Author’s response to reviews

Title: Malignancy during pregnancy in Japan: an exceptional opportunity for early diagnosis

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Author’s response to reviews:

We wish to express our appreciation to the reviewers for their insightful comments, which have helped us significantly improve the paper.

<Reviewer #1>

Good start for further investigative and educational work. You only need to proof read again as there are some minor grammatical errors.

Response:

We wish to thank the Reviewer #1 for this comment. Our revised paper has been edited and rewritten by an experienced scientific editor, who has improved the grammar and stylistic expression of the paper.

<Reviewer #2>

Major comment 1
A major concern is that only 50% of hospitals who were approached responded to the survey and there is no way to determine whether the hospitals that responded are representative of all Japanese hospitals. There are also no details given about how these hospitals identified cases of cancer diagnosed during pregnancy. One would assume that these are collected in hospital-based tumor registries, and that electronic medical records were searched for mention of pregnancy and dates of pregnancy and diagnosis of cancer were compared? Further details should be provided.

Response:

We wish to thank the Reviewer #2 for this comment. We recruited the questionnaires from training hospitals and clinical cancer centers, so community hospitals were not included in this study. We think that almost of malignant cases during pregnancy were referred to the training hospitals and clinical cancer centers (secondary or tertiary care hospitals) for further investigation, however, in accordance with the Reviewer's comment, we do not consider that 50% of the hospitals are representative of all Japanese hospitals. Therefore, we have cooled down our statement in the Text. We have changed to 'in the present study' from 'in Japan' in several places and removed 'in Japan' from the text (p3 line16, p8 line14, p10 line3, p10 line6).

In accordance with the Reviewer's comment, we have added the following text to the Methods (p7, lines 6-8).

Most of the cases has been collected in hospital-based tumor registries. Subsequently, the attending obstetrician or gynecologist has examined the clinical information of the cases from medical records.

Major comment 2

Another major concern is that there are virtually no details given about stage at diagnosis; this would seem particularly important for cervical cancer. Considering that the vast majority of these tumors were diagnosed by cytology, it seems unlikely that they are truly invasive cancers. Further details should be provided about stage at diagnosis. It may also be interesting to present histologic type of ovarian cancer.

Response:

In accordance with the Reviewer's comment, we have added the following text to the Results (p 8, lines 14-18 and p 9, lines 1-2)

The stage at diagnosis of 162 cases with cervical cancer in this study was as follows: 102 cases (63%) in CIN3, 16 cases (10%) in stage Ia, 33 cases (20%) in stage Ib, 5 cases (3%) in stage II, 2 cases (1%) in stage IV and 4 cases (3%) with unknown clinical stage.

The histologic type of 16 cases with ovarian cancer in this study was as follows: 5 cases with adenocarcinoma (2 endometrioid, 1 serous, 1 clearcell, and 1 mucinous type), 2 with serous borderline tumor, 4 with germcell tumor (3 immature teratoma and 1 dysgerminoma), 1 with
malignant transformation of mature teratoma, 1 with sertoli-lei'dich tumor, and 3 with unknown histology.

Minor comment 1

Background: lines 7-10, where were these studies conducted and what were the study designs?

Response:

In accordance with the Reviewer's comment, we have added the following text to the Background (p 5, lines 10-16)

Several reports on malignancies during pregnancy have been published6-11 (e.g. the American Cancer Society's Department of Epidemiology and Statistics reports for the United States and around the world, a population-based cohort study from the Cancer Registry and the Medical Birth Registry of Norway, and an international collaborative setting of institutional registry in Belgium, the Netherlands and Czech Republic). In these reports, gynecological tumors are among the malignancies most frequently diagnosed during pregnancy6-10, particularly those of cervical and ovarian origin11. When managing such tumors, the physician must be considered both fetal life preservation and the potential loss of the patient’s future reproductive capacity as a result of any chosen cancer therapy.

Minor comment 2

Increases in 'HPV-linked cervical cancer in women of younger age'; this statement needs a reference. Cervical cancer in general (at least in the U.S.) has been declining for many years, in part due to improved screening practices and treatment of early stage lesion. Please provide incidence trends for younger women in Japan.

Response:

As far as I searched, there is no paper mentioned increasing trend of 'HPV-linked cervical cancer in women of younger age, however it has been reported that the incidence rate of cervical cancer in 20 to 49-year-old females has been increasing in Japan.

Therefore, we have changed the following text in the Background (p. 5, lines 5-8)

This is also associated with increase in the incidence rate of cervical cancer in 20 to 49-year-olds has been seen in Japan6-8. This is assumed to be a result of a decline in the age of initial incidence of HPV infection due to a decline in the age of first sexual intercourse, in addition to low screening rate.

Moreover, we have also added the following reference.


Minor comment 3

The results refer to 'in Japan' in several places, but this was a census of at most ½ of the hospitals in Japan (or perhaps even lower since the questionnaires were sent to 'training hospitals' and clinical cancer centers only; community hospitals were not included?). It would be better to refer to the results 'in the present study'. Discussion, line 17-18, rate should be prevalence; again 'in Japan' is not accurate.

Response:

In accordance with the Reviewer’s comment, we have changed the following text to the Discussion (p.10, lines 10-12) and changed to 'in the present study' from 'in Japan' in several places.

The prevalence of cervical cancer for women in their twenties and thirties has risen dramatically over the past decade in several studies in Japan6-8.

We wish to thank the Reviewers again for their valuable comments.