Impact of Environmental Temperature on Clinical Outcomes and Tumor Microenvironment of Early-Stage Breast Cancer

Arya M Roy, MD, Spencer Rosario, PhD, Anthony George, MS, Qiang Hu, MD, PhD, John Carpten, PhD, Virginia F Borges, MD, Bryan Schneider, MD, Jill Kolesar, PharmD, MS, BCPS, FCCP, Christopher Moskaluk, MD, PhD, Craig Shriver, MD, FACS, Cindy Matsen, MD, Shridar Ganesan, MD, PhD, Sneha Phadke, DO, MPH, Wajeeha Razaq, MD, Kristopher Attwood, PhD, Shipra Gandhi, MD

1 Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA, 2 Moffitt Cancer Center, Tampa, FL, USA, 3 University of Southern California, Los Angeles, CA, USA, 4 University of Colorado Cancer Center, Denver, CO, USA, 5 Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN, USA, 6 University of Kentucky, Lexington, KY, USA, 7 University of Virginia, Charlottesville, VA, USA, 8 Murtha Cancer Center, Uniformed Services University, Bethesda, MD, USA, 9 Fred Hutchinson Cancer Center, University of Utah, Salt Lake City, UT, USA, 10 Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA, 11 Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA, 12 The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

https://doi.org/10.53876/001c.90822

BACKGROUND

Preclinical evidence using mouse model suggests that thermal/cold stress increases tumor growth by modulating the tumor microenvironment (TME); however, the clinical relevance of temperature on breast cancer (BC) outcomes is unknown. We aim to study the impact of environmental temperature on the pathological complete response (pCR) and survival of early-stage BC patients (pts).

METHODOLOGY

A multi-institutional study was conducted within the Oncology Research Information Exchange Network. We analyzed the clinical and genomic data for early-stage BC pts from 12 centers in different environment zones (5 warm and 7 cold) (based on average annual regional temperature obtained from National Centers for Environmental Information). Cox regression was used to measure the association of climate and overall/relapse-free survival (OS/RFS) after adjusting for co-variates. Raw feature counts were normalized, and differential expression analysis was carried out using DESeq2. Differential expression rank order was used for subsequent gene set enrichment analysis, performed using the cluster profile package in R.

RESULTS

Out of the 1,504 early-stage BC pts, 271 pts received neoadjuvant chemotherapy (NAC) (186 warm, 85 cold). Higher clinical T- and N-stages were observed in pts from warm compared to cold regions (p<0.001). Pts residing in cold regions had more comorbidities (57.6% vs 4.8%, p<0.001). Pts in warm regions had higher pCR, though not statistically significant (8% vs 2.5%, p=0.1). In the overall population, the OS (univariate (UV) HR= 0.48, 95% CI 0.27-0.64, p <0.001; adjusted HR (aHR)= 0.56, 95% CI 0.32 - 0.96, p= 0.03) and RFS (UV HR= 0.51, 95% CI 0.38 - 0.68, p<0.001; aHR= 0.52, 95% CI 0.36 - 0.75, p= 0.0005) were higher in pts from warm compared to cold regions (Table 1). RNA sequencing was performed on 826 tumors (443 warm, 383 cold) using pre-treatment samples. Naïve B-cells (mean: 0.09 vs 0.08, p=0.004), CD4 naïve T cells (0.03 vs 0.02, p= 0.0008), CD4+ memory T cells (0.03 vs 0.02, p= 0.04), gamma-delta T-cells (0.007 vs 0.004, p= 0.006) were higher in pts residing in cold compared to warm regions while CD8 T cells, T regulatory cells, macrophages, dendritic cells, natural killer cells were similar in both regions. Macrophage signaling, cholesterol metabolism and the pathway for negative regulation of cell migration in angiogenesis were upregulated in pts living in warm compared to cold regions.

Table 1. OS and RFS of patients living in warm vs cold environments.

<table>
<thead>
<tr>
<th>Regions (n)</th>
<th>5-yr OS (95% CI)</th>
<th>Median OS (months) (95% CI)</th>
<th>p-value</th>
<th>5-yr RFS (95% CI)</th>
<th>Median RFS (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold (782)</td>
<td>83 (76-86)%</td>
<td>157.7 (116.6-NR)</td>
<td>&lt;0.001</td>
<td>69 (62-76)%</td>
<td>108.4 (88.9-147.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warm (522)</td>
<td>95 (92-97)%</td>
<td>214.7 (205.3-NR)</td>
<td></td>
<td>83 (79-87)%</td>
<td>250.4 (129.9-250.4)</td>
<td></td>
</tr>
</tbody>
</table>
CONCLUSION

Early-stage BC pts living in cold have worse OS and RFS compared to warm regions. Our study is the first to report significant differences in the TME among these pts. To ensure the validity and robustness of these intriguing findings, larger multi-center studies should be conducted, encompassing detailed information on the duration of exposure to both warm and cold weather conditions.