=92) were shown 81cases normal endometrium, 6cases atrophy 3 cases hyperplasia and 2 cases polyp. Eight cases were missed from this group. There was however no case of malignancy in the study.

Histopathological examination:



Fig(1):photomicrograph of normal endometrium shows small, round and regular glands.They are widely separated by a stroma without edema, which contains small, regularly distributed blood vessels. Gland lining have slight pseudo stratification, occasional mitotic figures and a few clear cells. Stromal cells are uniform and small, with round to ovoid nuclei and occasional mitotic figures(Hematoxylin &Eosinstain x200).

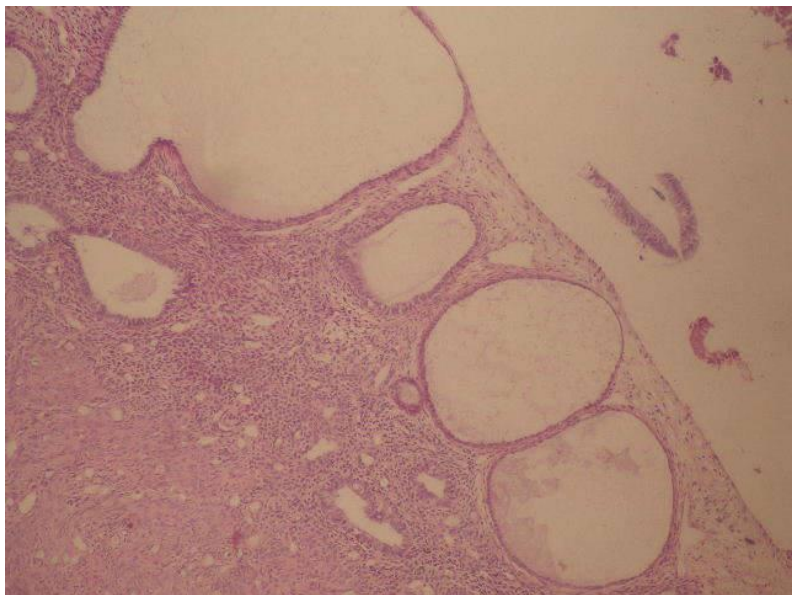


Fig.(2):photomicrograph of endometrium atrophy showing a thin endometrium with only a few residual glands surrounded by an atrophic somewhat fibrotic stroma. The glands vary from small to cystically dilated, but allare lined by a single layer of epithelial cells that are cuboidal to flattened.(Hematoxylin &Eosinstain x200).

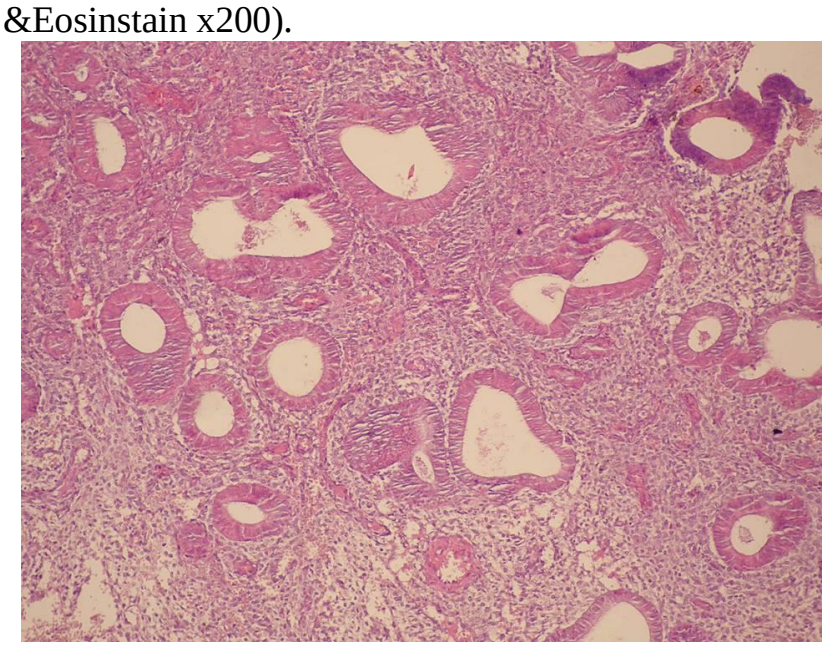


Fig.(3):photomicrographsimpleendometrium hyperplasiashowing increased glandular stromal ratio. The endometrial glandsare variable in shape and size with some cystification and lined by pseudostratified columnar epithelium. Stroma is compact and cellular. Endometrial biopsy(Hematoxylin &Eosinstain x200).

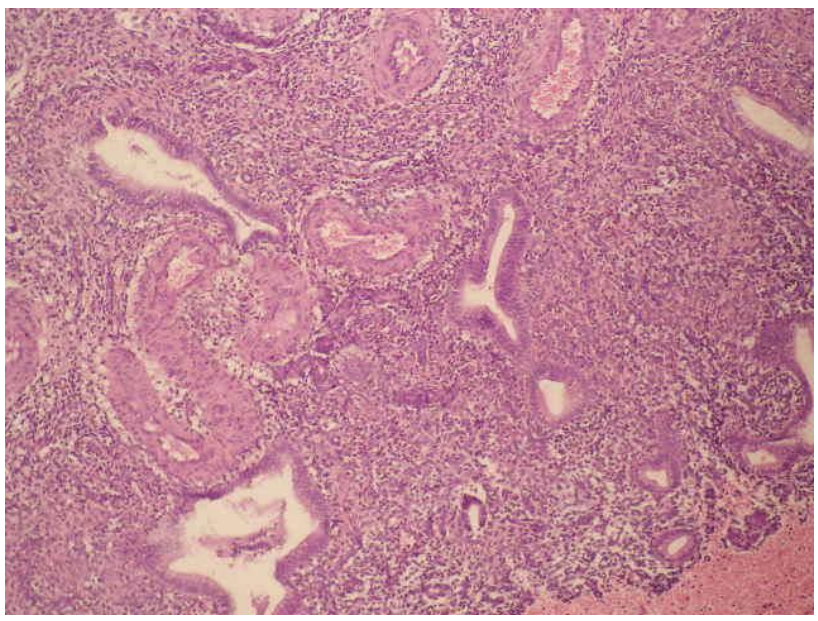


Fig.(4):photomicrographendometrium polyp showing relatively few glands in a fibrotic stroma rich in thick-walled blood vessels.Endometrial glands are branched and show some retention cysts. (Hematoxylin &Eosinstain x200).

DISCUSSION

Soybeans isoflavones enriched supplements are characterized by a predominance of genistein and daidzein compounds, which are metabolized to equol products (great benefit in hot flashes reduction(14, 15). Our study was carried out with soya beans boiled (contain 47 mg isoflavones). During the four months of the study, we observed a gradual decrease in hot flashes (39% at 16 weeks) and night sweats (29% at 16 weeks). These findings are in agreement with some studiesthat reveal a minimal effectofsoya beans on hot flushes.They find that soya beans lead to 45% reduction in hot flashes and control groupshow 30% reduction compared with 70% reduction inhot flushes with estrogen replacement therapy.These results have been reported in clinical studies that examined the effects of dietary intake of soybeans or isoflavones supplements on hot flashes (16,17). These inconsistent findings could be explained by the diversity of environmental studies, the origin of the soybeans, (isoflavones), the number of hot flashes at baseline, and individual metabolism (e.g., equol production) (18,19). According to The North American Menopause Society, treatment of vasomotor symptoms using isoflavones can be achieved with an initial dose of 50 mg/day for at least 12 weeks (20).This is in agreement with our study with a dose of isoflavones equal to 47 mg /day for at least 16 weeks.Taken together, one year treatment with soya beans was well tolerated by menopausal patients in our study. However, the contribution of this supplement to potential adverse effects was not evaluated. Nevertheless, the fact that isoflavones were well tolerated seems to confirm previous comparative, double-blind studies indicating no differences in the frequency of adverse events between isoflavonestreated and control groups(21).Most randomized controlled trials have reported that isoflavones supplements are generally safe, and our study is consistent with those findings (34),but the frequency of some adverse effectsreported in our studywere not effective for discontinuation study and may not related to soya beans.This agreement with studies(22-25)that reported no side effect in isoflavones supplementation doses ranged from 5 to 154mg/d and supplementation duration ranged from 3months to 3years.However longer-term studies are needed to evaluate the long-term safety of soy isoflavones supplements. Further studies are also necessary to assess the efficacy of soy isoflavones in racially and ethnically diverse populations.(26)

Endometrial carcinoma (EC) is the most common gynaecologic malignancy (20). Approximately 80% ofECs occur in postmenopausal women.Individual risk factors are obesity, high-fat diet, reproductive factors such as nulliparity and polycystic ovary syndrome, early menarche, and late menopause andincreased lifetime estrogen exposure(unopposed estrogen) have been linked to an increased risk of EC(27).Current evidence suggests that certain subsets of women at high risk of developing EC who have endometrial thickening on ultrasound and other positive findings (increased vascularity, inhomogeneity of endometrium, particulate fluid, and excessively thickened endometrium > 11 mm) should be referred to gynecologist for endometrial sampling and histopathology (28).

The present study shows no significant change in endometrial thickness in either treatment or control group.The baseline endometrial thickness in treatment group varied from 1.8±2.5mm to 1.5±2.3mm.This agree with other studies(22-25) .But a study (29) reported the absolute changes provided baseline and final endometrial thickness after intervention.Our analysis found that there was no significant effect of soybeans supplementation on endometrial thickness and EC risk (no cases of EC either by ultrasound or histopathology).In the other handZhang et al. performed a meta-analysis about soy intake and EC risk and found that soy food intake was associated with lower EC risk in 10 related observational studies (30). They found the highest reported soy intake compared with the lowest reduced the risk of EC by 19%. This finding shows that the intake of soy foods has a positive effect on human endometrial. Our results were contradictory with Zhang’s results since endometrial thickening is a risk factor of EC. Also Ollberding and his colleagues performed a prospective study followed up for an average of 13.6 years and observed an inverse association between dietary isoflavones intake and the risk of EC(31)

Ourresults also agree with subjects from Japanese and Asian women that had no significant decrease in endometrial thickness after isoflavones intervention, which was opposite to the response of North America subjects. This difference could be contributed by different genetic background and dietary

patterns between populations. Asian and African diet is rich in isoflavones due to more soy and soy products intake (7, 32,33), which might result to a higher background level of isoflavones in their body; and additional supplementation may not be beneficial. North American had less isoflavones intake from their regular diet and the supplementation might be more effective.(34).

We found that isoflavones supplementation might produce different effects on populations and the daily dose of isoflavones supplementation maybe important to the results due to first, the endometrial thickness may be affected by internal hormone exposure. Though 21 over 23 studies included only menopause women for the study, the different time duration after menopause might affect the endometrial thickness and response to hormone, which increase the heterogeneity of the study. The equol producer phenotype is important as it can reflect gut metabolite of soy isoflavones*in vivo* (35) In human, only 30%-50% of the population are capable of converting daidzein to equol and equol's biological activities differs from its parent compound (36,37). However, we could not get the information about equol producers in almost all the included studies.Additional large and long follow-up studies should be performed to confirm our results and explore the exact mechanism of isoflavones effect on endometrium.

CONCLUSION

Our study confirmed the efficacy of soybeans (isoflavones) supplement (47 mg/day) on vasomotor disorders(hot flashes and night sweats) inpost-menopausalwomen. Specifically, we found that soya beans treatment led to a significant decrease in the number of hot flashes and night sweats while displaying very good long-term tolerance.These results found no evidence to support that higher consumption of soy food and isoflavones is associated with the reduction of endometrium cancer risk in postmenopausal women. Future studies with a greater number of cases and more precise assessment of exposure variables or use of related biomarkers are required to verify these findings.

Limitations

A number of limitations should also be notedDespite our study was based on two climacteric symptoms whereas about forty of such symptoms have been described. Some participants received a cup of soya beans (94 mg /day) isoflavones but analyses were not based on the number of grain received. As it was a longitudinal symptom-based trial, the biochemistry of plasma estrogens should be combined with such analyses in future trials, and also in our study was small sample size and short follow-up period.The number of incident cancer cases was zero, reflecting no incidence of endometrial carcinoma (EC) in Egypt. Although our analysis on a continuous scale (47 mg/day soybeans isoflavones intake) showed no clear direction to decrease or increase in risk EC. Repeated measurement at regular intervals would likely provide a better estimate of exposure status. Obesity is a known risk factor of EC, and the effect of soy intake on EC risk in lean and obese women is interesting. The results of our study might not extrapolate to other populations. Confirmation of these results awaits further studies in larger and more diverse populations.

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الملخص العربى

تأثير الأيزوفلافون المتواجد فىفول الصويا على أعراض انقطاع الطمث و خطر الاصابة بسرطان بطانة الرحم فى النساء بعد سن اليأس " دراسة عشوائية محكومة."

اشرف قنصوه[1] وعبداللطيف البالشى[2]

قسم النساء والتوليد – مستشفى شبين الكوم التعليمى[1]

قسم الباثولوجى، كلية الطب – جامعة بنها[2]

هدف البحث إلى تحديد تأثير أيزوفلافونفول الصويا على أعراض إنقطاع الطمث (مثل الهبات الساخنة والتعرق الليلى) ومعدل سرطان بطانة الرحم عند النساء بعد سن اليأس.

واعتمد البحث على 200 سيدة بعد انقطاع الطمث من المترددات علىمستشفى شبين الكوم التعليمى فى الفترة من يوليو 2013 إلى يونيو 2014 وأخذ من كل منهن تاريخ مرضى مفصل واستثنيت السيدات من العينة اذا كانت اقل من 12شهر انقطاع طمث أو استئصال رحمى أو أى مرض عضوى فى الحوض مثل ورم ليفى - أورام سرطانية – نزيف مهبلى – التهابات فى الحوض- فشل فى الكبد – حساسية لفول الصويا وتم أخذ موافقة المريضة قبل البحث. وقسمت العينة إلى مجموعتين (**المجموعة المعالجة"**100سيدة " تم اختيارهن عشوائيا ممن تعانين من اعراض انقطاع الطمث مثل الهبات الساخنة ،و التعرق الليلى) وتم عمل استبيان للسيدات من حيث شدة الهبات الساخنة وعدد مرات الحدوث فى النهار، الليل ، وخلال اليوم الواحد وأيضا التعرق الليلى من حيث عدد مرات حدوثه خلال 16 أسبوع وعمل موجات فوق صوتية مهبلية لدراسة سمك وخطر الاصابة بسرطان بطانة الرحم من بداية البحث وأيضا بعد 3، 6 ، 12 شهرًا. وتم أخذ عينة من بطانة الرحم بعد 12 شهر بعد تناول فول الصويا كل هذه الخطوات تم اجراءها قبل وبعد تناول نصف كوب فول صويا مغلى = 8 ملاعق كبيرة تحتوى على 47 ملى جرام أيسوفلافون

مجموعة التحكم " 100سيدة " تعانين من أعراض انقطاع الطمث مثل الهبات الساخنة ،و التعرق الليلى) وتم أيضا عمل استبيان للسيدات من حيث شدة الهبات الساخنة وعدد مرات الحدوث فى النهار، الليل ، وخلال اليوم الواحد وأيضا التعرق الليلى من حيث عدد مرات حدوثه خلال 16 أسبوع وعمل موجات فوق صوتية مهبلية لدراسة سمك وخطر الاصابة بسرطان بطانة الرحم من بداية البحث وأيضا بعد 3، 6 ، 12 شهرًا. وتم أخذ عينة من بطانة الرحم بعد 12 شهر بدون تناول فول الصويا أيسوفلافون. وقد أخذت عينات من بطانة الرحم وارسلت إلى التحليل وقد أجيز هذا البحث من لجنة الأبحاث بالهيئة العامة للمعاهد والمستشفيات التعليمية

وقد دللت نتائج البحث على أن لفول الصويا تأثير ايجابى فى انخفاض عدد الهبات الساخنة فى النهار والليل والتعرق الليلى بعد مرور 16 أسبوع من العلاجحيث كانت (45%)، (42%)، (45%) منخفضة بالنهار والليل وخلال 24 ساعة على التوالى فى المجموعة المعالجة بفول الصويا بينما كانت مجموعة التحكم (29%)، (33%)، (30%) منخفضة على التوالى كما أنه لم توجد أى أعراض جانبية باستثناء حالة واحدة زيادة فى الوزن أكثر من 5% وثلاث حالات انتفاخ فى البطن وحالتين عانتا من الاسهال وحالتين فقط عانين من نزول نقاط دموية بسيطة من المهبل وجميع هؤلاء تم اجراء فحوصات اللازمة وأكملوا البحث . وقد أثبت البحث أنه لا يوجد دلالة للتغير فى سمك بطانة الرحم وخطر الاصابة بسرطان بطانة الرحم بعد 3 ، 6 ، 12 شهرا فى كل من المجموعتين.