

ORIGINAL ARTICLE

Body mass index and breast cancer: analysis of a nation-wide population-based prospective cohort study on 1 393 985 Taiwanese women

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BACKGROUND: Asian women have a younger age at onset of breast cancer and a lower body mass index (BMI) than Western women. The link between obesity and risk of breast cancer in Asian women is still elusive. We aimed to investigate the effect of BMI on the risk of incident breast cancer in Taiwanese women.

METHODS: A total of 1 393 985 women who had been cancer-free before recruitment and attended a nation-wide Taiwanese breast cancer-screening program between 1999 and 2009 were enrolled using a prospective cohort study. Obesity and other relevant variables (such as menopause status and other biochemical markers) were collected through in-person interviews, anthropometric measurements and blood samples at first screen. Incident breast cancers during follow-up were ascertained through the linkage of the cohort with the National Cancer Registry and the National Death Certification System.

RESULTS: A total of 6969 and 7039 incident breast cancer cases were identified among women enrolled before and after menopause, respectively. Compared with a BMI range of 18.5–23.9 kg m⁻², the incremental level of BMI in the enrolled women before menopause revealed a lack of statistically significant association with the risk of incident breast cancer (adjusted hazard ratio = 0.94, 0.98, 1.02, 1.01 and 0.82 for BMI < 18.5, 24–26.9, 27–29.9, 30–34.9 and ≥ 35, respectively), but the incremental level of BMI in the enrolled women after menopause led to a statistically significant incremental increase in the risk of breast cancer (adjusted hazard ratio = 0.78, 1.19, 1.31, 1.53 and 1.65 for BMI < 18.5, 24–26.9, 27–29.9, 30–34.9 and ≥ 35, respectively) after adjusting for other explanatory risk factors.

CONCLUSION: Obesity acts mainly as an influential promoter of the development of late-onset breast cancer after menopause in Taiwanese women.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women worldwide¹ and has recently increased markedly in Taiwan.² Excess body weight, an emerging problem worldwide, has been reported to be associated with elevated risks of many non-communicable chronic diseases.³ Although body mass index (BMI), which is generally used to define overweight or obese, varies among ethnicities and cannot completely reflect adiposity, excess body weight is one of the most important contributors to mortality worldwide⁴ and is considered an established factor for several types of cancer,^{5,6} including breast cancer. The evidence showing that high BMI has significant negative and positive associations with risk of breast cancer among pre- and post-menopausal women, respectively, is mainly from Western populations.^{5,7} However, inconclusive results have been reported from Asian populations such as Taiwanese women partly because the data used in the previous studies are too sparse and partly because the epidemiological profiles are different across ethnic groups, specifically in that the incidence of breast cancer in Asian women peaks at age 40–50 years, whereas it peaks at age 60–70 years in

Western women.⁸ Socio-economic profiles, lifestyles, cultures and genetic backgrounds related to occurrence of breast cancer in Asian population are also at odds with those in Western populations.^{8,9} Therefore, a better understanding of the similarities and differences between Asian and Western women in major breast cancer risk factors (such as BMI) could potentially be of great benefit to designing and providing more effective screening and primary prevention programs.

High BMI is associated with an elevated risk of breast cancer in post-menopausal women with consistent evidence.^{5,7,10–18} However, the association between obesity and breast cancer risk is controversial in pre-menopausal women,^{7,19,20} which may be attributed to different anthropometric measurements of body composition presentation (including BMI, body height or waist-to-hip ratio) and different study designs (such as cohort studies or case-control studies). As Asian people have been reported to have higher levels of body fat, more abdominal fat and less-lean mass than the other ethnic groups for a given BMI,^{19–21} such findings motivate us to test the postulate, 'Is the effect of BMI on breast cancer risk greater in Asian women?'

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In this study, we aimed to investigate the effect of current BMI on the risk of incident breast cancer in Taiwanese pre-menopausal and post-menopausal women using a large population-based cohort study. We also examined the effect of BMI on the age at breast cancer diagnosis during follow-up among women recruited in this cohort study.

MATERIALS AND METHODS

Study cohort

A nation-wide prospective non-selective breast cancer-screening program has been conducted in Taiwan since 1999 using three stepwise stages. The first population cohort launched in 1999, the second cohort launched in 2002, and the third cohort launched in 2005. The recruitment and follow-up of the first two cohorts have been previously described.²² In brief, in cohort I ($n=897\,806$), women aged 35 years or older at screening were invited via a governmental publicity campaign to enroll in this nation-wide cohort between 1999 and 2001. In cohort II ($n=301\,181$), women aged 50–69 years were invited to enroll in the program between 2002 and 2004. In the first two cohorts, all participants were screened via physical examination by public health nurses or by questionnaire, respectively, to exclude women at high risk of breast cancer prior to further ultrasonography and mammography. In cohort III ($n=595\,410$), women aged 40 years and older were invited between 2005 and 2009 to participate in the nation-wide breast cancer-screening program, which offered mammography every 2 years. Women ($n=311\,832$) who were repeatedly recruited in at least two of the three cohorts were identified, and only their first screen was retained in the final analyses. We excluded subjects who had not gone through menopause by age 60, those with incomplete data for height, weight, BMI or menopausal status, and subjects who at baseline were menopausal owing to surgical reasons. All enrolled subjects were considered to be free of breast cancer. A total of 1 393 985 women were included in the following analyses. All the subjects gave informed consent, and this nation-wide cancer-screening program was supported and approved by the Department of Health, Executive Yuan (No.1039900137).

All women recruited in these three cohorts were free of symptoms and underwent face-to-face interviews with public health nurses or health-care providers at recruitment for the collection of basic personal data including anthropometric measurements, menstrual and reproductive history, and family and medical history. BMI was calculated as weight (kilograms) divided by squared height (square meters) and obtained only at entry into the study. Values of BMI were grouped as follows according to recommendations for Taiwanese adults from the Department of Health, Executive Yuan: underweight (<18.5), normal-weight (18.5–23.9), overweight (24–26.9), mild obesity (27–29.9), moderate obesity (30–34.9) and morbid obesity (35 or more). Information on hormone usage was included in the questionnaires for cohorts II and III, but not for cohort I.

Follow-up and identification of cancer cases

All enrolled women were followed from the start of screening until 26 October 2012.² The incident breast cancer during follow-up was ascertained using the National Cancer Registry and the National Death Certification System. All hospitals in Taiwan have a legal obligation to actively report cases of treated or diagnosed cancer to the National Cancer Registry. In addition, any migration or death must be registered with the local household registration office in Taiwan; therefore, all deceased residents in Taiwan were included in the computerized national death certificate data. Regardless of emigration, we could trace the vital status of all participants through data linkage with the household registration and death certification systems. To investigate the relationship between baseline BMI and subsequent breast cancer cases in the breast cancer-screening program cohort and to identify breast cancers that may have already developed but would not be identified by screening, we further differentiated breast cancer diagnosed during follow-up as prevalent and incident breast cancer. Prevalent breast cancer cases were defined as subjects who had a positive screening result and were diagnosed with breast cancer. Other breast cancer cases diagnosed during follow-up were regarded as incident cases.

Statistical analysis

The data are presented as the number of patients along with the percentage, as shown in Table 1. The time to occurrence of breast cancer

was calculated from the date of the first screen to the diagnosis of incident breast cancer, death, loss to follow-up or the end of the study, whichever came first. The life-table method was used to show the actual number of breast cancer cases and their percent distribution according to BMI at enrollment and age of diagnosis of breast cancer for pre- and post-menopausal women. Cox proportional hazards regression models were used to assess the association between incident breast cancer and BMI, age at recruitment, family history of breast cancer, history of hormone usage, and reproductive factors including age at menarche, number of births, age at first full-term pregnancy and breast-feeding history. Hazard ratios were estimated using univariate and multi-variable regression models for all explanatory variables, including BMI, age at recruitment, family history of breast cancer, age at menarche, number of births, age at first full-term pregnancy and history of breastfeeding. Trends analyses were also performed for the level of BMI and other variables. All statistical analyses were performed using the PC version of the Statistical Analysis System (SAS, version 9.1; SAS Institute, Inc., Cary, NC, USA). All programming codes for the statistical analyses are available upon request (Chiou S-T and Chen H-H).

RESULTS

Among the 1 393 985 women enrolled in total, 503 007 women were pre-menopausal and 890 978 women were post-menopausal. A total of 8571 (including 1602 prevalent and 6969 incident cases of breast cancer) and 10 761 (including 3722 prevalent and 7039 incident cases of breast cancer) newly diagnosed cases of breast cancer were recorded during follow-up among pre- and post-menopausal women, respectively. Baseline demographic data are shown in Table 1.

Table 2 presents the associations between the baseline explanatory variables and the development of incident breast cancer according to menopausal status at recruitment. Only incident breast cancer cases were included in the final analyses. As expected, breast cancer risks were significantly higher in women with a family history of breast cancer and among those who had used hormones, and risks were significantly lower among those who had delayed menarche and those who had given birth. Among women with a history of childbirth, breastfeeding and high-order parity were associated with lower risks of breast cancer, whereas older age at first delivery was associated with increased risk. All associations remained significant in the baseline pre- and post-menopausal groups after adjusting for the explanatory factors with each other.

The relationship between baseline BMI and risk of incident breast cancer during follow-up is shown in Table 2 and Figure 1. High BMI was associated with increased risk of breast cancer in post-menopausal women, and this association remained after adjusting for all explanatory variables. A total of 6969 and 7039 incident breast cancer cases were identified among the enrolled women before and after menopause, respectively. Compared with the reference subgroup of BMI within 18.5–23.9 kg m⁻² that contained the largest number of enrolled subjects among all BMI subgroups, the incremental level of BMI at recruitment in the enrolled women before menopause was not statistically significantly associated with the risk of incident breast cancer (adjusted hazard ratio=0.94, 0.98, 1.02, 1.01 and 0.82 for BMI <18.5 , 24–26.9, 27–29.9, 30–34.9 and ≥ 35 , respectively), but the incremental level of BMI at recruitment in the enrolled women after menopause led to a statistically significant incremental increase in the risk of incident breast cancer (adjusted hazard ratio=0.78, 1.19, 1.31, 1.53 and 1.65 for BMI <18.5 , 24–26.9, 27–29.9, 30–34.9 and ≥ 35 , respectively) after adjusting for other explanatory risk factors. Although morbidly obese (BMI ≥ 35 kg m⁻²) women who were pre-menopausal at recruitment had a lower risk of developing incident breast cancer, this association was not statistically significant. Figures 1a and b show the cumulative incidence of breast cancer during follow-up by BMI among women who were pre- and post-menopausal at recruitment, respectively.

Table 1. The demographic and hormone-related characteristics of all recruited women

Factors	Pre-menopause N = 503 007			Post-menopause N = 890 978		
	Free of breast cancer N(%)	Prevalence breast cancer N(%)	Incidence breast cancer N(%)	Free of breast cancer N(%)	Prevalence breast cancer N(%)	Incidence breast cancer N(%)
Age at recruitment						
< 40	121 968(24.67)	141(8.80)	1702(24.42)	1005(0.11)	0(0.00)	11(0.16)
40–49	225 429(45.59)	450(28.09)	3962(56.85)	21 032(2.39)	39(1.05)	258(3.67)
50–59	147 039(29.74)	1011(63.11)	1305(18.73)	450 445(51.17)	2236(60.08)	3772(53.59)
60–69	0(0.00)	0(0.00)	0(0.00)	31 8301(36.16)	1353(36.35)	2522(35.83)
≥ 70	0(0.00)	0(0.00)	0(0.00)	89 434(10.16)	94(2.53)	476(6.76)
BMI						
< 18.5	15 384(3.22)	36(2.29)	224(3.34)	19331(2.46)	84(2.40)	103(1.71)
18.5–23.9	283 602(59.36)	936(59.58)	4161(62.02)	375 549(47.70)	1593(45.61)	2578(42.80)
24–26.9	114 707(24.01)	377(24.00)	1518(22.63)	237 766(30.20)	1093(31.29)	1939(32.19)
27–29.9	43 546(9.11)	154(9.80)	562(8.38)	105 322(13.38)	490(14.03)	923(15.32)
30–34.9	17 532(3.67)	62(3.95)	216(3.22)	42 716(5.43)	196(5.61)	417(6.92)
≥ 35	2993(0.63)	6(0.38)	28(0.42)	6599(0.84)	37(1.06)	63(1.05)
Age at menarche						
≤ 13	134 295(28.32)	526(33.80)	2091(31.41)	159 981(18.65)	950(25.75)	1345(19.70)
14	138 451(29.19)	440(28.28)	2008(30.16)	189 723(22.12)	977(26.48)	1578(23.12)
15	98 623(20.80)	290(18.64)	1303(19.57)	173 794(20.26)	731(19.81)	1429(20.93)
≥ 16	102 866(21.69)	300(19.28)	1256(18.86)	334 368(38.95)	1032(27.97)	2474(36.24)
Birth						
No	22 378(4.57)	136(8.57)	399(5.81)	35 302(4.02)	306(8.23)	399(5.70)
Yes	467 736(95.43)	1451(91.43)	6471(94.19)	842 123(95.98)	3414(91.77)	6600(94.30)
No. of birth^a						
1	35 762(7.65)	156(10.75)	643(9.94)	33 909(4.03)	255(7.47)	315(4.77)
2	186 266(39.82)	653(45.00)	2884(44.57)	159 867(18.98)	989(28.97)	1318(19.97)
≥ 3	245 708(52.53)	642(44.25)	2944(45.50)	648 347(76.99)	2170(63.56)	4967(75.26)
Age at full-term pregnancy^a						
≤ 22	92 818(26.33)	111(18.17)	1091(19.09)	328 738(39.86)	958(28.47)	2283(35.23)
23–25	107 326(30.44)	181(29.62)	1642(28.73)	274 274(33.26)	1089(32.36)	2116(32.65)
26–29	104 786(29.72)	202(33.06)	1914(33.48)	161 333(19.56)	885(26.30)	1459(22.51)
≥ 30	47 605(13.50)	117(19.15)	1069(18.70)	60 316(7.31)	433(12.87)	623(9.61)
Breast feeding^a						
No	211 953(44.72)	854(55.17)	3104(47.58)	193 792(22.44)	1382(37.62)	1626(23.98)
Yes	261 997(55.28)	694(44.83)	3420(52.42)	66 9749(77.56)	2292(62.38)	5155(76.02)
Family history						
No	472 375(96.52)	1473(92.41)	6573(95.27)	844 882(96.77)	3444(92.71)	6633(95.03)
Yes	17045(3.48)	121(7.59)	326(4.73)	28220(3.23)	271(7.29)	347(4.97)
Hormone therapy						
No	99 652(91.75)	845(92.86)	508(88.04)	366 358(81.96)	2444(82.71)	1718(77.11)
Yes	8963(8.25)	65(7.14)	69(11.96)	80 664(18.04)	511(17.29)	510(22.89)

^aAmong parous women.

The morbidly obese women recruited before menopause had a trend of lower cumulative incidence of breast cancer during the follow-up period (Figure 1a). The cumulative incidence of new breast cancers during follow-up increased with greater baseline BMI among women who were menopausal at recruitment (Figure 1b).

To further investigate the effects of baseline BMI on the age at diagnosis of breast cancer among pre- and post-menopausal women, we stratified all subjects according to baseline BMI and plotted the proportion of breast cancer diagnosed at different age bands during follow-up. As shown in Figure 2a, the peak percentage of breast cancer diagnosed at each age subgroup in pre-menopausal women with preceding morbidly obese (BMI $\geq 35 \text{ kg m}^{-2}$) tended to occur at an older age than those with lower baseline BMI. For women who were post-menopausal at

recruitment, as shown in Figure 2b, the percentage of breast cancer increased with the incremental level of BMI.

DISCUSSION

Because Asian women generally have lower BMI²³ and an earlier peak age of breast cancer incidence than Western women,⁸ it is therefore worthwhile to investigate the effect of BMI on the risk of incident breast cancer for pre-menopausal and post-menopausal Taiwanese women using a large prospective cohort study like our study design. We found BMI was a strong predictor of breast cancer for post-menopausal but not for pre-menopausal Taiwanese women. Obesity seems to mainly exert its effects on breast cancer among older women.

Table 2. Cox proportional hazards regression analyses for the crude HR and multiple variable-adjusted HR for risk of breast cancer in women recruited before and after menopause

Factors	Pre-menopause			Post-menopause		
	Crude HR	aHR	P-value	Crude HR	aHR	P-value
	(95% CI)	(95% CI)		(95% CI)	(95% CI)	
BMI (vs 18.5–23.9)						
< 18.5	0.94(0.82,1.07)	0.94(0.81,1.10)	0.9999 ^a	0.79(0.65,0.97)	0.78(0.63,0.96)	< 0.0001 ^a
24–26.9	0.95(0.90,1.01)	0.98(0.91,1.04)		1.13(1.06,1.20)	1.19(1.12,1.27)	
27–29.9	0.96(0.87,1.04)	1.02(0.93,1.13)		1.22(1.13,1.31)	1.31(1.21,1.41)	
30–34.9	0.93(0.81,1.06)	1.01(0.86,1.18)		1.41(1.27,1.56)	1.53(1.38,1.71)	
≥ 35	0.71(0.49,1.03)	0.82(0.54,1.24) ^b		1.50(1.17,1.92)	1.65(1.27,2.13)	
Age at recruitment (vs < 40)						
40–49	1.26(1.19,1.34)	1.39(1.30,1.48)	< 0.0001 ^a	1.11(0.61,2.03)	0.96(0.49,1.88)	< 0.0001 ^a
50–59	1.39(1.29,1.49)	1.72(1.56,1.90)		1.34(0.74,2.42)	1.25(0.65,2.41)	
60–69	—	—		1.07(0.59,1.93)	1.21(0.63,2.33)	
≥ 70	—	—		0.59(0.33,1.08)	0.73(0.37,1.41)	
Age at menarche (vs ≤ 13)						
14	0.91(0.85,0.97)	0.96(0.90,1.03)	< 0.0001 ^a	0.88(0.82,0.95)	0.94(0.87,1.02)	< 0.0001 ^a
15	0.83(0.83,0.89)	0.89(0.82,0.96)		0.83(0.77,0.90)	0.92(0.85,1.00)	
≥ 16	0.76(0.76,0.82)	0.82(0.76,0.89)		0.66(0.62,0.71)	0.78(0.72,0.84)	
Birth (vs no)						
Yes	0.73(0.66,0.81)	0.81(0.62,1.06)	0.1186	0.62(0.56,0.69)	0.67(0.54,0.83)	0.0003
No. of birth^c (vs 1)						
2	0.86(0.79,0.94)	0.91(0.82,1.00)	< 0.0001 ^a	0.89(0.79,1.01)	0.96(0.83,1.10)	< 0.0001 ^a
≥ 3	0.66(0.60,0.71)	0.76(0.69,0.85)		0.59(0.53,0.66)	0.80(0.70,0.92)	
Age at first full-term pregnancy^c (vs ≤ 22)						
23–25	1.29(1.20,1.39)	1.28(1.18,1.39)	< 0.0001 ^a	1.20(1.13,1.27)	1.15(1.08,1.23)	< 0.0001 ^a
26–29	1.54(1.43,1.66)	1.46(1.35,1.58)		1.57(1.47,1.68)	1.33(1.23,1.44)	
≥ 30	1.89(1.74,2.06)	1.69(1.54,1.87)		1.87(1.72,2.05)	1.51(1.36,1.68)	
Breast feeding^c (vs no)						
Yes	0.86(0.82,0.91)	0.94(0.89,0.99)	0.0243	0.67(0.63,0.71)	0.86(0.80,0.92)	< 0.0001
Family history (vs no)						
Yes	1.57(1.41,1.76)	1.39(1.22,1.59)	< 0.0001	2.02(1.81,2.24)	1.68(1.48,1.90)	< 0.0001
Hormone therapy (vs no)						
Yes	1.25(0.97,1.61)	—	—	1.25(1.13,1.38)	—	—

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazards ratio. aHR: adjusted hazard ratio calculated by multiple variable Cox proportional hazards regression model for the risk of breast cancer after adjustment for all the variables include BMI, age, age at menarche, birth history, number of birth, age at the first full-term pregnancy, breast-feeding history and family history of breast cancer. ^aP-value for trend. ^bP-value = 0.3575 for testing BMI ≥ 35 vs BMI < 35 (HR = 0.82, 95% CI = 0.54–1.25). ^cAmong parous women.

The precipitating effect of adiposity and obesity on the risk of breast cancer in post-menopausal women had been well established in all ethnicities.^{5–7,17} Such an association seems stronger in Asian populations than among Caucasian women in meta-analyses of previous studies.^{5,19,20,24} In this study, we not only confirmed the positive association between BMI and risk of breast cancer in the enrolled women after menopause, but also revealed that the risk of incident breast cancer was nearly twofold (adjusted odds ratio = 1.65) in morbidly obese women compared with women of normal-weight enrolled after menopause. Hence, the effect of BMI on the risk of breast cancer in Taiwanese women seems much higher than in women in Western countries.^{5,7,20,24} The higher impact of high BMI on the risk of breast cancer in Asian women, as shown in this study, might be explained by the greater adiposity in Asian women than in other ethnicities for a given BMI.¹⁹ Therefore, the WHO-recommended BMI level for overweight and obesity for Asians is quite different from the recommended level for Caucasians.²³

The biological mechanisms linking obesity to elevated risk of breast cancer have been explained by the higher rate of conversion of androgenic precursors to estrogens through the peripheral aromatization in adipose tissue.^{20,25} The high levels of insulin and insulin-like growth factor in response to obesity and increased estrogens levels have been found to stimulate the development and growth of cancer cells in both pre- and post-menopausal women.^{20,26} A trend of more frequent estrogen receptor-positive and hormone-dependent subtypes of breast cancer in post-menopausal women^{14,27} provides strong evidence to support the association between high BMI and risk of incident breast cancer among post-menopausal women.

The association between BMI and breast cancer risk among pre-menopausal women of different ethnicities remains controversial,^{5–7} especially among Asian women. Although some studies have reported an inverse relationship between BMI and breast cancer risk among Indian and Asian-American women,^{16,17,28} most studies among pre-menopausal Asian women

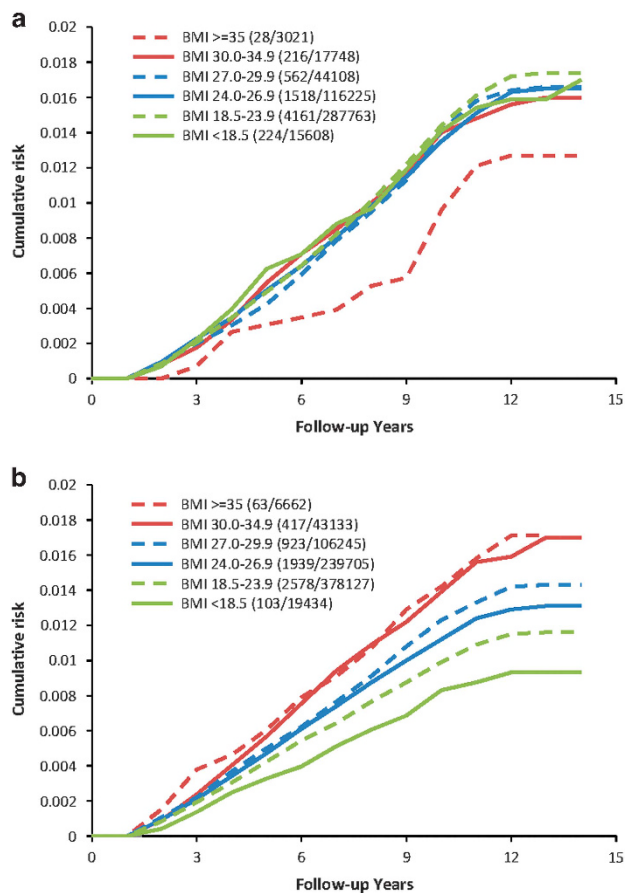


Figure 1. (a) The cumulative risk of breast cancer by six different BMI levels in women recruited before menopause. (b) The cumulative risk of breast cancer by six different BMI levels in women recruited after menopause.

from Japan, China, Hong Kong and Taiwan have suggested no association or a positive association between BMI and breast cancer risk.^{5,6,12–15,18,29,30} The main criticism of these previous Asian studies^{15,17,21,28,29,31,32} is the use of a case-control study design, small sample size, the failure of considering age onset of breast cancer and the narrow range of BMI, all of which could be solved by using a large population-based cohort study design as in the current study.

It is very interesting to note that morbidly obese women had a lower incidence of breast cancer before menopause, which was consistent with the previous finding that greater BMI during earlier periods of life may be inversely related to breast cancer risk.^{33–35} In our cohort, though morbidly obese women who were enrolled prior to menopause tended to be at lower odds of having early-onset breast cancer; however, this protective effect of morbid obesity disappeared and inverted at advanced age, which is upheld by growing evidence that the hormone receptor status of breast cancer leads to differential breast cancer risk based on race, obesity and age.^{36,37} Younger women (≤ 50 years) with obesity (BMI ≥ 30 kg m⁻²) have a higher prevalence of aggressive and hormone receptor-negative breast cancer,³⁶ whereas older women (> 50 years) with obesity have increased risk of hormone receptor-positive breast cancer.^{14,36} Moreover, it has been reported that greater body fatness and BMI during childhood, adolescence and young adulthood are associated with higher prevalence of anovulatory disorders such as polycystic ovary syndrome and infertility,^{38–40} resulting in lower estrogen levels, which, in turn, leads to lower breast cancer risk in women throughout life.^{41–43} However, anovulation itself cannot completely explain the reduced

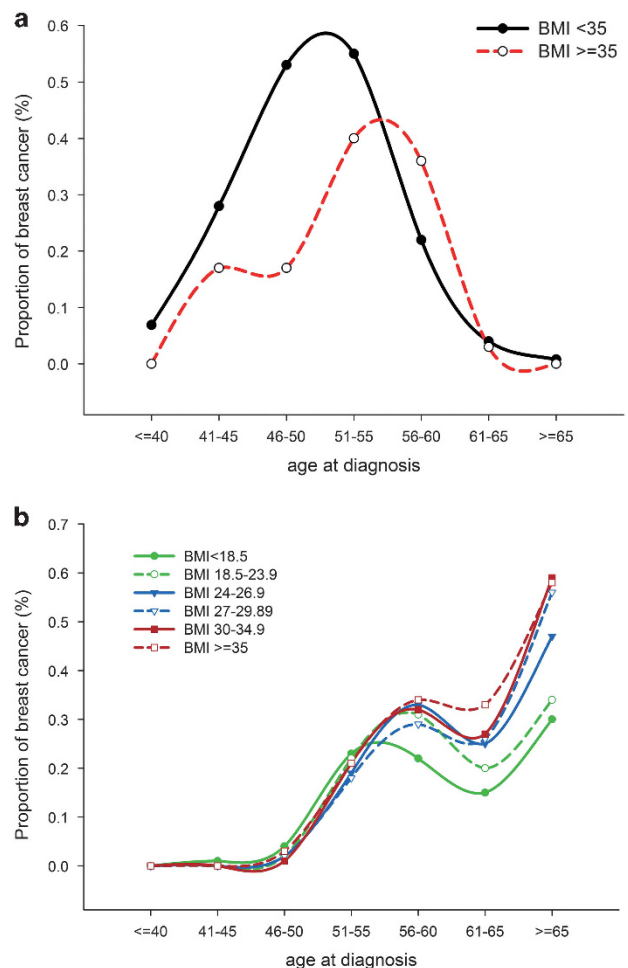


Figure 2. (a) The proportion of breast cancer diagnosed at seven age subgroups in women with and without preceding morbid obesity recruited before menopause. (b) The proportion of breast cancer diagnosed at seven age subgroups among different BMI levels in women recruited after menopause.

breast cancer risk in obese young women.³³ Recently, obesity has been reported to be associated with rapid decline in ovarian reserve⁴⁴ and early menopause.⁴⁵ Further studies are needed to investigate the relationship between histology, obesity and ovarian function on the risk of breast cancer.

Our study has some limitations. Although we found that morbidly obese women enrolled both before and after menopause have higher incidence of breast cancer diagnosed at advanced age, particularly from 56 years of age onward as shown in Figure 2, this might imply the association between adiposity and estrogen-dependent breast cancer diagnosed after menopause. However, the data on BMI at the time of breast cancer diagnosis, age of menopause, status of menopause at the time of breast cancer diagnosis and breast cancer histology (hormone receptor status) were not available in this study. Moreover, the influence of BMI at the time of breast cancer diagnosis and change in adiposity on the risk of breast cancer could also not be investigated in the present study. Therefore, these might limit the interpretation of the potential impact of BMI and obesity on the hormone-dependent subtype of breast cancer and its association with menopausal status in this study. Some individuals with breast cancer might have long-term survival or may not have early diagnosis using current screening methods. Therefore, to investigate the causal relationship between baseline BMI levels and risk of breast cancer, and to

avoid bias from over-representation of breast cancer cases, we only included incident breast cancer in all analyses. Another concern pertains to the sparsity of breast cancer cases among morbidly obese pre-menopausal women that precludes us from reaching the statistically significant result as shown in Table 2, suggesting further study with a larger sample size is needed to clarify the result.

Using a large prospective Taiwanese cohort study, we found that baseline BMI was not significantly associated with risk of incident breast cancer in women enrolled before menopause, but the higher the level of BMI, the higher the risk for incident breast cancer in women enrolled after menopause. Although morbid obesity seems to have a protective effect on the risk of breast cancer, especially in early-onset breast cancer in women enrolled before menopause, it was not statistically significant when confined to incident breast cancer cases. Our findings suggest that excess weight may act as an influential promoter for the late-stage development of post-menopausal breast cancer among Taiwanese women.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors made substantial contribution to the conception and design, analysis, and interpretation of data and to critical review of the manuscript. MJC carried out the design of the study, interpretation of the results and drafted the manuscript. WYYW performed the statistical analysis and helped to design the study and draft the manuscript. AMFY, JCYF, SLSC and SYHC helped in the data acquisition, interpretation of the data, conception and design of study and statistical analysis. HHC conceived and designed the study, coordinated the data collection and analysis, and revised the manuscript. STC carried out the administrative, technical and material support. All authors read and approved the final manuscript.

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