Obesity, Mammography Use and Accuracy, and Advanced Breast Cancer Risk

Karla Kerlikowske, Rod Walker, Diana L. Miglioretti, Arati Desai, Rachel Ballard-Barbash, Diana S. M. Buist, for the National Cancer Institute-Sponsored Breast Cancer Surveillance Consortium

**Background**

Being overweight or obese is associated with increased breast cancer risk and disease severity among postmenopausal women, but whether extent of mammography use and accuracy modify this association and further contribute to increases in disease severity at diagnosis among overweight and obese women is unclear.

**Methods**

We prospectively collected data during 1996–2005 on 287,115 postmenopausal women not using hormone therapy (HT) who underwent 614,562 mammography examinations; 4446 women were diagnosed with breast cancer within 12 months of a mammography examination. We calculated rates per 1000 mammography examinations of large (>15 mm), advanced-stage (IIb, III, or IV), high-grade (3 or 4), estrogen receptor (ER)–positive and –negative, and screen-detected and non-screen-detected breast cancer across body mass index (BMI, kg/m²) groups defined as normal (18.5–24.9), overweight (25.0–29.9), obese class I (30.0–34.9), and obese class II/III (≥35.0), adjusting for age, race/ethnicity, and mammography registry and use. All statistical tests were two-sided.

**Results**

Adjusted rates per 1000 mammography examinations of overall breast cancer increased across BMI groups (6.6 normal, 7.4 overweight, 7.9 obese I, 8.5 obese II/III; \( P_{\text{trend}} < .001 \)), as did rates of advanced disease, including large invasive (2.3 normal, 2.6 overweight, 2.9 obese I, 3.2 obese II/III; \( P_{\text{trend}} < .001 \)), advanced-stage (0.8 normal, 0.9 overweight, 1.3 obese I, 1.5 obese II/III; \( P_{\text{trend}} < .001 \)), and high nuclear grade (1.5 normal, 1.7 overweight, 1.7 obese I, 1.9 obese II/III; \( P_{\text{trend}} = .10 \)) tumors. Rates of ER-positive tumors increased across BMI groups (\( P_{\text{trend}} < .001 \)); rates of ER-negative tumors did not. Rates of screen-detected cancers were higher among overweight and obese women than normal and underweight women, but rates of non-screen-detected (false-negative) cancers were similar. Rates of advanced breast cancer increased across BMI groups regardless of extent of mammography use.

**Conclusions**

Patterns of mammography use and mammography accuracy are not the primary reasons for higher rates of advanced breast cancer among overweight and obese postmenopausal women not using HT; thus, biologic differences in breast tumor development and/or progression may be important.

J Natl Cancer Inst 2008;100:1724–1733

Excessive body weight is a substantial problem in the United States, with 36% of women aged 40–59 years being classified as overweight (body mass index [BMI] = 25–29.9 mg/kg²) and another 37% as obese (BMI = 30 mg/kg² or higher) (1,2). Being overweight or obese is associated with an increased risk of breast cancer among postmenopausal women, in particular among those who do not use hormone therapy (HT) (3–7). Increased weight has been associated with increased risk of larger tumor size and more advanced stage at diagnosis in premenopausal (8–10) and postmenopausal (6) women. The few studies of the association of advanced tumors and elevated BMI (6,7,11) have not taken into account mammography use or mammography accuracy or whether the magnitude of the association exists for both overweight and obese women compared with normal-weight women.

The mechanism of association between overweight or obesity and elevated risk of breast cancer and advanced cancer is likely to be complex, and the contributions of biologic vs nonbiologic effects that influence cancer detection have not been definitively

**Affiliations of authors:** Departments of Epidemiology and Biostatistics (KK) and General Internal Medicine Section, Department of Veterans Affairs, University of California, San Francisco, CA (KK); Group Health Center for Health Studies, Seattle, WA (RW, DLM, DSMB); Department of Biostatistics, University of Washington, Seattle, WA (DLM); Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, MD (AD); Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD (RBB).

**Correspondence to:** Karla Kerlikowske, MD, San Francisco Veterans Affairs Medical Center, General Internal Medicine Section, 111A1, 4150 Clement St, San Francisco, CA 94121 (e-mail: karla.kerlikowske@ucsf.edu).

See “Funding” and “Note” following “References.”

DOI: 10.1093/jnci/djn388

© The Author 2008. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.
determined. Postulated biologic mechanisms include increased serum sex hormones, particularly bioavailable estradiol (12); increased insulin and insulin-like growth factors (13,14); and increased inflammatory markers (15). Nonbiologic mechanisms include differential screening practices among overweight individuals (16–20) and differences in mammography accuracy (21,22). Obese white women are 17%–30% less likely to be screened with mammography within the previous 2 years than normal-weight white women (absolute difference of 8%–9%), even after adjustment for sociodemographic factors and access to health care (16–20). One study (21) reported that the sensitivity of mammography is higher among women with a BMI of 25 kg/m² and greater, although another (22) reported that the sensitivity did not differ by BMI.

We determined rates of breast cancer and advanced-stage disease within 1 year of a mammography examination across five standard BMI groups among women not using HT. Our goal was to examine whether extent of mammography use and accuracy modify this association and further contribute to increases in disease severity at diagnosis among overweight and obese women.

Subjects and Methods

Data Source

Data were pooled from seven mammography registries (California, North Carolina, New Hampshire, Vermont, Colorado, New Mexico, and Washington) that participate in the Breast Cancer Surveillance Consortium (23) (http://breastscreening.cancer.gov), which is funded by the National Cancer Institute. These registries collect information on mammography examinations that are performed in their defined catchment areas, which are two counties in California (San Francisco and Marin), 39 counties in North Carolina, 80% of the state of New Hampshire, 100% of the state of Vermont, 50% of the Denver metropolitan area, the Albuquerque metropolitan and surrounding areas, and the Puget Sound region of Group Health in Washington state. Each mammography registry annually links women in their registry to a state tumor registry or regional Surveillance, Epidemiology, and End Results (SEER) program that collects population-based cancer data. Some registries are also linked to pathology databases. Each registry obtains annual approval from their Institutional Review Board for consenting processes or a waiver of consent, enrollment of participants, and ongoing data linkages for research purposes. All registries have received Federal Certificates of Confidentiality that protect the identities of research subjects.

Subjects

The study sample included mammography examinations performed between January 1, 1996, and December 31, 2005, among postmenopausal women aged 40 years and older who were not currently using HT at the time of their mammography examination and who completed a self-administered questionnaire at the time of each examination that included a question about height and weight. We did not include postmenopausal women who self-reported using HT at the time of mammography and premenopausal women because increased BMI is either not associated or only very weakly associated with breast cancer risk in these women (4,6,7). We excluded mammography examinations among women with a history of breast cancer (n = 80665 or 10.3%), breast implants (n = 332 or 0.5%), missing race/ethnicity (n = 19843, 2.5%), or missing BMI (n = 66711 or 8.5%). After these exclusions, 287115 women and 614562 mammography examinations were included in the study. Mammography examinations that occurred after December 31, 2005, were not included to ensure at least 12 months for reporting cancers to tumor registries after the most recent mammography examination. Cancer ascertainment from cancer registries by participating mammography registries is estimated to be more than 94.3% complete during the study period (24).

Measurements and Definitions

Demographic and breast health history information were obtained on a self-administered questionnaire that included questions about race/ethnicity, previous mammography, menopausal status, history of oophorectomy, and height and weight. We categorized women as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native American/Native Alaskan, or other/mixed race. Mammography examinations were included if a woman reported both ovaries had been removed, her menstrual periods had stopped permanently for reasons other than hysterectomy, or if she was aged 55 years or older, which are factors that are consistent with criteria used in the literature to define a woman as postmenopausal (6,25,26). Height and weight were used to calculate BMI by dividing weight in kilograms by height squared.

CONTEXT AND CAVEATS

Prior knowledge

In postmenopausal women, obesity and being overweight are associated with increased risk of breast cancer and increased disease severity; however, it is unknown whether differences in mammography use and accuracy have a role in these associations.

Study design


Contribution

Increased body mass index (BMI) was associated with increased rates of breast cancer overall and advanced-stage disease per 1000 mammography examinations; it was not associated with rates of non-screen-detected breast cancers.

Implications

In the population studied, differences in mammography use and accuracy do not explain the higher rates of breast cancer among overweight and obese postmenopausal women who are not using HT.

Limitations

BMI calculations were based on self-reported height and weight measurements, and overweight women often underestimate their weight. Because few black, Hispanic, Native American, and Native Alaskan women with breast cancer were included in the study, rates of advanced breast cancer by BMI category adjusted for mammography use could not be calculated for these subgroups.

From the Editors
in meters squared (kg/m²). Mammography examinations were grouped into five standard BMI categories (<18.5 underweight, 18.5–24.9 normal weight, 25.0–29.9 overweight, 30.0–34.9 obese I, and ≥35.0 obese II/III) using nationally defined cut points (27). A total of 87% of women were assigned to the same BMI category on each of their mammography examinations, 3% started in the normal-weight category and subsequently had an examination when they were in the overweight or obese categories, 6% started as overweight or obese and subsequently had an examination when they were in a lower BMI category, and 4% were assigned to some other combination of categories.

We characterized mammography use according to type of examination and time interval between that examination and a woman’s most recent prior examination using a combination of dates that had been recorded in a database (90%) and self-reported dates from surveys only (10%). The time intervals used to characterize mammography use were as follows: within 1 year (9–17 months), within 2 years (18–29 months), or within 3 years or longer (>30 months). First screening examinations, which were defined as the first screening that was recorded in a mammography registry among women who self-reported no prior history of mammography, were combined with examinations that were performed 3 or more years apart because the rates of breast cancer by BMI category were similar in these groups. The prevalence of first screening examinations in this sample of postmenopausal women was low (2.2%) and similar across BMI categories. First diagnostic examinations, which were defined as mammography that was ordered for a breast problem among women with no prior history of mammography, were classified separately because the probability of cancer is much higher in these women than women in other groups. Women could have had more than one mammography examination during the study period; thus, the same woman could have examinations assigned to different mammography use categories.

Mammography examinations were interpreted using Breast Imaging Reporting and Data System (BI-RADS) (28) assessment categories and were classified as positive or negative using standard definitions (29). Mammographic breast density was categorized using BI-RADS categories of almost entirely fat, scattered fibroglandular densities, heterogeneously dense, or extremely dense.

Each mammography examination was followed for 365 days or until the next mammography examination, whichever came first, to determine breast cancer status, as is standard in mammography studies (25,26,28–32). Each breast cancer was associated with a mammography examination given the prior observations:

\[ p(Y_{i1}, \ldots, Y_{in} | X_i) = p(Y_{i1} = 1 | Y_{i0} = 0, \ldots, Y_{i(n-1)} = 0, X_{i1}, \ldots, X_{in}) \times p(Y_{i0} = 0 | Y_{i1} = 0, \ldots, Y_{i(n-1)} = 0, X_{i1}, \ldots, X_{in}) \]

where \( Y_{i1}, \ldots, Y_{in} \) indicate the \( n \) observations for the \( i \)th woman and \( X_i = (X_{i1}, \ldots, X_{im}) \) indicates the associated covariates (with \( X_{im} \) indicating covariates measured at the first mammography examination, \( X_{i2} \) indicating covariates measured at the second examination, etc.). Under the assumption that the probability of a first cancer diagnosis within 12 months of a mammography examination, given the covariates measured at that examination, does not depend on the observation number in the analysis or on covariates measured at other mammography examinations, the likelihood contribution for each woman’s sequence of mammography examinations reduces to the following:

\[ p(Y_{i1}, \ldots, Y_{in} | X_i) = p(Y_i = 1 | Y_{n} = 0) \times p(Y_{i0} = 0 | X_{i1}) \times \ldots \times p(Y_{in} = 0 | X_{in}). \]

**Statistical Analysis**

Frequency distributions of risk factors were determined by BMI categories. The main analysis used logistic regression to examine whether BMI was associated with the probability of a first breast cancer diagnosis within 12 months of a mammography examination as well as the probability of a first cancer diagnosis being advanced (large, advanced stage, or high grade at diagnosis) and being ER negative or ER positive. Separate logistic regression models were also fit for each cancer stage. All models were adjusted for age (using categories 40–49, 50–54, 55–59, 60–64, 65–69, ≥70 years), race/ethnicity (using categories above), and mammography registry. We adjusted for race/ethnicity because black women have a higher rate of advanced tumors than white women, in part because they are less likely to be adequately screened (31). Separate subgroup analyses were performed among white and Hispanic women. Subgroup analyses among black and Native American or Native Alaskan women were not possible given the small number of breast cancers (\( n = 75 \) and \( n = 42 \), respectively). Analyses were repeated with an additional adjustment for mammography use (as a categorical variable: 1 year, 2 years, ≥3 years or first screening examination, or first diagnostic mammography examination). We also compared results stratifying by mammography use. We did not adjust for breast density in the main analyses because BMI influences breast density (34). However, we did explore adjusting for breast density in a sensitivity analysis.

The analyses were performed at the level of a mammography examination. Each woman contributed a single examination that was associated with her first breast cancer diagnosis, one or more mammography examinations that were not associated with breast cancer, or one or more examinations that were not associated with cancer followed by an examination that was associated with her first breast cancer. The likelihood contribution from each woman that results from multiple mammography examinations with these possible outcome sequences (either no cancer events or a single cancer event for the last observation) can be written as a product of the probabilities of the outcome at each mammography examination given the prior observations:

The analyses repeated with an additional adjustment for mammography use. We did not adjust for breast density in the main analyses because BMI influences breast density (34). However, we did explore adjusting for breast density in a sensitivity analysis.

The analyses were performed at the level of a mammography examination. Each woman contributed a single examination that was associated with her first breast cancer diagnosis, one or more mammography examinations that were not associated with breast cancer, or one or more examinations that were not associated with cancer followed by an examination that was associated with her first breast cancer. The likelihood contribution from each woman that results from multiple mammography examinations with these possible outcome sequences (either no cancer events or a single cancer event for the last observation) can be written as a product of the series of conditional probabilities (\( p \)) of the outcome at each mammography examination given the prior observations:

\[ p(Y_{i1}, \ldots, Y_{in} | X_i) = p(Y_{i1} = 1 | Y_{i0} = 0, \ldots, Y_{i(n-1)} = 0, X_{i1}, \ldots, X_{in}) \times p(Y_{i0} = 0 | Y_{i1} = 0, \ldots, Y_{i(n-1)} = 0, X_{i1}, \ldots, X_{in}) \times \ldots \times p(Y_{in} = 0 | X_{in}) \]

where \( Y_{i1}, \ldots, Y_{in} \) indicate the \( n \) observations for the \( i \)th woman and \( X_i = (X_{i1}, \ldots, X_{im}) \) indicates the associated covariates (with \( X_{im} \) indicating covariates measured at the first mammography examination, \( X_{i2} \) indicating covariates measured at the second examination, etc.). Under the assumption that the probability of a first cancer diagnosis within 12 months of a mammography examination, given the covariates measured at that examination, does not depend on the observation number in the analysis or on covariates measured at other mammography examinations, the likelihood contribution for each woman’s sequence of mammography examinations reduces to the following:

\[ p(Y_{i1}, \ldots, Y_{in} | X_i) = p(Y_i = 1 | Y_{n} = 0) \times p(Y_{i0} = 0 | X_{i1}) \times \ldots \times p(Y_{in} = 0 | X_{in}). \]
This likelihood contribution is proportional to the binomial likelihood that considers all outcomes for a woman to be independent events. Therefore, we used logistic regression without additional adjustment for clustering within women. We used the likelihood ratio statistic to test for a linear trend for each outcome across increasing BMI groups, excluding underweight women in this calculation because that group was very small.

Given that our main analyses of interest model the probability of a first cancer diagnosis either conditional on or stratified by the time since last mammography examination, we believe that the above assumption, that the probability of cancer does not depend on the observation number in the analysis or on covariates measured at other mammography examinations, is reasonable. To assess potential effects of this assumption on the results, we refit the models for our main analyses but incorporating a covariate indicating each woman’s observation number, and the findings were unchanged. We also examined whether fitting the logistic regression model using generalized estimating equations with a working independence correlation structure and robust variance estimates (to account for potential correlation among mammograms performed on the same woman) altered the results. The results were practically identical to those of the logistic regression models without additional adjustment for clustering within women.

We estimated rates of cancer within 1 year of a mammography examination adjusted for the covariates collected at that examination from logistic regression models using marginal standardization, also known as predictive margins (35,36). This calculation entails first estimating the probability of cancer for each combination of age, race, and mammography registry based on the fitted logistic regression model. Then we estimated adjusted rates for each BMI category by calculating a weighted average of these probabilities, weighted by the overall proportion of women in the corresponding age, race/ethnicity, and mammography registry strata observed in the data. We repeated these rate estimates, also adjusting for or stratifying by mammography use. Rates of first breast cancer diagnosis per 1000 mammography examinations are slightly higher than SEER rates because women who undergo screening mammography are at higher risk for having occult breast cancer detected within 12 months of mammography and because the SEER program reflects screened and unscreened women (37).

We estimated screen-detected cancer (true positive) and non-screen-detected cancer (false negative) rates (per 1000 mammography examinations) and the sensitivity of screening mammography by BMI (<25 vs ≥25 kg/m²) and mammography use categories from logistic regression models adjusting for age, race/ethnicity, and mammography registry using marginal standardization, as described above.

We calculated the population attributable fraction of breast cancer, large invasive cancer, and advanced-stage breast cancer for a given level of BMI to estimate the proportion of advanced breast cancers in the mammography population that could be attributed to being overweight or obese (38). These calculations used the adjusted probabilities of cancer for each BMI category, which were estimated using marginal standardization and the fitted logistic regression model described above.

All statistical calculations were performed using SAS (version 9.1; SAS Institute, Cary, NC). All statistical tests were two-sided, and P values less than .05 were considered statistically significant.

**Results**

Among 287,115 postmenopausal women who were age 40 years and older (mean 63.9 years), 614,562 mammography examinations (96% screening, 4% diagnostic) were performed, and 4,446 women developed breast cancer within 12 months of an examination. Women aged 60–69 years and black and Native American or Native Alaskan women had the highest proportions of overweight and obese (Table 1). Almost entirely fat breast density was most prevalent among overweight and obese women. Mammography use decreased with increasing BMI, with 14.2% of women with a normal BMI having had mammography 3 or more years ago or a first screening or diagnostic examination compared with 19.3% of obese II/III women (P < .001). Few examinations were recorded as a first diagnostic examination, and the proportion was similar across BMI categories. A total of 18.5% of underweight women had mammography examinations 3 or more years ago or had a first screening or diagnostic examination (Table 1).

The rates per 1000 mammography examinations of breast cancer overall and of large, advanced-stage, and high nuclear grade invasive cancer adjusted for age, race/ethnicity, and mammography registry increased statistically significantly with higher BMI (data not shown), and the findings were similar when we additionally adjusted for mammography use (Table 2). Adjusted rates for breast cancer overall increased across BMI groups (6.6 normal, 7.4 overweight, 7.9 obese I, 8.5 obese II/III; P trend < .001) in the entire study population and similarly increased across BMI groups when limiting analyses to white (6.9 normal, 7.8 overweight, 8.2 obese I, 8.8 obese II/III; P trend < .001), Hispanic (4.9 normal, 5.6 overweight, 7.4 obese I–III; P trend = .002) women.

The rates of large invasive breast cancer (2.3 normal, 2.6 overweight, 2.9 obese I, 3.2 obese II/III; P trend < .001) and of advanced-stage breast cancer (0.8 normal, 0.9 overweight, 1.3 obese I, 1.5 obese II/III; P trend < .001) increased between 1.3- to 1.8-fold with each higher BMI category. Adjusted advanced breast cancer rates increased across BMI groups when analyses were limited to white women (0.8 normal, 0.9 overweight, 1.4 obese I, 1.5 obese II/III; P trend < .001) similar to that observed in the overall study population (Table 2). Too few black, Hispanic, and Native American or Native Alaskan women had advanced disease (n = 12, n = 67, and n = 8, respectively) to perform stratified analyses by BMI category.

The rate of high nuclear grade invasive breast cancer (1.5 normal, 1.7 overweight, 1.7 obese I, 1.9 obese II/III; P trend = .10) increased with each higher BMI category. The rate of ER-positive tumors increased with higher BMI (P trend < .001), but the rate of ER-negative tumors did not (P trend = .8). Underweight women had lower or similar rates of breast cancer overall and of large, advanced-stage, and high nuclear grade invasive cancer compared with women with a normal BMI (Table 2). Adjusting for breast density in all models either did not change or strengthened trends in results (data not shown).
Rates of advanced cancer across BMI groups from underweight to obese II/III were stratified by mammography use (within 1 year, within 2 years, or within 3 years or longer or first screening examination) to investigate whether differences in mammography use explain the differences by BMI (Figure 1). If the only influence of BMI on cancer risk was through the potential association of BMI with mammography use, then the rates of cancer would be the same across BMI categories for any given mammography use category but would still be successively higher among women who underwent less frequent mammography. We observed statistically significantly higher rates and odds of advanced-stage breast cancer across increasing BMI categories for women with 2 years (P trend < .001) and 3 years or more (P trend = .001) between mammography examinations and a non-statistically significant increasing trend for women with 1 year between mammography examinations (P trend = .1). Women with 3 years or more between mammography examinations had higher rates of advanced breast cancer across BMI categories than women who underwent more frequent mammography (Figure 1). The rate of increase or slope of linear trend in breast cancer rates across increasing BMI categories did not statistically significantly differ by mammography use for breast cancer overall (test for interaction, P = .19) or for large (test for interaction, P = .32), advanced-stage (test for interaction, P = .10), high nuclear grade (test for interaction, P = .62), ER-positive (test for interaction, P = .74), or ER-negative (test for interaction, P = .59) breast cancer. Although the increasing linear trend across BMI categories for advanced-stage disease was not as strong among the 1-year mammography group as it was among the other mammography groups, the results in Figure 1 illustrate that differences in mammography use only partially explain the differences in rates of advanced disease seen across BMI categories.

The proportions of breast cancers that were stage IIb or III/IV were highest among overweight and obese women (Table 3). The rate of breast cancer increased by between 0.3 and 0.5 cancers per 1000 mammography examinations from normal to obese II/III categories for early (stage 0 and I) and advanced (stage IIb or III/IV) stages (Table 3). Women who had their first diagnostic examination had high rates of breast cancer per 1000 examinations, regardless of BMI (204 normal, 209 overweight, 209 obese I, and 142 obese II/III).

We measured the rate of breast cancer by method of detection (screen- or non-screen-detected) and the sensitivity of mammography to determine whether a greater proportion of breast cancers not detected in overweight and obese women could have led to a higher rate of advanced disease. The rate of non-screen-detected cancer was low and did not vary by BMI, whereas the rate of screen-detected cancer was higher among overweight and obese women than among lower weight women. The sensitivity of screening mammography was similar or higher among overweight and obese compared with underweight and normal-weight women (Table 4).
Table 2. Rates and odds ratios (ORs) with 95% confidence intervals (CIs) of breast cancer and of large, advanced-stage, high-grade, and estrogen receptor (ER)–positive and –negative invasive breast cancer within 12 mo of a mammography examination per 1000 examinations by body mass index (BMI) category*  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Underweight</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese I</th>
<th>Obese II/III</th>
<th>$P_{\text{trend}}$†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer, n</td>
<td>80</td>
<td>1617</td>
<td>1505</td>
<td>780</td>
<td>464</td>
<td></td>
</tr>
<tr>
<td>Rate‡</td>
<td>6.8</td>
<td>6.6</td>
<td>7.4</td>
<td>7.9</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI) ‡</td>
<td>1.03 (0.82 to 1.30)</td>
<td>Reference</td>
<td>1.12 (1.05 to 1.21)</td>
<td>1.20 (1.10 to 1.31)</td>
<td>1.30 (1.17 to 1.45)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Large (n)§</td>
<td>20</td>
<td>554</td>
<td>528</td>
<td>293</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>Rate†</td>
<td>1.6</td>
<td>2.3</td>
<td>2.6</td>
<td>2.9</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI) ‡</td>
<td>0.71 (0.45 to 1.12)</td>
<td>Reference</td>
<td>1.16 (1.03 to 1.31)</td>
<td>1.31 (1.13 to 1.51)</td>
<td>1.42 (1.19 to 1.69)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Advanced stage (n)§</td>
<td>8</td>
<td>207</td>
<td>186</td>
<td>130</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Rate†</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>1.3</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI) ‡</td>
<td>0.78 (0.38 to 1.58)</td>
<td>Reference</td>
<td>1.10 (0.90 to 1.35)</td>
<td>1.56 (1.25 to 1.95)</td>
<td>1.82 (1.40 to 2.37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High grade (n)§</td>
<td>11</td>
<td>369</td>
<td>342</td>
<td>175</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Rate†</td>
<td>1.0</td>
<td>1.5</td>
<td>1.7</td>
<td>1.7</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI) ‡</td>
<td>0.64 (0.35 to 1.16)</td>
<td>Reference</td>
<td>1.10 (0.95 to 1.28)</td>
<td>1.13 (0.94 to 1.36)</td>
<td>1.21 (0.97 to 1.51)</td>
<td>.10</td>
</tr>
<tr>
<td>ER positive (n)§</td>
<td>47</td>
<td>875</td>
<td>848</td>
<td>439</td>
<td>257</td>
<td></td>
</tr>
<tr>
<td>Rate†</td>
<td>3.9</td>
<td>3.6</td>
<td>4.2</td>
<td>4.5</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI) ‡</td>
<td>1.10 (0.82 to 1.49)</td>
<td>Reference</td>
<td>1.17 (1.07 to 1.29)</td>
<td>1.25 (1.11 to 1.41)</td>
<td>1.34 (1.16 to 1.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ER negative (n)§</td>
<td>8</td>
<td>199</td>
<td>160</td>
<td>82</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Rate†</td>
<td>0.7</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI) ‡</td>
<td>0.86 (0.42 to 1.75)</td>
<td>Reference</td>
<td>0.96 (0.78 to 1.18)</td>
<td>0.98 (0.76 to 1.27)</td>
<td>0.95 (0.68 to 1.32)</td>
<td>.8</td>
</tr>
</tbody>
</table>

* Underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight 25.0–29.9 kg/m², obese I 30.0–34.9 kg/m² and obese II/III (≥35.0 kg/m²). Normal BMI (18.5–24.9) is the reference group. Multivariable analyses were adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native American/Native Alaskan, or other/mixed race), age (40–49, 50–54, 55–59, 60–64, 65–69, ≥70 y), and mammography use (within 1 y [9–17 mo], 2 y [18–29 mo], or 3 y or longer [≥30 mo] or first screening examination, or first diagnostic examination) and registry.

† Calculation excludes underweight women. $P_{\text{trend}}$ values (two-sided) were calculated using asymptotic chi-square distribution of the likelihood ratio statistic.

‡ Multivariable analyses were adjusted for race/ethnicity (non-Hispanic White, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native American/Native Alaskan or other/mixed race), age (40–49, 50–54, 55–59, 60–64, 65–69, ≥70 y), and mammography use (within 1 y [9–17 mo], 2 y [18–29 mo], or 3 y or longer [≥30 mo] or first screening examination, or first diagnostic examination) and registry.

§ Large invasive tumors greater than 15 mm in diameter, advanced stage IIb, III, or IV, high-grade invasive 3 or 4, estrogen receptor (ER)–positive or –negative invasive tumors.

Thus, it seems unlikely that differences in breast cancer detection across BMI categories led to a higher rate of advanced disease in obese and overweight women than among lower weight women. For women with a BMI of 25 kg/m² or greater who underwent mammography, the population attributable fraction for breast cancer, large invasive cancer, and advanced-stage breast cancer was 8.9%, 12.0%, and 16.3%, respectively, adjusting for age, race, and mammography registry and use.

Discussion

Among postmenopausal women not using HT, those who were overweight or obese had higher rates of breast cancer and advanced-stage disease than normal-weight women, regardless of mammography use before breast cancer diagnosis, suggesting that the relationship between BMI and cancer outcomes is not due chiefly to differences in mammography exposure. Moreover, differential cancer detection on mammography examinations across a range of BMI did not contribute to the higher rate of advanced disease observed among women with higher BMI because the rate of non-screen-detected breast cancer (ie, false-negative cancer) was similar among overweight and obese women compared with normal-weight and underweight women. Taken together, these findings suggest the difference in advanced-stage disease across BMI groups is only partly explained by mammography use or mammography accuracy; therefore, biologic differences in breast tumor development and/or progression are likely to contribute to the greater risk of advanced disease in overweight and obese women.

Three other studies (6,11,39) have examined whether obese postmenopausal women are more likely to be diagnosed with advanced-stage disease. One study (6) found that postmenopausal women are more likely to have regional or distant metastasis if their BMI is more than 25 kg/m²; their findings are more pronounced among women who self-reported one or fewer mammography examinations in the last 3 years compared with women who had more than one examination. A small study (11) found no association between BMI and advanced-stage disease among women younger than age 55 years or women aged 55 years and older. A study of modest size (39) showed that adult weight gain was associated with increased risk of regional or distant metastasis among women who regularly undergo screening mammography. We extend the literature by showing that rates of advanced-stage disease among postmenopausal women not on HT increased across increasing categories of BMI even after accounting for actual mammography use before breast cancer diagnosis. If differences in mammography use contributed to increasing rates of advanced-stage disease across BMI groups, one would expect primarily an increase in advanced disease or higher absolute increases in rates of advanced- vs early-stage disease with increasing BMI. However, we observed similar absolute increases in the rates of early and advanced stages of breast cancer with increasing BMI even after accounting for mammography use, which suggests that...
BMI categories. race, and registry distribution of the study population. Time between
Figure 1
body mass index (BMI) kg/m² and mammography use adjusted for age,
mammography examination per 1000 mammography examinations by
35.0 kg/m²). Tests for trend apply for normal BMI and higher

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>0.58 (0.14 to 2.35)</td>
<td>1.56 (0.37 to 6.52)</td>
<td>0.33 (0.05 to 2.36)</td>
</tr>
<tr>
<td>Normal</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
<td>1.0 (Referent)</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.04 (0.76 to 1.44)</td>
<td>1.23 (0.75 to 2.02)</td>
<td>1.23 (0.85 to 1.79)</td>
</tr>
<tr>
<td>Obese I</td>
<td>1.27 (0.86 to 1.87)</td>
<td>2.96 (1.83 to 4.79)</td>
<td>1.36 (0.88 to 2.10)</td>
</tr>
<tr>
<td>Obese II/III</td>
<td>1.42 (0.88 to 2.30)</td>
<td>3.15 (1.82 to 5.44)</td>
<td>2.13 (1.37 to 3.31)</td>
</tr>
<tr>
<td>P_total</td>
<td>.1</td>
<td>&lt;.001</td>
<td>.001</td>
</tr>
</tbody>
</table>

Elmore et al. (22) reported that the sensitivity of mammography did not vary by BMI yet reported a statistically significantly lower proportion of DCIS and a similar proportion of advanced-stage cancer among overweight and obese women compared with normal-weight women. We did not find a lower proportion of DCIS among overweight and obese women compared with normal-weight women and by examining these rates were able to show that the rates of DCIS and advanced disease increased with increasing BMI category.

We hypothesize that obese postmenopausal women are at higher risk of advanced-stage breast cancer than normal-weight women, in part because obesity increases exposure to high levels of circulating estradiol, which promotes and increases rate of tumor growth. Compared with postmenopausal women with a normal BMI, those with higher BMI have twofold higher levels of circulating estrogens and lower levels of sex hormone–binding globulin and thus more bioavailable estrogens (12). Although there is evidence that serum estradiol levels are associated with risk of incident breast cancer, we are unaware of any published studies that demonstrate an association between serum estradiol levels and extent of advanced invasive cancer. Indirect evidence from studies of exogenous hormone use demonstrates that use of estrogen and progestin postmenopausal HT for 5 years or more increases the likelihood of developing advanced-stage invasive breast cancer (25,41). The higher rate of advanced disease in long-term users of estrogen and progestin compared with nonusers suggests that sex hormones may act synergistically to promote tumorigenesis and more rapid tumor growth (42,43). The influence of hormones on rapid tumor growth is further supported by our observation that the rate of high nuclear grade, a marker of the biology of the tumor, increased with increasing BMI.
Table 3. Rates and odds ratios (ORs) with 95% confidence intervals (CIs) of breast cancer by stage groups within 12 mo of a mammography examination per 1000 examinations by body mass index (BMI), adjusted for age, ethnicity/race, and mammography registry and use*

<table>
<thead>
<tr>
<th>Stage</th>
<th>BMI category</th>
<th>0 (no. of cases)</th>
<th>1 (no. of cases)</th>
<th>IIa (no. of cases)</th>
<th>IIIb (no. of cases)</th>
<th>IIIIV (no. of cases)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underweight</td>
<td>Normal</td>
<td>Overweight</td>
<td>Obese</td>
<td>Obese III/IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>%†</td>
<td>%†</td>
<td>%†</td>
<td>%†</td>
<td>%†</td>
<td>Reference</td>
<td>0.59 (0.19 to 1.87)</td>
<td>Reference</td>
<td>1.05 (0.78 to 1.40)</td>
</tr>
<tr>
<td></td>
<td>23.0 (17)</td>
<td>17.5 (267)</td>
<td>17.1 (245)</td>
<td>16.4 (121)</td>
<td>20.0 (87)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.5</td>
<td>1.1</td>
<td>1.2</td>
<td>1.2</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1 (0.86 to 2.30)</td>
<td>Reference</td>
<td>1.12 (0.94 to 1.33)</td>
<td>1.14 (0.92 to 1.42)</td>
<td>1.46 (1.14 to 1.87)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>3.0</td>
<td>3.1</td>
<td>3.4</td>
<td>3.6</td>
<td>3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.96 (0.68 to 1.34)</td>
<td>Reference</td>
<td>1.09 (0.99 to 1.21)</td>
<td>1.16 (1.02 to 1.32)</td>
<td>1.18 (1.00 to 1.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.9 (14)</td>
<td>18.7 (285)</td>
<td>20.4 (288)</td>
<td>17.8 (131)</td>
<td>16.3 (71)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>1.2</td>
<td>1.2</td>
<td>1.4</td>
<td>1.3</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.02 (0.59 to 1.75)</td>
<td>Reference</td>
<td>1.22 (1.04 to 1.44)</td>
<td>1.13 (0.91 to 1.39)</td>
<td>1.13 (0.82 to 1.40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.8 (5)</td>
<td>7.0 (107)</td>
<td>7.1 (101)</td>
<td>8.5 (63)</td>
<td>9.7 (42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>0.4</td>
<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.96 (0.39 to 2.37)</td>
<td>Reference</td>
<td>1.16 (0.88 to 1.52)</td>
<td>1.45 (1.06 to 1.99)</td>
<td>1.70 (1.17 to 2.45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1 (3)</td>
<td>6.6 (100)</td>
<td>6.0 (85)</td>
<td>9.1 (67)</td>
<td>9.9 (43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>0.2</td>
<td>0.4</td>
<td>0.4</td>
<td>0.7</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>0.59 (0.19 to 1.87)</td>
<td>Reference</td>
<td>1.05 (0.78 to 1.40)</td>
<td>1.67 (1.22 to 2.29)</td>
<td>1.95 (1.35 to 2.83)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), obese I (30.0–34.9 kg/m²), and obese II/III (≥35.0 kg/m²). Normal BMI 18.5–24.9 is the reference group. Multivariable analyses were adjusted for race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native American/Native Alaskan, or other/mixed race), age (40–49, 50–54, 55–59, 60–64, 65–69, ≥70 y), and mammography use (within 1 y [9–17 mo], 2 y [18–29 mo], or 3 y or longer [≥30 mo] or first screening examination, or first diagnostic examination) and registry.
† Column percentage.
‡ Calculation excludes underweight women. P values (two-sided) were calculated using the asymptotic chi-square distribution of the likelihood ratio statistic.

This study has several strengths, including the large, population-based study sample, medical record documentation of mammography use and interpretation, large number of outcomes, and diversity by age, race/ethnicity, and geography. We also were able to examine the association of BMI and breast cancer among women not using HT, the group in whom the association is the strongest. Most reports dichotomize women into two BMI groups (≤25 kg/m²), whereas we were able to report results according to the five standard BMI categories.

Our study also has some potential limitations. Height and weight were self-reported rather than directly measured. Correlation of self-reported height and weight with measured height and weight has been reported to be high (44,45), yet overweight women tend to underestimate their weight. Misclassification of obese women to lower BMI categories because of inaccurate self-report, and exclusion of women who did not report their weight may have led to an underestimation of the true association between obese II/III and breast cancer. Although we were able to show the rate of breast cancer increased across BMI groups separately among white women and Hispanic women, we were not able to conduct subgroup analyses for black women or Native American or Native Alaskan women because of insufficient numbers of women with breast cancer. We also did not have sufficient numbers of black, Hispanic, and Native American or Native Alaskan women to report advanced disease rates by BMI category adjusted for mammography use. We conducted a prospective observational study; thus, we

Table 4. Sensitivity and 95% confidence intervals (CIs) of screening mammography and rate of screen-detected and non-screen-detected cancer within 12 mo of a mammography examination per 1000 screening examinations by body mass index (BMI) and mammography use group, adjusted for age, race, and mammography registry*.

<table>
<thead>
<tr>
<th>Measure</th>
<th>BMI category</th>
<th>1 y (95% CI)</th>
<th>2 y (95% CI)</th>
<th>≥3 y or first screen (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>BMI &lt;25.0 kg/m²</td>
<td>79.9 (76.3 to 82.7)</td>
<td>84.0 (79.3 to 87.6)</td>
<td>91.0 (86.9 to 93.7)</td>
</tr>
<tr>
<td></td>
<td>BMI ≥25.0 kg/m²</td>
<td>86.1 (83.5 to 88.1)</td>
<td>89.0 (85.9, 91.2)</td>
<td>92.6 (89.8 to 94.4)</td>
</tr>
<tr>
<td>P</td>
<td>.001</td>
<td>.04</td>
<td>.4</td>
<td></td>
</tr>
<tr>
<td>Screen-detected, rate per 1000 examinations†</td>
<td>BMI &lt;25.0 kg/m²</td>
<td>3.1 (2.8, 3.4)</td>
<td>4.3 (3.8 to 4.8)</td>
<td>7.4 (6.5 to 8.4)</td>
</tr>
<tr>
<td></td>
<td>BMI ≥25.0 kg/m²</td>
<td>4.0 (3.7 to 4.3)</td>
<td>5.8 (5.3 to 6.3)</td>
<td>9.2 (8.4 to 10.1)</td>
</tr>
<tr>
<td>P</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Non-screen-detected, rate per 1000 examinations†</td>
<td>BMI &lt;25.0 kg/m²</td>
<td>0.8 (0.7 to 1.0)</td>
<td>0.8 (0.6 to 1.1)</td>
<td>0.7 (0.5 to 1.1)</td>
</tr>
<tr>
<td></td>
<td>BMI ≥25.0 kg/m²</td>
<td>0.6 (0.6 to 0.8)</td>
<td>0.7 (0.6 to 0.9)</td>
<td>0.7 (0.6 to 1.0)</td>
</tr>
<tr>
<td>P</td>
<td>.1</td>
<td>.5</td>
<td>.9</td>
<td></td>
</tr>
</tbody>
</table>

* P values (two-sided) comparing BMI of <25.0 with ≥25.0 kg/m² were calculated using the asymptotic chi-square distribution of the likelihood ratio statistic.
† Breast cancer detected within 12 mo of positive screening mammography result.
‡ Breast cancer detected within 12 mo of negative screening mammography result.
cannot definitely prove causation. However, the dose response we observe of higher advanced breast rates with higher BMI after accounting for mammography use suggests that being overweight or obese contributes to higher risk of advanced breast cancer.

In summary, in this analysis of postmenopausal women not using HT, we observed higher rates of advanced-stage cancer among overweight and obese than normal-weight women, even after taking into account prior mammography exposure and accuracy. The association of higher BMI and advanced disease was moderate. However, because overweight or obesity is highly prevalent among postmenopausal women, a large number of advanced breast cancers may be attributed to being overweight or obese in the US population. Obesity is one of the few modifiable risk factors for breast cancer, and losing weight has been shown to decrease breast cancer risk in some observational studies (4). Screening mammography is the only secondary prevention measure that has been proven to decrease breast cancer mortality by detection of early-stage disease among women who undergo mammography every 1–2 years (46). Our results suggest that postmenopausal women who are overweight or obese—a large proportion in the United States (58% of women in our study)—should be encouraged to lose weight and to undergo routine screening mammography, two factors that may decrease the number of women who are diagnosed with advanced disease.

References

18. Ostbye T, Taylor DH, Yancy WS, Krause KM. Associations between obesity and receipt of screening mammography, papanicolaou tests, and influenza vaccination: results from the health and retirement study (hrs) and the asset and health dynamics among the oldest old (ahead) study. Am J Public Health. 2005;95(9):1623–1630.

**Funding**
NCI-funded Breast Cancer Surveillance Consortium cooperative agreement (U01CA63740, U01CA86076, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040). The collection of cancer incidence data used in this study was supported in part by several state public health departments and cancer registries throughout the United States. For a full description of these sources, please see: http://breastscreening.cancer.gov/work/acknowledgement.html.

**Note**
Manuscript received May 17, 2008; revised September 1, 2008; accepted September 30, 2008.