Circulating growth factors data associated with insulin secretagogue use in women with incident breast cancer

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Abstract

Oral drugs stimulating insulin production may impact growth factor levels. The data presented shows the relationship between pre-existing insulin secretagogues use, growth factor profiles at the time of breast cancer diagnosis and subsequent cancer outcomes in women diagnosed with breast cancer and type 2 diabetes mellitus. A Pearson correlation analysis evaluating the relationship between growth factors stratified by diabetes pharmacotherapy and controls is also provided.

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**Specifications Table**

| Subject area                      | Clinical and Translational Research |
|-----------------------------------|-------------------------------------|
| More specific subject area        | Biomarker Research, Cancer Epidemiology |
| Type of data                      | Tables                              |
| How data was acquired             | Tumor registry query was followed by vital status ascertainment, and medical records review |
|                                   | Luminex®-based quantitation of growth factors (epidermal growth factor, fibroblast growth factor 2, vascular endothelial growth factor, hepatocyte growth factor, platelet-derived growth factor BB, and tumor growth factor-β) from plasma samples was conducted. |
|                                   | A Luminex®200™ instrument with Xponent 3.1 software was used to acquire all data |
| Data format                       | Analyzed                            |
| Experimental factors              | Growth factors were determined from the corresponding plasma samples collected at the time of breast cancer diagnosis |
| Experimental features             | The dataset included 97 adult females with diabetes mellitus and newly diagnosed breast cancer (cases) and 194 matched controls (breast cancer only). Clinical and treatment history were evaluated in relationship with cancer outcomes and growth factor profiles. A growth factor correlation analysis was also performed. |
| Data source location              | United States, Buffalo, NY - 42° 53' 50.3592"N; 78° 52' 2.658"W |
| Data accessibility                | The data is with this article       |

**Value of the data**

- This dataset shows the observed relationship between baseline insulin secretagogues use, circulating growth factor levels at the time of cancer diagnosis and breast cancer outcomes.
- Reported data may guide future studies evaluating pharmacotherapy-induced growth factor modulation in breast cancer.
- These observations can assist future study design in evaluating the relationship between diabetes pharmacotherapy safety and circulating growth factors levels at the time of cancer diagnosis.

1. **Data**

Reported data represents the observed association between use of insulin secretagogues preceding breast cancer and the growth factor profiles at the time of cancer diagnosis in women with diabetes mellitus (Table 1). Data in Table 2 includes the observed correlations between growth factors stratified by type 2 diabetes mellitus pharmacotherapy and controls. C-peptide correlation with each of the studied growth factors is presented in Table 2, however details regarding its determination from plasma, association with cancer outcomes and insulin secretagogues use has been already reported by us [2].
| Biomarker | Biomarker grouping | Concentration | Control | No Secretagogue | Any Secretagogue | Unadjusted P-value (MVP) |
|-----------|--------------------|---------------|---------|-----------------|-----------------|-------------------------|
|           |                    |               |         |                 |                 | p¹                      |
|           |                    |               |         |                 |                 | p²                      |
|           |                    |               |         |                 |                 | p³                      |
|           |                    |               |         |                 |                 | Global test             |
| EGF       | Median, ng/ml      | –             | 20.26   | 29.60           | 26.63           | 0.002                   |
|           | (25th–75th)        |               | (12.25–37.04) | (18.76–56.42) | (15.35–53.77) | (0.002)                 |
|           | Quartiles          | 1.60–13.61    | 57 (29.4%) | 6 (12.8%)       | 10 (20.0%)      | 0.020                   |
|           |                    | 13.79–23.29   | 51 (26.3%) | 10 (21.3%)      | 12 (24.0%)      | 0.280                   |
|           |                    | 23.70–44.72   | 47 (24.2%) | 13 (27.7%)      | 12 (24.0%)      | 0.740                   |
|           |                    | 45.35–382.99  | 39 (20.1%) | 18 (38.3%)      | 16 (32.0%)      | 0.070                   |
|           | OS-Based Optimization | 1.60–113.10 | 5 (2.6%) | 49 (25.3%) | 14 (28.0%) | 0.220                   |
|           |                    | 116.01–382.99 | 5 (2.6%) | 3 (6.0%) | 14 (28.0%) | 0.430                   |
|           | DFS-Based Optimization | 1.60–5.20 | 12 (6.2%) | 4 (8.0%) | 4 (8.0%) | 0.490                   |
|           |                    | 5.39–382.99   | 182 (93.8%) | 46 (97.9%) | 46 (92.0%) | 0.240                   |
| FGF-2     | Median, pg/ml      | –             | 16.15   | 30.58           | 14.66           | 0.048                   |
|           | (25th–75th)        |               | (4.32–34.43) | (7.13–49.11) | (3.20–42.68) | (0.034)                 |
|           | Quartiles          | 1.60–4.18     | 49 (25.3%) | 10 (21.3%)     | 14 (28.0%)      | 0.220                   |
|           |                    | 4.76–17.34    | 51 (26.3%) | 9 (19.1%)      | 13 (26.0%)      | 0.620                   |
|           |                    | 17.51–39.78   | 52 (26.8%) | 11 (23.4%)     | 9 (18.0%)       | 0.430                   |
|           |                    | 40.30–1147.64 | 42 (21.6%) | 17 (36.2%)     | 14 (28.0%)      | 0.780                   |
|           | OS-Based Optimization | 1.60–10.15 | 72 (37.1%) | 15 (31.9%) | 19 (38.0%) | 0.510                   |
|           |                    | 10.21–1147.64 | 122 (62.9%) | 32 (68.1%) | 31 (62.0%) | 0.530                   |
|           | DFS-Based Optimization | 1.60–14.61 | 87 (44.8%) | 17 (36.2%) | 25 (50.0%) | 0.380                   |
|           |                    | 14.68–1147.64 | 107 (55.2%) | 30 (63.8%) | 25 (50.0%) | 0.380                   |
| HGF       | Median, pg/ml      | –             | 289     | 347             | 348             | 0.160                   |
|           | (25th–75th)        |               | (129–439) | (193–507) | (136–576) | 0.240                   |
| Biomarker | Biomarker grouping | Concentration | Control | No Secretagogue | Any Secretagogue | Unadjusted P-value (MVP) |
|-----------|--------------------|---------------|---------|-----------------|------------------|-------------------------|
|           |                    |               |         |                 |                  | p¹ | p² | p³ | Global test |
| Quartiles | 13.02–130.22       | 50 (25.8%)    | 11 (23.4%) | 12 (24.0%)      | 0.670            | 0.021 | 0.350 | 0.110 |
|           | 130.72–312.56      | 52 (26.8%)    | 10 (21.3%) | 11 (22.0%)      |                  |                  |                  |                  |
|           | 314.96–472.00      | 53 (27.3%)    | 13 (27.7%) | 7 (14.0%)       |                  |                  |                  |                  |
|           | 505.37–6728.77     | 39 (20.1%)    | 13 (27.7%) | 20 (40.0%)      |                  |                  |                  |                  |
| OS-Based  | 13.02–1148.76      | 188 (96.9%)   | 45 (95.7%) | 48 (96.0%)      | 0.660            | (0.770) | (0.960) | (0.840) | (0.960) |
| Optimization | 1169.11–6728.77   | 6 (3.1%)      | 2 (4.3%)   | 2 (4.0%)        | 0.000            | (0.250) | (0.460) | (0.640) |
| DFS-Based | 13.02–919.06       | 185 (95.4%)   | 44 (93.6%) | 44 (88.0%)      | 0.710            | 0.090 | 0.490 | 0.170 |
| Optimization | 920.11–6728.77   | 9 (4.6%)      | 3 (6.4%)   | 6 (12.0%)       |                  |                  |                  |                  |
| PDGF-BB   | Median, pg/ml (25th–75th) | 2055 (615–5402) | 1341 (309–2802) | 1105 (205–3211) | 0.100           | 0.037 | 0.710 | 0.053 |
|           | Quartiles          | 60–414        | 43 (22.2%) | 13 (27.7%)      | 17 (34.0%)       | 0.610 | 0.210 | 0.800 | 0.460 |
|           |                    | 440–1618      | 47 (24.2%) | 12 (25.5%)      | 14 (28.0%)       |                  |                  |                  |                  |
|           |                    | 1660–4332     | 49 (25.3%) | 13 (27.7%)      | 10 (20.0%)       |                  |                  |                  |                  |
|           |                    | 4355–15,480   | 55 (28.4%) | 9 (19.1%)       | 9 (18.0%)        |                  |                  |                  |                  |
| OS-Based  | 60–2687³           | 109 (56.2%)   | 34 (72.3%) | 35 (70.0%)      | 0.046           | 0.080 | 0.800 | 0.046 |
| Optimization | 2694–15,480      | 85 (43.8%)    | 13 (27.7%) | 15 (30.0%)      | (0.014)         | (0.035) | (0.940) | (0.017) |
| DFS-Based | 60–10,400¹         | 186 (95.9%)   | 44 (93.6%) | 49 (98.0%)      | 0.450           | 0.690 | 0.350 | 0.490 |
| Optimization | 10,944–15,480     | 8 (4.1%)      | 3 (6.4%)   | 1 (2.0%)        | (0.690)         | (0.710) | (0.450) | (0.690) |
| TGF-β     | Median, pg/ml (25th–75th) | 3007 (1996–4053) | 4063 (2678–4872) | 3425 (2417–4414) | 0.013 | 0.070 | 0.450 | 0.017 |
|           |                    | –             |          |                 |                  |                  |                  |                  |

Note: MBA® Wntrob et al./Data in Brief 11 (2017) 459–468
| Quartiles | 453–2151 | 57 (29.4%) | 7 (14.9%) | 9 (18.0%) | 0.060 | 0.110 | 0.440 | 0.052 |
|-----------|----------|------------|-----------|-----------|--------|--------|--------|--------|
|           | 2155–3157 | 52 (26.8%) | 11 (23.4%) | 10 (20.0%) |        |        |        |        |
|           | 3183–4303 | 43 (22.2%) | 11 (23.4%) | 18 (36.0%) |        |        |        |        |
|           | 4311–12,026 | 42 (21.6%) | 18 (38.3%) | 13 (26.0%) |        |        |        |        |

OS-Based Optimization

| Quartiles | 453–5545 | 176 (90.7%) | 39 (83.0%) | 43 (86.0%) | 0.130 | 0.330 | 0.680 | 0.260 |
|-----------|----------|------------|-----------|-----------|--------|--------|--------|--------|
|           | 5557–12,026 | 18 (9.3%) | 8 (17.0%) | 7 (14.0%) | (0.220) | (0.890) | (0.320) | (0.480) |

DFS-Based Optimization

| Quartiles | 453–1881 | 42 (21.6%) | 6 (12.8%) | 6 (12.0%) | 0.180 | 0.130 | 0.910 | 0.160 |
|-----------|----------|------------|-----------|-----------|--------|--------|--------|--------|
|           | 1907–12,026 | 152 (78.4%) | 41 (87.2%) | 44 (88.0%) | (0.210) | (0.470) | (0.800) | (0.370) |

VEGF Median, pg/ml (25th–75th)

| Quartiles | 1.60–43.56 | 52 (26.8%) | 8 (17.0%) | 13 (26.0%) | 0.210 | 0.680 | 0.120 | 0.320 |
|-----------|------------|------------|-----------|-----------|--------|--------|--------|--------|
|           | 44.52–97.48 | 51 (26.3%) | 9 (19.1%) | 16 (32.0%) |        |        |        |        |
|           | 97.87–192.64 | 45 (23.2%) | 16 (34.0%) | 8 (16.0%) |        |        |        |        |
|           | 194.47–4197.81 | 46 (23.7%) | 14 (29.8%) | 13 (26.0%) |        |        |        |        |

OS-Based Optimization

| Quartiles | 1.60–37.94 | 45 (23.2%) | 7 (14.9%) | 10 (20.0%) | 0.220 | 0.630 | 0.510 | 0.450 |
|-----------|------------|------------|-----------|-----------|--------|--------|--------|--------|
|           | 38.42–4197.81 | 149 (76.8%) | 40 (85.1%) | 40 (80.0%) | (0.150) | (0.810) | (0.570) | (0.370) |

DFS-Based Optimization

| Quartiles | 1.60–37.94 | 45 (23.2%) | 7 (14.9%) | 10 (20.0%) | 0.220 | 0.630 | 0.510 | 0.450 |
|-----------|------------|------------|-----------|-----------|--------|--------|--------|--------|
|           | 38.42–4197.81 | 149 (76.8%) | 40 (85.1%) | 40 (80.0%) | (0.150) | (0.810) | (0.570) | (0.370) |

Unadjusted p-values: $p^1$, compares no secretagogue versus control; $p^2$, compares any secretagogue versus control; $p^3$, compares any secretagogue versus no secretagogue (as per Kruskal–Wallis test); global test, compares all categories (as per Wilcoxon, type 3 error test); MVP denotes the p-value of each multivariate adjusted analysis corresponding to the earlier described unadjusted analyses. For more information, please see Section 2.7 below and our previously published analysis work flow1. MVP = p-value of the multivariate adjusted analysis. Epidermal growth factor (EGF), fibroblast Growth Factor 2 (FGF-2), hepatocyte growth factor (HGF), platelet-derived growth factor BB (PDGF-BB), tumor growth factor (TGF), vascular endothelial growth factor (VEGF).

Overall survival (OS)- and disease-free survival (DFS)-optimized growth factor ranges associated with poorer outcomes (i.e. the group with a lower survival probability) are represented in bold.
### Table 2
Growth factor correlations by secretagogues use.

| Compared Biomarkers | Group | Unadjusted Correlation | Adjusted Correlation |
|---------------------|-------|------------------------|----------------------|
|                     |       | Pearson Correlation 95% Confidence Interval | p-value | Pearson Correlation 95% Confidence Interval | p-value |
| C-Peptide EGF       | All Subjects (n=291) | -0.098 -0.210 to 0.018 | 0.096 | **-0.136 -0.247 to -0.020** | 0.021 |
|                     | Controls (n=194)     | -0.104 -0.242 to 0.037 | 0.147 | -0.141 -0.278 to 0.001 | 0.051 |
|                     | No Secretagogue (n=43) | -0.395 -0.622 to -0.108 | 0.008 | **-0.388 -0.624 to -0.087** | 0.012 |
|                     | Any Secretagogue (n=54) | 0.166 -0.106 to 0.416 | 0.226 | 0.229 -0.050 to 0.474 | 0.103 |
| C-Peptide FGF-2     | All Subjects (n=291) | -0.161 -0.271 to -0.047 | 0.006 | **-0.178 -0.288 to -0.064** | 0.002 |
|                     | Controls (n=194)     | -0.122 -0.259 to 0.019 | 0.089 | -0.125 -0.263 to 0.017 | 0.083 |
|                     | No Secretagogue (n=43) | -0.391 -0.619 to -0.103 | 0.008 | **-0.364 -0.607 to -0.059** | 0.019 |
|                     | Any Secretagogue (n=54) | -0.105 -0.362 to 0.168 | 0.448 | -0.071 -0.340 to 0.208 | 0.618 |
| C-Peptide HGF       | All Subjects (n=291) | 0.035 -0.080 to 0.150 | 0.549 | 0.006 -0.109 to 0.122 | 0.913 |
|                     | Controls (n=194)     | 0.173 0.033 to 0.306 | 0.016 | **0.165 0.024 to 0.300** | 0.0219 |
|                     | No Secretagogue (n=43) | -0.204 -0.475 to 0.103 | 0.186 | -0.275 -0.540 to 0.040 | 0.082 |
|                     | Any Secretagogue (n=54) | -0.034 -0.299 to 0.236 | 0.804 | -0.025 -0.299 to 0.252 | 0.861 |
| C-Peptide PDGF-BB   | All Subjects (n=291) | -0.111 -0.223 to 0.004 | 0.058 | -0.093 -0.206 to 0.023 | 0.116 |
|                     | Controls (n=194)     | -0.087 -0.176 to 0.105 | 0.618 | -0.082 -0.222 to 0.060 | 0.254 |
|                     | No Secretagogue (n=43) | -0.122 -0.408 to 0.185 | 0.432 | -0.134 -0.428 to 0.185 | 0.405 |
|                     | Any Secretagogue (n=54) | -0.068 -0.330 to 0.204 | 0.625 | -0.049 -0.321 to 0.229 | 0.730 |
| C-Peptide TGF-β     | All Subjects (n=291) | 0.063 -0.053 to 0.177 | 0.285 | 0.018 -0.098 to 0.133 | 0.767 |
|                     | Controls (n=194)     | -0.036 -0.176 to 0.105 | 0.618 | -0.064 -0.205 to 0.078 | 0.375 |
|                     | No Secretagogue (n=43) | 0.254 -0.050 to 0.515 | 0.096 | 0.230 -0.088 to 0.505 | 0.150 |
|                     | Any Secretagogue (n=54) | 0.035 -0.235 to 0.300 | 0.803 | 0.035 -0.243 to 0.308 | 0.807 |
| C-Peptide VEGF      | All Subjects (n=291) | -0.127 -0.238 to -0.012 | 0.030 | **-0.136 -0.247 to -0.020** | 0.021 |
|                     | Controls (n=194)     | -0.096 -0.233 to 0.046 | 0.184 | -0.095 -0.234 to 0.047 | 0.189 |
|                     | No Secretagogue (n=43) | -0.389 -0.617 to -0.100 | 0.009 | **-0.350 -0.596 to -0.043** | 0.024 |
|                     | Any Secretagogue (n=54) | 0.068 -0.203 to 0.330 | 0.622 | 0.119 -0.162 to 0.382 | 0.404 |
| EGF                 | All Subjects (n=291) | 0.730 0.672 to 0.780 | <0.001 | 0.734 0.675 to 0.783 | <0.001 |
|                     | Controls (n=194)     | 0.717 0.641 to 0.779 | <0.001 | 0.725 0.650 to 0.786 | <0.001 |
|                     | No Secretagogue (n=43) | 0.812 0.677 to 0.894 | <0.001 | 0.824 0.689 to 0.903 | <0.001 |
|                     | Any Secretagogue (n=54) | 0.307 0.042 to 0.531 | 0.022 | 0.342 0.072 to 0.564 | 0.013 |
| EGF                 | All Subjects (n=291) | 0.311 0.203 to 0.411 | <0.001 | 0.291 0.182 to 0.394 | <0.001 |
|                     | Controls (n=194)     | 0.107 -0.034 to 0.244 | 0.137 | 0.087 -0.055 to 0.226 | 0.229 |
|                     | No Secretagogue (n=43) | 0.544 0.291 to 0.726 | <0.001 | 0.583 0.332 to 0.757 | <0.001 |
|                     | Any Secretagogue (n=54) | 0.157 -0.115 to 0.408 | 0.252 | 0.127 -0.154 to 0.389 | 0.371 |
| EGF                 | All Subjects (n=291) | -0.023 -0.138 to 0.092 | 0.694 | -0.007 -0.123 to 0.108 | 0.900 |
|                     | Controls (n=194)     | 0.016 -0.125 to 0.157 | 0.824 | 0.009 -0.133 to 0.151 | 0.898 |
|                     | No Secretagogue (n=43) | -0.117 -0.403 to 0.190 | 0.451 | -0.093 -0.393 to 0.225 | 0.567 |
| | Any Secretagogue (n=54) | | | | |
|---|---|---|---|---|---|
| EGF (n=291) | 0.052 | -0.219 to 0.315 | 0.707 | -0.080 | -0.348 to 0.120 | 0.573 |
| Controls (n=194) | 0.196 | 0.082 to 0.304 | <0.001 | 0.172 | 0.058 to 0.282 | 0.003 |
| No Secretagogue (n=43) | 0.153 | -0.154 to 0.433 | 0.324 | 0.170 | -0.150 to 0.457 | 0.291 |
| FGF (n=291) | 0.621 | 0.545 to 0.687 | <0.001 | 0.627 | 0.552 to 0.693 | <0.001 |
| Controls (n=194) | 0.621 | 0.526 to 0.700 | <0.001 | 0.627 | 0.533 to 0.706 | <0.001 |
| No Secretagogue (n=43) | 0.662 | 0.451 to 0.803 | <0.001 | 0.691 | 0.483 to 0.825 | <0.001 |
| FGF-2 (n=291) | 0.336 | 0.075 to 0.554 | 0.012 | 0.366 | 0.101 to 0.583 | 0.007 |
| Controls (n=194) | 0.138 | 0.024 to 0.249 | 0.018 | 0.133 | 0.018 to 0.245 | 0.023 |
| No Secretagogue (n=43) | 0.264 | -0.040 to 0.523 | 0.084 | 0.299 | -0.014 to 0.558 | 0.058 |
| PDGF-BB (n=291) | 0.127 | 0.012 to 0.239 | 0.030 | 0.120 | 0.005 to 0.233 | 0.041 |
| Controls (n=194) | 0.054 | -0.087 to 0.194 | 0.453 | 0.048 | -0.095 to 0.189 | 0.509 |
| No Secretagogue (n=43) | 0.288 | -0.014 to 0.541 | 0.058 | -0.046 | -0.310 to 0.225 | 0.743 |
| PDGF-BB (n=291) | 0.805 | 0.760 to 0.842 | <0.001 | 0.805 | 0.760 to 0.842 | <0.001 |
| Controls (n=194) | 0.845 | 0.780 to 0.881 | <0.001 | 0.845 | 0.799 to 0.881 | <0.001 |
| No Secretagogue (n=43) | 0.754 | 0.586 to 0.859 | <0.001 | 0.763 | 0.592 to 0.868 | <0.001 |
| PDGF-BB (n=291) | 0.8 | 0.677 to 0.879 | <0.001 | 0.792 | 0.660 to 0.876 | <0.001 |
| Controls (n=194) | 0.057 | -0.058 to 0.171 | 0.328 | 0.074 | -0.042 to 0.188 | 0.208 |
| No Secretagogue (n=43) | 0.093 | -0.048 to 0.231 | 0.195 | 0.087 | -0.056 to 0.226 | 0.233 |
| PDGF-BB (n=291) | 0.247 | -0.022 to 0.483 | 0.069 | 0.226 | -0.053 to 0.472 | 0.107 |
| Controls (n=194) | 0.116 | 0.001 to 0.228 | 0.048 | 0.091 | -0.025 to 0.205 | 0.122 |
| No Secretagogue (n=43) | 0.113 | -0.028 to 0.250 | 0.116 | 0.099 | -0.043 to 0.238 | 0.170 |
| PDGF-BB (n=291) | 0.02 | -0.282 to 0.318 | 0.901 | -0.036 | -0.344 to 0.279 | 0.824 |
| Controls (n=194) | 0.294 | 0.029 to 0.521 | 0.029 | 0.304 | 0.031 to 0.535 | 0.028 |
| No Secretagogue (n=43) | 0.034 | -0.081 to 0.149 | 0.562 | 0.032 | -0.084 to 0.147 | 0.584 |
| PDGF-BB (n=291) | 0.031 | -0.110 to 0.171 | 0.666 | 0.025 | -0.118 to 0.166 | 0.736 |
| Controls (n=194) | 0.024 | -0.278 to 0.322 | 0.876 | 0.095 | -0.223 to 0.395 | 0.557 |
| No Secretagogue (n=43) | -0.091 | -0.350 to 0.182 | 0.513 | -0.078 | -0.346 to 0.202 | 0.584 |
| PDGF-BB (n=291) | -0.120 | -0.232 to -0.005 | 0.040 | -0.103 | -0.216 to 0.012 | 0.080 |
| Controls (n=194) | -0.145 | -0.280 to -0.004 | 0.044 | -0.155 | -0.290 to -0.013 | 0.032 |
| No Secretagogue (n=43) | -0.110 | -0.397 to 0.197 | 0.481 | -0.055 | -0.360 to 0.261 | 0.734 |
2. Experimental design, materials and methods

Evaluation of growth factor profile association with insulin secretagogue use and BC outcomes was carried out under two protocols approved by both Roswell Park Cancer Institute (EDR154409 and NHR009010) and the State University of New York at Buffalo (PHP0840409E). Demographic and clinical patient information was linked with cancer outcomes and growth factor profiles of corresponding plasma specimen harvested at BC diagnosis and banked in the Roswell Park Cancer Institute Data Bank and Bio-Repository.

2.1. Study population

As described in the original research article by Wintrob et al. [1], all incident breast cancer cases diagnosed at Roswell Park Cancer Institute (01/01/2003-12/31/2009) were considered for inclusion (n = 2194). Medical and pharmacotherapy history were used to determine the baseline presence of diabetes.

2.2. Inclusion and exclusion criteria

Inclusion criteria were as follows: minimum 18 years of age at diagnosis, presence of pre-existing diabetes at breast cancer diagnosis, and having available banked treatment-naïve plasma specimens in the Institute's Data Bank and Bio-Repository. That is, the blood had to be collected prior to the initiation of any cancer-related therapy (surgery, radiation or pharmacotherapy).

Subjects were excluded if they were male, had prior cancer history or unclear date of diagnosis, incomplete clinical records, type 1 or unclear diabetes status. For a specific breakdown of excluded subjects, please see the original research article by Wintrob et al. [1].

A total of 97 female subjects with breast cancer and baseline diabetes mellitus were eligible for inclusion in this analysis.

2.3. Control-matching approach

Each of the 97 adult female subjects with breast cancer and diabetes mellitus (defined as “cases”) was matched with two other female subjects diagnosed with breast cancer, but without baseline diabetes mellitus (defined as “controls”). The following matching criteria were used: age at diagnosis, body mass index category, ethnicity, menopausal status and tumor stage (as per the American Joint Committee on Cancer). Some matching limitations applied [1].

| PDGF-BB | VEGF |
|---------|------|
| Any Secretagogue (n=54) | 0.051 -0.220 to 0.314 0.716 0.059 -0.220 to 0.329 0.679 |
| All Subjects (n=291) | 0.078 -0.037 to 0.192 0.182 0.081 -0.035 to 0.195 0.168 |
| Controls (n=194) | **0.143** **0.003 to 0.279** 0.045 0.138 -0.004 to 0.275 0.056 |
| No Secretagogue (n=43) | 0.047 -0.257 to 0.342 0.764 -0.011 -0.321 to 0.302 0.947 |
| Any Secretagogue (n=54) | -0.107 -0.364 to 0.166 0.439 -0.047 -0.318 to 0.232 0.744 |
| All Subjects (n=291) | 0.100 -0.016 to 0.212 0.089 0.098 -0.018 to 0.211 0.096 |
| Controls (n=194) | 0.044 -0.098 to 0.184 0.542 0.040 -0.103 to 0.181 0.583 |
| No Secretagogue (n=43) | 0.208 -0.099 to 0.478 0.177 0.280 -0.035 to 0.544 0.077 |
| Any Secretagogue (n=54) | -0.033 -0.299 to 0.236 0.810 -0.034 -0.306 to 0.244 0.814 |

Significant correlations are displayed in bolded text. The differences that are only significant in either adjusted or unadjusted correlations are further denoted by an outline. Epidermal growth factor (EGF), fibroblast Growth Factor 2 (FGF-2), hepatocyte growth factor (HGF), platelet-derived growth factor BB (PDGF-BB), tumor growth factor (TGF), vascular endothelial growth factor (VEGF).
2.4. Demographic and clinical data collection

Clinical and treatment history was documented by medical chart review. Vital status was obtained from the Institute’s Tumor Registry, a local database updated biannually with data obtained from the National Comprehensive Cancer Networks’ Oncology Outcomes Database. Outcomes of interest were overall survival (death from breast cancer) and disease-free survival (breast cancer recurrence and/or death). Mean overall and disease-free survival were 113.3 and 107.3 months respectively, both with a minimum follow-up of 25.6 months. For additional details concerning data collection, specific definitions regarding censoring and drug use (including the number of insulin users per analyzed group), and a comprehensive demographic report, please see the original article by Wintrob et al. [1].

2.5. Plasma specimen storage and retrieval

All the plasma specimens retrieved from long-term storage were individually aliquoted in color coded vials labeled with unique, subject specific barcodes. Overall duration of freezing time was accounted for all matched controls ensuring that the case and matched control specimens had similar overall storage conditions. Only two instances of freeze-thaw were allowed between biobank retrieval and biomarker analyses: aliquoting procedure step and actual assay.

2.6. LuminexASSays

A total of 6 biomarkers (epidermal growth factor, fibroblast growth factor 2, vascular endothelial growth factor, hepatocyte growth factor, platelet-derived growth factor BB, and tumor growth factor-β) were quantified according to the manufacturer protocol. The following Luminex® biomarker panels were utilized in this study: TGFβ-64K (tumor growth factor-β), HCYTOMAG-60K (platelet-derived growth factor BB), and HAGP1MAG-12K (epidermal growth factor, fibroblast growth factor 2, vascular endothelial growth factor, and hepatocyte growth factor) produced by Millipore Corporation, Billerica, MA. C-peptide determinations were done according to the manufacturer protocol as previously reported [2].

2.7. Biomarker-pharmacotherapy association analysis

Biomarker cut-point optimization was performed for each analyzed biomarker. Biomarker levels constituted the continuous independent variable that was subdivided into two groups. Cut-point selection was determined by p-value optimization using the log rank method with respect to survival (both overall and disease-free) as the dependent variable with the condition of a minimum biomarker group size of 10 patients. The results of this analysis yielded the cut-point for each biomarker that would provide the most significant separation of a Kaplan-Meier survival probability curve by assigning the subject to their respective biomarker category, specifically above or below the identified cut-point. Thus identifying potential biomarker ranges associated with poorer outcomes, specifically, ranges associated with a lower survival probability. Quartiles were also constructed. The resultant biomarker categories were then ztested for association with type 2 diabetes mellitus therapy and controls by Fisher’s exact test. The continuous biomarker levels were also tested for association with diabetes therapy and controls across groups by the Kruskal–Wallis test and pairwise by the Wilcoxon rank sum. Multivariate adjustments were performed accounting for age, tumor stage, body mass index, estrogen receptor status, and cumulative comorbidity. The biomarker analysis was performed using R Version 2.15.3. Please see the original article for an illustration of the analysis workflow [1].

Correlations between biomarkers stratified by type 2 diabetes mellitus pharmacotherapy and controls were assessed by the Pearson method. Correlation models were constructed both with and without adjustment for age, body mass index, and the combined comorbidity index. Correlation analyses were performed using SAS Version 9.4.
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Transparency document. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.dib.2017.02.038.

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