Insulin secretagogue use and circulating inflammatory C–C chemokine levels in breast cancer patients

Zachary A.P. Wintroba, Jeffrey P. Hammel, George K. Nimako, Zahra S. Fayazi, Dan P. Gaile, Alan Forrester, Alice C. Ceacareanu

State University of New York at Buffalo, Dept. of Pharmacy Practice, NYS Center of Excellence in Bioinformatics and Life Sciences, 701 Ellicott Street, Buffalo, NY 14203, USA
Cleveland Clinic, Dept. of Biostatistics and Epidemiology, 9500 Euclid Ave., Cleveland, OH 44195, USA
State University of New York at Buffalo, Dept. of Biostatistics, 718 Kimball Tower, Buffalo, NY 14214, USA
The UNC Eshelman School of Pharmacy, Division of Pharmacotherapy and Experimental Therapeutics, Campus Box 7569, Chapel Hill, NC 27599, USA
Roswell Park Cancer Institute, Dept. of Pharmacy Services, Elm & Carlton Streets, Buffalo, NY 14263, USA

Article history:
Received 30 November 2016
Received in revised form 27 January 2017
Accepted 13 February 2017
Available online 16 February 2017

Keywords:
Inflammation
Inflammatory cytokines
Secretagouge
C–C chemokines
CCL-2
CCL-3
CCL-4
CCL-5
Breast cancer

Abstract
Monocytes’ infiltration into the tumor tissue and their activation to tumor-associated macrophages is an essential step in tumor development, also playing a critical role in an eventual metastasis. Stimulation of endogenous insulin production by oral insulin secretagogue treatment has the potential to interfere with the production and release of C–C chemokines, a group of potent inflammatory cytokines acting as monocyte chemo-attractants and influencing their behavior in the tumor microenvironment.

Studied plasma samples were collected under a previously reported study design involving a population of women diagnosed with breast cancer presenting with or without type 2 diabetes mellitus at the time of breast cancer diagnosis (Wintrob et al., 2017, 2016) [1,2]. The data presented here shows the relationship between pre-existing use of insulin secretagogue, the inflammatory C–C chemokine profiles at the time of breast cancer diagnosis,
Diabetes
Monocyte infiltration
Activated macrophage
Cancer outcomes
Cancer prognosis

and subsequent cancer outcomes. A Pearson correlation analysis stratified by secretagogue use and controls was implemented to evaluate the relationship between the investigated biomarkers and respectively each of these biomarkers and the other relevant reported cytokine datasets derived from the same patient population (Wintrob et al., 2017, 2016) [1,2].

© 2017 Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Specifications table

| Subject area | Clinical and Translational Research |
|--------------|-------------------------------------|
| More specific subject area | Biomarker Research, Cancer Epidemiology |
| Type of data | Tables |
| How data was acquired | The TYBRES study was designed to assess the relationship between utilization of specific diabetes mellitus pharmacotherapies, breast cancer outcomes, and biomarker profiles, of which the associations between medication use and adipokines’ circulation have been recently reported [1,2]. The data presented here was obtained by linking new biomarker profiles to the original TYBRES patient database. Tumor registry query was followed by vital status ascertainment, and medical records review as described [1,2]. Luminex®-based quantitation from plasma samples was conducted for the following inflammatory C–C chemokine ligands: Chemokine ligand 2, CCL-2 (monocyte chemoattractant protein 1, MCP-1); chemokine ligand 3, CCL-3 (macrophage inflammatory protein 1α, MIP-1α); chemokine ligand 4, CCL-4 (macrophage inflammatory protein 1β, MIP-1β); and chemokine ligand 5, CCL-5 (regulated on activation normal T cell expressed and secreted, RANTES). A Luminex®200™ instrument with Xponent 3.1 software was used to acquire all data |
| Data format | Analyzed |
| Experimental factors | Above described biomarkers were determined from the corresponding plasma samples collected at the time of breast cancer diagnosis. |
| Experimental features | This dataset included 97 adult female cases diagnosed with type 2 diabetes and incident breast cancer and 194 matched controls with newly diagnosed breast cancer, but no diabetes diagnosis. Clinical and treatment history were evaluated in relationship with cancer outcomes and C-C chemokine profiles. A correlation analysis was 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

- Monocytes' mobilization to the tumor location is a chemotactic response mediated by pro-inflammatory C–C chemokine ligands: CCL-2, CCL-3, CCL-4, and CCL-5 [3]. Their combined contribution determines specific tumor environment changes many of which are responsible for metastasis.
- CCL-2 was the first described tumor-derived factor while later has been found to also be elevated among type 2 diabetes patients [4,5]. CCL-2 promotes tumor metastasis through secretion of CCL-3. Given its crucial role, CCL-2 is currently explored as a diagnostic and prognostic biomarker [6–9]. CCL-4 and CCL-5 are reported to facilitate metastasis and contribute to disease progression [10–12]. CCL-5 is currently considered as a therapeutic target for breast cancer [13].
- Present data shows the observed relationship between history of insulin secretagogue use, circulating C–C chemokines at breast cancer diagnosis and cancer outcomes.
- This data provides additional detail for the design of future studies investigating the relationship between insulin production and inflammation leading to breast cancer metastasis.
- Our observations have the potential to guide research investigating the use of C–C chemokines as diagnostic and/or prognostic indicators.

1. Data

Reported data represents the observed association between use of insulin secretagogues preceding breast cancer and the inflammatory C–C chemokine profiles at the time of cancer diagnosis in women with diabetes mellitus (Table 1). Data in Table 2 includes the observed correlations between the measured biomarkers stratified by type 2 diabetes mellitus pharmacotherapy and controls, as well as correlations with other inflammatory adipokines reported by us in the past: tumor necrosis factor α, interleukin 1β and its receptor antagonist, and interleukin 6. The details regarding tumor necrosis factor α, interleukin 1β and its receptor antagonist, and interleukin 6 determination from plasma, their association with cancer outcomes and use of insulin secretagogues has been previously reported [1,2].

2. Experimental design, materials and methods

Evaluation of pro-inflammatory cytokine profiles 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 pro-inflammatory cytokine 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

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 [1,2].

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.
| Biomarker | Biomarker grouping | Concentration | Control | No secretagogue | Any secretagogue | Unadjusted p-value (MVP) |
|-----------|--------------------|---------------|---------|-----------------|-----------------|-------------------------|
| **CCL-2** (MCP-1, pg/ml) | Median | – | 304 (221–392) | 296 (252–382) | 301 (216–391) | 0.810 (0.610) |
| | Quartiles | 1.6 to 225.6 | 52 (26.0%) | 8 (17.0%) | 13 (26.0%) | 0.180 (0.900) |
| | | 227.7 to 302.5 | 42 (21.8%) | 17 (36.2%) | 13 (26.0%) | 0.050 (0.900) |
| | | 303.7 to 388.6 | 50 (25.0%) | 11 (23.4%) | 11 (22.0%) | 0.010 (0.300) |
| | | 391.9 to 4531.2 | 49 (25.4%) | 11 (23.4%) | 13 (26.0%) | 0.000 (0.200) |
| | OS-Based | 1.6 to 395.8 | 146 (75.6%) | 36 (76.6%) | 38 (76.0%) | 0.000 (0.700) |
| | Optimization | 398.5 to 4531.2 | 47 (24.4%) | 11 (23.4%) | 12 (24.0%) | 0.000 (0.500) |
| | DFS-Based | 1.6 to 170.4 | 22 (11.4%) | 3 (6.4%) | 6 (12.0%) | 0.000 (0.400) |
| | Optimization | 172.4 to 4531.2 | 171 (88.6%) | 44 (88.0%) | 44 (88.0%) | 0.000 (0.400) |
| **CCL-3** (MIP-1α, ng/ml) | Median | – | 3.82 (2.38–6.95) | 5.63 (3.18–10.09) | 3.86 (1.97–9.11) | 0.051 (0.160) |
| | Quartiles | 0.36 to 2.37 | 49 (25.3%) | 9 (19.1%) | 15 (30.0%) | 0.160 (0.360) |
| | | 2.41 to 4.02 | 53 (27.3%) | 9 (19.1%) | 11 (22.0%) | 0.160 (0.360) |
| | | 4.07 to 7.96 | 51 (26.3%) | 12 (25.5%) | 9 (18.0%) | 0.160 (0.360) |
| | | 8.11 to 390.27 | 41 (21.1%) | 17 (36.2%) | 15 (30.0%) | 0.160 (0.360) |
| | OS-Based | 0.36 to 4.02 | 102 (52.6%) | 18 (38.3%) | 26 (52.0%) | 0.080 (0.400) |
| | Optimization | 4.07 to 390.27 | 92 (47.4%) | 29 (61.7%) | 24 (48.0%) | 0.080 (0.400) |
| | DFS-Based | 0.36 to 4.02 | 102 (52.6%) | 18 (38.3%) | 26 (52.0%) | 0.080 (0.400) |
| | Optimization | 4.07 to 390.27 | 92 (47.4%) | 29 (61.7%) | 24 (48.0%) | 0.080 (0.400) |
| **CCL-4** (MIP-1β, pg/ml) | Median | – | 23.00 (16.54–32.87) | 28.74 (20.74–44.77) | 27.48 (20.20–37.74) | 0.009 (0.020) |
| | Quartiles | 1.60 to 17.56 | 56 (28.9%) | 8 (17.0%) | 9 (18.0%) | 0.009 (0.020) |
| | | 17.58 to 23.77 | 48 (24.7%) | 11 (23.4%) | 14 (28.0%) | 0.009 (0.020) |
| | | 23.92 to 34.81 | 48 (24.7%) | 12 (25.5%) | 14 (28.0%) | 0.009 (0.020) |
| | | 34.94 to 660.94 | 42 (21.6%) | 16 (34.0%) | 15 (30.0%) | 0.009 (0.020) |
| | OS-Based | 1.60 to 12.40 | 18 (9.3%) | 3 (6.4%) | 3 (6.4%) | 0.009 (0.020) |
| | Optimization | 12.58 to 660.94 | 176 (90.7%) | 44 (93.6%) | 47 (94.0%) | 0.009 (0.020) |
| | DFS-Based | 1.60 to 13.59 | 26 (13.4%) | 4 (8.5%) | 3 (6.0%) | 0.009 (0.020) |
| | Optimization | 13.69 to 660.94 | 168 (86.6%) | 43 (91.5%) | 47 (94.0%) | 0.009 (0.020) |
| **CCL-5** (RANTES, pg/ml) | Median | – | 7158 (3460–14543) | 5802 (4168–10391) | 5673 (3269–8904) | 0.640 (0.240) |

Z.A.P. Wintrob et al. / Data in Brief 11 (2017) 391–402
| Quartiles          | 0 to 3446 | 49 (25.3%) | 8 (17.0%) | 16 (32.0%) | 0.051 | 0.330 | 0.350 | 0.110 |
|-------------------|-----------|------------|-----------|------------|-------|-------|-------|-------|
|                   | 3500 to 6307 | 41 (21.1%) | 18 (38.3%) | 14 (28.0%) |       |       |       |       |
|                   | 6381 to 13442 | 48 (24.7%) | 13 (27.7%) | 11 (22.0%) |       |       |       |       |
|                   | 13442 to 57898 | 56 (28.9%) | 8 (17.0%) | 9 (18.0%)  |       |       |       |       |
| OS-Based Optimization | 0 to 3183 | 42 (21.6%) | 8 (17.0%) | 11 (22.0%) | 0.480 | 0.960 | 0.540 | 0.770 |
| DFS-Based Optimization | 0 to 16821 | 160 (82.5%) | 43 (91.5%) | 46 (92.0%) | 0.140 | 0.110 | 1.000 | 0.100 |
| Optimized biomarker ranges associated with poorer outcomes are represented in bold. Unadjusted p-values: p1, compares no insulin versus control; p2, compares any insulin versus control; p3, compares any insulin versus no insulin (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 workflow [1]. MVP = p-value of the multivariate adjusted analysis. Chemokine ligand 2, CCL-2 (monocyte chemoattractant protein 1, MCP-1); chemokine ligand 3, CCL-3 (macrophage inflammatory protein 1α, MIP-1α); chemokine ligand 4, CCL-4 (macrophage inflammatory protein 1β, MIP-1β); chemokine ligand 5, CCL-5 (regulated on activation normal T cell expressed and secreted, RANTES). |
| Compared biomarkers | Group | Unadjusted correlation | Adjusted correlation |
|---------------------|-------|------------------------|----------------------|
|                     |       | Pearson correlation | 95% confidence interval | p-Value | Pearson correlation | 95% confidence interval | p-Value |
| CCL-2 (MCP-1)       | CCL-3 (MIP-1α) | All subjects (n=291) | -0.042 | -0.156 to 0.074 | 0.480 | -0.043 | -0.158 to 0.073 | 0.463 |
|                     |       | Controls (n=194) | -0.034 | -0.174 to 0.108 | 0.636 | -0.029 | -0.170 to 0.114 | 0.695 |
|                     |       | No secretagogue (n=43) | -0.091 | -0.381 to 0.215 | 0.560 | -0.125 | -0.420 to 0.194 | 0.440 |
|                     |       | Any secretagogue (n=54) | -0.162 | -0.412 to 0.110 | 0.238 | -0.158 | -0.416 to 0.122 | 0.263 |
| CCL-2 (MCP-1)       | CCL-4 (MIP-1β) | All subjects (n=291) | 0.008 | -0.107 to 0.123 | 0.897 | 0.008 | -0.108 to 0.123 | 0.892 |
|                     |       | Controls (n=194) | -0.002 | -0.143 to 0.139 | 0.974 | 0.001 | -0.143 to 0.141 | 0.990 |
|                     |       | No secretagogue (n=43) | 0.057 | -0.248 to 0.351 | 0.716 | 0.048 | -0.268 to 0.354 | 0.768 |
|                     |       | Any secretagogue (n=54) | 0.078 | -0.194 to 0.339 | 0.574 | 0.082 | -0.198 to 0.350 | 0.564 |
| CCL-2 (MCP-1)       | CCL-5 (RANTES) | All subjects (n=291) | -0.172 | -0.281 to -0.058 | 0.003 | -0.174 | -0.283 to -0.059 | 0.003 |
|                     |       | Controls (n=194) | -0.257 | -0.384 to -0.121 | < 0.001 | -0.251 | -0.379 to -0.113 | < 0.001 |
|                     |       | No secretagogue (n=43) | 0.416 | 0.132 to 0.637 | 0.005 | 0.422 | 0.127 to 0.648 | 0.006 |
|                     |       | Any secretagogue (n=54) | -0.158 | -0.409 to 0.114 | 0.249 | -0.183 | -0.436 to 0.098 | 0.196 |
| CCL-2 (MCP-1)       | IL-1β | All subjects (n=291) | -0.037 | -0.151 to 0.078 | 0.529 | -0.036 | -0.151 to 0.080 | 0.545 |
|                     |       | Controls (n=194) | -0.008 | -0.148 to 0.133 | 0.916 | -0.016 | -0.158 to 0.126 | 0.821 |
|                     |       | No secretagogue (n=43) | -0.051 | -0.346 to 0.253 | 0.744 | -0.062 | -0.366 to 0.255 | 0.703 |
|                     |       | Any secretagogue (n=54) | -0.104 | -0.362 to 0.168 | 0.450 | -0.067 | -0.336 to 0.213 | 0.639 |
| CCL-2 (MCP-1)       | IL-1Ra | All subjects (n=291) | -0.014 | -0.129 to 0.101 | 0.815 | -0.011 | -0.127 to 0.104 | 0.849 |
|                     |       | Controls (n=194) | -0.007 | -0.148 to 0.134 | 0.923 | -0.004 | -0.146 to 0.138 | 0.953 |
|                     |       | No secretagogue (n=43) | -0.023 | -0.321 to 0.280 | 0.885 | -0.032 | -0.340 to 0.282 | 0.844 |
|                     |       | Any secretagogue (n=54) | 0.092 | -0.180 to 0.351 | 0.507 | 0.075 | -0.205 to 0.343 | 0.600 |
| CCL-2 (MCP-1)       | TNF-α | All subjects (n=291) | -0.013 | -0.128 to 0.102 | 0.824 | -0.008 | -0.123 to 0.108 | 0.899 |
|                     |       | Controls (n=194) | -0.001 | -0.142 to 0.140 | 0.987 | -0.018 | -0.159 to 0.125 | 0.808 |
|                     |       | No secretagogue (n=43) | -0.055 | -0.350 to 0.249 | 0.722 | -0.040 | -0.347 to 0.275 | 0.805 |
|                     |       | Any secretagogue (n=54) | 0.127 | -0.146 to 0.382 | 0.357 | 0.155 | -0.126 to 0.413 | 0.273 |
| CCL-2 (MCP-1)       | IL-6   | All subjects (n=291) | 0.010 | -0.105 to 0.124 | 0.870 | 0.007 | -0.109 to 0.122 | 0.910 |
|                     |       | Controls (n=194) | 0.015 | -0.126 to 0.156 | 0.831 | 0.016 | -0.126 to 0.158 | 0.825 |
|                     |       | No secretagogue (n=43) | 0.002 | -0.298 to 0.303 | 0.987 | 0.005 | -0.307 to 0.316 | 0.975 |
|                | CCL-3 | CCL-4 | IL-1β | CCL-5 | CCL-6 | TNF-α | IL-1Ra | CCL-4 | CCL-5 | IL-1β | CCL-3 | CCL-4 | CCL-6 | TNF-α | IL-1Ra | CCL-3 | CCL-4 | CCL-6 | TNF-α | IL-1Ra |
|----------------|-------|-------|-------|-------|-------|-------|--------|-------|-------|-------|-------|-------|-------|-------|--------|-------|-------|-------|-------|--------|
| All subjects   |       |       |       |       |       |       |        |       |       |       |       |       |       |       |        |      |      |      |      |        |
| Any secretagogue | 0.267 | 0.157 | -0.165 | 0.157 | 0.151 | 0.232 | 0.163 | -0.009 | -0.009 | -0.041 | 0.049 | 0.070 | 0.010 | 0.005 | -0.09 | 0.055 | 0.069 | 0.084 | 0.041 | 0.049 |
| Controls       | 0.239 | 0.102 | -0.243 | 0.091 | 0.112 | 0.223 | 0.116 | 0.092 | 0.092 | 0.022 | 0.085 | 0.174 | 0.001 | 0.010 | -0.11 | 0.055 | 0.069 | 0.084 | 0.041 | 0.049 |
| No secretagogue | 0.551 | 0.301 | -0.179 | 0.352 | 0.538 | 0.570 | 0.313 | 0.124 | 0.124 | -0.014 | 0.325 | 0.348 | -0.005 | -0.141 | -0.141 | 0.087 | 0.872 | 0.872 | 0.008 | -0.123 | 0.108 |
| Any secretagogue | 0.750 | 0.603 | -0.346 | 0.403 | 0.247 | 0.313 | 0.307 | 0.302 | 0.302 | 0.302 | 0.403 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | -0.123 | 0.108 |
| Controls       | 0.107 | 0.035 | -0.050 | 0.229 | 0.092 | 0.223 | 0.112 | 0.050 | 0.050 | 0.050 | 0.229 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 | 0.050 | -0.042 | 0.239 |
| No secretagogue | 0.014 | 0.288 | -0.288 | 0.313 | 0.538 | 0.570 | 0.313 | 0.124 | 0.124 | 0.124 | 0.313 | 0.124 | 0.124 | 0.124 | 0.124 | 0.124 | 0.124 | 0.124 | 0.124 | -0.123 | 0.108 |
| Any secretagogue | -0.086 | -0.346 | -0.346 | 0.186 | 0.247 | 0.313 | 0.307 | 0.302 | 0.302 | 0.302 | 0.403 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | 0.302 | -0.123 | 0.108 |

The table above provides the mean fold changes and the corresponding 95% confidence intervals for various cytokines in response to secretagogues. The statistical significance of the changes is indicated by p-values. For example, the mean fold change for CCL-3 in all subjects is 0.267 with a 95% confidence interval of 0.157 to 0.371, and the p-value is < 0.001, indicating a statistically significant increase. The table includes data for controls and no secretagogue conditions as well.
| Compared biomarkers | Group | Unadjusted correlation | Adjusted correlation |
|---------------------|-------|------------------------|----------------------|
|                     |       | Pearson correlation    | 95% confidence interval | p-Value | Pearson correlation | 95% confidence interval | p-Value |
|                     |       |                        |                      |         |                        |                      |         |
| CCL-4 (MIP-1β)      | Controls (n=194) | 0.217 | 0.079 to 0.347 | 0.002 | 0.217 | 0.078 to 0.348 | 0.002 |
|                     | No secretagogue (n=43) | 0.920 | 0.855 to 0.956 | < 0.001 | 0.920 | 0.852 to 0.957 | < 0.001 |
|                     | Any secretagogue (n=54) | 0.018 | −0.251 to 0.285 | 0.895 | 0.037 | −0.241 to 0.310 | 0.795 |
| CCL-4 (MIP-1β)      | IL-1Ra | All subjects (n=291) | 0.836 | 0.798 to 0.868 | < 0.001 | 0.836 | 0.798 to 0.868 | < 0.001 |
|                     | Controls (n=194) | 0.875 | 0.838 to 0.905 | < 0.001 | 0.875 | 0.838 to 0.905 | < 0.001 |
|                     | No secretagogue (n=43) | 0.861 | 0.757 to 0.923 | < 0.001 | 0.862 | 0.752 to 0.925 | < 0.001 |
|                     | Any secretagogue (n=54) | 0.365 | 0.107 to 0.576 | 0.006 | 0.420 | 0.163 to 0.623 | 0.002 |
| CCL-4 (MIP-1β)      | TNF-α | All subjects (n=291) | 0.438 | 0.340 to 0.527 | < 0.001 | 0.446 | 0.349 to 0.534 | < 0.001 |
|                     | Controls (n=194) | 0.421 | 0.298 to 0.531 | < 0.001 | 0.430 | 0.307 to 0.539 | < 0.001 |
|                     | No secretagogue (n=43) | 0.450 | 0.173 to 0.661 | 0.002 | 0.501 | 0.224 to 0.703 | < 0.001 |
|                     | Any secretagogue (n=54) | 0.067 | −0.238 to 0.360 | 0.667 | 0.376 | 0.112 to 0.591 | 0.006 |
| CCL-4 (MIP-1β)      | IL-6 | All subjects (n=291) | 0.334 | 0.228 to 0.433 | < 0.001 | 0.336 | 0.230 to 0.435 | < 0.001 |
|                     | Controls (n=194) | 0.317 | 0.184 to 0.438 | < 0.001 | 0.322 | 0.188 to 0.443 | < 0.001 |
|                     | No secretagogue (n=43) | 0.680 | 0.477 to 0.814 | < 0.001 | 0.693 | 0.486 to 0.826 | < 0.001 |
|                     | Any secretagogue (n=54) | 0.190 | −0.082 to 0.436 | 0.165 | 0.217 | −0.063 to 0.464 | 0.123 |
| CCL-5 (RANTES)      | IL-1β | All subjects (n=291) | 0.037 | −0.079 to 0.151 | 0.535 | 0.040 | −0.076 to 0.155 | 0.500 |
|                     | Controls (n=194) | 0.081 | −0.060 to 0.220 | 0.258 | 0.088 | −0.055 to 0.227 | 0.225 |
|                     | No secretagogue (n=43) | 0.056 | −0.249 to 0.350 | 0.722 | 0.065 | −0.251 to 0.369 | 0.687 |
|                     | Any secretagogue (n=54) | 0.095 | −0.178 to 0.353 | 0.494 | 0.098 | −0.182 to 0.364 | 0.489 |
| CCL-5 (RANTES)      | IL-1Ra | All subjects (n=291) | 0.008 | −0.107 to 0.123 | 0.895 | 0.008 | −0.107 to 0.124 | 0.888 |
|                     | Controls (n=194) | 0.011 | −0.130 to 0.152 | 0.874 | 0.013 | −0.129 to 0.155 | 0.857 |
|                     | No secretagogue (n=43) | 0.052 | −0.252 to 0.347 | 0.739 | 0.040 | −0.275 to 0.347 | 0.804 |
|                     | Any secretagogue (n=54) | −0.093 | −0.352 to 0.179 | 0.502 | −0.123 | −0.386 to 0.158 | 0.386 |
| CCL-5 (RANTES)      | TNF-α | All subjects (n=291) | −0.064 | −0.178 to 0.051 | 0.274 | −0.047 | −0.162 to 0.069 | 0.422 |
|                     | Controls (n=194) | −0.146 | −0.281 to −0.005 | 0.042 | −0.143 | −0.279 to −0.001 | 0.048 |
|                     | No secretagogue (n=43) | 0.067 | −0.238 to 0.360 | 0.667 | 0.089 | −0.229 to 0.390 | 0.582 |
|                     | Any secretagogue (n=54) | 0.104 | −0.168 to 0.362 | 0.451 | 0.103 | −0.178 to 0.368 | 0.470 |
| Chemokine Ligand | Group | Median | IQR | Mean | S.D. | Median | IQR | Mean | S.D. |
|------------------|-------|--------|-----|------|------|--------|-----|------|------|
| CCL-2 (MCP-1)    | All subjects (n=291) | 0.051 | 0.065 to 0.165 | 0.388 | 0.047 | 0.069 to 0.161 | 0.430 |
|                  | Controls (n=194) | 0.043 | 0.098 to 0.183 | 0.546 | 0.042 | 0.100 to 0.183 | 0.562 |
|                  | No secretagogue (n=43) | 0.038 | 0.266 to 0.334 | 0.810 | 0.052 | 0.264 to 0.358 | 0.749 |
|                  | Any secretagogue (n=54) | 0.126 | 0.147 to 0.381 | 0.362 | 0.166 | 0.115 to 0.422 | 0.242 |

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. Chemokine ligand 2, CCL-2 (monocyte chemoattractant protein 1, MCP-1); chemokine ligand 3, CCL-3 (macrophage inflammatory protein 1α, MIP-1α); chemokine ligand 4, CCL-4 (macrophage inflammatory protein 1β, MIP-1β); chemokine ligand 5, CCL-5 (regulated on activation normal T cell expressed and secreted, RANTES); tumor necrosis factor α, TNF-α; interleukin 1β, IL-1β; interleukin 1β receptor antagonist, IL-1Ra; interleukin 6, IL-6.
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. The specific treatment groups have been defined according to the mechanism of action of their respective diabetes pharmacotherapy. Receiving any of the following pharmacotherapies alone or in combination: sulfonylureas (glimepiride, glipizide, and glyburide), meglitinides (nateglinide, repaglinide), alpha-glucosidase inhibitors (acarbose, miglitol), glucagon-like peptide-1 receptor agonists (exenatide, liraglutide), led to assigning the subject to the “any secretagogue” user group, whereas the “no secretagogue” user group included patients receiving one or more of the following treatment options: biguanides (metformin) and thiazolidinediones (pioglitazone, rosiglitazone) or no oral pharmacotherapy [1]. Of note is that each of the two groups, any secretagogue and no secretagogue, included 11 and respectively 9 insulin users.

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 5 biomarkers – chemokine ligand 2, CCL-2 (monocyte chemoattractant protein 1, MCP-1); chemokine ligand 3, CCL-3 (macrophage inflammatory protein 1α, MIP-1α); chemokine ligand 4, CCL-4 (macrophage inflammatory protein 1β, MIP-1β); and chemokine ligand 5, CCL-5 (regulated on activation normal T cell expressed and secreted, RANTES) – were quantified according to the manufacturer protocol. The HCYTOMAG-60K Luminex® biomarker panel (Millipore Corporation, Billerica, MA) was utilized in this study. Tumor necrosis factor α, interleukin 1β, interleukin 1β receptor antagonist, interleukin 6, and interleukin 10 determinations were done according to the manufacturer protocol as previously reported [1,2].

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.

Funding sources

This research was funded by the following grant awards: Wadsworth Foundation Peter Rowley Breast Cancer Grant awarded to A.C.C. (UB Grant Number 55705, Contract CO26588).

Acknowledgments

Authors acknowledge the valuable help of Dr. Chi-Chen Hong with case-control matching.

Transparency document. Supplementary material

Transparency data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.dib.2017.02.031.

References

[1] Z. Wintrob, J.P. Hammel, T. Khoury, G.K. Nimako, H.-W. Fu, Z.S. Fayazi, D.P. Galle, A. Forrest, A.C. Ceacareanu, Insulin use, adipokine profiles and breast cancer prognosis, Cytokine 89 (2017) 45–61.
[2] Z. Wintrob, J.P. Hammel, G.K. Nimako, Z.S. Fayazi, D.P. Galle, A. Forrest, A.C. Ceacareanu, Circulating adipokines data associated with insulin secretagogue use in breast cancer patients, Data Brief 10 (2016) 238–247.
[3] D.M. Richards, J. Hettinger, M. Feuerer, Monocytes and macrophages in cancer: development and functions, Cancer Microenviron. 6 (2) (2013) 179–191.
[4] N. Kamei, K. Tobe, R. Suzuki, M. Ohsugi, T. Watanabe, N. Kubota, N. Ohtsuka-Kowatari, K. Kumagai, K. Sakamoto, M. Kobayashi, T. Yamauchi, K. Ueki, Y. Oishi, S. Nishimura, I. Manabe, H. Hashimoto, Y. Ohsishi, H. Ogata, K. Tokuyama, M. Tsumoda, T. Ide, K. Murakami, R. Nagai, T. Kadokawi, Overexpression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance, J. Biol. Chem. 281 (36) (2006) 26602–26614.
[5] J. Pann, Monocyte Chemochactant Protein 1 (MCP-1) in obesity and diabetes, Cytokine 60 (1) (2012) 1–12.
[6] J. Wang, Z.G. Zhuang, S.F. Xu, Q. He, Y.G. Shao, M. Jl, L. Yang, W. Bao, Expression of CCL2 is significantly different in five breast cancer genotypes and predicts patient outcome, Int. J. Clin. Exp. Med. 8 (9) (2015) 15684–15691.
[7] I. Tsaur, A. Noack, J. Makarevic, E. Oppermann, A.M. Waaga-Gasser, M. Gasser, H. Borgmann, T. Huesch, K.M. Gust, M. Reiter, D. Schilling, G. Bartsh, A. Haferkamp, R.A. Blaheta, CCL2 chemokine as a potential biomarker for prostate cancer: a pilot study, Cancer Res. Treat. 47 (2) (2015) 306–312.
[8] K. Izumi, A. Mizokami, H.P. Lin, H.M. Ho, H. Iwamoto, A. Maolake, A. Natsagdorj, Y. Kitagawa, Y. Kadono, H. Miyamoto, C. K. Huang, M. Namiki, W.J. Lin, Serum chemokine (CC motif) ligand 2 level as a diagnostic, predictive, and prognostic biomarker for prostate cancer, Oncotarget 7 (7) (2016) 8389–8398.
[9] J. Wu, X. Liu, Y. Wang, Predictive value of proproceptive serum CCL2, CCL18, and VEGF for the patients with gastric cancer, BMC Clin. Pathol. 13 (2013) 15.
[10] E. Azenshtein, G. Luboshtis, S. Shina, E. Neumark, D. Shahbazian, M. Weil, N. Wigler, I. Keydar, A. Ben-Baruch, The CC chemokine RANTES in breast carcinoma progression: regulation of expression and potential mechanisms of promalignant activity, Cancer Res. 62 (4) (2002) 1093–1092.
[11] G. Luboshtis, S. Shina, O. Kaplan, S. Engelberg, D. Nass, B. Lifshitz-Mercer, S. Chaitchik, I. Keydar, A. Ben-Baruch, Elevated expression of the CC chemokine regulated on activation normal T cell expressed and secreted (RANTES) in advanced breast carcinoma, Cancer Res. 59 (1999) 4681–4687.
[12] S. Sasaki, T. Baba, T. Nishimura, Y. Hayakawa, S. Hashimoto, N. Gotoh, N. Mukaida, Essential roles of the interaction between cancer cell-derived chemokine, CCL4, and intra-bone CCR5-expressing fibroblasts in breast cancer bone metastasis, Cancer Lett. 378 (1) (2016) 23–32.

[13] V. D’Esposito, D. Liguoro, M.R. Ambrosio, F. Collina, M. Cantile, R. Spinelli, G.A. Raciti, C. Miele, R. Valentino, P. Campiglia, M. De Laurentis, M. Di Bonito, G. Botti, R. Franco, F. Beguinot, P. Formisano, Adipose microenvironment promotes triple negative breast cancer cell invasiveness and dissemination by producing CCL5, Oncotarget 7 (17) (2016) 24495–24509.