**Mini-CAT Name\_\_\_JUN\_\_MA\_\_\_\_**

**Brief description of patient problem/setting:**

Within one week, there were three postmenopausal women with breast cancer came to our clinic for annual exam. All of them have BMI>25. I was wondering if obesity is a risk factor of breast cancer.

**Search Question:**

Are women with a BMI over 25, at increased risk for breast cancer, compared to those with a BMI below 25?

**Question Type:** What kind of question is this?

**Prevalence**  Screening Diagnosis

Prognosis Treatment Harms

I got five systematic review and/or meta-analysis articles. If there are not enough review articles, RCT and high quality cohort or case-control study articles are the second best to help because RCT studies can provide second highest level evidence and cohort or case-control studies can contain large amount of samples.

**PICO search terms:**

|  |  |  |  |
| --- | --- | --- | --- |
| **P** | **I** | **C** | **O** |
| postmenopausal women | obesity | without obesity | breast cancer |
| postmenopausal female | BMI over 25 | BMI below | breast malignancy |
| postmenopausal persons | obese | normal | breast malignant tumor |

**Search tools and strategy used:**

I used PubMed to search for “obesity+ postmenopausal breast cancer” in “systematic review” + “free full text” and found 51 articles.

I also used Cochrane to search for “obesity+ postmenopausal breast cancer” in “review”, and found 6 articles.

I also used ScienceDirect to search for “obesity+ postmenopausal breast cancer” in review articles with open access, and found 156 articles.

I also used Google Scholar to search for “obesity+ postmenopausal breast cancer” within recent 10 years, and found 91 articles.

Then, I read the titles and abstracts of these articles from the most recent article until I found four to six most related review articles.

**Results found:**

**Quantitative association between body mass index and the risk of cancer: A global Meta-analysis of prospective cohort studies.**

**Fang X, Wei J, He X, Lian J, Han D, An P, Zhou T, Liu S, Wang F, Min J.**

**Int J Cancer. 2018 Oct 1;143(7):1595-1603. doi: 10.1002/ijc.31553. Epub 2018 May 13.**

**PMID: 29696630**

Abstract:

Numerous studies have suggested that excess body weight is associated with increased cancer risk. To examine this putative association, we performed a systematic review and quantitative meta-analysis of cohort studies reporting body mass index (BMI) and the risk of 23 cancer types. PubMed, Embase, and Web of Science were searched for cohort studies, yielding 325 articles with 1,525,052 cases. Strong positive associations were observed between BMI and endometrial cancer (RR: 1.48), esophageal adenocarcinoma (RR: 1.45), and kidney cancer (RR: 1.20); weaker associations (RR < 1.20) were also found for several other cancer types. Interestingly, we found significant inverse associations between BMI and oral cavity (RR: 0.93), lung (RR: 0.91), premenopausal breast (RR: 0.95), and localized prostate (RR: 0.97) cancers. A male-specific association was found for colorectal cancer (p = 0.023), and a female-specific association was found for cancer in brain (p = 0.025) or kidney (p = 0.035). With respect to geography, the strongest positive association was found for total cancer in North America (p = 0.038). This comprehensive meta-analysis provides epidemiological evidence supporting the association between BMI and cancer risk. These findings can be used to drive public policies and to help guide personalized medicine in order to better manage body weight, thereby reducing the risk of developing obesity-related cancer.

Key points:

* significant inverse association between BMI and premenopausal breast cancer (RR: 0.95)
* significant positive association was observed between BMI and postmenopausal breast cancer (RR: 1.11)
* significant positive association was observed between BMI and unspecified breast cancer (RR: 1.06)

I chose it because it is new (2018) and relevant. It is a systematic review and meta-analysis article, including 27 prospective cohort studies for premenopausal breast cancer, 45 prospective cohort studies for postmenopausal breast cancer and 20 prospective cohort studies for unspecified breast cancer.

Link: <https://onlinelibrary.wiley.com/doi/pdf/10.1002/ijc.31553>

**Adult weight gain and adiposity-related cancers: a dose-response meta-analysis of prospective observational studies.**

**Keum N, Greenwood DC, Lee DH, Kim R, Aune D, Ju W, Hu FB, Giovannucci EL.**

**J Natl Cancer Inst. 2015 Mar 10;107(2). pii: djv088. doi: 10.1093/jnci/djv088. Print 2015 Feb. Review.**

**PMID: 25757865**

Abstract:

BACKGROUND:

Adiposity, measured by body mass index, is implicated in carcinogenesis. While adult weight gain has diverse advantages over body mass index in measuring adiposity, systematic reviews on adult weight gain in relation to adiposity-related cancers are lacking.

METHODS:

PubMed and Embase were searched through September 2014 for prospective observational studies investigating the relationship between adult weight gain and the risk of 10 adiposity-related cancers. Dose-response meta-analyses were performed using a random-effects model to estimate summary relative risk (RR) and 95% confidence interval (CI) for each cancer type. All statistical tests were two-sided.

RESULTS:

A total of 50 studies were included. For each 5 kg increase in adult weight gain, the summary relative risk was 1.11 (95% CI = 1.08 to 1.13) for postmenopausal breast cancer among no- or low-hormone replacement therapy (HRT) users, 1.39 (95% CI = 1.29 to 1.49) and 1.09 (95% CI = 1.02 to 1.16) for postmenopausal endometrial cancer among HRT nonusers and users, respectively, 1.13 (95% CI = 1.03 to 1.23) for postmenopausal ovarian cancer among no or low HRT users, 1.09 (95% CI = 1.04 to 1.13) for colon cancer in men. The relative risk of kidney cancer comparing highest and lowest level of adult weight gain was 1.42 (95% CI = 1.11 to 1.81). Adult weight gain was unrelated to cancers of the breast (premenopausal women, postmenopausal HRT users), prostate, colon (women), pancreas, and thyroid. An increase in risk associated with adult weight gain for breast cancer was statistically significantly greater among postmenopausal women (P(heterogeneity) = .001) and HRT nonusers (P(heterogeneity) = .001); that for endometrial cancer was alike among HRT nonusers (P(heterogeneity) = .04).

CONCLUSIONS:

Avoiding adult weight gain itself may confer protection against certain types of cancers, particularly among HRT nonusers.

Key points:

* An increase in risk associated with adult weight gain for breast cancer was statistically significantly greater among postmenopausal women (P(heterogeneity) = .001) and HRT nonusers (P(heterogeneity) = .001)
* Adult weight gain was unrelated to cancers of the breast (premenopausal women, postmenopausal HRT users).

I chose it because it is not old (2015) and relevant. It is a systematic review and meta-analysis article, including 17 observational studies in epidemiology studies (4 studies for premenopausal breast cancer and 13 studies for postmenopausal breast cancer).

Link: <https://academic.oup.com/jnci/article/107/2/djv088/2223074>

**Body mass index and risk of breast cancer: a nonlinear dose-response meta-analysis of prospective studies.**

**Xia X, Chen W, Li J, Chen X, Rui R, Liu C, Sun Y, Liu L, Gong J, Yuan P.**

**Sci Rep. 2014 Dec 15;4:7480. doi: 10.1038/srep07480.**

**PMID: 25504309**

Abstract:

The role of Body Mass Index (BMI) for Breast Cancer (BC) remains to be great interest for a long time. However, the precise effect of nonlinear dose-response for BMI and BC risk is still unclear. We conducted a dose-response meta-analysis to quantitatively assess the effect of BMI on BC risk. Twelve prospective studies with 4,699 cases identified among 426,199 participants and 25 studies of 22,809 cases identified among 1,155,110 participants in premenopausal and postmenopausal groups, respectively, were included in this meta-analysis. Significant non-linear dose-response (P < 0.001) association was identified between BMI and BC risk in postmenopausal women. Individuals with BMI of 25, 30, and 35 kg/m(2) yielded relative risks (RRs) of 1.02 [95% confidence interval (CI): 0.98-1.06], 1.12 (95% CI: 1.01-1.24), and 1.26 (95% CI: 1.07-1.50), respectively, when compared to the mean level of the normal BMI range. However, inverse result though not significant was observed in premenopausal women. In conclusion, the results of this meta-analysis highlighted that obesity contributed to increased BC risk in a nonlinear dose-response manner in postmenopausal women, and it is important to realize that body weight control may be a crucial process to reduce BC susceptibility.

Key points:

* Obesity contributed to increased breast cancer risk in a nonlinear dose-response manner in postmenopausal women.
* Inverse association of BMI with breast cancer was observed in premenopausal women, although the association was not significant.

I chose it because it is not old (2014) and most relevant. It is a systematic review and meta-analysis article, including 12 prospective studies of 4,699 cases identified among 426,199 women in premenopausal group and 25 prospective studies of 22,809 cases identified among 1,155,110 women in postmenopausal group.

Link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265780/pdf/srep07480.pdf>

**Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status.**

**Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A.**

**Epidemiol Rev. 2014;36:114-36. doi: 10.1093/epirev/mxt010. Review.**

**PMID: 24375928**

Abstract:

To assess the joint relationships among body mass index, menopausal status, and breast cancer according to breast cancer subtype and estrogen-progestin medication use, we conducted a meta-analysis of 89 epidemiologic reports published in English during 1980-2012 identified through a systematic search of bibliographic databases. Pooled analysis yielded a summary risk ratio of 0.78 (95% confidence interval (CI): 0.67, 0.92) for hormone receptor-positive premenopausal breast cancer associated with obesity (body mass index (weight (kg)/height (m)(2)) ≥30 compared with <25). Obesity was associated with a summary risk ratio of 1.39 (95% CI: 1.14, 1.70) for receptor-positive postmenopausal breast cancer. For receptor-negative breast cancer, the summary risk ratios of 1.06 (95% CI: 0.70, 1.60) and 0.98 (95% CI: 0.78, 1.22) associated with obesity were null for both premenopausal and postmenopausal women, respectively. Elevated postmenopausal breast cancer risk ratios associated with obesity were limited to women who never took estrogen-progestin therapy, with risk ratios of 1.42 (95% CI: 1.30, 1.55) among never users and 1.18 (95% CI: 0.98, 1.42) among users; too few studies were available to examine this relationship according to receptor subtype. Future research is needed to confirm whether obesity is unrelated to receptor-negative breast cancer in populations of postmenopausal women with low prevalence of hormone medication use.

Key points:

* Elevated postmenopausal breast cancer risk ratios associated with obesity were limited to women who never took estrogen-progestin therapy

I chose it because it is not old (2014) and most relevant. It is a systematic review and meta-analysis article including 89 epidemiologic studies.

Link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3873844/pdf/mxt010.pdf>

**Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis.**

**Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A.**

**PLoS One. 2012;7(12):e51446. doi: 10.1371/journal.pone.0051446. Epub 2012 Dec 7. Review.**

**PMID: 23236502**

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.Key points:

* There was an inverse but non-significant correlation between BMI and breast cancer risk during premenopausal period.
* There was a direct and significant correlation between BMI and breast cancer risk during postmenopausal period.

I chose it because it is not very old (2012) and most relevant. It is a systematic review and meta-analysis article including 15 cohort studies involving 2,104,203 subjects and 3,414,806 person-years and 35 case-control studies involving 71,216 subjects.

Link <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3517558/pdf/pone.0051446.pdf>

**Summary of Evidence**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author (Date) | | Level of Evidence | | Sample/Setting  (# of subjects/ studies, cohort definition etc. ) | | Outcome(s) studied | | Key Findings | | Limitations and Biases | |
| Fang X, Wei J, He X, Lian J, Han D, An P, Zhou T, Liu S, Wang F, Min J.  (2018) | | systematic review and meta-analysis | | 92 prospective cohort studies, including 20 studies of 34352 cases identified among 3377920 women in unspecified group, 27 studies of 38409 cases identified among 5179582 women in premenopausal group, and 45 studies of 97552 cases identified among 5843416 women in postmenopausal group. | | breast cancer | | significant inverse association between BMI and premenopausal breast cancer (RR: 0.95); significant positive association was observed between BMI and postmenopausal breast cancer (RR: 1.11);  significant positive association was observed between BMI and unspecified breast cancer (RR: 1.06) | | First, because of the observational nature of the studies included, residual confounding factors cannot be excluded, including the inherent issues associated with the original studies.  Secondly, they may have missed age-dependent effects combined with other risk factors.  Finally, high heterogeneity cannot be explained by most of subgroup analyses. | |
| Keum N, Greenwood DC, Lee DH, Kim R, Aune D, Ju W, Hu FB, Giovannucci EL.  (2015) | | systematic review and meta-analysis | | 17 observational studies (4 studies for premenopausal breast cancer and 13 studies for postmenopausal breast cancer) with sample size from 6160 to 99039. | | breast cancer | | An increase in risk associated with adult weight gain for breast cancer was statistically significantly greater among postmenopausal women (P(heterogeneity) = .001) and HRT nonusers (P(heterogeneity) = .001)  Adult weight gain was unrelated to cancers of the breast in premenopausal women and postmenopausal HRT users. | | All meta-analyses of observational studies are liable to the same potential biases. Measurement error in adult weight gain is particularly concerning, as dose-response meta-analyses incorporate absolute values of adult weight gain rather than ranking of it.  Additionally, studies were inconsistent in their adjustments for anthropometric measures, which affects interpretation of adult weight change. | |
| Xia X, Chen W, Li J, Chen X, Rui R, Liu C, Sun Y, Liu L, Gong J, Yuan P.  (2014) | | systematic review and meta-analysis | | 12 prospective studies of 4,699 cases identified among 426,199 women in premenopausal group and 25 prospective studies of 22,809 cases identified among 1,155,110 women in postmenopausal group. | | breast cancer | | Obesity contributed to increased breast cancer risk in a nonlinear dose-response manner in postmenopausal women.  Inverse association of BMI with breast cancer was observed in premenopausal women, although the association was not significant. | | Obesity could affect BC risk through impacting circulating endogenous estrogen levels. Additionally,  the methods restricted the number of studies  included. Furthermore, the definition of menopausal status varied  between different cohorts may lead to misclassification bias.  Moreover, it is considered that BMI may not be the valid indicator  for some people to assess the adiposity. | |
| Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A.  (2014) | | systematic review and meta-analysis | | 89 published epidemiological studies (cohort, case-control, and randomized trials) with  sample size from 39 to 10419 | | breast cancer | | Elevated postmenopausal breast cancer risk ratios associated with obesity were limited to women who never took estrogen-progestin therapy | | Publications were included in the  analysis only if the results could be considered in the 3 categories according to well-recognized cutpoints for obesity  based on body mass index as defined by the World Health  Organization.  Results in the analysis were a combination of adjusted relative risk estimates taken directly from the published papers  along with crude estimates.  Meta-analysis relies on the quality of the individual studies.  Many studies collected information on body mass index,  postmenopausal hormone use, and other factors by using  self-report rather than medical records or measured values. | |
| Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A.  (2012) | | systematic review and meta-analysis | | 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 | | breast cancer | | There was an inverse but non-significant correlation between BMI and breast cancer risk during premenopausal period.  There was a direct and significant correlation between BMI and breast cancer risk during postmenopausal period. | | 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, other potential confounding variables were not reported exactly in majority of the studies. Hence, they could not conduct subgroup analysis based on these variables. This issue may raise the possibility of the information bias. | |

**What is the clinical “bottom line” derived from these articles in answer to your question?**

**Question:** Are women with a BMI over 25, at increased risk for breast cancer, compared to those with a BMI below 25?

**Answer:** The first study showed significant positive association was observed between BMI and both unspecified breast cancer and postmenopausal breast cancer while significant inverse association between BMI and premenopausal breast cancer, which should be weighed most heavily since it is the newest systematic review and meta-analysis study with a large sample size.

The second study showed an increase in risk associated with adult weight gain for breast cancer was statistically significantly greater among postmenopausal women and HRT nonusers, but not in premenopausal women and postmenopausal HRT users, which should be weighed as the last since only 17 studies were included.

The third study showed that obesity contributed to increased breast cancer risk in a nonlinear dose-response manner in postmenopausal women, and inverse association of BMI with breast cancer was observed in premenopausal women, although the association was not significant, which should be weighed second since it is relatively new and has a large sample size.

The fourth study showed that elevated postmenopausal breast cancer risk ratios associated with obesity were limited to women who never took estrogen-progestin therapy, which should be weighed fourth since 89 studies did not include a very large size of samples.

The fifth study showed an inverse but non-significant correlation between BMI and breast cancer risk during premenopausal period, and a direct and significant correlation between BMI and breast cancer risk during postmenopausal period, which should be weighed third since it has large sample size although not very new.

**Conclusion:** Obese or overweight women (BMI>25) are at increased postmenopausal breast cancer risk, compared to women with BMI<25, although there is still debate about whether the conclusion applies for postmenopausal HRT users. In addition, obese or overweight women (BMI>25) are not at increased premenopausal breast cancer risk, compared to women with BMI<25, although there is debate about whether obesity decreases the risk of premenopausal breast cancer risk.

**Clinical significance:** It will provide the guide for breast cancer prevention about who should be screened for breast cancer, and also provide the guide for intervention such as weight loss.

**Concerns:** Further studies should be performed about the debates shown in the conclusion part.