**Supplementary Tables**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 1.** Distribution of cases and controls who were initially selected for the case-control study by final study status | | | | | | |
|  |  |  |  |  |  |  |
| **A. Collected tissue specimens and pathology review** | | | | | | |
|  |  |  | **Number of Cases** | | **Number of Controls** | |
|  |  |  | **No.** | **%** | **No.** | **%** |
|  |  |  |  |  |  |  |
| **Initially selected** | | | **316** | **100.0** | **1303** | **100.0** |
|  |  |  |  |  |  |  |
|  | **Excluded** | | **114** | **36.1** | **561** | **43.1** |
|  | - | No tissue blocks available | 61 | 19.3 | 388 | 29.8 |
|  | - | No DCIS component found | 18 | 5.7 | 74 | 5.7 |
|  | - | (Micro)invasive component present | 6 | 1.9 | 11 | 0.8 |
|  | - | LCIS present | 9 | 2.8 | 31 | 2.4 |
|  | - | Papillary lesion other than DCIS | 14 | 4.4 | 34 | 2.6 |
|  | - | Specimen not assessable | 5 | 1.6 | 12 | 0.9 |
|  | - | Other reason | 1 | 0.3 | 11 | 0.8 |
|  |  |  |  |  |  |  |
|  | **Administrative reason for exclusion** | | **2** | **0.6** | **268** | **20.6** |
|  | - | Selected as case, controls excluded | 2 | 0.6 | - | - |
|  | - | Selected as control, case excluded | - | - | 268 | 20.6 |
|  |  |  |  |  |  |  |
| **Total excluded** | | | **116** | **36.7** | **829** | **63.7** |
|  |  |  |  |  |  |  |
| **Total included in study** | | | **200** | **63.3** | **474** | **36.4** |
|  |  |  |  |  |  |  |
| **Duplicate controls** | | | **-** | **-** | **113** | **23.8** |
|  |  |  |  |  |  |  |
|  | **Case as control** | | **-** | **-** | **33** | **7.0** |
|  | - | Once | - | - | 28 | 5.9 |
|  | - | Twice | - | - | 5 | 1.1 |
|  |  |  |  |  |  |  |
|  | **Control** | | **-** | **-** | **72** | **15.2** |
|  | - | Once | - | - | 65 | 13.7 |
|  | - | Twice | - | - | 6 | 1.3 |
|  | - | Three times | - | - | 1 | 0.2 |
|  |  |  |  |  |  |  |
| **Total number of unique individuals in study** | | | **200** | **100.0** | **361** | **76.2** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| **B. Immunohistochemistry (IHC) assessment** | | | | | | |
|  |  |  | **Number of Cases** | | **Number of Controls** | |
|  |  |  | **No.** | **%** | **No.** | **%** |
|  |  |  |  |  |  |  |
| **Initially selected for IHC** | | | **200** | **100.0** | **474** | **100.0** |
|  |  |  |  |  |  |  |
|  | **Excluded** | | **12** | **6.0** | **26** | **5.5** |
|  | - | Insufficient tissue available | 12 | 6.0 | 26 | 5.5 |
|  |  |  |  |  |  |  |
|  | **Administrative reason for exclusion** | | **3** | **1.5** | **28** | **5.9** |
|  | - | Selected as case, controls excluded | 3 | 1.5 | - | - |
|  | - | Selected as control, case excluded | - | - | 28 | 5.9 |
|  |  |  |  |  |  |  |
| **Total excluded** | | | **15** | **7.5** | **54** | **11.4** |
|  |  |  |  |  |  |  |
| **Total included in IHC analysis** | | | **185** | **92.5** | **420** | **88.6** |
|  |  |  |  |  |  |  |
| **Duplicate controls** | | | **-** | **-** | **97** | **23.1** |
|  |  |  |  |  |  |  |
|  | **Case as control** | | **-** | **-** | **27** | **6.4** |
|  | - | Once | - | - | 23 | 5.5 |
|  | - | Twice | - | - | 4 | 1.0 |
|  |  |  |  |  |  |  |
|  | **Control** | | **-** | **-** | **61** | **14.5** |
|  | - | Once | - | - | 54 | 12.9 |
|  | - | Twice | - | - | 6 | 1.4 |
|  | - | Three times | - | - | 1 | 0.2 |
|  |  |  |  |  |  |  |
| **Total number of unique individuals in IHC analysis** | | | **185** | **100** | **323** | **76.9** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S2.** Clinical characteristics of 561 unique patients included in this study and of 669 patients not included in this case-control study. | | | | | | | |
| **Characteristics** | | **Included, No. (%)** | | **Not included, No. (%)** | | **P-value a** | |
| Overall | | 561 | (100.0) | 669 | (100.0) |  |  |
| Patient group | |  |  |  |  |  |  |
|  | Cases | 200 | (35.7) | 116 | (17.3) |  |  |
|  | Controls | 361 | (64.3) | 553 | (82.7) | <0.001 |  |
| Age at DCIS diagnosis, mean (range) | | 58 | (30 - 89) | 59 | (30 - 89) | 0.008 |  |
| Age at DCIS diagnosis (years) | |  |  |  |  |  |  |
|  | <40 | 33 | (5.9) | 29 | (4.33) |  |  |
|  | 40-49 | 74 | (13.2) | 108 | (16.1) |  |  |
|  | 50-59 | 225 | (40.1) | 210 | (31.4) |  |  |
|  | 60-69 | 160 | (28.5) | 178 | (26.6) |  |  |
|  | 70-79 | 52 | (9.3) | 105 | (15.7) |  |  |
|  | ≥80 | 17 | (3.0) | 39 | (5.8) | <0.001 |  |
| Year of DCIS diagnosis, mean (range) | | 1996 | (1989 - 2004) | 1997 | (1989 - 2004) | 0.17 |  |
| Period of DCIS diagnosis | |  |  |  |  |  |  |
|  | 1989-1998 (screening implementation phase) | 393 | (70.1) | 441 | (65.9) |  |  |
|  | 1999-2004 (full nationwide coverage) | 168 | (29.9) | 228 | (34.1) | 0.12 |  |
| Clinical presentation of DCIS | |  |  |  |  |  |  |
|  | Screen-detected | 282 | (50.3) | 273 | (40.8) |  |  |
|  | Non-screening-related | 230 | (41.0) | 332 | (49.6) | 0.001 |  |
|  | Unknown | 49 | (8.73) | 64 | (9.57) |  |  |
| a: For continuous variables, the p-value was calculated by unpaired T-test, and for categorical variables the p-value was calculated by chi-square test; Unknown clinical presentation was not included in the analysis. | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table S3.** Comparison of the 316 cases and 914 controls (unique) initially selected for the case-control study with the unique cases and controls included in this study | | | | | | | | | | |
|  |  |  | | |  |  | |  |  |  |
| **Cases** | |  | | |  |  | |  |  |  |
| Characteristics | | **Initial selection** | | | | **Included in study** | | |  |  |
|  |  | (*n* = 316) | | | | (*n* = 200) | | |  |  |
|  |  | n | | (%) | | n | | (%) | **P-value a** | |
| Age at DCIS diagnosis (years) | |  | |  | |  | |  |  |  |
|  | <40 | 16 | | (5.1) | | 14 | | (7.0) |  |  |
|  | 40-49 | 49 | | (15.5) | | 27 | | (13.5) |  |  |
|  | 50-59 | 109 | | (34.5) | | 79 | | (39.5) |  |  |
|  | 60-69 | 85 | | (26.9) | | 55 | | (27.5) |  |  |
|  | 70-79 | 41 | | (13.0) | | 19 | | (9.5) |  |  |
|  | ≥80 | 16 | | (5.1) | | 6 | | (3.0) | 0.48 |  |
| Year of DCIS diagnosis, mean (range) | | 1996 | | (1989 - 2004) | | 1996 | | (1989 - 2004) | 0.88 |  |
| Period of DCIS diagnosis | |  | |  | |  | |  |  |  |
|  | 1989-1998 (implementation phase) | 234 | | (74.1) | | 147 | | (73.5) |  |  |
|  | 1999-2004 (full nationwide coverage) | 82 | | (25.9) | | 53 | | (26.5) | 0.92 |  |
| Clinical presentation of DCIS | |  | |  | |  | |  |  |  |
|  | Screen-detected | 135 | | (42.7) | | 96 | | (48.0) |  |  |
|  | Non-screening-related | 155 | | (49.1) | | 89 | | (44.5) | 0.23 |  |
|  | Unknown | 26 | | (8.2) | | 15 | | (7.5) |  |  |
|  |  |  | |  | |  | |  |  |  |
|  |  |  | |  | |  | |  |  |  |
| **Controls** | |  | |  | |  | |  |  |  |
| Characteristics | | **Initial selection** | | | | **Included in study** | | |  |  |
|  |  | (*n* = 914) | | | | (*n* = 361) | | |  |  |
|  |  | n | (%) | | | n | (%) | | **P-value a** | |
| Age at DCIS diagnosis (years) | |  |  | | |  |  | |  |  |
|  | <40 | 46 | (5.0) | | | 19 | (5.3) | |  |  |
|  | 40-49 | 133 | (14.6) | | | 47 | (13.0) | |  |  |
|  | 50-59 | 326 | (35.7) | | | 146 | (40.4) | |  |  |
|  | 60-69 | 253 | (27.7) | | | 105 | (29.1) | |  |  |
|  | 70-79 | 116 | (12.7) | | | 33 | (9.1) | |  |  |
|  | ≥80 | 40 | (4.4) | | | 11 | (3.0) | | 0.30 |  |
| Year of DCIS diagnosis, mean (range) | | 1997 | (1989 - 2004) | | | 1997 | (1989 - 2004) | | 0.53 |  |
| Period of DCIS diagnosis | |  |  | | |  |  | |  |  |
|  | 1989-1998 (implementation phase) | 600 | (65.6) | | | 246 | (68.1) | |  |  |
|  | 1999-2004 (full nationwide coverage) | 314 | (34.4) | | | 115 | (31.9) | | 0.41 |  |
| Clinical presentation of DCIS | |  |  | | |  |  | |  |  |
|  | Screen-detected | 420 | (46.0) | | | 186 | (51.5) | |  |  |
|  | Non-screening-related | 407 | (44.5) | | | 141 | (39.1) | | 0.07 |  |
|  | Unknown | 87 | (9.5) | | | 34 | (9.4) | |  |  |
| a: For continuous variables, the p-value was calculated by paired T-test, and for categorical variables the p-value was calculated by chi-square test; Unknown clinical presentation was not included in the analysis. | | | | | | | | | | |

| **Table S4.** Multivariable analysis of histopathological characteristics and immunohistochemical markers independently associated with subsequent invasive disease | | | | | | |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |
|  |  | **DCIS cases** | | **DCIS controls** | |  |  |  |
|  |  | n | (%) | n | (%) | **OR (95% CI) a** | **P-value b** |  |
| Periductal fibrosis/COX-2 | | 185 |  | 420 |  |  |  |  |
|  | Absent/Low | 11 | (5.9) | 86 | (20.5) | 1.00 (reference) |  |  |
|  | Present/Low | 8 | (4.3) | 20 | (4.8) | 3.26 (1.13-9.42) |  |  |
|  | Absent/High | 102 | (55.1) | 213 | (50.7) | 3.82 (1.94-7.51) |  |  |
|  | Present/High | 59 | (31.9) | 92 | (21.9) | 4.87 (2.37-9.99) | <0.001 |  |
|  | N/A | 5 | (2.7) | 9 | (2.1) |  |  |  |
| Necrosis/COX-2 | |  |  |  |  |  |  |  |
|  | Absent/Low | 3 | (1.6) | 39 | (9.3) | 1.00 (reference) |  |  |
|  | Present/Low | 16 | (8.6) | 67 | (16.0) | 2.34 (0.63-8.66) |  |  |
|  | Absent/High | 37 | (20.0) | 76 | (18.1) | 5.07 (1.48-17.33) |  |  |
|  | Present/High | 124 | (67.0) | 230 | (54.8) | 5.76 (1.75-18.95) | 0.001 |  |
|  | N/A | 5 | (2.7) | 8 | (1.9) |  |  |  |
| Periductal fibrosis/HER2 | |  |  |  |  |  |  |  |
|  | Absent/Negative | 89 | (48.1) | 244 | (58.1) | 1.00 (reference) |  |  |
|  | Present/Negative | 31 | (16.8) | 65 | (15.5) | 1.25 (0.75-2.09) |  |  |
|  | Absent/Positive | 24 | (13.0) | 54 | (12.9) | 1.26 (0.74-2.17) |  |  |
|  | Present/Positive | 38 | (20.5) | 50 | (11.9) | 2.04 (1.23-3.38) | 0.050 |  |
|  | N/A | 3 | (1.6) | 7 | (1.7) |  |  |  |
| Necrosis/HER2 | |  |  |  |  |  |  |  |
|  | Absent/Negative | 35 | (18.9) | 107 | (25.5) | 1.00 (reference) |  |  |
|  | Present/Negative | 85 | (45.9) | 203 | (48.3) | 1.26 (0.80-1.99) |  |  |
|  | Absent/Positive | 5 | (2.7) | 9 | (2.1) | 1.72 (0.52-5.63) |  |  |
|  | Present/Positive | 57 | (30.8) | 95 | (22.6) | 1.84 (1.10-3.09) | 0.12 |  |
|  | N/A | 3 | (1.6) | 6 | (1.4) |  |  |  |
| Periductal fibrosis/Necrosis/COX-2 | |  |  |  |  |  |  |  |
|  | All other groupings | 19 | (10.3) | 106 | (25.2) | 1.00 (reference) |  |  |
|  | Negative/Negative/High | 28 | (15.1) | 66 | (15.7) | 2.39 (1.21-4.71) |  |  |
|  | Positive/Negative/High | 9 | (4.9) | 10 | (2.4) | 4.60 (1.62-13.03) |  |  |
|  | Negative/Positive/High | 74 | (40.0) | 147 | (35.0) | 2.90 (1.62-5.21) |  |  |
|  | Positive/Positive/High | 50 | (27.0) | 82 | (19.5) | 3.39 (1.81-6.34) | 0.002 |  |
|  | N/A | 5 | (2.7) | 9 | (2.1) |  |  |  |
| Fibrosis/Necrosis/HER2 | |  |  |  |  |  |  |  |
|  | All other groupings | 40 | (21.6) | 116 | (27.6) | 1.00 (reference) |  |  |
|  | Negative/Positive/Negative | 62 | (33.5) | 149 | (35.5) | 1.19 (0.74-1.91) |  |  |
|  | Positive/Positive/Negative | 23 | (12.4) | 53 | (12.6) | 1.15 (0.62-2.12) |  |  |
|  | Negative/Positive/Positive | 21 | (11.4) | 45 | (10.7) | 1.39 (0.73-2.66) |  |  |
|  | Positive/Positive/Positive | 36 | (19.5) | 50 | (11.9) | 2.02 (1.14-3.56) | 0.18 |  |
|  | N/A | 3 | (1.6) | 7 | (1.7) |  |  |  |
| Necrosis/HER2/COX-2 | |  |  |  |  |  |  |  |
|  | All other groupings | 13 | (7) | 65 | (15.5) | 1.00 (reference) |  |  |
|  | Positive/Negative/Low | 11 | (5.9) | 43 | (10.2) | 1.14 (0.45-2.89) |  |  |
|  | Negative/Negative/High | 32 | (17.3) | 71 | (16.9) | 2.12 (1.00-4.50) |  |  |
|  | Positive/Negative/High | 73 | (39.5) | 156 | (37.1) | 2.23 (1.13-4.41) |  |  |
|  | Positive/Positive/High | 50 | (27) | 72 | (17.1) | 3.43 (1.66-7.08) | 0.004 |  |
|  | N/A | 6 | (3.2) | 13 | (3.1) |  |  |  |
| a: Comparisons between DCIS cases and DCIS controls were made by multivariate conditional logistic regression.  b: P-values for overall effect were calculated by Wald-test.  N/A: Not assessable. N/As were not included in the analysis.  LR chi2 corrected for degrees of freedom were 6.34 for periductal fibrosis/COX-2, 5.18 for necrosis/COX-2, 2.60 for periductal fibrosis/HER2, 1.95 for necrosis/HER2, 4.39 for periductal fibrosis/necrosis/COX-2, 1.57 for periductal fibrosis/necrosis/HER2, and 3.83 for necrosis/HER2/COX-2. | | | | | | | | |