In this study, Gu et al. has found that Gamma Tocotrienol, a natural form of Vitamin E, suppressed the mammasphere formation through RAS/ERK pathway. Firstly, the authors found that mammaspheres enriched breast cancer stem cell population as evidenced by increased in CD44+CD24- expression. Based on this finding, they found that Gamma Tocotrienol inhibited the sphere formation from cells derived from cancers of breast, colon and cervical. Subsequent studies showed that SHP2 is the target of Gamma Tocotrienol mediating this effect. Finally, the authors found that RAS/ERK is the ultimate downstream target of Gamma Tocotrienol determining the survival of mammaspheres. There are several concerns of this paper.

1. In order to prove the effect of Gamma Tocotrienol on breast cancer stem cells, the authors should examine the effect of Gamma Tocotrienol on expression of CD44 and CD24.

2. The authors found that Gamma Tocotrienol completely suppressed mammasphere formation at 5ug/ml. Is this dose lethal or toxic to the cancer cells?

3. The effect of Gamma Tocotrienol on SHP1 is not obvious (even opposite in the result obtained in western blot analysis). Therefore, the author cannot conclude that SHP1 is the target of Gamma Tocotrienol.

4. Can the authors account for the difference in the results obtained in Figure 3A and C?

5. The authors should quantitate the protein expression in Figure 5C.

6. The quality of western blot in Figure 4A and 5D are very poor. The proteins concentration is not normalized. The western blot should be rerun to confirm the effect of Gamma Tocotrienol on p-SHP2 and elevated expression of p-SHP-2 in mammaspheres.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

'I declare that I have no competing interests'