외표지

의학석사 학위논문

한국 여성에서의 체질량 지수에 따른 분자생물학적 분류별 유방암 위험도: 사례 대조군 연구

Body mass index and risk of breast cancer molecular subtypes in Korean women : a case control study

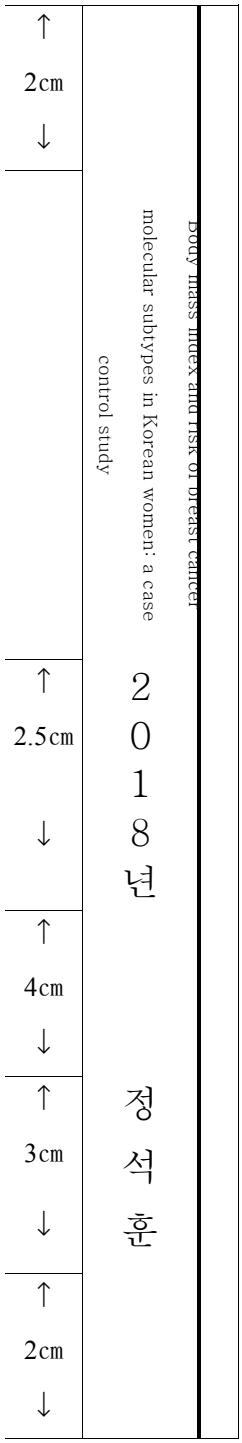
2018년 2월

서울대학교 대학원

협동과정 종양생물학전공

정 석 훈

표지측면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지도 교수 박 수 경

이 논문을 의학석사 학위논문으로 제출함
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정 석 훈

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Body mass index and risk of breast cancer molecular subtypes in Korean women

: a case control study

by

Seok Hun Jeong

A thesis submitted to the Interdisciplinary program in Cancer Biology in partial fulfillment of the requirements for the Degree of Master of Science in Medicine at Seoul National University College of Medicine

January 2018

Approved by Thesis Committee:

Professor _____Chairman

Professor _____Vice

chairman

Professor _____

Abstract

Body mass index and risk of breast cancer molecular subtypes in Korean women: a case control study

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Seoul National University

College of Medicine

Background: Obesity has been suggested as a risk factor for postmenopausal breast cancer. However, the effects of obesity on developing different subtypes of breast cancer remain unclear, particularly for premenopausal women.

Methods: This study aims to evaluate the association between body mass index (BMI, kg/m2) and risks of the subtypes including Luminal A (ER and PgR + and HER2− and Ki−67<14%), Luminal B−HER2 negative (ER + and HER2 − and (Ki−67≥14% or PgR −)), Luminal B−HER2 positive (ER + and HER2 + and any Ki−67, any PgR), HER2−express (ER− and PgR− and HER2 +), Triple negative (ER− and PgR− and HER2 −). Based on a community−based case−control study design, a total of 101,274 female breast cancer patients (35−80 years old) diagnosed between 2003 and 2010 were individually matched by age to healthy women (1:2 ratios of cases and controls). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using multivariate logistic regression with normal weight (BMI 18.5−22.9) as the reference group of exposures.

Results: For post-menopausal women, breast cancer risk of Luminal B-her negative type increased in the obese II group (BMI≥30) (OR: 3.22 CI: 2.41-4.31), which showed similar results for other subtypes. For pre-menopausal women, being underweight (BMI <18.5) was related to increased risk of Luminal A (OR: 1.23 CI: 1.09-1.39). In addition, the obese II group (BMI≥30) was more likely to develop basal-like breast cancer (OR: 1.63 CI: 1.29-2.05). For those with BC family history for pre-menopausal women, being underweight (BMI <18.5) was related to increased risk of HER2 express (OR: 2.41 CI: 1.21-4.80) and Triple-negative (OR: 1.98 CI: 1.22-3.22).

Conclusions: Our findings suggest that BMI can be an important predictor of the breast cancer subtypes for both post- and pre-menopausal women.

Keywords: Breast cancer, body mass index, obesity, molecular subtype

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I. Introduction

1. Background

Breast cancer has been reported as the most common female cancer in the developing and developed countries. [1, 2] In particular, the incidence of female breast cancer in Korea has been increasing since 1999 and 47.7 age-standardized incident cases per 100,000 populations were reported as one of the leading primary cancer sites in 2014. [3] Breast cancer is one of the most common cancers in women 35-64 years of age in Korea. Considering relatively young ages of diagnosis and growing burden of the disease, breast cancer is the foremost public health concerns in Korea. However, further evidence is needed to stratify the risk of subtypes of breast cancer according to the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) status and

promote targeted prevention strategies.

2. Obesity and breast cancer molecular subtype

It has been well known that obesity a significant risk factor for postmenopausal breast cancer. [4-6] In contrast, obesity is a controversial factor for premenopausal breast cancer. According to previous studies, the risk of breast cancer increases with obesity, [7] some are irrelevant, [8] and some decrease. [9, 10]

Among the various potential mechanism explaining the relationship between obesity and breast cancer, estrogen hypothesis suggests that obese postmenopausal women have a lack of sex hormone binding globulin (SHBG) in serum and increase the bioavailable estrogen concentration. [11] However, in obese premenopausal women, the menstrual cycle is long, irregular, and has many anovulatory cycles, resulting in reduced total estrogen exposure. [12]

Breast cancer risk factors by molecular subtypes are known to vary

according to menopausal status and ethnicity [13]. For example, in Asian women, the frequency of Luminal A is low and the frequencies of Luminal B and HER2-expression are high compared to white women. [14] A meta-analysis of recent Asian women has shown that the risk of breast cancer increases with weight gain in hormone receptor-negative subtypes. According to a case-control study in the same paper, the risk increased significantly in pre-menopausal women when body weight was increased in Triple negative breast cancer (OR = 2.51 95% CI = 1.53-4.12). [15] Also, the higher the waist-to-hip circumference, the greater the risk of breast cancer in triple-negative subtypes. In particular, triple negative subtypes have been linked to the BRCA1 pathway. [16]

Although premenopausal women have been reported to have different breast cancer risk according to subtypes and BMI, most

have been studied in the West and lack data in Asia. [17]

3. Objectives

For the purpose of this study : First, analyze association with BMI on the risk for each BC subtype and hormone receptor among premenopausal and postmenopausal women Second, analyze the effect of BC family history on the relationship between BMI and each BC subtype and hormone receptor among premenopausal and postmenopausal women. We used data from a large multi-center case-control study, which allowed us to we classify the subtypes, Luminal A, Luminal B HER2 positive, Luminal B HER2 negative, Triple negative and HER2 express type.

II. Materials and methods

1. Study design and study population

For case ascertainment, we used the Nationwide Korean Breast Cancer Society Data (KBCS) [18]. The data collection was started in 1996 and it includes nationwide 102 general hospitals with over 400 beds (41 university hospitals and 61 surgical training hospitals). From 2001, an online cancer registration program has been launched, and physicians at participating hospitals have been able to directly enter patients' information via the web-based database system. The definition of the case group is that the female breast cancer patients who were recruited between 2003 and 2010 have no loss of BMI and hormone receptor.

For controls, we used the data of the Health Examinees Study (HEXA), a subset of Korean genome and epidemiology study

(KoGES). [19] It has been previously described in detail. In brief, HEXA is a community-based cohort, and study subjects were recruited from 2004 to 2013 for people aged between 40 and 75. Among the total of 173,357 subjects, 114,063 were the women. In order to reduce the period bias, the control group was restricted to those who were recruited until 2009. Excluding 506 breast cancer patients, 75,648 were included for the eligible subjects for the control group.

Age at enrollment was used to match cases and controls to exclude age-related effects of breast cancer development. The matching method was G-match algorithm of SAS 9.4, and case: control was matched 1: 2 based on age ±5 years. Finally, a total of 101,274 case-control data were generated with 33,758 cases and 67,516 controls for the final analyses. This study was approved by the

Institutional Review Boards of Seoul national university hospital biomedical research institute (IRB number: 0909-048-295).

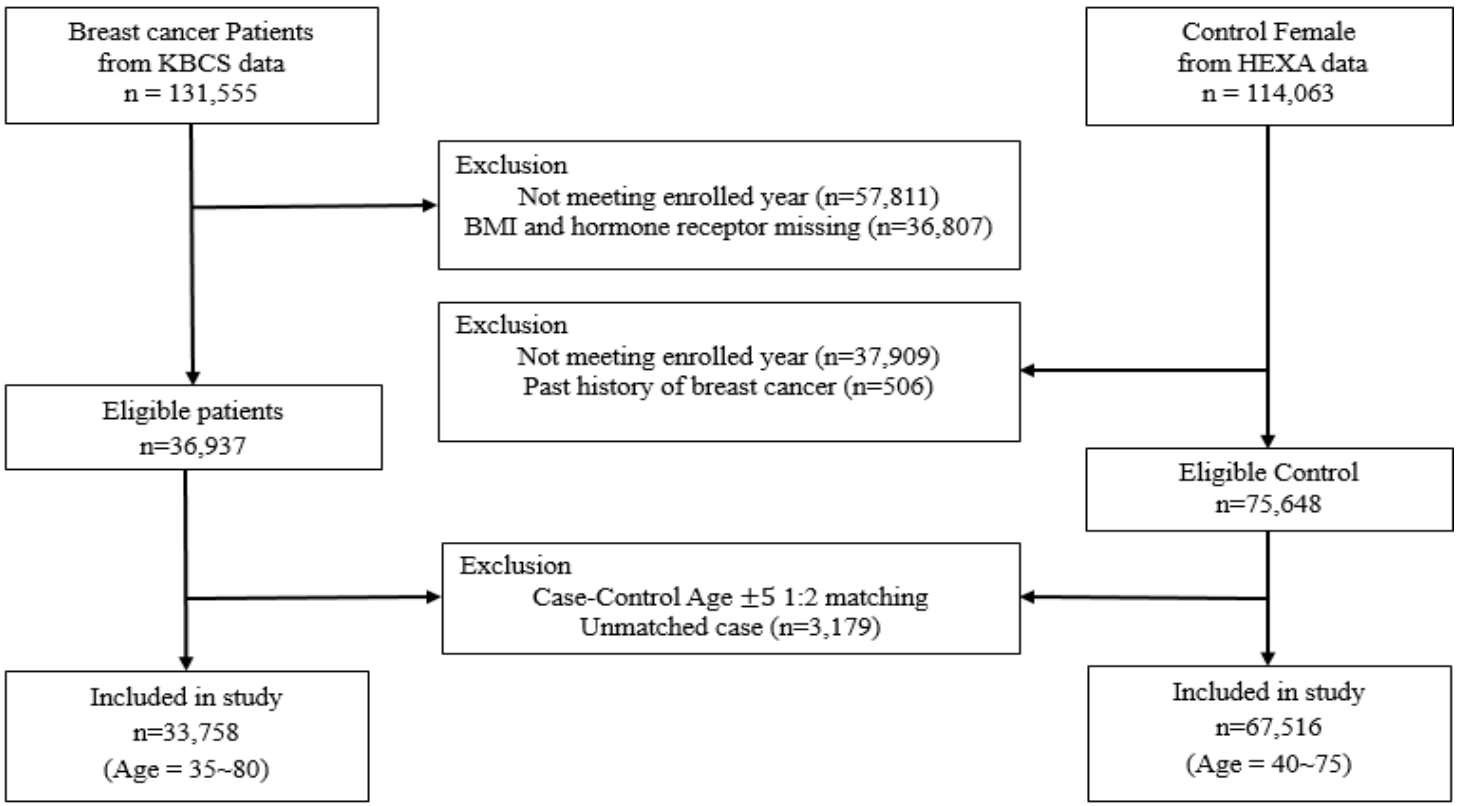

Figure 1. Selection process for study population in the KBCS, 2003−2010

2. Data collection

The required items to be filled out are the patient's unique resident registration number as a personal identifier, gender, age, surgical procedure and cancer stages based on the United States Joint Committee on Cancer classification. Additional items including information about potential risk factors of breast cancer, such as BC family history, lifetime duration lactation, duration of hormone replacement therapy (HRT), duration of oral contraceptive (OC) use, age at first birth, number of births and age at menopause, which were acquired based on personal interviews. The clinical, pathologic and laboratory findings were also recorded as biological markers, estrogen receptor (ER), progesterone receptor (PR), immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), Ki-67 antibody percent. The information related to patients'

treatment procedures were also collected.

Those who with missing values in BMI or hormone receptor (ER, PR) were excluded. In order to match the control group with the enrollment time, 33,758 individuals who were entered from 2003 to 2010 were finally selected.

For both cases and controls, anthropometric factors were measured at enrollment. BMI was calculated using the measured body weight (kg) divided by the squared height(m). and it was classified according to the WHO Asia-Pacific standard BMI as underweight (<18.5), normal (18.5-22.9), overweight (23-24.9), obese I (25-29.9) and obese II (30 or more). [20]

i. Molecular subtype

This study is a nationwide data and it does not control all the machines or drugs used in Immunohistochemistry in each hospital. Based on the results of ER, PgR, Cerb2-FISH, Cerb2-IHC, and Ki-67 performed at each hospital, HER2 was determined to be positive for Cerb2-FISH positive or Cerb2-IHC 3+.[21] In addition, the Ki-67 index was determined to be high for 14% or more of tumor cells were immunostained according to the guidelines of 'St Gallen International expert Consensus'. The subtype were classified into 5types: Luminal A (ER and PgR + and HER2- and Ki-67<14%), Luminal B-HER2 negative (ER + and HER2 - and (Ki-67≥14% or PgR -)), Luminal B-HER2 positive (ER + and HER2 + and any Ki-67, any PgR), HER2-express (ER- and PgR- and HER2 +), Triple negative (ER- and PgR- and HER2 -). [22] When the ki67 value

was measured, it could be classified as Luminal B-HER negative, but it was included as Luminal A when it was missing.

3. Statistical analysis

We did imputation of missing values of reproductive factors (age at menarche, number of children, first full-term pregnancy age, duration of breast feeding, duration of OC, duration of HRT, menopausal state) in missforest methods (R version 3.3.1). [23, 24] descriptive analyses, continuous variables such as age, BMI, duration of OC, lifetime duration lactation, duration of HRT were analyzed by t-test to compare mean difference by groups in Table1 whereas we used analysis of variance (ANOVA) test in Table 2. Categorical variables such as BC family history, past history of hysterectomy, past history of oophorectomy and past history of cancer were analyzed by Chi-square test (or Fisher's exact test) to compare differences between groups. The risk according to BMI for each subtype of breast cancer was stratified by menopausal state. The

odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using multivariate logistic regression models adjusted for age, BC family history, age at (menarche, first full-term pregnancy), number of children, past history of (hysterectomy, oophorectomy), duration of (breast feed, OC, HRT) adjustment. All statistical analyses were performed by SAS version 9.4. (SAS Institute Inc, Cary, NC, U.S.A).

III. Results

1. Baseline characteristics of study participants

Baseline characteristics of the 101,274 women in the study were described in Table 1. There were statistically significant differences in risk factors (age, BMI, age at menarche, first full-term pregnancy age, number of full-term birth, duration of breastfeeding, duration of HRT, duration of OC, status of familial breast cancer, medical history (hysterectomy, oophorectomy, ovarian cancer and thyroid cancer)) related to breast cancer, but these statistical differences seem to be due to the large sample size. From Table 1, BMI has the same mean value but standard deviation(SD) is different by 0.3 between BC cases and control. For age at menarche, the difference for mean value is 0.1 and for SD is 0.1. The number of full-term pregnancies and lifetime duration of lactation were higher in the control group,

while the BC family history and duration of OC were higher in the patient group.

Table 1. The selected characteristics of study population in the Korea Breast Cancer Study (KBCS), 2003 – 2010

	BC cases (N=33,758)	Controls (N=67,516)
	Mean (SD)	**Mean (SD)**
Age	48.9 (9.0)	51.5 (8.2)
BMI (Kg/m^2)	23.6 (3.2)	23.6 (2.9)
Age at menarche (years)	15.1 (1.8)	15.2 (1.8)
Age at FFTP[1] (years)	26.4 (3.6)	26.0 (3.4)
Number of FTP[1]	2.1 (0.9)	2.3 (1.0)
Breastfeeding duration[2] (months)	15.8 (17.0)	22.0 (25.3)
OC use (months)	4.7 (13.0)	4.3 (15.8)
Age at menopause[3]	49.1 (4.9)	48.9 (5.0)
HRT use[3] (months)	4.9 (16.4)	6.1 (17.0)
	N (%)	**N (%)**
BC Family history[4]	2,540 (7.5)	1,097 (1.6)
Nullparous women	729 (2.2)	775 (1.2)
No experience of breastfeeding[2]	8,644 (25.6)	11,695 (17.3)
Hysterectomy	2,707 (8.0)	7,154 (10.6)
Oophorectomy	1,013 (3.0)	4,485 (6.6)
Past history of ovarian cancer	24 (0.1)	15 (0.0)
Past history of thyroid cancer	515 (1.5)	460 (0.7)

Affiliation: BC, breast cancer; BMI, body mass index; FFTP, first full-term pregnancy; FTP, full-term pregnancy; OC, oral contraceptives; HRT, hormone replacement therapy

1. Among parous women
2. Among breastfed women
3. Among postmenopausal women
4. Among first- and second-degree relatives

2. Objective #1: association with BMI on the risk for each BC subtype and hormone receptor among premenopausal and postmenopausal women.

The risk of BC stratified by premenopausal and postmenopausal women according to BMI, pathologic subtype, presence of hormone receptor, and expression of HER2 is shown in Table 2 and 3. In premenopausal obese II women, the risk increased only in the Basal-like subtype (OR = 1.63 95% CI = 1.29-2.05). In the other subtypes, a partial increase showed in obese I (HER2- Luminal B, OR = 1.19, 95% CI = 1.02-1.39, HER2 Express OR = 1.34, 95% CI = 1.17-1.52), but not in obese II premenopausal women. On the other hand, there was no significant result of any subtype in the underweight group. In the obese II postmenopausal women, the risk of breast cancer increased regardless of the subtype. The subtypes

with the highest risk were HER− Luminal B (OR = 3.22 95% CI = 2.41−4.31) and the lowest subtype was HER2 Express (OR = 1.66 95% CI = 1.33−2.07). The difference was almost double (p−heterogeneity in obese II postmenopausal women = 0.001). The difference in the presence of hormone receptors in obese women was significant among premenopausal women (HR+ OR = 1.23 95% CI = 1.07−1.41, HR− OR = 1.56 95% CI = 1.33−1.84) (P−heterogeneity = 0.029). On the other hand, there was no difference in postmenopausal women according to the presence of hormone receptors. (HR + OR = 2.14 95% CI = 1.91−2.39, HR− OR = 2.01 95% CI = 1.77−2.28) (P−heterogeneity = 0.468).

Table 2. Association between body mass index (BMI) and each pathological subtype of breast cancer[1] in the Korea Breast Cancer Study (KBCS), 2003−2010

BMI (Kg/m^2)	Luminal A	HER2- Luminal B	HER2+ Luminal B	HER2 Express	Triple-negative
			OR (95% CI)[2]		
Total women					
<18.5	1.23 (1.09-1.39)	1.26 (0.97-1.65)	1.35 (1.11-1.65)	1.21 (0.97-1.50)	1.37 (1.15-1.62)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.95 (0.90-0.99)	1.02 (0.91-1.14)	0.99 (0.91-1.08)	1.04 (0.96-1.13)	1.05 (0.98-1.13)
25-29.9	1.19 (1.13-1.25)	1.35 (1.21-1.50)	1.13 (1.04-1.24)	1.19 (1.10-1.29)	1.36 (1.26-1.46)
≥30	1.57 (1.41-1.74)	1.89 (1.52-2.35)	1.29 (1.06-1.57)	1.38 (1.15-1.66)	1.98 (1.72-2.29)
Premenopausal women					
<18.5	1.18 (1.03-1.36)	1.18 (0.88-1.60)	1.18 (0.94-1.50)	1.07 (0.81-1.41)	1.15 (0.93-1.41)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.95 (0.89-1.02)	1.05 (0.91-1.21)	1.02 (0.91-1.14)	1.09 (0.97-1.24)	1.14 (1.03-1.25)
25-29.9	1.05 (0.98-1.13)[35]	1.19 (1.02-1.39)[35]	1.08 (0.96-1.22)[35]	1.34 (1.17-1.52)[3]	1.39 (1.26-1.54)[3]
≥30	1.07 (0.90-1.28)[45]	1.17 (0.81-1.69)[45]	1.06 (0.79-1.42)[45]	1.17 (0.84-1.61)[4]	1.63 (1.29-2.05)[45]
Postmenopausal women					
<18.5	1.02 (0.78-1.34)	0.92 (0.47-1.81)	1.54 (1.03-2.29)	1.14 (0.79-1.65)	1.29 (0.91-1.83)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	1.09 (1.00-1.17)	1.22 (1.02-1.47)	1.08 (0.94-1.24)	1.05 (0.94-1.18)	1.09 (0.97-1.22)
25-29.9	1.53 (1.42-1.64)[35]	1.91 (1.61-2.26)[35]	1.37 (1.20-1.56)[35]	1.21 (1.08-1.34)[3]	1.46 (1.31-1.62)[3]
≥30	2.37 (2.07-2.73)[45]	3.22 (2.41-4.31)[45]	1.77 (1.35-2.32)[45]	1.66 (1.33-2.07)[4]	2.48 (2.05-3.00)[45]

1. Total BC was classified to 5 subtypes by the expression status of the ER, PR (Immunohistochemistry), HER2 (FISH), and Ki−67 index (based on the guidelines by the St Gallen International Expert Consensus'). The classification criteria of 5 subtypes were as follows: Luminal A (ER and PgR + and HER2− and Ki−67<14%), Luminal B−HER2 negative (ER + and HER2 − and (Ki−67≥14% or PgR −)), Luminal B−HER2 positive (ER + and HER2 + and any Ki−67, any PgR), HER2−express (ER− and PgR− and HER2 +), Triple negative (ER− and PgR− and HER2 −). Korean BC cases were composed of Luminal A 30.8%, Luminal B (HER2−) 12.4%, Luminal B (HER2+) 9.6%, HER2 Express 11.5%, Triple Negative 15.9%, and Unclassified BC 19.8%.

2. Unconditional logistic regression model adjusted for age, BC family history, age at menarche, number of children, hysterectomy, oophorectomy, first full-term pregnancy age, breast feeding duration, oral contraceptive duration.
3. [Light gray shade] Each subtype in the obese I (BMI of 25-29.9 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity < 0.001 in total women; <0.001 in premenopausal women; <0.001 in postmenopausal women)
4. [Dark gray shade] Each subtype in the obese II (BMI of ≥30 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity=0.001 in total women; 0.059 in premenopausal women; 0.001 in postmenopausal women).
5. [Solid lines] Both ORs between premenopausal and postmenopausal women in each obese I and obese II had statistical heterogeneity in association (P-heterogeneity <0.001 and <0.001 for Luminal A; <0.001 and <0.001 for HER2-Luminal B; 0.009 and 0.012 for HER2+Lumina B; 0.006 for Basal-like (Obese II only), respectively)

Table 3. Association with body mass index (BMI) on the risk of each BC subtype by hormone receptor (HR) or HER2 status in the Korea Breast Cancer Study (KBCS), 2003−2010

BMI (Kg/m^2)	HR+	HR-	HER2+	HER2-
			OR (95% CI)[2]	
Total women				
<18.5	1.24 (1.13-1.37)	1.27 (1.13-1.43)	1.27 (1.12-1.43)	1.25 (1.13-1.37)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.99 (0.95-1.03)	1.04 (0.99-1.09)	1.01 (0.96-1.07)	1.00 (0.96-1.04)
25-29.9	1.24 (1.19-1.29)	1.28 (1.22-1.34)	1.20 (1.14-1.27)	1.28 (1.23-1.33)
≥30	1.68 (1.54-1.83)	1.82 (1.65-2.01)	1.60 (1.44-1.78)	1.80 (1.65-1.95)
Premenopausal women				
<18.5	1.19 (1.06-1.33)	1.15 (0.99-1.33)	1.17 (1.01-1.35)	1.18 (1.05-1.32)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.99 (0.94-1.05)	1.08 (1.01-1.16)	1.04 (0.97-1.12)	1.02 (0.96-1.07)
25-29.9	1.10 (1.04-1.17)[23]	1.28 (1.19-1.37)[2]	1.17 (1.09-1.26)	1.16 (1.10-1.23)[3]
≥30	1.23 (1.07-1.41)[3]	1.56 (1.33-1.84)[3]	1.36 (1.14-1.61)[3]	1.33 (1.16-1.52)[3]
Postmenopausal women				
<18.5	1.08 (0.88-1.33)	1.14 (0.90-1.43)	1.19 (0.93-1.51)	1.06 (0.87-1.29)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	1.07 (1.01-1.14)	1.05 (0.98-1.13)	1.04 (0.97-1.12)	1.08 (1.01-1.14)
25-29.9	1.43 (1.35-1.52)[33]	1.29 (1.21-1.38)[3]	1.26 (1.17-1.35)[3]	1.44 (1.36-1.53)[33]
≥30	2.14 (1.91-2.39)[3]	2.01 (1.77-2.28)[3]	1.81 (1.57-2.08)[45]	2.24 (2.01-2.49)[45]

1. Unconditional logistic regression model adjusted for age, BC family history, age at menarche, number of children, hysterectomy, oophorectomy, first full−term pregnancy age, breast feeding duration, oral contraceptive duration.

2. [Light gray shade] Each subtype by HR status in the obese I (BMI of 25−29.9 Kg / m^2) and obese II (BMI of ≥30 Kg / m^2) had a statistical heterogeneity in association (P−heterogeneity=0.001 in premenopausal women; 0.023 in postmenopausal women)

3. [Light gray shade] Each subtype by HER2 status in the obese I (BMI of 25−29.9 Kg / m^2) had a statistical heterogeneity in association (P−heterogeneity=0.029 in premenopausal women; 0.023 in postmenopausal women)
4. [Dark gray shade] Each subtype by HER2 status in the obese II (BMI of ≥30 Kg / m^2) had a statistical heterogeneity in association (P−heterogeneity=0.005 for Obese I postmenopausal women; 0.018 for Obese II postmenopausal women)
5. [Solid lines] Both ORs between premenopausal and postmenopausal women in each obese I and obese II had statistical heterogeneity in association (P−heterogeneity <0.001 and <0.001 for HR+; 0.016 for HR− (Obese II only); 0.012 for HER2+ (Obese II only); <0.001 and <0.001 for HER2−, respectively

3. Objective #2: the effect of BC family history on the relationship between BMI and each BC subtype and hormone receptor among premenopausal and postmenopausal women.

Table 4-7 shows the stratified analysis according to BC family history. There was no statistically significant difference between the two groups and this might be because of the small number of people with BC family history. However, some unusual patterns were found. First, the risk of breast cancer significantly increased in the HER2 subtype (OR = 2.41 95% CI = 1.21-4.80) and Basal-like subtype (OR = 1.98 95% CI = 1.22-3.22) in pre-menopausal women with BMI less than 18.5. Premenopausal women with basal-like subtypes showed the opposite risk when stratified by BC family history. As noted above, there was an increase in underweight women with BC

family history, but not in underweight women without BC family history (Triple negative OR = 1.16 95% CI = 0.96−1.40). On the other hand, in obese II premenopausal women with basal-like subtypes with BC family history did not show any significant effect (OR = 1.14 95% CI = 0.53−2.47), but risk for obese II women who did not have BC family history increased (OR = 1.66 95% CI = 1.32−2.10). In obese II postmenopausal women, the risk of breast cancer increased regardless of BC family history. However, there were some differences by subtypes and also some subtypes showed significant risk (HER2+ Luminal B OR = 1.04 95% CI = 0.32−3.40, HER2 express OR = 1.69 95% CI = 0.75−3.78).

Table 4. Association with body mass index (BMI) on the risk for each BC subtype[1] among total women classified by breast cancer (BC) family history in the Korea Breast Cancer Study (KBCS), 2003−2010

BMI (Kg/m^2)	Luminal A	HER2- Luminal B	HER2+ Luminal B	HER2 Express	Triple-negative
			OR (95% CI)[2]		
BC Family history+					
<18.5	1.40 (0.80-2.44)	1.19 (0.41-3.48)	1.08 (0.43-2.73)	2.11 (0.94-4.73)	1.66 (0.85-3.22)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.95 (0.74-1.21)	1.15 (0.75-1.77)	1.08 (0.74-1.57)	0.96 (0.65-1.41)	1.17 (0.86-1.59)
25-29.9	1.17 (0.92-1.49)	0.87 (0.54-1.39)	0.93 (0.63-1.40)	1.38 (0.95-2.00)	1.44 (1.05-1.97)
≥30	2.32 (1.40-3.83)	2.29 (0.99-5.32)	1.18 (0.49-2.83)	1.45 (0.65-3.25)	2.55 (1.36-4.78)
BC Family history−					
<18.5	1.21 (1.07-1.37)	1.27 (0.96-1.68)	1.37 (1.12-1.68)	1.15 (0.92-1.45)	1.32 (1.10-1.58)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.96 (0.91-1.01)	1.02 (0.91-1.15)	0.99 (0.91-1.08)	1.05 (0.96-1.14)	1.05 (0.98-1.14)
25-29.9	1.19 (1.14-1.26)[3]	1.40 (1.25-1.57)[3]	1.15 (1.05-1.26)[3]	1.18 (1.08-1.29)[3]	1.36 (1.26-1.47)[3]
≥30	1.53 (1.37-1.71)[3]	1.87 (1.49-2.35)[3]	1.30 (1.06-1.59)[3]	1.38 (1.15-1.66)[3]	1.97 (1.70-2.29)[3]

1. Total BC was classified to 5 subtypes by the expression status of the ER, PR (Immunohistochemistry), HER2 (FISH), and Ki−67 index (based on the guidelines by the St Gallen International expert Consensus'). The classification criteria of 5 subtypes were as follows: Luminal A (ER and PgR + and HER2− and Ki−67<14%), Luminal B−HER2 negative (ER + and HER2 − and (Ki−67≥14% or PgR −)), Luminal B−HER2 positive (ER + and HER2 + and any Ki−67, any PgR), HER2−express (ER− and PgR− and HER2 +), Triple negative (ER− and PgR− and HER2 −). Korean BC cases were composed of Luminal A 30.8%, Luminal B (HER2−) 12.4%, Luminal B (HER2+) 9.6%, HER2 Express 11.5%, Triple Negative 15.9%, and Unclassified BC 19.8%.

2. Unconditional logistic regression model adjusted for age, age at menarche, number of children, hysterectomy, oophorectomy, first full−term pregnancy age, breast feeding duration, oral contraceptive duration.

3. [Light gray shade] Each subtype in the obese I (BMI of 25−29.9 Kg / m^2) and obese II (BMI of ≥30 Kg / m^2) had a statistical heterogeneity in association (P−heterogeneity=0.003 and 0.002 in family history− group, respectively)

Table 5. Association with body mass index (BMI) on the risk for each BC subtype[1] among premenopausal and postmenopausal women classified by breast cancer (BC) family history in the Korea Breast Cancer Study (KBCS), 2003−2010

BMI (Kg/m^2)	Luminal A	HER2- Luminal B	HER2+ Luminal B	HER2 Express	Triple-negative
			OR (95% CI)[2]		
Premenopausal women					
BC Family history+					
<18.5	1.21 (0.81-1.79)	1.32 (0.52-3.34)	0.74 (0.27-2.03)	2.41 (1.21-4.80)[6]	1.98 (1.22-3.22)[6]
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.77 (0.62-0.96)	0.88 (0.53-1.46)	1.04 (0.71-1.54)	1.07 (0.66-1.73)	1.11 (0.83-1.50)
25-29.9	0.95 (0.76-1.18)[7]	0.87 (0.50-1.52)[7]	0.89 (0.57-1.39)	1.31 (0.79-2.15)	1.20 (0.87-1.66)
≥30	0.93 (0.54-1.61)[7]	1.75 (0.63-4.87)[7]	1.25 (0.50-3.13)	0.83 (0.20-3.41)	1.14 (0.53-2.47)[7]
BC Family history−					
<18.5	1.19 (1.03-1.36)	1.18 (0.86-1.61)	1.21 (0.95-1.54)	1.01 (0.75-1.36)[6]	1.16 (0.96-1.40)[6]
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.95 (0.89-1.02)	1.03 (0.89-1.20)	1.00 (0.89-1.13)	1.08 (0.95-1.23)	1.11 (1.00-1.23)
25-29.9	1.05 (0.98-1.13)[5,7]	1.20 (1.03-1.40)[5,7]	1.08 (0.95-1.22)[5]	1.32 (1.15-1.51)[5]	1.38 (1.24-1.54)[5]
≥30	1.06 (0.90-1.28)[5,7]	1.15 (0.79-1.68)[5,7]	1.05 (0.77-1.42)[5]	1.20 (0.86-1.66)[5]	1.66 (1.32-2.10)[5,7]
Postmenopausal women					
BC Family history+					
<18.5	2.22 (1.19-4.16)[4]	0.19 (0.06-0.64)[4]	2.15 (0.67-7.08)[4]	0.17 (0.08-0.38)[3,4,6]	0.22 (0.11-0.43)[4,6]
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.90 (0.68-1.19)	1.12 (0.65-1.94)	0.82 (0.48-1.41)	0.79 (0.49-1.28)	0.94 (0.61-1.45)
25-29.9	1.37 (1.07-1.76)[3,7]	0.85 (0.48-1.53)[3,7]	0.90 (0.53-1.52)[3]	1.30 (0.85-1.97)[3]	1.38 (0.93-2.05)[3]
≥30	3.09 (2.07-4.61)[4,7]	2.36 (0.96-5.79)[4,7]	1.04 (0.32-3.40)[4]	1.69 (0.75-3.78)[4]	3.30 (1.81-6.04)[4,7]
BC Family history−					
<18.5	0.95 (0.72-1.26)	1.03 (0.52-2.02)	1.52 (1.00-2.30)	1.19 (0.83-1.72)[6]	1.35 (0.95-1.91)[6]
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	1.06 (0.98-1.15)	1.17 (0.96-1.42)	1.06 (0.91-1.22)	1.03 (0.92-1.15)	1.07 (0.95-1.20)
25-29.9	1.42 (1.32-1.53)[5,7]	1.81 (1.52-2.16)[5,7]	1.28 (1.12-1.47)[5]	1.10 (0.98-1.23)[5]	1.36 (1.22-1.52)[5]
≥30	2.06 (1.79-2.38)[5,7]	2.91 (2.15-3.93)[5,7]	1.61 (1.22-2.13)[5]	1.45 (1.15-1.82)[5]	2.21 (1.82-2.69)[5,7]

1. Total BC was classified to 5 subtypes by the expression status of the ER, PR (Immunohistochemistry), HER2 (FISH), and Ki-67 index (based on the guidelines by the St Gallen International expert Consensus'). The classification criteria of 5 subtypes were as follows: Luminal A (ER and PgR + and HER2- and Ki-67<14%), Luminal B-HER2 negative (ER + and HER2 - and (Ki-67≥14% or PgR -)), Luminal B-HER2 positive (ER + and HER2 + and any Ki-67, any PgR), HER2-express (ER- and PgR- and HER2 +), Triple negative (ER- and PgR- and HER2 -). Korean BC cases were composed of Luminal A 30.8%, Luminal B (HER2-) 12.4%, Luminal B (HER2+) 9.6%, HER2 Express 11.5%, Triple Negative 15.9%, and Unclassified BC 19.8%.
2. Unconditional logistic regression model adjusted for age, age at menarche, number of children, hysterectomy, oophorectomy, first full-term pregnancy age, breast feeding duration, oral contraceptive duration.
3. OR was estimated by the Cochran-Mantel-Haenszel equation with Yates' correction
4. [Dark gray shade] Each subtype in the underweight (BMI < 18.5 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity <0.001 in BC Family history+postmenopausal women)
5. [Light gray shade] Each subtype in the obese I (BMI of 25-29.9 Kg / m^2) and obese II (BMI of ≥30 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity <0.001 and 0.037 in BC Family history- premenopausal women; <0.001 and 0.002 in BC Family history- postmenopausal women)
6. [Solid lines] The four ORs among BC family history+ premenopausal and postmenopausal women and BC family history- premenopausal and postmenopausal women in underweighted group (BMI < 18.5 Kg / m^2) had statistical heterogeneity in association (P-heterogeneity <0.001 for HER2 Express; <0.001 for Basal-like, respectively)
[Solid lines] The four ORs among BC family history+ premenopausal and postmenopausal women and BC family history- premenopausal and postmenopausal women in obese I group (BMI of 25-29.9 Kg / m^2) and obese II group (BMI of ≥30 Kg / m^2) had statistical heterogeneity in association (P-heterogeneity <0.001 and <0.001 for Luminal A; 0.001 and 0.002 for HER2- Luminal B, respectively; 0.043 for Basal-like (Obese II only))

Table 6. Association with body mass index (BMI) on the risk of each BC subtype by hormone receptor (HR) or HER2 status among total women classified by breast cancer (BC) family history in the Korea Breast Cancer Study (KBCS), 2003−2010

BMI (Kg/m^2)	HR+	HR-	HER2+	HER2-
BC Family history+				
<18.5	1.47 (1.13-1.90)	1.82 (1.33-2.49)	1.59 (1.10-2.28)	1.59 (1.25-2.02)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.87 (0.77-0.98)	0.97 (0.83-1.14)	0.95 (0.80-1.12)	0.89 (0.79-0.99)
25-29.9	1.03 (0.92-1.17)	1.20 (1.03-1.41)	1.09 (0.92-1.29)	1.10 (0.98-1.23)
≥30	1.97 (1.57-2.47)[2]	2.20 (1.66-2.91)[2]	1.94 (1.42-2.67)	2.11 (1.71-2.62)
BC Family history-+				
<18.5	1.24 (1.12-1.37)	1.26 (1.11-1.42)	1.26 (1.11-1.43)	1.24 (1.12-1.37)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.98 (0.95-1.02)	1.03 (0.99-1.09)	1.01 (0.96-1.06)	1.00 (0.96-1.04)
25-29.9	1.24 (1.19-1.29)	1.28 (1.22-1.34)	1.20 (1.14-1.27)	1.28 (1.23-1.33)
≥30	1.66 (1.52-1.81)[2]	1.80 (1.62-1.99)[2]	1.58 (1.42-1.77)	1.77 (1.63-1.93)

1. Unconditional logistic regression model adjusted for age, family history of breast cancer, age at menarche, number of children, hysterectomy, oophorectomy, first full−term pregnancy age, breast feeding duration, oral contraceptive duration.
2. [Solid lines] The four ORs among BC family history+ premenopausal and postmenopausal women and BC family history− premenopausal and postmenopausal women in obese II group (BMI of ≥30 Kg / m^2) had statistical heterogeneity in association (P−heterogeneity for HR+; 0.167 for HR−; 0.188)

Table 7. Association with body mass index (BMI) on the risk of each BC subtype by hormone receptor (HR) or HER2 status among premenopausal and postmenopausal women classified by breast cancer (BC) family history in the Korea Breast Cancer Study (KBCS), 2003−2010

BMI (Kg/m^2)	HR+	HR-	HER2+	HER2-
		OR (95% CI)[1]		
Premenopausal women				
BC Family history+				
<18.5	1.20 (0.89-1.63)	1.84 (1.32-2.57)[7]	1.48 (0.98-2.21)	1.41 (1.08-1.85)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.87 (0.74-1.01)	1.04 (0.85-1.28)	1.01 (0.81-1.26)	0.89 (0.77-1.04)
25-29.9	0.93 (0.79-1.10)	1.13 (0.90-1.40)	1.01 (0.79-1.29)	0.99 (0.85-1.16)
≥30	1.32 (0.92-1.89)	1.50 (0.95-2.37)	1.61 (1.00-2.61)	1.29 (0.91-1.82)
BC Family history+				
<18.5	1.20 (1.06-1.35)	1.14 (0.98-1.32)[7]	1.17 (1.01-1.36)	1.18 (1.05-1.33)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.99 (0.94-1.05)	1.08 (1.00-1.15)	1.04 (0.97-1.11)	1.01 (0.96-1.07)
25-29.9	1.11 (1.04-1.17)	1.27 (1.19-1.37)	1.17 (1.09-1.26)	1.16 (1.10-1.23)
≥30	1.22 (1.06-1.40)	1.56 (1.33-1.84)	1.34 (1.13-1.60)	1.32 (1.16-1.51)
Postmenopausal women				
BC Family history+				
<18.5	1.71 (1.02-2.88)[3]	0.37 (0.09-1.50)[2,3]	1.02 (0.42-2.52)	1.31 (0.74-2.32)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	0.97 (0.80-1.18)	0.97 (0.75-1.25)	0.94 (0.72-1.23)	0.99 (0.82-1.19)
25-29.9	1.23 (1.02-1.48)	1.33 (1.06-1.69)	1.20 (0.93-1.54)	1.30 (1.09-1.56)
≥30	2.85 (2.10-3.85)	2.91 (2.00-4.22)	2.27 (1.47-3.50)	3.20 (2.41-4.23)[8]
BC Family history+				
<18.5	1.04 (0.84-1.29)	1.16 (0.92-1.46)	1.18 (0.92-1.51)	1.04 (0.85-1.27)
18.5-22.9	1.00	1.00	1.00	1.00
23-24.9	1.07 (1.01-1.14)	1.05 (0.98-1.13)	1.04 (0.97-1.13)	1.07 (1.01-1.14)
25-29.9	1.44 (1.36-1.53)[4]	1.29 (1.21-1.38)[4]	1.26 (1.17-1.36)[5]	1.45 (1.37-1.53)[5]
≥30	2.11 (1.89-2.37)	1.97 (1.73-2.25)	1.79 (1.55-2.07)[6]	2.21 (1.98-2.46)[6,8]

1. Unconditional logistic regression model adjusted for age, family history of breast cancer, age

at menarche, number of children, hysterectomy, oophorectomy, first full-term pregnancy age, breast feeding duration, oral contraceptive duration.
2. OR was estimated by the Cochran-Mantel-Haenszel equation with Yates'correction
3. [Light gray shade] Each subtype by HR status in the underweight (BMI < 18.5 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity =0.045 in BC Family history+ postmenopausal women)
4. [Light gray shade] Each subtype by HR status in obese I (BMI of 25-29.9 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity =0.015 in BC Family history+ postmenopausal women)
5. [Dark gray shade] Each subtype by HER2 status in the obese I (BMI of 25-29.9 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity=0.003 for postmenopausal women)
6. [Dark gray shade] Each subtype by HER2 status in the obese II (BMI of ≥30 Kg / m^2) had a statistical heterogeneity in association (P-heterogeneity=0.022 for postmenopausal women)
7. [Solid lines] Both ORs between BC family history+ premenopausal women and BC family history- premenopausal women in underweighted group (BMI < 18.5 Kg / m^2) had statistical heterogeneity in association (P-heterogeneity = 0.01 for HR-)
8. [Solid lines] Both ORs between BC family history+ postmenopausal women and BC family history- postmenopausal women in the obese II (BMI of ≥30 Kg / m^2) had statistical heterogeneity in association (P-heterogeneity = 0.016 for HER-)

IV. Discussions

Our results have shown that obesity can play an important role in increasing breast risk differently depending on the tumor subtype (Luminal A, Luminal B her positive, Luminal B her negative, Triple negative/basal-like and HER2 type). In our study, the association of BMI and breast cancer subtypes were different according to their menopausal status. This supports that histological classification is appropriate for understanding etiology.

The results of previous studies on the risk of BMI and breast cancer subtypes according to menopause state are very limited. In a case-control study (Polish Breast Cancer Study (PBCS) n=804 invasive cases) (16) in Poland, except for the triple negative subtype, the tendency to protect the obesity was not statistically significant, but obesity of triple negative (p-heterogeneity = 0.003) was observed

as a risk factor compared with luminal A. Also case-case of Carolina Breast Cancer Study (CBCS) study (n = 1,424 in situ and invasive cases) (13) showed that pre-menopausal obesity was found to be a risk factor for basal subtype like compared to luminal A subtype, but there was no statistically significant difference in other types. The Life After Cancer Epidemiology (LACE) (n=2,544 invasive cases) [25] study also showed significant differences compared to luminal A subtype in the premenopausal and obese triple negative subtype. In addition, the subtypes (luminal B, HER2 expression) showed higher OR than luminal A subtype, but not statistically significant. On the other hand, there was no difference in postmenopausal women between groups. In the Washington State (WS) (n=2,386) case-control study [26] of postmenopausal women, it was not statistically significant, but it suggested that there is a heterogeneity among the

subtypes in the postmenopausal women.

Our results are similar to previous studies in premenopausal women with basal-like subtype. However, postmenopausal women with HER2 expression have different results. There was a significant difference in the risk of breast cancer due to BMI before menopause and the BC risk tended to increase as the obesity increased in the HER2 expression (p-trend = 0.03) and basal-like subtype(p-trend = 0.02). And in basal-like subtype, OR was 1.63 in obese premenopausal women (BMI≥30). In the postmenopausal obese group, ORs of HER2 negative group (luminous A, B (HER negative) and basal-like) were higher than HER2 negative group (Luminal B (HER positive) and HER2 expression). Obesity was a risk factor in all subtypes after menopause, but BC risk in Luminal B subtype (HER positive) was also found to increase in underweight.

Our result is that there is a clear heterogeneity in the risk of developing breast cancer before and after menopause, which is consistent with previous studies. It is associated with BMI and hormone receptors (ER, PR, HER2) in breast cancer patients. [27-33] There are many known hypotheses about the development of breast cancer, but it can't be denied that estrogen concentration in blood is important. In fact, obesity in postmenopausal women has a high activity of aromatase enzyme that converts androstenedione into estrogen in adipose tissue and maintains a high level of estrogen level. [34] However, there is not sufficient evidence for other receptors and its related molecular biologic mechanisms.

The strength of our study is the nationwide large-scale data. In fact, there are 91,651 female breast cancer outbreaks among Korean women between 2003 and 2010 [35] , and this study is highly

representative, because it is the result of 33,758 which is 36.8% of the entire female breast cancer outbreaks in Korea between 2003 and 2010. Therefore, it is thought that generalizability is relatively high in Asia race with breast cancer risk distribution similar to Korea. The anthropometric factors were measured at enrollment, which may minimize recall bias for exposure status. In addition, the data included comprehensive medical and epidemiologic data based on a standardized study protocols.

The limitations of this study are as follows: First, the data did not include lifestyle factors including physical exercise, smoking and drinking. Missing information for genetic testing such as BRCA mutation information, were not evaluated. Second, most of the previous studies were conducted on Westerners such as Americans, Caucasians, and African Americans. This study was conducted for

Koreans only, and the results may be different. [36] Third, despite age matching, the age difference was 2.6 years old. This is because the average age of the control group is higher than the average age of the cases, and the control group of the lower age was not sufficiently available. Fourth, the unclassified is an equivocal with IHC 2+. According to the guideline [37], additional FISH should be done to distinguish the HER2 receptor. But we have not been able to do it in our study. Sixth, about one-third of the patients in the country were used, but data collected from hospitals with over 400 beds could lead to selection bias.

V. Conclusion

In summary, we used a case-control analysis to assess the association between BMI and breast cancer subtypes to observe significant heterogeneity of association by tumor subtype. Our findings indicated that obesity can be an independent predictor of all breast cancer subtypes in post-menopausal women, while both underweight and obesity can accelerate the selected subtypes among pre-menopausal breast cancer patients. These different associations by subtype can support that breast cancer is a heterogeneous disease defined by presence of hormone receptors with distinct etiologic pathways. Future studies will need to focus on analyzing other known risk factors besides BMI and identifying the molecular biologic causes.

Supplementary table 1. The selected characteristics of breast cancer (BC) cases according to molecular and pathological classification[1] in the Korea Breast Cancer Study (KBCS), 2003 – 2010

BMI (Kg/m^2)	Luminal A	HER2- Luminal B	HER2+ Luminal B	HER2 Express	Triple-negative	Unclassified
	N=10,390	N=4,182	N=3,232	N=3,883	N=5,380	N=6,691
	Mean (SD)					
Age	48.5 (8.6)	50.4 (9.4)	48.2 (8.5)	50.7 (8.9)	48.5 (9.3)	48.5 (8.9)
BMI (Kg/m^2)	23.5 (3.2)	23.8 (3.3)	23.4 (3.3)	23.7 (3.2)	23.8 (3.3)	23.6 (3.3)
Age at menarche (years)	15.0 (1.7)	15.3 (1.8)	15.1 (1.8)	15.3 (1.81)	15.2 (1.8)	15.2 (1.8)
Age at FFTP[2] (years)	26.6 (3.6)	26.3 (3.7)	26.4 (3.6)	26.0 (3.5)	26.1 (3.5)	26.5 (3.6)
Number of FTP[2]	2.1 (0.9)	2.2 (1.0)	2.1 (0.9)	2.3 (1.0)	2.2 (1.0)	2.1 (0.9)
Breastfeeding duration[3] (months)	14.6 (16.6)	17.1 (17.5)	15.5 (16.9)	18.5 (17.2)	16.1 (16.8)	15.5 (17.9)
OC use (months)	4.5 (12.9)	5.6 (14.7)	5.1 (13.3)	5.0 (11.4)	5.7 (12.7)	4.6 (12.5)
Age at menopause[4]	48.9 (5.2)	49.3 (4.7)	49.1 (4.9)	49.6 (4.4)	49.1 (4.7)	49.1 (5.2)
HRT use[4] (months)	4.7 (16.7)	6.1 (17.6)	4.9 (16.7)	6.0 (17.3)	4.6 (15.9)	4.7 (15.5)

Affiliation: BC, breast cancer; BMI, body mass index; FFTP, first full-term pregnancy; FTP, full-term pregnancy; OC, oral contraceptives; HRT, hormone replacement therapy

1. Total BC was classified to 5 subtypes by the expression status of the ER, PR (Immunohistochemistry), HER2 (FISH), and Ki-67 index (based on the guidelines by the St Gallen International expert Consensus'). The classification criteria of 5 subtypes were as follows: Luminal A (ER and PgR + and HER2- and Ki-67<14%), Luminal B-HER2 negative (ER + and HER2 - and (Ki-67≥14% or PgR -)), Luminal B-HER2 positive (ER + and HER2 + and any Ki-67, any PgR), HER2-express (ER- and PgR- and HER2 +), Triple negative (ER- and PgR- and HER2 -). Korean BC cases were composed of Luminal A 30.8%, Luminal B (HER2-) 12.4%, Luminal B (HER2+) 9.6%, HER2 Express 11.5%, Triple Negative 15.9%, and Unclassified BC 19.8%.

2. Among parous women
3. Among breastfed women
4. Among postmenopausal women

Supplementary table 2. Association between body mass index (BMI) and each pathological subtype of breast cancer in the Korea Breast Cancer Study (KBCS), 2003–2010. Analysis results from sources without imputation*.

BMI (Kg/m^2)	Luminal A	HER2- Luminal B	HER2+ Luminal B	HER2 Express	Triple-negative
	N=6,272	N=2,462	N=1,839	N=2,361	N=3,256
			OR (95% CI)[1]		
Premenopausal women					
<18.5	1.24 (1.06–1.45)	1.09 (0.84–1.42)	1.20 (0.94–1.55)	1.10 (0.87–1.37)	1.16 (0.93–1.43)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.92 (0.85–0.99)	1.04 (0.92–1.17)	0.97 (0.86–1.10)	1.10 (0.97–1.25)	1.14 (1.03–1.26)
25-29.9	0.97 (0.89–1.05)	1.17 (1.03–1.33)	1.00 (0.87–1.14)	1.33 (1.16–1.51)	1.38 (1.24–1.53)
≥30	0.93 (0.76–1.13)	1.28 (0.96–1.71)	1.00 (0.73–1.38)	1.16 (0.83–1.60)	1.60 (1.27–2.02)
Postmenopausal women					
<18.5	1.00 (0.73–1.37)	1.18 (0.80–1.73)	1.51 (0.97–2.33)	1.15 (0.79–1.67)	1.30 (0.91–1.85)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	1.09 (0.99–1.19)	1.00 (0.88–1.13)	1.07 (0.93–1.25)	1.02 (0.91–1.14)	1.06 (0.95–1.19)
25-29.9	1.46 (1.34–1.60)	1.37 (1.23–1.54)	1.32 (1.14–1.52)	1.09 (0.98–1.22)	1.35 (1.21–1.51)
≥30	2.35 (2.01–2.75)	1.81 (1.46–2.25)	1.67 (1.27–2.24)	1.45 (1.16–1.81)	2.25 (1.85–2.72)

1.Unconditional logistic regression model adjusted for age, family history of breast cancer, age at menarche,

number of children, hysterectomy, oophorectomy, first full-term pregnancy age, breast feeding duration, oral contraceptive duration.

* Excludes subjects without menopausal data in the selection process of data

* Excludes 6,691 subjects for unclassified

Supplementary table 3. Association with body mass index (BMI) on the risk for each BC subtype[1] among premenopausal and postmenopausal women classified by breast cancer (BC) family history in the Korea Breast Cancer Study (KBCS), 2003−2010. Analysis results from sources without imputation*.

BMI (Kg/m^2)	Luminal A	HER2- Luminal B	HER2+ Luminal B	HER2 Express	Triple-negative
	N=6,272	N=2,462	N=1,839	N=2,361	N=3,256
			OR (95% CI)[1]		
BC Family history +					
Premenopausal women					
<18.5	1.39 (0.91-2.12)	1.10 (0.48-2.55)	0.84 (0.30-2.33)	**2.47 (1.24-4.94)**	**2.03 (1.24-3.30)**
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.83 (0.66-1.04)	0.72 (0.46-1.14)	1.05 (0.69-1.57)	1.06 (0.66-1.72)	1.12 (0.83-1.50)
25-29.9	0.91 (0.71-1.16)	1.03 (0.67-1.60)	0.83 (0.51-1.35)	1.28 (0.78-2.12)	1.19 (0.86-1.64)
≥30	0.79 (0.41-1.50)	1.67 (0.72-3.88)	1.37 (0.55-3.44)	0.80 (0.19-3.32)	1.10 (0.51-2.38)
Postmenopausal women					
<18.5	**2.28 (1.09-4.76)**	1.27 (0.40-4.10)	1.61 (0.38-6.81)	-	-
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.95 (0.69-1.32)	0.87 (0.59-1.29)	0.91 (0.52-1.60)	0.78 (0.49-1.26)	0.93 (0.60-1.43)
25-29.9	**1.40 (1.04-1.88)**	1.07 (0.74-1.56)	1.00 (0.57-1.74)	1.28 (0.84-1.95)	1.37 (0.92-2.03)
≥30	**3.89 (2.51-6.03)**	1.60 (0.79-3.26)	0.79 (0.19-3.33)	1.68 (0.75-3.77)	**3.28 (1.80-6.01)**
BC Family history -					
Premenopausal women					
<18.5	**1.26 (1.08-1.47)**	1.11 (0.85-1.46)	1.25 (0.97-1.62)	1.05 (0.77-1.41)	1.13 (0.91-1.42)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	0.91 (0.84-0.98)	1.04 (0.92-1.17)	0.95 (0.84-1.08)	1.09 (0.95-1.24)	**1.12 (1.01-1.24)**
25-29.9	0.97 (0.89-1.05)	**1.17 (1.03-1.33)**	1.00 (0.87-1.14)	**1.31 (1.15-1.50)**	**1.37 (1.23-1.53)**
≥30	0.92 (0.75-1.13)	1.23 (0.91-1.66)	0.97 (0.70-1.35)	1.16 (0.83-1.62)	**1.61 (1.27-2.04)**
Postmenopausal women					
<18.5	0.91 (0.65-1.27)	1.12 (0.75-1.67)	1.45 (0.92-2.29)	1.18 (0.81-1.71)	1.33 (0.94-1.90)
18.5-22.9	1.00	1.00	1.00	1.00	1.00
23-24.9	1.08 (0.98-1.19)	1.00 (0.88-1.13)	1.08 (0.92-1.25)	1.02 (0.91-1.14)	1.06 (0.94-1.19)
25-29.9	**1.47 (1.34-1.60)**	**1.40 (1.25-1.57)**	**1.34 (1.15-1.55)**	1.09 (0.97-1.22)	**1.35 (1.21-1.51)**
≥30	**2.26 (1.93-2.66)**	**1.83 (1.46-2.28)**	**1.73 (1.30-2.31)**	**1.43 (1.14-1.81)**	**2.19 (1.80-2.67)**

1.Unconditional logistic regression model adjusted for age, age at menarche, number of children, hysterectomy, oophorectomy, first full-term pregnancy age, breast feeding duration, oral contraceptive duration.

* Excludes subjects without menopausal data in the selection process of data

* Excludes 6,691 subjects for unclassified

Supplementary table 4. Association with body mass index (BMI) on the risk for each BC subtype[1] among postmenopausal women classified by use of hormone replacement therapy (HRT) in the Korea Breast Cancer Study (KBCS), 2003−2010. Analysis results from sources without imputation*.

BMI (Kg/m^2)	Luminal A	HER2− Luminal B	HER2+ Luminal B	HER2 Express	Triple−negative
	N=2,271	N=1,255	N=729	N=1,304	N=1,405
	OR (95% CI)[1]				
Postmenopausal women with never HRT used					
<18.5	1.13 (0.75−1.71)	1.35 (0.81−2.26)	1.35 (0.69−2.67)	1.09 (0.63−1.89)	1.10 (0.66−1.84)
18.5−22.9	1.00	1.00	1.00	1.00	1.00
23−24.9	1.14 (1.01−1.29)	1.04 (0.88−1.24)	1.25 (1.01−1.55)	1.18 (1.01−1.38)	1.12 (0.96−1.31)
25−29.9	1.66 (1.48−1.86)	1.59 (1.36−1.86)	1.50 (1.22−1.85)	1.21 (1.03−1.41)	1.51 (1.31−1.74)
≥30	2.93 (2.40−3.56)	2.31 (1.74−3.07)	2.16 (1.47−3.16)	1.91 (1.43−2.54)	2.75 (2.16−3.50)
Postmenopausal women with ever HRT used					
<18.5	0.85 (0.55−1.32)	0.93 (0.54−1.61)	1.51 (0.87−2.63)	1.13 (0.70−1.83)	1.44 (0.91−2.29)
18.5−22.9	1.00	1.00	1.00	1.00	1.00
23−24.9	1.09 (0.97−1.24)	1.02 (0.97−1.20)	1.01 (0.83−1.24)	0.93 (0.80−1.08)	1.05 (0.89−1.23)
25−29.9	1.38 (1.23−1.55)	1.30 (1.12−1.51)	1.29 (1.07−1.56)	1.08 (0.93−1.26)	1.27 (1.09−1.48)
≥30	1.97 (1.58−2.45)	1.48 (1.09−2.01)	1.38 (0.92−2.07)	1.13 (0.81−1.57)	1.78 (1.33−2.37)

1.Unconditional logistic regression model adjusted for age, BC family history, age at menarche, number of

children, hysterectomy, oophorectomy, first full-term pregnancy age, breast feeding duration, oral contraceptive duration.

* Excludes subjects without menopausal data in the selection process of data

* Excludes 6,691 subjects for unclassified

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초 록

서론: 비만은 폐경 후 여성에서 유방암 위험요인으로 잘 알려져 있다. 그러나 세부 유방암과 체중과 유방암의 관련성이 아직 불명확하고 특히 폐경 전 여성에서는 연구가 부족한 실정이다.

방법: 본 연구는 사회 기반 사례 대조군 연구로 2003년에서 2010년 사이에 모집된 35세이상 80에 이하의 한국 여성을 사례군과 대조군을 1:2로 매칭하여 총 101,274명의 자료를 이용하여 체질량지수 (BMI, kg/m2)와 세부 유방암 아형 Luminal A (ER and PgR + and HER2- and Ki-67<14%), Luminal B-HER2

negative (ER + and HER2 − and (Ki−67≥14% or PgR −)), Luminal B−HER2 positive (ER + and HER2 + and any Ki−67, any PgR), HER2−express (ER− and PgR− and HER2 +), Triple negative (ER− and PgR− and HER2 −). 간의 관련성 분석하였다.

결과: 폐경 후 여성에서는 세부 유방암의 아형에 상관 없이 고도비만(BMI≥30)일 때 유방암 위험이 증가하는 것으로 나타났는데, 그 중 가장 크게 증가한 아형은 HER−Luminal B 이다. (OR: 3.22 CI: 2.41−4.31) 폐경 전 여성에서는 저체중(BMI<18.5)일 때 Luminal A (OR: 1.23 CI: 1.09−1.39)로 증가하고, 고도비만(BMI≥30)에서는 Triple negative 아형에서 유방암 위험이 증가한 것으로 관찰되었다. (OR: 1.63 CI: 1.29−2.05). 유방암 가족력이 있는 경우 폐경 전 저체중 여성에서 HER2 express 아형 (OR: 2.41 CI: 1.21−4.80) 과 Triple negative 아형 (OR: 1.98 CI: 1.22−3.22)의 위험이 증가한 것으로 관찰되었다.

결론: 체질량지수는 세부 유방암 아형의 지표로서 폐경 전, 폐경

후 여성에서 모두 중요한 역할을 한다.

주요어: 유방암, 병리학적 아형, 비만, 체질량지수

학 번: (2016-22022)