PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Impact of Functional Limitations on Long-term Outcomes among African-American and White Women with Breast Cancer: A Cohort Study
AUTHORS	Izano, Monika; Satariano, William; Hiatt, Robert; Braithwaite, Dejana

VERSION 1 - REVIEW

REVIEWER	John P Pierce, Professor, University of California, San Diego, USA I have no competing interests
REVIEW RETURNED	10-Jun-2013

THE STUDY	Study Design: • Multiple hypotheses were tested in a relatively small sample size (n=975 with complete data). Is the study sufficiently powered to examine differences in the impact of physical functioning on mortality by race? • Furthermore, the baseline physical functional assessment was conducted within 2 and 4 months of initial breast cancer diagnosis. Do you have an estimate of the proportion of women that were still recovering, or receiving treatment for breast cancer? Would a physical functional limitation during treatment have the same long-term health implication as a physical functional limitation post treatment? • The long follow-up period (upwards of 20 years) implies that some women were followed until they were 100+ years. What is the advantage of including such a long follow-up period? Does modeling cause of death at for women at age 100 years have public health relevance? Representative of Actual Patients: • Most of the women included in the study were treated for breast cancer in the 1980's. Therefore, women in the study did not receive the current standard of care. Is there evidence to suggest that the findings are generalizable to breast cancer survivors receiving treatment in 2013? Discussion of key findings and study limitations: • A more extensive explanation of key findings (as the relate to study objectives) is needed in the discussion section. Description/Appropriateness of Statistical Methods: • Page 12, Line 50: How were the Cox models stratified by age at diagnosis? This needs elaboration in your description of statically methods. • Page 13, Line 15: More details regarding the justification and procedures used for examining effect modification are needed. Were interactions tested before models were stratified? • Table 2: Each component of physical functioning was examined in

	model 2. Do you have reason to believe that each component of physical functioning is independently related to breast cancer outcomes (i.e., are correlations between individual components low)? • Table 3: Were functional limitations (continuous variable) and functional limitations (dichotomous variable) examined in the same model? If so, what was the justification for this? • It appears that a proportion of the study participants had no physical limitations, which implies that the physical limitations variable is right censored. Is it appropriate to treat it as a continuous variable (i.e., without transformation)?
RESULTS & CONCLUSIONS	• This study appeared to have three primary objectives (page 5), however these study objectives were not revisited and/or described in the discussion section of the paper. • Additionally, no discussion of the information from Tables 2 and 3 were provided. Is this information important? • Overall study conclusion is that functional limitations and functional limitations are linked to survival after breast cancer. What is novel about this finding? Haven't these findings already been demonstrated by Braithwaite (2010) and Sehl (2013)?

REVIEWER	Heidi D. Klepin, MD, MS Wake Forest School of Medicine I have no competing interests
REVIEW RETURNED	09-Jul-2013

THE STUDY	1. Was there an association between chemotherapy use and functional limitation or functional decline in this cohort? Please clarify in the methods whether chemotherapy and/or hormonal therapy was captured and included in the modeling. It is mentioned in the methods as available data but the "treatment" variable reported on page 11 line 11, mentions only surgery. 2. Please clarify terms used for staging. On page 10 the categories are local, regional, and remote. On page 12 (line 19) they refer to local, remote or distant but not regional.
RESULTS & CONCLUSIONS	1. Given the disparities reported in the results regarding differences in function and in mortality outcomes by race, a comment on these results in the abstract and in the discussion would strengthen the paper. 2. Additional comments in the discussion regarding mechanisms underlying differential "predictors" of all-cause versus cancer specific mortality would be helpful. This is particularly important when thinking about how one might use functional assessment in clinic to change outcomes.
REPORTING & ETHICS	Statement re informed consent required.
GENERAL COMMENTS	The authors present a well written manuscript examining the impact of self-report functional limitations and functional decline during the year following breast cancer diagnosis using data from a large cohort study. The findings are of interest to an oncology audience and provide some new insights into relationships between functional status, age, race, BMI and mortality. The manuscript could be strengthened by spending a little more time in the discussion on several of the main study findings including differential results regarding all cause and breast cancer specific mortality. This might elucidate next steps in considering how this information could be used to impact practice. Additionally, understanding race related

	disparities in outcome and function was a primary focus of the paper and results but not mentioned in the abstract or addressed in the discussion. Additional Comments: 1. Were the models in Table 3 adjusted for race? 2. Please provide p values for Kaplan Meier curves.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

John P Pierce, Professor, University of California, San Diego, USA

Study Design:

Multiple hypotheses were tested in a relatively small sample size (n=975 with complete data). Is the study sufficiently powered to examine differences in the impact of physical functioning on mortality by race?

-The issue of statistical power was addressed during the design phase of the study and was considered adequate. Our ability to detect significant differences in the effect of functional limitations and decline on mortality is a testament to the presence of sufficient power to detect such differences.

Furthermore, the baseline physical functional assessment was conducted within 2 and 4 months of initial breast cancer diagnosis. Do you have an estimate of the proportion of women that were still recovering, or receiving treatment for breast cancer? Would a physical functional limitation during treatment have the same long-term health implication as a physical functional limitation post treatment?

-Unfortunately, data on whether participants were recovering or receiving treatment at the time of the baseline interview are not available for this cohort. However, we initially conducted analyses assessing the association with mortality of functional limitations measured both at the baseline and 12 months interviews. Since the association with mortality of functional limitations at 3 and 12 months

and mortality were similar, we chose to report only the former. Additionally, we believe that any changes in physical functioning between these two time points would be captured by our measures of functional decline.

The long follow-up period (upwards of 20 years) implies that some women were followed until they were 100+ years. What is the advantage of including such a long follow-up period? Does modeling cause of death at for women at age 100 years have public health relevance?

-The advantage of including a long follow-up period is that it permitted the evaluation of the long-term survival disadvantages of women with functional limitations. Although the maximum follow-up in HFW is 28 years, median follow-up was 11 years (interquartile range: 4.5-22.4). At the end of the follow-up, participants had a median age of 77 year (interquartile range: 68-85; 99th percentile: 98; maximum: 101). While it is true that modeling the cause of death for the older women in this cohort may have implications for a relatively small proportion of the general population, the proportion of older women with breast cancer is increasing1. More than 50% of new invasive breast cancer cases diagnosed each year in the United Sates occur among women aged 65 years and older, and rates rise dramatically with advancing age1. With the increasing life expectancy and aging of women in the United States and worldwide, the absolute number of breast cancer cases among older women is expected to increase substantially over the coming decades. As the number of older women with breast cancer increases, we believe that identifying factors that may improve survival is important for older as well as younger women.

Representative of Actual Patients:

Most of the women included in the study were treated for breast cancer in the 1980's. Therefore, women in the study did not receive the current standard of care. Is there evidence to suggest that the findings are generalizable to breast cancer survivors receiving treatment in 2013?

-It is true that women in the Health and Functioning in Women with Breast Cancer (HFW) study did not receive the current standard of care and that functional limitations may be of less concern for breast cancer survivors receiving less invasive modern treatments. We have acknowledged this limitation of our study in our discussion, on page 17. However, the impact of functional limitations and

decline is primarily exerted on mortality from causes other than breast cancer, and the role of breast cancer treatment is less relevant with respect to that outcome.

Discussion of key findings and study limitations:

A more extensive explanation of key findings (as the relate to study objectives) is needed in the discussion section.

-We thank the reviewer for his comment. We have revised the first paragraph of the discussion section as follows: “We found that the presence of functional limitations after breast cancer diagnosis,

including difficulties in mobility (walking half a mile) and in upper-body limitations (pushing or pulling

large objects, writing or handling small objects) were associated with statistically significant increases

in the risk of other-cause mortality compared to those with breast cancer without such limitations in this biracial cohort of breast cancer survivors. Overall, functional limitations were more prevalent among African-American women. Race was a significant predictor of mortality in univariate models, but the association was no longer significant in covariate-adjusted models. These findings suggest that factors other than functional limitations are responsible for racial disparities in the survival of women with breast cancer. In evaluating whether the effect of functional limitations varies across strata of breast cancer stage at diagnosis, we found that the presence of functional limitations was statistically significantly associated with other-cause mortality in women with localized disease, but not in women with regional and remote disease. Conversely, functional decline was associated with increased risk of other-cause mortality in women with regional and remote disease, but not in women

with localized disease. Analyses stratified by BMI revealed that the number of functional limitations was positively associated with other-cause mortality in overweight and obese women, but not in women of normal weight. Each unit of functional decline and decline in lower-body function (the ability to sit for an hour or longer) were both significantly associated with increased risk of breast cancer mortality. Functional decline was positively associated with breast cancer mortality in obese women. These findings underscore the prognostic role of obesity among breast cancer survivors."

Description/Appropriateness of Statistical Methods:

Page 12, Line 50: How were the Cox models stratified by age at diagnosis? This needs elaboration in your description of statically methods.

-We thank the reviewer for his comment. We have revised the statistical methods section to clarify that, when the proportionality of hazards assumption was violated, we stratified multivariable models by age at the time of breast cancer diagnosis, to allow for separate baseline hazard functions for each age.

Page 13, Line 15: More details regarding the justification and procedures used for examining effect modification are needed. Were interactions tested before models were stratified?

-Indeed, we tested for interactions between covariates in our analyses. We have added a statement in the statistical methods section (page 12) to indicate that these tests were carried out. However, our interest was to evaluate the presence of effect modification, which differs conceptually from interaction. While interaction asks whether the joint effect of two concurrent exposures is different from the totality of the two effects considered separately, effect modification addresses whether one exposure varies across strata of the second3. In this study, we were interested in the latter: we wanted to assess whether the impact of functional limitations and decline on mortality was different among obese women compared to women of normal weight. Similarly, we were interested in assessing whether the impact of functional limitations differed across strata of breast cancer stage at

diagnosis. For this reason, we conducted analyses separately for subgroups defined by categories of

the effect modifier of interest. We have also indicated this in the statistical analyses section which states: “To evaluate effect modification we conducted analyses separately for subgroups defined by BMI (<25, 25-30, >30) at the baseline interview and stage of breast cancer (local, remote or distant) at

diagnosis.”

Table 2: Each component of physical functioning was examined in model 2. Do you have reason to believe that each component of physical functioning is independently related to breast cancer outcomes (i.e., are correlations between individual components low)?

-Reports on the prognostic role of functional limitations have been mixed. Case-control studies have found that upper body limitations are more prevalent among women with breast cancer4 and that among women with breast cancer, upper body functional limitations are associated with increased risk

of advanced stage disease5. On the other hand in the general population, lower body function appears to be a more significant predictor of mortality6 7. Considering each component separately allowed us to distinguish between upper and lower body limitations, as well as their components, at the cost of parsimony. The evaluation of the independent effects of the individual functional limitations

was one of the objectives of this study, particularly since summary measures of functional limitations

have been previously evaluated8.

Table 3: Were functional limitations (continuous variable) and functional limitations (dichotomous variable) examined in the same model? If so, what was the justification for this?

-We apologize for the confusion. Continuous and dichotomous measures of functional limitations were

examined in separate models. We have updated the “Functional Limitation Assessment” to reflect the

distinction.

It appears that a proportion of the study participants had no physical limitations, which implies that

the physical limitations variable is right censored. Is it appropriate to treat it as a continuous variable (i.e., without transformation)?

-Authors are unclear about the reviewer's comment regarding the right censoring of the exposure. The number of functional limitations in this instance is simply an explanatory variable measured at baseline. Much like in a setting where the exposure of interest is a particular disease history, the study includes subject with and without the disease at a particular time. Whether participants the disease in the future is not relevant for this particular measure.

Results and Conclusions:

This study appeared to have three primary objectives (page 5), however these study objectives were not revisited and/or described in the discussion section of the paper.

-We thank the reviewer for his comment. The objectives set forth on page 5 were: (1) the evaluation of the long-terms effects of functional limitations and functional decline on mortality, (2) assessing whether functional limitations explain racial disparities in survival, and (3) evaluating effect modification by stage and categories of body mass index. The first paragraph of the discussion section was revised to address these objectives and is listed in our response to one of the reviewer's earlier comments.

Additionally, no discussion of the information from Tables 2 and 3 were provided. Is this information important?

-We thank the reviewer for his comment. While a reference to "Table 2" was present in the results section, in-text references to "Table 3" were missing. We have revised the text of the results section to

include references to this table.

Overall study conclusion is that functional limitations and functional limitations are linked to survival

after breast cancer. What is novel about this finding? Haven't these findings already been

demonstrated by Braithwaite (2010) and Sehl (2013)?

-In Braithwaite et al. functional limitations were weighted equally and categorized as a binary variable

(0 vs. 1 or more)8. This study did not evaluate functional decline or individual functional limitations.

Sehl at al. evaluated decline in physical functioning as measured by the Physical Function Index (PF-

10) in the year following breast cancer diagnosis9. This study assessed changes in physical

performance, but not individual or summary measures of functional limitation. To our knowledge our

study is the first to evaluate the association of both individual functional limitations and functional

decline with survival among breast cancer patients.

Reviewer #2

Heidi D. Klepin, MD, MS

1. Was there an association between chemotherapy use and functional limitation or functional decline

in this cohort? Please clarify in the methods whether chemotherapy and/or hormonal therapy was

captured and included in the modeling. It is mentioned in the methods as available data but the

“treatment” variable reported on page 11 line 11, mentions only surgery.

-Examining the association between chemotherapy use and functional limitations was beyond the

scope of our study and was not explored in this analysis. However, data on adjuvant treatment was

obtained from the SEER registry and combines both chemotherapy and/or hormonal therapy. It has

been shown that adjuvant therapy utilization as captured in SEER registries at the time that the HFW

cohort was assembled, was underreported10. Therefore, we did not create separate categories of the

treatment variable for women who received chemotherapy and/or hormonal therapy in addition to

partial or radical mastectomy. The methods section on pages 10-11 was updated as follows: “In

addition to information on surgery (no surgery, partial mastectomy, or modified radical mastectomy)

provided by the MDCSS files, physicians completed a supplementary survey regarding chemotherapy

and hormonal therapy administered on an outpatient basis. However, adjuvant therapy utilization has

been shown to be underreported in SEER registries10, resulting in a small the number of participants

with evidence of chemotherapy and/or hormonal therapy treatment in addition to partial or radical mastectomy. Less than 30 women received no surgery. We combined data from the MDCSS files and physician surveys to create a two-level treatment variable (no surgery or partial mastectomy, and modified radical mastectomy)." For the reviewer's interest, we have provided below the distribution of

adjuvant therapy utilization, for women with and without functional limitations. There were no statistical differences in the distribution of adjuvant therapy utilization among women with and without

functional limitations (P value for Pearson's .2 = 0.43).

Evidence of chemo/hormonal therapy No Evidence of chemo/hormonal therapy

0 Functional limitations 139 154

= 1 Functional limitations 305 377

2. Please clarify terms used for staging. On page 10 the categories are local, regional, and remote. On page 12 (line 19) they refer to local, remote or distant but not regional.

-We thank the reviewer for her comment. The correct categories for staging are: local, regional and remote. We have corrected the information on page 12 as follows: "To evaluate effect modification we

conducted analyses separately for subgroups defined by BMI (<25, 25-30, >30) at the baseline interview and stage of breast cancer (local, regional or remote) at diagnosis."

3. Given the disparities reported in the results regarding differences in function and in mortality outcomes by race, a comment on these results in the abstract and in the discussion would strengthen

the paper.

-Although functional limitations were more prevalent among African-American women in this cohort,

race was a significant predictor of mortality in univariate models, but we observed no residual racial disparity in survival after adjusting for other predictors. We agree that this wasn't made abundantly clear in discussion and abstract and updated both sections accordingly. In the abstract (page 2) we

now state: “Functional limitations and decline did not explain racial disparities in the survival of this cohort.” We have revised the first paragraph of the discussion section (page 15) to state: “We found that the presence of functional limitations after breast cancer diagnosis, including difficulties in mobility (walking half a mile) and in upper-body limitations (pushing or pulling large objects, writing or handling small objects) were associated with statistically significant increases in the risk of other-cause mortality compared to those with breast cancer without such limitations in this biracial cohort of breast cancer survivors. Overall, functional limitations were more prevalent among African-American women in this cohort. Race was a significant predictor of mortality in univariate models, but the association was no longer significant in covariate-adjusted models. These findings suggest that factors other than functional limitations are responsible for racial disparities in the survival of women with breast cancer.”

We are currently investigating which factors do in fact explain racial disparities in survival in this cohort.

2. Additional comments in the discussion regarding mechanisms underlying differential “predictors” of all-cause versus cancer specific mortality would be helpful. This is particularly important when thinking about how one might use functional assessment in clinic to change outcomes.

-We thank the reviewer for her suggestion. While we agree that the elucidation of the potential biological mechanisms linking functional limitations and cause-specific mortality is important to breast cancer survivors and health-care providers, we believe that an important next step is the validation of our findings in other cohorts, ideally in settings where functional limitations and other covariates are captured longitudinally. On page 17, we have added a section to our discussion which states: “In this study, we have shown that functional limitations differentially impact breast cancer-specific and other-cause mortality. Specifically, we observed that functional limitations measured at baseline predicted

other-cause mortality, particularly among non-obese women and those with localized disease. On the

other hand, functional decline was associated with breast cancer-specific mortality, particularly among

overweight and obese women. Prior to probing potential mechanisms linking physical functioning and

cause-specific mortality, these findings should be validated in other cohorts of breast cancer survivors

with employing measures of functional limitations and other covariates, to verify the nature of the

association between various aspects of physical functioning and cause-specific mortality. Identifying

populations most likely to benefit from targeted interventions to enhance functional status is the first

step toward improving outcomes following breast cancer diagnosis."

Statement re informed consent required.

-The following sentence was added to the section describing the study population: "This study was

approved by the Committee on Human Research at the University of California, San Francisco."

The authors present a well written manuscript examining the impact of self-report functional limitations

and functional decline during the year following breast cancer diagnosis using data from a large

cohort study. The findings are of interest to an oncology audience and provide some new insights into

relationships between functional status, age, race, BMI and mortality. The manuscript could be

strengthened by spending a little more time in the discussion on several of the main study findings

including differential results regarding all cause and breast cancer specific mortality. This might

elucidate next steps in considering how this information could be used to impact practice. Additionally,

understanding race related disparities in outcome and function was a primary focus of the paper and

results but not mentioned in the abstract or addressed in the discussion.

-We thank the reviewer for her valuable suggestions. We have expanded the first paragraph of the

discussion section (page 15), to state: "We found that the presence of functional limitations after

breast cancer diagnosis, including difficulties in mobility (walking half a mile) and in upper-body

limitations (pushing or pulling large objects, writing or handling small objects) were associated with statistically significant increases in the risk of other-cause mortality compared to those with breast cancer without such limitations in this biracial cohort of breast cancer survivors. Overall, functional limitations were more prevalent among African-American women. Race was a significant predictor of mortality in univariate models, but the association was no longer significant in covariate-adjusted models. These findings suggest that factors other than functional limitations are responsible for racial disparities in the survival of women with breast cancer. In evaluating whether the effect of functional limitations varies across strata of breast cancer stage at diagnosis, we found that the presence of functional limitations was statistically significantly associated with other-cause mortality in women with localized disease, but not in women with regional and remote disease. Conversely, functional decline was associated with increased risk of other-cause mortality in women with regional and remote disease, but not in women with localized disease. Analyses stratified by BMI revealed that the number of functional limitations was positively associated with other-cause mortality in overweight and obese women, but not in women of normal weight. Each unit of functional decline and decline in lower-body function (the ability to sit for an hour or longer) were both significantly associated with increased risk of breast cancer mortality. Functional decline was positively associated with breast cancer mortality in obese women. These findings underscore the prognostic role of obesity among breast cancer survivors."

Additional Comments:

1. Were the models in Table 3 adjusted for race?

-All models in Tables 2 & 3 were adjusted for race. The footnotes to the tables were corrected to reflect this.

2. Please provide p values for Kaplan Meier curves.

-We thank the reviewer for the opportunity to reconsider the reporting of P values for the log-rank tests in Figures 2a and 2b. A significant P value in the current setting would indicate that the survival distributions of two or more subgroups defined by race and burden of functional limitations were different, but would provide no information about the subgroups in which these differences may occur.

In order to provide a more complete picture of differences in survival distributions, a listing of log-rank

P values for relevant pair-wise subgroup comparisons is provided in the Appendix. In-text references to the appendix have also been added in pages 14 and 15 of the manuscript.

References:

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VERSION 2 – REVIEW

REVIEWER	John P Pierce Professor Moores UC San Diego Cancer Center USA
REVIEW RETURNED	06-Aug-2013

THE STUDY	Breast Cancer treatment in the 1980s limits generalizability as there have been major advances in treatment. However, the limitations issues are still very relevant today
GENERAL COMMENTS	The authors have been very responsive to previous comments

REVIEWER	Heidi D. Klepin Wake Forest University, Comprehensive Cancer Center
REVIEW RETURNED	26-Aug-2013

GENERAL COMMENTS	Reviewer comments addressed adequately.