PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	An Applied Investigation of Person- and Context-Specific Factors on Post-operative Recovery and Clinical Outcomes of Patients undergoing Gastrointestinal cancer surgery: Multi-centre European study
AUTHORS	Markar, Sheraz; Mavroveli, Stella; Petrides, Konstantinos; Scarpa, Marco; Christophe, Veronique; Castoro, Carlo; Mariette, C.; Lagergren, Pernilla; Hanna, George

VERSION 1 - REVIEW

REVIEWER	Naoki Nakaya Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University 2-1 Seiryo, Sendai 980-8573, Japan
REVIEW RETURNED	01-May-2016

GENERAL COMMENTS	This study design paper focused on the psychosocial variables that contribute to better physical and mental health following gastrointestinal cancer (GIC) surgery. However the manuscript was well written and the numerical simulations are well performed, the manuscript had some critical issues as follows. Question 1. The authors clarify the hypothesis why psychosocial variables link to post-operative cancer outcome. For example, biological mechanisms [HPA-axis, immune, etc], lifestyle, or other……Further, the authors have to classify psychosocial factors clearly (trait-, state-, social support, or other) and should argue. Question 2. For the association between personality traits and cancer survival, the authors cited Ref. 9 (Nakaya N, et al.2006). This manuscript was old, and the number of subjects was very few. I feel the authors should change an article to quote as follows; Nakaya N, Bidstrup PE, Saito-Nakaya K, et al. Personality traits and cancer risk and survival based on Finnish and Swedish registry data. Am J Epidemiol. 2010;172(4):377–85. Adelita V. Ranchor AV, Sanderman R, Coyne J. Invited Commentary: Personality as a Causal Factor in Cancer Risk and Mortality—Time to Retire a Hypothesis? Am J Epidemiol. 2010;172(4):386-8. Question 3.

	A preceding study clarified that the association between depression and the risk of cancer survival was largely confounded by clinical state variables (clinical stage, PS, and clinical symptoms) [Nakaya N, Saito-Nakaya K, Akechi T, et al. Negative psychological aspects and survival in lung cancer patients. Psychooncology. 2008;17(5):466-73.]. The conclusion about the association between psychosocial factors and cancer survival will not be provided when the above phenomenon do not clear. Question 4. Define the main outcome (all-cause mortality, disease specific mortality, or other). Further, is sample size enough? Question 5. The authors should show the variables of lifestyles (smoking, body mass index, etc) and socioeconomic situations in the method section.

REVIEWER	Roel Hompes Oxford University Hospitals NHS Foundation Trust
REVIEW RETURNED	11-May-2016

GENERAL COMMENTS	Thank you for the opportunity to review your study protocol. This is a very interesting subject and in the field of digestive surgery needs further exploration. So your study is very timely. In regards to the timeline of the questionnaires, have the authors taken into account that the pathway for colorectal cancer patients is somewhat different from the patients with upper GI cancers ? The majority of patients with colon cancer will not require neo-adjuvant treatment, unless the present with synchronous liver metastases. The longterm outlook for these patients is of course worse and will clearly impact on their psychological well being. A proportion of patients who present with rectal cancer will require neo-adjuvant treatment and will fit in the flow chart. However the majority of these patient will end up with a temporary ileostomy which will be closed after the patent complete their adjuvant treatment (in majority of cases > 6 months after their surgery). The presence of an ileostomy, the potential for poor functional outcome after rectal cancer surgery clearly are important factors for the patients psychological status. Are the authors planning to capture their proposed questionnaires before and after ileostomy closure, even if this might be 6 months after the index surgery ? Are they planning to capture functional questionnaires (colorectal, urological, sexual function) and correlate these with the psychological questionnaires ?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
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Institution and Country

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Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
This study design paper focused on the psychosocial variables that contribute to better physical and mental health following gastrointestinal cancer (GIC) surgery.
However the manuscript was well written and the numerical simulations are well performed, the manuscript had some critical issues as follows.

Question 1.
The authors clarify the hypothesis why psychosocial variables link to post-operative cancer outcome. For example, biological mechanisms [HPA-axis, immune, etc], lifestyle, or other……Further, the authors have to classify psychosocial factors clearly (trait-, state-, social support, or other) and should argue.

RESPONSE: At present, there is insufficient evidence to identify the precise mechanism by which psychological variables affect postoperative cancer outcomes. However, extant data, albeit inadequate, point to a cumulative effect of biological mechanisms, personality and social factors, lifestyle impacts, and extent of adherence to postoperative goals [page 5 line 16].

Question 2.
For the association between personality traits and cancer survival, the authors cited Ref. 9 (Nakaya N, et al.2006). This manuscript was old, and the number of subjects was very few. I feel the authors should change an article to quote as follows;

Nakaya N, Bidstrup PE, Saito-Nakaya K, et al. Personality traits and cancer risk and survival based on Finnish and Swedish registry data. Am J Epidemiol. 2010;172(4):377–85.

Adelita V. Ranchor AV, Sanderman R, Coyne J. Invited Commentary: Personality as a Causal Factor in Cancer Risk and Mortality—Time to Retire a Hypothesis? Am J Epidemiol. 2010;172(4):386-8.

RESPONSE: Thank you for bringing these references to our attention. We have now amended our manuscript accordingly. [page 15 line 27].

Question 3.
A preceding study clarified that the association between depression and the risk of cancer survival was largely confounded by clinical state variables (clinical stage, PS, and clinical symptoms) [Nakaya N, Saito-Nakaya K, Akechi T, et al. Negative psychological aspects and survival in lung cancer patients. Psychooncology. 2008;17(5):466-73.]. The conclusion about the association between psychosocial factors and cancer survival will not be provided when the above phenomenon do not clear.

RESPONSE: We have previously established, in the context of gastrointestinal cancer, the adverse prognostic effects of postoperative psychiatric morbidity, independent of cancer stage [Bouras et al.,

Ann Surg 2015 PMID:26649592].
The primary aim of our study is to assess postoperative psychiatric morbidity within 30-days of surgery, with a further objective to identify key measurable and modifiable preoperative psychological factors that can significantly affect this. Specifically with respect to taking into account potentially confounding variables, our design controls for several such, including tumor stage, postoperative symptoms and socioeconomic status [page 13 line 7].

Question 4.
Define the main outcome (all-cause mortality, disease specific mortality, or other).
Further, is sample size enough?

RESPONSE: We have defined the primary outcome for the study in the revision as postoperative psychiatric morbidity within 30-days of surgery [page 11 line 7] and described the sample size (power) calculation [page 12 line 8]. The power calculation was performed by a statistician, who confirmed that our target sample size will be sufficient for the purposes of this research.

Question 5.
The authors should show the variables of lifestyles (smoking, body mass index, etc) and socioeconomic situations in the method section.

RESPONSE: We have expanded the archive data section to describe the additional information on lifestyle factors that will be collected as part of the study [page 9 line 6].

Reviewer: 2

Reviewer Name
Roel Hompes

Institution and Country
Oxford University Hospitals NHS Foundation Trust

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
Dear Authors,

thank you for the opportunity to review your study protocol. This is a very interesting subject and in the field of digestive surgery needs further exploration. So your study is very timely.

In regards to the timeline of the questionnaires, have the authors taken into account that the pathway for colorectal cancer patients is somewhat different from the patients with upper GI cancers ? The majority of patients with colon cancer will not require neo-adjuvant treatment, unless the present with synchronous liver metastases. The longterm outlook for these patients is of course worse and will clearly impact on their psychological well being.

RESPONSE: Many thanks for this valuable comment. We have amended Figure 1 to indicate the proportion of colorectal patients who will not receive neoadjuvant therapy and will thus be psychologically profiled at four time-points (at diagnosis, 1 month, 6 and 12 months post surgery). Patients with metastatic disease have a very different prognosis to those without non-metastatic disease, and thus are excluded from this study [added page 12 line 3].

A proportion of patients who present with rectal cancer will require neo-adjuvant treatment and will fit in the flow chart. However the majority of these patient will end up with a temporary ileostomy which will be closed after the patent complete their adjuvant treatment (in majority of cases > 6 months after their surgery). The presence of an ileostomy, the potential for poor functional outcome after rectal cancer surgery clearly are important factors for the patients psychological status. Are the authors planning to capture their proposed questionnaires before and after ileostomy closure, even if this might be 6 months after the index surgery ?

RESPONSE: This is a very good point. We have amended the protocol to include in the demographic data collection information on ileostomy status, and have also added an additional time-point at 12 months to capture patients following ileostomy closure.

Are they planning to capture functional questionnaires (colorectal, urological, sexual function) and correlate these with the psychological questionnaires ?

RESPONSE: We have amended the protocol to include utilisation of functional questionnaires at the same time points as the psychological screening [page 11 line 17].

VERSION 2 – REVIEW

REVIEWER	Mr Roel Hompes Oxford University Hospitals NHS Foundation Trust Department of Colorectal Surgery
REVIEW RETURNED	17-Jul-2016

GENERAL COMMENTS	I'm satisfied all comments have bee answered correctly and the manuscript changed accordingly.