Gynecologic Oncology 140 (2016) 184–190

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Body mass index and mortality in endometrial cancer: A systematic review and meta-analysis

Angeles Alvarez Secord [a,*], Vic Hasselblad [b], Vivian E. Von Gruenigen [c], Paola A. Gehrig [d], Susan C. Modesitt [e], Victoria Bae-Jump [d], Laura J. Havrilesky [a]

[a] Division of Gynecology Oncology, Department of Obstetrics and Gynecology, Duke Cancer Institute, Duke University Medical Center, Durham, NC, USA
[b] Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA
[c] Division of Gynecology Oncology, Department of Obstetrics and Gynecology, Summa Health System, Akron, OH, USA
[d] Division of Gynecology Oncology, Department of Obstetrics and Gynecology, University of North Carolina in Chapel Hill, Chapel Hill, NC, USA
[e] Division of Gynecology Oncology, Department of Obstetrics and Gynecology, University of Virginia, Charlottesville, VA, USA

HIGHLIGHTS

- Increased BMI is associated with increased all-cause mortality in women with endometrial cancer.
- Women with a BMI ≥ 40 have the highest risk of death.

ARTICLE INFO

Article history:
Received 18 August 2015
Received in revised form 22 October 2015
Accepted 28 October 2015
Available online 31 October 2015

Keywords:
Body mass index
Obesity
Mortality
Survival
Endometrial cancer

ABSTRACT

Objective. To evaluate the association between body mass index (BMI) and mortality in women with endometrial cancer.

Methods. A systematic review was performed utilizing a Medline search with Mesh keywords 'endometrial neoplasms' and ('body mass index' or 'obesity') and ('survival analysis' or 'mortality' or 'survivor' or 'survival') for studies published prior to June 2013. Inclusion criteria included studies that assessed associations between BMI and survival in endometrial cancer patients. Two investigators independently reviewed the title and abstract and full-text of articles for inclusion or exclusion decision; discordant decisions were adjudicated by a third reviewer. A random-effects model was constructed that was comparable to the standard random-effects models used in the meta-analysis of odds ratios. The model was fitted using SAS PROC NLMIXED.

Results. 1451 studies were identified and reviewed in duplicate, 18 met inclusion criteria. A random-effects meta-analysis demonstrated significantly higher odds of mortality with increasing BMI in endometrial cancer patients. Specifically the odds ratios were 1.01, 1.17, 1.26, and 1.66 for BMI categories of 25–29.9, 30–34.9, 35–39.9, and 40+, respectively. The odds ratio for all-cause mortality in endometrial cancer patients with a BMI ≥ 40 compared to those with a BMI < 25 was 1.66 (CI: 1.10–2.51, $p = 0.02$). A single dose–response model indicated that a 10% increase in BMI resulted in a 9.2% increase in the odds of all-cause mortality ($p = 0.007$).

Conclusion. Increased BMI is significantly associated with increased all-cause mortality in women with endometrial cancer, with the highest risk for those with a BMI ≥ 40.

Contents

* Corresponding author at: Division of Gynecologic Oncology, Duke University Medical Center, BOX 3079, Durham, NC 27710, USA.
E-mail address: angeles.secord@dm.duke.edu (A.A. Secord).

http://dx.doi.org/10.1016/j.ygyno.2015.10.020
0090-8258/

1. Introduction

Obesity is a known risk factor for endometrial cancer with obese women having a 2–5 fold higher incidence of endometrial cancer [1]. In addition, 62% of American women are overweight or obese [2]. While the relationship between obesity, measured by body mass index (BMI), and increased risk of endometrial is well established, there is conflicting data regarding BMI and survival in women diagnosed with endometrial cancer. Understanding the relationship between BMI and survival outcomes in women with endometrial cancer is extremely important as endometrial carcinoma is the most common gynecologic malignancy in the United States. Approximately 54,870 new endometrial cancer diagnoses are estimated in 2015 with 10,170 deaths expected from this disease [3]. There has been an alarming increase in endometrial cancer cases; incidence rates increased by 2.4% from 2007 to 2011 according to the latest report form the American Cancer Society Cancer Statistics [3]. The increase in the prevalence of obesity and endometrial cancer highlights the need to understand the effects of obesity on endometrial cancer outcomes and mortality.

There have been conflicting results in the literature regarding the association between BMI and survival in women with endometrial cancer. Some studies have demonstrated either improved survival (the obesity paradox) or no difference in survival between non-obese and obese endometrial cancer survivors. However, other studies have demonstrated a significant association between BMI and decreased survival. Calle and colleagues conducted a prospective study to evaluate the relationship between BMI and the risk of death from all cancers and reported that the endometrial cancer survivors with a BMI > 40 had a 6.25 fold increased relative risk (RR) of death compared to those who were of normal weight [4].

While a systematic review regarding survival outcomes and obesity in endometrial cancer has been published, a meta-analysis has not been performed [5]. Therefore, we performed a systematic review and meta-analysis, to evaluate the association between BMI and survival in women with endometrial cancer. Information gleaned from this analysis will help determine if BMI is associated with survival in endometrial cancer patients. In addition, our results, if positive, will inform clinical trials to evaluate BMI-reducing strategies aimed at improving survival in women with endometrial cancer.

2. Methods

2.1. Sources

This systematic review and meta-analysis was conducted in accord with guidelines for Meta-Analysis of Observational Studies in Epidemiology guidelines (http://edmgr.ovid.com/ong/accounts/moose.pdf). A systematic review was performed utilizing a Medline search using exploded Mesh keywords 'endometrial neoplasms' and ('body mass index' or 'obesity') and ('survival analysis' or 'mortality' or 'survivor' or 'survival'). Furthermore, we obtained additional sources by manually reviewing references in papers and from American Society of Clinical Oncology (ASCO) Communications: Cancer in the News.

Inclusion and exclusion criteria were developed based on patient population, comparators, outcomes, and language criteria. Study inclusion criteria were as follows: study included women with endometrial cancer; study evaluated survival outcomes based on BMI, a surrogate for obesity; the study included a comparison group; the study reported a quantitative association between BMI and survival outcomes; the study was peer-reviewed and written in the English. There were no time limitations or exclusion based on study design. There also were no limitations regarding sample size, treatment type, or selection of controls. Study exclusion criteria were as follows: study results could not be interpreted in the context of hazard ratios (HR); or publication type is editorial, review, or letter to the editor.

Titles and abstracts of identified articles were reviewed by one reviewer (AAS) and independently confirmed by a second reviewer (LH, SM, VV, VBJ, PAG) for potential inclusion in the study. Articles included by either reviewer were subjected to full-text screening. All articles were independently reviewed by two investigators who determined if each article was included or excluded for data abstraction. One researcher (AAS) abstracted the data from all the studies, and the second reviewer (LH, SM, VV, VBJ, PAG) completed a second independent abstraction file. The abstraction files were merged and compared alongside the original article to assess for accuracy and completeness. Quality of individual studies was assessed using the approach described in Agency for Healthcare and Research Quality's Methods Guide for Effectiveness and Comparative Effectiveness Reviews and Guyatt et al. [6,7] The quality of the individual studies were graded by 2 authors (AAS, LH) and summary quality ratings of high, moderate, low, and very low were assigned to each study [7].

The quantitative synthesis for survival outcomes was challenging based on heterogeneity of the studies, statistical design, reporting of results, and observational study designs. There was substantial heterogeneity in BMI (continuous or categorical variables); the type of BMI categories; and adjustment variables. Performing a meta-analysis on the effect of BMI on total mortality was challenging as individual studies reported the hazard ratios/odds ratios for different BMI intervals. Therefore, we assumed that the logarithm of each odds ratio could be described by a linear model. The model included a random effects term, σ^2, as well as terms for BMI categories: less than 25, 25 to 29.9, 30 to 34.9, 35 to 39.9, and 40+. Independent variables were used to create the BMI category desired.

If every study used the same five intervals for BMI, then the analysis would be relatively straightforward. However, most studies used a subset of those intervals. For example, the Arem et al. study used the first three categories (<25 kg/m^2, 25 to <30, 30 to <35), but grouped the remaining values into a single category, 35+ (35 to 39.9, and 40+) [8]. In order to use this study as reported it was necessary to estimate the fraction of the sample in each of the last two categories. The primary assumption was that BMI values are lognormally distributed. The maximum likelihood methods were used to estimate the parameters of the distribution based on the observed frequencies and intervals reported [9]. From this we estimated the fractions to be 0.154 and 0.077 for the 35 to 39.9, and the 40+ categories, respectively. Instead of using independent variables with all zeros except for a one for either the 35 to 39.9 category or for the 40+ categories, the normalized values of 0.667 and 0.333 for those variables were used.

Survival outcome measures varied between the studies and included progression-free survival (PFS), disease-free survival (DFS), overall survival (OS), all-cause mortality, relative risk of mortality, death, death-rate, recurrence frequency, recurrence risk, recurrence-free survival (RFS), and cancer-specific survival (CSS). Studies were required to report hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) or to provide adequate data to allow the 95% CI to be calculated. The primary analysis was based on all-cause mortality, because not all studies uniformly reported PFS, DFS, RFS, and/or CSS.

The general strategy for analysis was to construct a random-effects model that was comparable to the standard random-effects models