HOW TO MANAGE THE OBESE CANCER PATIENT

BY RENEHAN, ET AL

SUPPLEMENTAL MATERIAL

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Table S1 Proportion of cancer patients that are obese (BMI ≥ 30 kg/m^2) by cancer types and settings

Authors, ref.	Cancer type	Setting	Trial/ study name	No. of patients†	% obese
Crosbie et al. [1]	Endometrial cancer	Early stage - surgery	ASTEC	1408	47.0
Munstedt et al. 2008 [2]	Endometrial	Mainly stage I-III	German consortium	1180	38.6
Hakimi et al. 2013 [3]	Renal cell carcinoma	Undergoing surgery	Memorial Sloan-Kettering Cancer Centre	2119	42.1
Bokey et al. 2014 [4]	Rectal cancer	Undergoing resection	Perth, Australia	255	37.2
Meyerhardt et al. 2004 [5]	Rectal cancer	Adjuvant	USA Intergroup Trial 0114	1688	18.1
Melis et al. 2013 [6]	Oesophageal adenoacrcinoma	Undergoing surgery	Moffitt Cancer Centre	540	34.6
STARSurg collaborative 2016 [7]	Several malignancy; mainly gastrointestinal	Surgery for any malignancy	STARSurgUK	2129	26.2
Mullen et al. 2008 [8]	Several malignancy; mainly gastrointestinal	Surgery for any malignancy	ACS-NSQIP database	2258	25.4
Sincrope et al. 2013 [9]	Colon cancer	Adjuvant therapies	ACCENT trial consortium	25,291	17.6
Munstedt et al. 2008 [2]	Ovarian cancer	Mainly stage I-III	German consortium	824	15.4
Barrett et al. 2008 [10]	Ovarian cancer	81% FIGO stage III/IV	SCOTROC I	1067	12.0
Fischer et al. 2013 [11]	Breast cancer*	Breast reconstruction	ACS-NSQIP database	15937	27.1
Goodwin 2013 [12]	Breast cancer	Hormonal therapy	ATAC	4939	27.3

Goodwin 2013 [12]	Breast cancer	Hormonal therapy	BIG 1-98	4760	23.0
Goodwin 2013 [12]	Breast cancer	Hormonal therapy	TEAM	4700	23.3
Goodwin 2013 [12]	Breast cancer	Hormonal therapy	ABCSG	1684	10.8
Gennari et al. 2016 [13]	Early Breast cancer	Adjuvant chemotherapy	IBIS 3	1066	21.0
Widschwender et al. 2015 [14]	Early high-risk breast cancer	Chemotherapy	SUCCESS A	3754	20.9
Wong et al. 2014 [15]	Breast cancer including 33% with metastatic disease.	Doxorubicin chemotherapy	All Asian patients in Singapore	84‡	14.3
Simkens et al. 2011 [16]	Colorectal cancer	Metastatic	CAIRO	796	12.0
Simkens et al. 2011 [16]	Colorectal cancer	Metastatic	CAIRO2	730	12.0

*proportion with malignancy not specified.
† total number of patients in cohort.
‡ This is a small sample size study but included as it was a detailed Asian population.

Case studies to illustrate effects of sample size and composition

1. Small study size can yield both type 1 (Table S2) and type 2 (Table S3) statistical errors in relationships of proportions of interest (e.g. complications) and BMI categories.

Table S2 Data from Arndt et al. Patient delay and stage of diagnosis among breast cancer patients in Germany – a population based study[17]

	BMI categories			
	Normal weight (n = 126)	Overweight (n = 80)	Obese (n = 70)	P value
Proportions of patients with delay				
< 1 month	73.0	57.5	57.1	
1 – 3 months	13.5	27.5	15.0	
> 3 months	13.5 (n = 17)	17.4 (n = 13)	25.7 (n = 17)	0.02

The study concluded that obesity was associated with delayed presentation, but the numbers here are small and might have occurred by chance.

Table S3 Data from Melis et al. Body mass index and perioperative complications after oesophagectomy for adenocarcinoma: a systematic database review [6]

	BMI categories			
	Normal weight (n = 155)	Overweight (n = 198)	Obese (n = 187)	P value
30-day mortality (%)	1.3	1.5	2.7	0.7
30-day mortality (n)	2	3	5	

The study concluded that there was no significant difference (for 30-day mortality) across the BMI categories, but this might simply reflect an underpowered study. A peri-operative mortality of 2.7% in obese patients is double that in normal weight patients (1.3%), which might be clinically significant

Studies should seek to justify their conclusions taking account the size and power of the cohort. This is nicely illustrated by the Determining Surgical Complications in the Overweight (DISCOVER) study protocol. This is a multicentre observational prospective cohort study to evaluate the role of obesity as a risk factor for postoperative complications in general surgery (UK), and in their protocol the power calculation reads as follows: "to detect a significant difference between obese patients (BMI ≥ 30) and patients with healthy weight (BMI 18.5–24.99), a total of 3550 patients would provide 80% power to detect a 35% increase in the postoperative complication rate from 8% to 10.8% (α=0.05)".[18]

2. Tabulations with greater than 2 rows of interest (e.g. histological grade) can be difficult to interpret (Table S4).

Table S4 Data from Widschwendter et al. The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial (N: 3754) [14]

	BMI categories					
	Normal weight	Overweight	Obese I	Obese II	Obese III	P value
Nodal status (%)						< 0.001*
pN0	37.5	30.6	27.6	37.9	40.4	
pN1	44.9	46.7	47.8	38.4	33.3	
pN2	12.1	14.4	17.0	13.6	12.3	
pN3	4.3	7.8	7.2	10.2	14.0	
Histological grade (%)						0.126*
G1	4.6	4.9	4.9	4.5	1.8	
G2	48.2	47.7	46.0	46.3	38.6	
G3	46.3	47.0	48.7	49.2	59.6	

* Mantel-Haenszel linear-by-linear association chi-square test

The data for nodal status looks reasonably straightforward – the proportion with N3 stage increases with increasing BMI, but for example, the proportional changes of N0 (node

negative) with increasing BMI is more difficult to interpret. For histological grade, the p value is not significant but the increasing proportions of G3 tumors with increasing BMI seems reasonably clear-cut.

3. With an increasing size of the proportions of obese within a cohort, there is an increased likelihood of statistical significant for the same effect size between obese versus normal weight (Table S5).

Table S5 Data from two simulated scenarios – colorectal and endometrial cancers – with contrasting proportions of BMI categories. We simulate an average event rate (say a complication) of 30% in 1000 patients and we fix the effect size (absolute) difference between normal weight and obesity at 10%

	BMI categories			
	Normal weight	Overweight	Obese	P value*
Colorectal cancer†				
BMI category, n (%)	390 (39)	400 (40)	210 (21)	
Event rate, n (%)	97 (25)	130 (32)	72 (35)	0.015
Endometrial cancer‡				
BMI category, n (%)	220 (22)	320 (32)	460 (46)	
Event rate, n (%)	55 (25)	84 (26)	161 (35)	0.006

*Overall chi-squared
† Taken from in-house data on 569 patients undergoing adjuvant chemotherapy.
‡ Taken from the ASTEC surgery in early endometrial trial.[1]

Table S6 Overview of studies evaluating relationships between elevated BMI and non-cancer prognosis by various cancer types*

Cancer type	Authors (year)	Studies/ Total cancers	Events	Summary conclusion	Summary estimates	Adjustments
Breast cancer (BC)	Chan et al. 2014 [19]	37 population-based cohort; 28 treatment cohorts; 14 secondary analyses of RCT	213,075 Two studies on CVD deaths: 151; Five studies on non-cancer deaths; 2704		**Non- cancer mortality** (BMI < 12 months post-diagnosis) Versus normal BMI, Overweight: 0.96 (0.83-1.11) Obese : 1.29 (0.99-1.68) **CVD mortality** (BMI pre-diagnosis) Versus normal BMI, Overweight: 1.01 (0.80-1.29) Obese: 1.60 (0.66-3.87)	
Breast cancer (BC)	Kwan et al. 2012 [20]	After Breast Cancer Pooling Project. Breast† 1990-2006 Total no: 14,948	All deaths: 2,140 BC deaths: 1,423 Non-BC deaths: 717	Women who were obese II and III before breast cancer diagnosis were at the greatest risk of non-BC deaths. "Morbidly obese women were also at increased risk of death from breast cancer."	**Non-breast cancer mortality** Versus normal BMI, Overweight: 1.01 (0.91-1.12) Obese I: 1.13 (0.90-1.42) Obese II: 1.40 (1.02-1.92) Obese III: 3.01 (2.09-4.33) **BC mortality** **Breast cancer mortality** Versus normal BMI, Overweight: 1.04 (0.92-1.18) Obese I: 1.12 (0.94-1.32) Obese II: 0.92 (0.68-1.24) Obese III: 1.40 (1.00-1.96)	Adjusted for age at diagnosis, AJCC stage, race/ethnicity, education, menopausal status, hormone receptor status, surgery, chemotherapy, radiation therapy, hormonal therapy, smoking, comorbidity, and physical activity
Colorectal cancer (CRC)	Campbell et al. 2012 [21]	Cancer Prevention Study II Nutrition Cohort 1992-2008 Total no: 2,303	All deaths: 851 CRC deaths: 380 CVD deaths: 153	Pre-diagnosis BMI (mean, 7 years before CRC diagnosis), obese BMI was associated with higher risk of mortality resulting from all causes, CRC, and CVD. Post-diagnosis BMI (mean, 1.5 years after diagnosis) was not associated with all-cause, CVD or cause-specific mortality.	**CVD mortality** **Pre-diagnosis BMI** HR (95% CIs) per 5 kg/m^2: 1.28 (1.04-1.58) **Post-diagnosis BMI** HR (95% CIs) per 5 kg/m^2: 1.06 (0.84-1.33)	Adjusted for age at diagnosis, smoking status, physical activity, red meat intake, SEER summary stage at diagnosis, and sex
Endometrial (EC)	Ward et al. 2012 [22]	SEER registries, 1973-88 Total no:	All deaths: 23,934 EC deaths: 4,150	"cardiovascular disease is the leading cause of death among endometrial cancer patients and survivors"	**Cardiovascular deaths:** Localised low-grade: 42% Localised high-grade: 34% Advanced low-grade: 27%	Unadjusted

33,232	CVD deaths: 8,777	Advanced high-grade: 15% **EC deaths:** Localised low-grade: 7% Localised high-grade: 26% Advanced low-grade: 33% Advanced high-grade: 56%

*Information directly from published systematic reviews/ meta-analyses – rather than directly from primary studies.
BMI: body mass index. CI: confidence interval. CVD: cardiovascular disease. SEER: Surveillance, Epidemiology, and End Results.
†Three of the cohorts specifically recruited breast cancer patients: the Shanghai Breast Cancer Survival Study (SBCSS), the Life after Cancer Epidemiology (LACE) Study [16], and the Women's Healthy Eating and Living (WHEL) Study. The fourth cohort included women with breast cancer diagnosed in the prospective Nurses' Health Study (NHS) cohort.

Table S7 Overview of studies evaluating relationships between elevated BMI and quality of life by various cancer types*

Cancer type	Authors (year)	Studies/ Total cancers	When BMI measured	Assessment tools	Summary conclusion	Summary estimates	Comments
Multiple cancer types: breast, prostate, colorectal, bladder, uterine, skin melanoma cancer survivors	Blanchard et al. 2010 [23]	ASC SCS-II Cross-sectional design, Total N: 36,372 This analysis: 3,241	Any time during survivorship	Godin Leisure-Time Exercise Questionnaire; RAND-36 manual	"…healthy-weight and/or overweight cancer survivors reported significantly better physical functioning compared with their obese counterparts …….overweight colorectal cancer survivors reported significantly better mental health compared with obese survivors"	Physical component composite score; main effect of BMI category Breast: P = 0.001 Prostate: P = 0.005 Colorectal: P = 0.002 Uterine: P = 0.001 Skin melanoma: P = 0.034	Adjusted for age, education, number of co-morbidities and physical activity
Breast cancer (BC)	Paxton et al. 2012 [24]	Within the WHEL study, N: 3013		SF 36-Item Health Survey	Obesity is associated with "functional decline among cancer survivors"		No controls. Associations between obesity and QoL were mixed.
Breast cancer (BC)	Connor et al. 2016 [25]	Long-Term Quality of Life Study: 200 cases/survivors (69 Hispanic, 131 NHW) & 251 controls (79 Hispanic, 172 NHW).	Baseline & follow-up interviews	SF 36-Item Health Survey	"… obesity at baseline and follow-up interviews was associated with reduced physical health, regardless of survivor/control status and that obesity at baseline interview was associated with reduced QoL for mental health among survivors."	Mental health SF-36 Obesity at baseline among survivors: β = −13.30, SE = 4.00, p = 0.001; Obesity at baseline among controls: β = −1.14, SE = 2.71, p = 0.674	Control population included. Comparison between Hispanic and NHW. No adjustment for multiple testing
Colorectal cancer (CRC)	Jansen et al. 2010 [26]	Meta-analysis of ten studies; two specifically evaluated BMI and QoL from same population (Wisconsin)	259 female CRC survivors. BMI measured post diagnosis		"Female survivors with higher BMI at the time of follow-up had lower physical QoL even when controlling for number of comorbidities, age and education. Higher BMI was associated with worse scores in physical functioning, role physical, bodily pain, general health and vitality. Psychological QoL was not associated with BMI."		No equivalent studies for male survivors
Prostate cancer (PCa)	Allott et al. 2013 [27]	Systematic review; five studies identified that evaluated			"Several small retrospective observational studies reported mixed findings between obesity and Qol among PCa survivors treated with radical prostatectomy (RP) or radiotherapy. The prospective multicentre Boston study among 1201 PCa survivors treated with RP or radiotherapy reported an		Whether these findings are indicative of obesity, physical inactivity, or an interaction between

		obesity and QoL			independent association of obesity with reduced vitality and worse QoL. Obesity was associated with worse pre-treatment vitality, which has a negative impact on post-treatment QoL. Erectile function following RP is determined by erectile function pre-surgery and is not independently associated with obesity. Obese and inactive men were 26% more likely to be incontinent versus normal weight physically active men after RP."		the two is unclear. There are potential confounding due to race and ethnicity
Endometrial cancer	Smits et al. 2015 [28]	Meta-analysis of four studies: 2 cross-sectional; 1 retrospective; 1 prospective Total N: 1362	At time of questionnaire completed (3 studies); at diagnosis (1 study)		".....obese survivors had a significantly poorer physical functioning, social functioning and role functioning when compared to non-obese women. Emotional functioning and cognitive functioning did not show significant differences".	**Obese versus non-obese** (BMI ≥ 30 kg/m^2 v < 30 kg/m^2) poorer physical functioning: MD:−11.61 (95% CI: −18.66 to −4.55) social functioning: MD: −4.37 (95% CI: −7.75 to −1.00) role functioning: MD: −5.44 (95% CI: −8.90 to −1.98)	The authors recognised the high risk of bias "associated with non-randomisation, patient attrition, and selective reporting." While all studies adjusted for several potential confounders only one study adjusted for socio-demographic factors and comorbidities.
Ovarian cancer	Smits et al. 2015 [29]	Single institution, 2008-2013 Total N: 176	Any time during survivorship	EORTC QLQ-C30	"Increasing BMI is associated with poorer quality-of-life outcomes in terms of physical and emotional functioning in ovarian cancer survivors"	**Mean (SD) global QoL score:** Normal BMI: 67.9 (25.9) Overweight: 62.0 (30.0) Obese: 58.6 (28.6)	There were wide SDs on most scores and statistically significant differences were borderline

*Information directly from published systematic reviews/ meta-analyses – rather than directly from primary studies.
BMI: body mass index. QoL: quality of life. MD: mean difference. CI: confidence interval. SD: standard deviation.
WHEL: Women's Health Eating and Living Study. NHW: non-Hispanic Whites.
ASC SCS-II: American Cancer Society's Study of Cancer Survivors II.
EORTC: European Organization for Research and Treatment of Cancer.

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