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LETTER TO THE EDITOR

The adjacent to tumor sample trap

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To the Editor,

A cancer biomarker has one fundamental characteristic: to be different between normal and cancer cells.

Translating the use of biomarkers to clinical practice remains a challenge in oncology. A large number of these markers are proposed daily, but they are rarely consolidated as useful tools for clinicians. To favor this translation, innovative strategies are being attempted, including multicenter collaborative efforts.

Among these initiatives, The Cancer Genome Atlas has arisen as one of the most robust public data banks, because the commonest tumors were widely studied by rigorous methods.

Nevertheless, at least for gastric cancer, most of these investigations that search for relevant biomarkers, including The Cancer Genome Atlas, carry the potential bias of lacking true normal samples to compare with cancer samples. Most gastric cancer biomarkers discovered by molecular analysis resulted from comparisons between tumor samples and adjacent-to-tumor samples, which were considered normal samples [1–4].

Although their appearance is normal, adjacent-to-tumor samples possess molecular alterations that are not sufficient to cause them to look like and be diagnosed as cancer tissue, but strongly differentiate them from true normal tissues.

Because most gastric cancer experiments to discover cancer biomarkers consider different expression patterns between cancer samples and adjacent-to-cancer samples instead of normal samples, important discrepancies could result from equivocal interpretations.

In 1953, Slaughter et al. [5] proposed the basic idea of the cancer field effect in an attempt to explain the occurrence of multiple cancers or cancer recurrence in a given organ. Many scientists have subsequently demonstrated that instead of being normal, tissue adjacent to tumor cells already exhibits genetic [6] and epigenetic [5, 7–14] aberrations.

Searching for putative cancer biomarkers by comparing cancer samples with adjacent-to-cancer samples will most likely provide markers of progression from cancer fields to cancer, instead of resulting in the discovery of the earliest markers of cancer, because normal tissues are not compared.

According to the field effect hypothesis, this current strategy, although lacking the capability to identify initial events of carcinogenesis, provides robust information regarding the field effect phenomenon and is an important source of data to be incorporated into integral analyses that include cancer, adjacent-to-cancer, and normal samples. Nevertheless, the inclusion of normal samples from noncancer patients who were not exposed to the main carcinogens, such as *Helicobacter pylori*, would improve the ability to interpret carcinogenesis and, consequently, better translate the use of biomarkers to clinical practice.

For gastric cancer, addition of samples from noncancer patients to allow integral analysis of normal, cancer, and adjacent-to-cancer sample data is feasible because endoscopy is usually performed in noncancer patients. Thus, selecting adequate samples from volunteers seems reasonable, taking into account all ethical regulations.

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Moreover, referring to adjacent-to-tumor samples as normal samples can lead to misinterpretations, including missing the identification of potential biomarkers expressed in both tumor and adjacent-to-tumor tissues in patterns different from those in true normal tissue. We can reasonably propose the addition of samples from noncancer patients, whenever accessible, to enhance the potential benefits of large multicenter cancer investigations.

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Compliance with ethical standards

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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