Dear editors,

Thank you very much for offering us an opportunity to resubmit our manuscript after reversing. We have made extensive revisions according to the reviewers' comments. I hope you can give us another opportunity to further revise our manuscript if some limitations remain in the manuscript.

Looking forward to hearing from you,

Best regards,
Ningli Chai

Replies to Reviewer #1: Thank you very much for your positive comments, which might be of great help to improve the quality of our manuscript.

1. The authors used the term 'esophageal squamous cell neoplasia (ESCN)', 'esophageal cancer' and 'squamous cell carcinoma' alternatively. However, ESCN includes low-grade intraepithelial neoplasia (LIN), high-grade intraepithelial neoplasia (HIN), squamous cell carcinoma in situ, squamous cell carcinoma. Nevertheless, the authors conducted this study using 92 ESCN consisted of HIN and squamous cell carcinoma. If the authors want to take the term ESCN, 'esophageal cancer' and 'squamous cell carcinoma' should be discarded as an alternative term. If the authors want to take the term esophageal cancer or squamous cell carcinoma, HIN should not be collected as a research materials.

Reply:
Thanks for your constructive suggestions. We completely agreed your proposal

and have revised an easily misunderstood ‘esophageal cancer’ and some 'squamous cell carcinoma' to' esophageal squamous cell neoplasia (ESCN)'.

2. Immunohistochemical expression pattern should be revised as SGK3 rather than ERBB3 (page 8, the last sentence).

Reply:
Thanks for your kind comment. The word "ERBB3" has been changed to "SGK3"

3. Figure 1: 1) LIN is not categorized into esophageal cancer. 2) EP indicates HIN and squamous cell carcinoma in situ.

Reply:
Thank you very much for your positive and constructive comments. We have read your opinion carefully and the term ‘esophageal cancer’ has been changed to ‘esophageal neoplasia’.

4. Figure 2: 1) All figures (A~D) are HIN? Give the classification of the neoplasia to each photos. 2) There is no cytoplasmic membranous staining of the SGK3 anywhere. C showed only nuclear staining and D showed nuclear staining with cytoplasmic overstaining only.

Reply:
Our study had the highest percentage of high-grade intraepithelial neoplasia (HIN), so the images we chose were all HIN. The definition of SGK3 positive was based on the nuclear staining, so we have changed ‘cytoplasmic membranous staining’ to ‘nuclear staining’. And our images were confirmed and selected by pathologists again, they showed varying degree of nuclear staining.

5. Table 1: Differentiated types High Middle Low should be revised as Well-differentiated Intermediate differentiated Poorly differentiated

Reply:

Thanks for your kind comment. Based on your suggestions, we renamed the degree of differentiation of squamous cell carcinoma.

Replies to Reviewer #2: First of all, thank you very much for your positive and constructive comments and suggestions.

1. Most of patients did not experience recurrence or metastasis. Please list the cause of death of both group (SGK3-overexpression and SGK3-normal).

Reply:

The cause of death of both group were showed in the table.

	SGK3-overexpression	SGK3-normal
Death from ESCN	6	1
Death from pneumonia	3	1
Death from coronary disease	3	1
Death from other cause	3	0

2. Please explain in the discussion why the overexpression of SGK3 resulted in worse prognosis although the complete resection was performed.

Reply:

Thank you very much for your positive and constructive comments. In the discussion, the reason why the overexpression of SGK3 resulted in worse prognosis can be simply summarized as relies on the PI3K/protein kinase B (AKT) signaling pathway to regulate tumor cell progression and is aberrantly expressed in a variety of tumors.

3. Please exclaim the clinical impact about examining IHC for SGK3 in ESCN. For example, if we detected ESCN and perform a biopsy before treatment, the result of IHC for SGK3 in specimen would affect decision-making about treatment (endoscopic resection, surgical resection, chemotherapy, radiotherapy) ?

Reply:

That's a good question. Since IHC for SGK3 in ESCN showed that overexpression of SGK3 is an independent factor in prognosis, IHC staining of SGK3 could be used to determine the population with high mortality. Thus, active measures, including shortening the follow-up intervals and using moderate radiotherapy or chemotherapy, can be taken to improve the survival of patients with SGK3 overexpression.

4. More than half of ESCNs overexpressed SGK3. This finding mean that SGK3-normal ESCN has a better outcome, rather than the explanation that SGK3-overexpressed ESCN has a worse outcome.

Reply:

Undoubtedly, SGK3-normal ESCN has a better outcome in our study. In contrast, SGK3-overexpressed ESCN has a worse outcome. This is a different perspective on the SGK3 expression state. In this study, more than half of ESCNs overexpressed SGK3 and 15 patients with SGK3 overexpression died during the follow-up period. Only 3 patients with SGK3-normal died. Thus, we speculated that SGK3 may be associated with poor prognosis and made a further analysis from this perspective。

5. Please unify the name of the control group (normal or negative).

Reply:

The use of normal and negative to describe the control group might result in misunderstanding. Therefore, based on your comments, we have changed all the control group into SGK3 normal group.