Peer Review File

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Reviewer A

Comment: editing the whole discussion is needed!

Reply: Thank you for your valuable feedback regarding the Discussion section. We appreciate your constructive suggestions, which have allowed us to further refine our manuscript. Below, I will respond to your comments in four points (a-d).

a. Reorganizing Logic and Adjusting Narrative Structure

   We have carefully reviewed and made adjustments to the logical structure of the discussion section. Specifically, we moved the original fourth paragraph to the third paragraph (see **line 229-238** in the revised manuscript). The updated sequence of the discussion section is as follows: (1) the reasons for the predominance of luminal-type BC in DPBOC cases in this study; (2) the criteria for defining the time interval between the two primary tumors; (3) discussion of demographic factors, particularly race, that influence survival differences; (4) discussion of key findings: the time interval as an independent prognostic factor for DPBOC, survival primarily determined by OC, and the impact of OC staging and pathology type; (5) summary of the reasons behind the survival differences between the two groups; (6) discussion of the study's limitations. Additionally, at the end of each key findings section, we have provided corresponding clinical and research recommendations to highlight the significance of this study.

b. Strengthening the Discussion of Key Findings and Highlighting Clinical and Research Significance

   We have added further details to the discussion of the three key findings in this study. In the fourth paragraph of the discussion, we revised the statement: "with the median time interval (48 months) as the cutoff value, the hazard ratio of ≥48 months were 0.323 (95% CI=0.264-0.395), 0.527 (95% CI=0.305-0.908) and 0.707 (95% CI=0.559-0.894), respectively. This indicates that the longer the time interval, the lower the risk for patients to develop adverse outcomes." to: "Using the median interval of 48 months as the cutoff, patients with intervals ≥48 months exhibited significantly lower risks of adverse outcomes, with hazard ratios of 0.323 (95% CI=0.264-0.395) for OS, 0.527 (95% CI=0.305-0.908) for BCSS, and 0.707 (95% CI=0.559-0.894) for OCSS. These results

suggest that longer time intervals between FPC and SPC diagnosis are associated with improved survival outcomes." This revision provides a clearer presentation of how time intervals affect survival outcomes (see **line 250-255** in the revised manuscript). We then revised the remaining portion of the paragraph to extend the discussion from a research perspective to clinical relevance. Specifically, we discussed how the time interval affects survival outcomes and suggested how clinicians could use this information to develop more comprehensive diagnostic and treatment plans, ensuring that the study findings are effectively translated into clinical practice (see **line 255-262** in the revised manuscript). At the end of the fifth paragraph, we added: "These findings underscore the critical importance of considering distant metastasis (M stage) when evaluating early-stage tumors, as it can significantly influence survival outcomes. From a clinical perspective, when determining treatment strategies for DPBOC and assessing patient survival, careful consideration should be given to the pathological type and TNM stage of OC. Prioritizing the monitoring of OC and developing personalized management plans based on the presence of metastasis could help optimize disease control and improve patient outcomes." This addition first explains why T0-stage OC is associated with higher mortality risk, emphasizing the impact of M stage on survival. We then summarize the key content of this section and provide clinical suggestions for monitoring and treatment priorities for DPBOC patients (see **line 282-288** in the revised manuscript). The sixth paragraph of the discussion primarily explores the impact of OC pathological types on DPBOC survival. At the end of this paragraph, we added: "However, as this study did not collect data on BRCA mutations or treatment-related factors, we were unable to fully analyze the impact of these variables on patient survival. Future studies should incorporate genetic profiles and treatment data to further investigate the complex effects of different OC pathological types on survival outcomes. From a clinical perspective, our findings highlight the importance of personalized monitoring and treatment strategies for clear cell OC patients. Given their elevated risk of recurrence and drug resistance, more proactive interventions and follow-up strategies are essential to improving survival outcomes." This addition suggests key variables and details that future studies should consider, ensuring the study results remain highly relevant to researchers. Based on our data, we also highlight the importance of clear cell OC in DPBOC patients and provide recommendations for clinicians (see **line 298-305** in the revised manuscript).

c. Improving Language Expression for Conciseness, Logic, and Accuracy

We have reviewed the language used in the discussion section to ensure clarity, accuracy, and to remove redundant expressions. For example, we revised the sentence:

"We also found that about 40% of patients developed SPC within 24 months of being diagnosed FPC, suggesting that the 2 years after FPC diagnosis is a high incidence period of SPC." to: "Notably, 40% of patients developed SPC within 24 months, highlighting this period as a critical window of high SPC incidence." This revision simplifies the sentence while emphasizing the important finding, setting the stage for discussing its clinical implications (see **line 246-247** in the revised manuscript). Additionally, we changed the following sentence: "Moreover, one thing can be sure that longer the time since diagnosis of FPC, the lower the probability of developing SPC, as is indicated in many studies including the current one." to: "Furthermore, consistent with previous findings, our results suggest that the probability of developing SPC decreases as the time interval from FPC diagnosis lengthens." This revision reduces the stacking of short phrases and enhances readability while making the key finding clearer (see **line 247-249** in the revised manuscript). We also added the word "Importantly" before "Table 4" to better transition to the next key point (see **line 249** in the revised manuscript). To avoid fragmenting the clinical significance, we deleted the sentence: "Therefore, in clinical work, we should pay more attention to the pathological type and TNM stage of OC in DPBOC patients and prioritize monitoring and treatment for OC." This was removed to improve readability and the flow of the argument. We moved the sentence: "The BRCA is not included in our study, so it is not sufficient enough to attribute the higher proportion of serous carcinoma and stage III and IV OC in the BO group to gene mutations." to a later section, where we provide a unified explanation for why BRCA gene mutations are not discussed in this study. This ensures better contextual coherence (see **line 277-279** in the revised manuscript). Lastly, since the fifth paragraph focuses on the impact of tumor staging on survival, we moved the sentence: "Table 4 shows that the death risk of T0 in OC is higher than that of T2, T3, and T4. After analyzing the data, we found that the 4 T0 stage OC patients were all M1 stage, and 2 of them died of OC, which led to multivariate Cox regression showing that T0 was a high risk." from the sixth paragraph to the fifth, adding "Additionally," before it to improve the logical flow of the discussion and ensure a clearer allocation of content (see **line 279-282** in the revised manuscript).

d. Addition of Discussion on Statistical Methods

The explanation regarding the exclusion of T and N staging in the BCSS analysis was insufficient in the original manuscript. Therefore, in the revised manuscript (see **line 319-324**), we have provided a detailed explanation of this approach and discussed its impact on the generalizability of the results, as well as alternative methods that could be considered.

Changes in the text: **line 229-238**: "The proportion of white people in this study (897, 83.5%) is higher than that of black people (70, 6.5%), but the mortality rate of white people is lower (50.9% vs. 57.1%). This indicates that through white women have higher BC and OC occurrence, black women have higher death rate, such is consistent with previous findings[24]. Many studies have shown that black women have a higher *BRCA* mutation rate than white women[25,26], which seems to suggest that *BRCA* test is necessary for black women. However, Armstrong et al. found that after the *BRCA1/2* mutation probability, socioeconomic characteristics and other factors are adjusted, the possibility of black women with BC and OC family history to receive *BRCA1/2* assessment is lower than white women other same condition[27], suggesting that the poor prognosis of the disease may be due to the fact that some black women cannot receive timely *BRCA* test and effective clinical prevention and treatment."

line 250-255: "Using the median interval of 48 months as the cutoff, patients with intervals ≥48 months exhibited significantly lower risks of adverse outcomes, with hazard ratios of 0.323 (95% CI=0.264-0.395) for OS, 0.527 (95% CI=0.305-0.908) for BCSS, and 0.707 (95% CI=0.559-0.894) for OCSS. These results suggest that longer time intervals between FPC and SPC diagnosis are associated with improved survival outcomes."

line 255-262: "Clinically, these findings underscore the importance of intensive follow-up during the early years after FPC diagnosis, particularly within the first two years when the risk of SPC is highest. Currently, BC patients in mainland China are generally reexamined every 3 months within the first 2 years post-surgery, focusing primarily on breast ultrasound, abdominal ultrasound, and chest CT. However, ovarian examinations are often overlooked. Given the significant impact of OC on the prognosis of BC patients, it is strongly recommended that routine gynecological evaluations, particularly ovarian assessments, be incorporated into follow-up protocols. Early and comprehensive surveillance for SPC could potentially enhance patient outcomes by enabling timely intervention."

line 282-288: "These findings underscore the critical importance of considering

distant metastasis (M stage) when evaluating early-stage tumors, as it can significantly influence survival outcomes. From a clinical perspective, when determining treatment strategies for DPBOC and assessing patient survival, careful consideration should be given to the pathological type and TNM stage of OC. Prioritizing the monitoring of OC and developing personalized management plans based on the presence of metastasis could help optimize disease control and improve patient outcomes."

line 298-305: "However, as this study did not collect data on BRCA mutations or treatment-related factors, we were unable to fully analyze the impact of these variables on patient survival. Future studies should incorporate genetic profiles and treatment data to further investigate the complex effects of different OC pathological types on survival outcomes. From a clinical perspective, our findings highlight the importance of personalized monitoring and treatment strategies for clear cell OC patients. Given their elevated risk of recurrence and drug resistance, more proactive interventions and follow-up strategies are essential to improving survival outcomes."

line 246-247: "Notably, 40% of patients developed SPC within 24 months, highlighting this period as a critical window of high SPC incidence."

line 247-249: "Furthermore, consistent with previous findings, our results suggest that the probability of developing SPC decreases as the time interval from FPC diagnosis lengthens."

line 249: "Importantly,"

line 277-279: "Moreover, the BRCA is not included in our study, so it is not sufficient enough to attribute the higher proportion of serous carcinoma and stage III and IV OC in the BO group to gene mutations."

line 279-282: "Additionally, table 4 shows that the death risk of T0 in OC is higher than that of T2, T3, and T4. After analyzing the data, we found that the 4 T0 stage OC patients were all M1 stage, and 2 of them died of OC, which led to multivariate Cox regression showing that T0 was a high risk."

line 319-324: "Additionally, the T and N stages of BC were excluded from the Cox regression analysis for BCSS due to the absence of BC-related deaths in certain subgroups, which could lead to biased or unstable estimates. Although this exclusion may limit the generalizability of conclusions related to tumor size and lymph node involvement, key prognostic factors were retained to ensure the robustness of the analysis. Alternative methods, such as penalized Cox regression, could be explored in future studies with larger sample sizes to address this limitation."

Reviewer B

Comment 1: The statistical results could be summarized more concisely to improve readability. For example, highlight the main survival outcomes and their implications in a clear, reader-friendly format, such as bullet points or a concise table within the main text.

Reply 1: Thank you for your valuable feedback. Below, I will respond to your comments in five points (a-e).

a. The key content of the Demographic Characteristics section is to describe how the two groups were formed and their basic demographic information. Since only the racial composition showed a significant difference, no changes have been made to this section.

b. In the Pathological Characteristics section, the order of descriptions has been adjusted. We first describe the pathological characteristics of BC and OC in the overall population, followed by a comparison of these characteristics between the two groups. The revision highlights the significant differences in the pathological features of OC between the groups. Please refer to **line 138-146** of the revised manuscript for details.

c. The Survival Analysis section describes the survival differences between the two groups from three perspectives: Kaplan-Meier survival curves, cumulative survival rates, and detailed survival data. To clarify where the survival differences lie, we added the statement "Patients in the OB group had significantly superior survival outcomes than those in the BO group, with the differences primarily reflected in OS and OCSS." on **line 157-158** of the revised manuscript. Additionally, we removed the redundant sentence "The OB group did not reach the median OS." to make the description more concise. To emphasize that OC primarily determines the survival outcomes of DPBOC, we revised the original statement "with 6.1% succumbing to BC and 33.1% to OC." to "with significantly more deaths attributed to OC than to BC (33.1% vs. 6.1%)." on **line 161-162**.

d. The Univariate and Multivariate Analyses section contains six paragraphs. The first paragraph explains the statistical challenges encountered during the regression analysis and the corresponding solutions. The second paragraph provides a summary of the independent influencing factors. The following four paragraphs discuss significant influencing factors. In the third paragraph, we removed the sentence "For OCSS, the death risk of patients diagnosed with

FPC at the age range between 66-76 was 1.393 times (95% CI=1.034-1.877, P=0.029) higher than those diagnosed at the age of 18-66." to reduce the presentation of non-essential results and highlight the key statement: "the age of FPC diagnosis had a greater impact on survival compared to the age of SPC diagnosis." Additionally, we corrected an error where "the age of FPC diagnosis had a greater impact on survival compared to the age of SPC diagnosis" was mistakenly written as "the age of SPC diagnosis had a greater impact on survival compared to the age of SPC diagnosis." These changes can be found on **line 182** of the revised manuscript. The fifth paragraph has been summarized, with a concluding statement added at the beginning of the paragraph to better present the results. Please refer to **line 192** of the revised manuscript for details. In the sixth paragraph, the original sentence "For OS, the death risk of T1 and T2 in OC was lower than T0 (HR=0.134, 95%CI=0.044-0.410, P<0.001; HR=0.277, 95%CI=0.091-0.844, P=0.024); For OCSS, the death risk of T1 in OC was lower than T0 (HR=0.086, 95%CI=0.020-0.378, P=0.001)" was overly complex and redundant. We integrated and reorganized the sentences to improve logical flow and coherence. Please refer to **line 199-202** of the revised manuscript for the updated content.

e. Additionally, in accordance with the journal's requirements, we have added a Highlight Box in the manuscript to present the key statistical results more intuitively and enhance the overall readability of the article. Please refer to **line 59** of the revised manuscript for details.

Changes in the text: **line 138-146**: "Regarding OC, the predominant pathological type, tumor stage, T stage, N stage, and M stage respectively correspond to serous carcinoma (526, 40.9%), stage III (411, 38.3%), T3 (526, 49.0%), N0 (795, 74.0%), and M0 (839, 78.1%). A comparison between the two groups reveals that there were no statistically significant differences between the two groups in BC-related aspects (P>0.05). However, significant differences were observed in the pathological characteristics of OC. Specifically, the BO group had a higher proportion of serous carcinoma (52.8% vs. 42.8%, P<0.001), stages III and IV (68.6% vs. 46.7%, P<0.001), T3 (56.2% vs. 37.2%, P<0.001), N1 (17.7% vs. 14.2%, P=0.009), and M1 (25.9% vs. 15.4%, P<0.001) compared to the OB group."

line 157-158: "Patients in the OB group had significantly superior survival outcomes than those in the BO group, with the differences primarily reflected in OS and OCSS."

line 161-162: "with significantly more deaths attributed to OC than to BC (33.1%

vs. 6.1%)."

line 182: "the age of FPC diagnosis had a greater impact on survival compared to age of SPC diagnosis."

line 192: "The survival for patients with higher BC tumor stages is worse."

line 199-202: "For OS and OCSS, the death risk of T1 in OC was lower than that of T0 (OS: HR=0.134, 95%CI=0.044-0.410, P<0.001; OCSS: HR=0.086, 95%CI=0.020-0.378, P=0.001), while the death risk of T2 in OC was significantly lower than that of T0 for OS (HR=0.277, 95%CI=0.091-0.844, P=0.024)."

line 59: "Key findings: Time interval is an independent influence factor of DPBOC. The longer the time after being diagnosed FPC, the lower the risk for patients to develop SPC and with better prognosis. The survival outcome of DPBOC is mainly determined by OC, and the prognosis of patients with BC as FPC is worse than that of patients with OC as FPC."

Comment 2: Explicitly discuss the clinical importance of findings such as the role of time intervals, tumor stage, and pathological type in influencing survival outcomes. This will ensure the findings resonate with practitioners and researchers alike.

Reply 2: Thank you for your valuable suggestions. We have carefully revised the manuscript to better highlight the clinical importance of our findings as you suggested. Below, I will respond to your comments in three points (a-c).

a. In the third paragraph of the Discussion section, we made several modifications based on the reviewer's suggestions, as outlined below:
   First, we revised the original sentence "We also found that about 40% of patients developed SPC within 24 months of being diagnosed FPC, suggesting that the 2 years after FPC diagnosis is a high incidence period of SPC." to "Notably, 40% of patients developed SPC within 24 months, highlighting this period as a critical window of high SPC incidence." This modification uses concise and clear wording to emphasize this important finding and lays the foundation for the subsequent discussion of its clinical significance. Please refer to **line 246-247** in the revised manuscript for details.
   Next, we modified the original sentence "Moreover, one thing can be sure that longer the time since diagnosis of FPC, the lower the probability of developing SPC, as is indicated in many studies including the current one." to "Furthermore, consistent with previous findings, our results suggest that the probability of developing SPC decreases as the time interval from FPC diagnosis lengthens."

This change reduces the stacking of short sentences and improves readability, while also making the significance of this finding more prominent. Please refer to **line 247-249** in the revised manuscript for details.

To enhance the coherence and logical flow of the paragraph, we added "Importantly," before "Table 4," which provides a smooth transition to the key statistical results. Please refer to **line 249** in the revised manuscript for details.

Subsequently, we revised the original sentence "with the median time interval (48 months) as the cutoff value, the hazard ratio of ≥48 months were 0.323 (95% CI=0.264-0.395), 0.527 (95% CI=0.305-0.908) and 0.707 (95% CI=0.559-0.894), respectively. This indicates that the longer the time interval, the lower the risk for patients to develop adverse outcomes." to "Using the median interval of 48 months as the cutoff, patients with intervals ≥48 months exhibited significantly lower risks of adverse outcomes, with hazard ratios of 0.323 (95% CI=0.264-0.395) for OS, 0.527 (95% CI=0.305-0.908) for BCSS, and 0.707 (95% CI=0.559-0.894) for OCSS. These results suggest that longer time intervals between FPC and SPC diagnosis are associated with improved survival outcomes." This revision improves the clarity of how time intervals influence survival outcomes, making the results easier to understand. Please refer to **line 250-255** in the revised manuscript for details.

Finally, we fully revised the remaining part of this paragraph. We extended the discussion beyond presenting the study results by connecting them to clinical implications. We provided specific recommendations to guide clinicians on how to apply these findings to develop more comprehensive diagnostic and treatment plans, further enhancing the connection between research outcomes and clinical practice. Please refer to **line 255-262** in the revised manuscript for details.

b. In the fifth paragraph of the Discussion section, we made several modifications to improve the logic and structure, as outlined below:

First, we deleted the original sentence, "Therefore, in clinical work, we should pay more attention to the pathological type and TNM stage of OC in DPBOC patients and prioritize monitoring and treatment for OC," to avoid fragmented clinical interpretations and improve the paragraph's readability and coherence.

Next, we moved the sentence, "The BRCA is not included in our study, so it is not sufficient enough to attribute the higher proportion of serous carcinoma and stage III and IV OC in the BO group to gene mutations," to the latter part of the paragraph. This adjustment unifies the explanation of why BRCA gene analysis was not included in the study and strengthens the connection between the

preceding and following content. Please refer to the revised manuscript, **line 277-278**, for details.

Since the main discussion of the fifth paragraph focuses on the impact of tumor stage on survival outcomes, we relocated the sentence from the sixth paragraph: "Table 4 shows that the death risk of T0 in OC is higher than that of T2, T3, and T4. After analyzing the data, we found that the 4 T0 stage OC patients were all M1 stage, and 2 of them died of OC, which led to multivariate Cox regression showing that T0 was a high risk." This sentence was moved to the fifth paragraph, with "Additionally," added to the beginning to smoothly connect it to the surrounding context. This adjustment clarifies the organization and ensures that the content is more logically distributed. Please see **line 279-282** in the revised manuscript.

At the end of this paragraph, we added the following concluding statement: "These findings underscore the critical importance of considering distant metastasis (M stage) when evaluating early-stage tumors, as it can significantly influence survival outcomes. From a clinical perspective, when determining treatment strategies for DPBOC and assessing patient survival, careful consideration should be given to the pathological type and TNM stage of OC. Prioritizing the monitoring of OC and developing personalized management plans based on the presence of metastasis could help optimize disease control and improve patient outcomes." This addition first explains the reason for the higher mortality risk associated with T0-stage OC, emphasizing the significant influence of M stage on survival outcomes. Then, it summarizes the key points of the paragraph and links them to clinical practice by providing recommendations for monitoring and treatment strategies for DPBOC patients. For details, please refer to **line 282-288** in the revised manuscript.

c. In the sixth paragraph of the Discussion section, we primarily discuss the impact of OC pathological types on the survival outcomes of DPBOC patients. At the end of this paragraph, we included the following statement: "However, as this study did not collect data on BRCA mutations or treatment-related factors, we were unable to fully analyze the impact of these variables on patient survival. Future studies should incorporate genetic profiles and treatment data to further explore the complex effects of different OC pathological types on survival outcomes. From a clinical perspective, our findings highlight the importance of personalized monitoring and treatment strategies for clear cell OC patients. Given their elevated risk of recurrence and drug resistance, more proactive interventions and follow-up strategies are essential to improving survival

outcomes." This addition first identifies key variables and details that future studies should take into consideration, ensuring that the study's findings maintain strong relevance for researchers. Building on the current data, we then highlight the clinical importance of clear cell OC in DPBOC patients and provide actionable recommendations for clinical practitioners. Specifically, we emphasize the need for personalized monitoring and proactive management strategies for clear cell OC patients to optimize their survival outcomes. For further details, please refer to **line 298-305** in the revised manuscript.

Changes in the text: **line 246-247**: "Notably, 40% of patients developed SPC within 24 months, highlighting this period as a critical window of high SPC incidence."

line 247-249: "Furthermore, consistent with previous findings, our results suggest that the probability of developing SPC decreases as the time interval from FPC diagnosis lengthens."

line 249: "Importantly,"

line 250-255: "Using the median interval of 48 months as the cutoff, patients with intervals ≥48 months exhibited significantly lower risks of adverse outcomes, with hazard ratios of 0.323 (95% CI=0.264-0.395) for OS, 0.527 (95% CI=0.305-0.908) for BCSS, and 0.707 (95% CI=0.559-0.894) for OCSS. These results suggest that longer time intervals between FPC and SPC diagnosis are associated with improved survival outcomes."

line 255-262: "Clinically, these findings underscore the importance of intensive follow-up during the early years after FPC diagnosis, particularly within the first two years when the risk of SPC is highest. Currently, BC patients in mainland China are generally reexamined every 3 months within the first 2 years post-surgery, focusing primarily on breast ultrasound, abdominal ultrasound, and chest CT. However, ovarian examinations are often overlooked. Given the significant impact of OC on the prognosis of BC patients, it is strongly recommended that routine gynecological evaluations, particularly ovarian assessments, be incorporated into follow-up protocols. Early and comprehensive surveillance for SPC could potentially enhance patient outcomes by enabling timely intervention."

line 277-278: "Moreover, the *BRCA* is not included in our study, so it is not sufficient enough to attribute the higher proportion of serous carcinoma and stage III and IV OC in the BO group to gene mutations."

line 279-282: "Additionally, table 4 shows that the death risk of T0 in OC is higher

than that of T2, T3, and T4. After analyzing the data, we found that the 4 T0 stage OC patients were all M1 stage, and 2 of them died of OC, which led to multivariate Cox regression showing that T0 was a high risk."

line 282-288: "These findings underscore the critical importance of considering distant metastasis (M stage) when evaluating early-stage tumors, as it can significantly influence survival outcomes. From a clinical perspective, when determining treatment strategies for DPBOC and assessing patient survival, careful consideration should be given to the pathological type and TNM stage of OC. Prioritizing the monitoring of OC and developing personalized management plans based on the presence of metastasis could help optimize disease control and improve patient outcomes."

line 298-305: "However, as this study did not collect data on BRCA mutations or treatment-related factors, we were unable to fully analyze the impact of these variables on patient survival. Future studies should incorporate genetic profiles and treatment data to further investigate the complex effects of different OC pathological types on survival outcomes. From a clinical perspective, our findings highlight the importance of personalized monitoring and treatment strategies for clear cell OC patients. Given their elevated risk of recurrence and drug resistance, more proactive interventions and follow-up strategies are essential to improving survival outcomes."

Comment 3: Provide a more thorough justification for excluding variables with high collinearity. Clearly explain how the collinearity diagnosis was performed, perhaps including variance inflation factor (VIF) thresholds, to validate the exclusion process.

Reply 3: Thank you for your insightful comment regarding the collinearity diagnosis and the exclusion of variables. We have provided a more detailed explanation as follows (a-c).

a. Justification for Excluding Variables with High Collinearity: In multivariate Cox regression analysis, high collinearity between variables can lead to unreliable coefficient estimates, inflated standard errors, and unstable model results. To ensure the robustness of our model and minimize these issues, we excluded variables exhibiting significant collinearity based on the VIF.
b. Collinearity Diagnosis Method: We conducted a comprehensive collinearity diagnosis using the VIF to identify variables with high collinearity. A VIF threshold of 5 was used as the cutoff for exclusion, as recommended in the literature for identifying multicollinearity concerns. Variables with VIF values

exceeding this threshold were excluded to improve model stability and interpretability.

c. Changes Made to the Manuscript: We revised the sentence "After the collinearity diagnosis, based on the Variance Inflation Factor (VIF) value, we excluded the variables with large collinearity from the multivariate Cox analysis and incorporated the remaining variables" to "A collinearity diagnosis was performed using the Variance Inflation Factor (VIF), with a threshold of 5. Variables with VIF values exceeding 5 were excluded from the multivariate Cox analysis, while the remaining variables were incorporated into the final model." This revision clearly explains the collinearity diagnosis process. Please refer to **line 170-172** in the revised manuscript.

Changes in the text: "A collinearity diagnosis was performed using the Variance Inflation Factor (VIF), with a threshold of 5. Variables with VIF values exceeding 5 were excluded from the multivariate Cox analysis, while the remaining variables were incorporated into the final model."

Comment 4: The exclusion of T and N stages from BCSS analysis should be more thoroughly explained. Discuss how this exclusion might affect the generalizability or interpretation of results and whether alternative statistical methods could address the lack of BC-related deaths in these subgroups.

Reply 4: Thank you for your valuable suggestion regarding the exclusion of T and N stages from the BCSS analysis. We have further clarified this exclusion and its implications as follows (a-d).

a. Justification for Excluding T and N Stages: As noted in the manuscript, the T stage and N stage of BC were excluded from the Cox regression analysis for BCSS because certain subgroups within these stages had not experienced BC-related deaths. Including variables with zero or extremely low event counts can result in biased or unstable estimates within the Cox regression model, leading to unreliable or overly inflated hazard ratios. To avoid this issue, we excluded these variables and focused on those with sufficient events for meaningful analysis.

b. Impact on the Generalizability and Interpretation of Results: We acknowledge that the exclusion of T and N stages may affect the generalizability of the results, particularly for interpretations related to tumor size or lymph node involvement. However, we have ensured that other key variables related to prognosis, such

as OC-related factors and overall clinical characteristics, are included in the analysis to maintain the robustness of the findings. Additionally, given that BC-related deaths were minimal in these subgroups, their exclusion is unlikely to significantly alter the primary conclusions of the study.

c. Alternative Approaches to Addressing the Issue: We considered alternative statistical approaches, such as penalized Cox regression (e.g., LASSO or ridge regression) or stratified Cox models, which can handle low event counts. However, these methods may introduce additional complexity and were not applicable in this study due to the limited sample size and subgroup distributions. Future studies with larger cohorts or different statistical designs could address this limitation more comprehensively.
d. In the final paragraph of the discussion, we included an explanation of how this exclusion could impact the generalizability and interpretation of the results. Additionally, we discussed whether alternative statistical methods could address the issue of the lack of BC-related deaths in these subgroups. Please refer to **line 319-324** in the revised manuscript.

Changes in the text: "Additionally, the T and N stages of BC were excluded from the Cox regression analysis for BCSS due to the absence of BC-related deaths in certain subgroups, which could lead to biased or unstable estimates. Although this exclusion may limit the generalizability of conclusions related to tumor size and lymph node involvement, key prognostic factors were retained to ensure the robustness of the analysis. Alternative methods, such as penalized Cox regression, could be explored in future studies with larger sample sizes to address this limitation."

Comment 5: Compare and contrast the study's findings with existing research on dual primary breast and ovarian cancers. Highlight areas where the study corroborates or diverges from previous studies to provide context and demonstrate its contribution to the field.

Reply 5: Thank you for this insightful and constructive comment. Below, we have addressed this comment from two perspectives (a-b).

a. The original reference [25] was removed due to its retraction. Consequently, we deleted the citation and removed the following segment from the third paragraph of the Discussion section: "He et al. found that about 50% of DPBOC patients developed SPC within the first 60 months after being diagnosed with FPC, and more than 70% occurred within the first 120 months[25]. The number

of patients by these two time points is even larger in this study, with 64% by 60 months and 90% by 120 months." After re-evaluating relevant literature, we compared the 5- and 10-year SPC incidence rates with data from newly identified references, emphasizing the shorter time interval between the onset of the two cancers. The specific revisions are provided in **line 241-246** of the updated manuscript.

b. Our review of recent studies on DPBOC revealed that very few have concurrently examined the time interval between the two cancers and provided a detailed assessment of the associated risk factors. The key findings of our study include three important aspects: (1) the time interval is an independent influencing factor for DPBOC; (2) OC primarily determines the survival outcomes of DPBOC; (3) patients with BC as FPC have a worse prognosis than those with OC as the FPC. First, consistent with previous studies on dual primary cancers, we reaffirmed that the time interval is an independent risk factor. Second, our study is among the first to establish that DPBOC survival outcomes are primarily driven by OC. We further investigated this relationship by analyzing multiple factors, including pathological types, tumor staging (TNM), and cancer staging, areas that have been minimally explored in prior research.

Changes in the text: "Additionally, our study found that about 64% of DPBOC patients developed SPC within the first 60 months after being diagnosed FPC, and 90% occurred within the first 120 months. This proportion is higher than that reported in a study by Ying Song et al., indicating that the time interval between the two cancers in our study is shorter. However, it is important to note that the study by Ying Song et al. focused on metachronous double primary cancers, which may have influenced the observed differences[29]."

Comment 6: Include a more robust discussion on the novelty of findings, such as the impact of the time interval between cancers on survival outcomes, to underline the study's significance.

Reply 6: Thank you for your valuable suggestion to include a more robust discussion on the novelty of our findings. In response, we have carefully revised the manuscript to enhance the clarity and significance of our discussion. The key modifications are as follows (a-b).

a. Emphasizing the Critical Importance of Intensive Follow-Up During the First

Two Years: In the original manuscript, we briefly mentioned that "the 2 years after FPC diagnosis is a high incidence period of SPC" but did not provide sufficient elaboration on its clinical significance or explain why this period is particularly critical. To address this, we have expanded the discussion to emphasize the need for close monitoring during the first two years, supported by specific data, such as the finding that 40% of patients developed SPC within 24 months of FPC diagnosis. This evidence highlights the first two years as a high-risk period for SPC. Additionally, we have proposed recommendations for frequent follow-up, particularly for BC patients post-surgery, and emphasized the necessity of incorporating ovarian examinations into routine follow-up protocols. By integrating data analysis with clinical practice, we believe these revisions significantly enhance the practical relevance and clinical applicability of our findings. Please refer to the revised manuscript at **line 241-262**.

b. Highlighting the Impact of OC on Survival Outcomes and Proposing Personalized Management Strategies: We have made partial revisions to the 5th and 6th paragraphs of the Discussion section to improve the logical flow of the article and further emphasize the key conclusion that OC plays a dominant role in determining the survival outcomes of DPBOC patients. In these revisions, we provide a more detailed explanation of how OC-related factors, including pathological type and advanced stage, independently influence survival outcomes. Furthermore, we have proposed personalized clinical management strategies that prioritize the monitoring and treatment of OC, given its significant impact on survival. By incorporating these strategies into clinical practice, we aim to better demonstrate the importance of our findings and their potential contribution to improving patient outcomes. Please refer to the revised manuscript at **line 277-288** and **line 298-305**.

Changes in the text: **line 241-262**: "Additionally, our study found that about 64% of DPBOC patients developed SPC within the first 60 months after being diagnosed FPC, and 90% occurred within the first 120 months. This proportion is higher than that reported in a study by Ying Song et al., indicating that the time interval between the two cancers in our study is shorter. However, it is important to note that the study by Ying Song et al. focused on metachronous double primary cancers, which may have influenced the observed differences[29].Notably, 40% of patients developed SPC within 24 months, highlighting this period as a critical window of high SPC incidence. Furthermore, consistent with previous findings, our results suggest that the probability of developing SPC decreases as the time interval from FPC diagnosis lengthens.

Importantly, table 4 shows that the time interval was an independent influencing factor of OS, BCSS, and OCSS (P<0.001; P=0.021; P=0.004). Using the median interval of 48 months as the cutoff, patients with intervals ≥48 months exhibited significantly lower risks of adverse outcomes, with hazard ratios of 0.323 (95% CI=0.264-0.395) for OS, 0.527 (95% CI=0.305-0.908) for BCSS, and 0.707 (95% CI=0.559-0.894) for OCSS. These results suggest that longer time intervals between FPC and SPC diagnosis are associated with improved survival outcomes. Clinically, these findings underscore the importance of intensive follow-up during the early years after FPC diagnosis, particularly within the first two years when the risk of SPC is highest. Currently, BC patients in mainland China are generally reexamined every 3 months within the first 2 years post-surgery, focusing primarily on breast ultrasound, abdominal ultrasound, and chest CT. However, ovarian examinations are often overlooked. Given the significant impact of OC on the prognosis of BC patients, it is strongly recommended that routine gynecological evaluations, particularly ovarian assessments, be incorporated into follow-up protocols. Early and comprehensive surveillance for SPC could potentially enhance patient outcomes by enabling timely intervention."

line 277-288: "Moreover, the *BRCA* is not included in our study, so it is not sufficient enough to attribute the higher proportion of serous carcinoma and stage III and IV OC in the BO group to gene mutations. Therefore, more researches are needed to confirm it. Additionally, table 4 shows that the death risk of T0 in OC is higher than that of T2, T3, and T4. After analyzing the data, we found that the 4 T0 stage OC patients were all M1 stage, and 2 of them died of OC, which led to multivariate Cox regression showing that T0 was a high risk. These findings underscore the critical importance of considering distant metastasis (M stage) when evaluating early-stage tumors, as it can significantly influence survival outcomes. From a clinical perspective, when determining treatment strategies for DPBOC and assessing patient survival, careful consideration should be given to the pathological type and TNM stage of OC. Prioritizing the monitoring of OC and developing personalized management plans based on the presence of metastasis could help optimize disease control and improve patient outcomes."

line 298-305: "However, as this study did not collect data on BRCA mutations or treatment-related factors, we were unable to fully analyze the impact of these variables on patient survival. Future studies should incorporate genetic profiles and treatment data to further investigate the complex effects of different OC pathological types on survival outcomes. From a clinical perspective, our findings highlight the importance of personalized monitoring and treatment strategies for clear cell OC patients. Given

their elevated risk of recurrence and drug resistance, more proactive interventions and follow-up strategies are essential to improving survival outcomes."

Comment 7: Expand the practical implications of the findings. For instance, emphasize the need for personalized monitoring strategies based. It could be useful the use of a image to clarify the top concepts.

Reply 7: Thank you for your valuable suggestion. We have expanded the practical significance of our research findings and emphasized the necessity of personalized monitoring and treatment strategies in the following areas (a-c).

a. The first two years as a high-risk period for SPC, emphasizing the importance of intensive follow-up: Our analysis revealed that 40% of patients developed SPC within the first 24 months after FPC diagnosis, highlighting this period as a critical high-risk phase for SPC. Based on these findings, we recommend frequent follow-up for BC patients post-surgery, with an emphasis on incorporating ovarian-related examinations into routine care. This section integrates our research results with practical clinical strategies, providing physicians with evidence-based guidance for developing personalized follow-up plans and enhancing the clinical relevance of the study. Please refer to the revised manuscript at **line 246-262**.
b. Emphasizing the critical role of OC in determining survival outcomes for DPBOC: Our findings demonstrate that in DPBOC patients, ovarian cancer, rather than breast cancer, is the primary determinant of survival outcomes. Therefore, we recommend prioritizing the monitoring of ovarian cancer in clinical management. This expanded discussion not only deepens the interpretation of our results but also offers practical guidance for physicians to focus more precisely on OC during clinical assessments. Please refer to the revised manuscript at **line 284-288**.
c. Clarifying survival differences among various pathological types of ovarian cancer and emphasizing the need for personalized monitoring: We identified a high mortality rate for SOC (40.1%) and found that patients with clear cell OC had an even higher risk of death compared to those with SOC. Additionally, clinical observations indicate that clear cell OC patients have a lower 5-year survival rate and are more prone to recurrence and drug resistance. These findings underscore the importance of personalized monitoring and treatment for clear cell OC patients, including more frequent follow-up and proactive

interventions to improve prognosis. Please refer to the revised manuscript at **302-305**.

Changes in the text: **line 246-262**: “Notably, 40% of patients developed SPC within 24 months, highlighting this period as a critical window of high SPC incidence. Furthermore, consistent with previous findings, our results suggest that the probability of developing SPC decreases as the time interval from FPC diagnosis lengthens. Importantly, table 4 shows that the time interval was an independent influencing factor of OS, BCSS, and OCSS (P<0.001; P=0.021; P=0.004). Using the median interval of 48 months as the cutoff, patients with intervals ≥48 months exhibited significantly lower risks of adverse outcomes, with hazard ratios of 0.323 (95% CI=0.264-0.395) for OS, 0.527 (95% CI=0.305-0.908) for BCSS, and 0.707 (95% CI=0.559-0.894) for OCSS. These results suggest that longer time intervals between FPC and SPC diagnosis are associated with improved survival outcomes. Clinically, these findings underscore the importance of intensive follow-up during the early years after FPC diagnosis, particularly within the first two years when the risk of SPC is highest. Currently, BC patients in mainland China are generally reexamined every 3 months within the first 2 years post-surgery, focusing primarily on breast ultrasound, abdominal ultrasound, and chest CT. However, ovarian examinations are often overlooked. Given the significant impact of OC on the prognosis of BC patients, it is strongly recommended that routine gynecological evaluations, particularly ovarian assessments, be incorporated into follow-up protocols. Early and comprehensive surveillance for SPC could potentially enhance patient outcomes by enabling timely intervention.”

line 284-288: “From a clinical perspective, when determining treatment strategies for DPBOC and assessing patient survival, careful consideration should be given to the pathological type and TNM stage of OC. Prioritizing the monitoring of OC and developing personalized management plans based on the presence of metastasis could help optimize disease control and improve patient outcomes.”

line 302-305:“From a clinical perspective, our findings highlight the importance of personalized monitoring and treatment strategies for clear cell OC patients. Given their elevated risk of recurrence and drug resistance, more proactive interventions and follow-up strategies are essential to improving survival outcomes.”