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Editorial

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Biomarker Research in World Journal of Oncology

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In this issue of World Journal of Oncology, Desai et al review carcinoembryonic antigen (CEA), carbohydrate antigen-19-9 (CA19-9), CA125, prostate surface antigen (PSA) and other cancer biomarkers [1], and Chen et al report vascular endothelial growth factor-C (VEGF-C) as a lung adenocarcinoma prognostic biomarker [2]. Biomarker research has gained such popularity during the last 30 years that the publication count on the topic increases exponentially every year. There were more than 74,000 publications in 2022 alone, and more than 1,100,000 manuscripts total with the keyword "biomarker" searchable in the PubMed database (searched February 2023). According to the United States National Cancer Institute, "biomarker" is defined as "A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition." As such, cancer biomarkers can be functionally classified into diagnostic (screening) biomarkers, prognostic biomarkers, and predictive biomarkers, where the latter two are the ones that most people presume when the word "biomarker" is used in the context of cancer management. It is important to note that prognostic biomarkers are associated with cancer outcomes, while predictive biomarkers discriminate response to therapy. For instance, cancer staging defined by the American Joint Committee on Cancer (AJCC) is a prognostic biomarker, such that patients with stage IV cancer have worse survival compared to the other stages. Chen et al claim that VEGF-C is a prognostic biomarker because they found that when its gene expression was low, it was associated with better overall survival in lung adenocarcinoma. One example of a predictive biomarker is programmed death-ligand 1 (PD-L1) expression because anti-PD1 immunotherapy targets that mechanism, although it is reported that some patients respond to the therapy even without detectable PD-L1 expression for unknown reasons. Purwanto et al reported in World Journal of Oncology that PD-L1 gene expression was associated with worse overall survival in Indonesian triple-negative breast cancer patients who did not receive anti-PD1 immunotherapy, and thus PD-L1 was evaluated as a prognostic biomarker in this case [3]. This finding was not replicated in Mexican women [4].

The expressions of breast cancer biomarkers such as the estrogen receptor and the human epidermal growth factor 2 (HER2) receptor determine whether the target therapies (hormonal therapy and anti-HER2 targeted therapy, respectively) are applicable, and therefore they are predictive biomarkers. Indeed, the distribution of these biomarkers in Nigerian women was reported by Adeniji et al [5], in Jamaican women by Copeland et al [6], and in Mexican women by Macari et al [7] in World Journal of Oncology. Estrogen receptor status is a critical predictive biomarker not only for hormonal therapies that directly interact with the receptor or its signaling, but for other targeted therapies such as cyclin-dependent kinase (CDK) 4 and 6 inhibitors that also have therapeutic effects only in this population [8, 9].

Given the powerful predictive biomarkers of estrogen, progesterone, and HER2 receptors expressions, it is typical for breast cancer to be divided into subtypes that correspond to receptor expression status: 70% are luminal (estrogen receptor-positive), 10-15% are HER2-overexpressing, and 10-20% are triple-negative. This typical classification scheme is changing with a recognition of a new predictive biomarker, "HER2-low". Traditional HER2-targeted therapy using trastuzumab or pertuzumab was indicated only for HER2-overexpressed breast cancers determined as 3+ staining by immunohistochemistry or 2+ staining by immunohistochemistry and positive by fluorescent *in situ* hybridization (FISH). However, Modi et al recently reported in the New England Journal of Medicine (July 2022) that HER2-low tumors, currently defined as HER2 1+ or 2+ by immunohistochemistry with negative FISH, are treatable using trastuzumab deruxtecan, a HER2 targeting antibody-topoisomerase 1 inhibitor conjugate [10]. Apparently, approximately 50-60% of non-HER2 overexpressing and 35% of triple-negative breast cancers are HER2-low [11, 12]. To this end, the predictive biomarker distribution in breast cancer is now 50% HER2-low, 25% luminal, 15% HER2 overexpressing, and 10% triple-negative [13].

As such, the discovery of predictive biomarkers can

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change how we recognize a cancer, and this is most likely one of the reasons for the recent explosion of publications on this topic. Therefore, we predict that the race to identify powerful predictive biomarkers will continue. Ultimately, prognostic biomarkers that identify patients with poor survival odds but do not provide treatment information are less useful than predictive biomarkers. To this end, our group has also been aggressively pursuing this line of research not only to identify single gene expression biomarkers (maternal embryonic leucine zipper kinase (MELK) [14], inositol-trisphosphate 3-kinase (ITPKC) [15], androgen receptor [16]), but also scores combining multiple gene expressions (5-gene score [17], 4-gene score [18], 3-gene score [19]), cell infiltrations (regulatory T cells [20], T-helper 2 (Th2) cells [21]) and activation of signaling pathways (E2F targets [22], G2M checkpoint [23]). We expect to receive more manuscript submissions to the World Journal of Oncology on this end in the near future.

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None to declare.

Conflict of Interest

None to declare.

Author Contributions

Conceptualization and design of study: KT. Editing of the paper: KT and MGKB.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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