Pacific University

CommonKnowledge

School of Physician Assistant Studies

College of Health Professions

Summer 8-10-2019

Seaweed Consumption and Its Effect on Breast Cancer

Alyssa MouaLee

Thanita Pradhanang

Seaweed Consumption and Its Effect on Breast Cancer

Abstract

Background: Breast cancer remains the most common cancer in women worldwide. Interestingly, breast cancer incidence varies dramatically among countries. Japan, in particular, has relatively low breast cancer (BC) rates when compared to those in Western countries. Daily consumption of seaweed has been proposed as one of the factors in explaining the difference in incidence rates of BC. The high concentrations of polysaccharides in seaweed have been reported in many studies to have anti-cancer effects as well as chemoprotective effects. The aim for this review is to look at the potential benefits of seaweed consumption and its effect on breast cancer.

Methods: Exhaustive search of available medical literature was performed using MEDLINE-Ovid, Science Direct, Web of Science and CINAHL. Keywords used included: breast cancer, breast neoplasm and seaweed. Studies were assessed for quality using GRADE criteria.

Results: The systematic literature search yielded 311 articles for review. After screening the titles and abstracts, 3 articles met the eligibility criteria. Two of the studies were randomized control trials and 1 was a case-control observational study. These studies showed an association between seaweed consumption and lower rates of breast cancer.

Conclusion: Daily consumption of seaweed may play an important role in decreasing the incidence of breast cancer in women.

Keywords: Seaweed, breast cancer, breast neoplasm

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

Keywords
breast cancer, breast neoplasm, seaweed

Seaweed Consumption and Its Effect on Breast Cancer

Thanita Pradhanang
and
Alyssa MouaLee

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 2019

Faculty Advisors: Heather T. Porst, MBA, PA-C
Mark Pedemonte, MD

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

[Redacted for privacy]

Abstract

Background: Breast cancer remains the most common cancer in women worldwide. Interestingly, breast cancer incidence varies dramatically among countries. Japan, in particular, has relatively low breast cancer (BC) rates when compared to those in Western countries. Daily consumption of seaweed has been proposed as one of the factors in explaining the difference in incidence rates of BC. The high concentrations of polysaccharides in seaweed have been reported in many studies to have anti-cancer effects as well as chemoprotective effects. The aim for this review is to look at the potential benefits of seaweed consumption and its effect on breast cancer.

Methods: Exhaustive search of available medical literature was performed using MEDLINE-Ovid, Science Direct, Web of Science and CINAHL. Keywords used included: breast cancer, breast neoplasm and seaweed. Studies were assessed for quality using GRADE criteria.

Results: The systematic literature search yielded 311 articles for review. After screening the titles and abstracts, 3 articles met the eligibility criteria. Two of the studies were randomized control trials and 1 was a case-control observational study. These studies showed an association between seaweed consumption and lower rates of breast cancer.

Conclusion: Daily consumption of seaweed may play an important role in decreasing the incidence of breast cancer in women.

Keywords: Seaweed, breast cancer, breast neoplasm

Acknowledgements

To our family and friends, thank you for all your support.

Table of Contents

List of Tables

List of Abbreviations

BC	Breast cancer
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
uPAR	Urinary human urokinase plasminogen activator receptor
IGF-1	Insulin-like growth factor
P1/P2	Placebo
ER+	Estrogen-receptor positive
ER-	Estrogen-receptor negative

Seaweed Consumption and Its Effect on Breast Cancer

BACKGROUND

Breast cancer remains the most common cancer in women worldwide. Interestingly, breast cancer incidence varies dramatically among countries. The biggest consumers of seaweed today are in Asia and include Japan, China, Korea, and the Philippines.[1] Japan, in particular, has relatively low breast cancer (BC) rates when compared to those in Western countries. When comparing rates of BC between Japan and the United States, the rates are much higher in the US. According to the US Cancer statistics 2008 working group, the average BC incidence rates in US women is 118 per 100 000, whereas Japan has an average of 20 per 100 000.[2] Although genetic predisposition has been proposed as part of BC susceptibility, this difference is also thought to be related to dietary preferences. Seaweed, in particular, has been proposed as one of the dietary factors in explaining the lower rates of BC in Japan.

Seaweed is consumed on a daily basis in traditional Japanese diets. It is often incorporated in different types of meals such as soups, garnishes, teas, sauces, or salads. It is estimated that an average person in Japan consumes about 7.3 grams of seaweed per day.[3] The high contents of polysaccharides in seaweeds have been

suggested to have anti-cancer effects.[4] Fucoidan, a natural polysaccharides found in brown seaweed *Laminaria*, has been shown to inhibit cancer growth through induction of cell cycle arrest and apoptosis.[5] In addition to it's anti-cancer effects, fucoidan has also been shown to have a protective effect against the toxicity associated with chemotherapy and radiation. Ikegushi et al examined the effect of fucoidan on colorectal cancer patients who received 5-fluorouracil as part of their treatments. The group of patients who received 6 months of liquid fucoidan reported no side effects such as allergic dermatitis from chemotherapy. They also reported significant decrease in generalized fatigue from 60% to 10% when compared to the control group.[8]

Thus, there is considerable interest in associations between high seaweed consumption and breast cancer risk. The aim for this review is to evaluate the benefits of seaweed consumption and its protective effects against breast cancer.

METHODS

A comprehensive literature search was completed using MEDLINE-Ovid, Science Direct, Web of Science and CINAHL. Completion of the search was done using the terms "breast cancer",

"breast neoplasm", "seaweed" and "study". The titles and abstracts

from the search were evaluated for inclusion based on eligibility

criteria. The references from relevant articles were also evaluated for

inclusion. The eligibility criteria consisted of literature assessing

seaweed and its effects on breast cancer on human subjects, use of

the English language, and study completion within the last 15 years.

Literature included in the review were evaluated for quality of evidence

using the Grading of Recommendations, Assessment, Development

and Evaluation (GRADE) Working Group Guidelines.[6] The level of

evidence from each article was downgraded as needed based on its

limitations, indirectness, inconsistency, imprecision and publication

bias. Additional evaluation for observational studies included quality

upgrades based on large magnitude of effects, dose-response gradient

and plausible confoundings.

RESULTS

The systematic literature search yielded 311 articles for review.

After screening the titles and abstracts and eliminating duplicates, 3

articles met the eligibility criteria and were included in the review.

There were two randomized control trials[8, 9] and one case-control

observational study[4] (See Table 1). The search yielded multiple studies

which evaluated the effects of seaweed on breast cancer but the subjects were non-human leading to the exclusion of these studies from the review.

Yang et al

Yang et al[4] is a retrospective observational study evaluating the relationship between seaweed consumption, specifically gim and miyeok--which are the 2 most common types of seaweed consumed in Korea--and the risk of breast cancer. The study participants included 362 Korean women between the ages of 30-65 years. Cases and controls were recruited between October 2004 through June 2006. Cases included Korean women who were histologically confirmed to have breast cancer and controls were patients recruited from other clinics within the same hospital. Both cases and controls were interviewed by questionnaires about their "general characteristics, menstrual and reproductive history, family history of breast cancer, smoking and drinking habits, intake of multivitamins, the average time spent on exercising" and dietary intake. Dietary intake was collected by a food frequency questionnaire (FFQ) which included 121 food items, 2 of which were gim and miyeok.[4]

The amount of gim consumed was evaluated by quintiles and frequency and the amount of miyeok consumed was evaluated by quartiles and frequency as there was not enough miyeok consumed to

group them into quintiles. From the data collected, 3 models of comparison were used to evaluate the relationship between seaweed consumption and the risk of breast cancer. The study first assessed the quintiles of gim intake and the quartiles of miyeok intake with the risk of breast cancer. The first model did not apply any adjustments. The second model applied adjustments to variables that were significantly different which included multivitamin intake, number of children, breastfeeding, education, exercise and oral contraceptive use resulting in an OR of 0.43 (95% CI, 0.26, 0.70) for the last quintile (P for trend, 0.002).[4] The third model adjusted further dietary factors which included consumption of energy, ß-carotene, vitamin C, folate, vitamin E, and soya protein. After adjustments of the confounding factors, an inverse correlation between gim intake by quintiles and the risk of breast cancer was seen within all 3 models (OR, 0.47; 95% CI. 0.29, 0.75 for the last quintile in comparison with the lowest quintile; P for trend, 0.003). The frequency of gim intake was also analyzed with the same 2 models. The first 2 models also showed an inverse relationship with the risk of breast cancer and gim intake until the third model in which there was no significant relationship. The frequency and quartiles of miyeok intake did not show any correlation with the risk of breast cancer when analyzed within the 3 models above.[4]

Teas et al (2011)

Teas et al,[8] a randomized control trial study, was completed to evaluate the relationship between seaweed and soy intake and levels of IGF-1. IGF-1 is an important biomarker associated with increased risk of postmenopausal breast cancer according to a meta-analysis done on 17 studies. The study participants included healthy postmenopausal women of European-American descent. Recruitment into the randomized, placebo-crossover study was done by word of mouth, physician referral, and newspaper ads. Of the 33 women who enrolled in the study, only 30 fit the inclusion criteria. Three women were excluded as they were currently on tamoxifen which is known to decrease IGF-1 levels.[8]

Thirty women were randomly assigned into placebo and treatment groups by a computer generator. The groups were divided into 5 g/day of seaweed powder (10 capsules) or 5 g/day of maltodextrin for 7 weeks. During the 7th week of the 5 g/day of either seaweed or maltodextrin, participants were also required to take a daily soy supplement. After the 7 weeks there was a 3-week washout period followed by switching to the alternate treatment for an additional 7 weeks. At the end of each treatment period, fasting blood samples were taken for IGF-1 testing.[8]

Analysis of the results was done using simple descriptive statistics. Of the 30 women, only 27 completed the entire study. The data from the first 3 collections of the 3 women who withdrew from the study was included in the end results. This was possible as the study met criteria for the intention-to-treat approach. Two withdrew due to mild side effects, 1 from gastroesophageal reflux and the other from a skin rash and itchy eyes. The third woman withdrew due to recommendations from her naturopathic provider.[8]

The end results yielded a significant difference in IGF-1 levels which increased based on whether they took the placebo or seaweed with soy. With placebo intake, the mean IGF-1 level was at 16.9 nmol/L and increased by 25% when soy was added during the 7th week (21.2 nmol/L for soy vs 16.9 nmol/L for placebo; P = 0.0001). With seaweed and soy intake, the mean level of IGF-1 increase was reduced by about 40% (21.2 nmol/L for soy alone vs 19.4 nmol/L; P = 0.01).[8]

Teas et al (2013)

This randomized control study[9] aimed to evaluate the effect of dietary seaweed on levels of urinary human urokinase plasminogen activator receptor (uPAR) in 15 healthy, postmenopausal American women. Increased concentrations of uPAR have been found to be associated with the rapid progression of BC. Participants, aged 50-66

years old, were recruited to a single-blinded placebo-controlled study for 3 months through Palmetto Health Tumor Registry.[9]

All 15 participants had a negative mammogram for BC and did not consume dietary seaweed on a normal basis. Five who had never been diagnosed with BC were placed in a control group and the other 10 were BC survivors who were placed in either an estrogen receptor positive (ER+) group or estrogen receptor negative (ER-) group. Participants ingested 10 capsules (5 g/day) of placebo (P1) filled with maltodextrin for 1-month, then seaweed (*Undaria*) for 1-month (S), followed by a placebo washout period (P2) for 1 month. Blood and urine samples were obtained at the end of each treatment period. The concentration of uPAR was then analyzed by ELISA. The evaluation of uPAR levels was used in this study as a possible biomarker for protective properties of seaweed against BC.[9]

Following seaweed supplementation, all 3 groups showed a decreased in urinary uPAR concentrations by about 50%; however, the concentration was reversed after the second placebo treatment. P1, 1.5 (95% CI, 0.9-2.1); S, 0.9 (95% CI, 0.6-1.1); and P2, 1.7 (95% CI, 1.2-2.2)

DISCUSSION

Breast cancer has been one of the most prevalent cancers among women for many years. Despite the advances in early detection and treatment, it continues to take thousands of lives each year in the US. When comparing incidences of BC, there is a decrease in rates of breast cancer among women in Japan versus women in the US.[9] This profound finding has been proposed to be caused by the differences in dietary intake, specifically seaweed. This has led to multiple studies evaluating the potential use of seaweed as an anti-cancer agent. According to the 3 studies in this systematic review, seaweed has been found to be a possible contributing factor in decreasing the risk of breast cancer.

The first of the 3 articles reviewed, Yang et al,[4] was a case-control study looking at dietary intake of seaweed and the risk of breast cancer. The study overall was done well and took into consideration 3 models of adjustments to allow for confounding factors. Despite the adjustments, it is a retrospective observational study relying on patient recall which makes it less reliable. Participants were asked to recall their diet intake during a 12-month period within the last 3 years which may lead to inaccuracy of answers. The questionnaire used open ended questions which may lead to

differences in interpretation between participants. The population

studied included a broad range of women between the ages of 30 and

65 and was based in 1 hospital which may restrict the ability to apply

findings to the general population. The article also did not include

detailed information on data collection. The differences in diet between

women who participated in the study and women who did not may

also be another limitation. Yang et al[4] only evaluated 2 types of

seaweed and excluded others which are commonly consumed as well.

Additional studies are needed to evaluate more types of seaweed

consumed in various populations to be able to further evaluate its

potential. The study found a significant relationship between gim

intake and the decreased risk of breast cancer, but because it is a

retrospective observational study, the correlation does not give a

concrete relationship that seaweed consumption is the cause of

decreased risk of breast cancer. Despite the limitations with Yang et

al,[4] the dose dependent relationship between gim intake and

decreased risk of breast cancer is promising and warrants additional

studies to further evaluate its potential.

The second article reviewed, Teas et al (2011),[8] studied the

effects of soy and seaweed consumption on IGF-1 levels. The study

included a randomized, placebo-controlled crossover design.

Treatment allocation was blinded with computer generation. All

participants began the study with the same prognostic variables including age, BMI, weight, physical exercise, parity, breast cancer treatments, and baseline IGF-1 levels. Despite the positive aspects of the study mentioned above, there were a few limitations affecting it's quality. There was only a total of 30 women who completed the entire study. The small number of participants were of European-American descent and were recruited from Massachusetts limiting the applicability to those of Asian-Western descent. This would be important to include as the Asian diet, specifically Japanese and Koreans, most commonly include seaweed and soy in their diets. Including Asian-Americans in the study could possibly reveal further significant findings. Teas et al (2011)[8] only included 1 type of seaweed, Alaria esculenta (L.), which can only be found in Ireland or Great Britain. This also limits the applicability of findings as this seaweed is not commonly consumed around the world. The dietary intake of the participants is unknown which can significantly affect the levels of IGF-1. IGF-1 levels are known to be affected by tomatoes, dairy and green tea. By evaluating their dietary intake, adjustments could be made if there are any significant differences in diets affecting the outcome. The end results overall yielded a significant difference depending on placebo or seaweed intervention. Although the baseline and follow up IGF-1 levels were all within normal range, there was a

reduction in the level of IGF-1 increase with seaweed. Despite the

limitations, the results are promising and should be further studied

with a larger sample size, inclusion of women from various

backgrounds, and evaluation of other dietary factors.

The last article reviewed was another study done by Teas et al

(2013).[9] The study evaluated the effects of seaweed on urokinase-type

plasminogen activator receptor (uPAR). The increased concentrations

of uPAR have been associated with the presence of breast cancer and

poorer prognosis.[9] The study included a single-blinded, placebo-

controlled design but did not mention how treatment allocation was

performed. Adherence to the treatment was maintained with clinic

visits and urinary iodine testing. Participant demographics had no

significant differences but there were some important differences with

prognostic variables. Participants who had survived breast cancer had

higher levels of FSH indicating possible variables in hormone levels

which can affect outcomes. The study also tested the effects of only 1

type of seaweed, Undaria pinnatifida, which is most commonly eaten

in Japan. Only seaweed with the highest amounts of fucoidan, a

component of seaweed found to have anti-cancer effects, was used in

the study. This left out other common types of seaweed that are also

commonly eaten in Japan. Dietary variables were also not included and

could have affected the levels of uPAR tested. The study included a

small sample size of 15 participants limiting precision. The uPAR levels were found to decrease by about 50% with 5g/day of seaweed.

All 3 studies found significant relationships between seaweed consumption and the risk of breast cancer. They each evaluated a different type of seaweed making it difficult to determine which one is the most effective in decreasing the risk of breast cancer. Yang et al,[4] despite being a case-control study, had a significant dose response gradient. The following 2 randomized control trials[8,9] had the same author leading to some publication bias and small sample sizes limiting their quality. Despite bias and small sample sizes, they both yielded interesting connections to cancer-related biomarkers which is promising for future studies. Although these studies support the potential use of seaweed consumption in decreasing the risk of breast cancer, further studies are needed before inclusion of seaweed in interventional practice.

CONCLUSION

Although the potential benefits of seaweed need to be further investigated, the studies suggest that there is a direct association between seaweed consumption and a decreased risk of breast cancer. Such findings provide a possible explanation as to why the incidence of BC remains lower in the seaweed-consuming populations. However,

the vast variety of seaweeds as well as different ways that they are

consumed make it difficult to estimate which type of seaweed and the

actual daily intake it would require to obtain anti-cancer effects. It

should also be noted that each species of seaweed is made up of

different biochemical compositions. Thus, the effects reported in the

studies only applied to particular types of seaweed*, Porphyra sp and*

Undaria. Although the mechanisms in how seaweed provides

protective effects against breast cancer is not fully understood, this

review has compiled some evidence that seaweed could play a critical

role as a source of anti-cancer agent.

References

1. Yuan Y (2008) Marine algal constituents. In: Shahidi F and Barrow C(eds) Marine nutraceuticals and functional foods. CRC, Florida

2. US Cancer Statistics Working Group (2007) United States Cancer Statistics: 2004 Incidence and Mortality. U.S. Department of Health and Human Services CfDCa, Institute PaNC, Atlanta

3. Teas J. The dietary intake of laminaria,a brown seaweed, and breast cancer prevention. *Nutrition and Cancer*. 1982;4(3):217-222. doi:10.1080/01635588209513760.

4. Yang YJ, Nam S-J, Kong G, Kim MK. A case–control study on seaweed consumption and the risk of breast cancer. *British Journal of Nutrition*. 2010;103(9):1345-1353. doi:10.1017/S0007114509993242

5. Atashrazm F, Lowenthal RM, Woods GM, Holloway AF, Dickinson JL. Fucoidan and Cancer: A Multifunctional Molecule with Anti-Tumor Potential. Mar Drugs. 2015;13(4):2327-2346. doi:10.3390/md13042327.

6. Ikeguchi, M.; Yamamoto, M.; Arai, Y.; Maeta, Y.; Ashida, K.; Katano, K.; Miki, Y.; Kimura, T. Fucoidan reduces the toxicities of chemotherapy for patients with unresectable advanced or recurrent colorectal cancer. Oncol. Lett. 2011, 2, 319–322

7. GRADE home. http://gradeworkinggroup.org/. Accessed July 18, 2018.

8. Teas J, Irhimeh MR, Druker S, et al. Serum IGF-1 Concentrations Change With Soy and Seaweed Supplements in Healthy Postmenopausal American Women. *Nutr Cancer*. 2011;63(5):743-748. doi:10.1080/01635581.2011.579383

9. Teas J, Vena S, Cone DL, Irhimeh M. The consumption of seaweed as a protective factor in the etiology of breast cancer: proof of principle. *J Appl Phycol*. 2013;25(3):771-779. doi:10.1007/s10811-012-9931-0.

10. Murphy C, Hotchkiss S, Worthington J, McKeown SR. The potential of seaweed as a source of drugs for use in cancer chemotherapy. Journal of Applied Phycology. 2014;26(5):2211-2264.doi:10.1007/s10811-014-0245-2.

Table 1: Quality Assessment of Reviewed Articles

Outcome	Number of studies	Study Designs	Downgrade Criteria					Upgrade Criteria	Quality
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Risk of Breast Cancer	1	Observation	Not serious	Not Serious	Not Serious	Serious[a]	Not likely	Dose-Response Gradient	Very Low
IGF-1 levels	1	RCT	Not serious	Serious[b]	Not Serious	Serious[a]	Likely[c]	None	Very Low
uPAR levels	1	RCT	Not serious	Serious[b]	Not serious	Serious[a]	Likely[c]	None	Very Low

[a] Small sample size
[b] Reliance on surrogate outcomes
[c] Same authors published both RCTs.