Data Article

Dataset on growth factor levels and insulin use in patients with diabetes mellitus and incident breast cancer

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A R T I C L E   I N F O

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A B S T R A C T

Growth factor profiles could be influenced by the utilization of exogenous insulin. The data presented shows the relationship between pre-existing use of injectable insulin in women diagnosed with breast cancer and type 2 diabetes mellitus, the growth factor profiles at the time of breast cancer diagnosis, and subsequent cancer outcomes. A Pearson correlation analysis evaluating the relationship between growth factors stratified by insulin use and controls is also provided.
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 |
|                                      | Luminox®-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 Luminox®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 represents the observed relationship between injectable insulin use, circulating growth factors at breast cancer diagnosis and outcomes.
- Reported data has the potential to guide future research evaluating insulin-induced growth factor modulation in breast cancer.
- Our observations may assist future studies in evaluating the relationship between insulin safety and effectiveness and growth factors production in cancer.

1. Data

Reported data represents the observed association between use of injectable insulin 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 use of injectable insulin has been previously reported by us [1].
Table 1
Growth factor associations with insulin use.

| Biomarker | Biomarker grouping | Concentration (ng/ml) | Control | No insulin | Any insulin | Unadjusted p-value (MVP) | p1 | p2 | p3 | Global test |
|-----------|--------------------|-----------------------|---------|------------|-------------|-------------------------|-----|-----|-----|-------------|
| **EGF (ng/ml)** | Median (25–75th) | 20.26 (12.25–37.04) | 28.70 (16.55–56.15) | 31.50 (17.62–54.76) | | 0.002 | 0.049 | 0.920 | 0.003 |
| Quartiles | 1.60–13.61 | 57 (29.4%) | 12 (15.8%) | 3 (15.0%) | 0.019 | (0.140) | 0.930 | (0.023) |
| | 13.79–23.29 | 51 (26.3%) | 17 (22.4%) | 5 (25.0%) | 0.212 | 0.360 | 1.000 | 0.080 |
| | 23.70–44.72 | 47 (24.2%) | 20 (26.3%) | 5 (25.0%) | 0.920 | (0.930) | (0.930) | (0.930) |
| | 45.35–382.99 | 39 (20.1%) | 27 (35.5%) | 7 (35.0%) | 0.003 | (0.023) | (0.023) | (0.023) |
| **OS-Based Optimization** | 1.60–113.10 | 189 (97.4%) | 69 (90.8%) | 19 (95.0%) | 0.042 | 0.450 | 1.000 | 0.060 |
| | 116.01–382.99 | 5 (2.6%) | 7 (9.2%) | 1 (5.0%) | 0.360 | 0.180 | 0.470 | 0.360 |
| **DFS-Based Optimization** | 1.60–5.20 | 12 (6.2%) | 4 (5.3%) | 1 (5.0%) | 1.000 | 1.000 | 1.000 | 1.000 |
| | 5.39–382.99 | 182 (93.8%) | 72 (94.7%) | 19 (95.0%) | 0.060 | 0.270 | 0.990 | 0.990 |
| **OS-Based Optimization** | 1.60–10.15 | 72 (37.1%) | 27 (35.5%) | 6 (30.0%) | 0.810 | 0.530 | 0.640 | 0.810 |
| | 10.21–1147.64 | 122 (62.9%) | 49 (64.5%) | 14 (70.0%) | (0.810) | (0.370) | (0.430) | (0.630) |
| **DFS-Based Optimization** | 1.60–14.61 | 87 (44.8%) | 34 (44.7%) | 7 (35.0%) | 0.990 | 0.400 | 0.440 | 0.690 |
| | 14.68–1147.64 | 107 (55.2%) | 72 (44.3%) | 13 (65.0%) | (0.810) | (0.370) | (0.430) | (0.630) |
| **HGF (pg/ml)** | Median (25–75th) | 16.15 (4.32–34.43) | 22.00 (4.83–44.44) | 17.39 (10.04–94.06) | 0.230 | 0.160 | 0.450 | 0.220 |
| Quartiles | 1.60–4.18 | 49 (25.3%) | 19 (25.0%) | 4 (20.0%) | 0.480 | 0.180 | 0.470 | 0.360 |
| | 4.76–17.34 | 51 (26.3%) | 16 (21.1%) | 6 (30.0%) | 0.028 | 0.360 | 0.170 | 0.060 |
| | 17.51–39.78 | 52 (26.8%) | 18 (23.7%) | 2 (10.0%) | 0.810 | 0.530 | 0.640 | 0.810 |
| | 40.30–1147.64 | 42 (21.6%) | 23 (30.3%) | 8 (40.0%) | 0.028 | 0.360 | 0.170 | 0.060 |
| **OS-Based Optimization** | 1.60–10.15 | 72 (37.1%) | 27 (35.5%) | 6 (30.0%) | 0.810 | 0.530 | 0.640 | 0.810 |
| | 10.21–1147.64 | 122 (62.9%) | 49 (64.5%) | 14 (70.0%) | (0.810) | (0.370) | (0.430) | (0.630) |
| **DFS-Based Optimization** | 1.60–14.61 | 87 (44.8%) | 34 (44.7%) | 7 (35.0%) | 0.990 | 0.400 | 0.440 | 0.690 |
| | 14.68–1147.64 | 107 (55.2%) | 72 (44.3%) | 13 (65.0%) | (0.810) | (0.370) | (0.430) | (0.630) |
| **PDGF-BB (pg/ml)** | Median (25–75th) | 2055 (615–5402) | 1178 (200–2939) | 1955 (317–3824) | 0.019 | 0.470 | 0.480 | 0.060 |
| Quartiles | 13.02–130.22 | 50 (25.8%) | 21 (27.6%) | 2 (10.0%) | 0.028 | 0.360 | 0.170 | 0.060 |
| | 130.72–312.56 | 52 (26.8%) | 16 (21.1%) | 5 (25.0%) | 0.710 | 0.500 | 1.000 | 0.640 |
| | 314.96–472.60 | 53 (27.3%) | 12 (15.8%) | 7 (35.0%) | (0.780) | (0.860) | (0.850) | (0.970) |
| | 505.37–6728.77 | 39 (20.1%) | 27 (35.5%) | 6 (30.0%) | 0.370 | 0.090 | 0.390 | 0.110 |
| **OS-Based Optimization** | 13.02–1148.76 | 188 (96.0%) | 73 (96.1%) | 19 (95.0%) | 0.910 | (0.350) | (0.170) | (0.560) |
| | 1169.11–6728.77 | 6 (3.1%) | 3 (3.9%) | 1 (5.0%) | 0.110 | 0.560 | 0.560 | 0.560 |
| **DFS-Based Optimization** | 13.02–919.06 | 185 (95.4%) | 70 (92.1%) | 17 (85.0%) | 0.019 | 0.470 | 0.480 | 0.060 |
| | 920.11–6728.77 | 9 (4.6%) | 6 (7.9%) | 3 (15.0%) | (0.015) | (0.150) | (0.590) | (0.039) |
Table 1 (continued)

| Biomarker | Biomarker grouping | Concentration (ng/ml) | Control | No insulin | Any insulin | Unadjusted p-value (MVP) |
|-----------|--------------------|-----------------------|---------|------------|-------------|-------------------------|
|           |                    |                       |         |            |             | $p^1$       | $p^2$ | $p^3$ | Global test |
|           |                    |                       |         |            |             |            |       |       |             |
|           |                    | 1660–4332             | 49 (25.3%) | 16 (21.1%) | 7 (35.0%) | 0.015      | 0.450 | 0.520 | 0.046         |
|           |                    | 4355–15480            | 55 (28.4%) | 14 (18.4%) | 4 (20.0%) | (0.007)   | (0.120) | (0.580) | (0.020)         |
|           | OS-Based Optimization | 60–2687              | 109 (56.2%) | 55 (72.4%) | 13 (65.0%) | (0.560)   | (0.150) | (0.220) | (0.380)         |
|           |                   | 2694–15480            | 85 (43.8%) | 21 (27.6%) | 7 (35.0%) | (0.450)   | (0.120) | (0.580) | (0.020)         |
|           | DFS-Based Optimization | 60–10400            | 186 (95.0%) | 72 (94.7%) | 20 (100%) | 0.740      | 1.000 | 0.580 | 0.790          |
|           |                   | 10944–15480           | 8 (4.1%) | 4 (5.3%) | 0 (0%) | (0.520) | (0.580) | (0.520) | (0.120)         |
| TGF-β (pg/ml) | Median (25–75th) | –                     | 3007 (1996–4053) | 3425 (2413–4608) | 4096 (3039–4903) | 0.032 | 0.029 | 0.410 | 0.018 |
|           | Quartiles | 453–2151            | 57 (29.4%) | 14 (18.4%) | 2 (10.0%) | 0.015      | 0.450 | 0.520 | 0.046         |
|           |          | 2155–3157            | 52 (26.8%) | 18 (23.7%) | 3 (15.0%) | (0.007)   | (0.120) | (0.580) | (0.020)         |
|           |          | 3183–4303            | 43 (22.2%) | 20 (26.3%) | 9 (45.0%) | (0.560)   | (0.150) | (0.220) | (0.380)         |
|           |          | 4311–12026           | 42 (21.6%) | 24 (31.6%) | 6 (30.0%) | (0.580)   | (0.420) | (0.650) | (0.480)         |
|           | OS-Based Optimization | 453–5545             | 176 (90.7%) | 64 (84.2%) | 17 (85.0%) | 0.130      | 0.420 | 1.000 | 0.230 |
|           |                   | 5557–12026           | 18 (9.3%) | 12 (15.8%) | 3 (15.0%) | (0.430)   | (0.480) | (0.990) | (0.710)         |
|           | DFS-Based Optimization | 453–1881            | 42 (21.6%) | 10 (13.2%) | 2 (10.0%) | 0.120      | 0.380 | 1.000 | 0.190 |
|           |                   | 1907–12026           | 152 (78.4%) | 66 (86.8%) | 18 (90.0%) | (0.220)   | (0.510) | (0.750) | (0.390)         |
| VEGF (pg/ml) | Median (25–75th) | –                     | 95.07 (40.78–189.51) | 111.90 (45.66–226.14) | 96.26 (64.90–291.86) | 0.300    | 0.380 | 0.910 | 0.450 |
|           | Quartiles | 1.60–43.56           | 52 (26.8%) | 17 (22.4%) | 4 (20.0%) | 0.680      | 0.660 | 0.570 | 0.770 |
|           |          | 44.52–97.48          | 51 (26.3%) | 17 (22.4%) | 7 (35.0%) | (0.460)   | (0.710) | (0.980) | (0.650)         |
|           |          | 97.87–192.64         | 45 (23.2%) | 21 (27.6%) | 3 (15.0%) | (0.370)   | (0.420) | (0.800) | (0.480)         |
|           |          | 194.47–4197.81       | 46 (23.7%) | 21 (27.6%) | 6 (30.0%) | (0.370)   | (0.420) | (0.800) | (0.480)         |
|           | OS-Based Optimization | 1.60–37.94           | 45 (23.2%) | 14 (18.4%) | 3 (15.0%) | 0.390      | 0.580 | 1.000 | 0.620 |
|           |                   | 38.42–4197.81        | 149 (76.8%) | 62 (81.6%) | 17 (85.0%) | (0.370)   | (0.420) | (0.800) | (0.480)         |
|           | DFS-Based Optimization | 1.60–37.94           | 45 (23.2%) | 14 (18.4%) | 3 (15.0%) | 0.390      | 0.580 | 1.000 | 0.620 |
|           |                   | 38.42–4197.81        | 149 (76.8%) | 62 (81.6%) | 17 (85.0%) | (0.370)   | (0.420) | (0.800) | (0.480)         |

*Overall survival (OS)- and disease-free survival (DFS)-optimized growth factor ranges associated with poorer outcomes are represented in bold. BLQ = below limit of quantitation.

$p^1$ = pairwise comparison of controls with the no insulin group, $p^2$ = pairwise comparison of controls with the any insulin group, and $p^3$ = pairwise comparison of the no insulin and any insulin groups. Global Test = significance test across all groups. 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).
2. Experimental design, materials and methods

Evaluation of growth factor profile association with injectable insulin 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 Table 2

| 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 Insulin (n=77)      | -0.104               | -0.321 to 0.123 | 0.365 | -0.064               | -0.289 to 0.167 | 0.584 |
|                     |                        | Any Insulin (n=20)     | -0.476               | -0.758 to -0.042 | 0.029 | -0.414               | -0.746 to 0.083 | 0.089 |
| 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 Insulin (n=77)      | -0.224               | -0.426 to 0.000 | 0.049 | -0.209               | -0.417 to 0.021 | 0.072 |
|                     |                        | Any Insulin (n=20)     | -0.540               | -0.793 to -0.127 | 0.011 | -0.427               | -0.753 to 0.068 | 0.079 |
| 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 | 0.021 |
|                     |                        | No Insulin (n=77)      | 0.050                | -0.176 to 0.271 | 0.663 | 0.006                | -0.234 to 0.223 | 0.962 |
|                     |                        | Any Insulin (n=20)     | -0.361               | -0.693 to 0.097 | 0.110 | -0.363               | -0.718 to 0.142 | 0.142 |
| 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 Insulin (n=77)      | -0.15                | -0.562 to 0.076 | 0.190 | -0.138               | -0.355 to 0.094 | 0.240 |
|                     |                        | Any Insulin (n=20)     | 0.359                | -0.100 to 0.691 | 0.112 | 0.319                | -0.191 to 0.693 | 0.202 |
| 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 Insulin (n=77)      | 0.145                | -0.082 to 0.357 | 0.206 | 0.135                | -0.096 to 0.353 | 0.248 |
|                     |                        | Any Insulin (n=20)     | 0.195                | -0.271 to 0.587 | 0.403 | 0.215                | -0.296 to 0.631 | 0.398 |
| 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 Insulin (n=77)      | -0.244               | -0.444 to -0.021 | 0.031 | -0.216               | -0.423 to 0.014 | 0.063 |
| EGF                 | FGF-2                  | 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 Insulin (n=77)      | 0.709                | 0.577 to 0.805   | <0.001 | 0.724               | 0.594 to 0.817   | <0.001 |
|                     |                        | Any Insulin (n=20)     | 0.895                | 0.750 to 0.958   | <0.001 | 0.907               | 0.755 to 0.966   | <0.001 |
| EGF                 | HGF                    | 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 Insulin (n=77)      | 0.002                | -0.222 to 0.226  | 0.984 | 0.025               | -0.204 to 0.252  | 0.829 |
|                     |                        | Any Insulin (n=20)     | 0.902                | 0.765 to 0.961   | <0.001 | 0.909               | 0.760 to 0.967   | <0.001 |
| EGF                 | PDGF-BB                | 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  | 0.889 |
|                     |                        | No Insulin (n=77)      | -0.010               | -0.233 to 0.214  | 0.931 | -0.107               | -0.328 to 0.124  | 0.361 |
|                     |                        | Any Insulin (n=20)     | -0.136               | -0.546 to 0.326  | 0.563 | -0.124               | -0.571 to 0.379  | 0.630 |
Table 2 (continued)

|    | EGF | TGF-β | GFR | VEGF | PDGF-BB | TGF-β |
|----|-----|-------|-----|------|---------|-------|
| All Subjects (n=291) | 0.196 | 0.082 | 0.304 | <0.001 | 0.172 | 0.058 | 0.282 | 0.003 |
| Controls (n=194) | 0.191 | 0.052 | 0.323 | 0.007 | 0.165 | 0.023 | 0.300 | 0.022 |
| No Insulin (n=77) | 0.181 | -0.045 | 0.389 | 0.113 | 0.205 | -0.024 | 0.414 | 0.077 |
| Any Insulin (n=20) | 0.067 | -0.387 | 0.495 | 0.775 | 0.123 | -0.379 | 0.570 | 0.632 |
| All Subjects (n=291) | 0.621 | 0.545 | 0.687 | <0.001 | 0.627 | 0.552 | 0.693 | <0.001 |
| Controls (n=194) | 0.621 | 0.526 | 0.700 | <0.001 | 0.627 | 0.533 | 0.706 | <0.001 |
| No Insulin (n=77) | 0.683 | 0.542 | 0.787 | <0.001 | 0.691 | 0.549 | 0.794 | <0.001 |
| Any Insulin (n=20) | 0.648 | 0.288 | 0.847 | 0.001 | 0.686 | 0.307 | 0.877 | 0.001 |
| All Subjects (n=291) | 0.138 | 0.024 | 0.249 | 0.018 | 0.133 | 0.018 | 0.245 | 0.023 |
| Controls (n=194) | 0.003 | -0.138 | 0.144 | 0.965 | -0.004 | -0.146 | 0.138 | 0.955 |
| No Insulin (n=77) | -0.157 | -0.368 | 0.069 | 0.17 | -0.128 | -0.347 | 0.103 | 0.274 |
| Any Insulin (n=20) | 0.761 | 0.480 | 0.900 | <0.001 | 0.817 | 0.554 | 0.932 | <0.001 |
| All Subjects (n=291) | 0.059 | -0.056 | 0.173 | 0.328 | 0.070 | -0.046 | 0.184 | 0.234 |
| Controls (n=194) | 0.124 | -0.017 | 0.261 | 0.0835 | 0.117 | -0.026 | 0.254 | 0.108 |
| No Insulin (n=77) | 0.012 | -0.212 | 0.236 | 0.916 | 0.011 | -0.218 | 0.239 | 0.923 |
| Any Insulin (n=20) | -0.061 | -0.490 | 0.392 | 0.795 | 0.034 | -0.454 | 0.506 | 0.897 |
| All Subjects (n=291) | 0.127 | 0.012 | 0.239 | 0.030 | 0.120 | 0.005 | 0.233 | 0.041 |
| Controls (n=194) | 0.054 | -0.087 | 0.194 | 0.453 | 0.048 | -0.095 | 0.189 | 0.509 |
| No Insulin (n=77) | 0.216 | -0.009 | 0.419 | 0.058 | 0.234 | 0.006 | 0.439 | 0.043 |
| Any Insulin (n=20) | -0.061 | -0.490 | 0.392 | 0.795 | -0.035 | -0.507 | 0.453 | 0.892 |
| All Subjects (n=291) | 0.805 | 0.760 | 0.842 | <0.001 | 0.805 | 0.760 | 0.842 | <0.001 |
| Controls (n=194) | 0.845 | 0.780 | 0.881 | <0.001 | 0.845 | 0.799 | 0.881 | <0.001 |
| No Insulin (n=77) | 0.787 | 0.683 | 0.859 | <0.001 | 0.785 | 0.678 | 0.859 | <0.001 |
| Any Insulin (n=20) | 0.832 | 0.617 | 0.932 | <0.001 | 0.834 | 0.591 | 0.939 | <0.001 |
| All Subjects (n=291) | 0.057 | -0.058 | 0.171 | 0.328 | 0.074 | -0.042 | 0.188 | 0.208 |
| Controls (n=194) | 0.093 | -0.048 | 0.231 | 0.195 | 0.087 | -0.036 | 0.226 | 0.233 |
| No Insulin (n=77) | 0.186 | -0.039 | 0.394 | 0.103 | 0.221 | -0.007 | 0.428 | 0.056 |
| Any Insulin (n=20) | -0.063 | -0.492 | 0.390 | 0.790 | -0.105 | -0.558 | 0.395 | 0.623 |
| All Subjects (n=291) | 0.116 | 0.001 | 0.228 | 0.048 | 0.091 | -0.025 | 0.205 | 0.122 |
| Controls (n=194) | 0.113 | -0.028 | 0.250 | 0.116 | 0.099 | -0.043 | 0.238 | 0.170 |
| No Insulin (n=77) | 0.210 | -0.015 | 0.414 | 0.065 | 0.188 | -0.043 | 0.399 | 0.107 |
| Any Insulin (n=20) | 0.017 | -0.429 | 0.456 | 0.944 | 0.071 | -0.424 | 0.533 | 0.784 |
| All Subjects (n=291) | 0.034 | -0.081 | 0.149 | 0.562 | 0.032 | -0.084 | 0.147 | 0.584 |
| Controls (n=194) | 0.031 | -0.110 | 0.171 | 0.666 | 0.025 | -0.118 | 0.166 | 0.736 |
| No Insulin (n=77) | -0.174 | -0.383 | 0.052 | 0.127 | -0.126 | -0.344 | 0.196 | 0.283 |
| Any Insulin (n=20) | 0.548 | 0.139 | 0.797 | 0.009 | 0.650 | 0.246 | 0.861 | 0.003 |
| All Subjects (n=291) | -0.120 | -0.232 | -0.005 | 0.040 | -0.103 | -0.216 | 0.012 | 0.080 |
| Controls (n=194) | -0.145 | -0.280 | -0.004 | 0.044 | -0.155 | -0.290 | -0.013 | 0.032 |
| No Insulin (n=77) | 0.007 | -0.217 | 0.231 | 0.952 | 0.054 | -0.176 | 0.279 | 0.644 |
| Any Insulin (n=20) | -0.212 | -0.598 | 0.255 | 0.363 | -0.264 | -0.661 | 0.248 | 0.296 |
corresponding plasma specimen harvested at BC diagnosis and banked in the Roswell Park Cancer Institute Data Bank and Bio-Repository.

2.1. Study population

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

All adult women with pre-existing diabetes at breast cancer diagnosis having available banked treatment-naïve plasma specimens (blood collected prior to initiation of any cancer-related therapy – surgery, radiation or pharmacotherapy) in the Institute’s Data Bank and Bio-Repository were included.

Subjects were excluded if they 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].

2.4. Demographic and clinical data collection

Clinical and treatment history was documented as previously described [1]. Vital status was obtained from the Institute’s Tumor Registry, a database updated biannually with data obtained from the National Comprehensive Cancer Networks’ Oncology Outcomes Database. Outcomes of interest were breast cancer recurrence and/or death.
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. Luminex® assays

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: TGFB-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 that optimized the log rank test among all possible cut-point selections yielding a minimum of 10 patients in any resulting group. Quartiles were also constructed. The resultant biomarker categories were then tested 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. Supplementary material

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