Collaborative modeling of the impact of obesity on race-specific breast cancer incidence and mortality

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Abstract Obesity affects multiple points along the breast cancer control continuum from prevention to screening and treatment, often in opposing directions. Obesity is also more prevalent in Blacks than Whites at most ages so it might contribute to observed racial disparities in mortality. We use two established simulation models from the Cancer Intervention and Surveillance Modeling Network (CISNET) to evaluate the impact of obesity on race-specific breast cancer outcomes. The models use common national data to inform parameters for the multiple US birth cohorts of Black and White women, including age- and race-specific incidence, competing mortality, mammography characteristics, and treatment effectiveness. Parameters are modified by obesity (BMI of $\geq 30$ kg/m$^2$) in conjunction with its age-, race-, cohort- and time-period-specific prevalence. We measure age-standardized breast cancer incidence and mortality and cases and deaths attributable to obesity. Obesity is more prevalent among Blacks than Whites until age 74; after age 74 it is more prevalent in Whites. The models estimate that the fraction of the US breast cancer cases attributable to obesity is 3.9–4.5 % (range across models) for Whites and 2.5–3.6 % for Blacks. Given the protective effects of obesity on risk among women <50 years, elimination of obesity in this age group could increase cases for both the races, but decrease cases for women $\geq 50$ years. Overall, obesity accounts for 4.4–9.2 % and 3.1–8.4 % of the total number of breast cancer deaths in Whites and Blacks, respectively, across models. However, variations in obesity prevalence have no net effect on race disparities in breast cancer mortality because of the opposing effects of age on risk and patterns of age- and race-specific prevalence. Despite its modest impact on breast cancer control and race disparities, obesity remains one of the few known modifiable risks for cancer and other diseases, underlining its relevance as a public health target.

Keywords Simulation modeling · Breast cancer · Disparities · Obesity

Introduction

The burden of breast cancer has been decreasing over time [1, 2], but mortality gaps between Black and White women have been persistent [3]. The higher mortality rate for Black women is particularly striking now, given virtually equivalent screening rates and lower incidence than White women [4, 5]. Racial differences in breast cancer outcome are cast on a backdrop of an obesity epidemic that disproportionately affects Black women. Currently, more than 50 % of Black women are obese (defined as a BMI of $\geq 30$ kg/m$^2$), compared to 32.0 % of White women [6, 7] but there are exceptions to this overall trend, with Whites having higher rates of obesity after age 74 [6–8].
Obesity exerts numerous, often opposing effects on the chain of events leading to possible death from breast cancer. It increases breast cancer incidence in post-menopausal women, but reduces risk in pre-menopausal women [9–13]. Obesity also leads to more favorable tumor types [13, 14], greater sensitivity of detection [15], but more advanced stage [16–18], lower treatment effectiveness [19, 20], and greater competing mortality [8, 21, 22]. The Institute of Medicine recently noted that simulation modeling is particularly useful for evaluating the net impact of a factor such as obesity that affects multiple points in a disease process differentially [23]. Modeling is also helpful in evaluating the role obesity plays in racial disparities by providing a “virtual laboratory” to evaluate the impact of varying conditions that cannot be readily tested in the population, such as the net impact of reductions in obesity prevalence on breast cancer rates [24, 25].

In this article, we use two established, independent simulation models to evaluate how obesity affects breast cancer incidence and mortality in US Black and White women. We also investigate how much of the disparity in breast cancer mortality is due to the differential prevalence of obesity. Our results are intended to inform debates about effective strategies to reduce racial gaps in breast cancer mortality and reduce the burden of breast cancer for all women.

Methods

The two models, called MISCAN and SPECTRUM, were developed within the Cancer Intervention and Surveillance Modeling Network (CISNET) [26] and were exempt from institutional review board approval. The models have been described in detail elsewhere [2, 24, 27, 28]. Briefly, both are discrete event-driven, continuous-time state transition models that project US breast cancer population trends in the absence of screening or treatment and then overlay screening and adjuvant treatment diffusion over time. Breast cancer is depicted as having a preclinical screen-detectable period (sojourn time) and a clinical detection point. On the basis of mammography sensitivity (or thresholds of tumor size detection), screening identifies disease in the preclinical screen-detectable period and results in the identification of earlier stage or smaller, more curable tumors than might occur via clinical detection, resulting in reduced breast cancer mortality. Age at diagnosis, estrogen-receptor (ER) and human epidermal growth factor-2 (HER2) status and tumor size- or stage-specific treatment have independent effects on probability of a cure (or survival). Women can die of breast cancer or of other causes.

MISCAN portrays tumor growth, where tumors can be detected once they are larger than a detection threshold and cured if the diameter at detection is below a fatal threshold. In SPECTRUM, tumors progress through stages, with screening effects due to age- and stage-shifts and treatment reducing the hazard of death. In both, ductal carcinoma in situ (DCIS) can regress, remain and be diagnosed, or progress to invasive cancer. In previous collaborations, the models generated similar estimates of incidence and mortality [2, 24, 29].

Model parameters

Using data from clinical trials and epidemiological studies, the models employ a common set of parameters to portray race-specific effects and then superimpose the impact of obesity on each parameter (Table 1). Each includes model-specific parameters to represent sojourn, lead, and dwell time within stages or tumor diameter growth times and stage distribution or tumor size [2, 24, 27, 28].

Demographic data and obesity

The population consists of cohorts of US Black and White women born between 1890 and 2010 [30]. We start in 1890 to project prevalent cancers in the 1970s. Women are assigned to being obese or non-obese based on rates observed for their age, birth cohort, race, and the calendar year using prevalence data from the National Health and Nutrition Examination Survey I (1970–1975), II (1976–1980), III (1988–1994), and 1999–2004 [8]. These data are extrapolated to 2009–2010 using the most recent NHANES data [7]. We do not allow transitions from obese to non-obese (or back again to obese) because there are insufficient data on how such transitions would affect all the model parameters.

Breast cancer incidence

Breast cancer incidence in the absence of screening is based on an age-period-cohort (APC) model [31]. We extrapolate forward based on rates in 2000 so do not capture the more recent decrease in incidence [32]. The APC model is adapted for Black women using an age-specific relative risk (RR) based on Black versus White incidence [24]. Based on a synthesis of studies, obesity is modeled as increasing breast cancer incidence in post-menopausal women by a RR of 1.25 and decreasing rates in pre-menopausal women by a RR of 0.60 [9–11, 33].

Mammography

The dissemination of mammography is depicted based on the age of receipt of the first mammography and the interval between subsequent mammograms using data from the Breast Cancer Surveillance Consortium (BCSC)
This parameter was extended using BCSC data to include different screening rates and intervals for Blacks and Whites [36, 37]. Mammography use does not generally vary by BMI (except for the extremes for underweight and extremely obese) [38], so we assume obesity has no effect on mammography dissemination.

Sensitivity and specificity of mammographic screening for DCIS and invasive cancer were estimated by age group (under and over 50), screening round (first or subsequent), and obesity group using unpublished BCSC data [39]. There was no difference in test characteristics by race.

### Stage distribution

The tumor stage distribution in the absence of screening for Black and White women was estimated from the SEER Table 1: Common model input parameters

| Parameter                | Race-specific Source | Obesity-specific Source | Source |
|--------------------------|----------------------|-------------------------|--------|
| Births                   | Birth cohorts born from 1890 to 2000 by race [30] | –                      | [74, 75] |
| Obesity prevalence      | Race, cohort and year-specific [74, 75] | –                      | [9–11, 33] |
| Incidence                | Age-period cohort model with age-specific relative risk of Black versus White incidence [24, 31] | For obese (BMI > 30) vs. non-obese: <50: RR 0.6 (95 % CI 0.4–1.0) 50+: RR 1.25 (95 % CI 1.1–2.0) Assume obesity effect equal by race | [9–11, 33] |
| Mammography use          | Dissemination based on age- and race-specific rates for first and subsequent exams and intervals between screenings. [34–37] | Assume obesity does not affect rate of screening | [38] |
| Mammography sensitivity  | Age-specific rates for first and subsequent screening exams; equal by race based on unpublished BCSC data. [39] | BMI-specific Unpub. BCSC data | – |
| Sojourn time             | 2 years if age ≤40 | Assume sojourn time is equal across BMI categories. | – |
| ER/HER2                  | Regression model using NCCN data from 2,646 women [24] | Risk of ER+ breast cancer, obese vs. non-obese: <50: RR 0.86 (95 % CI 0.77–0.95) 50+: RR 1.78 (95 % CI 1.50–2.11) Assume no effect HER2 | [14] |
| Mean stage dwell time    | DCIS 5 years | Assume no effect of obesity | – |
| Stage distribution       | Unscreened varies by age, race and year [40], Unpub. BCSC data | BMI-specific stage Unpub. BCSC data | – |
|                          | Screened varies by age and race | –                      | – |
| Survival without Rx      | Survival by race from SEER in 1975–1979 [40] | Assume no effect of obesity on breast cancer-specific survival | – |
| Treatment dissemination  | Blacks 22 % less likely to receive chemo; 10 % (≤age 50) to 15 % (age 50+) less likely to get hormonal Rx than Whites [43, 44] | Obesity has no effect on treatment dissemination | [52] |
| Treatment effectiveness  | Meta-analyses of randomized trial results; assume treatment effectiveness is equal by race [47–51] | Reduce hazard ratios by 0.55 for obese ER-negative women who receive dose reductions; 30 % of obese women have a dose-reduction [19, 20] | – |
| Other cause mortality    | Age-, race-, and cohort-specific all-cause mortality rates by year [54, 55] | NHANES-linked mortality database [8] | – |
data in 1975–1979 before widespread use of mammography [40] and updated over time using race-specific BCSC data for unscreened (clinically detected) women. Stage distributions among screened women were estimated using race-specific BCSC data from 1996 to 2007 by screening intervals and first versus subsequent screen detection (unpublished data).

Obesity is associated with more advanced tumors at diagnosis overall [16, 41] and in Blacks and Whites [17, 18], even after accounting for mammography use [15]. Therefore, we used BCSC data stratified by BMI and age group to represent the impact of obesity on stage for unscreened and screened women of both races.

Tumor biomarkers

We estimated the joint distribution of ER and HER2 status by age, year, stage, and race using data from 1997 to 2005 [24, 42]. As obesity affects the rate of ER+ tumors differentially by menopausal status [14], we applied RRs of 0.86 and 1.78 to the probability of having ER+ cancer among obese women <50 and 50+, respectively. We assumed that

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**Fig. 1** Model predicted age-adjusted breast cancer incidence and mortality by model, race and calendar year versus observed SEER rates for US women age 25+. The figure shows the comparison between model predictions and observed SEER rates for breast cancer incidence and mortality from 1975 to 2015, with separate plots for different models (SPECTRUM, MISCAN) and race (white, black).
obesity had no direct impact on ER– tumors. There were insufficient data on obesity and HER2, so we assumed that obesity had no impact on HER2 distribution.

Treatment

Age-, year-, AJCC stage (or tumor size), and ER/HER2-specific use of adjuvant hormonal and chemotherapy as disseminated from 1975 to 2000 was estimated from NCI’s Patterns of Care studies [43, 44] and updated through 2010 using unpublished data from the National Comprehensive Cancer Network (NCCN) Outcomes Database. Compared to White women, Black women were 22 % less likely to receive multi-agent chemotherapy and 10 % (age <50) to 15 % (age 50+) less likely to receive hormonal therapy. These Black–White differences were applied to the treatment dissemination curves. Obese and non-obese women had similar treatment patterns and obesity did not modify treatment in Blacks [45].

Women with ER+ invasive tumors receive hormonal treatment (tamoxifen from 1980 to 1999; tamoxifen if <50 years and anastrozole if ≥50 years from 2000 to present) and non-hormonal treatment (CMF or anthracycline-based regimen from 1975 to 1999; anthracycline-based plus taxanes from 2000 to present). Women with ER– invasive tumors receive non-hormonal therapy only. Women with DCIS and ER+ tumors receive hormonal therapy. Women with HER2+ tumors received trastuzumab beginning in 2005 [46].

Treatment effectiveness is based on RCTs [47–50]. Hormonal and chemotherapy regimens are equally effective in Black and White women [51]. We adjusted survival to reflect the fact that ~30 % of obese patients experience dose reductions and that ER– cases having dose-reductions experience decrements in survival of 55 % [52, 53].

Table 2 Projected breast cancer incidence in 2012 among women 25+ by race, obesity, and model

| Model          | White                  | Black                  |
|----------------|------------------------|------------------------|
|                | Obese | Non-obese | All | Obese | Non-obese | All |
| SPECTRUM model | Age-adjusted incidence rate per 100,000 | 300.3 | 267.4 | 277.4 | 247.6 | 223.7 | 229.8 |
|                 | # of cases |   | 91,688 | 175,643 | 267,331 | 11,619 | 17,461 | 29,080 |
|                 | Proportion of cases in the US population attributable to obesity | 4.5 % |  |  | 3.6 % |  |
| MISCAN model   | Age-adjusted incidence rate per 100,000 | 290.7 | 258.2 | 267.5 | 252.7 | 223.0 | 229.7 |
|                 | # of cases |   | 88,989 | 172,768 | 261,757 | 11,463 | 17,717 | 29,180 |
|                 | Proportion of cases in the US population attributable to obesity | 3.9 % |  |  | 2.5 % |  |

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* For comparability the model outputs for both race groups are age adjusted using the standard US million-population

b The number of cases is calculated from the model projected age- and race-specific rates, the age- and race-specific population distribution projected for 2010, and the age- and race-specific prevalence of obesity
c The attributable fraction of cases in the overall US population that are due to obesity is estimated by the prevalence of obesity * (incidence in obese – incidence in non-obese)/(prevalence of obesity * incidence in obese + (1 – prevalence of obesity) * incidence in non-obese)
No adjustment was applied for ER+ patients. We assumed that the impact of dose reductions was the same across all race groups and that obesity had no effects on treatment effectiveness of hormonal or trastuzumab therapy [9].

**Mortality**

SEER data from 1975 to 1979 were used to estimate breast cancer survival before screening and adjuvant treatment was available. Age-, race- and cohort-specific non-breast cancer mortality were calculated by subtracting breast cancer from all-cause mortality [54, 55]. The impact of obesity on non-breast cancer mortality was derived from NHANES-mortality linked data [8].

**Analysis**

The models simulate 1975–2020 age-adjusted breast cancer incidence and mortality rates for Black and White obese and non-obese women; adjustment is based on the standard US million population. This common referent population allows comparisons of results, as the age distributions of the population differ by race and obesity status. Overall, the US rates were estimated using a prevalence-weighted sum of the age-adjusted rates for the obese and non-obese women. Age-specific rates by race are used with the projected 2010 age-specific distribution of the respective populations [56] weighted by obesity prevalence to calculate numbers of cases and deaths. Additionally, we calculate the fraction of cases and deaths attributable to obesity. Finally, we investigate the effect of obesity on the difference in mortality between White and Black women, after considering the effect of race-differences in demographics, incidence, natural history, screening use alone, adjuvant treatment use alone, and both screening and treatment. To this end, we sequentially substitute parameter values relating to these factors in the White version of the models with corresponding values from the Black version. In the final step, we add the prevalence of obesity among Blacks to the models. At each step, we compute the fraction of the mortality difference between White and Black women explained by each factor. The predicted breast cancer mortality rates at each step are also compared to the 3-year average of observed rates for Black women [3].

**Model validation**

The model validation has been described in previous publications [27, 28]. Results from two models provide implicit cross-validation, a range of plausible impacts of obesity, and a measure of uncertainty. Internal reliability was evaluated by combining incidence and mortality rates for obese and non-obese women in proportion to their age- and race-specific prevalence of obesity to verify that we reproduced overall population rates. Reliability of the model adaptations for obesity was also evaluated by comparing model outputs to observed SEER data.

**Results**

Observed incidence trends were accurately reproduced by both models. Mortality rates are reproduced for White women, and the shape of the curve is similar for Blacks, but lower than SEER (Fig. 1). The models mirror observed data showing that stage distribution (or tumor size) is more favorable in White than in Black women, but the models predict a slightly more favorable distribution for Blacks than actually observed (Fig. 2).

Impact of obesity on incidence

Obesity increases the incidence of breast cancer for both races, and the fraction of cases attributable to obesity is similar for Whites (3.9–4.5 %, across models) and Blacks (2.5–3.6 %) (Table 2; Fig. 3). The net impact of obesity on incidence is the result of opposing risk by age. The predicted incidence in obese women <50 years is 37–47/100,000 for Whites and 32–44/100,000 for Blacks. Among non-obese White and Black women <50 years, the corresponding rates are 47–60/100,000 and 43–60/100,000, respectively. Thus, elimination of obesity would actually increase the number of cases among women <50 years. For women aged 50+, obesity accounts for 5.5–6.4 % and 5.3–8.1 % of cases for White and Black women, respectively (data not shown).

Impact of obesity on breast cancer mortality

Obesity increases mortality rates for both race groups and accounts for 4.4–9.2 % and 3.1–8.4 % of the total deaths for Whites and Blacks, respectively, across models (Table 3; Fig. 4). This translates into 1,400–3,552 deaths in Whites and 148–412 deaths in Blacks that could be avoided each year if obesity were eliminated. Among women <50 years, obesity decreases death rates given the large decrease in incidence associated with its protective effects. For women age 50+ of both race groups, obesity accounts for about 5.1–11.5 % of the deaths in the overall US population.

Obesity and impact on Black–White differences in rates

The observed age-adjusted mortality rate was 33.9/100,000 in Whites and 48.1/100,000 in Blacks from 2007 to 2009.
In Table 4, these values are compared to model predictions based on sequential replacement of parameter values in the White model by those from the Black model to test how much the higher prevalence of obesity in Black compared to White women affects the differences in mortality. As can be seen in Step 6, there is no net effect of race differences in obesity prevalence on mortality disparities. This result occurs because the higher prevalence of obesity among Black versus White women decreases cases and deaths among the oldest women. Thus, differences in obesity prevalence do not account for the net age-adjusted mortality disparities between Blacks and Whites.

Discussion

This is the first study to use collaborative modeling to evaluate the impact of obesity on breast cancer incidence and mortality in White and Black women and to assess whether differences in obesity prevalence account for race disparities in mortality. We found that obesity accounts for...
about 3–4 % of the cases and 3–9 % of the deaths in both the race groups. Variations in obesity prevalence have no net effect on the mortality differences between Blacks and Whites.

The overall modest impact of obesity represents the balance of an increase in cases/deaths among a large number of post-menopausal women and a decrease among a smaller number of pre-menopausal women. The obesity attributable fraction of 5.3–8.1 % of cases among White and Black women 50 years and older we observed is similar to, but lower than prior US (8.9 %) [15] and UK estimates (8.7 %) because those included both overweight and obese women [57]. If obesity were eliminated we could avoid more than 12,000 cases among White women and 1,000 in Black women. There are few measures that can prevent so many breast cancer cases, except perhaps Tamoxifen use by high-risk women [58].

Obesity accounts for <10 % of breast cancer deaths across race groups. For colorectal cancer, elimination of obesity and other risk factors could reduce mortality by up to 16 % [59]. Decreasing obesity has other important effects on health, such as reductions in risk of other cancers and heart disease, and could lower health care costs [21, 22, 60], making it an important public health target.

Obesity is a modest but potentially meaningful target in reducing the burden of breast cancer, but it does not appear to account for net racial differences in age-adjusted mortality. This conclusion is consistent with the recent finding of Lu et al. [63] that obesity did not affect breast cancer survival in Blacks ages 35–64, although it had a modest impact for Whites. Unfortunately, that study did not have information on treatment. Others have found that adjusting for obesity does not remove Black–White differences in deaths from breast cancer [64, 65].

Our approach builds on and extends prior modeling of the impact of obesity on cancer outcomes [59] by incorporating the impact of obesity on incidence, screening, and treatment parameters and examining results separately by race. Despite the strengths of our approach, there are some caveats that should be considered in evaluating the results. First, although weight can change over the life course [25], we modeled obesity as constant after onset given the unavailability of data to link changes in weight to the multiple input parameters. This may underestimate the impact of obesity because a transition from non-obese to obese around menopause, which is a common pattern, maximizes risk during both periods. Next, as in other models we consider two categories of obesity:

| Table 3 Projected breast cancer mortality in 2012 among women 25+ by race, obesity, and model |
|-----------------------------------------------|
| White | Non-obese | All (weighted sum of obese + non-obese) | Black | Non-obese | All (weighted sum of obese + non-obese) |
|-----------------------------------------------|
| SPECTRUM model | Age-adjusted mortality rate per 100,000 | 44.8 | 33.4 | 36.6 | 47.8 | 36.3 | 39.2 |
| # of deaths from breast cancer | 14,363 | 24,398 | 38,761 | 2,059 | 2,872 | 4,931 |
| Proportion of deaths in the US population attributable to obesity | 9.2 % | 8.4 % |
| MISCAN Model | Age-adjusted mortality rate per 100,000 | 35.8 | 30.9 | 32.2 | 41.1 | 36.0 | 37.3 |
| # of deaths from breast cancer | 10,780 | 21,052 | 31,832 | 1,846 | 2,863 | 4,709 |
| Proportion of deaths in the US population attributable to obesity | 4.4 % | 3.1 % |

* For comparability the model outputs for both race groups are age adjusted using the standard US million-population

* The number of deaths was calculated from the model projected age- and race-specific rates, the age- and race-specific population distribution projected for 2010, and the age and race-specific prevalence of obesity

* The attributable fraction of deaths in the overall US population that are due to obesity is estimated by prevalence of obesity * (mortality in obese – mortality in non-obese)/(prevalence of obesity * mortality in obese + (1 – prevalence of obesity) * mortality in non-obese)
of obesity [59] but do not consider an overweight category or body fat distribution, given the paucity of consistent epidemiological data across parameters for a wider range of characterizations. Others have not found a difference in estimates of risk [66] or survival [67] based on different categorizations of weight and there is no consistent evidence to suggest that level of obesity interacts with race in its effects on cancer incidence [66]. Obesity is also the net result of diet and physical activity, and these factors may affect survival [68, 69]. However, it remains difficult to separately estimate the impact of these components (or their molecular correlates) [70–73] on the prevention, screening, treatment, and survival parameters included in the models. This is an important area for future research [25]. Until then, our results are useful as obesity is the most robustly related to breast cancer outcomes among measures of energy balance [66, 67].

Overall, these results represent the first comprehensive examination using comparative modeling of obesity and how it affects the entire breast cancer process from risk of disease to the type of disease at presentation and treatment impact in the context of competing mortality. The results indicate that obesity exerts a modest impact on breast cancer and does not explain net race disparities in outcome. However, obesity remains one of the few known modifiable risk factors for this and other diseases, increasing its relevance as a public health target for all women.
Table 4 Model predictions of breast cancer mortality differences between Black and White women ages 25+ in the US in 2012—impact of prevalence of obesity

| Step 1: | Step 2: | Step 3: | Step 4: | Step 5: | Step 6: | Model predicted (White) | SEER observed 2007–2009 (White) | Model predicted (Black) | SEER observed 2007–2009 (Black) |
|---------|---------|---------|---------|---------|---------|-------------------------|-------------------------------|-------------------------|--------------------------------|
| Mortality per 100,000 | 36.6 | 30.7 | 36.9 | 37.5 | 38.9 | 39.6 | 39.4 | 39.4 |
| Difference (observed – predicted) | 17.4 | 11.2 | 10.6 | 9.2 | 8.5 | 8.7 |
| % explained by replaced value | 35.6 % | 3.6 % | 11.7 % | 15.5 % | No net effect |
| Total explained | 50.2 % |

**SPECTRUM model**

White value replaced with Black value is indicated in bold

We used model output for 2007-2009 for these comparisons because this is the most recent year that data are available from SEER. In other analyses and tables, we include model projected rates to 2012.

* Calculated as the ratio of reduction of the difference between observed and predicted mortality rate and the maximum difference. So, in SPECTRUM substituting Black natural history parameters into the White model, after adjusting for the lower incidence in Blacks than Whites explains 35.61 % of the Black-White differences based on a reduction in the difference from 17.43 to 11.22 per 100,000, or 6.21 per 100,000 of the 17.43, i.e., 35.61 %. If we consider the Black screening rates in the White model, given Black natural history and incidence, we see that the difference drops from 11.22 to 10.60, or 0.62 per 100,000 of the 17.43 %, or 3.59 %. Treatment results in Step 4 are compared to Step 2. Step 5 is also compared to Step 2. In the final step, Step 6 is compared to Step 5. No net effect occurs because the higher prevalence of obesity among Black versus White women under age 50 causes a net decrease in cases and mortality, a net increase from ages 50 to 74 and a net decrease from age 75+, as White women have a higher prevalence of obesity than Blacks at the oldest ages.
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Conflict of interest None.

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