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Visceral obesity measured by Computed Tomography and breast cancer

비만으로 인한 유방암 발생의 영향 연구: 복부비만도 측정과 그 외 생활 요인

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ABSTRACT

Visceral obesity measured by Computerized Tomography and breast cancer

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Cancer statics in Korea has been the highest causes of death with steadily increasing. In annual rate of change, the most prevalent cancer was breast cancer in female. Incidence rates of breast cancer have been rising in South Korea, with change in intake of high fat western diet, reproductive patterns, lack of physical activity, obesity, and rising stress level the main contributory. Therefore to find obesity as risk factors on breast, assess proper to usual dietary intake, estimated abdominal obesity, and related personality factors.

The study was case – control study and approved by the Institutional Review Board of the National Cancer Center (NCC2014-0124). The patient groups were set as newly diagnosed cancer patients (breast cancer who visited at the Korean National Cancer Center hospital from August 1st, 2014 to May 29th, 2015. Undiagnosed cancer person as control group, who visited Korean National Cancer Center hospital for the health examination service by national health insurance from September 1st, 2011 to September 30th, 2014.

The breast cancer patients were 255 female aged ranges from 32 to 82 years with a mean age of 52.6 years old and that of the control participants were 222 female aged ranges from 27 to 62 years with a mean of 52.3 years old. All cancer patients were only for a newly diagnosed cancer without any related to cancer treatment as take any chemotherapy, radiation therapy and surgery before the start of the study.

Dietary intake was assessed with the semi-quantitative food frequency questionnaire (FFQ) method (developed for cancer research in Korea) at the onset of this validation study in 2012. All participants were asked to an additional question about behavior questionnaire (regular dietary pattern, family history, breast feeding, parity, physical activity, other disease, stress level, hobby, smoking, alcohol, level of education, menarche and menopause) with FFQ.

All CT examinations of related breast cancer study were

performed on the 64-Multi detector row computed tomography system (Lightspeed VCT, Discovery HD 750; GE Healthcare system, Milwaukee, WI, USA). Measuring abdominal fat was used to approximate a level at the umbilicus or the fourth lumbar vertebra, which is a valid virtually all the information on abdominal fat in human.

Breast cancer patients had a lower dietary fiber intake (adjusted for total calories, $p = 0.003$), moderate higher animal lipid, and higher abdominal fat ratio than control groups. Abdominal fat ratio is more effect on premenopausal women for risk of breast cancer than in postmenopausal women.

There were no significant associations between personality factors (physical activity, menarche, BMI, and stress perception) and breast cancer risk, while risk of breast cancer was a positive first degree of family history with moderate and moderate inverse association with education level. Effect of physical activity was show stronger inversely association in hormone positive groups. There were no significant associations of smoking and alcohol consumption to incidence of breast cancer.

However, compared normal subjects, breast cancer patients have more association between breast cancer risks and increased in abdominal fat. Breast cancer risk was positive associated with obesity in total women, also the more positive associated with obesity categorized in post-menopausal women. While obesity may influence breast cancer risk in post-menopausal women, the

opposing effects that association between breast cancer and pre-menopausal women when obesity is protective for breast cancer risk. Abdominal distribution fat is metabolic indicators in breast cancer women, and may play a role in the pre-menopausal breast cancer risk (Harris et al., 2011), though more effect of visceral fat on breast cancer incidence in post-menopausal women.

There were no correlation between total calories intake and all of anthropometric measurements (BMI, abdominal fat ratio). Abdominal total fat was highest positive correlation with all of anthropometric measurements $p < 0.001$), exclude abdominal fat ratio ($r = 0.43$).

To know cancer mortality, subjects were categorized into two groups by histological grade score (< 2, ≥ 2)), high histological grade patients were marginal negative relation with intake of dietary fiber ($p = 0.06$ for adjust for total calories). Abdominal fat ratio was statistical significant difference in low and high breast cancer malignant.

In conclusion, this study shows clear association of breast cancer with high dietary animal fat and low dietary fiber intake. In addition, abdominal fat ratio is useful as an indicator of risk factor on breast as well malignancy.

Key words: Breast cancer, CT, obesity, fat ratio, FFQ

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Chapter I. Introduction

1. Background

As the economy developed, people have more plenty of food to eat and improved living standard than past in South Korea. As not happy for affluent living standards, we have faced with problem to solve which adverse effects from increased in malnutrition, inactive lifestyle pattern, and psychological stress due to changing complicated society (The Korean National Health and Nutrition Examination Survey : KNHANES 2010; Hong et al., 2011). In accordance with increasing total caloric intakes and decreasing physical activity, prevalence of overweight (body mass index, BMI $\geq$ 25 kg/㎡) and obesity (BMI $\geq$ 30 kg/㎡) were in Korea has been continue to increase, reached 55% and 32% respectively, in aged over 20 years in KNHANES 2010 (Figure I-1). Especially in obesity was continuing to increase with all of gender but overweight was only with male continues to grow (Figure I-2).

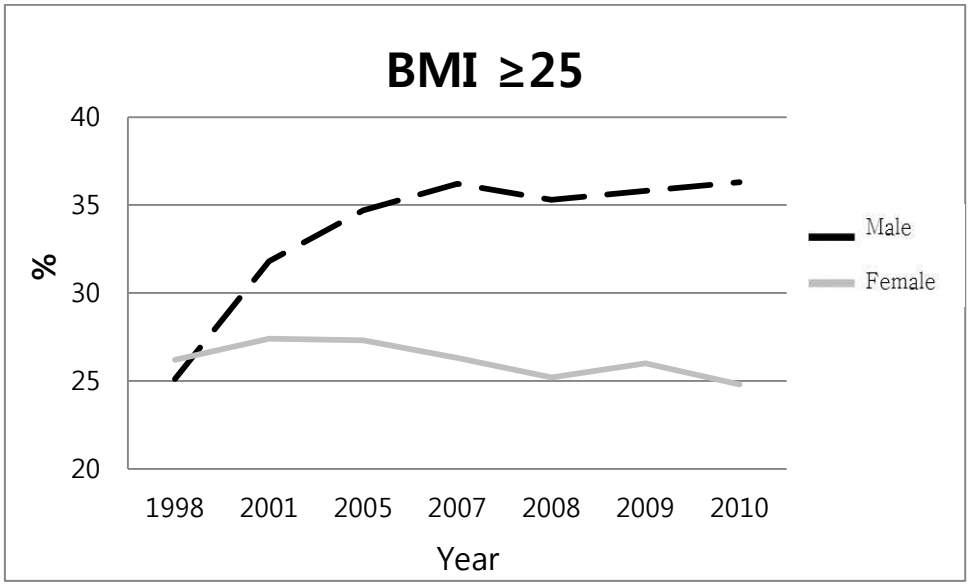


Figure I-1. Trends in overweight among Korean adults (BMI ≥ 25) (KNHNES 2010).

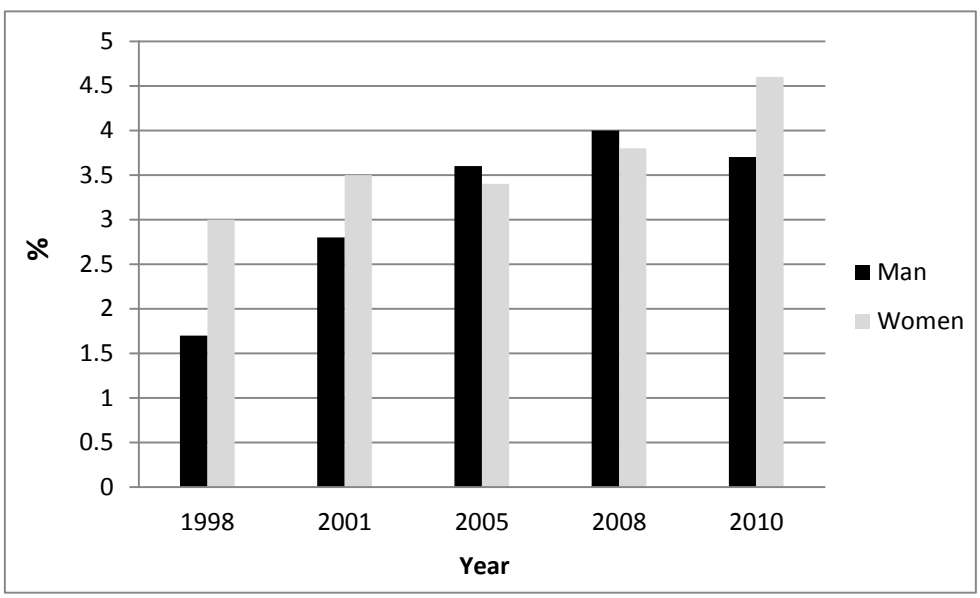


Figure I-2. Trends in obesity among Korean adults (BMI ≥ 30) (KNHNES 2010).

There are many risk factors for cause of cancer; human carcinogens include smoking, asbestos, aflatoxins and radiation, associated with chronic infections include hepatitis virus (HBV, HCV), papillomaviruses (HPV) and Helicobacter pylori. In addition to the recent rising recognition, role of lifestyle factors including diet, physical activity, and alcohol consumption (World Cancer Research; WCR). Furthermore, 30-40% of all cancer cases could be reduced by optimal nutrition, regular physical activity and the prevention of obesity (World Cancer Research Fund/American Institute for Cancer Research 1997; Stewart and Kleihues, 2003). In Figure I-3, "World cancer report 2003" announced overweight and obesity from diet and report estimates for the causes of cancer. In addition, the American Institute for Cancer Research and WCR reported that there is evidence for a relation between obesity and postmenopausal breast cancers (Freedland and Platz. 2007).

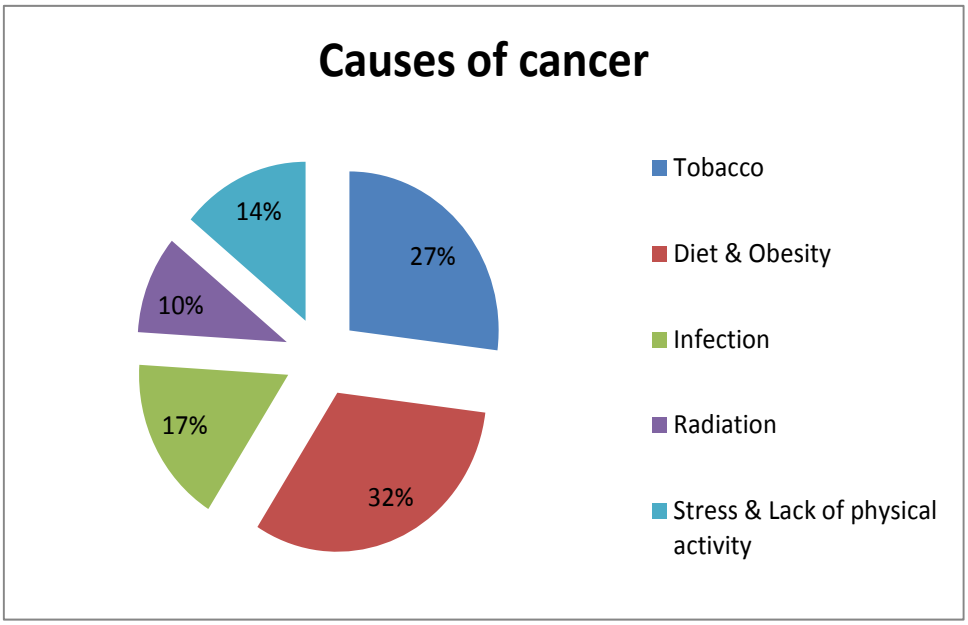
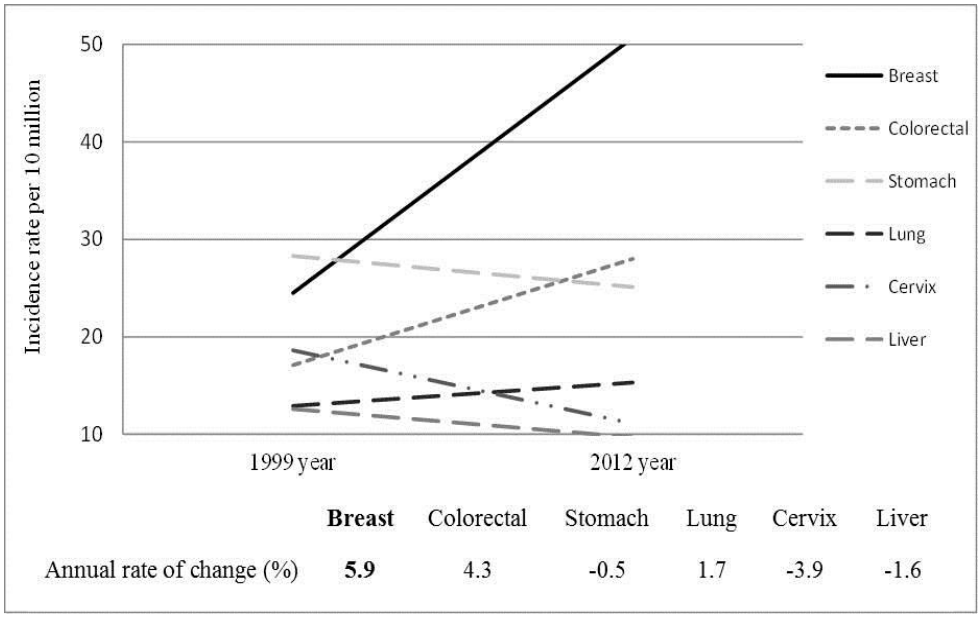


Figure I-3. Estimated percentage of cancer causes (World cancer report 2003).

Cancer statics in Korea has been the highest causes of death with steadily increasing since 1983 (Korea National Statistical Office 2009; Korean National Cancer Information Center 2014). Age-standardized rates of major cancer incidence in male were highest for stomach cancer (61%), followed by colorectal cancer (51.4%) lung cancer (45%), liver cancer (35.2%), and prostate cancer (27%) and for female were breast cancer (120.4%), colorectal cancer (28%), stomach (25.1%), lung cancer (15.3%), cervix cancer (11.1%), and liver cancer (9.7%) exclude thyroid cancer (Korean National Cancer Information Center 2014). But in annual rate of change (%), the most prevalent cancer was breast cancer (5.9%) in female and prostate cancer (11.4%) in male

(Figure I-4, 5)(Korean National Cancer Information Center 2014). Also in worldwide, breast cancer is the most frequently and the second most diagnosed cancer in each sex, and responsible for 23% (1.38 million) and 14% (903,500) of the total new cancer cases in 2008 in respectively (Boyle et al., 2008).

Incidence rates of breast cancer has been rising in South Korea, with change in intake of high fat western diet, reproductive patterns, lack of physical activity, obesity, and rising stress level the main contributory factors (Antoni et al ., 2006; Stewart et al., 2003; Boyle et al., 2008; KNHANES 2010; Korean National Cancer Information Center 2014). Similar results shows from migrants studies as a shifting pattern, there are evident migrant from low-risk countries to areas of higher risk show remarkable increases in the incidence rates (for example, Korean, Chinese, Filipino, Filipino, Vietnamese, and Japanese living in the United States)(McCracken et al.,2007).



	Breast	Colorectal	Stomach	Lung	Cervix	Liver
Annual rate of change (%)	**5.9**	4.3	-0.5	1.7	-3.9	-1.6

Figure I-4. Trends in incidence rate of female major cancers exclude thyroid cancer (From Korean National Cancer Information Center 2014).

Meanwhile, in most prospective studies for relation between obesity and risk of cancer, analysis has been approach to the limited due to using a single method of obesity obtained from nutrient intake or estimated of abdomen or BMI. Therefore these have cannot help studying with limitation of relation between obesity and cancer due to no proper research not only a complex factor affecting for obesity also obesity as a risk factor for cancer. As a result, obesity research is necessary to evaluate this relation in more detail of increased risks of cancer, thorough out the research on overall obesity factors (abdominal fat, nutrient intake, physical activity, stress).

1.1. Obesity and cancer risk

Although obesity has been recognized as cause of type II diabetes and cardiovascular diseases, the relationship between obesity and cancer has received less attention than its other disease effects (Stewart and Kleihues, 2003; von Hafe et al., 2004; Hamilton et al, 2011; Vona-Davis et al., 2007). According to previous study, higher Body Mass Index (BMI) are a greater affect the cancer risk than are those with low BMI (Stewart and Kleihues, 2003; Renehan et al, 2008; Lahmann et al, 2004) Especially, there was strength relation between BMI and colorectal, breast cancer incidence than any other cancers (Lahmann et al, 2004; Wright et al, 2007). Many epidemiological studies indicate that adiposity contributes to the increased incidence of cancer, and assessed that 15-20% of all cancer deaths in the United States. (Calle et al., 2003; Stewart and Kleihues, 2003; Calle and Kaaks. 2004). Postmenopausal breast cancer patients (post-menopausal) with BMI $\geq$ 40.0 have death rates that are three times higher than very thin patients with BMI < 20.5 (Petrelli et al., 2002)but negatively associated with risk of premenopausal breast cancer (Weiderpass E et al., 2004 ; Michels et al., 2006). The mechanisms for the negative association are poorly understood. Previous researches have shown associations between body fat distribution and hormone levels and metabolic markers in women with a range of BMIs, sug-gesting that body fat distribution may play a role in the risk of

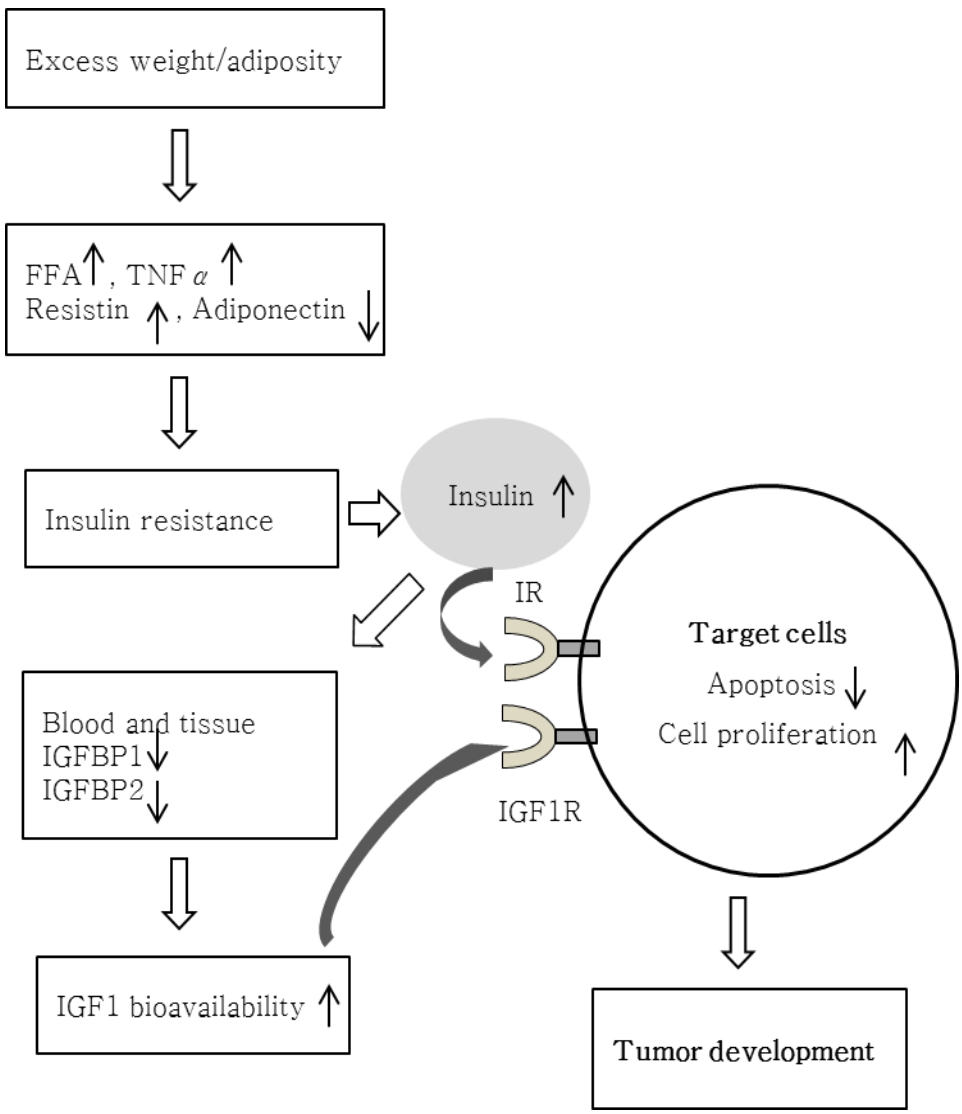
premenopausal breast cancer (Holly et al., 2011). Also obesity with breast cancer patients is associated both with reduced likelihood of survival and increased likelihood of recurrence, irrespective of menopausal status and after adjustment for clinical stage and therapy (Rock and Denmark. 2002; Stephenson and Rose. 2003).

However general known that abdominal obesity, defined by BMI measurement was not ideal reflect the amounts and the site of deposition of the adipose in comparison to measurement obtained from Computed Tomography (CT) is not better predictor of cancer incidence (Weits et al., 1998; van der Kooy et al., 1993; Pickhardt et al., 2012).

Adipose tissue has composed of subcutaneous and visceral. Subcutaneous adipose is the defined as layer of subcutaneous tissue, whereas visceral adipose is within the main cavities of the abdomen known as organ fat or intra-abdominal fat. Visceral adipose is more metabolically active than subcutaneous adipose, as it has high lypolytic activity and release large amounts of free fatty acids (Heymsfield et al., 2004); so optimal measurements of adipose would consider both the amounts and the site of deposition of the adipose (Calle and Kaaks. 2004). Generally similar age, gender, BMI has same % body fat distribution. But despite their similar BMI or WC, visceral fat content has variation in age, sex, and race (Camhi et al, 2011).

The assessment of fat distribution has important issue in obesity research because this visceral fat seems to be most

strongly associated with not only metabolic disorders but also cancer (von Hafe et al, 2004; Hamilton et al, 2011; Vona-Davis et al, 2007).



FFA: free fatty acids; TNF α: tumor-necrosis factor-α; IGF1: insulin-like growth factor 1; IGFBP: IGF-binding protein; SHBP: sex hormone-

binding globulin; IR: insulin receptor.

Figure I-5. Mechanism of obesity on growth-factor production to cancer development (Calle and Kaaks 2004).

Figure I-5 show that effects of obesity on act as tumor development. Grown release from adipose tissue of free fatty acids (FFA), tumor-necrosis factor-α (TNFα) and resistin, and reduced release of adiponectin contribute to the development of insulin resistance. Increased insulin levels lead to insulin-like growth factor binding protein 1, 2 (IGFBP 1, 2), and cause upturn level of IGF 1 bioavailability. Results in, high level of insulin and IGF 1 signal to promote cellular proliferation and inhibit apoptosis in many tissues so that might leads to tumorigenesis (Calle and Kaaks 2004).

1.2. Risk factors on breast cancer

Recently in, breast cancer are show quite marked higher incidence rate in each sex in South Korea that having common or similar to factors (positively associated with risk of cancer suggested by epidemiologic studies) such as dietary animal fat intake, as opposed intake of vegetable and fruits, alcohol, obesity, family history, environmental or life-style, stress hormone and age, except different characteristics of disease dependent sex (Willett 1997; Stewart and Kleihues 2003; Ferlay et al., 2004; Bostwick et al., 2004; Korean National Cancer Information Center 2014).

Table I-1 shows that detail of risk factors breast cancer with relative risk.

Table I-1. Risk factors on breast cancer (McPherson, et al., 2000; Boyle et al 2008)

Factor	Relative risk	High risk group
Age	>10	Elderly
Age at menarche	3	Menarche before age 11
Age at first full pregnancy	3	First child in early 40s
Family history relative when young	>2	Breast cancer in first degree
Previous benign disease	4-5	Aypical hyperplasia
Cancer in other breast	>4	
Diet	1.5	High intake of saturated fat
Body weight (postmenopasusal)	2	BMI>35
Alcohol consumption	1.3	Excessive intake
Exposure to ionizing radiation	3	Abdonrmal exposure in young females after age 10
Oral contraceptives	1.24	Current use

Hormone replacement therapy	1.35	Use for ≥10 years
Diethylstibestrol	2	Use during pregnancty

1.3. Characteristics of nutrient intake and stress in south Korea

According to the KNHANES, average daily intake of animal foods was 8.7 fold increases from 32g in 1969 to 278.6g in 2005 and during the same period, fat intake was 2.7 fold increases from 16.9g to 46g (Kim et al. 2009). In accordance with changing nutrient intake, annual incidence rates per million persons on breast cancer was second fold increases from 24.5 persons in 1999 to 50 persons in (Ministry of Health and Welfare 2007, 2010).

Additionally characteristic of malnutrition in South Korea is long time and distance commute at city, increased in women's social activity, growing eat out and irregular dietary pattern include starving the morning, sustainable growth total energy intake, and increased alcoholic drink(Hong et al. 2011; Kim 1996; Kang et al. 2011). Especially in frequency eat out can cause overeating and over intake of fat and sodium nutrient than in house (Na et al. 2010;

Song et al. 2013). Changing these eating habit are not only causing diabetes, hypertension, cardiovascular disease also risk factor to incidence of cancer (Hanf et al. 2005; Vucenik and Stains, 2012; Patel, 2014).

Meanwhile, Korea ' s annual suicide rate is trend in increasing and the most highest among Organization for Economic Cooperation for Development (OECD) (Korea National Statistical Office. 2014).

Stress can also risk factor drive for cancer. Therefore risen of cortisol level from psychological stress is not only largely responsible for the down regulation of immune system but also cause of breast cancer (Carlson et al., 2003).

2. Purposes

The purpose of this study was to conduct a case control study for normal subjects and cancer patients within a prospective and retrospective study on the risk factor and relation to breast cancer using combined the results from the abdominal fat ratio, Food Frequency Questionnaire (FFQ), and relevant to personality questionnaires data.

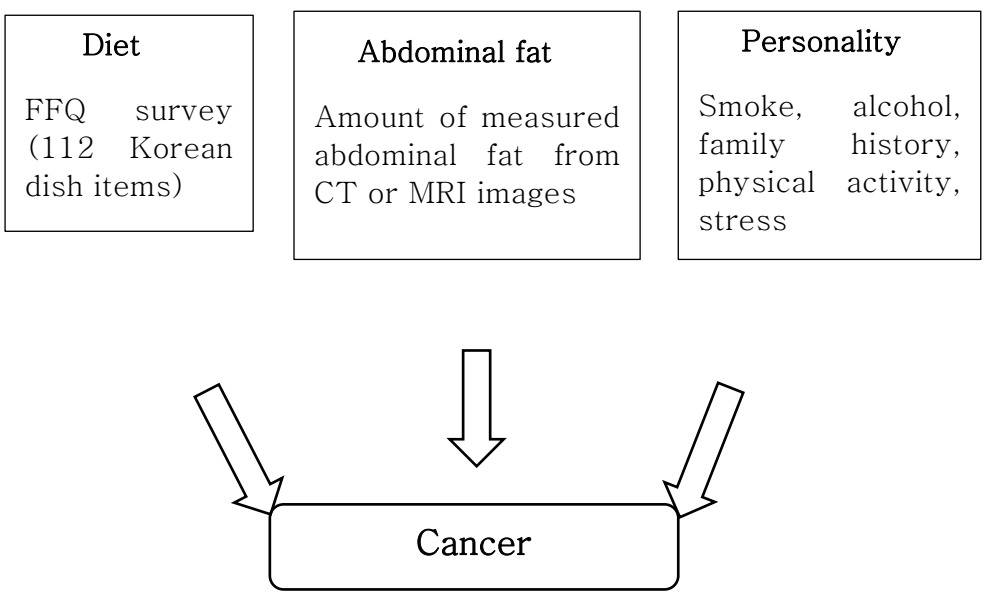


Figure I-6. Study scheme by affecting factor for cancer.

The details of purposes in this study are following;

1. To examine association between the dietary pattern and risk factor for cancer, evaluate the intake of cancer patients of nutrients estimated by semi-quantitative.

2. In order to examine the abdominal fat ratio by computed tomography (CT), verify linking presence of excess fat in the abdomen as a risk factor for cancer incidence.

3. In order to evaluate the association between statuses of behavioral characteristics included stress, physical activity level and spend leisure time and risk factor for cancer.

Chapter II. Risk factors on breast cancer

1. Introduction

World widely, breast cancer is the most incidence cancer among women and over 411,000 deaths results from breast cancer annually (Parkin et al., 2005; Stewart and Kleihues, 2003). Korea has low breast cancer incidence rates increased from 43.8 (per 100,000 women-years) in 2009 to 50.7 (per 1000,000 women-years) in 2012) compared with developed countries, but breast cancer is the first common cancer among women and recent incidence rates is trends in rising rapidly (Korean National Cancer Information Center 2014).

Actual rising breast cancer rates is due to adoption of western lifestyles that tend to promote delayed childbirth, decreased physical exercise, and intake of fatty dietary habits associated with earlier menarche, all of which have been associated with increasing rates of postmenopausal breast cancer (Cho et al., 2003; Bray 2004; Parkin 2006; Porter. 2008).

Breast cancers are often pathologic featured by estrogen and progesterone receptor status. On the basis of many studies, the incidence rate for estrogen receptor-positive cancers increasing trend intake of animal fat such as intake of red meat and high-fat dairy foods (heterocyclic amines in cooked meat, heme iron, exogenous hormone residues) effects on the risk of breast cancers through hormone receptors (Cho et al., 2003; Althuis et al., 2004; Cho et al., 2006).

Additionally, abdominal fat is linked to the development of

breast cancer result from higher levels of estrogen derived from aromatization of androstenedione within the larger fat stores (Harvie et al., 2003). Abdominal fat comprises subcutaneous and visceral compartment and correlate of the amounts of visceral fat and breast cancer risk due to mammary gland is affected by the estrogen level, visceral fat is usually positive correlated with levels of free steroid hormones, and the adipose tissue perform important endocrine function (La Guadia and Giammanco 2001; Stephenson and Rose 2003; Vucenik and Stains 2012). Therefore ideally measurement of the abdominal fat compartment on breast cancer risk should rely on technique such as CT (Weits et al., 1998; Pickhad et al., 2012). There are many factors and complexity contribute for abdominal fat accumulation but major factor of obesity is characterized by excess consumption of high energy dense food and sedentary lifestyle (stewart and Kleihues 2003; Jean and Isabelle 2006).

This study was case-control research, designed to assess obesity as a risk factor on breast cancer using usual dietary intake, estimated abdominal obesity, and related personality factors.

2. Materials and Methods

2.1. Study design and Subjects

This study is a case control and case only study with breast cancer patients who visited at the Korean National Cancer Center hospital from August 1st, 2014 to May 29th, 2015. Control group is normal healthy participants without cancer who visited Korean National Cancer Center hospital (NCC) for the health examination service by national health insurance and for the personal medical health check-up service from September 1st, 2011 to September 30th, 2014 and retrospective study. During that time, the total number of newly diagnosed breast cancer patient visiting NCC was 1887. Among them, the number of CT scanned patient was 256, which diagnosed for breast cancer work up, but exclude patients that performed on surgery, radiation, and chemo therapy in NCC or other hospitals. So the total number of patient is 256 female. In that case of control group, the number of visited NCC for the health examination service during that time was about 49000. Among them, the number of confirmed normal with CT scanned participant and fully filled questionnaire was 222. So the number of normal participant is 222 female.

The target participants were set as newly diagnosed with breast cancer and undiagnosed cancer person as control. The breast cancer patients were 256 female aged ranges from 32 to 82 years

with a mean age of 52.6 years old and that of the control participants were 222 female aged ranges from 27 to 62 years with a mean of 52.3 years old. All cancer patients were only for a newly diagnosed cancer without any related to cancer treatment as take any chemotherapy, radiation therapy and surgery before the start of the study. All normal participants were not take any medications and excluded if they had a personal history of cancer.

All of cancer patients were age matched with controls in case-control study. Case only study was conducted with all cancer patients (150 patients) for related histological grade. There was no significant difference in age between the cancer patients and control participants were closely matched.

2.2. Participants information

All patient's profile information (height, weight, tumor size, lymph node, estrogen, and progesterone receptor) obtained from institutional electronic medical record (EMR). Each subject's weight and height were gathered from the nurse's information sheet that was recorded at each admission interview to calculate for the BMI. BMI (kg^{-2}) was calculated as body weight in kilograms divided by height in meters squared. In addition to the patient's tumor size and lymphatic invasion data was established postoperatively by surgery and estrogen and progesterone receptor level obtained from blood sample report in EMR.

Histologic grade is associated with prognostic information or

malignancy in breast cancer and into 3 groups according to malignancy, including tubular formations (grade III), nuclear grade (grade II), and mitotic activity (grade I). The evaluation of this grade is determined by pathologists that tumor specimen from our institution the preoperative biopsy. Therefore this grade is used for malignancy factor on breast cancer according to obesity in this study also obtained from pathology report section in EMR.

The study was approved by the Institutional Review Board of the National Cancer Center (NCC2014-0124) and written informed consent was obtained from all participants.

2.3. FFQ

Many evaluation of dietary assessment instruments have been used to study how diet relates to cancers and chronic diseases. Of the many instruments used, FFQ have been the primary method in epidemiological studies to estimate individual long-term dietary intakes of foods and nutrients due to its ability to identify usual dietary patterns (Park et al, 2012; Mirmiran et al, 2010). Therefore the FFQ is designed to assess dietary variables that are hypothesized to affect the occurrence of obesity and cancer. Dietary intake was assessed with the semi-quantitative FFQ method (developed for cancer research in Korea) at the onset of this validation study in 2012. The current FFQ instrument consisted of 112 Korean dishes and foods which are highly consumed by

frequency and amount, or which contribute substantially to nutrition intake in adults based on the diet intake reported by participants in the KNHANES. And this FFQ is evaluated the validity and reliability at the Asian Pacific J Cancer Prev 2012;13(2):545-552.

The food items were listed in food and dish groups:

Grains-6 items; noodle and dumping -11; cereal and snack -5; sweets -5; Legumes - 6; nuts and seeds -12; potatoes -2 ; vegetables -32; kimchi - 8; mushrooms -4; soup - 5; fruits - 12; meat and its products -16; eggs -2; fish and shellfish - 21; seaweeds - 3; milk and dairy products - 4; beverage - 11. The consumption frequency (never or seldom, once a month, 2-3 times a month, one to two times a week, three to four times a week, five to six times a week, once a day, twice a day or three times or more every day) of categories diversified among dish types to allow participants to clarify their on a daily intake with greater specificity. The collected frequency for each food item was change a daily intake.

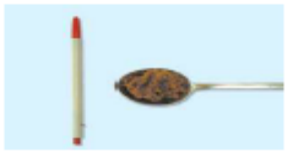
Figure II-1 show the use of FFQ example and Table II-1 listed food items of FFQ in this study.

(사진 4-1. 땅콩)

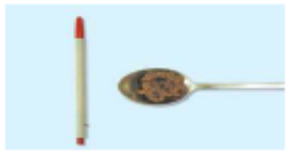
(사진 4-2. 땅콩)

(사진 4-3. 땅콩)

(사진 5-1. 된장)



(사진 5-2. 된장)



(사진 5-3. 된장)

	지난 1년간 평균 섭취빈도									평균 1회 섭취분량
	거의 안먹음	월		주			일			
		1회	2-3회	1-2회	3-4회	5-6회	1회	2회	3회	
케익/쇼코파이	○	○	○	○	○	○	○	○	○	○ 4개 ○ 1개 ○ 1개 반
피자/햄버거	○	○	○	○	○	○	○	○	○	○ 큰 것 4개 ○ 큰 것 1개 ○ 큰 것 1개 반
선식/미숫가루	○	○	○	○	○	○	○	○	○	○ 2큰술 ○ 3큰술/선식 1봉지 ○ 4큰술
쿠키/크래커/스낵	○	○	○	○	○	○	○	○	○	○ 반봉지 이하 ○ 반봉지 ○ 1봉지
사탕/초콜릿	○	○	○	○	○	○	○	○	○	○ 3개/반개 ○ 5개/한개 ○ 7개/한개 반
땅콩/아몬드/잣	○	○	○	○	○	○	○	○	○	○ 사진 4-1(반줌) ○ 사진 4-2(한줌) ○ 사진 4-3(한줌 반)
콩/콩자반 (초콩포함, 콩밥제외)	○	○	○	○	○	○	○	○	○	○ 사진 4-1(반줌) ○ 사진 4-2(한줌) ○ 사진 4-3(한줌 반)
된장국/청국장/된장/쌈장	○	○	○	○	○	○	○	○	○	○ 사진 5-1(1그릇) ○ 사진 5-2(1그릇) ○ 사진 5-3(1그릇 반)

Figure II-1. An example of semi-quantitative food frequency questionnaire included portion size aids consisting of pencil and a full-size picture

Table II-1. Listed in food items

Food or food group	Food items

Grains	White rice, multi-grain rice, Mixed multi-grain rice, Rice with beans, roasted and ground grains
Noodle and dumpling	Rice cakes, Ramyon (a Korean instant noodle), dumpling, Udong, Chinese noodle, Buckwheat noodles, Korean cold noodle, Rice cake soup, Stir-fried glass noodles and vegetables
Flour and bread	Bread, Sandwich, Toast, Red bean bread, Hoppang (a Korean red bean style bread), Sponge cake, Donut, Cream bread, Cake, Choco-pie, Pizza, Hamburger
Cereal and snack	Cereals, Snack, Biscuit, Cookies, Cracker
Sweets	Jam, honey, Sugar, Chocolate, Candy
Legumes	Soybean curd, Soybean milk, Tofu, Muk, Deodeok, Balloon flower
Nuts and seeds	Pine nuts, Walnuts, Peanuts, Almond, Bean, Doenjang, Doenjang soup, Cheonggukjang, Ssamjang, Bean sprouts, Perilla seeds
Potatoes	Potatoes, Sweet potatoes
Vegetables	Spinach, Lettuce, Perilla leaf, Salad, Spinach, Lettuce, Perilla leaf, cabbage, Kale, Chicory, Bok choy, Broccoli, Shepherd’ s purse, Beet, Curled mallow, Mugwort, Outer leaves, Bracken, Sweet potato beans, Pepper leaves, Brachycarpa,

	Seasoned aster, Crwon daisy, Chives, Water parsley, Cucumber, Carrot, Onion, Green chili, Green pumpkins, Aged amber,
Kimchi	Kimchi, Kkagdugi, Watery kimchi made of sliced radishes, Korean lettuce, Green onion kimchi, Pickled vegetables, Pickled radish, Chinese cabbage
Mushrooms	Oyster mushroom, Black mushroom, Button mushroom,
Soup	Ox bone soup, Beef-bone soup, Short rib soup, Beef stew, Yukgaejang
Fruits	Straw berry, Water melon, Melon, Peach, Plum, Banana, Persimmon, Mandarin, Pear, Apple, Orange, Grapes, Tomato
Meat and its products	Pork, Beef, Fried chicken, Ham, Sausage, Bacon, Bossam, Jangjorim, Sausage, Organ meats, Seonji, Sundae, Steak, Dog meat, Whole chicken soup, Whole chicken soup with ginseng
Eggs	Egg, Qualil egg
Fish and shellfish	Sashimi, Mackerel, Saury, Janpanese Spanish mackerel, Hairtail, Eel, Croaker, Sea bream, Halibut, Pollack, Squid, Small octopus, Anchovy, Tuna, Salted seafood, Shellfish, Whelk, Oyster, Fish cake, Blue crab, Shrimp

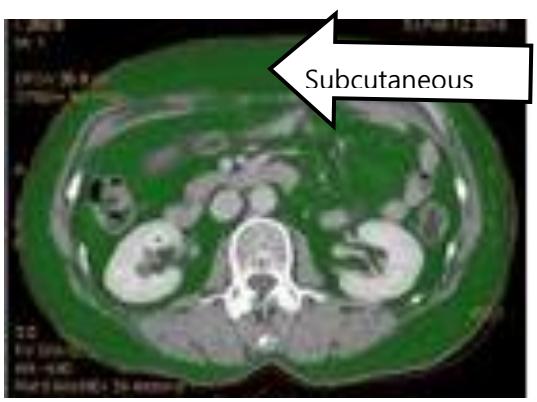
Seaweeds	Laver, Kelp, Sea mustard
Milk and dairy products	Milk, Yogurt, Cheese, Ice cream
Beverage	Coffee, Instant coffee, Green tea, Citrus tea, Green plum tea, Aloes, Persimmon punch, Jujube tea, Black herbal tea, Sikhye

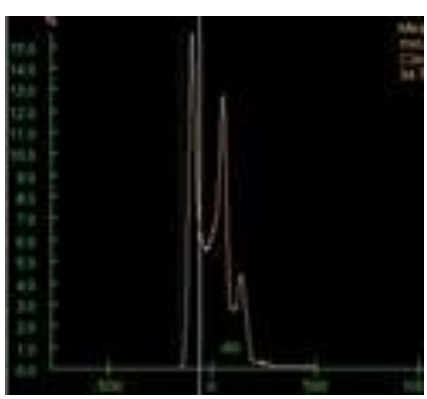
To improve the participants understanding, FFQ was developed with instruction on how to complete the questionnaire using portion size aids consisting of color photographs of pencil and a full-size picture of major dishes. The portion sizes of intake for each dish were categories: a 1/2 serving size, a serving size, and a 1.5 serving size. For mixed dishes, nutrients of FFQ were calculated according to their ingredients. Each foods and dishes were based on the basic recipes of CAN-Pro (Computer Aided Nutritional Analysis Program).

The FFQ asked subjects to report their average frequency and amount of consumption food intake in the past year. The participant's entire FFQ were conducted via a face-to-face interviewed by same trained investigator oneself (trained FFQ dietary interview from research institute, National Cancer Center, Korea) throughout the study.

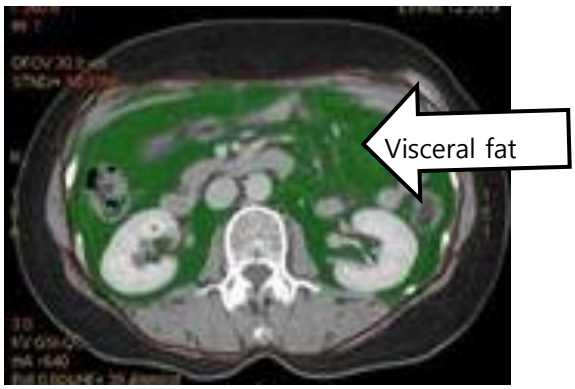
2.4. Abdominal fat ratio

All CT examinations of related breast cancer study were performed on the 64-Multi detector row computed tomography system (Lightspeed VCT, Discovery HD 750; GE Healthcare system, Milwaukee, WI, USA). CT Exposure parameters were kVp 120, auto exposure control mA (mA range: 100 ~ 350), and pitch 1:1. Imaging data were reconstructed every 10 mm.Measuring abdominal CT image was used to approximate a level at the umbilicus or the fourth lumbar vertebra, which is a valid virtually all the information on abdominal fat in human (Weits et al, 1998; van der Kooy et al 1993; Perry et al, 2012)). To quantify the subject's adipose tissue, all CT images were transferred to a commercially available workstation computer (Advantage Windows Workstation, version 4.5, GE Healthcare) and then measure the total adipose tissue volume (TAT; figure II-2(a)) and visceral adipose tissue (VAT; figure II-2(c)) with CT numbers from -50 and -250 Hounsfield Units (HU) (figure II-2(b)), which correspond to adipose tissue at umbilicus level (II-3).





(a) (b)



(c)

Figure II-2. Measurements of abdominal fat from a CT image.

a. Total adipose tissue (shaded) within which all of abdominal area.

b. Histogram of CT numbers obtained from a CT image.

c. Visceral adipose tissue (shaded) within which intra-abdomen.

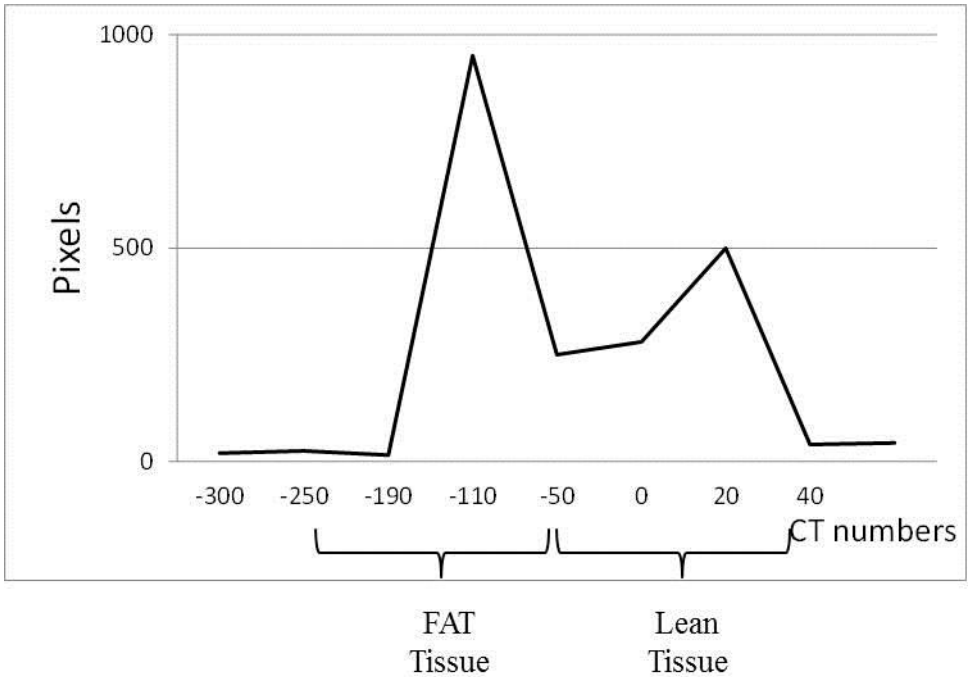


Figure II-3. Histogram of CT numbers obtained from an umbilicus level image. The maximum peak represents fat and the smaller peak represents lean tissue. The admissible range of CT numbers classified as fat was −50 to −250.

All visceral fat measurements were taken by a single radiology technologist throughout the study. But to minimize measurement errors by a single person, measurements of abdominal fat were performed randomly assigned by using a double blind random allocation (blanked participant' s information) with permuted duplication data assignments identified by other person.

SAT and fat ratio was calculated using the following equations;

SAT = TAT - VAT

Fat ratio % = (VAT / TAT) × 100

In addition, a randomly dividing the case and control sample 30 participants (by SPSS random selection procedures), to eliminate measurement error by one person. Intrapersonal differences between Test 1 and Test 2 were subsequently tested separately, measured by two trained radiology technologists that using only identifies number with measurement computer (AW4.5) and each in the same method, except for other participant's information. The random sample cases were abdominal fat ratio of 36.9% with a mean age of 56.8 years old and that of the control participants were abdominal fat ratio of 32.4% with a mean age of 53.8 years old. To compare intra-personal difference in measurement of visceral fat performed correlation and chi-square test. The value of correlation (r) and chi-square (p) between the two measurements was represents a similar relationship in each case and control (visceral fat: r = 0.98, p = 0.24. fat ratio: r = 0.96, p = 0.23 in case; visceral fat: 0.98, p = 0.23. fat ratio: r = 0.99, p =0.23 in control).

2.5. Personality factors (questionnaire survey)

All participants were asked to an additional question about behavior questionnaire (regular dietary pattern, family history,

physical activity, other disease, stress level, hobby, smoking, alcohol, level of education, menarche and menopause) with FFQ.

2.5.1. Physical activity

The physical activity data from the questionnaire related to physical activity and an average MET score (a multiple of resting metabolic equivalent rate) were summarized according to the physical activities recorded (occupation, whether or not performing regular exercise, exercise types, duration and times per week)(Craig et al., 2003). The collected physical activity is estimate the followed by scoring the short form of international physical activity questionnaire (IPAQ) (IPAQ Research Committee. 2004). Each activity was assigned MET score with standard resting metabolic rate of 1.0 (4.184 kJ) · kg^{-1} · h^{-1} and range from 0.9 (sleeping) to 19 METs (running at 10.9 mph) (Ainsworth et al., 2000; Craig et al., 2003). MET is considered a resting metabolic rate obtained during rest sitting based on the energy cost of actual movement. MET score is classifying the MET intensity of physical activities (light, < 3.3 METs; moderate, 4 METs; vigorous, > 8 METs), frequency (measured in days per week) and duration (time per day). MET-minute scores are equivalent to kilocalories for a 60 kilogram person. Kilocalories may be obtained from MET-minutes using the following formula: MET-min x (weight in kilograms/60 kilograms).

Table II-2 shows the example of major types of activities convert to MET score (IPAQ Research Committee 2004).

Table II-2. MET energy Example of compendium of physical activities modified from Ainsworth's study.

Major activities	Activity type or intensity	MET estimate
Occupational	Vigorous	8
	Moderate	4
	Walking (Vigorous)	5
	Walking (Moderate)	3.3
Transport	Sitting	1
	Walking	3.3
	Cycling (Vigorous)	8
	Cycling (Moderate)	6
Household	Vigorous	3
Leisure	Vigorous (weight	8

	training)	
	Moderate (golf)	4
	Walking	3.3

Expressed as MET-min per week: MET score x minutes of activity x events per week using the following sample calculation method:

Total MET-min/week= (walk METs *min*days) + (moderate METs*min*days) + Vigorous METs*min*days)

MET levels	MET-min/week for 30 min episode, 5 tiems/week
Walking = 3.3 METs	3.3*30*5 = 495 MET-min/week
Moderate intensity = 4.0 METs	4.0*30*5= 600 MET-min/week
Vigorous intensity = 8.0 METs	8.0*30*5= 1,200 MET-min/week
	Total =2,295 MET-min/week

2.5.2. Stress

To evaluate the relationships of usual psychological response to breast cancer, we added related stress item in behavior questionnaire. Related stress items is a 3-item questionnaire that "How much under stress usually and then answering in following scale", "Usually you doing for stress relief if under stress" and "Do you have something like hobby for relaxation" Stress scale is scored on a 5-point Likert scale, with responses ranging from no stress (a score of 1), mild, moderate, much and extreme stress (a score of 5) depending on intensity level. We calculated a score of subjects to assess cause cancer.

2.5.3. Smoking and alcohol consumption

For those causal associations between a smoking or alcohol consumed and cancer, we added in behavior questionnaire and asked to all subjects. The smoking questions included smoking status and screening questions to identify smokers as those who had age started use, usual duration and amounts consumed per day, and drinkers as those who had usual consumed kind of alcohol (beer, soju, rice wine, and whisky), number of intake on week, amount per one time over their entire lifetime.

2.5.4. Nutrient intake habit

In this study, FFQ designed to describe individual dietary

habits over a 1 year period. Therefore for more accuracy assessed FFQ, asked to subjects whether or not difference in usual dietary intake pattern compared to over the past year. And asked that “How frequency dietary intake classified depending on morning, lunch, dinner?” and frequency range is every day, 5 ~ 6 times per week, 3 ~ 4 times per week, 1 ~ 2 times per week, and not eating. In addition asked that “How much amount of usually diet intake?” and amount range is always eaten full, middle amount of eaten, small amount of eaten, and irregular amount of eaten.

2.5.5. Other disease and family history

All study participants completed a brief questionnaire regarding history of medical illnesses and cancer in the family (first and second degree relatives) because breast cancer have influenced by genetically inherited so can be increased risk according to family history of breast cancer (McPherson, et al., 2000; Boyle et al 2008). Personality questionnaire include questions “Does anyone in your family or close relatives have a history of cancer” and “Do you have any medical diseases before or present?”

2.5.6. Menstruation, Parity, and breastfeeding

Variations of woman's reproductive history which may be indicative of risk for developing breast cancer. To determine

whether menstrual affect breast cancer, study participants completed questionnaires menopausal status, age at menarche, parity, and breastfeeding.

2.6. Analysis

We conducted a combined (personality factors and FFQ) analysis of the collected data to evaluate the case-control. All means and distributions of demographic and characteristics were examined using the t-tests and chi-square tests. Multiple regression analysis was conducted to determine which of the many variables on breast cancer after using the normal transformed variables. Among the relevant variables, odds ratios and 95% confidence intervals (CIs) were analyzed by entered logistic regression. Statistical analysis was performed using SPSS statistics v. 20 (SPSS Inc., Chicago, IL, USA), and p values < 0.05 were considered statistically significant.

3. Results

3.1 Comparison of characteristic and distribution

Table II-3 show the detail of demographic characteristics in this study.

Table II-3. Socio-demographic characteristics of breast cancer cases and non-cancer controls

	Case-control n=234 (Questionnaire data n=147)		Control n =211 (except breast feeding and parity n =101)		P
	No.	%	No.	%	
Age at diagnosis (year)					0.08
<39	26	11.1	8(3)	3.7(2.7)	
40-49	93	39.7	55(26)	23.5(23.6)	
50-59	68	29.1	127(48)	54.3(43.6)	
≥60	47	20.0	22(15)	9.4(13.6)	
Body mass index (kg/㎡)					
<20	30	12.8	38 (20)	18.0(18.1)	0.00
20-24.9	132	56.4	133(68)	63.0(61.8)	
25-29.9	58	24.7	38(20)	18.0(18.1)	
≥30	14	5.9	2(2)	0.94(1.8)	

First-degree family history of breast cancer					0.05
No	208	88.9	197(102)	93.4(93.5)	
Yes	26	11.1	14(6)	6.6(6.6)	
Age at menarche					0.001
12 or less	23	9.8	(2)	(1.8)	
13	47	20.0	(14)	(12.7)	
14	43	18.3	(39)	(35.4)	
15 or older	122	52.1	(61)	(55.4)	
Smoking					0.90
Never smoked	(99)	(91)	(66)	(84.6)	
Past smoker	(7)	(6)	(7)	(8.9)	
Current smoker	(3)	(3)	(5)	(6.4)	
Alcohol					0.85
Non-drinker	(71)	(65)	(35)	(44.8)	
Past drinker	(5)	(5)	(6)	(7.6)	
Current drinker	(33)	(30)	(37)	(47.4)	
Total energy expenditure from recreational physical activity (MET/week)					0.001
<0-500	(9)	(8.2)	11	14.1	
500-1000	(4)	(44.9)	24	30.7	
1001-2000	(26)	(23.8)	31	39.7	
>2001	(3)	(27.5)	12	15.3	
NA					
Dietary energy (Kcal/day)					0.60
<1058	(12)	(11)	(8)	(12.8)	

1059−1300	(19)	(17.4)	(7)	(14.1)	
1301−1600	(26)	(23.8)	(11)	(20.5)	
1601−1999	(25)	(22.9)	(20)	(26.9)	
≥2000	(26)	(23.8)	(17)	(25.6)	
Abdominal fat ratio (%)					0.86
<29.9	101	43.1	90(43)	42.6(39.0)	
30−49.9	117	50.1	113(62)	53.5(56.3)	
>50	16	6.8	8(5)	3.7(4.5)	
Histologic grade					
1	45	19.2			
2	104	44.4			
3	83	35.5			
Positive lymph nodes					
No	161	68.8			
Yes	73	31.2			
ER/PR status					
ER+	148	63.2			
ER−	86	36.7			
PR+	112	47.8			
PR−	122	52.2			

P value in case−control: Chi square tests

ER: estrogen receptor, PR: progesterone receptor, MET: metabolic equivalent rate

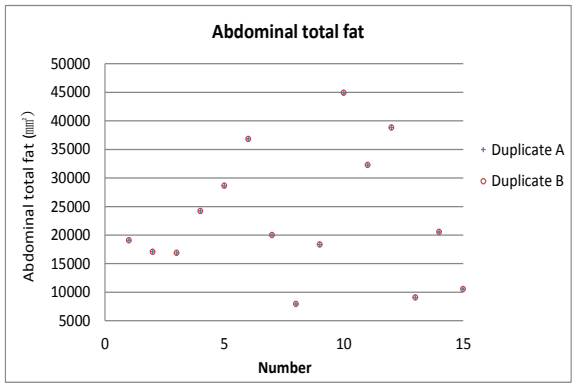
† Results from t test

† values are meant ± SE.

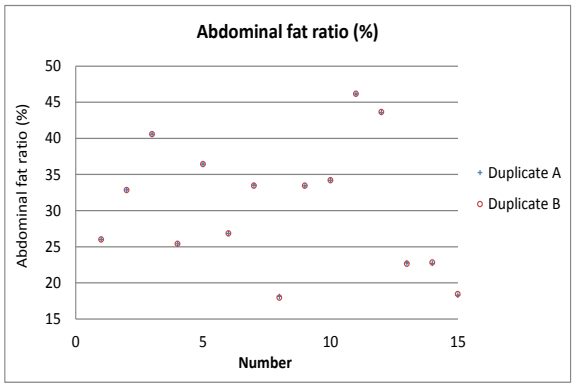
General characteristics of sum daily intake of nutrients estimated by FFQ and abdominal fat ratio are presented in Table II-4. There were no statistically significant differences (t-test) with no energy adjusted between cases and controls in most of sum daily intake of nutrients that is total energy ($p = 0.82$), vegetable protein ($p = 0.16$), vegetable lipid ($p = 0.40$), animal protein ($p = 0.78$), animal lipid ($p = 0.43$), glucose ($p = 0.62$), and abdominal fat ratio ($p = 0.02$). However compared with controls, cases had a lower dietary fiber intake (16.2 ± 5.9 for case, 20.1 ±8.1 for control; $p = 0.005$) with statistical significant difference and higher abdominal fat ratio (33.3% ± 8.2 for case, 30.6% ± 8.5 for control; $p=0.001$) with a significant positive correlation. Moreover adjusted for total calories, showing significant relation with dietary fiber and abdominal fat ratio ($p = 0.003$; $p = 0.001$ respectively).

The comparison of the two duplicate samples (Figure II-4), with an almost perfectly matched scatter plot, demonstrates the validation of the abdominal fat measurement. All visceral fat measurements were taken by a single radiology technologist throughout the study. But to minimize measurement errors and ascertained with validation, measurements of abdominal fat were performed randomly assigned by using a double blind random allocation (blanked participant's information) with duplicate-permuted data assignments (additionally submitted to the laboratory as 15 blind duplicate data in total subject data) identified by other person. Intra duplicate data correlation coefficients (r) between

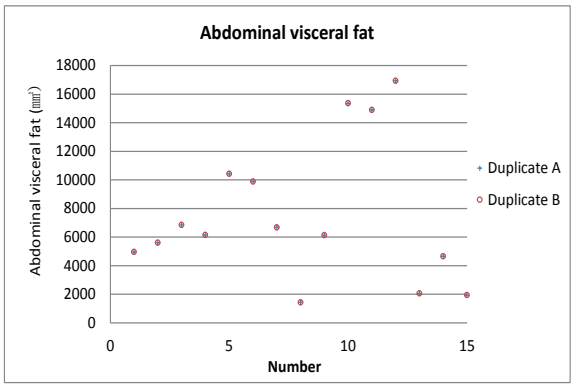
blind duplicate data were 0.99 for abdominal total, visceral, subcutaneous fat, and abdominal fat ratio. Duplicate data neither are nor used for this study.


Abdominal total fat
Abdominal total fat (㎟)
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
5
10
15
Number
Duplicate A
Duplicate B

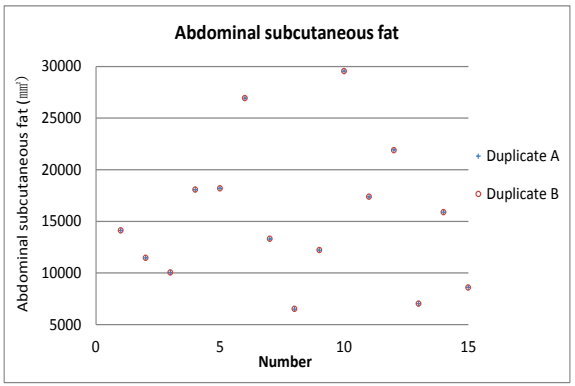
(a)


Abdominal fat ratio (%)
Abdominal fat ratio (%)
50
45
40
35
30
25
20
15
0
5
10
15
Number
Duplicate A
Duplicate B

(b)


Abdominal visceral fat
Abdominal visceral fat (㎟)
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
0
5
10
15
Number
Duplicate A
Duplicate B

(c)


Abdominal subcutaneous fat
Abdominal subcutaneous fat (㎟)
30000
25000
20000
15000
10000
5000
0
5
10
15
Number
Duplicate A
Duplicate B

(d)

Figure II-4 Scatter plot – comparison of abdominal distribution fat results between duplicated samples A and B. (a) comparison of abdominal total fat results between duplicated samples A and B. (b) comparison of abdominal fat ratio results between duplicated samples A and B. (c) comparison of abdominal visceral fat results between duplicated samples A and B. (d) comparison of abdominal subcutaneous fat results between duplicated samples A and B.

Table II-4. General characteristics of breast cancer patients and normal participants (age matched): the sum daily intake of nutrients (n=300).

	Cancer patients (Mean ± S.D)	Normal participants (Mean ± S.D)	p	^p
Total calories (kcal)	1706.1±449.6	1726.4±595.6	0.82	.
Vegetable protein (g)	34.9±10.1	37.8±14.2	0.16	0.23
Animal protein (g)	23.4±13.7	22.8±12.5	0.78	0.69

Vegetable lipid (g)	17.4±11.3	15.9±9.5	0.40	0.46
Animal lipid (g)	17.4±11.3	15.9±9.5	0.43	0.37
Glucose (g)	294.9±83.3	302.1±105.5	0.62	0.81
Dietary fiber (g)	16.2±5.9	20.1±8.1	**0.005	**0.003
Visceral fat (㎟)	8783.8 ± 4422. 2	6601.2 ± 3622.9	< 0.000	

Results were statistically analyzed with t-test (p: crude t-test; ^p: adjusted for total calories)

*, p < 0.05 compared to control

**, p < 0.005 compared to control

***, p < 0.001 compared to control

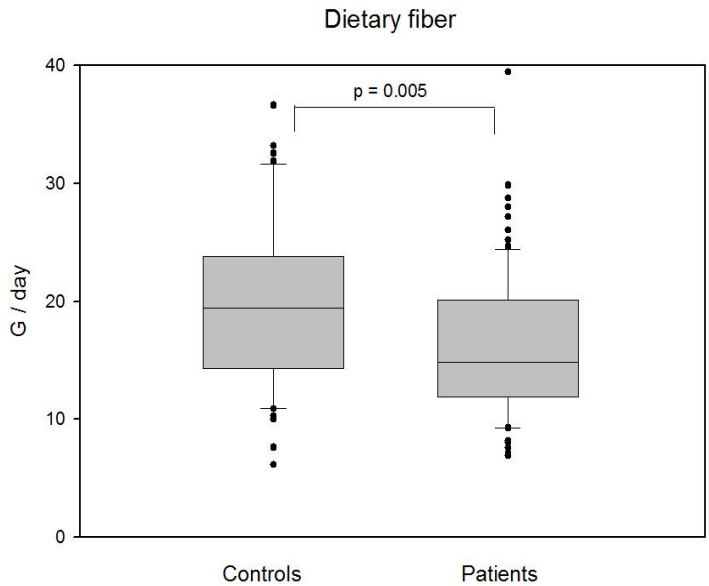


Figure II-5. Dietary fiber diagram: comparison between breast cancer patients and controls (normal participants). The breast cancer patients had significantly lower dietary fiber intakes with unadjusted total consumption compared to controls (p= 0.005; t-test), ・Circles represent outliers.

Figure II-5 depicts the diagram of contribution and association with statistical significant difference between breast cancer patients and normal participants in detail. Moreover adjust for total consumption and divided into categories (The median stratified by nutrients variable respectively), dietary fiber was changed more high statistical significant (p = 0.003).

In addition, multiple regression analysis with adjust for total calories was used to examine the relationship of sum daily intake of nutrients variables to incidence of breast cancer in case control study. As shown Table II-4, incidence of breast cancer were

positively associated with animal lipid (β = 2.18, p = 0.001), while negatively associated with dietary fiber (β = 2.20, p = 0.000).

Table II-5. The effects of sum daily intake of nutrients with adjust for total calories on breast cancer risk in case-control study (n=300).

Variables	β	95% (CI)		p-value
		Lower	Upper	
Vegetable protein	0.15	-0.001	0.013	0.83
Animal protein	0.10	-0.001	0.009	0.13
Vegetable lipid	-0.45	-0.057	0.001	0.06
Animal lipid	2.18	0.087	0.123	***0.001
Glucose	-0.15	-0.002	0.003	0.57
Dietary fiber	-2.20	-0.204	-0.102	***0.000

Results were statistically analyzed with multiple regression (P: significant with adjust for total calories)

*, $p < 0.05$ compared to control

**, $p < 0.005$ compared to control

***, $p < 0.001$ compared to control

List the food items with adjusted for total calories in the Table II-6 that were may be related to the effect on breast cancer in case control study. Similar result from sum daily intake of nutrients (Table II-5), breast cancer patients had a higher intake of related animal food items (Chicken: $p = 0.01$; Pork belly: $p = 0.01$), while lower intake of vegetables and fruits (Pepper leaves; $p = 0.05$; Tangerine: $p = 0.006$; Other Kimchi: $p = 0.05$; other vegetable: $p = 0.03$; Sliced radish kimchi: $p = 0.02$; Perilla leaf: $p = 0.02$; Cabbage kimchi: $p = 0.02$; Lettuce: $p = 0.05$; Tomato: $p = 0.04$).

Table II-6. A comparison of average intake of food items among total food items obtained from FFQ survey relate to breast cancer between breast cancer patients and normal (n=300)

Food items (g)	Cancer patients	Control	p
Processed meat	225.58 ± 505.51	201.73 ± 721.78	0.81
Dog meat	16.09 ± 46.80	9.24 ± 51.61	0.53
Chicken	197.07 ± 431.45	51.34 ± 49.52	*0.01
Beef	1287.33 ± 2112.84	1560.55 ± 1743.62	0.32
Organ meats	291.22 ± 508.35	158.88 ± 296.01	0.07
Pork belly	2917.80 ± 3630.27	1786.09 ± 1970.99	*0.01
Pork pan-broiling	1928.84 ± 2789.66	1807.29 ± 3758.32	0.82
Boiled pork	27.60 ± 170.75	13.16 ± 35.37	0.52
Bracken	36.83± 84.90	71.77 ± 18.54	0.07
Pepper leaves	52.61 ± 107.33	86.30 ± 116.19	*0.05
Tangerine	303.3 ± 315.55	613.51 ± 886.20	*0.006
Other kimchi	184.90 ± 294.42	334.18 ± 898.73	0.05
Other vegetable	56.93 ± 174.21	230.57 ± 580.	*0.03
Button mushroom	58.09 ± 110.66	105.02 ± 293.74	0.17
Sliced radish kimchi	300.36 ± 510.56	564.76 ± 777.34	*0.02
Watery kimchi	93.70 ± 333.70	170.88 ± 421.01	0.13
Oyster	115.19 ± 168.42	181.71 ± 402.68	0.15

mushroom			
Aged amber	55.43 ± 51.64	57.54 ± 146.78	0.08
Carrot	223.74 ± 467.95	430.97 ± 1431.80	0.21
Perilla leaf	98.56 ± 120.39	167.68 ± 231.86	*0.02
Straw berry	111.37 ± 176.88	113.26 ± 129.19	0.68
Pickled radish	230.60 ± 515.41	315.64 ± 588.83	0.17
Banana	214.15 ± 325.03	134.47 ± 177.14	0.59
Pear	59.20 ± 151.36	30.55 ± 58.53	0.17
Cabbage soup	81.48 ± 152.30	80.89 ± 236.02	0.98
Cabbage kimchi	1119.00 ± 1119.63	15965.74 ± 1147.10	*0.02
Peach	85.10 ± 132.26	57.77 ± 91.70	0.17
Apple	199.77 ± 293.29	274.23 ± 389.68	0.23
Lettuce	241.23 ± 179.56	388.75 ± 352.95	*0.05
Water melon	101.89 ± 103.24	200.20 ± 317.95	**0.007
Spinach	350.47 ± 265.15	436.37 ± 1227.66	0.60
Crown daisy	60.13 ± 99.28	90.79 ± 107.73	0.08
Green pumpkin	195.63 ± 220.11	255.94 ± 284.81	0.64
Onion	55.65 ± 54.72	49.80 ± 59.02	0.57
Orange	46.35 ± 76.58	66.13 ± 123.972	0.19
Cucumber	164.62 ± 335.23	113.87 ± 131.16	0.27
Pickled vegetables	62.16 ± 146.26	43.42 ± 77.46	0.37

Oriental melon	99.06 ± 157.33	157.33 ± 343.28	0.11
Bean sprouts	894.81 ± 790.86	1080.11 ± 2928.74	0.68
Tomato	203.53 ± 319.81	348.14 ± 442.99	*0.04
Grapes	55.90 ± 134.36	34.02 ± 40.10	0.20
Green chilli	111.99 ± 147.79	134.96 ± 143.96	0.26

P was significant difference with adjust for total calories

*, $p < 0.05$ compared to control

**, $p < 0.005$ compared to control

3.2 Risk factors for breast cancer

Table II-7 shows general distribution abdominal fat and BMI among all of subjects. To risk of breast cancer via anthropometric factors such as abdominal visceral fat, stratification of the factors into the tertile, this performed logistic regression. Table II-8 shows the crude and adjusted odds ratios of breast cancer. Increased of abdominal visceral fat and BMI were shows positive associated with breast incidence. But neither measured abdominal fat nor BMI was strongly associated with breast incidence in total subjects. For example, the multivariable-adjusted odds ratio of breast cancer for the highest vs the lowest tertile of abdominal fat ratio and of visceral fat were 1.34 (95% CI =0.82 to 2.16) and 1.51 (95% CI = 0.91 to 2.51). The odds ratio of breast cancer for the highest vs the lowest tertile of BMI was 2.49 (95% CI =1.52 to 4.08). Table II-9 shows the crude and adjusted odds ratios of breast cancer according to menstruation status. But neither measured abdominal fat nor BMI was strongly associated with breast cancer incidence in total subjects. Measured abdominal fat was opposite associated with breast cancer incidence according to menstruation status. For example, the multivariable-adjusted odds ratio of breast cancer for the highest vs the lowest tertile of pre and post-menopausal subjects of abdominal fat ratio were 0.86(95% CI = 0.44 to 1.62) and 1.50 (95% CI = 0.75 to 2.98). Post-menopausal subjects were the more positively associated with breast cancer incidence than pre-menopausal.). Thus post-

menopausal subjects were more effect of abdominal visceral fat on breast cancer risk than pre-menopausal. Abdominal subcutaneous fats, the multivariable-adjusted odds ratio of breast cancer for the highest vs the lowest tertile of pre-menopausal subjects were 0.51 (95% CI =0.25 to 1.02), the lowest inverse associated with breast cancer incidence.

However BMI was positively associated with the risk of breast cancer unrelated to menstruation status. The multivariable-adjusted odds ratio of breast cancer for the highest vs the lowest tertile of BMI categorized as pre-menopausal was 1.88 (95% CI = 0.94 to 3.76)) and categorized as post-menopausal was 4.35 (95% CI = 2.04 to 9.84). Therefore breast cancer risks were the more positively associated with post-menopausal subjects than pre-menopausal.

Table II-7. Comparison of abdominal distribution fat and BMI in all subjects

Subjects		Control (n=211) Mean ± S.D	Case (n=234) Mean ± S.D	p
Age (y)		52.11(±6.49)	51.02(±10.11)	0.10
Abdominal total fat (mm^2)	Total	23403.0(±8704.3)	23279.1(±10068.2)	0.96
	Pre-menopause	21143.3(±7716.2)	19476.5 (±9324.0)	0.17
	Post-menopause	25362.7(±9063.7)	28125.7(±8858.4)	0.27
Abdominal visceral fat (mm^2)	Total	7992.6(±4549.6)	8186.7(±5424.8)	0.64
	Pre-menopause	6725.8(±3862.5)	6151.1(±4604.1)	0.34
	Post-menopause	9091.3(±4823.7)	10781.1(±5301.1)	0.60
Abdominal	Total	15410.3(±5242.8)	15092.4(±5614.9)	0.61

subcutaneous fat (mm^2)	Pre-menopause	14417.5(±4794.5)	13325.4(±5432.5)	0.13
	Post-menopause	16271.3(±5479.0)	17344.6(±5027.1)	0.89
Abdominal fat ratio (%)	Total	32.6(±8.80)	32.6(±10.55)	0.91
	Pre-menopause	30.92(±8.0)	29.3(±9.65)	0.22
	Post-menopause	34.19(±9.24)	36.8(±10.1)	0.19
BMI	Total	22.4(±2.6)	23.6(±3.4)	0.01
	Pre-menopause	21.9(±2.6)	22.9(±3.2)	0.10
	Post-menopause	22.9(±2.6)	24.9(±3.1)	0.28

Results were statistically analyzed with t-test (2 tailed)

Table II-8. Odds ratios and 95% CI on breast cancer risk in relation to anthropometric factors (distribution of abdominal fat and BMI) in case-control study

Factors	Tertile (range)	No. (%) of participants		Crude	Multivariate*
		Case	Control	Odds ratio(95%CI)	Odds ratio(95%CI)
Abdominal Fat ratio (%)	Reference (< 27.84)	88(37.9)	70(33.2)		
	1st vs 2nd(27.85-34.79)	51(21.9)	70(33.2)	0.57 (0.35-0.91)	0.62 (0.38-1.02)
	1st vs 3rd (≥ 34.80)	93(40.0)	71(33.6)	1.09 (0.59-1.68)	1.34(0.82-2.16)
Abdominal total fat (㎟)	Reference (< 18120)	78(33.3)	70(33.2)		
	1st vs 2nd(18121-27112)	80(34.1)	70(33.2)	1.02 (0.65-1.61)	1.10(0.69-1.76)
	1st vs 3rd (≥ 27113)	76(32.4)	71(33.6)	0.96 (0.60-1.51)	1.12 (0.68-1.84)
Abdominal visceral fat (㎟)	Reference (< 4894)	72(30.7)	70(33.2)		
	1st vs 2nd(4895-9149)	77(32.9)	70(33.2)	1.10 (0.69-1.74)	1.26 (0.78-2.04)

	1st vs 3rd (≥9150)	85(36.3)	71(33.6)	1.18 (0.74−1.86)	1.51 (0.91−2.51)
Abdominal subcutaneous fat (㎟)	Reference (< 12786)	86(36.7)	70(33.2)		
	1st vs 2nd(12787−17156)	71(30.3)	70(33.2)	0.82 (0.52−1.30)	0.86 (0.53−1.37)
	1st vs 3rd (≥17157)	77(32.9)	71(33.6)	0.88 (0.56−1.38)	0.96 (0.56−1.53)
BMI	Reference (< 20.89)	57(24.5)	70(33.1)		
	1st vs 2nd(20.90−23.28)	61(26.2)	70(33.1)	1.08 (0.66−1.77)	1.17 (0.71−1.94)
	1st vs 3rd (≥23.29)	115(49.3)	71(33.6)	2.02 (1.27−3.20)	2.49 (1.52− 4.08)

* Odds ratio adjusted for age, menopause, and family history

a, Age: year

b, Menstruation: 1, postmenopausal; 2, premenopausal

c, Family history: 1, positive family history; 2, negative family history

Table II-9. Odds ratios and 95% CI on breast cancer risk in relation to anthropometric factors (distribution of abdominal fat and BMI) classified as pre and post-menopausal status in case-control study

Factors		Tertile (range)	No.(%)of participants		Crude	Multivariate*
			Case	Control	Odds ratio(95%CI)	Odds ratio(95%CI)
Abdominal fat ratio	Pre-menopause	Reference (< 26.87)	65(51.1)	33(33.6)		
		1st vs 2nd(26.88-33.43)	23(18.1)	33(33.6)	0.41 (0.21-0.80)	0.48 (0.23-0.98)
		1st vs 3rd (>33.44)	39(30.7)	32(32.6)	0.60 (0.32-1.12)	0.86(0.44-1.62)
	Post-menopause	Reference (< 29.88)	27(26.4)	38(33.6)		
		1st vs 2nd(29.89-37.19)	24(23.5)	38(33.6)	0.89 (0.43-1.80)	0.86 (0.40-1.76)
		1st vs 3rd (≥37.20)	51(50.0)	37(32.7)	1.94 (1.01-3.71)	1.50(0.75-2.98)
Abdominal total fat (㎟)	Pre-menopause	Reference (< 16803)	54(41.5)	33(33.6)		
		1st vs 2nd(16804-24329)	47(36.2)	33(33.6)	0.87 (0.46-1.62)	0.85 (0.44-1.64)
		1st vs 3rd (≥24330)	29(22.3)	32(32.6)	0.55 (0.28-1.07)	0.63 (0.31-1.26)

	Post-menopause	Reference (< 19875)	16(15.6)	38(33.6)		
		1^{st} vs 2^{nd}(19876-30013)	46(45.0)	38(33.6)	2.87 (1.39-5.93)	2.55 (1.20-5.43)
		1^{st} vs 3^{rd} (≥30014)	40(39.2)	37(32.7)	2.56 (1.23-5.35)	1.84 (0.84 -4.02)
Abdominal visceral fat (㎟)	Pre-menopause	Reference (< 4198)	51 (39.2)	33(33.6)		
		1^{st} vs 2^{nd}(4199-6998)	40 (30.9)	33(33.6)	0.78 (0.41-1.48)	0.83 (0.42-1.63)
		1^{st} vs 3^{rd} (≥6999)	39 (30.0)	32(32.6)	0.78 (0.41-1.49)	0.98 (0.49-1.93)
	Post-menopause	Reference (< 6016)	17 (16.6)	38(33.6)		
		1^{st} vs 2^{nd}(6017-10615)	42 (41.1)	38(33.6)	2.47 (1.20-5.08)	2.13 (1.01-4.53)
		1^{st} vs 3^{rd} (≥10616)	43 (42.1)	37(32.7)	2.59 (1.26-5.34)	1.81(0.83-3.89)
Abdominal subcutaneous fat (㎟)	Pre-menopause	Reference (< 11951)	60 (46.1)	33(33.6)		
		1^{st} vs 2^{nd}(11952-16630)	40 (30.7)	33(33.6)	0.66 (0.35-1.24)	0.61 (0.31-1.19)
		1^{st} vs 3^{rd} (≥16632)	30 (23.0)	32(32.6)	0.51 (0.26-0.99)	0.51 (0.25-1.02)
	Post-menopause	Reference (< 13507)	26 (25.5)	38(33.6)		
		1^{st} vs 2^{nd}(13508-18089)	36 (35.3)	38(33.6)	1.38 (0.70-2.72)	1.33 (0.66-2.68)
		1^{st} vs 3^{rd} (≥18090)	40 (39.2)	37(32.7)	1.56 (0.80-3.08)	1.35 (0.67-2.74)

BMI	Pre-menopause	Reference (< 20.43)	35(27.1)	33(33.6)		
		1st vs 2nd(20.44-22.48)	40(31.0)	33(33.6)	1.14 (0.58-2.21)	1.30(0.64-2.68)
		1st vs 3rd (≥22.49)	54 (41.8)	32(32.6)	1.59(0.83-3.04)	1.88 (0.94-3.76)
	Post-menopause	Reference (< 21.75)	12(11.7)	38(33.6)		
		1st vs 2nd(21.76-23.92)	25(24.5)	38(33.6)	2.07 (0.93-4.62)	1.65 (0.70-3.88)
		1st vs 3rd (≥23.93)	65(63.7)	37(32.7)	4.94 (2.35-10.40)	4.35 (2.04-9.84)

* Odds ratio adjusted for age, menopause, parity, menarche, breast feeding, and family history

a, Age: year

b, Menstruation: 1, post-menopausal; 2, pre-menopausal

c, Parity: 1, never; 2, ever

d, Menarche: year

e, breast feeding: 1, never; 2, ever

f, Family history: 1, positive family history; 2, negative family history

To the more effect on breast cancer incidence by distribution of abdominal fat was another assessed subgroup by adding a parity, menarche, and breast feeding variable by use of odds ratio classified as median. Similar result from Table II-9, increased of abdominal visceral fat was showing positive associated with breast incidence (Table II-10). Hence, the multivariable-adjusted odds ratio of breast cancer for the highest vs the lowest median of abdominal fat ratio and of visceral fat were 1.09 (95% CI =0.68 to 1.87) and 1.05 (95% CI = 0.62 to 1.79). But subcutaneous fat, the odds ratio of breast cancer for the highest vs the lowest median was 0.74 (95% CI =0.45 to 1.21), show inverse association with breast cancer incidence.

Table II-10. Odds ratios and 95% CI on breast cancer risk in relation to distribution of abdominal fat in sub group case-control study

Factors	Median (range)	No. (%) of participants		Crude	Multivariate*
		Case	Control	Odds ratio(95%CI)	Odds ratio(95%CI)
Abdominal Fat ratio (%)	Reference (< 31.87)	123(52.8)	55(50)		
	1st vs 2nd(≥31.88)	111(47.8)	55(50)	0.88 (0.56-1.39)	1.09 (0.68-1.87)
Total fat (㎟)	Reference (< 23403)	131(56.5)	55(50)		
	1st vs 2nd(≥23404)	101(43.5)	55(50)	0.88 (0.56-1.39)	1.13(0.68-1.89)

Visceral fat (㎟)	Reference (< 7769)	128(55.2)	55(33.2)		
	1st vs 2nd(≥7770)	104(44.8)	55(33.2)	0.81 (0.51−1.28)	1.05 (0.62−1.79)
Subcutaneous fat (㎟)	Reference (< 15769)	140(60.3)	55(33.2)		
	1st vs 2nd(≥15770)	104(39.6)	55(33.2)	0.65 (0.41−1.03)	0.74 (0.45−1.21)

* Odds ratio adjusted for age, menopause, parity, menarche, breast feeding, and family history

a, Age: year

b, Menstruation: 1, post−menopausal; 2, pre−menopausal

c, Parity: 1, never; 2, ever

d, Menarche: year

e, breast feeding: 1, never 2, ever

f, Family history: 1, positive family history; 2, negative family history

Table II-11 Odds ratios and 95% CI on breast cancer risk in relation to distribution of abdominal fat classified as pre and post-menopausal status in sub group case-control study

Factors		Median (range)	No. (%) of participants		Crude	Multivariate*
			Case	Control	Odds ratio(95%CI)	Odds ratio(95%CI)
Abdominal fat ratio	Pre-menopause	Reference (< 31.41)	79(62.4)	23(50)		
		1st vs 2nd(≥ 32.42)	47(37.3)	23(50)	0.60 (0.30-1.17)	0.86 (0.39-1.91)
	Post-menopause	Reference (< 31.93)	40(37.7)	32(50)		
		1st vs 2nd(≥ 31.94)	66(62.2)	32(50)	1.60 (0.85-2.98)	1.29 (0.59-2.79)
Total fat (㎟)	Pre-menopause	Reference (< 21824)	87(69.0)	23(50)		
		1st vs 2nd(≥ 21825)	39(30.9)	23(50)	0.46 (0.22-0.89)	0.58 (0.26-1.27)
	Post-menopause	Reference (< 24492)	41(38.7)	32(50)		
		1st vs 2nd(≥ 24493)	65(61.3)	32(50)	1.58 (0.84-2.97)	1.42 (0.72-2.78)

Visceral fat (㎟)	Pre-menopause	Reference (< 7095)	87 (68.3)	23(50)		
		1st vs 2nd(≥ 7096)	39 (30.9)	23(50)	0.46 (0.22-0.89)	0.73 (0.33-1.61)
	Post-menopause	Reference (< 8378)	38 (35.8)	32(50)		
		1st vs 2nd(≥ 8379)	68 (64.2)	32(50)	1.72 (0.92-3.22)	1.47 (0.74-2.93)
Subcutaneous fat(㎟)	Pre-menopause	Reference (< 14686)	84 (66.6)	23(50)		
		1st vs 2nd(≥ 14687)	42 (33.3)	23(50)	0.50 (0.25-0.99)	0.45 (0.20-0.99)
	Post-menopause	Reference (< 15786)	49 (46.2)	32(50)		
		1st vs 2nd(≥ 15787)	57 (53.7)	32(50)	1.16 (0.62-2.16)	1.06 (0.54-2.07)

* Odds ratio adjusted for age, menopause, parity, menarche, breast feeding, and family history

a, Age: year

b, Menstruation: 1, post-menopausal; 2, pre-menopausal

c, Parity: 1, never; 2, ever

d, Menarche: year

e, breast feeding: 1, never 2, ever

f, Family history: 1, positive family history; 2, negative family history

Table II-11 shows crude and adjusted odds ratio of breast cancer incidence according to menstruation status in subgroup, similar pattern from Table II-9. Also subgroups, visceral fat effect on breast cancer risks were the more positively associated with post-menopausal subjects than pre-menopausal. The multivariable-adjusted odds ratio of breast cancer for the highest vs the lowest median of visceral fat categorized as pre and post-menopausal were 0.73 (95% CI =0.33 to 1.61) and 1.47 (95% CI = 0.74 to 2.93).

3.3 Comparison of characteristic and distribution between pre and post menopause

To know difference in intake of nutrients on breast cancer risk depending on status of menstruation, subjects were categorized as pre and post menopause. As shown Table II-10, the sum daily intake of nutrients with crude and adjust for total calories analysis was no significant difference in total calories (p=0.49), vegetable protein (p=0.03 for adjust for total calories), glucose, and dietary fiber between pre and post-menopause in breast cancer patients. Also abdominal fat ratio was moderate statistical difference in analysis (p = 0.001). However in case of animal lipid, pre-menopause women were more intake than post-menopause in breast cancer patients and show statistically significant with crude and adjusting total calories (p = 0.009 for crude analysis; p = 0.03 for adjust for total calories). In spite of post-menopause women was intake lower total calories than pre-menopause women, post-menopause women were more intake of vegetable protein and animal lipid with adjusting total calories analysis (p = 0.03; p = 0.03 respectively). And post menopause women were moderate more intake of glucose (p = 0.08), though lower intake of total calories than pre menopause women.

Table II- 12. Comparison of the sum daily intake of nutrients and abdominal fat ratio, which pre and post menopause in breast cancer patients (n=150)

	Pre menopause (Mean ± S.D)	Post menopause (Mean ± S.D)	^p	†p
Total calories (kcal)	1711.0±521.3	1669.9±474.1	0.49	
Vegetable protein (g)	33.4±9.4	35.4±9.6	0.55	*0.03
Animal protein (g)	25.0±13.7	20.9±11.6	0.07	0.57
Vegetable lipid (g)	13.4±7.8	12.3±7.5	0.25	0.15
Animal lipid (g)	20.0±11.9	14.7±8.5	** 0.009	*0.03

Glucose (g)	287.7±74.4	295.7±84.4	0.87	0.08
Dietary fiber (g)	15.4±5.8	16.3±5.9	0.62	0.14
Abdominal fat ratio (%)	30.7±8.3	35.2±7.6	0.001	

*, $p < 0.05$ compared to control

**, $p < 0.005$ compared to control

^ p was crude t-test

† p was adjusted for total calories

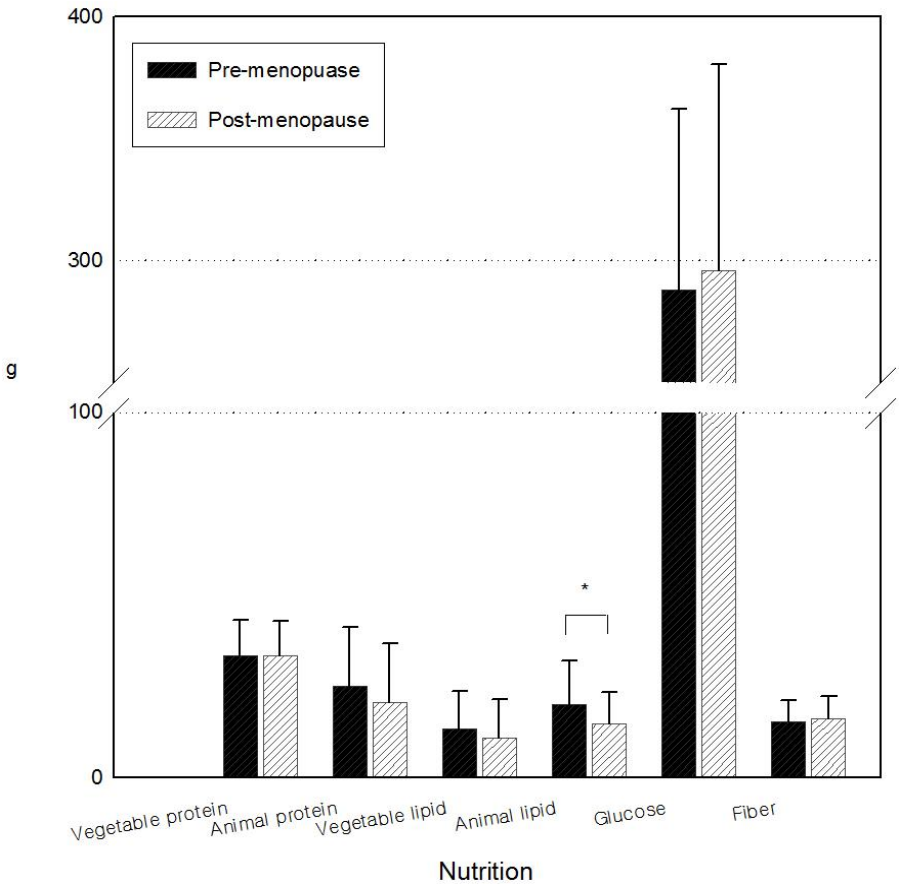


Figure II-6 Comparison of sum daily intake of nutrients between pre and post menopause breast cancer patients.

The star symbol (*) indicate statistically significant differences with adjust for total calories by t-test.

*; $p < 0.05$

Figure II-6 depicts the comparison of sum daily intake of

nutrients between breast cancer patients and normal participants.

Multiple linear regression analysis was conducted to evaluate the association between breast cancer incidence and personality factors independently of the variables such as family history, menarche, education level, physical activity in age matched case control study. Risk of breast cancer was a positive first degree of family history with moderate and higher cross sectional with high association, and moderate inverse association with education level (Table II-13).

Table II-13. The effects of personality factors on breast cancer risk in case and control

Variables	β	95% (CI)		p-value
		Lower	Upper	
Fat ratio (%)	0.16	-2.03	-0.11	0.02
Visceral fat (㎟)	0.26	0.00	0.001	0.01
Education (year)	-0.14	-0.21	0.05	0.09
Menarche (year)	-0.25	-0.12	-0.05	0.00

Menstruation (0, 1)[a]	0.05	−0.12	0.07	0.63
Breastfeeding (0, 1)[b]	−0.14	−0.25	−0.03	0.01
Parity (0, 1)[c]	0.09	−0.02	0.09	0.23
Family history (0,1)[d]	0.07	−0.28	0.04	0.15
Physical activity (MET score)	−0.04	−0.02	0.10	0.17
Smoking status (0,1,2)[e]	0.09	−0.01	0.35	0.24
Alcohol consumption (0,1)[f]	0.11	−0.00	0.22	0.11

a, Menstruation: 0, postmenopausal; 1, premenopausal

b, Breastfeeding: 0, No; 1, Yes

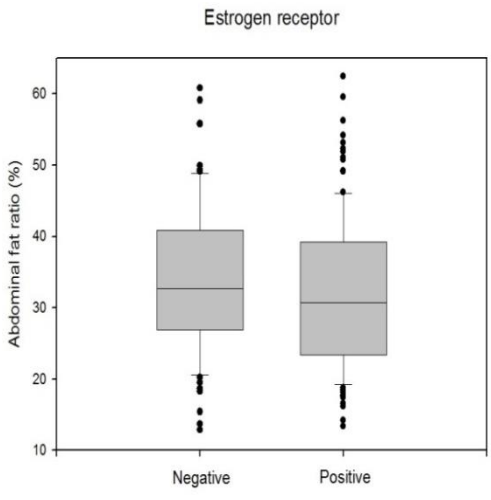
c, Parity: 0: No child birth; 1, more than one child birth

d, family history: 0, positive family history; 1, negative family history

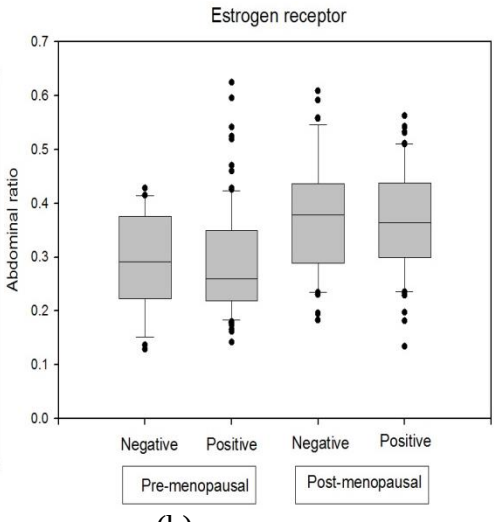
e, smoking status: 0, never smoking; 1, past smoking; 2, current smoking

f, alcohol consumption: 0, never consumption; 1, current consumption

3.4 Association between distribution fat and hormone status



(a)



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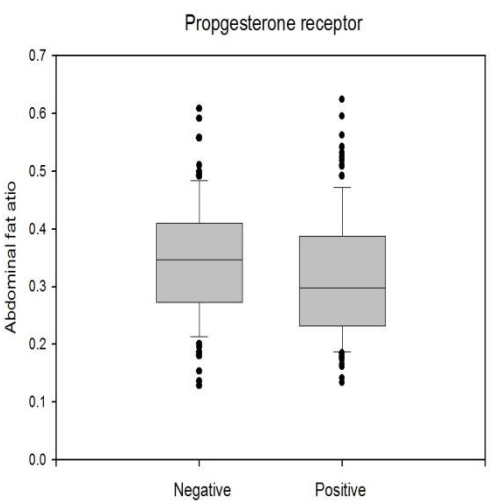
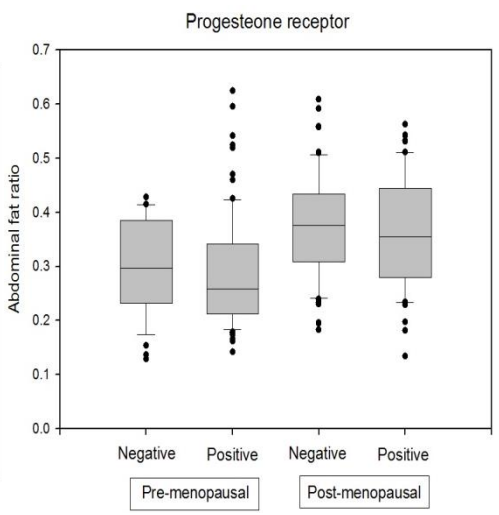


(c)



(d)

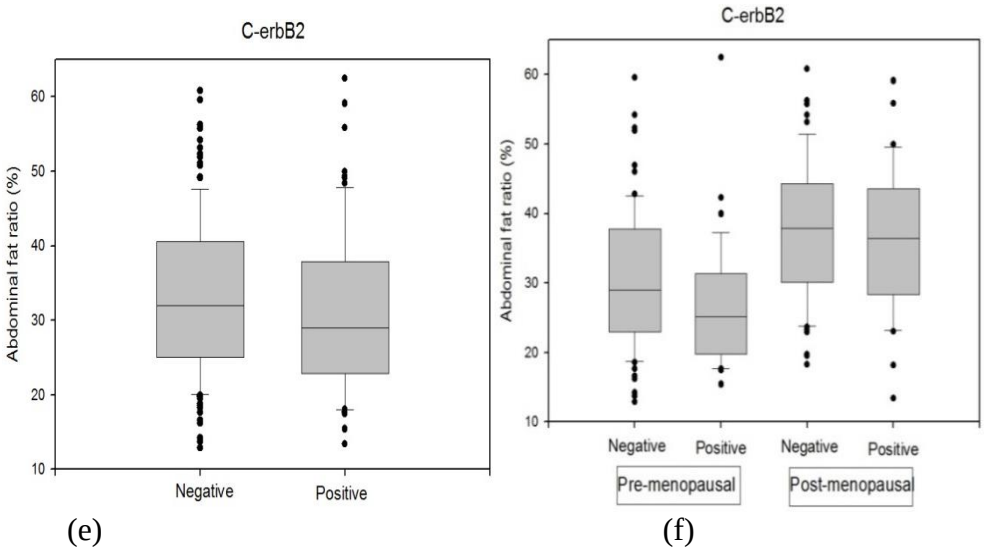


Figure II-7 Abdominal fat ratio and hormone status diagram in breast cancer patients. Generally negative hormone patients had higher abdominal fat ratio than positive hormone patients in total breast cancer patients (estrogen receptor, p = 0.12; progesterone receptor, p = 0.06; Herceptin, p = 0.43 for t-test). (a) Diagram of abdominal fat ratio and classified as estrogen receptor score. (b) Diagram of abdominal fat ratio and classified as estrogen receptor score according to menstruation status. (c) Diagram of abdominal fat ratio and classified as progesterone receptor score. (d) Diagram of abdominal fat ratio and classified as progesterone receptor score according to menstruation status. (e) Diagram of abdominal fat ratio and classified as Herceptin score. (f) Diagram of abdominal fat ratio and classified as Herceptin score according to menstruation status. · Circles represent outliers.

Figure II-7 and Table II-14 show association between

hormone status and anthropometric factors. Generally hormone negative patients had higher abdominal fat ratio than positive hormone patients in total breast cancer patients (estrogen receptor, p = 0.12; progesterone receptor, p = 0.06; Herceptin, p = 0.43). Pre-menopausal patients, hormone negative score was the more differenced average abdominal fat ratio (estrogen receptor, p = 0.41; progesterone receptor, p = 0.33; Herceptin, p = 0.02) than post-menopausal and positive hormone score (estrogen receptor, p = 0.72; progesterone receptor, p = 0.91; Herceptin, p = 0.58). Thus hormones negative of pre-menopausal subjects were more effect of distribution abdominal fat on breast cancer risk than post-menopausal. However BMI was show not a similar pattern with measured distribution of abdominal fat.

Table II-14. Comparison of average anthropometric factors (distribution of abdominal fat and BMI) and classified as hormone in breast cancer patients.

Hormone	Subjects	score	No.(%) of participants	Average : p									
				Total abdominal fat(㎟)		Visceral fat (㎟)		Subcutaneous fat (㎟)		Abdominal fat ratio (%)		BMI	
Estrogen receptor (ER)	Total patients	Negative	69(30.5)	24596.6	0.21	9028.6	0.11	15567.9	0.47	33.9	0.18	23.6	0.98
		Positive	157(69.5)	22775.1		7778.9		14996.1		31.9		23.6	
	Pre-menopausal	Negative	28(24.8)	19049.7	0.63	5936.8	0.67	1312.8	0.63	29.0	0.93	22.4	0.64
		Positive	97(75.2)	19939.3		6305.1		13634.1		19.1		22.7	
	Post-menopausal	Negative	41(41.1)	28384.6	0.81	11140.0	0.60	17244.6	0.87	37.3	0.72	24.5	0.25
		Positive	61(58.9)	27951.6		10539.8		17411.8		36.5		25.2	
Progesterone	Total patients	Negative	89(39.38)	24822.8	0.06	9153.9	0.02	15668.8	0.27	34.4	0.02	23.7	0.78

receptor (PR)		Positive	137(40.62)	22362.2		7515.1		14847.1		31.3		23.6	
	Pre-menopausal	Negative	37(32.8)	19948.8	0.86	6414.5	0.74	13534.3	0.98	29.8	0.56	22.3	0.49
		Positive	88(67.2)	19652.2		6142.		13510.2		28.8		22.8	
	Post-menopausal	Negative	52(55.8)	28290.9	0.83	11103.1	0.51	17187.7	0.74	37.6	0.41	24.7	0.44
		Positive	50(44.2)	27953.9		10446.1		17507.8		36.0		25.2	
Herceptin	Total patients	Negative	156(68.7)	24101.5	0.14	8597.7	0.27	15503.8	0.12	33.4	0.43	24.0	0.28
		Positive	71(31.3)	22204.1		7553.6		14651.1		30.9		23.1	
	Pre-menopausal	Negative	89(71.2)	21063.4	**0.00**	6905.0	**0.00**	14158.3	**0.03**	30.3	**0.02**	23.0	0.06
		Positive	36(28.8)	16468.4		4535.6		1193.7		26.0		21.9	
	Post-menopausal	Negative	67(65.6)	28137.2	0.82	10846.1	0.84	17291.0	0.53	37.3	0.58	25.3	0.65
		Positive	35(24.4)	28103.8		10656.6		17447.1		35.9		24.3	

a, Estrogen and progesterone were classified as Remmele score

≥3 = positive

0−2 = negative

b, P: t−test (2−tailed)

Table II−15. Odds ratios and 95% CI on estrogen receptor change in relation to distribution of abdominal fat in breast cancer patients

Factors	Menopause status	Median (range)	No. (%) of participants		Odds ratio(95%CI)
			Positive	Negative	
Abdominal Fat ratio	All of breast cancer patients	Reference (< 31.24)	80(71.80)	33(29.20)	
		1st vs 2nd(≥ 31.25)	74(64.92)	40(35.08)	1.31 (0.74−2.29)

(%)	Pre-menopause	Reference (< 26.65)	51(80.96)	12(19.04)	
	breast cancer patients	1st vs 2nd(≥ 26.66)	43(69.35)	19(30.75)	1.87 (0.82-4.30)
	Post-menopause	Reference (< 36.82)	31 (60.79)	20 (39.21)	
	breast cancer patients	1st vs 2nd(≥ 36.83)	29 (56.87)	22 (43.13)	1.17 (0.53-2.58)
Abdominal total fat (㎟)	All of breast cancer patients	Reference (< 22115)	80(71.80)	33(29.20)	
		1st vs 2nd(≥22116)	74(64.92)	40(35.08)	1.31 (0.74-2.29)
	Pre-menopause	Reference (< 18175)	47 (74.60)	16 (25.40)	
	breast cancer patients	1st vs 2nd(≥ 18176)	45 (72.58)	17 (27.42)	1.11 (0.50-2.45)
	Post-menopause	Reference (< 27711)	31 (60.79)	20 (39.21)	
	breast cancer patients	1st vs 2nd(≥ 27712)	30 (58.82)	21 (41.18)	1.0 (0.45-2.20)

Abdominal visceral fat (㎟)	All of breast cancer patients	Reference (< 7200)	81(71.69)	32(28.31)	
		1st vs 2nd(≥7201)	73(64.04)	41(35.96)	1.42 (0.81−2.48)
	Pre−menopause breast cancer patients	Reference (< 4978)	51 (80.95)	12 (19.05)	
		1st vs 2nd(≥ 4979)	43 (69.35)	19 (31.75)	1.87 (0.82−4.30)
	Post−menopause breast cancer patients	Reference (< 9804)	31 (60.79)	20 (39.21)	
		1st vs 2nd(≥ 9805)	29 (56.86)	22 (43.14)	1.27(0.57−2.79)

Table II−16. Odds ratios and 95% CI on progesterone receptor change in relation to distribution of abdominal fat in breast cancer patients

Factors	Menopause status	Median (range)	No. (%) of participants		Odds ratio(95%CI)
			Positive	Negative	

Abdominal Fat ratio (%)	All of breast cancer patients	Reference (< 31.24)	74(65.49)	39(34.51)	
		1^{st} vs 2^{nd}(≥31.25)	55(48.25)	59(51.75)	2.03 (1.19−3.47)
	Pre−menopause breast cancer patients	Reference (< 26.65)	47(74.61)	16(25.39)	
		1^{st} vs 2^{nd}(≥ 26.66)	37(59.67)	25(40.33)	1.98 (0.92−4.25)
	Post−menopause breast cancer patients	Reference (< 36.82)	22 (43.24)	29 (56.86)	
		1^{st} vs 2^{nd}(≥ 36.83)	23 (45.09)	28 (54.91)	0.92 (0.42−2.01)
Abdominal total fat (㎟)	All of breast cancer patients	Reference (< 22115)	71(62.83)	42(37.17)	
		1^{st} vs 2^{nd}(≥22116)	58(51.32)	56(48.78)	1.63 (0.96−2.27)
	Pre−menopause breast cancer patients	Reference (< 18175)	45 (71.42)	18 (28.58)	1.47 (0.69−3.12)
		1^{st} vs 2^{nd}(≥ 18176)	39 (62.90)	23 (37.10)	

	Post-menopause breast cancer patients	Reference (< 27711)	23 (45.09)	28 (54.91)	
		1st vs 2nd(≥ 27712)	22 (43.13)	29 (56.87)	1.08 (0.49-2.36)
Abdominal visceral fat (㎟)	All of breast cancer patients	Reference (< 7200)	74(65.48)	39(34.52)	
		1st vs 2nd(≥7201)	55(48.25)	59(51.75)	2.03 (1.19-3.47)
	Pre-menopause breast cancer patients	Reference (< 4978)	47 (74.60)	16 (25.39)	1.98 (0.92-4.24)
		1st vs 2nd(≥ 4979)	37 (59.67)	25 (40.32)	
	Post-menopause breast cancer patients	Reference (< 9804)	23 (45.09)	28 (54.91)	
		1st vs 2nd(≥ 9805)	22 (43.13)	29 (62.87)	1.08 (0.49-2.36)

Table II-17. Odds ratios and 95% CI on Herceptin change in relation to distribution of abdominal fat in breast cancer patients

Factors	Menopause status	Median (range)	No. (%) of participants		Odds ratio(95%CI)
			Positive	Negative	
Abdominal Fat ratio (%)	All of breast cancer patients	Reference (< 31.24)	73(64.60)	40(35.40)	
		1st vs 2nd(≥31.25)	31(27.19)	83(72.81)	1.46 (0.83-2.58)
	Pre-menopause breast cancer patients	Reference (< 26.65)	25 (39.68)	38 (60.32)	
		1st vs 2nd(≥ 26.66)	11(17.74)	51 (82.26)	2.90 (1.33-6.95)
	Post-menopause breast cancer patients	Reference (< 36.82)	19 (37.25)	32 (62.75)	
		1st vs 2nd(≥ 36.83)	16 (31.37)	35 (68.63)	1.20 (0.57-2.94)
Abdominal total fat	All of breast cancer patients	Reference (< 22115)	36(31.85)	77(68.25)	
		1st vs 2nd(≥22116)	35(30.70)	79(69.30)	1.05 (0.60-1.85)

(㎟)	Pre-menopause breast cancer patients	Reference (< 18175)	21 (33.33)	42 (66.66)	1.56 (0.71-3.42)
		1st vs 2nd(≥ 18176)	15 (24.19)	47 (63.81)	
	Post-menopause breast cancer patients	Reference (< 27711)	17 (33.33)	34 (66.66)	
		1st vs 2nd(≥ 27712)	18 (36.30)	33 (64.70)	0.91 (0.40-2.07)
Abdominal visceral fat (㎟)	All of breast cancer patients	Reference (< 7200)	41(36.28)	72(43.72)	
		1st vs 2nd(≥7201)	30(26.31)	84(73.69)	1.59 (0.90-2.80)
	Pre-menopause breast cancer patients	Reference (< 4978)	21 (33.33)	42 (66.66)	
		1st vs 2nd(≥ 4979)	15 (24.19)	47 (63.81)	1.56 (0.71-3.42)
	Post-menopause breast cancer patients	Reference (< 9804)	19 (37.25)	32 (62.75)	
		1st vs 2nd(≥ 9805)	16 (31.37)	35 (28.63)	1.29 (0.57-2.94)

Thus hormones negative of pre-menopausal subjects were more effect of distribution abdominal fat on breast cancer risk than post-menopausal. However BMI was show not a similar pattern with measured distribution of abdominal fat.

Table II-15 to 17 show crude odds ratios of hormone negative score classified as median of abdominal distribution fat factors. Similar result from Table 6, increased of abdominal visceral fat was showing positive associated with hormone negative score in breast cancer patients. For example, the odds ratio of estrogen hormone receptor for the highest vs the lowest median of abdominal fat ratio and of visceral fat were 1.31 (95% CI = 0.74 to 2.29) and 1.42 (95% CI = 0.81 to 2.48); the odds ratio of progesterone hormone receptor for the highest vs the lowest median of abdominal fat ratio and of visceral fat were 2.03 (95% CI = 1.19 to 3.47); odds ratio of Herceptin for the highest vs the lowest median of abdominal fat ratio and of visceral fat were 1.46 (95% CI = 0.83 to 2.58) and 1.59 (95% CI = 0.90 to 2.80). But assessed depending on menopause status, the association value between abdominal distribution fat and hormone status were the more differenced than for total breast cancer patients. The status of hormone negative patients had higher abdominal fat ratio or visceral fat than positive hormone patients in total breast cancer patients. The odds ratio of estrogen hormone receptor; progesterone; Herceptin for the highest

vs the lowest median of abdominal fat ratio and of visceral fat in pre-menopausal patients were 1.87 (95% CI = 0.82 to 4.30) and 1.87 (95% CI = 0.82 to 4.30); 1.98 (95% CI = 0.92 to 4.25) and 1.98 (95% CI = 0.92 to 4.24); 2.90 (95% CI = 1.33 to 6.95) and 1.56 (95% CI = 0.71 to 3.42), the difference in odds ratio between pre-and post-menopausal were 0.6 (ER on visceral) to 1.8 fold elevation (PR on fat ratio). Thus generally higher distributions of abdominal fat ratio or visceral fat with breast cancer patients were the more effect on hormone negative receptor than hormone positive receptor.

Table II-18. Comparison of associated with estrogen receptor (ER) and progesterone receptor (PR) for status of lymph node metastasis of breast cancer, stratified by menopausal status in breast cancer patients

		95% (CI)		
	β	Lower	Upper	p
Postmenopausal				
ER (0, 1)[a]	0.09	−0.038	0.083	0.46
PR(0, 1)[a]	−0.08	−0.092	0.045	0.50

Premenopausal				
ER (0, 1)[a]	0.03	−0.059	0.076	0.79
PR (0, 1)[a]	−0.05	−0.07	0.053	0.71

Result from multiple regressions

a, hormone receptor status: 0 = negative receptor;
1 = positive receptor

Table II−19. Comparison of associated with estrogen receptor (ER) and progesterone receptor (PR) for histological grade of breast cancer, stratified by menopausal status in breast cancer patients

		95% (CI)		
	β	Lower	Upper	p
Postmenopausal				
Estrogen (0, 1)[a]	−0.40	−0.113	−0.031	0.00
Progesterone(0, 1)[a]	−0.01	−0.050	0.043	0.87
Premenopausal				
Estrogen (0, 1)[a]	−0.32	−0.123	−0.019	0.00
Progesterone(0, 1)[a]	−0.12	−0.077	0.024	0.30

Result from multiple regressions

a, hormone receptor status: 0 = negative receptor;

1 = positive receptor

Table II-18 and II-19 shows that association between hormone level (estrogen and progesterone receptor) and status of lymph node metastasis, and association between hormone level (estrogen and progesterone receptor) and histological grade in respectively, stratified by menopausal status in breast cancer patients. This study result shows that no statistical association between lymph node metastasis and hormone level, stratified by menopausal status. But similar associations with hormone level in pre and postmenopausal women. Unlike association with lymph node metastasis, in case of association with histological grade, higher level of estrogen receptor more negatively association with histological grade in pre and postmenopausal women (β = −0.27 for post-menopausal, β = −0.29 for pre-menopausal). Like result with estrogen receptor, also negatively associations between higher progesterone level and histological grade in breast cancer patients (β = −0.12 for post-menopausal, β = −0.18 for pre-menopausal) (Table II-12).

3.5 Association with breast cancer histological grade

Gneral characteristics of subjects and sum daily intake of nutrients categorized as low and high of Histological grade (<2 or ≥2) are presented in Table II-20. There were no statistically significant differences only sum daily intakes of nutrients with adjust for total calories but also age, cross sectional and physical activity depending on low or high histological grade. However abdominal fat ratio was positive association with breast cancer morality (histological grade).

To histological grade of breast cancer via anthropometric factors such as BMI and abdominal fat ratio for histological grade, stratification of the factors into the quartile, which performed logistic regression.

Table II-20. Association of nutrient factors and personality factors on breast cancer depending on histological grade in breast cancer patients

	Histological grade (< 2) Mean ± S.D	Histological grade (≥2) Mean ± S.D	p	^p
Total calories (kcal)	1696.3 ± 536.1.	1721.9 ± 503.4	0.72	
Vegetable protein (g)	34.7 ±10.0	34.9 ± 10.1		0.62
Animal protein (g)	23.0 ± 14.8	24.3 ± 13.7		0.77
Vegetable lipid (g)	12.8 ± 9.4	13.9 ± 8.6		0.48
Animal lipid (g)	17.1 ± 12.7	19.1 ± 11.1		0.44

Glucose (g)	295.1 ± 90.7	293.5 ± 75.1		0.62
Dietary fiber (g)	16.0 ± 5.4	16.0 ± 6.6		0.53
Age (y)	51. ±9.2	52.7 ± 7.7	0.54	
Visceral fat (㎟)	7784 ± 4449	8919± 4411	0.18	
Physical activity (MET score)	914.5 ± 577.9	926.5 ± 622.5	0.91	

p : crude t-test

^P : t-test with adjusted for total calories

Table II-21. The effects of anthropometric and other factors on histological grade in relation to anthropometric factors (in breast cancer patients

		95% (CI)		
	β	Lower	Upper	p
BMI	−0.07	−0.05	0.02	0.46
Cross sectional (㎟)	0.004	0.00	0.00	0.97
Visceral fat(㎟)	0.16	0.000	0.00	0.36
Family history (0. 1)[a]	0.09	−0.17	0.35	0.49
Menopause (0, 1)[b]	0.04	−0.12	0.24	0.52
Menarche (Y)	0.07	−0.03	0.10	0.282
Estrogen	−0.34	−0.10	−0.03	0.000

Progesterone	−0.08	−0.05	0.02	0.386

Result from linear regressions

a, family history: 0, first degree of family history = no; 1, first degree of family history = yes

b, menopause: 0, post menopause; 1, pre menopause

Table II−22. The effects of anthropometric and other factors on lymph node in relation to anthropometric factors in breast cancer patients

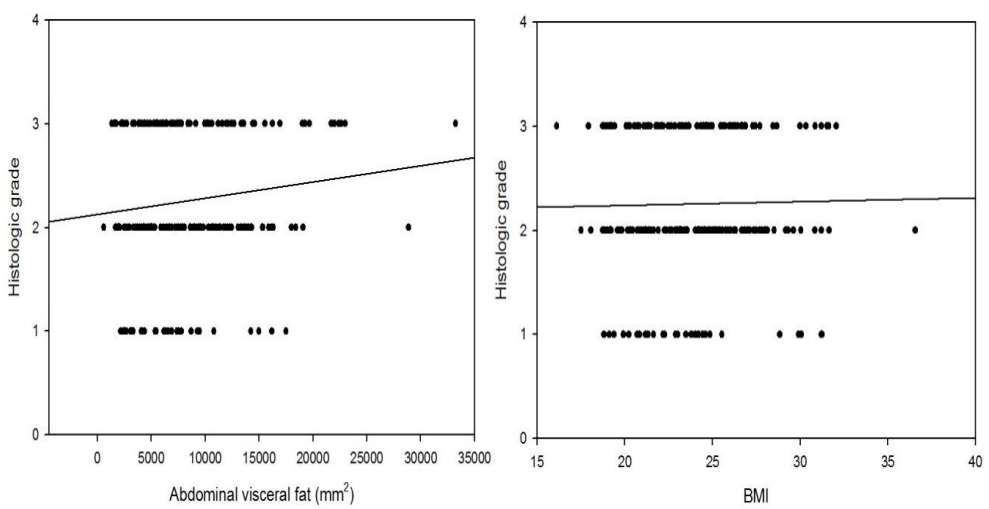
Factors		95% (CI)		p
	β	Lower	Upper	
BMI (kg/m^2)	−0.03	−0.06	0.04	0.74
Cross sectional (㎟)	−0.03	0.00	0.00	0.81
Visceral fat(㎟)	0.06	−2.38	2.51	0.77
Family history (0. 1)[a]	−0.01	−0.42	0.32	0.76

Menopause (0, 1)[b]	0.04	−0.18	0.32	0.59
Menarche (Y)	0.08	−0.03	0.15	0.23
Estrogen	0.02	−0.04	0.05	0.82
Progesterone	−0.01	−0.05	0.04	0.89

Result from linear regressions

a, family history: 0, first degree of family history = no; 1, first degree of family history = yes

b, menopause: 0, post menopause; 1, pre menopause



(a) (b)

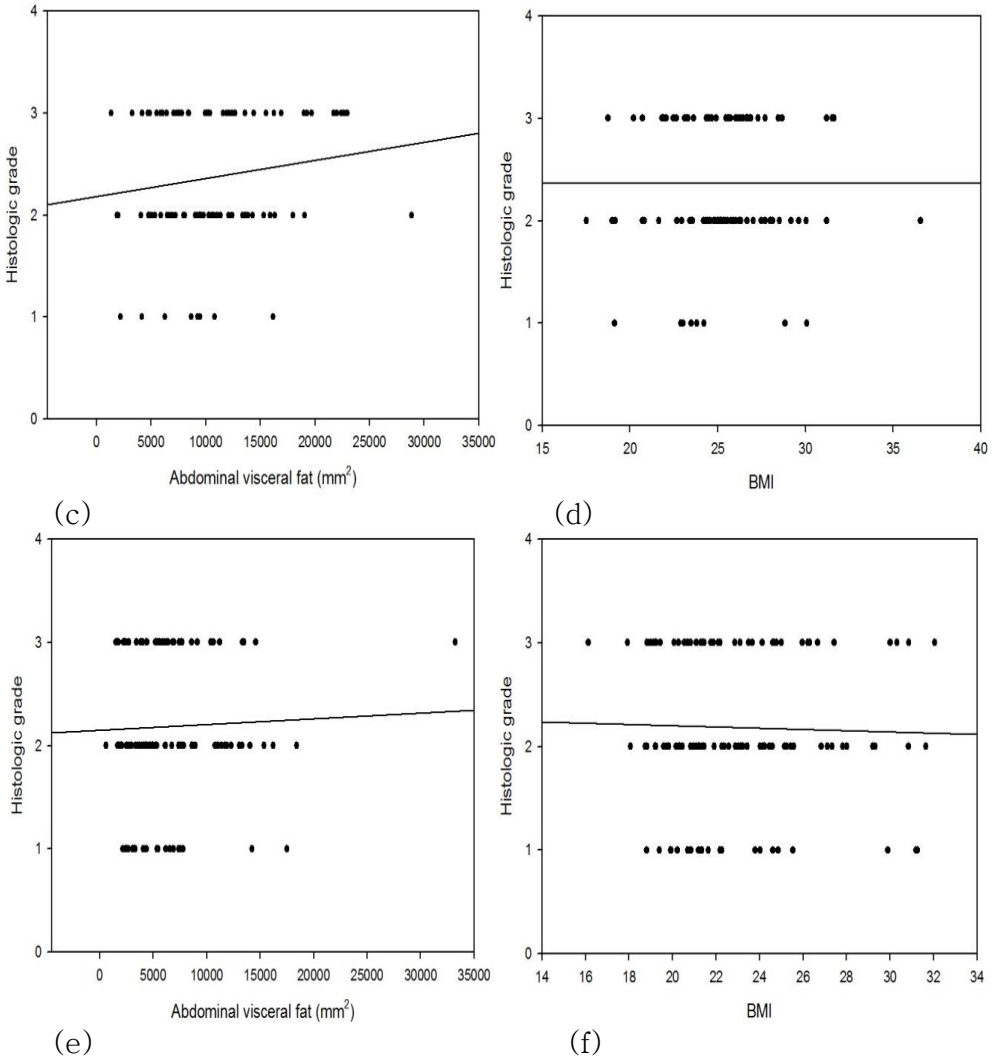


Figure II-8 A simple scatter - regression graph, abdominal visceral fat or BMI effect on histological grade of breast cancer in breast cancer patients. (a) Correlation between abdominal visceral fat and histological grade. A positive relation show histological grade (r = 0.13, p = 0.07 for Pearson correlation). (b) Correlation

between BMI and histological grade. No relation show with BMI (r = 0.01, p = 0.79 for Pearson correlation). (c) Correlation between abdominal visceral fat and histological grade in post-menopausal. A positive relation show histological grade (r = 0.07, p = 0.67 for Pearson correlation; r = 0.17). (d) Correlation between BMI and histological grade in post-menopausal. No relation show with BMI (r = 0.01, p = 0.98 for Pearson correlation). (e) Correlation between abdominal visceral fat and histological grade in pre-menopausal. A positive relation show histological grade (r = 0.15, p = 0.14 for Pearson correlation). (f) Correlation between BMI and histological grade. No relation show with BMI (r =- 0.03, p = 0.74 for Pearson correlation).

Figure II-8 show abdominal visceral fat and BMI effect on Histologic grade. Higher abdominal visceral fat was positive relation with histological grade (r = 0.13, p = 0.07 for Pearson correlation), but weak statistical association. However BMI was no relation with histologic grade in any case.

3.6 Association with smoking and alcohol

There were no significant associations of smoking and alcohol consumption to incidence of breast cancer by binary regression model (Table II-23), in case and control study.

Table II-23. Odds ratios and 95% CI on breast cancer risk in relation to smoking and alcohol consumption in case-control study

	Odds ratio	(95% CI)	
		Lower	Upper
Smoking			
Never	1.0 (Referent)		
Ever	0.93	0.224	3.870
Current	0.26	0.053	1.325
P for trend	0.47		
Alcohol			
Never	1.0(Referent)		
Ever	0.66	0.345	1.245
Current	0.78	0.131	2.569
P for trend	0.19		

4. Discussions

The prevalence of overweight and obesity are increasing globally and has become common health conditions. It is well known that overweight is associated with increased incidence of certain type cancers (Ferlay J et al 2002, 2004; Stewart et al 2003). Many studies have shown that obesity increases the risk of breast cancer, especially cohort study with postmenopausal women (Ferlay J et al 2002, 2004; Stewart et al 2003; Porter P. 2008; Cynthia et al 2014).

May be greater consumption of Fruits and vegetables are moderate change related to women hormonal altered from animal fat intakes. It is unclear which components of fruits and vegetables are preventing cancer, but there are some possible mechanisms. Fruits and vegetables are 100 potentially beneficial vitamins, minerals, fiber, and phytochemicals (lycopene, phenolic compounds, and flavonoids) associated with a modest reduction in the risk of breast cancer (Byers et al, 2002; Kushi, et al 2010).

In this case-control study, I observed significant inversely relationships between dietary fiber and risk of breast cancer (differenced in case and control $p = 0.003$; $\beta = -2.20$ adjusted for total calories), and weak positively relationships between animal lipid (differenced in case and control $p = 0.37$; $\beta = 2.18$ adjusted for total calories). However I observed no significant relations between other nutrients and risk of breast cancer. Such

results are consistent with previous studies reporting association between consumption of fruits and vegetables and risk of breast cancer. In contrast with our findings, however, many studies reported that inconsistent with intake of diet (animal fat intake or fruit and vegetables) as a risk factor on breast cancer (Smith-Warner et al, 2001, Pierece, J. P et al 2007), while results of this study is show strong associated with intake of high fat or low fruit and vegetables as a risk factor on breast cancer.

There is good evidence that breast cancer may be the result of the Western diet and lifestyle. Breast cancer is rare in Japanese women living on Japan (21.1 per 100,000 populations), but when they migrate to the U. S, their incidence of breast cancer (49.4 per 100,000 populations) approaches the average U.S risk within one generation (Shimizu et al 1991).

Some healthy diet food alone was not significantly protective breast cancer due to a lot of effect of factors on breast cancer, but breast cancer patients are lower intake of fruit and vegetables such as tomato, water melon, lettuce, cabbage kimchi, perilla leaf, pepper leaves, and tangerine and high intake of animal lipid such as pork belly and chicken was higher significant risk of cancer in this study. Tomatoes are popular in Korea. Tomato products contain lycopene as phytochemicals has been proposed to protect against cell cycle proliferation of mammary human cancer (Prakash et al., 2001). A recent relevant study was reported the no association between lycopene consumption and breast cancer

(Sesso et al., 2005), but may be there seemed to be different effects for estrogen receptor status breast cancer. In this study, intake of pepper, including pepper leaves and pepper chilli, is statistical significant or mild difference between breast cancer patients and normal participants. Still inconsistent with flavonoid, flavonol is also a major component of pepper, which may have a protective effect on breast cancer risk in animal and epidemiologic studies (Bosetti et al., 2005). Remained still controversial effect of citrus on breast cancer risk (Malin et al., 2003; Jung et al., 2012), this study show intake of Korean tangerine may be associated with a reduced risk of breast cancer due to intake of cancer patients lower statistically significant than those normal participants. Other fruit and vegetables are (Kimchi, perilla leaf, lettuce, and water melon) were significantly difference between case and control, but has been no evidence for significantly associated with breast cancer.

From previous studies, breast cancer is higher among women intake a western diet, which is consistent with consumption of animal fat food items (chicken, pork, and beef) also strong positive association animal fat (pork and chicken) and breast cancer risk in this study. However, this association has not been found in prospective studies. That reason with inconsistent result among relate to breast cancer risk is due to risk factors on breast cancer vary greatly and complex. 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine compound of heterocyclic amines,

made from overcooked foods are reported strong mutagenic in various investigations (Felton et al., 2002). Another biological plausibility of an association between animal fat and breast cancer risk is effect on mammary carcinogenesis in animals. Eicosanoids are belong to a complex family of lipid fatty acids potent regulator that the generation of free radicals and mutagenic compounds like as malondialdehyde by lipid peroxidation and the meditation of genes that are entailed mammary carcinogenesis (Boyd et al ., 2003)

In the developed countries (U.S.A), aging is related to an increased incidence rate of breast cancer (Figure II-7) as well as previous related to study show same result (Timothy et al., 2001). However in Korea revealed a striking difference in peak incidence, the age-specific incidence rate was showing a increasing to their 40s and a decreasing trend in incidence with aging (Figure III-7). Therefore the median age of newly diagnosed breast cancer in Korea in 2012 was found to be 49 years and a 12 younger than that in U.S.A. (median age 61 years between 2003 and 2007) (Ries . 2008; Korean National Cancer Information Center. 2014). Under 40s in Korea was adapted western diet and life style in earnest (intake of high fat and low vegetable), but over 50s was more intake traditional diet (intake of high vegetable and low animal product) than that under 40s. Thus, changing lifestyles might increase the risk of breast cancer, especially in premenopausal Korean women.

Also this study result show similarly. Namely, because of that reason, evidence that effect on risk factor on breast cancer and may be increased in a risk factor on breast cancer in 30 ~ 40s in Korea.

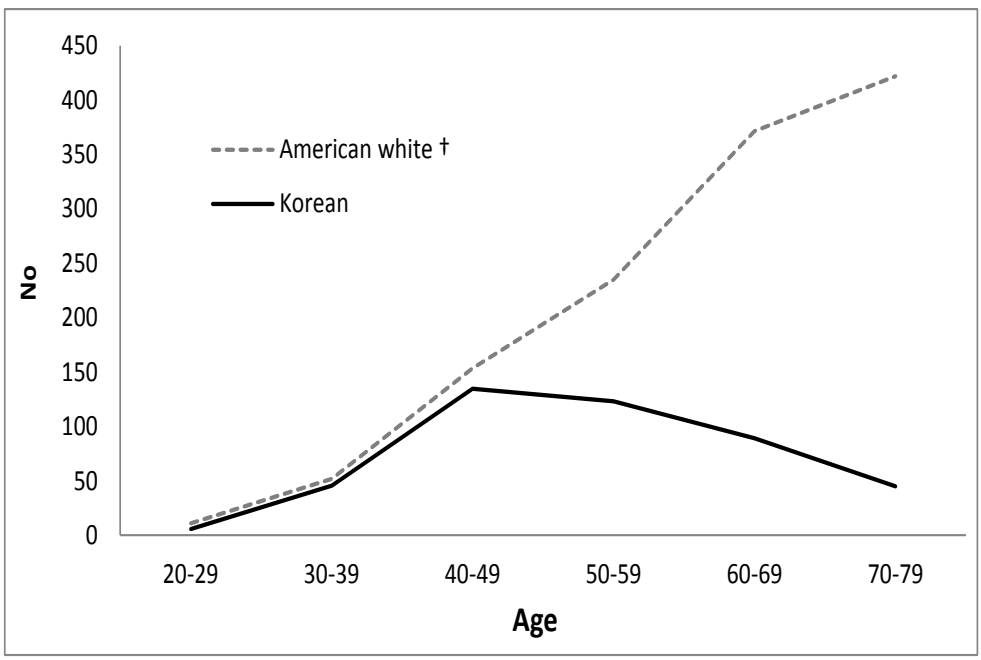


Figure II-9. Comparison of increase in age-specific crude incidence rates of breast cancer between U.S.A and Korean breast cancer patients (data from the surveillance, epidemiology and end results (SEER) 17 data (2003-2007)). No is patients number per 100,000 women

Otherwise a dietary fat that is a prominent component of the Western diet is existed as related to leading to activate estrogen hormone level (Key er al., 1988). Therefore higher estrogen level promoter of mammary tumor cell growth and induced normal DNA

adduction (Liehr et al., 1986; IARC, 1999). The source of estrogens in postmenopausal women is from the convert androgens of stored adipose to estrogens, while the ovaries are the primary source of estrogens in the premenopausal women (Feigelson and Henderson, 1996). Thus obesity is more associated with risk of breast cancer in postmenopausal women. However many studies related to breast cancer have been inconsistent with associations between estrogen receptor positive or negative tumors and obesity for risk of breast cancer. According to slattery's et al study in 2007, estrogen receptor negative tumors were associated with obesity among non-Hispanic white women, while opposite relationships were shown among Hispanic women. That reason is the genetic differences in these relationships (Slattery et al, 2007).

Though estrogen receptor is known to risk factor on breast cancer, restricting to associations between hormone status and breast cancer risk in this study, because normal participants were not include hormone assay in health examination service by national health insurance. Therefore analysis only associated with histological grade or status of lymph node metastasis in breast cancer patients, stratified by hormone status. Consistent with previous study reported, this study result shown that patients with estrogen receptor negative are more association with histological grade of breast cancer than positive women in postmenopausal women.

Determination of hormone status of invasive breast cancer is useful as a prognostic and metabolic factor and has become standard practice in the treatment of this cancer (Bauer, et al., 2007). Previous studies have found associations between body fat distribution and hormone receptor status. Thus abdominal distribution fat is metabolic indicators in breast cancer women, and may play a role in the pre-menopausal breast cancer risk (Harris et al., 2011), though more effect of visceral fat on breast cancer incidence in post-menopausal women. Classified as menopause status, abdominal distribution fat were similar results depending on hormone status in post-menopausal women. In this study, ER/PR/Herceptin negative breast cancers that founded markers of rapid growth, a reflection of their poor biological character (Darling, et al., 2001; Rose, et al., 2004). We used a classification system and logistic regression approach to analyze the association between abdominal distribution fat and hormone status. Our finding (Table 6 ~ 9) that higher abdominal distribution fat (abdominal visceral fat) with breast cancer patients were elevated odds ratio for ER/PR/Herceptin negative status (1.31 to 2.03; odds ratio of ER/PR/Herceptin for the highest vs the lowest median of abdominal visceral fat) than ER/PR/Herceptin positive. Also abdominal visceral fat was more associated with risk of ER/PR/Herceptin negative breast cancer than with the risk of ER/PR/Herceptin positive breast cancer suggests that visceral fat may influence the risk of breast cancer, especially in pre-menopausal women. Generally breast

cancer patients with ER/PR/Herceptin positive are lower risks of mortality after their diagnosis compared to ER/PR/Herceptin negative women (Dunnwald and Rossinq. 2007; Denni et al., 2011). Our finding with previous related studies provide evidence to support that abdominal adiposity may influence the risk of pre-menopausal breast cancer through sex hormone-independent pathways.

Few studies have classified ER and PR status by abdominal fat distribution, but related studies that have examined breast cancer risk factors by either ER or PR status separately have shown inconsistent results. But many related studies provided that similar result on the association between risk factors and outcome.

Oestrogen and progesterone affect the rate of cell division which causes proliferation of breast epithelial cells and may involve biological independent of hormonal exposure (Carmichael and Bates. 2004). But the causal pathways for ER and PR status breast cancer are not fully understood. PR status may play a role in the incidence of breast cancer and estrogen augment (Nancy, et al., 1991; Robert, et al., 2004). Maehele et al reported that, obese with PR negative breast cancer patients have a 1.53 higher risk of lymph node metastases than non-obese women, but not this association with ER (Maehele, et al., 2004). According to previous study, ER and PR positive status was a stronger marker for the advantage of adjuvant endocrine treatment than hormone positive status (Ferno et al., 2000; Ellis, et al., 2001; Bardou, et al., 2003). Moreover, clinical

studies have confirmed that a benefit response rate in ER and PR positive cancers compared with ER positive and PR negative cancers (Ellis, et al., 2001), and also PR positive cancers was a more good response tamoxifen compared with ER negative cancer (Early Breast Cancer Trialists). PR and ER positive cancers derive the greatest good response from adjuvant hormone therapy. If ER or PR is only present, this benefit reduces by almost half. Because the PR is regulated by ER pathway in breast, PR is synthesized by cancer cells that are promoted by estrogens through an interaction with ER (Bardou, et al., 2003). Therefore PR status is improves the better biomarker of hormonal responses than ER because ER may be present but not functional in some breast cancer patients (Table II-15 ~ 17). The bio mechanistic links between obesity and breast cancer risk and PR are likely to be more complex than a simple dependence on changes in ER and PR balance (Suzuki, et al., 2009; McFall, et al., 2015). Unlike obesity is positive associated with post-menopause women, many studies reported protective relationship between obese and pre-menopause women. A growth frequency of anovulation of low progesterone level in the lutal phase, may partially explain the related to pre-menopausal breast cancer (Barnett, 2003; Kaaks, et al., 1998). But bio-mechanism of estradiol shows to be almost remained for ovulatory cycle and decreased for anovulatory cycle (Kaaks, et al., 1998; Pike, et al., 1993). After menopause, ovarian secretion of progesterone ends, and estrogens secreted mainly by the conversion of androgens in

adipose tissue, remained steroid hormones foster breast cancer (Kaaks, et al., 1998; Pike, et al., 1993). According to Pike et al study, that contrasting effects were association with obesity in the pre and post-menopausal status can be explained by the estrogen augmented by progestogen hypothesis (Kaaks, et al., 1998; Pike, et al., 1993). According to previous studies related to obesity and hormone status for breast cancer, a high BMI and a high glycemic load diets were modestly significant increase in ER and PR negative status among pre-menopausal women, especially PR status was more associated with obesity than ER status, although using BMI or as obesity (Esfahlan, et al., 2011; Suzuki, et al., 2009; Larsson, et al., 2009; Zong, et al., 2014; McFall, et al., 2015). Also our results present ER and PR negative were associated with abdominal visceral fat among pre-menopausal women (PR was more associate with visceral fat compared with ER) compared with post-menopausal women. However, among post-menopausal women, we observed similar ER and PR status level for abdominal distribution fat compared with pre-menopausal women case.

Hormonal therapy is suitable for patients with ER/PR/Herceptin positive, not candidates for patients with hormone receptors negative (Julie, et al 2002; Emad et al., 2007). Especially Herceptin negative cancers are more likely to be poorly differentiated, of higher histological grade, associated with a higher recurrence rate, so lack the benefit of trastuzumab-based therapy like as specific targets therapy (Pichon, et al., 1996; Emad, et al.,

2007; Perez, et al., 2010). Visceral fat is also related with worse prognosis and poor treatment outcome in breast cancer, while hormone positivity in breast cancer is related to a good prognosis (Rose, et al., 2004). Therefore treatments options for these triple-negative breast cancer patients classified as ductal carcinoma are more limited. Furthermore, hormone negative tumors are the peak of breast cancer death occur range from 2 to 4 years after diagnosis, while women with positive have a consistent long term death (Jatoi et al, 2007).

As shown Figure II-9, the rate of estrogen receptor positive breast cancer increased from 49.6% in 1996 to 70.0% in 2010 in South Korea. That reason is the increase in young breast cancer patients with estrogen positive due to changing into westernization (Devi et al 2012).

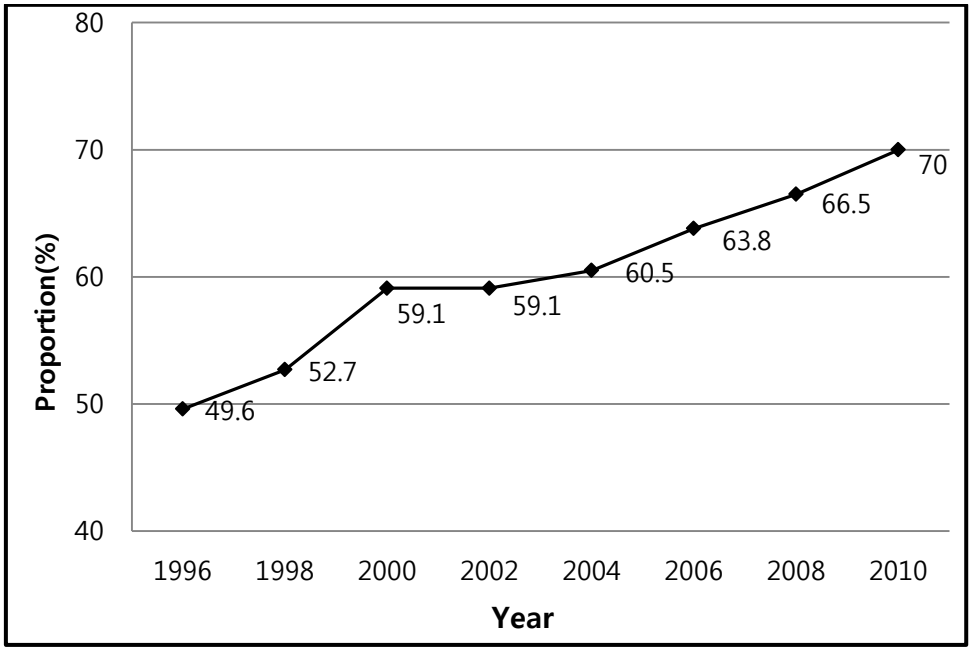


Figure II-10. The trend in estrogen receptor positive breast cancer in Korea (data adapted from Ko et al., 2012)

Breast cancer is influenced by hormonal factors, differing effects of adiposity on menopausal status. Therefore may be associated with nutrient consumption stronger for histological grade of breast cancer to premenopausal compared with postmenopausal patients, I was compared with nutrients stratified by menopausal status. Most studies have shown no evidence of an interaction by menstruation status (Smith-Warner et al, 2001). Like these studies, I also found no evidence that interacted with low fruits and vegetables consumption stronger for high compared with low histological grade of breast cancer groups. But two groups (low or high histological grade of breast cancer) were similar consumed

dietary fiber also other nutrients. Thus I found no evidence that adoption of dietary fiber effects on lower histological grade of breast cancer ($p = 0.53$ adjust for total calories). This result is consistent with previous studies reported (Pierece, J. P et al 2007).

Higher visceral fat is a recognized risk factor for breast cancer in post-menopausal women, whereas in pre-menopausal women there is a negative relationship between the abdominal fat and breast cancer risk. However, regardless of menopausal status, breast cancer patients who are more likely to have an adverse effect on breast cancer prognosis than those who are non-obese. That is, abdominal fat has a poor outcome (higher histological grade), but with a difference; the effects are similar in both pre- and post-menopausal women. Also our data from association between histologic grade and distribution of abdominal fat provide to support hypothesis that effect on breast cancer risk according to hormone receptor status. Related microarray studies have found that correspond a distinct gene expression profiles, strong correlation between the histologic grade and hormonal receptor status (Sorlie, et al., 2003; Sotiriou, et al., 2003). But BMI, no associated with histologic grade in any hormone receptor.

Though estrogen receptor is known to risk factor on breast cancer, restricting to associations between hormone status and breast cancer risk in this study, because normal participants were not include hormone assay in health examination service by national health insurance. Therefore analysis only associated with

histological grade in breast cancer patients, stratified by hormone status.

Some cohort studies have been weak correlation between BMI and breast cancer than case-control studies (Yong et al., 1996; Carroll. 1988). Still previous study shows that obscurity link obesity via conventional anthropometric measurements and breast cancer risk. A reason for such outcomes could be classical anthropometric measures such as weight and BMI. Breast cancer associated with obesity may be influenced by the distribution of body fat than classical anthropometric measure (Carroll, 1998). An increase in central obesity has been reported to contribute to the risk of breast cancer. Consistent with previous study, this study result show that central obesity has association with breast cancer (Kwan et al., 2014; Fukuda et al 2015), but body indicators such as BMI was a little or no effects on breast cancer than central obesity. Generally Asian populations have tend to higher abdominal and visceral adiposity compared to Caucasians (Fukuda et al, 2015; Lim et al, 2011; Amadou et al, 2013), it is not clear that reason, but it may be related to genetic factor to higher amount of visceral fat (Lim et al, 2011; Amadou et al, 2013).

The mechanisms by which abdominal obesity risk of increases breast cancer that presents to be an independent predictor of insulin resistance, associated with an increased level of FFA, TNFα, and resistin, lower levels of sex hormone-binding protein and increased bioavailability of oestradiol compared to

general lean body (Figure I-5)(Calle and Kaaks 2004; Amadou et al, 2013). Therefore high level of insulin and IGF 1 signal to promote cellular proliferation and inhibit apoptosis in many tissues so that might leads to tumorigenesis (Calle and Kaaks 2004).

Body fat distribution may be more important to the risk of hormone status breast cancer during a woman's reproductive years, when ovarian hormones predominate, because abdominal fat distribution may reflect a greater accumulation of more biologically active fat. This reason that is the influence of obesity on the biological process, such as tumor necrosis factor alpha (TNF-α), plasminogen activator inhibitor-1 (PAI-1), and leptin than non-obese women (Kern, et al., 1995; Eriksson, et al., 1998;Considine, et al., 1996). Adipose tissue has composed of subcutaneous and visceral. Subcutaneous adipose is the defined as layer of subcutaneous tissue, whereas visceral adipose is within the main cavities of the abdomen known as organ fat or intra-abdominal fat. Visceral adipose is more metabolically active and hormonal changes than subcutaneous adipose, and it is correlated with metabolic and hormonal changes, including insulin action (hyperinsulinemia and insulin resistance), increased levels of free fatty acids, decrease sex hormone- binding globulin levels, and elevated bioavailability of estradiol (Kirschner, et al., 1990; Bruning, et al., 1992; Julie, A., et al 2002; Harvie, et al., 2003; Harris, et al., 2011), which may play a role related with increased breast cancer risk, although subcutaneous fat may play a similar role (Julie, A., et al 2002;

Robert et al., 2004; Vona-Davis, etal., 2007; Boonyaratanakornkit, V. and Pateetin, P. 2015).

Abdominal visceral fat on breast cancer was more positive effect on the risk and histological grade in premenopausal women than postmenopausal women (Harvie et al, 2003) (Table II-12). There were no associations between intake of total calories and body indicators (BMI, abdominal fat). Also was weak correlation with abdominal fat ratio than visceral fat. Thus BMI was inappropriate body indicator as risk factor on breast cancer.

Breast cancers were effect on more visceral fat compared to subcutaneous fat than controls, as measured by computed tomography. Using CT has afforded an insight into cross sectional body image also quantification of body fat. Previous studies have presented CT to be an accurate method for measuring body fat distribution (van der Kooy, 1993; Weits, 1998; Carroll, 1998).

Education level and socio-economic status might reflect beneficial habits such as specific dietary habits and physical activity, which in turn, may be relevant to reproductive pattern (Gandini et al, 2000). In this study, higher education level was inverse association with risk of breast cancer, and with histological grade of breast cancer in postmenopausal women. But there were neutral association between education level and histological grade of breast cancer in premenopausal women. That reason, under 40s years generation (after 1970's birth) in Korea has grown up with economic development in prosperity, and changing lifestyle pattern

than before generation (postmenopausal women). This result is consistent with incidence of breast cancer in Korea.

In this study, physical activity was low related with risk of breast cancer, and inconsistent with histological grade of breast cancer, stratified by menopausal status. According to related to breast cancer study reported that consistently inverse associated with physical activity. That reason is due to limitations in the using unsuitable survey tool in this study. Later study needed more an accurate tool to estimate physical activity for subjects.

Early age menarche had a strong effect on premenopausal breast cancer risk; with risk is inverse association with increasing age. According to previous study, women who had menarche age less than 11 years have an increased risk of breast cancer compared to women experiencing menarche over 15 years (relative risk 3)(McPherson et al., 2000; Clavel-Chapelon and E3N-EPIC group. 2002). There are show no inversely associations between age of menarche and risk of breast cancer in this study. Because no statistically difference in age between case (mean age and S.D for normal participants: 15.1 $\pm$ 1.8) and control (mean age and S.D for normal participants: 14.9 $\pm$ 1.7) due to age matched for subjects ($p < 0.05$) and all of subjects' age were approximately over 15 years.

Effect of first degree of family history on breast cancer has shown positively association with long been recognized as a significant risk factor on breast cancer.

As a result, depending on histological grade, there are no nutrition and personality factors for histological grade on breast cancer except for abdominal fat ratio. That is only abdominal fat ratio is associated with risk or histological grade of breast cancer.

Generally related to breast cancer study reported that smoking was not associated with a raised risk of breast cancer in postmenopausal women, but increasing breast cancer only in premenopausal women when exposure before age 16 years (Band et al., 2002; Hamajima et al., 2002).

Generally similar age, gender, BMI has same % body fat distribution. But despite their similar BMI, visceral fat content has variation in age, sex, and race (Camhi et al, 2011). The assessment of fat distribution has important issue in obesity research because this visceral fat seems to be most strongly associated with not only metabolic disorders but also cancer (von Hafe et al, 2004; Hamilton et al, 2011; Vona-Davis et al, 2007). Therefore underlying mechanisms for association between adiposity and breast cancer risk are poorly understood (Julie, A., et al 2002; Sinicrope, F. A. and Dannenberg, A. J. 2011). However using CT has afforded an insight into cross sectional body image also quantification of body fat. Previous studies have presented CT to be an accurate method for measuring body fat distribution (van der Kooy, 1993; Weits, 1998; Carroll, 1998). Ideally measurement of the abdominal fat compartment on breast cancer risk should rely on technique such as CT, which provide the best overall predictor of breast cancer

(Weits et al., 1998).

Alcohol consumption is neutral or moderate positively associated with breast cancer risk in most epidemiologic studies (McPherson et al., 2000; Hamajima et al., 2002). Consistent with previous study, this study also show no statistically significant association with alcohol consumption.

Despite the common misperception that breast cancer is largely a problem of developed countries, an increasing at a more rapid rate of breast cancer incidence in developing income countries than developed countries (Ferlay et al., 2004). Actually ongoing research, largely breast cancer patients were exposure to poor occupational environmental such as exposure to solvents and pesticides, and night shift work (Band et al., 200; Hansen, 2001).

In Korea, trends in breast cancer incidence has been steadily increasing, so needed regular checkup and screening activity for prevent breast cancer risk. Using specific variable alone was not significantly associated with breast cancer.

III. Summary and limitation

In conclusion, these results indicate that intake of higher animal products and lower dietary fiber may influence the risk of breast cancer. Also the findings of this study support physical activity may be associated with lower risk of breast cancer. Abdominal fat ratio obtained from cross-sectional image is strong association with risk and histological grade, useful things a good biomarker for not only breast cancer risk also than any other anthropometric measurements. Our results suggest that healthy lifestyle behaviors recommend for nutrition and physical activity behavior may be associated with lower risk of cancer.

In contrast to other diseases, this study is necessary to a number of subjects because of a most difficult and complicated area of study related to diet and cancer remains at present (Boyle et al., 2008). This study had several limitations. First, study subjects were too small size to assess a reliable association with breast cancer risk.

Although the FFQ in this study was specifically designed for estimating cancer, total energy intake was generally found that low estimated among previous studies with this FFQ format (Park et al., 2012), while comparing with other FFQ format. And generally cancer patients visited NCC has low income and low socio-economic status in this study, so under estimated for total energy

intake.

May be differenced result of nutrient obtained from CAN-pro between patients and normal subjects due to difference in estimator for patients and normal subjects, although using same FFQ format and CAN-pro analysis in patients and normal subjects.

Abdominal fat ratio was directly measured visceral fat and subcutaneous fat thickness via the adapted for dedicated computer at the umbilicus level based on CT in this study. To reduced measurement error, conducting 2 times repeated measured. But the value of visceral and subcutaneous fat is can be varied by assessing method and choosing measurement of body part due to subjective evaluation by the man.

Another limitation is selection bias that may occur, which is inherent in retrospective normal subjects and possibility that certain type of subjects visit in this study hospital, although age-matched for case-control subjects and assessed by categorized as characteristics.

There are not able to determined incident of cancer depending on study on only intake of dietary and measurement of anthropometric due to a lot of effect of factors on cancer. The purpose of present study has been to know association between obesity and breast cancer. As progression in this study, investigator directly to meet cancer patients felt seemed that only effect of obesity on cancer incidence but also most of cancer patients have been experienced high level of stress in meanwhile, although this

study result showed no associated with stress level. Therefore further study is needed for association between stress level and risk of cancer from using optimized measurement tool for perceived stress.

IV. Overall Discussion and Conclusions

I focused on breast cancer because this cancer has the most prevalent cancer in Korea, similar good prognosis in the early diagnosis stage, and hormonally dependent, while differently expressed and degree of physical impairment (Korean National Cancer Information Center 2014).There are several mechanism can explain the rising incidence of cancers, but these cancer risks can vary over the 10 fold exposure by environment factors. In related evolution study indicate that the breast cancer appeared with development of mammals, and dietary adaptation to changing Western diet and sedentary life style pattern as evolution, there has been allow insufficient time to biological selection a proper defense for human biology system (Coffey, 2001). There has been an another evident that as people migrate from Asia to the United States, the low risks observed in their mother land begin to rise with spent time and subsequent generations toward those approached incidence level in the general United States population (Shimizu et al., 1991; Grover and Martin, 2002). Also incidence rates of breast cancer has been rising in South Korea, that factors may result with change in intake of high fat western diet, reproductive patterns, lack of physical activity, obesity, and rising stress level the main contributory factors (Antoni et al., 2006; Stewart et al., 2003; Boyle et al., 2008; KNHANES 2010; Korean National Cancer Information Center 2014).

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Abstract in Korea (국문 초록)

비만으로 인한 유방암 발생의 영향 연구: 복부비만도 측정과 그 외 생활 요인

최근 우리나라의 암 발생률은 꾸준히 증가추세에 있고 그 중에서도 유방암의 경우 갑상선암을 제외했을 때 여성에서 가장 높은 증가 추세를 보이고 있는 암이다. 유방암은 그 동안 선진국에서 주로 발병하는 것으로 알려진 암 종이지만 서구화된 식습관과 생활 행태 변화로 인하여 국내에서도 발생률이 증가하는 것으로 추정하고 있다. 따라서 국내 환경에 맞는 적절한 영양 조사와 내장 지방 분포와 같은 정확한 비만도 영향 측정을 통해 우리나라에서 증가율 1위를 보이고 있는 유방암암 발생의 원인 관계를 찾고자 한다.

본 연구는 환자와 정상군 비교를 하는 환자-대조군 연구이고 본 연구를 위하여 임상시험 윤리위원회 (IRB) 승인을 받았다 (NCC2014-0124). 환자군은 2014년 8월 1일부터 2015년 5월 22일 까지 국립암센터를 방문하여 유방암과 전립선암을 진단받고 수술과 항암치료 그리고 방사선 치료를 시작하지 않은 초진을 대상으로 하였고, 정상군은 2011년 11월부터 2014년 11월 30일까지 공단검진을 목적으로 국립암센테를 방문한 정상인을 대상으로 하였다. 모든 연구 대상자들 중에서 CT (유방암 연구) 검사를 시행하지 않은 경우 연구 결과에 포함하지 않았다. 유방암 연구는 환자 총 255명에 평균 50.5세 (29 – 75세)이고 정상군은 총 220명에 평균 54.5세 (37 – 70세) 이다. 각 대상자들의 영양 조사는 국립암센터 연구소에서 암환자 연구를 위해

개발한 FFQ를 이용하여 연구자 본인이 환자 대상으로 직접 시행하고 분석하였다. 정상군의 경우 동일한 FFQ에서 나온 영양 결과를 활용하였다. 더불어 모든 연구 대상자들의 생활 요인 평가를 위하여 암 가족력, 흡연, 음주 상태, 운동, 생리 정보(여성의 경우 초경과 폐경 여부) 등을 추가적으로 설문 조사하였다. 대상자들의 비만 측정은 단면 영상 정보를 제공해줄 수 있는 CT 영상의 배꼽 주위에서의 내장 지방과 피하지방을 전용 분석 컴퓨터를 활용하여 측정 하였다.

유방암 연구 결과 유방암 환자가 정상인 보다 총 열량을 보정하였을 때 식이 섬유를 통계적으로 유의하게 적은 양을 섭취하였고 ($p = 0.003$) 동물성 영양소는 큰 차이를 보이지 안았으나 유방암 발생의 영향 관계에서는 ($\beta = 2.18$, $p = 0.001$) 명확한 결과를 보였다. 유방암 환자 중 폐경 전 젊은 여성이 폐경 후 노인 여성 보다 통계적 유의한 육식을 섭취하여 40대에 유방암 발생과 서구화된 음식 섭취 변화 차이를 확연히 보여주고 있다. 비만의 유방암 발생 위험 영향 요인 척도 평가는 BMI에서는 무상관, 허리둘레 척도와는 미약한 양의 상관 관계를 보였지만 복부 내장 지방의 경우 정상군과 확연한 차이를 ($p = 0.02$) 보였을 뿐만 아니라 악성도 영향 상관성도 ($r = 0.26$) 보였다. 이런 복부 비만과 유방암 악성도의 양의 상관성은 폐경 후 여성에서는 양성관계를 폐경 전 여성에서는 반비례 관계를 나타냈다. 한편 초경 연령, 학력, 운동량, 흡연, 음주에 따른 유방암 발생과는 뚜렷한 영향 관계를 보이지 않았다.

결론적으로 본 연구를 통해서 국내에서도 유방암 발생은 높은 동물성 지방과 낮은 식이 섬유로 인하여 그 위험도가 증가됨을 알 수 있고 가속화되고 있는 서양식습관의 위험성을 홍보하는데 활용될 수 있을 것으로 기대한다. 또한 유방암의 발생 위험도와 복부 비만도의 연관성이

높아 암 발생의 지표로서 유용성을 보였다.

주요어: 유방암, 비만, 복부 비만도, FFQ

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