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EPIDEMIOLOGY

Prevalence of breast cancer-related risk factors in underweight premenopausal women: the Korea National Health and Nutrition Examination Survey IV–VI

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Abstract

Purpose This study aimed to examine the prevalence and trends of breast cancer-related risk factors and characteristics in premenopausal underweight Korean women according to birth year cohort.

Methods Socioeconomic and breast cancer-related risk factors were investigated in 13,415 premenopausal women using nationwide cross-sectional surveys performed between 2007 and 2015. Underweight was defined as body mass index < 18.5 kg/m^2. Multivariable models were created using complex sample procedures.

Results Underweight women comprised 9.5% of the sample. Compared with those who were obese or of normal weight, underweight women were characterized by younger age, higher rate of metropolitan residence, higher economic status, more education, higher rates of non-manual employment and unmarried status, lower rate of early menarche, higher rates of nulliparity, lower parity, alcohol consumption, and never having breastfed, and lower levels of high physical activity. Multivariable analysis showed that underweight women had a significantly lower rate of early menarche, lower parity, higher nulliparity, older age at first delivery, and lower levels of high physical activity compared to premenopausal women with normal weight. These trends were more apparent among women born in recent years.

Conclusions Underweight Korean premenopausal women exhibit distinctive features associated with an increased risk of breast cancer, except for a lower rate of early menarche. These associations were prominent in recent generations. Assessment of the association between underweight and premenopausal breast cancer risk should focus on promoting healthy lifestyles to reduce breast cancer risk.

Keywords Body mass index · Breast neoplasms · Premenopausal · Risk factors · Underweight

Purpose

Obesity determined by body mass index (BMI) is significantly associated with an increased risk of breast cancer, with a reciprocal association according to menopausal status. Based on strong evidence, the Continuous Update Project (CUP) report by the World Cancer Research Fund (WCRF) International/American Institute for Cancer Research (AICR) in 2017 suggests a probable association between body fat content and decreased premenopausal breast cancer risk, and a convincing association between obesity and increased postmenopausal breast cancer risk [1]. However, it remains unclear whether underweight status is a protective factor or a risk factor for breast cancer development. Nevertheless, guidelines recommend maintaining life-long lean body weight without being underweight [2].

As the number of obese women has increased over the last 4 decades, the worldwide prevalence of underweight women has decreased from 14.6 to 9.7%; however, the prevalence of underweight in women in South Asian countries was still 24.0% in 2014 [3]. Importantly, underweight can be

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a form of malnutrition and can lead to many health problems including impaired immunity [4, 5]. Underweight is also associated with increased risk of mortality in the general population and in breast cancer patients and survivors [6, 7]. This suggests that underweight may be a discriminative risk category for human disease including cancer. Jewish Israeli adolescents with BMI < 5th percentile showed a 15% increased risk for premenopausal breast cancer compared to those with a healthy BMI in the 5th-<85th percentile [8]. Japanese pooled analysis demonstrated higher hazard ratios (HRs) without statistical significance for premenopausal breast cancer in women with BMI < 19 kg/m^2 compared to those with BMI 23–< 25 kg/m^2 [9]. However, BMI < 22 kg/m^2 was positively associated with increased risk of premenopausal breast cancer, with reduced risk for BMI > 22 kg/m^2 in a population-based UK cohort study [10]. Moreover, several studies reported non-significant decreases in HR with a wide confidence interval (CI) in underweight women [11–13].

Considering the inverse association between BMI and breast cancer risk according to menopausal status and the higher prevalence of premenopausal breast cancer in Korea than in Western countries [1, 14], it is desirable to examine the prevalence of risk factors and the association with breast cancer in underweight young women. In addition, this should be the starting point for a comprehensive management program for underweight individuals, based on the widely accepted concept of P4 medicine, i.e., predictive, personalized, preventive, and participatory approaches [15]. Herein, we aimed to examine the prevalence of breast cancer-related risk factors according to BMI and mainly focused on characteristics of underweight Korean premenopausal women. This study also aimed to analyze and compare recent risk factor trends according to birth year cohort.

Methods

Data and subject selection

The Korea National Health and Nutrition Examination Survey (KNHANES) is a cross-sectional and nationally representative survey conducted by the Korea Centers for Disease Control and Prevention (KCDC) since 1998. Details of the data resource profile have been described elsewhere [16]. To examine recent risk factor patterns relevant to breast cancer, the KNHANES phase IV (2007–2009), V (2010–2012), and VI (2013–2015) were selected. Using raw datasets for 73,353 cases, exclusion criteria were as follows: male sex, post- or undetermined menopausal status, unknown BMI, age < 20 or > 60 years, and self-reported history of any type of cancer. Finally, 13,415 premenopausal women were included in the analysis. Data from the KNHANES are publicly available (http://knhanes.cdc.go.kr) and personal information was anonymized when data were released. The Institutional Review Board of the KCDC approved the study and informed consent had been obtained from all participants [16]. Thus, ethics approval was not required for this study.

Risk factors and covariables

The KNHANES data comprise a health interview, health examination, and nutrition survey. Demographic variables and breast cancer-related risk factors commonly collected through phases IV–VI of the KNHANES were chosen but duration of breast feeding was only surveyed since 2010 (KNHANES V–VI). Anthropometric height and weight were measured by trained nurses using a standardized procedure. BMI was calculated by dividing body weight (kg) by the square of height (m^2) and categorized as underweight (< 18.5 kg/m^2), normal weight (18.5–25 kg/m^2), or obese (≥ 25 kg/m^2) [17]. Birth year cohorts were generated by survey year minus age and categorized into prior to 1965, 1966–1975, 1976–1985, and 1986–1995. Type of residence was classified as metropolitan [the capital city (Seoul), its surrounding area (Gyeonggi), and 6 other metropolitan cities (Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan)], urban [Dong in Provinces (Gangwon, Chungbuk, Chungnam, Jeonbuk, Jeonnam, Gyeongbuk, Gyeongnam, and Jeju)], and rural (Eup and Myeon in Provinces), according to administrative divisions in Korea. Individual income was categorized into quartile levels and education status was divided into middle school or less, high school, and college or higher. Occupation was classified as follows: non-manual worker (managers, experts and related workers, and office workers), manual worker (sales and services, agriculture, forestry, fishery, engineering, assembling, technical work, and manual labor), and unemployed (housewives, students, and no jobs).

Age at menarche was classified into 3 categories based on age distribution of the first menstrual period: early (≤ 12 years), normal (13–15 years), and late (≥ 16 years). Parity (0–1, 2–3, and ≥ 4) and age at first delivery (nulliparous, ≤ 24, 25–29, and ≥ 30 years) were assessed as categorical variables. Duration of breast feeding was divided into never, 1–12, and ≥ 13 months but was collected between 2010 and 2015. Thus, subgroup analyses including duration of breast feeding were performed using the KNHANES V–VI datasets. Use of oral contraceptives (ever vs. never) and lifetime experience of alcohol drinking (ever vs. never) were used as categorical variables. Physical activity in the KNHANES had been surveyed using the short form of the International Physical Activity Questionnaire (IPAQ) between 2007 and 2013 but the instrument was changed to the Global Physical Activity Questionnaire (GPAQ) in

2014. The Korean version of the GPAQ showed a positive correlation with the IPAQ (Spearman's rho = 0.446–0.767) [18], with categories (low, intermediate, and high) in this study based on the combined analysis guidelines of both instruments [19, 20].

Statistical analysis

The KNHANES sampled participants using a multistage clustered probability method and weighted subjects to represent the Korean population by accounting for the complex survey design, non-response to survey, and post-stratification [16]. All statistical analyses were conducted using a complex sample procedure. Data weights were created based on the year of survey and the stratification and cluster variables provided by the KNHANES. We calculated unweighted frequencies and weighted proportions for categorical variables or weighted means with standard error (SE) for continuous data to present general characteristics and prevalence of risk factors. Categorical parameters were compared using the Chi-square test and continuous measurements were analyzed using the complex sample general linear model and post hoc Bonferroni correction. The odds ratio (OR) and 95% CI were calculated using complex sample logistic regression analysis after adjusting for socioeconomic parameters to investigate prevalence of low- or high-risk factors in underweight or obese groups, compared to those with normal weight. All statistical tests were 2-sided and P values < 0.05 were considered statistically significant. SPSS version 23.0 (IBM Inc., Armonk, NY, USA) was used for all analyses.

Results

Underweight, normal weight, and obese women accounted for 9.5% (SE 0.3), 69.7% (SE 0.5), and 20.8% (SE 0.4) of the sample, respectively. The mean BMI in underweight, normal, and obese groups was 17.6 kg/m^2, 21.6 kg/m^2, and 28.0 kg/m^2, respectively. The mean age was 30.1 years for underweight, 35.8 years for normal weight, and 38.5 years for obese groups. Table 1 shows the general characteristics of the study population according to BMI. More than half of the underweight women were in their 20 s and obesity was present in a significantly higher proportion of women aged > 40 years. More women in the underweight group resided in metropolitan areas, while more of the obese women lived in rural areas. Underweight women had a higher proportion of income in the 4th quartile but obese women had a higher proportion in the 1st quartile. More than half of underweight women had college-level or higher education but a higher proportion with education level of middle school or lower was noted in the obese group. A higher proportion of underweight women were non-manual workers, while manual workers were frequently obese. More than half of underweight women were unmarried and approximately 85% of obese women were married.

The distribution of risk factors for breast cancer is shown in Table 2. The mean age at menarche was 13.54 (SE, 0.057) years in the underweight group, 13.64 (SE 0.022) years in the normal weight group, and 13.58 (0.041) years in the obese group ($P = 0.220$). Obese women had a higher proportion of those with early (≤ 12 years) or late (≥ 16 years) menarche. Mean parity in underweight, normal weight, and obese groups was 1.12 (SE 0.05), 2.07 (SE 0.02), and 2.60 (SE 0.04), respectively. Two-thirds of underweight women had ≤ 1 pregnancy but 28.3% of obese women had parity of ≥ 4. The mean age at first delivery was 27.22 (SE, 0.176) years in underweight women, 26.77 (SE 0.055) years in normal weight women, and 26.19 (0.103) years in obese women ($P < 0.001$). More than half of the underweight group was nulliparous. More than 80% of obese women had delivered and approximately one-third had a first delivery at age ≤ 24. Use of oral contraceptives was not statistically different among groups. Although a very small proportion of the overall population reported no history, obese women frequently reported no lifetime experience of alcohol consumption. The underweight group had a higher proportion of those with low levels of physical activity, while obese women had a higher proportion of those with high levels of physical activity. The duration of breast feeding was investigated in 8,828 participants in the KNHANES V–VI. The mean duration in underweight, normal weight, and obese groups was 4.50 (SE 0.377), 8.62 (SE 0.213), and 11.26 (SE 0.446) months, respectively. More than two-thirds of underweight women had never experienced breast feeding but more than 30% of obese women reported a total duration of breast feeding of > 1 year.

After adjusting for age alone in model 1 and general characteristics in model 2, the ORs for prevalence of low- or high-risk factors associated with breast cancer in underweight and obese women were compared to those in normal weight women, with reference to the highly prevalent category in the KNHANES IV-VI (Table 3). Underweight women had a significantly lower rate of early age at menarche, and obese women had a significantly higher rate compared to those with normal weight. Underweight women had a significantly lower number of pregnancies and obese women had a significantly higher number. Thus, significantly more underweight women were nulliparous or were older at first delivery. Younger age at first delivery was highly prevalent in obese women; in model 2, significantly more obese women were nulliparous or were older at first delivery, compared to those in the normal weight group. Underweight women had a significantly lower prevalence of high levels of physical activity, while obese women had a higher prevalence.

Table 1 General characteristics of the study population

	Underweight [$n=1141$ (%, SE)]	Normal [$n=9456$ (%, SE)]	Obesity [$n=2818$ (%, SE)]	Total [$n=13{,}415$ (%, SE)]	P value
KNHANES					
IV	353 (26.3, 1.5)	3265 (29.1, 0.6)	964 (27.5, 1.0)	4582 (28.5, 0.6)	0.063
V	438 (38.6, 1.8)	3339 (35.9, 0.7)	1022 (39.1, 1.2)	4799 (36.9, 0.7)	
VI	350 (35.0, 1.8)	2852 (35.0, 0.7)	832 (33.4, 1.1)	4034 (34.6, 0.6)	
Birth year					
1949–1965	61 (4.6, 0.7)	1685 (15.9, 0.4)	739 (23.7, 0.9)	2485 (16.5, 0.4)	< 0.001
1966–1975	285 (19.8, 1.3)	3820 (36.4, 0.6)	1172 (38.8, 1.1)	5277 (35.3, 0.5)	
1976–1985	479 (39.2, 1.7)	2815 (31.4, 0.6)	698 (27.1, 1.0)	3992 (31.2, 0.6)	
1986–1995	316 (36.4, 1.8)	1136 (16.4, 0.6)	209 (10.4, 0.8)	1661 (17.0, 0.5)	
Age (yrs)					
20s	526 (55.6, 1.7)	2032 (27.4, 0.6)	417 (19.1, 1.0)	2975 (28.3, 0.5)	< 0.001
30s	433 (30.4, 1.5)	3699 (35.2, 0.6)	932 (30.9, 1.0)	5064 (33.9, 0.5)	
40s	170 (13.4, 1.1)	3186 (32.6, 0.6)	1159 (40.7, 1.1)	4515 (32.4, 0.5)	
50s	12 (0.7, 0.2)	539 (4.8, 0.2)	310 (9.4, 0.6)	861 (5.4, 0.2)	
Residence					
Metropolitan	576 (51.2, 1.9)	4598 (50.4, 0.9)	1227 (45.1, 1.3)	6401 (49.4, 0.8)	< 0.001
Urban	440 (37.6, 1.9)	3707 (38.1, 1.1)	1101 (38.4, 1.4)	5248 (38.1, 1.0)	
Rural	125 (11.2, 1.3)	1151 (11.5, 0.8)	490 (16.5, 1.3)	1766 (12.5, 0.8)	
Income (quartile)					
1st	254 (24.8, 1.6)	2099 (23.9, 0.6)	850 (32.6, 1.1)	3203 (25.8, 0.6)	< 0.001
2nd	230 (22.0, 1.5)	2285 (25.1, 0.6)	229 (27.3, 1.0)	3294 (25.3, 0.5)	
3rd	286 (24.4, 1.5)	2483 (25.9, 0.6)	645 (22.5, 1.0)	3414 (25.1, 0.5)	
4th	355 (28.7, 1.6)	2482 (25.1, 0.6)	525 (17.7, 0.9)	3362 (23.9, 0.6)	
Education					
≤ Middle school	36 (3.4, 0.6)	759 (7.7, 0.3)	479 (16.3, 0.8)	1274 (9.1, 0.3)	< 0.001
High school	429 (39.2, 1.7)	4156 (45.0, 0.7)	1452 (52.4, 1.1)	6037 (46.0, 0.6)	
≥ College	675 (57.4, 1.7)	4516 (47.2, 0.7)	878 (31.4, 1.1)	6069 (44.9, 0.6)	
Occupation					
Non-manual worker	424 (36.6, 1.6)	2844 (30.6, 0.6)	579 (21.0, 0.9)	3847 (29.2, 0.5)	< 0.001
Manual worker	204 (17.8, 1.3)	2369 (25.4, 0.5)	993 (35.0, 1.1)	3566 (26.7, 0.5)	
Unemployed	512 (45.6, 1.8)	4199 (44.0, 0.6)	1236 (44.0, 1.1)	5947 (44.1, 0.5)	
Marital status					
Married	631 (48.0, 1.8)	7400 (73.8, 0.7)	2448 (84.1, 0.9)	10,479 (73.5, 0.6)	< 0.001
Unmarried	509 (52.0, 1.8)	2038 (26.2, 0.7)	364 (15.9, 0.9)	2911 (26.5, 0.6)	

SE standard error, *KNHANES* Korean National Health and Nutrition Examination Survey

To examine models that included duration of breast feeding, complex sample logistic regression analyses were again performed using the KNHANES V-VI datasets (Table 4). Underweight women had lower prevalence of early menarche and high levels of physical activity and higher prevalence of older age at first delivery, with statistical significance. Obese women had higher prevalence of early menarche, younger age at first delivery, and high levels of physical activity, with statistical significance. Higher parity in model 1 and higher nulliparous rate in model 2 showed statistical significance in obese women, similar to the results in Table 3.

To assess risk factor trends according to BMI stratified by generation, the mean values of reproductive parameters were compared according to birth year cohorts in Fig. 1. Older age at menarche in underweight women was significantly more common among those born after 1976. Lower parity in underweight women was statistically significant among those born between 1966 and 1985. Older age at first delivery and shorter duration of breast feeding in underweight women showed borderline significance among those born between 1966 and 1975 and between 1976 and 1985, respectively. The rates of alcohol consumption and levels

Table 2 Prevalence of risk factors for breast cancer

	Underweight [$n=1141$ (%, SE)]	Normal [$n=9456$ (%, SE)]	Obesity [$n=2818$ (%, SE)]	Total [$n=13{,}415$ (%, SE)]	*P* value
Age at menarche (yrs)					
≤12	255 (24.8, 1.6)	2208 (25.5, 0.6)	753 (29.0, 1.0)	3216 (26.2, 0.5)	<0.001
13–15	771 (65.3, 1.7)	6045 (62.3, 0.6)	1640 (57.1, 1.1)	8456 (61.5, 0.5)	
≥16	112 (9.9, 1.0)	1170 (12.2, 0.4)	411 (13.9, 0.8)	1693 (12.3, 0.3)	
No. of parity					
0–1	685 (66.6, 1.6)	3140 (38.0, 0.7)	644 (26.4, 1.0)	4469 (38.3, 0.6)	<0.001
2–3	342 (24.8, 1.4)	4294 (42.0, 0.6)	1350 (45.3, 1.1)	5986 (41.1, 0.5)	
≥4	113 (8.6, 0.9)	2007 (20.0, 0.5)	816 (28.3, 1.0)	2936 (20.6, 0.4)	
Age at first delivery (yrs)					
Nulliparous	535 (56.2, 1.8)	2170 (28.2, 0.7)	414 (18.2, 0.9)	3119 (28.7, 0.6)	<0.001
≤24	114 (9.8, 1.0)	1798 (18.7, 0.5)	805 (28.6, 1.0)	2717 (19.9, 0.4)	
25–29	303 (22.5, 1.4)	3862 (39.1, 0.6)	1127 (38.5, 1.1)	5292 (37.4, 0.5)	
≥30	151 (11.6, 1.0)	1426 (14.0, 0.4)	414 (14.7, 0.8)	1991 (14.0, 0.4)	
OCs use					
Ever	113 (10.9, 1.1)	1097 (11.7, 0.4)	352 (12.3, 0.7)	1562 (11.8, 0.3)	0.538
Never	1027 (89.1, 1.1)	8358 (88.3, 0.4)	2463 (87.7, 0.7)	11,848 (88.2, 0.3)	
Alcohol drinking					
Ever	1063 (94.1, 0.8)	8702 (92.6, 0.3)	2534 (90.4, 0.6)	12,299 (92.3, 0.3)	<0.001
Never	77 (5.9, 0.8)	730 (7.4, 0.3)	275 (9.6, 0.6)	1082 (7.7, 0.3)	
Physical activity					
Low	498 (43.0, 1.8)	3650 (38.8, 0.6)	1019 (36.8, 1.1)	5167 (38.8, 0.5)	<0.001
Intermediate	478 (43.2, 1.8)	3776 (40.5, 0.6)	1055 (38.0, 1.1)	5309 (40.2, 0.5)	
High	160 (13.8, 1.2)	1975 (20.7, 0.5)	730 (25.2, 0.9)	2865 (21.0, 0.4)	
Duration of breast feeding (months, n = 8828)					
Never	493 (68.5, 1.8)	2629 (46.4, 0.8)	676 (38.7, 1.4)	3798 (46.9, 0.7)	<0.001
1–12 months	164 (18.1, 1.5)	1791 (27.1, 0.7)	534 (27.8, 1.2)	2489 (26.3, 0.6)	
≥13	131 (13.5, 1.3)	1767 (26.5, 0.7)	643 (33.6, 1.3)	2541 (26.7, 0.6)	

yrs years; *No*. number, *OCs* oral contraceptives

of physical activity varied according to BMI in the overall population (Table 2). Alcohol consumption according to BMI was not significantly different when stratified by birth cohort; however, the lower rate of high levels of physical activity in underweight women was significant among those born between 1966 and 1995, as shown in Fig. 2.

Discussion

In the current study, underweight Korean premenopausal women had unique socioeconomic characteristics: younger age at the time of the survey, higher rate of metropolitan residence, higher economic status and level of education, and higher rates of non-manual employment and unmarried status. Similar to Japanese and Chinese studies, underweight women were likely to be younger [21, 22]. This could reflect inappropriate perceptions of body size and intense desire for thinness among younger women [23]. Higher prevalence of underweight in most developing countries is frequently reported in rural women and lower socioeconomic levels [24, 25]. In contrast, underweight Korean premenopausal women were likely to be highly prevalent in metropolitan areas and have higher socioeconomic status [26].

Importantly, underweight premenopausal Korean women had distinctive breast cancer-related factors: lower rates of early menarche and parity, less likelihood of having breastfed, higher likelihood of having consumed alcohol, and lower rate of high levels of physical activity. Early age at menarche was inversely associated with BMI [27], but other factors were associated with an increased risk of breast cancer development. Multivariate analysis performed with adjustment for socioeconomic parameters showed that lower rates of early menarche and parity, older age at first delivery, and a lower rate of high levels of physical activity were significant in underweight women. Trends in obese women showed an inverse association compared to those in women

Table 3 Adjusted odds ratios in KNHANES IV–VI (2007–2015)

	Underweight vs. normal				Obesity vs. normal			
	Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at menarche (yrs)								
≤12	0.617 (0.514–0.740)	<0.001	0.618 (0.514–0.743)	<0.001	1.585 (1.402–1.792)	<0.001	1.664 (1.468–1.887)	<0.001
13–15	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥16	1.094 (0.854–1.401)	0.478	1.114 (0.863–1.439)	0.408	1.001 (0.860–1.164)	0.993	0.880 (0.753–1.029)	0.108
No. of parity								
0–1	1.357 (1.049–1.755)	0.020	1.327 (1.022–1.723)	0.033	0.830 (0.675–1.020)	0.076	0.878 (0.717–1.075)	0.208
2–3	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥4	0.927 (0.715–1.202)	0.569	0.933 (0.720–1.208)	0.597	1.181 (1.044–1.336)	0.008	1.126 (0.992–1.278)	0.067
Age at first delivery (yrs)								
Nulliparous	1.488 (1.131–1.959)	0.005	1.485 (1.024–2.154)	0.037	0.944 (0.738–1.207)	0.646	1.408 (1.024–1.936)	0.035
≤24	0.922 (0.707-1.200)	0.544	0.947 (0.721–1.243)	0.693	1.469 (1.294–1.668)	<0.001	1.191 (1.042–1.361)	0.011
25–29	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥30	1.406 (1.092–1.811)	0.008	1.411 (1.095–1.818)	0.008	1.149 (0.982–1.344)	0.083	1.175 (1.002–1.377)	0.047
OCs use								
Ever	1.021 (0.805–1.294)	0.864	1.035 (0.812–1.319)	0.782	0.982 (0.838–1.151)	0.822	0.926 (0.789–1.088)	0.351
Never	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Alcohol								
Ever	0.891 (0.661–1.202)	0.449	0.856 (0.634–1.157)	0.312	0.857 (0.717–1.024)	0.090	0.860 (0.717–1.030)	0.102
Never	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Physical activity								
Low	1.129 (0.957–1.332)	0.150	1.104 (0.935–1.303)	0.242	0.982 (0.874–1.103)	0.760	0.958 (0.851–1.078)	0.471
Intermediate	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
High	0.642 (0.515–0.802)	<0.001	0.650 (0.518–0.815)	<0.001	1.259 (1.110–1.428)	<0.001	1.218 (1.071–1.383)	0.003

In a model 1, age alone was adjusted

In a model 2, age, residence, income, education, occupation, and marital status were adjusted

vs. versus, *OR* odds ratio, *CI* confidence interval

of normal weight, and these patterns seemed more prominent among recent birth cohorts.

Several meta-analyses have addressed the association between BMI and breast cancer risk in premenopausal women. Ursin et al. [28] reported that an 8-unit increase in BMI was associated with a relative risk (RR) of 0.70 in cohort studies and 0.88 in case–control studies. Renehan et al. [29] found that a 5 kg/m^2 increase in BMI was associated with an RR of 0.92 (95% CI 0.88–0.97). The authors also found a significant inverse association between BMI and breast cancer risk in North American and European/Australian populations, as well as a positive association in Asian-Pacific populations. Recent reevaluation of dose–response meta-analyses confirmed a weak level of evidence for the association between BMI and premenopausal breast cancer (RR 0.95; 95% CI 0.93–0.98) [30]. Similarly, each 5 kg/m^2 increase was inversely associated with an RR of 0.95 in stratified analyses in Africans and Caucasians, while a significant positive association with an RR of 1.05 was found in Asian women according to a meta-analysis by Amadou et al. [31]. Subsequent dose–response meta-analyses found an RR of 0.98–0.99 per 5 kg/m^2 increase in BMI [32, 33]. Among premenopausal women, however, Xia et al. [34] and Chen et al. [35] found no significant association between BMI and premenopausal breast cancer risk in each meta-analysis. Although most meta-analyses and the CUP report by the WCRF/AICR suggested an inverse association between BMI and premenopausal breast cancer risk, the impact of underweight on breast cancer development has not been fully analyzed, especially considering heterogeneous BMI effects according to ethnicity. In most studies, overweight or obese women predominated, underweight women were underrepresented, underweight women were included in a control group and combined with those of normal weight as a reference group, or the underweight group was excluded. Considering that more than half of underweight Korean women were in their 20 s but had a lower rate

Table 4 Adjusted odds ratios in KNHANES V-VI (2010–2015)

	Underweight vs. normal				Obesity vs. normal			
	Model 1		Model 2		Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at menarche (yrs)								
≤12	0.667 (0.539–0.826)	<0.001	0.656 (0.529–0.814)	<0.001	1.525 (1.316–1.766)	<0.001	1.587 (1.366–1.844)	<0.001
13–15	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥16	1.160 (0.870–1.545)	0.312	1.173 (0.872–1.577)	0.291	1.032 (0.858–1.241)	0.737	0.906 (0.749–1.096)	0.309
No. of parity								
0–1	1.128 (0.817–1.556)	0.464	1.100 (0.793–1.526)	0.568	0.782 (0.609–1.004)	0.054	0.840 (0.659–1.072)	0.161
2–3	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥4	0.873 (0.639–1.194)	0.395	0.896 (0.657–1.220)	0.485	1.215 (1.039–1.421)	0.015	1.142 (0.973–1.341)	0.105
Age at first delivery (yrs)								
Nulliparous	1.353 (0.896–2.043)	0.150	1.243 (0.753–2.052)	0.395	1.029 (0.751–1.410)	0.857	1.510 (1.029–2.217)	0.035
≤24	0.894 (0.640–1.248)	0.509	0.898 (0.639–1.263)	0.536	1.524 (1.296–1.793)	<0.001	1.222 (1.030–1.451)	0.022
25–29	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥30	1.379 (1.018–1.869)	0.038	1.372 (1.012–1.860)	0.042	1.110 (0.918–1.342)	0.280	1.134 (0.936–1.374)	0.197
Duration of breast feeding (months)								
Never	1.110 (0.810–1.522)	0.514	1.136 (0.825–1.564)	0.434	1.086 (0.896–1.318)	0.400	1.070 (0.880–1.300)	0.498
1–12	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥13	0.866 (0.647–1.158)	0.331	0.867 (0.647–1.162)	0.338	1.103 (0.931–1.308)	0.257	1.066 (0.898–1.267)	0.465
OCs use								
Ever	1.206 (0.904–1.610)	0.203	1.248 (0.932–1.672)	0.137	1.031 (0.832–1.278)	0.778	0.983 (0.792–1.220)	0.876
Never	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Alcohol								
Ever	0.832 (0.574–1.206)	0.331	0.788 (0.542–1.144)	0.210	0.881 (0.699–1.111)	0.284	0.870 (0.687–1.102)	0.248
Never	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Physical activity								
Low	1.068 (0.878–1.299)	0.509	1.059 (0.872–1.287)	0.562	1.013 (0.882–1.164)	0.850	0.970 (0.843–1.117)	0.675
Intermediate	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
High	0.618 (0.463–0.825)	0.001	0.623 (0.465–0.836)	0.002	1.279 (1.088–1.504)	0.003	1.244 (1.055–1.467)	0.010

In a model 1, age alone was adjusted

In a model 2, age, residence, income, education, occupation, and marital status were adjusted

of high levels of physical activity, weight control might instead be a consequence of sustained adolescent physiology [36].

A cross-sectional study of university students in 23 countries revealed that underweight was associated with a significant increase in unadjusted OR for physical inactivity level, although the adjusted OR did not show statistical significance [37]. In the 2013 Behavioral Risk Factor Surveillance System study, underweight women showed a significantly increased OR for physical inactivity compared to those in the desirable weight group (OR 1.57; 95% CI 1.36–1.81) [38]. The OR was similar to that in overweight or obese class I categories and suggested that adverse health consequences of physical inactivity might be present in both underweight and overweight or obese individuals [38]. Since BMI and physical activity levels are modifiable over a lifetime and younger generations are potential targets of future disease, maintaining a healthy lifestyle should be promoted in younger underweight populations.

As potential limitations of this study, breast cancer risk in underweight women could not be directly calculated because the KNHANES data were not longitudinal. Moreover, risk factors such as breast biopsy histopathology, familial history of breast cancer, and genetic predisposition including the presence of *BRCA* 1/2 mutations were not included in the analysis. Most variables including BMI, parity, and physical activity status were not fixed risk categories and were modifiable throughout the lifetime. BMI determined during survey periods may not represent lifetime BMI status, especially in older participants, although multivariable-adjusted models were analyzed. Therefore, interpretation of the current results should be cautious, as cause-and-effect

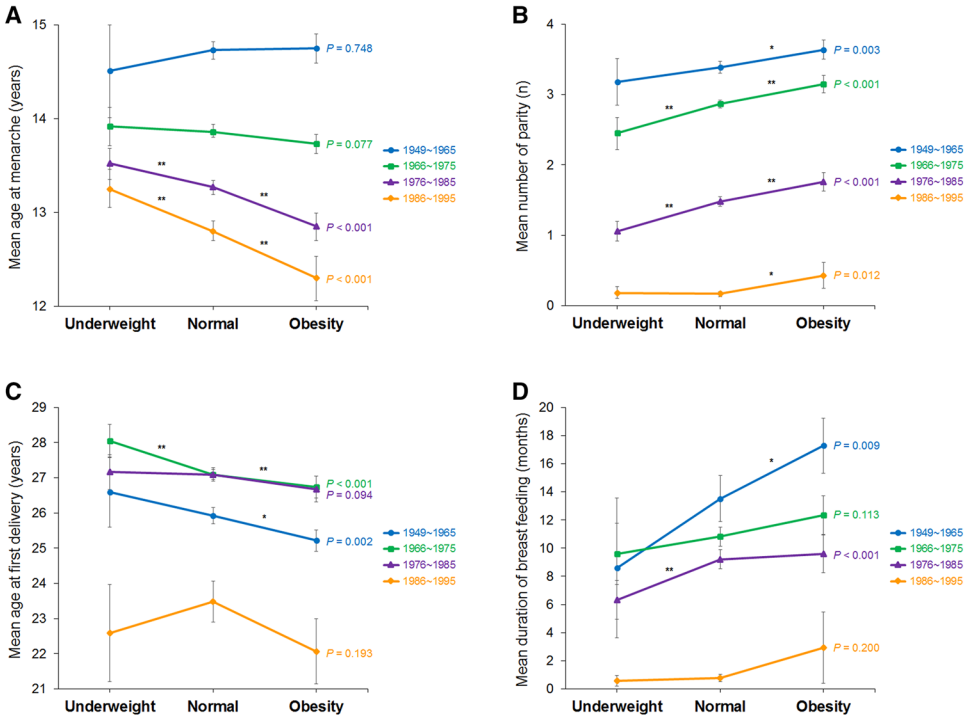

Fig. 1 Mean and 95% confidence interval for risk factors according to birth year in underweight, normal weight, and obese premenopausal women. **a** Age at menarche, **b** parity, **c** age at first delivery, and **d** duration of breast feeding. Blue line shows women born before 1965; green line, between 1966 and 1975; purple line, between 1976 and 1985; and orange line, between 1986 and 1995. Overall *P* value corrected with the Bonferroni method is presented for each birth year group. Normal weight, reference group; **P* value < 0.05; ***P* value < 0.001

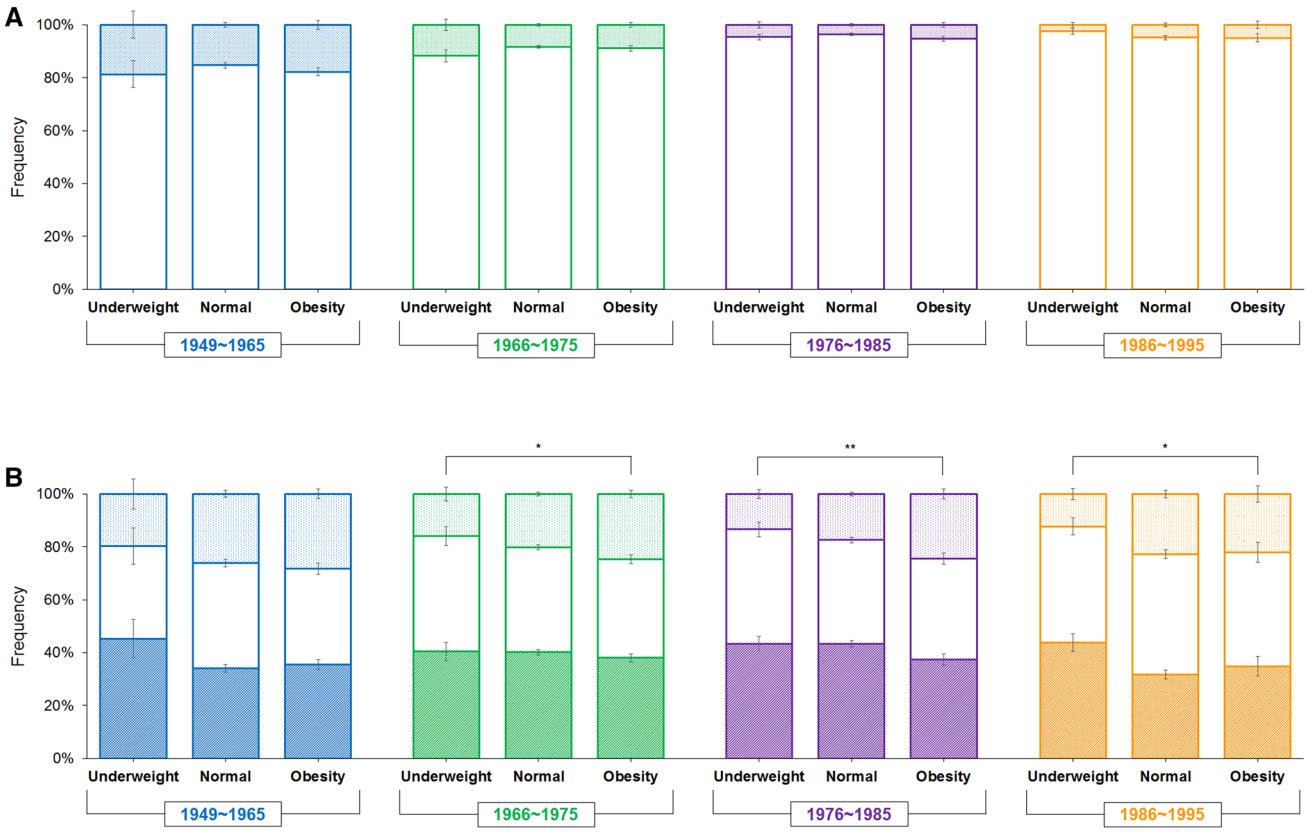

Fig. 2 Frequency of alcohol consumption and physical activity according to body mass index when stratified by birth year cohort. **a** Alcohol consumption and **b** physical activity. Dotted and white areas in **a** represent history of never or ever drinking alcohol, respectively, and dotted, white, and dashed areas in **b** represent high, intermediate, and low levels of physical activity, respectively. Blue line shows women born before 1965; green line, between 1966 and 1975; purple line, between 1976 and 1985; and orange line, between 1986 and 1995. Error bars show standard errors for each proportion. **P* value < 0.05; ***P* value < 0.001

relationships could be identified in this study. Based on the self-reporting nature of the KNHANES study and missing variables such as duration of breast feeding, potential recall and selection bias could not be excluded, although the relatively young premenopausal study population was likely to have intact memory. Finally, only 2 instruments were used for assessment of physical activity level, although a positive correlation between instruments was demonstrated. Nevertheless, the strength of our study was based on analysis of datasets from a large population-based study representing nationwide estimates with study periods of 9 years.

Conclusions

Underweight Korean premenopausal women presented unique characteristics of socioeconomic status and distinctive features associated with increased risk of breast cancer, except for the lower rate of early age at menarche. These characteristics showed an inverse association in obese women compared to those in women of normal weight, and the patterns were prominent in more recent generations. Further research on the association between underweight status and premenopausal breast cancer risk should focus on promotion of healthy lifestyles and nutritional support in young and underweight premenopausal women to prevent future breast cancer and disease.

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Compliance with ethical standards

Conflict of interest The authors have no potential conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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