Supplementary Online Content

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**eTable 5.** Multivariate Fine-Gray Competing Risk Models for Breast Cancer–Specific Mortality: Comparison of Interval Breast Cancers and Breast Cancers Detected by Screening After Controlling for Baseline Health and Tumor Characteristics Among Participants in the Control Arms

**eFigure.** Interval Breast Cancer Definition Flowchart

This supplementary material has been provided by the authors to give readers additional information about their work.
**eTable 1. Unadjusted Fine-Gray Competing Risk Models for Breast Cancer–Specific Mortality**

| Variable                                      | Hazard Ratio (95% Confidence Interval) | P Value |
|------------------------------------------------|----------------------------------------|--------|
| Breast Cancer Type                            |                                        |        |
| Screening-detected                            | 1.00 (reference)                       |        |
| Interval breast cancer <1 yr                  | 1.92 (1.39-2.65)                       | <0.001 |
| Interval breast cancer 1-2.5 yrs              | 1.20 (0.90-1.58)                       | 0.21   |
| Age at diagnosis                              | 0.99 (0.98-1.01)                       | 0.39   |
| Race                                          |                                        |        |
| White                                         | 1.00 (reference)                       |        |
| African American                              | 1.54 (1.06-2.23)                       | 0.02   |
| Hispanic                                      | 2.51 (1.47-4.29)                       | <0.001 |
| Asian                                         | 0.63 (0.24-1.68)                       | 0.36   |
| Other                                         | 1.59 (0.66-3.86)                       | 0.30   |
| Income                                        |                                        |        |
| <$10,000                                      | 1.00 (reference)                       |        |
| $10,000 - $19,999                             | 1.28 (0.59-2.74)                       | 0.53   |
| $20,000 - $34,999                             | 1.07 (0.52-2.22)                       | 0.85   |
| $35,000 - $49,999                             | 1.15 (0.55-2.40)                       | 0.71   |
| $50,000 - $74,999                             | 0.84 (0.40-1.78)                       | 0.65   |
| >$75,000                                      | 0.94 (0.44-1.99)                       | 0.86   |
| Smoking                                       |                                        |        |
| Never smokers                                 | 1.00 (reference)                       |        |
| Current smokers                               | 1.38 (0.87-2.20)                       | 0.17   |
| Ever smokers                                  | 1.20 (0.94-1.53)                       | 0.15   |
| Alcohol                                       |                                        |        |
| Never drinkers                                | 1.00 (reference)                       |        |
| <1 drink/month                                | 0.59 (0.36-0.96)                       | 0.03   |
| <1 drink/week                                 | 0.72 (0.47-1.10)                       | 0.13   |
| ≥7 drinks/week                                | 0.76 (0.51-1.15)                       | 0.19   |
| Past drinkers                                 | 0.97 (0.64-1.47)                       | 0.90   |
| Number of mammogram scans before diagnosis    | 0.95 (0.90-1.00)                       | 0.07   |
| Family history                                |                                        |        |
| No                                            | 1.00 (reference)                       |        |
| Yes                                           | 0.94 (0.71-1.26)                       | 0.69   |
| Lymph Node                                    |                                        |        |
| No                                            | 1.00 (reference)                       |        |
| Yes                                           | 4.53 (3.54-5.79)                       | <0.001 |
| Size                                           | 1.03 (1.02-1.03)                       | <0.001 |
| Stage                                         |                                        |        |
| In Situ                                       | 1.00 (reference)                       |        |
| Localized                                     | 3.06 (1.69-5.55)                       | <0.001 |
| Variable                                      | Hazard Ratio | 95% CI   | p-value |
|-----------------------------------------------|--------------|----------|---------|
| Regional                                     | 11.95        | (6.63-21.56) | <0.001 |
| Distant                                      | 114.22       | (52.53-248.40) | <0.001 |
| BMI (kg/m²) at baseline                      |              |          |         |
| Normal (<25)                                  | 1.00         | (reference) |         |
| Overweight (≥25)                             | 1.13         | (0.86-1.48) | 0.40    |
| Height (cm) at baseline                      | 0.99         | (0.97-1.01) | 0.25    |
| Waist-to-hip ratio at baseline               |              |          |         |
| Normal (<0.80)                               | 1.00         | (reference) |         |
| Overweight (≥0.80)                           | 1.29         | (1.01-1.65) | 0.04    |
| HT Arm Status                                |              |          |         |
| Not randomized to HT                         | 1.00         | (reference) |         |
| Estrogen-alone intervention                  | 0.95         | (0.55-1.63) | 0.85    |
| Estrogen-alone control                       | 1.37         | (0.91-2.05) | 0.13    |
| Estrogen + Progestin Intervention            | 1.08         | (0.77-1.52) | 0.64    |
| Estrogen + Progestin control                 | 0.83         | (0.54-1.27) | 0.39    |
| DM Arm Status                                |              |          |         |
| Not randomized to DM                         | 1.00         | (reference) |         |
| Intervention                                 | 0.87         | (0.63-1.20) | 0.41    |
| Control                                      | 1.00         | (0.75-1.32) | 0.98    |
| Ever full-term birth                         |              |          |         |
| No                                           | 1.00         | (reference) |         |
| Yes                                          | 0.65         | (0.36-1.20) | 0.17    |
| Comorbidity at baseline                      |              |          |         |
| 0                                            | 1.00         | (reference) |         |
| 1                                            | 0.96         | (0.71-1.29) | 0.78    |
| 2                                            | 1.11         | (0.71-1.75) | 0.64    |
| ≥3                                           | 1.52         | (0.80-2.86) | 0.20    |
| Histology                                    |              |          |         |
| Ductal                                       | 1.00         | (reference) |         |
| Lobular                                      | 2.09         | (1.51-2.89) | <0.001  |
| Ductal + Lobular                             | 1.16         | (0.81-1.68) | 0.42    |
| Others                                       | 3.28         | (1.48-7.25) | 0.003   |
| Molecular Subtype                            |              |          |         |
| ER+ and/or PR+/HER2-                         | 1.00         | (reference) |         |
| ER+ and/or PR+/HER2+                         | 0.85         | (0.51-1.42) | 0.53    |
| ER- and/or PR+/HER2+                         | 2.60         | (1.53-4.40) | <0.001  |
| Triple Negative                              | 2.47         | (1.62-3.77) | <0.001  |
| ER+/HER2 unknown                             | 0.92         | (0.66-1.28) | 0.62    |
| ER-/HER2 unknown                             | 2.11         | (1.31-3.39) | 0.002   |
| Others                                       | 0.85         | (0.60-1.20) | 0.34    |

Each row represents a unique unadjusted Fine-Gray Competing Risk model with that one variable and breast-cancer-specific mortality only included in the model. Numbers in cells represent the hazard ratios, 95% confidence intervals and p-values from that unadjusted risk model. Missing categories are not reported in the table. Variables found significantly related with breast-cancer-specific mortality in these unadjusted models were include in the multi-variate models unless specifically stated.
**eTable 2. Comparison of Tumor Characteristics Between Women With a Diagnosis of Breast Cancer Detected by Screening vs Women With a Diagnosis of Interval Breast Cancer Among Participants Not in HT Trial**

| Participant Characteristics | All Interval Breast Cancer (N=841) | Breast cancer detected by screening (N=1,042) | OR \(^5\) (95% CI) | OR \(^5\) (95% CI) | OR \(^5\) (95% CI) | OR \(^5\) (95% CI) | OR \(^5\) (95% CI) | OR \(^5\) (95% CI) | P Value\(^1,2\) | P Value\(^1,2\) |
|-----------------------------|------------------------------------|------------------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------|----------------|
| Tumor size, cm              | 1.59 (1.41)                        | 1.45 (1.27)                                    | 0.03                | 0.03                | <0.001              | 0.41                |
| Stage                       | 0.25                               | 0.25                                           |                     |                     | 0.003               | 0.87                |
| In Situ                     | 151 (18.30)                        | 219 (21.20)                                    | 1.00                | 1.00                | 124 (19.59)         | 1.00                |
| Localized                   | 502 (60.85)                        | 622 (60.21)                                    | 1.17 (0.92-1.49)    | 1.11 (57.81)        | 1.45 (0.93-2.27)    | 1.11 (0.86-1.43)    |
| Regional                    | 162 (19.64)                        | 185 (17.91)                                    | 1.27 (0.95-1.71)    | 49 (25.52)          | 2.15 (1.29-3.57)    | 113 (17.85)         | 1.08 (0.78-1.49) |
| Distant                     | 10 (1.21)                          | 7 (0.68)                                       | 2.07 (0.77-5.56)    | 5 (2.60)            | 5.79 (1.72-19.53)   | 5 (0.79)            | 1.26 (0.39-4.06) |
| Grade                       | 0.73                               | 0.73                                           | 0.52                | 0.52                |                     | 0.83                |
| Well differentiated          | 178 (23.99)                        | 234 (25.43)                                    | 1.00                | 1.00                | 136 (23.57)         | 1.00                |
| Moderately differentiated    | 317 (42.72)                        | 380 (41.30)                                    | 1.10 (0.86-1.40)    | 69 (41.82)          | 1.01 (0.67-1.54)    | 248 (42.98)         | 1.12 (0.86-1.46) |
| Poorly differentiated        | 195 (2638)                        | 232 (25.22)                                    | 1.11 (0.84-1.45)    | 46 (27.88)          | 1.11 (0.70-1.74)    | 149 (25.82)         | 1.11 (0.82-1.48) |
| Anaplastic                  | 52 (7.01)                          | 74 (8.04)                                      | 0.92 (0.62-1.39)    | 8 (4.85)            | 0.60 (0.27-1.34)    | 44 (7.63)           | 1.02 (0.67-1.57) |
| Unknown/not done            | 99                                 | 122                                           |                     |                     |                     | 71                  |
| Lymph Node Involvement       | 0.37                               | 0.37                                           | 0.02                | 0.02                |                     | 0.96                |
| Yes                         | 181 (21.57)                        | 207 (19.90)                                    | 1.11 (0.89-1.39)    | 53 (27.46)          | 1.52 (1.07-2.16)    | 128 (19.81)         | 0.99 (0.78-1.27) |
| No                          | 658 (78.43)                        | 833 (80.10)                                    | 1.00                | 1.00                | 518 (80.19)         | 1.00                |
| Molecular Type\(^4\)        | 0.19                               | 0.19                                           | 0.05                | 0.05                |                     | 0.39                |
| ER+/HER2-                   | 322 (68.95)                        | 390 (74.14)                                    | 1.00                | 1.00                | 260 (71.04)         | 1.00                |
| ER+/HER2+                   | 72 (15.42)                        | 70 (13.31)                                     | 1.25 (0.87-1.79)    | 17 (16.83)          | 1.53 (0.84-2.77)    | 55 (15.03)          | 1.18 (0.80-1.74) |
| ER-/HER2+                   | 25 (5.35)                         | 29 (5.51)                                      | 1.04 (0.60-1.82)    | 9 (8.91)            | 1.95 (0.88-4.32)    | 16 (4.37)           | 0.83 (0.44-1.55) |
| Triple Negative             | 48 (10.28)                        | 37 (7.03)                                      | 1.57 (1.00-2.47)    | 13 (12.87)          | 2.21 (1.11-4.39)    | 35 (9.56)           | 1.42 (0.87-2.31) |
| ER+/HER2 unknown            | 45                                 | 224                                           |                     |                     |                     | 121                 |
| ER-/HER2 unknown            | 40                                 | 45                                            |                     |                     |                     | 30                  |
| Others\(^\d\)               | 37                                 | 247                                           |                     |                     |                     | 37                  |
| Histology Type              | 0.19                               | 0.19                                           | 0.06                | 0.06                |                     | 0.36                |
| Ductal                      | 635 (75.69)                        | 827 (79.60)                                    | 1.00                | 1.00                | 494 (76.47)         | 1.00                |
| Lobular                     | 84 (10.01)                         | 83 (7.99)                                      | 1.32 (0.96-1.82)    | 27 (13.99)          | 1.91 (1.19-3.05)    | 57 (8.82)           | 1.15 (0.81-1.64) |
| Ductal + Lobular            | 110 (13.11)                       | 121 (11.65)                                    | 1.18 (0.90-1.56)    | 24 (12.44)          | 1.16 (0.73-1.87)    | 86 (13.31)          | 1.19 (0.88-1.60) |
| Others\(^\d\)               | 10 (1.19)                          | 8 (0.77)                                       | 1.63 (0.64-4.15)    | 1 (0.52)            | 0.73 (0.09-5.91)    | 9 (1.39)            | 1.88 (0.72-4.91) |

1. Chi-square tests are used for categorical variables and t-tests are used for continuous variables.
2. Missing categories are excluded from statistical analysis.
3. “Others” include “Borderline, Ordered/Results not available, Unknown/Not done, Missing”. *In data submissions earlier than November 2014, borderline ER/PR was not classified with positive ([https://seer.cancer.gov/seerstat/databases/ssf/breast-subtype.html](https://seer.cancer.gov/seerstat/databases/ssf/breast-subtype.html)).
4. P-values were calculated excluding “ER+/HER2 unknown”, “ER-/HER2 unknown” and “Others” categories.
5. Odds ratios stand for odds of being in the “interval breast cancer” group. Interval breast cancers were sub-divided by their inter-screening period - those diagnosed within 1 year of last screen or 1 – 2.5 years since last screen.
### eTable 3. Multivariate Fine-Gray Competing Risk Models for Breast Cancer–Specific Mortality: Comparison of Interval Breast Cancers and Breast Cancers Detected by Screening After Controlling for Baseline Health and Tumor Characteristics Among Participants Not in HT Trial

| Model | Breast cancer detected by screening | Interval breast cancer ≤1 yr HR (95% CI) | Interval breast cancer 1-2.5 yr HR (95% CI) |
|-------|------------------------------------|------------------------------------------|---------------------------------------------|
| Model 1<sup>2</sup> | 1.00 (reference) | 1.58 (1.00-2.48) | 1.27 (0.92-1.77) |
| Model 2<sup>3</sup> | 1.00 (reference) | 1.53 (0.98-2.39) | 1.21 (0.86-1.70) |
| Model 3<sup>4</sup> | 1.00 (reference) | 1.53 (0.98-2.39) | 1.20 (0.85-1.70) |
| Model 4<sup>5</sup> | 1.00 (reference) | 1.59 (1.02-2.48) | 1.21 (0.86-1.70) |
| Model 5<sup>6</sup> | 1.00 (reference) | 1.46 (0.93-2.30) | 1.18 (0.83-1.66) |
| Model 6<sup>7</sup> | 1.00 (reference) | 1.39 (0.90-2.17) | 1.21 (0.86-1.70) |
| Model 7<sup>8</sup> | 1.00 (reference) | 1.41 (0.90-2.22) | 1.17 (0.82-1.67) |

1. This table reports a series of sequential multivariate models where a new variable is added to each model. Numbers in cells represent the Hazard Ratios and 95% confidence intervals computed from the Fine-Grey competing risk model. Time is calculated as the time between diagnosis date and end-of follow-up. Interval breast cancers were sub-divided by their inter-screening period - those diagnosed within 1 year of last screen or 1 – 2.5 years since last screen.
2. Model 1: Fine-Gray Competing Risk Models for breast cancer-specific mortality by breast cancer type adjusting for molecular subtype as the covariate
3. Model 2 includes all variables in model 1 with additional adjustment for histology
4. Model 3 includes all variables in model 2 with additional adjustment for dietary modification trial arm
5. Model 4 includes all variables in model 3 with additional adjustment for WHR
6. Model 5 includes all variables in model 4 with additional adjustment for tumor size
7. Model 6 includes all variables in model 5 with additional adjustment for lymph node involvement
8. Model 7 includes all variables in model 6 with additional adjustment for other common risk factors for breast cancer (age at diagnosis, race/ethnicity, family history of breast cancer, comorbidity, total number of mammograms before diagnosis, age at menarche, age at first birth, income, education, smoking status, alcohol intake and BMI)
**Table 4.** Multivariate Fine-Gray Competing Risk Models for Breast Cancer–Specific Mortality: Comparison of Interval Breast Cancers and Breast Cancers Detected by Screening After Controlling for Baseline Health and Tumor Characteristics: Replacing the Survival Time From “Diagnosis Date to Death/End-of-Follow-up Date” With “Date of Last Mammogram to Death/End-of-Follow-up Date”

| Model | Breast cancer detected by screening | Interval breast cancer <1 yr HR (95% CI) | Interval breast cancer 1-2.5 yr HR (95% CI) |
|-------|-------------------------------------|------------------------------------------|---------------------------------------------|
| Model 1<sup>2</sup> | 1.00 (reference) | 1.80 (1.30-2.50) | 1.13 (0.85-1.50) |
| Model 2<sup>3</sup> | 1.00 (reference) | 1.63 (1.17-2.27) | 1.08 (0.80-1.44) |
| Model 3<sup>4</sup> | 1.00 (reference) | 1.65 (1.17-2.31) | 1.12 (0.82-1.53) |
| Model 4<sup>5</sup> | 1.00 (reference) | 1.68 (1.19-2.36) | 1.13 (0.83-1.54) |
| Model 5<sup>6</sup> | 1.00 (reference) | 1.45 (1.02-2.06) | 1.07 (0.78-1.46) |
| Model 6<sup>7</sup> | 1.00 (reference) | 1.10 (0.76-1.60) | 1.08 (0.78-1.49) |
| Model 7<sup>8,9</sup> | 1.00 (reference) | 1.00 (0.68-1.48) | 1.00 (0.71-1.39) |

1. This table reports a series of sequential multivariate models where a new variable is added to each model. Numbers in cells represent the Hazard Ratios and 95% confidence intervals computed from the Fine-Gray competing risk model. Time is calculated as the time between diagnosis date and end-of-follow-up. Interval breast cancers were sub-divided by their inter-screening period - those diagnosed within 1 year of last screen or 1 – 2.5 years since last screen.

2. Model 1: Fine-Gray Competing Risk Models for breast cancer-specific mortality by breast cancer type adjusting for molecular subtype as the covariate.

3. Model 2 includes all variables in model 1 with additional adjustment for histology.

4. Model 3 includes all variables in model 2 with additional adjustment for hormone replacement therapy clinical trial arm and dietary modification trial arm.

5. Model 4 includes all variables in model 3 with additional adjustment for WHR.

6. Model 5 includes all variables in model 4 with additional adjustment for tumor size.

7. Model 6 includes all variables in model 5 with additional adjustment for lymph node involvement.

8. Model 7 includes all variables in model 6 with additional adjustment for other common risk factors for breast cancer (age at diagnosis, race/ethnicity, family history of breast cancer, comorbidity, total number of mammograms before diagnosis, age at menarche, age at first birth, income, education, smoking status, alcohol intake and BMI).

9. If adding the common risk factors in Model 7 before adding tumor size and lymph node into the model, the corresponding HR (95%CI)=1.62 (1.13-2.33) for interval breast cancer<1 yr and 1.11 (0.81-1.53) for interval breast cancer 1-2.5 yr.
**Table 5.** Multivariate Fine-Gray Competing Risk Models for Breast Cancer–Specific Mortality: Comparison of Interval Breast Cancers and Breast Cancers Detected by Screening After Controlling for Baseline Health and Tumor Characteristics Among Participants in the Control Arms

| Model   | Breast cancer detected by screening HR (95% CI) | Interval breast cancer ≤1 yr HR (95% CI) | Interval breast cancer 1-2.5 yr HR (95% CI) |
|---------|-----------------------------------------------|-----------------------------------------|------------------------------------------|
| Model 1 | 1.00 (reference)                              | 1.56 (0.98-2.50)                        | 1.20 (0.84-1.72)                         |
| Model 2 | 1.00 (reference)                              | 1.41 (0.88-2.26)                        | 1.08 (0.74-1.59)                         |
| Model 3 | 1.00 (reference)                              | 1.44 (0.89-2.31)                        | 1.10 (0.75-1.61)                         |
| Model 4 | 1.00 (reference)                              | 1.39 (0.86-2.24)                        | 1.08 (0.73-1.61)                         |
| Model 5 | 1.00 (reference)                              | 1.32 (0.84-2.09)                        | 1.16 (0.78-1.72)                         |
| Model 6 | 1.00 (reference)                              | 1.20 (0.75-1.93)                        | 0.98 (0.65-1.48)                         |

1. This table reports a series of sequential multivariate models where a new variable is added to each model. Numbers in cells represent the Hazard Ratios and 95% confidence intervals computed from the Fine-Grey competing risk model. Time is calculated as the time between diagnosis date and end-of-follow-up. Interval breast cancers were sub-divided by their inter-screening period - those diagnosed within 1 year of last screen or 1 – 2.5 years since last screen.

2. Model 1: Fine-Gray Competing Risk Models for breast cancer-specific mortality by breast cancer type adjusting for molecular subtype as the covariate

3. Model 2 includes all variables in model 1 with additional adjustment for histology

4. Model 3 includes all variables in model 3 with additional adjustment for WHR

5. Model 4 includes all variables in model 4 with additional adjustment for tumor size

6. Model 5 includes all variables in model 5 with additional adjustment for lymph node involvement

7. Model 6 includes all variables in model 6 with additional adjustment for other common risk factors for breast cancer (age at diagnosis, race/ethnicity, family history of breast cancer, comorbidity, total number of mammograms before diagnosis, age at menarche, age at first birth, income, education, smoking status, alcohol intake and BMI)
**eFigure.** Interval Breast Cancer Definition Flowchart

1. **WHI Study eligibility mammogram**
   - Abnormal
   - Normal
     - Excluded from the study
     - Enrolled to study

2. **First on study mammogram**
   - Suspicious
   - Normal
     - Symptomatic
     - Interval Breast Cancer

3. **Diagnostic mammogram**
   - Suspicious
   - Normal
     - Symptomatic
     - Interval Breast Cancer

4. **Next screening mammogram**
   - Suspicious
   - Normal
     - Symptomatic
     - Interval Breast Cancer

5. **Subsequent mammogram**

Additional Notes:
- **High Surveillance**
  - Screen-detected Breast Cancer
  - Follow up

- **Screen-detected Breast Cancer**