

LETTER TO THE EDITOR

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# The status of *Her2* amplification and *Kras* mutations in mucinous ovarian carcinoma

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## Abstract

Jayson GC et al. remarked in *Lancet* that nearly 100% of mucinous ovarian cancer cases have *Kras* mutation as well as a high frequency of *Her2* amplification. Using the Abbott PathVysion *Her2* DNA Probe Kit and *Kras* mutant-enriched PCR Kits (FemtoPath<sup>®</sup>), 21 samples of primary ovarian mucinous cystadenocarcinomas from Taiwanese patients were examined to determine the status of *Her2* amplification and *Kras* mutations. Our results showed the *Her2* amplification rates were 33.33%, while the *Kras* mutation rates were 61.90%. We present here our results in order to enlighten the readership that the ~100% *Kras* mutant frequency and the high *Her2* amplification rate reported by Jayson et al. may be too exaggerated to be applicable into all populations. Additionally, we report another 2 novel *Kras* mutations (A11V, V14I).

**Keywords:** *Kras* mutation, *Her2* amplification, Mucinous ovarian carcinoma

## Main text

We read with great interest the work by Jayson et al. in *Lancet* (Oct. 2014). The authors presented a comprehensive review of outstanding quality. They remarked that mucinous ovarian carcinoma has a nearly 100% human V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*Kras*) mutation as well as a high frequency of human epidermal growth factor receptor 2 (*Her2*) amplification [1]. However, we respectfully disagree with Jayson et al.'s opinion.

Literature reviews revealed that in mucinous ovarian carcinoma, the frequency of *Her2* amplification/over-expression is estimated to be between 18 and 35% [2], and the presence of human *Kras* mutations is 13 to 60% [3–5]. This preliminary report aims to enlighten the readership that the ~100% *Kras* mutant frequency and the high *Her2* amplification rate in mucinous ovarian carcinoma may be higher than what has been observed in other studies, including our own.

Briefly, genomic DNA was extracted from formalin-fixed, paraffin-embedded tissue blocks of 21 cases of mucinous ovarian carcinoma. All the donors' identities have been permanently deleted. Abbott PathVysion *Her2* DNA Probe Kit and the 2013 American Society of Clinical

Oncology/College of American Pathologists (ASCO/CAP) breast cancer scoring methods were used to examine for *Her2* FISH ratio. The *Kras* mutant-enriched polymerase chain reaction (PCR) Kits (FemtoPath<sup>®</sup>) and a following direct sequencing method were applied to analyze exon 2 of the *Kras* gene. The reason why we choose *Kras* exon 2 to analyze is because *Kras* gene mutations are mainly known to cluster in several hotspots, with exon 2 (codons 12 and 13) being most commonly affected [6–9].

The prevalence of *Kras* mutations and *Her2* amplification within 21 Taiwanese mucinous ovarian carcinoma cases is shown in Table 1, which indicates that the amplification rate of *Her2* was 33.33% ( $n = 7$ ), while the mutation rate of *Kras* was 61.90% ( $n = 13$ ). Additionally, the rates of co-existing *Kras* mutations and *Her2* amplification were 9.52% ( $n = 2$ ) (Table 1). However, there was a lack of statistically significant association between *Her2* amplification and *Kras* mutations ( $p = 0.057$ ).

Of the 13 cases of mucinous ovarian carcinoma with *Kras* mutations, 12 cases had a single missense mutation, which was composed of G12V in 4 cases, G12D in 5 cases, G12A in 1 case and A11V in 2 cases. The remaining 1 case had triple missense mutations—A11V, G13N and V14I. Moreover, both A11V and V14I were novel discoveries, based on the Catalogue of Somatic Mutations in Cancer (COSMIC) database [10].

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**Table 1** The prevalence and relationship of *Kras* mutations and *Her2* amplification in mucinous ovarian carcinoma

	<i>Her2</i> non-amplification	<i>Her2</i> amplification	Total
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
<i>Kras</i> wild type	3 (14.29)	5 (23.81)	8 (38.10)
<i>Kras</i> mutation	11 (52.38)	2 (9.52)	13 (61.90)
Total	14 (66.67)	7 (33.33)	21 (100.00)
<i>P</i> value	0.056 <sup>a</sup>		

*n* (%) number (percentage)<sup>a</sup>Fisher's exact test

## Conclusion

Both *Her2* amplification and *Kras* activating mutations are not mutually exclusive, which indicates that *Her2/Kras*/mitogen-activated protein kinases (MAPK) is a crucial pathway in the carcinogenesis of mucinous ovarian neoplasms. Targeting this pathway seems to be a viable therapeutic option for patients with recurrent or advanced stage mucinous ovarian carcinoma. Treatment selection based on the molecular alterations of *Her2* and *Kras* can possibly produce superior therapeutic effects compared with nonselective treatments. Additionally, functional impacts of these 2 novel *Kras* mutations (A11V, V14I) are still unknown; further studies using bioinformatics tools and molecular modeling are encouraged.

## Abbreviations

ASCO/CAP: American Society of Clinical Oncology/College of American Pathologists; COSMIC: Catalogue of Somatic Mutations in Cancer; *Her2*: Human epidermal growth factor receptor 2 gene; ICH: International Conference on Harmonization; *Kras*: V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog gene; MAPK: Mitogen-activated protein kinases; PCR: Polymerase chain reaction

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## Availability of data and materials

Please contact the author for data requests.

## Authors' contributions

KLC and CPH provided the specimens and wrote the manuscript. MYL analyzed the data. WRC performed the experiments. All authors read and approved the final manuscript.

## Competing interests

The authors declare that they have no competing interests.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

Our research was conducted in accordance with the International Conference on Harmonization (ICH) guidelines and compliant with all applicable regulations for

the protection of human subjects for research, including review and approval by the Institutional Review Board of the Chung-Shan Medical University Hospital, Taichung, Taiwan.

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