10.1148/radiol.2019182599

# Appendix E1

## Imputation Procedure

96 of the 222 biopsied calcifications used for the final analysis had a first recorded size of 0 because the corresponding mammogram did not show any calcifications. For these calcifications, the start of growth may have occurred at any time between the first recorded mammogram (at time $t_1$ with lesion size $l_1 = 0$) and the second mammogram (at time $t_2$ with lesion size $l_2 > 0$). To account for this possibility, we used a multiple imputation procedure to predict the time of initiation for these 96 calcifications. More precisely, to enable the subsequent use of log-transformed response models, we imputed the time $\hat{t}_1 \in (t_1, t_2)$ when the lesion would have reached size $0.5mm$. We proceeded as follows.

***Step 1.*** We redefined values of $l_1 = 0$ as missing and used the PROC MI routine to impute missing values based on race, age at diagnosis, biopsy finding, time from mammogram to diagnosis for mammograms 1–3, and lesion size for mammograms 1–3. This resulted in a completed data set with imputed $\hat{l}_1$ at time $t_1$. 100 imputed data sets were created.

***Step 2***. Next, in each of the 96 calcifications with imputed first mammogram size, we replaced the imputed lesions size $\hat{l}_1$ by $\min\left(\hat{l}_1, 0\right)$ because (i) for $\hat{l}_1 \geq 0$ we thus remained consistent with the recorded value of 0 mm, and (ii) for $\hat{l}_1 < 0$ we allowed for the time of initiation of the calcifications to occur after the time of the first mammogram $t_1$.

***Step 3***. For each case of biopsied calcification with imputed mammogram size of $min\left(\hat{l}_1, 0\right)$ at time $t_1$, we then used a univariable linear regression model (lesion size regressed on time) to estimate the time $\hat{t}_1 \in (t_1, t_2)$ when the calcifications reached the size of 0.5 mm. This was done separately for each case of biopsied calcifications and imputation.

***Step 4.*** For each imputed case of biopsied calcifications, we replaced the first mammogram time and size $\left(t_1, \hat{l}_1\right)$ with $(\hat{t}_1, 0.5mm)$. Of note, each imputed data set consisted thus of the original data for the 126 cases with positive first mammogram size and imputed first mammogram time and size $(\hat{t}_1, 0.5mm)$ for the 96 calcifications with recorded first mammogram size of 0 mm.

All 100 imputed data sets were used in subsequent linear mixed effects modeling. Analyses were stratified by imputation number and estimates were combined using PROC MIANALYZE.

# Appendix E2

## Model Selection

**Model selection was performed between the three proposed linear mixed effects models with untransformed, square root-transformed, and log-transformed response variables (long-axis length), respectively. Based on the Akaike Information Criterion (AIC), and as shown in the table below, the log-transformed model yields the best fit (lowest AIC). Of note, the results of the log-transformed model are also presented in Table 2.**

| Effect | Linear Mixed Effects Model | | Linear Mixed Effects Model with Square Root Transformation | | Linear Mixed Effects Model with Log Transformation | |
|---|---|---|---|---|---|---|
| | Parameter Estimate (95% CI) | *P* Value | Parameter Estimate (95% CI) | *P* Value | Percent Change (95% CI)* | *P* Value |
| Intercept | 6.07 (0.37, 11.76) | .04 | 2.25 (1.32, 3.19) | <.001 | 336.6 (121.1, 762.4) | <.001 |
| Diagnosis | | | | | | |
| DCIS | 7.44 (3.42, 11.47) | <.001 | 0.89 (0.43, 1.35) | <.001 | 69.1 (29.5, 120.8) | <.001 |
| Benign | REF | | REF | | | |
| Time to diagnosis (y) | 1.60 (1.29, 1.91) | <.001 | 0.42 (0.36, 0.48) | <.001 | 67.7 (56.2, 80.1) | <.001 |
| Age at diagnosis (y) | 0.09 (0.00, 0.18) | .05 | 0.01 (0.00, 0.03) | .04 | 1.2 (0.1, 2.2) | .03 |
| Breast density | | | | | | |
| Fatty | −3.91 (−9.32, 1.49) | .16 | −0.41 (−1.33, 0.50) | .37 | −25.2 (−62.2, 47.7) | .40 |
| Scattered fibroglandular | −2.37 (−6.30, 1.57) | .24 | −0.42 (−1.06, 0.23) | .21 | −25.0 (−53.6, 21.0) | .24 |
| Heterogeneously dense | −2.91 (−6.76, 0.93) | .14 | −0.44 (−1.07, 0.19) | .17 | −23.7 (−52.1, 21.3) | .25 |
| Extremely dense | REF | | REF | | REF | |
| Race | | | | | | |
| Black | −0.64 (−2.56, 1.28) | .52 | 0.10 (−0.22, 0.42) | .52 | 9.1 (−13.7, 38.0) | .47 |
| White | REF | | REF | | REF | |
| Time * diagnosis | | | | | | |
| DCIS | 3.05 (1.49, 4.61) | <.001 | 0.32 (0.15, 0.50) | <.001 | 17.0 (0.5, 36.1) | .04 |
| Benign | REF | | REF | | REF | |
| No. of converging imputations | 100 | | 100 | | 100 | |
| AIC | 4692.23 (4685.67, 4718.10) | | 1895.43 (1883.98, 1920.99) | | 1850.46 (1832.65, 1877.16) | |
| | **Variance-Covariance of Random Effects, Median (Range)**** | | | | | |
| DCIS | | | | | | |
| Intercept-intercept | 268.45 (262.90, 272.85) | | 3.09 (3.02, 3.18) | | 0.76 (0.70, 0.84) | |
| Intercept-time | 6.42 (6.23, 6.53) | | 0.05 (0.05, 0.06) | | 0.006 (0.004, 0.007) | |
| Time-time | 0.27 (0.26, 0.27) | | 0.003 (0.002, 0.003) | | 0.001 (0.001, 0.002) | |
| Benign | | | | | | |
| Intercept-intercept | 62.51 (61.53, 63.25) | | 1.20 (1.18, 1.22) | | 0.50 (0.47, 0.53) | |
| Intercept-time | 0.64 (0.61, 0.65) | | 0.007 (0.007, 0.008) | | −0.003 (−0.003,−0.002) | |
| Time-time | 0.008 (0.007, 0.009) | | 0.0004 (0.0003, 0.0004) | | 0.0006 (0.0006, 0.0007) | |
| Residual/scale | 9.64 (9.48, 10.38) | | 0.21 (0.20, 0.23) | | 0.28 (0.27, 0.30) | |

* *For each model coefficient* $\hat{\beta}$ *estimated on the log-transformed scale, percent change on the natural scale was calculated as* $100*(e^{\hat{\beta}}-1)$.

** AIC and variance-covariance estimates are reported as median (range) of all converging imputation models. REF refers to the reference standard for calculations.

# Appendix E3

## Goodness of Fit

**A modified *R*-squared was computed for each model fit as 1-(Sum of Squared Residuals of Full Model/Sum of Squared Residuals of Intercept-Only Model). For the full model, residuals were estimated from the fitted model for each patient using the best linear unbiased predictors (BLUPs). The following table summarizes the modified *R*-squared values for the different models.**

| Model | Modified *R*-squared |
|---|---|
| Imputed data–median (range) | |
| Linear mixed effects model | 0.79 (0.77, 0.79) |
| LMM with square root transformation | 0.82 (0.80, 0.83) |
| LMM with log transformation | 0.78 (0.76, 0.80) |
| Original data | |
| Linear mixed effects model | 0.75 |
| LMM with square root transformation | 0.80 |

The following figure illustrates the model fit by comparing the raw data means (symbols) against the means of the model predictions (lines; based on the BLUPs). For each data point and corresponding model prediction, the time was rounded to the nearest full year, and for each year, the respective data and model means are shown.

# Appendix E4

## Sensitivity Analysis

**Results of the mixed effects models with unstructured covariance and time to diagnosis * diagnosis interaction without imputation. Only the untransformed and square root transformations are evaluated; the analysis is not applicable to the log-transformed model due to the presence of 0-valued entries. The results are similar to those with imputation shown in Table 2.**

| Effect | Linear Mixed Effects Model | | LMM with Square Root Transformation | |
|---|---|---|---|---|
| | Parameter Estimate (95% CI) | *P* Value | Parameter Estimate (95% CI) | *P* Value |
| Intercept | 5.65 (–0.04, 11.35) | .05 | 2.27 (1.31, 3.23) | <.001 |
| Diagnosis | | | | |
| DCIS | 7.03 (2.96, 11.09) | .001 | 0.82 (0.37, 1.28) | .001 |
| Benign | REF | | REF | |
| Time to diagnosis (y) | 1.57 (1.27, 1.87) | <.001 | 0.52 (0.45, 0.58) | <.001 |
| Age at diagnosis (y) | 0.10 (0.006, 0.18) | .04 | 0.02 (0.001, 0.03) | .04 |
| Breast Density | | | | |
| Fatty | –3.74 (–9.23, 1.74) | .18 | –0.46 (–1.41, 0.49) | .34 |
| Scattered fibroglandular | –2.83 (–6.81, 1.15) | .16 | –0.42 (–1.09, 0.25) | .21 |
| Heterogeneously dense | –2.91 (–6.80, 0.99) | .14 | –0.45 (–1.09, 0.20) | .18 |
| Extremely dense | REF | | REF | |
| Race | | | | |
| Black | –0.11 (–2.07, 1.85) | .91 | 0.11 (–0.22, 0.44) | .51 |
| White | REF | | REF | |

| | | | | |
|---|---|---|---|---|
| Time to diagnosis * diagnosis | | | | |
| DCIS | 2.86 (1.28, 4.44) | <.001 | 0.28 (0.10, 0.47) | .003 |
| Benign | REF | | REF | |
| AIC | 4741.96 | | 2132.21 | |
| | **Variance-Covariance of Random Effects** | | | |
| DCIS | | | | |
| Intercept-intercept | 268.27 | | 2.98 | |
| Intercept-time | 6.63 | | 0.05 | |
| Time-time | 0.28 | | 0.003 | |
| Benign | | | | |
| Intercept-intercept | 63.22 | | 1.10 | |
| Intercept-time | 0.60 | | 0.003 | |
| Time-time | 0.006 | | 0.0005 | |
| Residual/scale | 11.92 | | 0.35 | |

# Appendix E5

## Model of Non–high-grade DCIS versus High-grade DCIS

### Mixed effects models with unstructured covariance and time*diagnosis interactions with imputed data (100 imputed data sets). Diagnosis included as High-grade DCIS, Non–high-grade DCIS, and Benign.

| **Effect** | **LMM with Log Transformation** | |
|---|---|---|
| | **Percent Change (95% CI)*** | ***P* Value** |
| Intercept | 340.6% (122.1%, 774.1%) | <.001 |
| Diagnosis | | |
| High-grade DCIS | 95.0% (31.2%, 189.8%) | .001 |
| Non–high-grade DCIS | 55.4% (11.7%, 116.2%) | .009 |
| Benign | REF | |
| Time to diagnosis (y) | 67.9% (56.4%, 80.3%) | <.001 |
| Age at diagnosis (y) | 1.2% (0.1%, 2.2%) | .03 |
| Breast density | | |
| Fatty | –24.5% (–61.5%, 47.9%) | .41 |
| Scattered fibroglandular | –24.9% (–53.5%, 21.2%) | .24 |
| Heterogeneously dense | –23.4% (–51.8%, 21.6%) | .26 |
| Extremely dense | REF | |
| Race | | |
| Black | 9.3% (–14.3%, 39.4%) | .47 |
| White | REF | |
| Time * diagnosis | | |
| High-grade DCIS | 50.8% (12.5%, 102.0%) | .006 |
| Non–high-grade DCIS | 1.48% (–12.6%, 17.9%) | .85 |
| Benign | REF | |
| No. of converging imputations | 100 | |
| AIC | 1846.18 (1827.74, 1874.04) | |
| Variance-covariance of random effects | | |
| High-grade DCIS | | |
| Intercept-intercept | 0.63 (0.48, 0.71) | |
| Intercept-time | 0.02 (0.01, 0.02) | |

| | |
|---|---|
| Time-time | 0.002 (0.002, 0.003) |
| Non–high-grade DCIS | |
| Intercept-intercept | 0.88 (0.83, 0.99) |
| Intercept-time | –0.0002 (–0.0009, 0.001) |
| Time-time | 0.0007 (0.0007, 0.0008) |
| Benign | |
| Intercept-intercept | 0.51 (0.48, 0.56) |
| Intercept-time | –0.002 (–0.003, –0.002) |
| Time-time | 0.0006 (0.0006, 0.0007) |
| Residual/scale | 0.28 (0.26, 0.30) |

* For each model coefficient $\hat{\beta}$ estimated on the log-transformed scale, percent change on the natural scale was calculated as 100*( $e^{\hat{\beta}} - 1$) .

Growth rates estimated from model outlined above.

| Diagnosis | Annual Growth Rate |
|---|---|
| High-grade DCIS | 153.1% (90.5%, 236.2%) |
| Non–high-grade DCIS | 70.4% (49.3%, 94.5%) |
| Benign | 67.9% (56.4%, 80.3%) |

# Appendix E6

## Model of ER-positive versus ER-negative DCIS

### Mixed effects models with unstructured covariance and time*diagnosis interactions with imputed data (100 imputed data sets). Diagnosis included as ER-positive DCIS, ER-negative DCIS, and Benign.

| Effect | LMM with Log Transformation | |
|---|---|---|
| | Percent Change (95% CI)* | *P* Value |
| Intercept | 343.1% (121.7%, 785.3%) | <.001 |
| Diagnosis | | |
| ER-positive DCIS | 58.9% (19.2%, 111.9%) | .002 |
| ER-negative DCIS | 136.5% (31.7%, 324.7%) | .004 |
| Benign | REF | |
| Time to diagnosis (y) | 67.8% (56.2%, 80.1%) | <.001 |
| Age at diagnosis (y) | 1.1% (0.08%, 2.2%) | .04 |
| Breast density | | |
| Fatty | –24.8% (–62.3%, 50.0%) | .42 |
| Scattered fibroglandular | –23.2% (–52.6%, 24.4%) | .28 |
| Heterogeneously dense | –23.3% (–52.0%, 22.6%) | .27 |
| Extremely dense | REF | |
| Race | | |
| Black | 9.3% (–14.3%, 39.3%) | .47 |
| White | REF | |
| Time * diagnosis | | |
| ER-positive DCIS | 9.9% (–5.2%, 27.3%) | .21 |
| ER-negative DCIS | 66.8% (6.7%, 160.8%) | .02 |
| Benign | REF | |

| | |
|---|---|
| No. of converging imputations | 100 |
| AIC | 1850.64 (1831.92, 1877.42) |
| Variance-covariance of random effects | |
| ER-positive DCIS | |
| Intercept-intercept | 0.76 (0.68, 0.86) |
| Intercept-time | –0.001 (–0.002, 0.001) |
| Time-time | 0.001 (0.0009, 0.001) |
| ER-negative DCIS | |
| Intercept-intercept | 0.85 (0.55, 0.93) |
| Intercept-time | 0.03 (0.02, 0.03) |
| Time-time | 0.003 (0.003, 0.003) |
| Benign | |
| Intercept-intercept | 0.52 (0.49, 0.59) |
| Intercept-time | –0.002 (–0.003, –0.002) |
| Time-time | 0.0006 (0.0006, 0.0007) |
| Residual/scale | 0.28 (0.26, 0.30) |

* For each model coefficient $\hat{\beta}$ estimated on the log-transformed scale, percent change on the natural scale was calculated as 100*( $e^{\hat{\beta}} - 1$) .

Growth rates estimated from model outlined above.

| **Diagnosis** | **Annual Growth Rate** |
|---|---|
| ER-positive DCIS | 84.3% (61.9%, 109.8%) |
| ER-negative DCIS | 179.9% (80.0%, 335.1%) |
| Benign | 67.8% (56.2%, 80.1%) |