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Review

Effect of Body Mass Index on Breast Cancer during Premenopausal and Postmenopausal Periods: A Meta-Analysis

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Abstract

Objective: There is no universal consensus on the relationship between body mass index (BMI) and breast cancer. This meta-analysis was conducted to estimate the overall effect of overweight and obesity on breast cancer risk during pre- and post-menopausal period.

Data Sources: All major electronic databases were searched until April 2012 including Web of Knowledge, Medline, Scopus, and ScienceDirect. Furthermore, the reference lists and related scientific conference databases were searched.

Review Methods: All prospective cohort and case-control studies investigating the association between BMI and breast cancer were retrieved irrespective of publication date and language. Women were assessed irrespective of age, race and marital status. The exposure of interest was BMI. The primary outcome of interest was all kinds of breast cancers confirmed pathologically. Study quality was assessed using the checklist of STROBE. Study selection and data extraction were performed by two authors separately. The effect measure of choice was risk ratio (RR_i) and rate ratio (RR_a) for cohort studies and odds ratio (OR) in case-control studies.

Results: Of 9163 retrieved studies, 50 studies were included in meta-analysis including 15 cohort studies involving 2,104,203 subjects and 3,414,806 person-years and 35 case-control studies involving 71,216 subjects. There was an inverse but non-significant correlation between BMI and breast cancer risk during premenopausal period: OR = 0.93 (95% CI 0.86, 1.02); RR_i = 0.97 (95% CI 0.82, 1.16); and RR_a = 0.99 (95% CI 0.94, 1.05), but a direct and significant correlation during postmenopausal period: OR = 1.15 (95% CI 1.07, 1.24); RR_i = 1.16 (95% CI 1.08, 1.25); and RR_a = 0.98 (95% CI 0.88, 1.09).

Conclusion: The results of this meta-analysis showed that body mass index has no significant effect on the incidence of breast cancer during premenopausal period. On the other hand, overweight and obesity may have a minimal effect on breast cancer, although significant, but really small and not clinically so important.

Introduction

Breast cancer is the most common cancer in women both in the developed and the developing countries, comprising 16% of all female cancers. It is estimated that breast cancer led to 519,000 death in women in 2004 [1]. Although breast cancer is thought to be a common cancer in the developed countries, a majority (69%) of all breast cancer deaths occurs in developing world. Indeed, increase life expectancy, increase urbanization and adoption of western lifestyles have increased the incidence of breast cancer in the developing countries [1,2]. A recent study indicated that breast cancer is the leading cause of cancer and cancer related mortality in woman worldwide so that cause-specific mortality rate increases with age among postmenopausal women with hormone receptor-positive breast cancer [3].

The etiology of breast cancer is not well known. However, several risk factors have been suggested to have an influence on the development of this malignant tumor including genetic, hormonal, environmental, sociobiological and physiological factors [2]. Weight gain and obesity is another potential risk factor which may influence the incidence of breast cancer. There are numerous observational studies which have investigated the correlation between obesity and breast cancer. However the results are inconsistent. Some researchers believe that body mass index greater than 30 may increase the risk of breast cancer both in pre- and postmenopausal periods [4–7] whereas others claim that obesity may reduce the risk of breast cancer during premenopausal period but increase the risk during postmenopausal period [8–11].

There is no universal consensus on the relationship between BMI and breast cancer. To date, a few meta-analyses have been conducted to estimate a summary measure of the effect size of overweight and obesity on breast cancer. However, these studies were limited to the English language studies cited by Medline [12,13]. Thus, the present up-to-date meta-analysis was conducted to assess the results of both cohort and case-control studies addressing the correlation between BMI and breast cancer cited

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by all major international electronic databases in order to estimate the overall effect of body mass index (BMI) on breast cancer risk.

Materials and Methods

Searching

We planned to include cohort and case-control studies addressing the association between body mass index and breast cancer. We developed a search strategy using and combing a set of keywords including breast cancer, body mass index, waist hip ratio, obesity, overweight, body size, cohort studies, case-control studies, and observational studies. We search all major electronic databases including Web of Knowledge (January 1945 to April 2012); Medline (January 1950 to April 2012); Scopus (January 1973 to April 2012); ScienceDirect (January 1823 to April 2012).

In order to find additional references, we scanned the reference lists of all retrieved studies. In addition, we contacted authors of retrieved studies for additional unpublished studies. Furthermore, the following conference databases were searched for unpublished data until April 2012:

- American Society of Clinical Oncology; available from: www.asco.org
- American Cancer Society; available from: www.cancer.org
- International Agensy for Research on Cancer; available from: www.iarc.fr

Criteria for including studies

We included prospective cohort studies and case-control studies investigating the association between BMI and breast cancer irrespective of publication date and language. The retrospective cohort and matched case-control studies were excluded. We included those apparently healthy women irrespective of age, race and marital status. The exposure of interest was obesity and overweight using BMI. The term 'BMI' is a commonly used index to classify overweight and obesity in adults and is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Based on the World Health Organization classification [14] $BMI<18.5$ is considered as underweight, $18.5 \leq BMI < 25$ as normal weight, $25 \leq BMI < 30$ as overweight, and $BMI \geq 30$ as obese. The primary outcome of interest was breast cancer of any type which was confirmed pathologically. We planned to include all kinds of breast cancers irrespective of pathological characteristics and stage of the tumor.

Data collection and validity assessment

Two authors (ZC and ADI) read the retrieved publications separately in order to identify the studies that would meet the inclusion criteria of this review. The authors were not blinded to the authors' names of the publications, journals, and results. Any disagreements were resolved by adjudication with a third author (JP). The inter-authors reliability based on kappa statistics was 85%.

Two authors (ZC and ADI) extracted the data from the included studies. The variables which were extracted for data analysis included study design, year and location of study conduction, sample size, number of outcomes, mean age, gender, and body mass index. The extracted data were entered in the electronic data sheet. In cases of missing data or need for clarification, study authors were contacted.

We intended to assess the risk of bias of the included studies using the recommended checklist of STROBE [15] Two authors (ZC and ADI) assessed the studies independently. The items which were evaluated for judgment about cohort studies included (a) state specific objectives of the study; (b) present key elements of study design; (c) give the eligibility criteria; (d) clearly define exposure (here obesity and overweight); (e) clearly define outcome (here breast cancer); and (f) explain how loss to follow-up was addressed. The last item was merely evaluated for cohort studies.

Measures of exposure effect and data analysis

The effect measure of choice for cohort studies was risk ratio (RR_i) and rate ratio (RR_a) and that of case-control studies was odds ratio (OR). RR_i was defined as the probability of a disease in exposed people to the probability of the disease in unexposed people in a cohort study. RR_a was defined as the proportion of a disease in exposed people to a specified person-year (a statistical measure representing one person at risk of development of a disease during a period of 1 year) in a cohort study. OR was the proportion of the exposed population in whom disease has developed over the proportion of the unexposed population in whom disease has developed in a case-control study [16].

Meta-analysis was performed to obtain summary measure with 95% confidence interval (CI). Both Review Manager 5 [17] and Stata 11 (StataCorp, College Station, TX, USA) were employed for data analysis. Data were analyzed and the results were reported using random effect models [18].

Heterogeneity and publication bias

We explored statistical heterogeneity using the chi-squared (χ^2 or Chi^2) at the 5% significance level ($P<0.05$). We quantified inconsistency across studies results using I^2 statistic [19]. We also estimated the between-study variance using tau-squared (τ^2 or Tau^2) statistic [20]. We used funnel plot to investigate publication bias visually [20] as well as Begg's [21] and Egger's [22] tests to assess publication bias statistically.

Results

Description of studies

We retrieved 9163 studies up to April 2012, including 8370 references through searching electronic databases, 241 references through conference databases, 546 references through checking reference lists, and six references through personal contact with studies' authors. Of 9163 retrieved references, 2680 references were excluded because of duplication, 6273 references did not relate to the objective of this review, and 160 references did not meet the eligibility criteria. Eventually, we included 50 studies in the meta-analysis including 15 cohort studies [4–6,10,15,23–32] involving 2,104,203 people and 3,414,806 person-years and 35 case-control studies [8,9,33–65] involving 71,216 people. Some case-control and cohort studies evaluated breast cancer during premenopausal period, some during postmenopausal period and some during both periods. Thus, some studies presented only once and some others presented more than once in forest plots. However, the total number of 35 case-control and 15 cohort studies were included in meta-analysis.

Effect of exposure

The effect of BMI on breast cancer risk during pre- and postmenopausal period was assessed using odds ratio (OR) (Figure 1 and 2) in case-control studies and using risk ratio (RR_i) (Figure 3 and 4) and rate ratio (RR_a) (not shown) in cohort studies.

The results of both case-control and cohort studies showed that increase in BMI during premenopausal period reduced the risk of breast cancer: $OR = 0.93$ (95% CI 0.86, 1.02); $RR_i = 0.97$ (95% CI 0.82, 1.16); and $RR_a = 0.99$ (95% CI 0.94, 1.05). That means

Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Overweight						
Berstad 2010	17	39	60	112	1.0%	0.67 [0.32, 1.39]
Chow 2005	20	41	42	101	1.1%	1.34 [0.65, 2.77]
Coates 1999	14	55	21	88	1.0%	1.09 [0.50, 2.38]
Enger 2000	31	57	42	90	1.2%	1.36 [0.70, 2.65]
Friedenreich 2002	10	72	52	203	1.0%	0.47 [0.22, 0.98]
Hall 2000	75	176	74	134	2.0%	0.60 [0.38, 0.95]
John 2010	106	208	163	261	2.4%	0.62 [0.43, 0.90]
Kruk 2007	114	229	477	958	2.9%	1.00 [0.75, 1.33]
Magnusson 2005	113	232	247	484	2.7%	0.91 [0.67, 1.25]
Mathew 2008	90	244	187	464	2.7%	0.87 [0.63, 1.19]
Sangaramoorthy 2011	170	376	325	746	3.1%	1.07 [0.83, 1.37]
Shu 2001	195	469	298	560	3.1%	0.63 [0.49, 0.80]
Titus-Ernstoff 1998	256	524	560	1405	3.4%	1.44 [1.18, 1.76]
Trentham-Dietz 1997	309	586	604	1162	3.4%	1.03 [0.84, 1.26]
Verla-Tebit 2005	324	867	990	2632	3.7%	0.99 [0.84, 1.16]
Wrensch 2003	472	938	1342	2608	3.7%	0.96 [0.82, 1.11]
Subtotal (95% CI)		**5113**		**12008**	**38.3%**	**0.92 [0.81, 1.05]**
Total events	2316		5484			
Heterogeneity: Tau² = 0.04; Chi² = 44.76, df = 15 (P < 0.0001); I² = 66%						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.1.2 Obese						
Adebamowo 2003	29	54	91	246	1.4%	1.98 [1.09, 3.58]
Berstad 2010	283	586	1342	2608	3.5%	0.88 [0.74, 1.05]
Chow 2005	5	13	21	88	0.5%	1.99 [0.59, 6.76]
Coates 1999	272	549	604	1162	3.4%	0.91 [0.74, 1.11]
Enger 2000	110	228	477	958	2.9%	0.94 [0.70, 1.26]
Friedenreich 2002	102	221	247	484	2.7%	0.82 [0.60, 1.13]
Hall 2000	120	238	163	261	2.4%	0.61 [0.43, 0.87]
Hirose 2003	165	1398	1167	11877	3.6%	1.23 [1.03, 1.46]
Hu 1997	18	92	66	190	1.4%	0.46 [0.25, 0.83]
John 2010	179	451	298	560	3.1%	0.58 [0.45, 0.74]
Jordan 2009	12	174	20	610	1.0%	2.19 [1.05, 4.56]
Kim 2009	579	1428	771	2139	3.8%	1.21 [1.05, 1.39]
Kruk 2007	33	77	187	464	1.8%	1.11 [0.68, 1.81]
Magnusson 2005	338	684	703	1394	3.5%	0.96 [0.80, 1.15]
Mathew 2008	65	125	560	1405	2.4%	1.63 [1.13, 2.36]
McCredie 1998	62	142	287	534	2.4%	0.67 [0.46, 0.97]
Mezzetti 1998	198	399	791	1433	3.3%	0.80 [0.64, 1.00]
Sangaramoorthy 2011	61	165	74	134	1.9%	0.48 [0.30, 0.76]
Shin 2009	512	918	1564	3114	3.7%	1.25 [1.08, 1.45]
Shu 2001	52	102	738	1535	2.2%	1.12 [0.75, 1.68]
Tian 2007	25	60	116	222	1.5%	0.65 [0.37, 1.16]
Titus-Ernstoff 1998	17	36	42	101	1.0%	1.26 [0.59, 2.70]
Trentham-Dietz 1997	313	867	990	2632	3.7%	0.94 [0.80, 1.10]
Tung 1999	43	65	106	173	1.4%	1.24 [0.68, 2.25]
Verla-Tebit 2005	82	326	214	830	2.8%	0.97 [0.72, 1.30]
Wrensch 2003	7	18	60	112	0.6%	0.55 [0.20, 1.53]
Subtotal (95% CI)		**9416**		**35266**	**61.7%**	**0.94 [0.84, 1.06]**
Total events	3682		11699			
Heterogeneity: Tau² = 0.06; Chi² = 99.31, df = 25 (P < 0.00001); I² = 75%						
Test for overall effect: Z = 0.96 (P = 0.34)						
Total (95% CI)		**14529**		**47274**	**100.0%**	**0.93 [0.86, 1.02]**
Total events	5998		17183			
Heterogeneity: Tau² = 0.05; Chi² = 144.47, df = 41 (P < 0.00001); I² = 72%						
Test for overall effect: Z = 1.54 (P = 0.12)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						

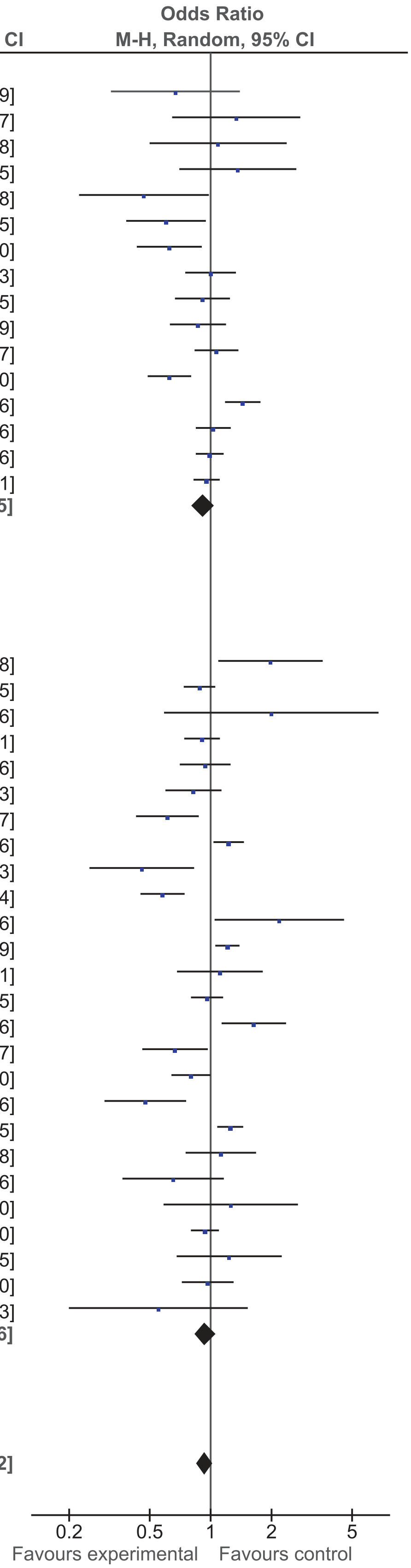

Figure 1. Forest plot of odds ratio estimates of breast cancer in premenopausal period by overweight and obesity.
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Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 Overweight						
Barnes 2011	1309	1931	4818	7165	3.1%	1.03 [0.92, 1.14]
Berstad 2010	579	1205	918	1847	3.0%	0.94 [0.81, 1.08]
Chow 2005	42	84	28	61	0.9%	1.18 [0.61, 2.28]
Enger 2000	290	565	489	1032	2.7%	1.17 [0.95, 1.44]
Friedenreich 2002	187	377	385	766	2.4%	0.97 [0.76, 1.25]
Hall 2000	140	299	114	232	1.9%	0.91 [0.65, 1.28]
Kruk 2007	221	439	205	500	2.4%	1.46 [1.13, 1.89]
La Vecchia 1997	252	445	751	1406	2.6%	1.14 [0.92, 1.41]
Li 2000	120	238	237	467	2.1%	0.99 [0.72, 1.35]
Li 2006	333	649	344	739	2.6%	1.21 [0.98, 1.49]
Magnusson 1998	538	1160	1536	3341	3.0%	1.02 [0.89, 1.16]
Mathew 2008	297	482	559	1009	2.6%	1.29 [1.04, 1.61]
Montazeri 2008	51	98	23	63	0.9%	1.89 [0.99, 3.61]
Sangaramoorthy 2011	119	268	79	148	1.7%	0.70 [0.47, 1.04]
Shu 2001	125	246	292	660	2.2%	1.30 [0.97, 1.75]
Titus-Ernstoff 1998	28	56	42	89	0.9%	1.12 [0.57, 2.18]
Trentham-Dietz 1997	1061	2360	2663	6415	3.2%	1.15 [1.05, 1.27]
Wrensch 2003	49	111	124	213	1.4%	0.57 [0.36, 0.90]
Subtotal (95% CI)		**11013**		**26153**	**39.7%**	**1.08 [1.00, 1.17]**
Total events	5741		13607			
Heterogeneity: Tau² = 0.01; Chi² = 35.16, df = 17 (P = 0.006); I² = 52%						
Test for overall effect: Z = 1.97 (P = 0.05)						
1.2.2 Obese						
Adebamowo 2003	31	47	73	146	0.9%	1.94 [0.98, 3.84]
Barnes 2011	259	364	4818	7165	2.5%	1.20 [0.95, 1.52]
Berstad 2010	394	845	918	1847	2.9%	0.88 [0.75, 1.04]
Chow 2005	30	48	28	61	0.7%	1.96 [0.91, 4.25]
Enger 2000	151	424	489	1032	2.5%	0.61 [0.49, 0.78]
Friedenreich 2002	199	390	385	766	2.5%	1.03 [0.81, 1.32]
Hall 2000	137	277	114	232	1.9%	1.01 [0.71, 1.44]
Hirose 2003	294	1576	745	6402	3.0%	1.74 [1.50, 2.02]
Hu 1997	27	78	36	105	1.0%	1.01 [0.55, 1.88]
Kim 2009	444	1038	261	801	2.7%	1.55 [1.28, 1.87]
Kruk 2003	44	86	29	93	1.0%	2.31 [1.26, 4.25]
Kruk 2007	122	219	205	500	2.1%	1.81 [1.31, 2.49]
La Vecchia 1997	244	448	751	1406	2.6%	1.04 [0.84, 1.29]
Li 2000	122	208	237	467	2.0%	1.38 [0.99, 1.92]
Li 2006	249	492	344	739	2.5%	1.18 [0.94, 1.48]
Magnusson 1998	715	1346	1536	3341	3.1%	1.33 [1.17, 1.51]
Mathew 2008	76	123	559	1009	1.8%	1.30 [0.89, 1.91]
Mezzetti 1998	611	1267	966	2055	3.0%	1.05 [0.91, 1.21]
Montazeri 2008	42	71	23	63	0.8%	2.52 [1.25, 5.06]
Rosato 2011	578	1125	3291	5817	3.1%	0.81 [0.71, 0.92]
Sangaramoorthy 2011	156	359	79	148	1.8%	0.67 [0.46, 0.99]
Shin 2009	543	1066	825	1813	2.9%	1.24 [1.07, 1.45]
Shoff 2000	1389	2855	3225	7576	3.2%	1.28 [1.17, 1.39]
Shu 2001	83	156	292	660	1.9%	1.43 [1.01, 2.03]
Tian 2007	49	74	54	132	1.1%	2.83 [1.56, 5.13]
Titus-Ernstoff 1998	30	55	42	89	0.9%	1.34 [0.68, 2.64]
Trentham-Dietz 1997	1197	2464	2663	6415	3.2%	1.33 [1.21, 1.46]
Tung 1999	68	146	84	223	1.6%	1.44 [0.94, 2.20]
Wrensch 2003	28	78	124	213	1.2%	0.40 [0.23, 0.69]
Subtotal (95% CI)		**17725**		**51316**	**60.3%**	**1.21 [1.08, 1.34]**
Total events	8312		23196			
Heterogeneity: Tau² = 0.06; Chi² = 183.59, df = 28 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
Total (95% CI)		**28738**		**77469**	**100.0%**	**1.15 [1.07, 1.24]**
Total events	14053		36803			
Heterogeneity: Tau² = 0.04; Chi² = 230.41, df = 46 (P < 0.00001); I² = 80%						
Test for overall effect: Z = 3.69 (P = 0.0002)						
Test for subgroup differences: Chi² = 2.58, df = 1 (P = 0.11), I² = 61.2%						

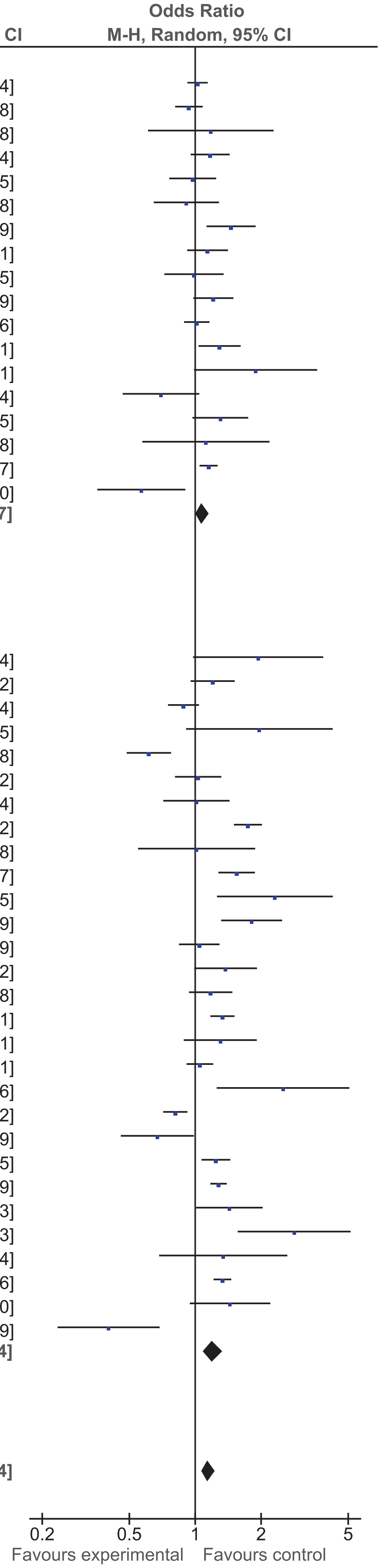

Figure 2. Forest plot of odds ratio estimates of breast cancer in postmenopausal period by overweight and obesity.
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women who were overweight or obese during premenopausal ages were at lower risk of breast cancer compared to women with normal weight although the observed inverse correlation was not statistically significant.

The results of both case-control studies and cohort studies showed that overweight and obesity in postmenopausal period increased slightly the risk of breast cancer: OR = 1.15 (95% CI 1.07, 1.24); $RR_i = 1.16$ (95% CI 1.08, 1.25); and $RR_a = 0.98$ (95% CI 0.88, 1.09). That means the women who were overweight or obese during postmenopausal period were significantly at higher risk of breast cancer.

The effect of overweight and obesity on the breast cancer risk was evaluated separately. According to the RR_i and OR values, obese women had lower risk of breast cancer compared to overweight women during premenopausal period. However, the correlation was reversed during postmenopausal period so that obese women were at higher risk of breast cancer compare to overweight women although the difference was not statistically significant.

We classified the cohort studies based on the selected items of the recommended checklist of STROBE into high-quality (33%) [10,23,25,27,66], intermediate-quality (54%) [4–6,24,28,30–32] and low-quality (13%) [26,29]. Similarly, the case-control studies were also classified into high-quality (74%) and intermediate-quality (26%). There was no statistically significant difference between the results of studies with different quality in both pre- and postmenopausal periods (Table 1).

Heterogeneity and publication bias

The between studies heterogeneity was assessed using the Chi^2 test and the I^2 statistics. The results of Chi^2 test indicated that case-control studies were significantly heterogeneous ($P<0.001$). The I^2 statistics for premenopausal period was 72% and for that of postmenopausal period was 80% (Figures 1 and 2). On the contrary, the results of cohort studies were homogenous ($P = 0.220$). The I^2 statistics for premenopausal period was 32.8% and for postmenopausal period was 34.5% (Figures 3 and 4).

Of 42 case-control studies (Figure 1) assessed the effect of BMI on breast cancer risk during premenopausal period, 24 studies reported negative associations (9 out of which were statistically significant) and 18 studies reported positive associations (7 out of which were statistically significant). Of 47 case-control studies (Figure 2) investigated the effect of BMI on breast cancer during postmenopausal period, 11 studies reported negative associations (5 out of which were statistically significant) and 36 studies reported positive associations (14 out of which were statistically significant). Of eight cohort studies (Figure 3) assessed the effect of BMI on breast cancer during premenopausal period, six studies reported negative associations (one out of which were statistically significant) and two studies reported positive associations (one out of which were statistically significant). Of 16 cohort studies (Figure 4) investigated the effect of BMI on breast cancer during postmenopausal period, no study reported negative associations while all 16 studies reported positive associations (9 out of which were statistically significant).

We assessed publication bias using the funnel plot as well as Begg's and Egger's tests. The studies scattered nearly symmetrically on both side of the vertical line reflecting absence of publication bias. The results of Begg's and Egger's tests for both OR and RR_i estimated in pre- and postmenopausal periods confirmed the absence of publication bias (Figure 5).

	Exposed		Unexposed			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI
1.1.1 Overweight						
Barlow 2006	212	69476	460	142416	21.2%	0.94 [0.80, 1.11]
Sonnenschein 1999	24	1129	60	2252	9.0%	0.80 [0.50, 1.27]
Tehard 2006	27	2954	170	15586	10.8%	0.84 [0.56, 1.26]
Weiderpass 2004	104	17411	259	61144	18.0%	1.41 [1.12, 1.77]
Subtotal (95% CI)		**90970**		**221398**	**59.1%**	**1.01 [0.77, 1.31]**
Total events	367		949			
Heterogeneity: Tau² = 0.05; Chi² = 10.59, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.1.2 Obese						
Barlow 2006	147	50513	460	142416	20.1%	0.90 [0.75, 1.08]
Sonnenschein 1999	25	1094	60	2252	9.2%	0.86 [0.54, 1.36]
Tehard 2006	2	695	170	15586	1.5%	0.26 [0.07, 1.06]
Weiderpass 2004	23	4607	259	61144	10.2%	1.18 [0.77, 1.80]
Subtotal (95% CI)		**56909**		**221398**	**40.9%**	**0.91 [0.71, 1.18]**
Total events	197		949			
Heterogeneity: Tau² = 0.02; Chi² = 4.53, df = 3 (P = 0.21); I² = 34%						
Test for overall effect: Z = 0.70 (P = 0.49)						
Total (95% CI)		**147879**		**442796**	**100.0%**	**0.97 [0.82, 1.16]**
Total events	564		1898			
Heterogeneity: Tau² = 0.03; Chi² = 16.60, df = 7 (P = 0.02); I² = 58%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%						

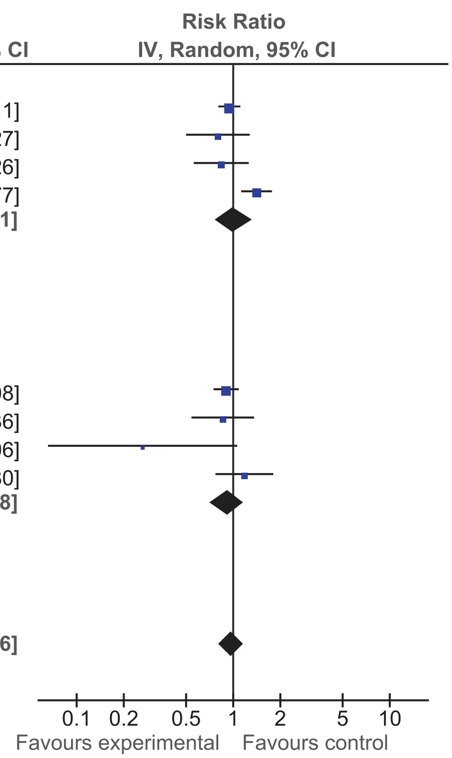

Figure 3. Forest plot of risk ratio estimates of breast cancer in premenopausal period by overweight and obesity.
doi:10.1371/journal.pone.0051446.g003

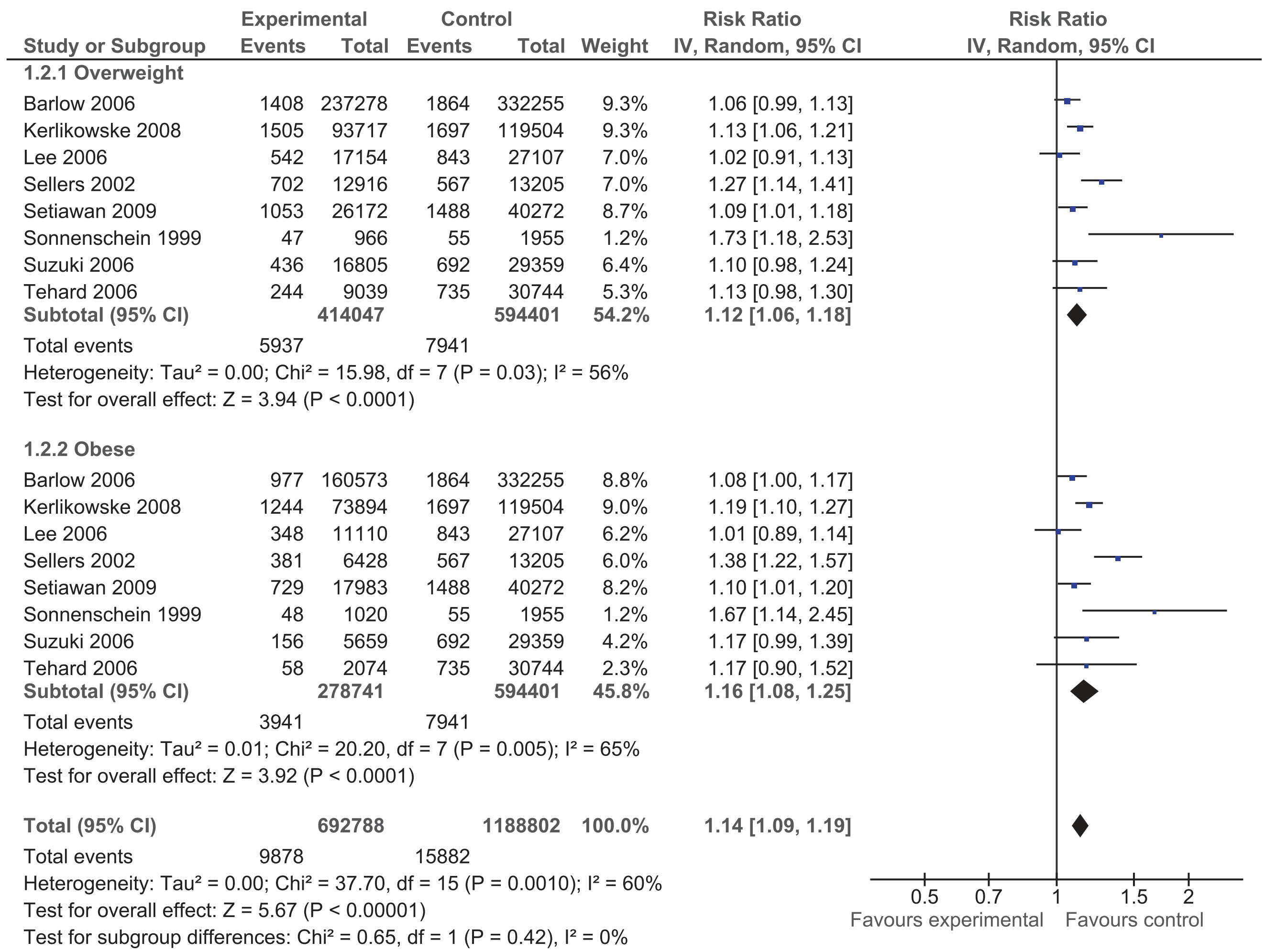

Figure 4. Forest plot of risk ratio estimates of breast cancer in postmenopausal period by overweight and obesity.
doi:10.1371/journal.pone.0051446.g004

Discussion

The results of this meta-analysis revealed that BMI during premenopausal period can decrease the risk of breast cancer by 0.07 although the association was not statistically significant. Contrary, increase in BMI during postmenopausal period can significantly increase the risk of breast cancer by 0.21. This evidence means that BMI is not a protective factor against breast cancer during premenopausal period. However, BMI is a weak but significant risk factor for breast cancer during postmenopausal

Table 1. Effect of body mass index on incidence of breast cancer by quality of the studies, menopausal period, and study design.

	High Quality		Moderate Quality		Low Quality	
Period	**Effect Size**	**Q-test**	**Effect Size**	**Q-test**	**Effect Size**	**Q-test**
Study design	**(95% CI)**	***P* value**	**(95% CI)**	***P* value**	**(95% CI)**	***P* value**
Premenopausal						
Case-control (OR)	0.93 (0.84, 1.02)	0.001	0.98 (0.79, 1.21)	0.020	No data	-
Cohort (RR_i)	No data	-	0.97 (0.82, 1.16)	0.020	No data	-
Cohort (RR_a)	1.02 (0.92, 1.13)	0.360	0.98 (0.91, 1.05)	0.010	No data	-
Postmenopausal						
Case-control (OR)	1.18 (1.08, 1.29)	0.001	1.08 (0.96, 1.22)	0.001	No data	-
Cohort (RR_i)	1.01 (0.93, 1.10)	0.010	1.11 (1.06, 1.16)	0.020	1.22 (1.13, 1.32)	0.040
Cohort (RR_a)	0.99 (0.90, 1.08)	0.001	0.96 (0.60, 1.54)	0.001	No data	-

doi:10.1371/journal.pone.0051446.t001

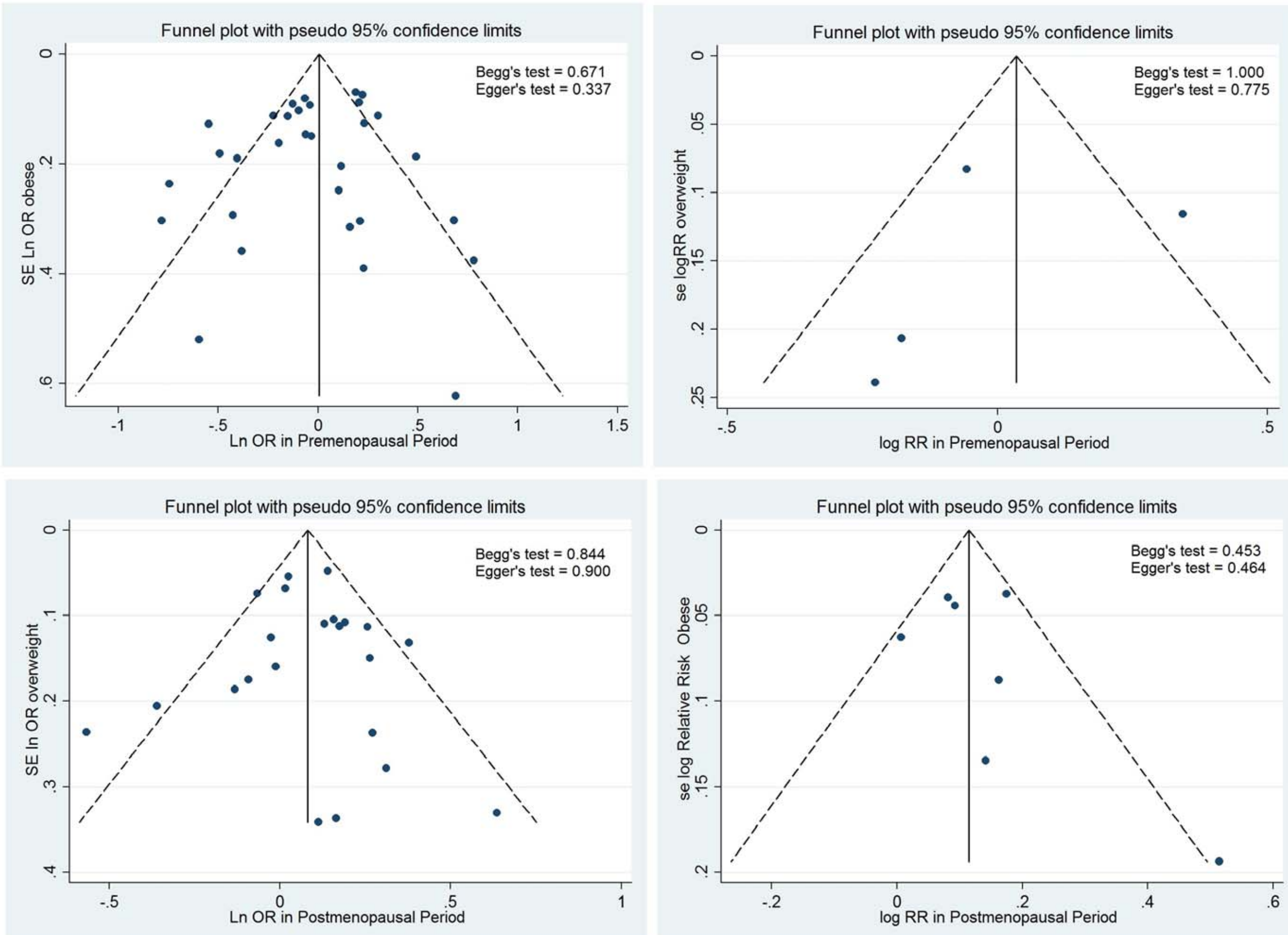

Figure 5. Funnel plot of included studies in pre postmenopausal and postmenopausal period by study design.
doi:10.1371/journal.pone.0051446.g005

period, although its effect is really small and not clinically important. The stronger the association, the more likely it is that the relation is causal while a weak association is more likely to be confounded although a weak association does not rule out causal connection [16]. Furthermore, increase in BMI during premenopausal period decreases the risk of breast cancer while increases the risk during postmenopausal period. This implies the presence of interaction between BMI and menopausal period. In such situation, the association should be assessed for each period separately and it is not reasonable to pool the data to estimate overall effect of BMI on breast cancer risk.

Suzuki et al [13] conducted a similar meta-analysis in order to assess the effect of BMI on breast cancer risk. They retrieved 31 references including nine cohort and 22 case-control studies indexed in Medline until December 2007. They reported that overweight during premenopausal period would decrease the risk of breast cancer; OR = 0.80 (95% CI 0.70, 0.92); while it might increase the risk of cancer during post menopausal period; OR = 1.89 (95% CI 1.52, 2.36). The results of their meta-analysis were rather different from ours. One reason was that we searched and retrieved the relevant references from all major international databases while Suzuki et al had searched only Medline database which might introduce selection bias in their results.

Another meta-analysis with same topic was conducted by Ryu et al [12]. They searched Medline database until 1999 and retrieved 12 case-control studies. They reported that overweight and obesity could increase the risk of breast cancer 1.56 times. However, they did not report the effect of body mass index on breast cancer during pre- and postmenopausal period separately. Furthermore, they had limited the search to the English language literatures indexed in Medline. This issue might also introduce selection bias in their results.

There was evidence of heterogeneity (small *P* value of Chi^2 test and large I^2 statistic) among the results of the included studies. However, care must be taken in the interpretation of the statistical tests for heterogeneity. The Chi^2 test has low power when the sample size is small. On the other hand, the test has high power in detecting a small amount of heterogeneity that may be clinically unimportant when there are many studies in a meta-analysis [20]. Therefore, we can attribute major part of the observed heterogeneity in the results to the number of studies (including 15 cohort and 35 case-control studies) included in the meta-analysis and the large sample size (involving 2,104,203 participants in cohort studies and 71,216 participants in case-control studies).

Regardless of the effect of overweight and obesity on breast cancer, there are several well-documented risk factors for breast cancer. A familial history of breast cancer, reproductive factors associated with prolonged exposure to endogenous estrogens, such as early menarche, late menopause, late age at first childbirth are among the most important risk factors for breast cancer.

Exogenous hormones such as oral contraceptive and hormone replacement therapy also exert a higher risk for breast cancer. Furthermore, alcohol use, and physical inactivity are among the modifiable risk factors for breast cancer [67].

There were a few limitations and potential biases in this meta-analysis. First, 15 studies seemed potentially eligible to be included in this meta-analysis but the full texts were not accessible. This issue may raise the possibility of selection bias. Second, we intended to assess the effect of other potential confounding variables such as onset of menarche, onset of menopause, smoking status, oral contraceptive consumption, and family history of breast cancer. However, these variables were not reported exactly in majority of the studies. Hence, we could not conduct subgroup analysis based on these variables. This issue may raise the possibility of the information bias. Despite its limitations, this meta-analysis could present strong evidence about the correlation between BMI and breast cancer by retrieving 9163 studies from all major databases and including 50 studies in the meta-analysis (15 cohort studies having 2,104,203 people and 3,414,806 person-years and 35 case-control studies involving 71,216 people).

In addition, our work brought some new information about the relationship between BMI and breast cancer, including (a) consolidation of the data to obtain summary measure of odds ratio, risk ratio, and rate ratio estimates regarding the effect of BMI on breast cancer; (b) non-significant inverse correlation between overweight and obesity and the incidence of breast cancer during premenopausal period; (c); significant direct correlation between overweight and obesity and the incidence of breast cancer during postmenopausal period; (d) the impact of various variables on the correlation between BMI and breast cancer such as studies designs, period of menopause, various types of BMI, and quality of the studies.

Conclusion

The results of this meta-analysis showed that body mass index has no significant effect on the incidence of breast cancer during premenopausal period. On the other hand, overweight and obesity may have a minimal effect on breast cancer, although significant, but really small and not clinically so important.

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Author Contributions

Conceived and designed the experiments: ZC JP ADI. Performed the experiments: ZC JP ADI. Analyzed the data: ZC JP ADI. Contributed reagents/materials/analysis tools: ZC JP ADI. Wrote the paper: ZC JP ADI TH NE.

References

1. World Health Organization (2012) Breast cancer: prevention and control. WHO.
2. World Health Organization (2006) Guidelines for management of breast cancer. Nasr: EMRO Technical Publications Series.
3. van de Water W, Markopoulos C, van de Velde CJH, Seynaeve C, Hasenburg A, et al. (2012) Association between age at diagnosis and disease-specific mortality among postmenopausal women withHormone receptor–positive breast cancer. JAMA 307: 590–597.
4. Barlow WE, White E, Ballard-Barbash R, Vacek PM, Titus-Ernstoff L, et al. (2006) Prospective breast cancer risk prediction model for women undergoing screening mammography. J Natl Cancer Inst 98.
5. Sonnenschein E, Toniolo P, Terry MB, Bruning PF, Kato I, et al. (1999) Body fat distribution and obesity in pre- and postmenopausal breast cancer. Int J Epidemiol 28: 1026–1031.
6. Tehard B, Clavel-Chapelon F, grp EN (2006) Several anthropometric measurements and breast cancer risk: results of the E3N cohort study. International Journal of Obesity 30: 156–163.
7. Tian YF, Chu CH, Wu MH, Chang CL, Yang T, et al. (2007) Anthropometric measures, plasma adiponectin, and breast cancer risk. Endocr Relat Cancer 14: 669–777.
8. Mathew A, Gajalakshmi V, Rajan B, Kanimozhi V, Brennan P, et al. (2008) Anthropometric factors and breast cancer risk among urban and rural women in South India: a multicentric case-control study. Br J Cancer 99: 207–213.
9. Montazeri A, Sadighi J, Farzadi F, Maftoon F, Vahdaninia M, et al. (2008) Weight, height, body mass index and risk of breast cancer in postmenopausal women: a case-control study. Bmc Cancer 8: 278.
10. Palmer JR, Adams-Campbell LL, Boggs DA, Wise LA, Rosenberg L (2007) A prospective study of body size and breast cancer in black women. Cancer Epidemiology Biomarkers & Prev 16: 1795–1802.
11. Loi S, Milne RL, Friedlander ML, E MMR, Giles GG, et al. (2005) Obesity and outcomes in premenopausal and postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 14: 1686–1691.
12. Ryu SY, Kim C-B, Nam CM, Park JK, Kim KS, et al. (2001) Is body mass index the prognostic factor in breast cancer? : a meta-analysis. J Korean Med Sci 16: 610–614.
13. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A (2009) Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status-a meta-analysis. Int J Cancer 124: 698–712.
14. World Health Organization (2012) 10 facts on obesity. WHO.
15. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, et al. (2007) Strengthening the reporting of observational studies in epidemiology (STROBE): explanation andelaboration. PLoS Med 4: 1628–1654.
16. Gordis L (2008) Epidemiology. Philadelphia: Saunders.
17. RevMan (2008) Review Manager (RevMan) [Computer program]. RevMan. Version 5.0 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.
18. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177–188.
19. Higgins JPT, Thompson SG, Deeks JJ, Altman D (2003) Measuring inconsistency in meta-analyses. BMJ 327: 557–560.
20. Higgins JPT, Green S (2008) Cochrane handbook for systematic reviews of interventions Version 5.0.0 [updated February 2008]. The Cochrane Collaboration.
21. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088–1101.
22. Egger M, Davey SG, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629–634.
23. Brinton LA, Richesson D, Leitzmann MF, Gierach GL, Schatzkin A, et al. (2008) Menopausal hormone therapy and breast cancer risk in the NIH-AARP diet and health study cohort. Cancer Epidemiol Biomarkers & Prev 17: 3150–3160.
24. Huang ZP, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, et al. (1997) Dual effects of weight and weight gain on breast cancer risk. JAMA 278: 1407–1411.
25. Kaaks R, Van Noord PA, Den Tonkelaar I, Peeters PH, Riboli E, et al. (1998) Breast-cancer incidence in relation to height, weight and body-fat distribution in the dutch "DOM" cohort. Int J Cancer 76: 647–651.
26. Kerlikowske K, Walker R, Miglioretti DL, Desai A, Ballard-Barbash R, et al. (2008) Obesity, mammography use and accuracy, and advanced breast cancer risk. J Natl Cancer Inst 100: 1724–1733.
27. Lee S, Kolonel L, Wilkens L, Wan P, Henderson B, et al. (2006) Postmenopausal hormone therapy and breast cancer risk: the multiethnic cohort. Int J Cancer 118: 1285–1291.
28. Michels KB, Terry KL, Willett WC (2006) Longitudinal study on the role of body size in premenopausal breast cancer. Arch Intern Med 166: 2395–2402.
29. Sellers TA, Davis J, Cerhan JR, Vierkant RA, Olson JE, et al. (2002) Interaction of waist/hip ratio and family history on the risk of hormone receptor-defined breast cancer in a prospective study of postmenopausal women. Am J Epidemiol 155: 225–233.
30. Setiawan VW, Monroe KR, Wilkens LR, Kolonel LN, Pike MC, et al. (2009) Breast cancer risk factors defined by estrogen and progesterone receptor status. Am J Epidemiol 169: 1251–1259.
31. Suzuki R, Rylander-Rudqvist T, Ye WM, Saji S, Wolk A (2006) Body weight and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status among Swedish women: a prospective cohort study. Int J Cancer 119: 1683–1689.
32. Weiderpass E, Braaten T, Magnusson C, Kumle M, Vainio H, et al. (2004) A prospective study of body size in different periods of life and risk of

premenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 13: 1121–1127.
33. Adebamowo CA, Ogundiran TO, Adenipekun AA, Oyesegun RA, Campbell OB, et al. (2003) Waist-hip ratio and breast cancer risk in urbanized Nigerian women. Breast Cancer Res 5: R18–24.
34. Berstad P, Coates RJ, Bernstein L, Folger SG, Malone KE, et al. (2010) A case-control study of body mass index and breast cancer risk in white and african-american women. Cancer Epidemiol Biomarkers Prev 19: 1532–1544.
35. Coates RJ, Uhler RJ, Hall HI, Potischman N, Brinton LA, et al. (1999) Risk of breast cancer in young women in relation to body size and weight gain in adolescence and early adulthood. Br J Cancer 81: 167–174.
36. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L (2000) Body size, physical activity, and breast cancer hormone receptor status: Results from two case-control studies. Cancer Epidemiol Biomarkers Prev 9: 681–687.
37. Friedenreich CM, Courneya KS, Bryant HE (2002) Case-control study of anthropometric measures and breast cancer risk. Int J Cancer 99: 445–452.
38. Hall IJ, Newman B, Millikan RC, Moorman PG (2000) Body size and breast cancer risk in black women and white women: The Carolina breast cancer study. Am J Epidemiol 151: 754–764.
39. Hirose K, Takezaki T, Hamajima N, Miura S, Tajima K (2003) Dietary factors protective against breast cancer in Japanese premenopausal and postmenopausal women. Int J Cancer 107: 276–282.
40. Hu YH, Nagata C, Shimizu H, Kaneda N, Kashiki Y (1997) Association of body mass index, physical activity, and reproductive histories with breast cancer: a case-control study in Gifu, Japan. Breast Cancer Res Treat 43: 65–72.
41. John EM, Sangaramoorthy M, Phipps AI, Koo J, Horn-Ross PL (2010) Adult body size, hormone receptor status, and premenopausal breast cancer risk in a multiethnic population: the San Francisco Bay Area breast cancer study. Am J Epidemiol 173: 201–216.
42. Jordan S, Lim L, Vilainerun D, Banks E, Sripaiboonkij N, et al. (2009) Breast cancer in the thai cohort study: An exploratory case-control analysis. The Breast 18: 299–303.
43. Kim Y, Park SK, Han W, Kim DH, Hong YC, et al. (2009) Serum high-density lipoprotein cholesterol and breast cancer risk by menopausal status, body mass index, and hormonal receptor in korea. Cancer Epidemiol Biomarkers Prev 18: 508–515.
44. Kruk J (2007) Association of lifestyle and other risk factors with breast cancer according to menopausal status: a case-control study in the region of western pomerania (Poland). Asian Pac J Cancer Prev 8: 513–524.
45. Kruk J, Aboul-Enein HY (2003) Occupational physical activity and the risk of breast cancer. Cancer Detect Prev 27: 187–192.
46. La Vecchia C, Negri E, Franceschi S, Talamini R, Bruzzi P, et al. (1997) Body mass index and post-menopausal breast cancer: an age-specific analysis. Br J Cancer 75: 441–414.
47. Li CI, Malone KE, Daling JR (2006) Interactions between body mass index and hormone therapy and postmenopausal breast cancer risk (United States). Cancer Causes Control 17: 695–703.
48. Li CI, Stanford JL, Daling JR (2000) Anthropometric variables in relation to risk of breast cancer in middle-aged women. Int J Epidemiol 29: 208–213.
49. Magnusson C, Baron J, Persson I, Wolk A, Bergstrom R, et al. (1998) Body size in different periods of life and breast cancer risk in post-menopausal women. Int J Cancer 76: 29–34.
50. Magnusson CM, Roddam AW, Pike MC, Chilvers C, Crossley B, et al. (2005) Body fatness and physical activity at young ages and the risk of breast cancer in premenopausal women. Br J Cancer 93: 817–824.
51. McCredie MRE, Dite GS, Giles GG, Hopper JL (1998) Breast cancer in Australian women under the age of 40. Cancer Causes Control 9: 189–198.
52. Mezzetti M, La Vecchia C, Decarli A, Boyle P, Talanmini R, et al. (1998) Population attributable risk for breast cancer: diet, nutrition, and physical exercise. J Natl Cancer Inst 90: 389–394.
53. Rosato V, Bosetti C, Talamini R, Levi F, Montella M, et al. (2011) Metabolic syndrome and the risk of breast cancer in postmenopausal women. Ann Oncol.
54. Sangaramoorthy M, Phipps AI, Horn-Ross PL, Koo J, John EM (2011) Early-Life factors and breast cancer risk in hispanic women: the role of adolescent body size. Cancer Epidemiol Biomarkers Prev 20: 2572–2582.
55. Shin A, Matthews CE, Shu XO, Gao YT, Lu W, et al. (2009) Joint effects of body size, energy intake, and physical activity on breast cancer risk. Breast Cancer Res Treat 113: 153–161.
56. Shoff SM, Newcomb PA, Trentham-Dietz A, Remington PL, Mittendorf R, et al. (2000) Early-life physical activity and postmenopausal breast cancer: Effect of body size and weight change. Cancer Epidemiol Biomarkers Prev 9: 591–595.
57. Shu XO, Jin F, Dai Q, Shi JR, Potter JD, et al. (2001) Association of body size and fat distribution with risk of breast cancer among Chinese women. Int J Cancer 94: 449–455.
58. Tian YF, Chu CH, Wu MH, Chang CL, Yang T, et al. (2007) Anthropometric measures, plasma adiponectin, and breast cancer risk. Endocr Relat Cancer 14: 669–677.
59. Titus-Ernstoff L, Longnecker MP, Newcomb PA, Dain B, Greenberg ER, et al. (1998) Menstrual factors in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev 7: 783–789.
60. Trentham-Dietz A, Newcomb PA, Storer BE, Longnecker MP, Baron J, et al. (1997) Body size and risk of breast cancer. Am J Epidemiol 145: 1011–1019.
61. Tung HT, Tsukuma H, Tanaka H, Kinoshita N, Koyama Y, et al. (1999) Risk factors for breast cancer in Japan, with special attention to anthropometric measurements and reproductive history. Jpn J Clin Oncol 29: 137–146.
62. Verla-Tebit E, Chang-Claude J (2005) Anthropometric factors and the risk of premenopausal breast cancer in Germany. Eur J Cancer Prev 14: 419–426.
63. Wrensch M, Chew T, Farren G, Barlow J, Belli F, et al. (2003) Risk factors for breast cancer in a population with high incidence rates. Breast Cancer Res 5: R88–R102.
64. Chow LWC, Lui KL, Chan JCY, Chan TC, Ho PK, et al. (2005) Association between body mass index and risk of formation of breast cancer in chinese women. Asian J Surg 28: 1791–1784.
65. Barnes BBE, Steindorf K, Hein R, Flesch-Janys D, Chang-Claude J (2011) Population attributable risk of invasive postmenopausal breast cancer and breast cancer subtypes for modifiable and non-modifiable risk factors. Cancer Epidemiol 35: 345–352.
66. van den Brandt PA, Dirx MJM, Ronckers CM, vandenHoogen P (1997) Height, weight, weight change, and postmenopausal breast cancer risk: the netherlands cohort study. Cancer Causes Control 8: 39–47.
67. Lacey JVJr, Kreimer AR, Buys SS, Marcus PM, Chang SC, et al. (2009) Breast cancer epidemiology according to recognized breast cancer risk factors in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Cohort. BMC Cancer 9: 84.