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EDITORIAL

Is C3c structure useful as biomarkers for epithelial ovarian cancer?

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Unlike to high possibility to eradicate cervical cancer by a very highly effective strategy, including human papilloma virus (HPV) vaccination and cytology-based plus HPV-based screening (combo test),[1–3] epithelial ovarian cancer (EOC) is still a big challenge due to the absence of cost-effective screening method and uncertainty of main etiology. Additionally, indulgent clinical course and symptom-free clinical presentation make an early diagnosis nearly impossible, and the advanced stage is a result when the confirmed diagnosis is made.[4] Moreover, the incidence of EOC is continuously increasing.[5] All result in a high mortality rate of EOC patients.[6] In fact, EOC is the most lethal female genital tract cancer and is also associated with a heavy socioeconomic burden in the world.[4–6] Although better understandings of pathophysiology of cancers plus far advance in modern medicine may help to combat many types of cancers effectively, there is no doubt that cancer stage is still the most powerful and independent risk factor for both progression-free survival (PFS) and overall survival (OS).[7–9] The limitation still apparently exists, even though therapy based on biomarkers-targeted therapy, genomic investigation, and following multimodality approach has provided cancer patient with a promising and exciting therapeutic efficacy.[7,8,10–13] These aforementioned new landscapes of treatment of choice not only improve both PFS and OS rates but also apparently maintain the quality of life (QoL) in these cancer survivors after treatment.[7–13] All strongly hint us the importance of an early diagnosis and following prompt adequate and effective therapy.[1–3] Therefore, many bench and bed researchers are eagerly searching for more biomarkers to make the dream come true. One of the articles published in the *Journal of Chinese Medical Association* (*JCMA*) is a typical example which addressed this topic. Dr. Chen et al[14] attempted to offer a better tool to fill in the gap. They found redefined complement C3c structures have significant increase in the plasma of EOC patients. This article is interesting and worthy of further discussion.

Dr. Chen et al[14] found canonical complement C3 derivatives as C3c having a strong correlation between increased plasma levels and occurrence and progression of EOC. Although the current study is worthy of applause, the many uncertainties are still against their claimed value. For example, the hypothesis of increased plasma C3c concentration being closely and positively correlated with occurrence and progression of EOC may not be really supported by Dr. Chen et al's[14] study. Although Dr. Chen et al's[14] study has claimed that p value between the results of healthy controls and stage I EOC group was <0.001 using two-tailed t test, the majority of either healthy controls or stage I EOC patients have plasma C3c concentration less than 1.0 μg/mL, and the higher mean of plasma C3c concentration may be secondary to the confounding effect by outliners of some stage I EOC patients. Therefore, the authors' conclusion may be stayed in a high possibility to overstate their findings. The value of canonical C3c concentration acting as biomarker for occurrence of EOC may be in doubt.

Additionally, the difference between stage I and stage II EOC cannot be found in their article. If the biomarkers are valuable as shown by authors with the observation canonical C3c demonstrated a strong correlation between increased plasma levels and the progression of EOC, why their canonical C3c concentration fails to show the positive correlation to EOC stage? Moreover, the scatter and wide distribution of plasma canonical C3c concentration in EOC is found in Dr. Chen et al's[14] study, regardless of whether early-stage EOC or advanced-stage EOC is classified. All are further against the potential role of using C3c acting as a biomarker for EOC, regardless of whether the occurrence or the progression roles are claimed.

The authors tried to explain the function of C3c by their description as "enhanced C3c formation in patients with EOC is a process considered to be a marker of inflammatory condition."[14] However, the aforementioned claims seem to support the alternation of C3c is an end product secondary to patients having EOC. Since if elevated plasma level of C3c cannot appear before the occurrence of EOC, what is the value of plasma level of C3c for clinical use? Finally, the age factor and menstrual cycles are not included in the current study, so it is hard to convince the audience to accept their blindly optimistic claims. A predicament of C3c is very similar to that of CA 125, since many clinical situations and age factor may influence the alternating serum level of CA 125.[15,16]

Taken together, we should respect the scientists' effort and also congratulate Dr. Chen et al's[14] success to publish their work. However, the success of the bench work is not always representative of the useful bed work. Moreover, statistical significance is not a clinical meaning. Enlarging the study subjects into the real homogeneous population

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and conducting longitudinal study design in place of cross-section study design may offer a better chance to show the clinical meanings. Without these, the data presentation should be cautious.

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