

Influence of body weight changes on survival in patients undergoing chemotherapy for epithelial ovarian cancer

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Abstract. – **OBJECTIVE:** Epithelial ovarian cancer is a highly fatal gynecologic malignancy with a poor prognosis. Therefore, identification of new modifiable prognostic factors is important. Due to the fact that the effect of body weight changes during chemotherapy for EOC is still not very well known we aimed to describe, considering evidence, role of body weight changes in relation to survival.

MATERIALS AND METHODS: Between October 2014 and August 2015 we systematically searched the following databases: Medline, Scopus, Web of Science and EMBASE to identify the studies describing the influence of body weight changes on survival in patients undergoing chemotherapy for EOC.

RESULTS: We identified 601 potentially relevant publications, however finally only one article was included for data extraction and analysis. The overall survival in the selected paper was significantly associated with body weight changes during the first-line chemotherapy. Nevertheless, no influence on progression free survival was found.

CONCLUSIONS: The analyzed data provides initial evidence, showing poorer overall survival associated with body weight loss and improved overall survival associated with body weight gain during primary chemotherapy for epithelial ovarian cancer. Prospective and retrospective trials are an urgent calling to confirm this conclusion.

Key Words:

Body weight, Ovarian cancer, Progression free survival, Overall survival.

Introduction

Epithelial ovarian cancer (EOC) is a highly fatal gynecologic cancer with over 150,000 deaths occurring worldwide annually¹. Around 70% of EOC cases are diagnosed in an advanced stage resulting in low 5-year survival rates². Although some prognostic factors including advanced tumor stage, residual disease after primary surgery, histologic type and grade, age at diagnosis, performance status, presence of ascites and even race³ have been shown to be important, the identification of new modifiable prognostic factors is an urgent calling⁴. Therefore, since a few years increasing attention in regard to the body weight changes is observed.

Obesity has been recognized as an important factor related with an increased risk of malignancy. Although, the association between obesity and cancer survival is still unclear⁵, recent data showed 6% increase of ovarian cancer risk per each of 5 BMI units⁶. Moreover, obesity can be related to weak adverse effect on the EOC survival⁷. On the other hand, both malnutrition and weight loss, common in patients suffering from cancer, affect the response and tolerance to treatment and therefore result in a poor survival⁸. There are also some studies suggesting that body weight gain in EOC patients is related to poor prognosis⁹; however, those results are conflicting with other data suggesting improved survival¹⁰.

Due to contradictory results in regard to body weight changes during chemotherapy and survival in EOC patients we decided to perform our analysis. The aim was to describe, considering available evidence the role of body weight changes in EOC patients undergoing chemotherapy in relation to survival.

Materials and Methods

Search Strategy

Between October 2014 and August 2015 we have systematically searched the following databases: MEDLINE, SCOPUS, WEB OF SCIENCE and EMBASE. We aimed to identify the experimental (intervention studies) and observational (individual) studies describing the influence of body weight changes on survival in patients undergoing chemotherapy for EOC. Search strategy was restricted to human, English language and following type of document: article, review, book and book chapter. The search based upon the listed below following index terms and title or abstract: #1 Body weight OR body size OR body weight changes OR weight gain OR weight loss and #2 Epithelial ovarian cancer OR ovarian cancer; Search #1 AND #2; #3 survival"; Search #2 AND #3; Search #1 AND #2 and #3

The protocol was registered in "PROSPERO International prospective register of systematic reviews" PROSPERO 2014:CRD42014014890 and is available on http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014890

Inclusion and Exclusion Criteria

The studies including women with EOC, indicating the changes in body weight during chemotherapy and showing its relation to patient's survival were included in our investigation. Only studies in which an assessment of body weight changes based on anthropometry measurements were included. Trials with following design were analyzed: experimental (intervention studies), randomized controlled trial, non-randomized trial, observational (individual), cohort study, case-control study, cross-sectional study (surveys) and ecologic studies (population). There was no restriction due to the date of publication. We excluded the articles, which did not meet inclusion criteria (studies performed in healthy population, animal studies, other than mentioned above type of documents, articles in any other language than English).

Data Extraction and Analysis

The selection process was based on an assessment of the following order: 1. Titles, 2. Abstracts and 3. Full text and was performed parallel by two independent researchers for each database. All disagreements between the researchers were solved after consultation with the review coordinator. The exact process flow sheet is presented on Figure 1.

Eligible studies were evaluated according to the number of participants, study design, stage of disease according to The International Federation of Gynecology and Obstetrics (FIGO) classification, changes in body weight or Body Mass Index (BMI) defined as body weight divided by the square of height and length of progression free survival (PFS) defined as the time elapsed between treatment initiation and tumor progression and finally overall survival (OS) defined as the time between diagnosis and death for any reason.

Results

Search Results

We identified 601 potentially relevant publications. After titles and abstracts evaluation 108 articles were included. Subsequently, after exclusion of paper duplication 55 papers were assigned for full-text review. Finally only one article was included for data extraction and analysis (Figure 2).

Study and Population Characteristic (Table I)

Only one article was included for data extraction and analysis. Full characteristic of study population was not available in selected publication¹⁰; however, we analyzed cited references and completed the information based on the primary published data that focused on the same population¹¹. Among study population, 86% were White, 6.3% Black, 5% Hispanic and 2.7% represents other ethnicity. At the baseline mean value of BMI was 24.9 kg/m² (range: 13.7-52.9). Of the 790 patients 645 completed all six cycles of chemotherapy and the full data describing the body weight changes were available for analysis.

Body Weight Changes due to Chemotherapy

In regard to chemotherapy regimen, the authors compared in selected article the body weight changes in both cisplatin/paclitaxel (cisplatin 75 mg/m² plus a paclitaxel 135 mg/m² in 24-hr infusion) and carboplatin/paclitaxel (car-

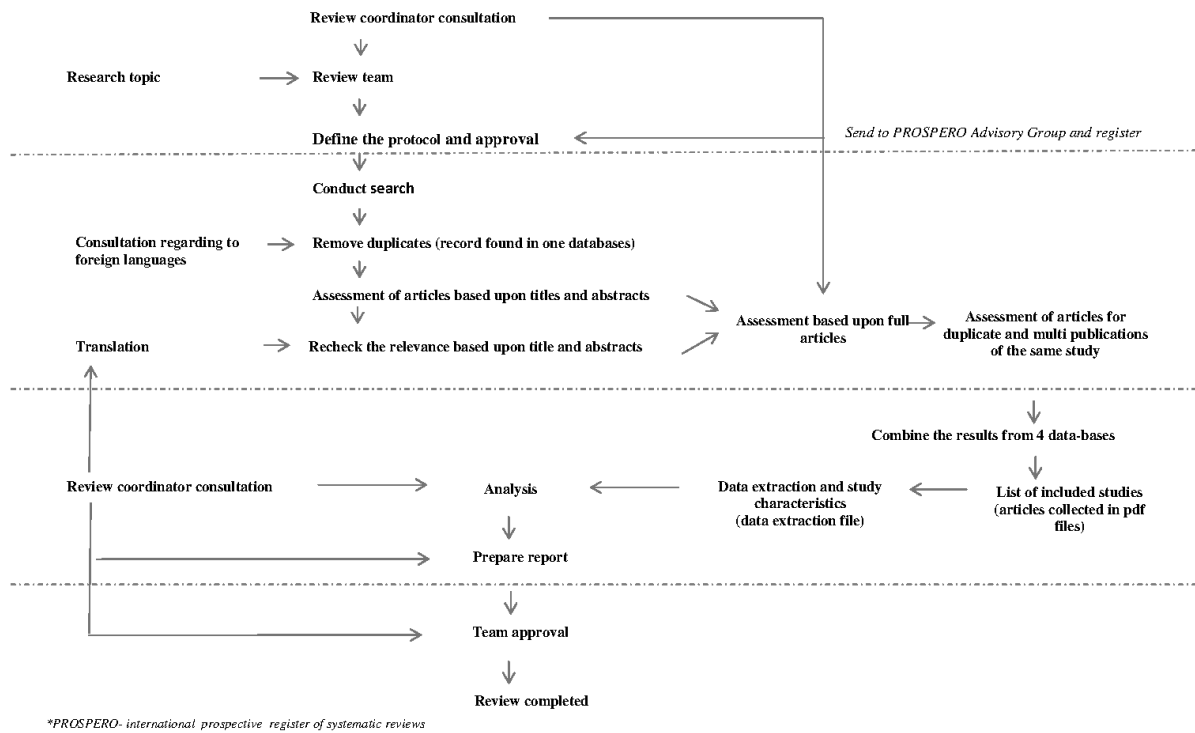


Figure 1. Process flow sheet.

boplatin AUC=7.5 plus paclitaxel 175 mg/m² in 3-hr infusion) treatment groups indicating the significant differences over the treatment period. Patients treated with cisplatin/paclitaxel experienced -2.2 kg loss of body weight after the first cycle of chemotherapy and did not regain weight through the treatment. In contrary, patients treated with carboplatin/paclitaxel lost 1.2 kg of body weight respectively, but regained weight through the treatment. Body weight loss

was observed in 51% of patients treated with cisplatin/paclitaxel and 35% of patients treated with carboplatin/paclitaxel¹⁰.

Body Weight Changes in Relation to Survival

The OS in selected data was significantly associated with body weight changes during first line chemotherapy. Median OS was correlated with body weight changes during chemotherapy (Ta-

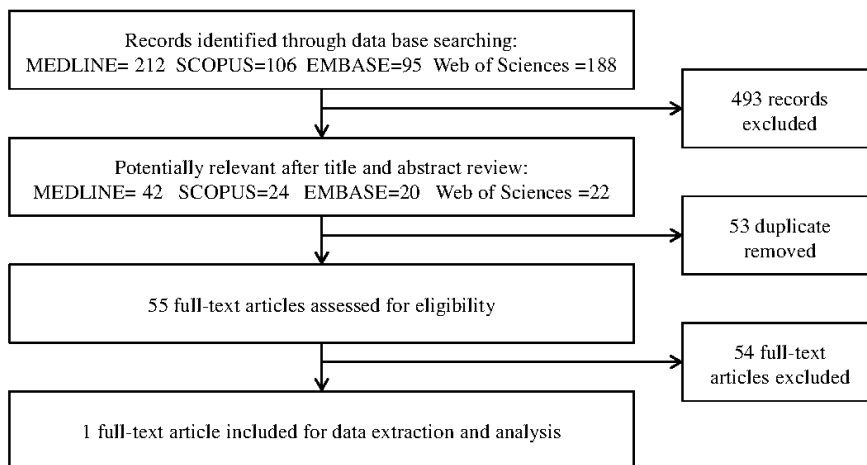


Figure 2. Flow diagram of the study selection process.

Table I. Study and population characteristic.

Study	Number of participants	Study design	FIGO stage	Chemotherapy regimen	Age	Ethnicity
Hess L et al. 2007	790	RCT (retrospective)	III	cisplatin/paclitaxel versus carboplatin /paclitaxel	21-90*	86% white, 6.3% black, 5% hispanic 2.7% other*

*Ozolas et al 2003; N/A- not available; FIGO- The International Federation of Gynecology and Obstetrics

ble II). The shortest OS was estimated for patients who lost weight of more than 5% (48.0 months) and the longest OS for those who gain weight of more than 5% (68.2 months). In multivariate analysis authors estimated that a 5% increase in body weight during chemotherapy was related to a 7% decrease in risk of death (HR=0.93; 95% CI= 0.88-0.99, $p=0.01$). No significant association of body weight changes during chemotherapy with PFS was found¹⁰.

Discussion

In this systematic review, we carefully evaluated the literature on the body weight changes in women undergoing chemotherapy for EOC. Only one article was included into the analysis¹⁰ showing the need for further broadened investigation in this topic. It was shown that body weight gain (>5%) during first line chemotherapy for advanced EOC is associated with improved OS (median 68.2 months), whereby the body weight loss (>5%) with poor OS (median 48.0 months)¹⁰.

Some studies in EOC patients found that obese women have a poorer outcome in comparison to the normal weight patients^{12,13}. However, other data based on the assessment of BMI value indicated no differences in survival^{2,5,14}. The meta-analysis of 14 studies published by

Protani et al⁷ showed slightly poorer survival among obese, than in non-obese women (HR, 1.17; 95% CI, 1.03-1.34) and a slightly stronger association in case if only women with a BMI over 30 kg/m² were included (HR, 1.20) in comparison to women who suffered from overweight (HR, 1.14). Nevertheless, due to a large amount of inter-study variation, no solid conclusions were stated. Recently, Bae et al² showed that high BMI (overweight, obese I and II) has no influence on the survival in advanced EOC patients. However, the overweight and obese I (BMI 30-34.9 kg/m²) subgroup of EOC patients with serous histology and after optimal surgery presented better survival than the patients with normal weight. Unfortunately, in any of the above mentioned publications changes in body weight during chemotherapy were evaluated.

On the other hand, Hess et al¹⁰ suggests that women who gain weight during chemotherapy present improvement in OS. This could be firstly due to the fact that no pre and post-surgery body weight data were analyzed. Authors compared only body weight at the start of chemotherapy and at the time of the sixth cycle of chemotherapy. Gil et al¹⁵ showed that women with EOC loss the weight due to major surgery of about 4% (-3 kg) and regained it slowly over the following year. However authors suggest that an apparent weight gain would be due to patients regaining weight that was lost fol-

Table II. Survival according to body weight changes in EOC patients undergoing chemotherapy.

Study	Baseline anthropometry	Body weight change	OS [months]	PFS [months]
Hess L et al. 2007	Mean BMI 24.9 [kg/m ²]	>5% decrease	48.0	N/A
	51.1% normal weight,	0-5% decrease	49.3	N/A
	30.6% overweight	0-5% increase	61.1	N/A
	18.2% obese	>5% increase	68.2	N/A

N/A- not available; OS – Overall Survival; PFS – Progression Free Survival.

lowing surgery. Secondly weight gain may be influenced by changes of dietary habits after the cancer diagnosis and changes in physical activity. Dietary habits changes, often in a pro-healthy direction were shown in ovarian¹⁶, breast¹⁷ and colorectal cancer^{18,19}. However little is known about this effect on survival in EOC patients. Nagle et al²⁰ observed survival advantage in EOC patients who reported higher intake of vegetables (cruciferous vegetables in particular) and vitamin E as well as modest positive trends with lactose, calcium and dairy products. Physical activity was indicated as a positive prognostic factor for survival in EOC patients¹²; however, most patients undergoing chemotherapy for different cancer sites decrease their physical activity^{15,19}. This fact can also contribute to weight change due to the decreased energy expenditure.

Loss of body weight was noticed as an important negative prognostic factor in the past. Ansell et al²¹ indicated cut-off in body weight loss during chemotherapy that can be recognized as a negative prognostic factor if exceeds 10%. Similarly Kim et al²² showed, that underweight patients with weight loss $\geq 10\%$ achieve poor PFS and OS in comparison to those with weight loss $< 10\%$ (PFS, median value, 3.5 vs. 16.8 months; OS, median value, 23.7 versus 58.1 months). Weight loss is also recognized as a symptom at the time of diagnosis (10% in FIGO I-II and 30% in FIGO IV patients) and can be associated with decreased PFS (10.7 vs. 15.4 months, $p = 0.023$)²³. Kim et al²² compared PFS and OS in groups of underweight, overweight and obese patients and in those characterized by normal body weight. As a result, only in patients with underweight status after treatment poor OS was noted.

Body weight changes might be also associated with side effect of treatment including taste changes or chemotherapy induced nausea and vomiting (CINV). Taste disorders are found in about 86% of individuals undergoing chemotherapy²⁴, most commonly if treated i.e. with carboplatin, cisplatin and paclitaxel²⁵. CINV are observed much more common if cisplatin was applied, in comparison to carboplatin²⁶. In the selected study the authors showed 51% and 35% weight loss in patients who received cisplatin/paclitaxel and carboplatin/paclitaxel regimen respectively. Nonetheless no differences in both PFS and OS between those two groups were found¹¹.

Hess et al¹⁰ the authors did not collected data describing body weight after the completion of six cycles of first line chemotherapy. Therefore, it is unclear whether changes in body weight or future treatment regimens could impact survival. Backes et al⁹ analyzed BMI changes over the time and indicated potentially increased risk of progression in patients who gained their weight within the six months after finishing the chemotherapy (HR: 1.68, 95% CI: 0.87-3.26). It was also suggested that the risk of progression was increased in those patients who were normal- or underweight after surgery compared to those who were considered obese. However, despite fat tissue in obese subjects results in higher concentration of circulating estrogens, ovarian cancer is not being recognized as hormone sensitive and this mechanism cannot be responsible for increased risk in obese patients.

There are some limitations in the interpretation of described data mostly due to the fact that only one published paper was included into the analysis. Selected article presented a retrospective analysis of the data from phase III clinical trial. Unfortunately, the results from the selected study refer only to BMI changes before starting chemotherapy and after the completion of treatment. No data were presented concerning pre-surgery body weight measurements, body weight in follow up and at the time of progression. There was also lack of information regarding to food intake and physical activity as well as body weight changes in subgroups according to baseline BMI values (underweight vs. normal weight vs. obese).

Future Directions

Prospective trials are needed to indicate whether body weight changes influence on survival in EOC. Study protocol should include body weight at the time of diagnosis (pre- and post surgery), during the chemotherapy and in follow-up. Body weight changes (weight gain or weight loss) should be indicated as intended or not-intended and might be applied with addition of different nutritional screening tools (Nutritional Risk Score – NRS, Subjective Global Assessment – SGA, Patient Generated – Subjective Global Assessment – PG-SGA, Mini Nutritional Assessment – MNA). Even more information might give body composition analysis and its changes over the time. The changes in nutritional intake, behavior, physical activity and in quality of life should not be omitted as important factors influencing changes in body weight.

Conclusions

The analyzed data provides initial evidence, showing poorer OS associated with body weight loss and improved overall survival associated with body weight gain during primary chemotherapy for EOC. Prospective and retrospective trials are an urgent calling to confirm this conclusion.

Conflicts of interest

The authors declare no conflicts of interest.

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