Impact of Weight Change on Cancer Prognosis

Professor Andrew G Renehan
PhD FRCS FRCS(GenSurg)

The Christie NHS Foundation Trust and
Manchester Cancer Research Centre
Division of Molecular & Clinical Cancer Sciences, School of Medical Sciences,
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Excess weight & cancer risk (no argument)

WCRF: obesity-related cancers	
1	Post-menopausal breast
2	Endometrial
3	Ovarian
4	Advanced prostate
5	Colorectal
6	Kidney
7	Pancreatic
8	Liver
9	Gallbladder
10	Gastric cardia
11	Oesophageal adenocarcinoma

BMI & incident cancer: causal associations

Bradford-Hill criteria	
1	Strength of association
2	Consistency
3	Specificity
4	Temporality
5	Biological gradient
6	Plausibility
7	Coherence
8	Experimental evidence
9	Analogy

(additional) Bristol criteria	
10	Appropriate adjustment for key confounding factors
11	Measurement error
12	Assessment of residual confounding
13	Lack of alternative explanations (e.g. dose-capping)

Lawlor et al. Lancet 2004;363:1724-27

This debate

Impact of BMI on:

incident cancer ≈ post-diagnosis outcome

Excess weight (or weight gain) after cancer diagnosis

Might have adverse effect on:

1. Oncological outcomes (i.e. prognosis)
2. Other co-morbidities (e.g. CDV, type 2 diabetes)
3. Quality of life
4. Second primary (obesity-related) cancers
5. ?others

WCRF breast cancer survivors report

"…… there is a link between having a healthy BMI - both before and after diagnosis - and surviving breast cancer.

However there are other factors that might explain why women who are overweight or obese have a greater risk of dying from the disease ……"

Present analysis: umbrella review of systematic reviews

Cancer types

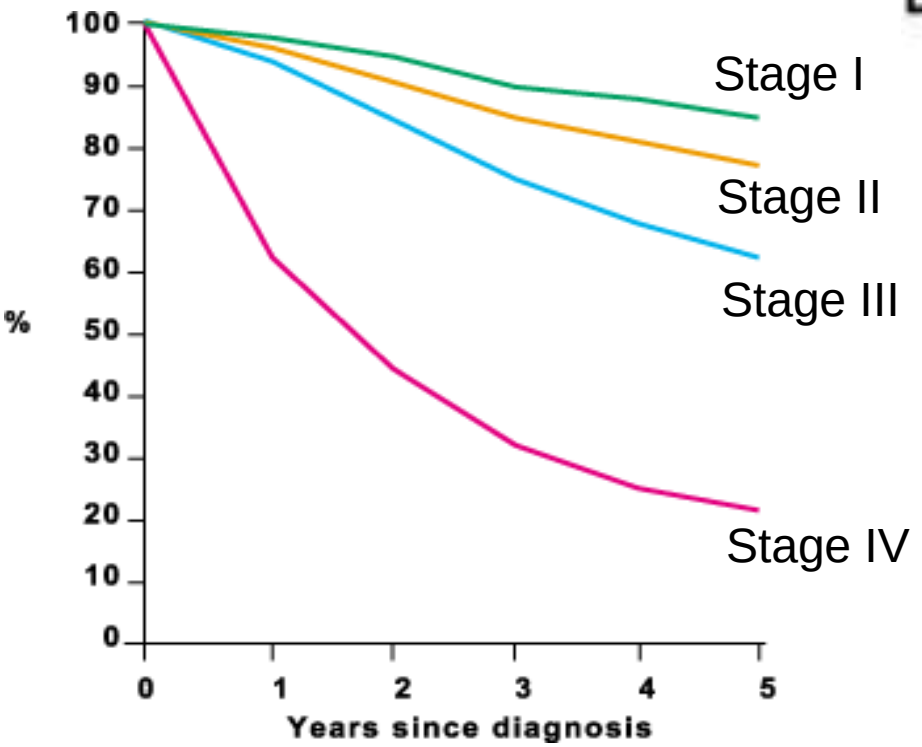
1. Breast cancer
2. Colorectal cancer
3. Prostate cancer
4. Endometrial cancer
5. Ovarian cancer

Appropriate adjustment for key confounding factors

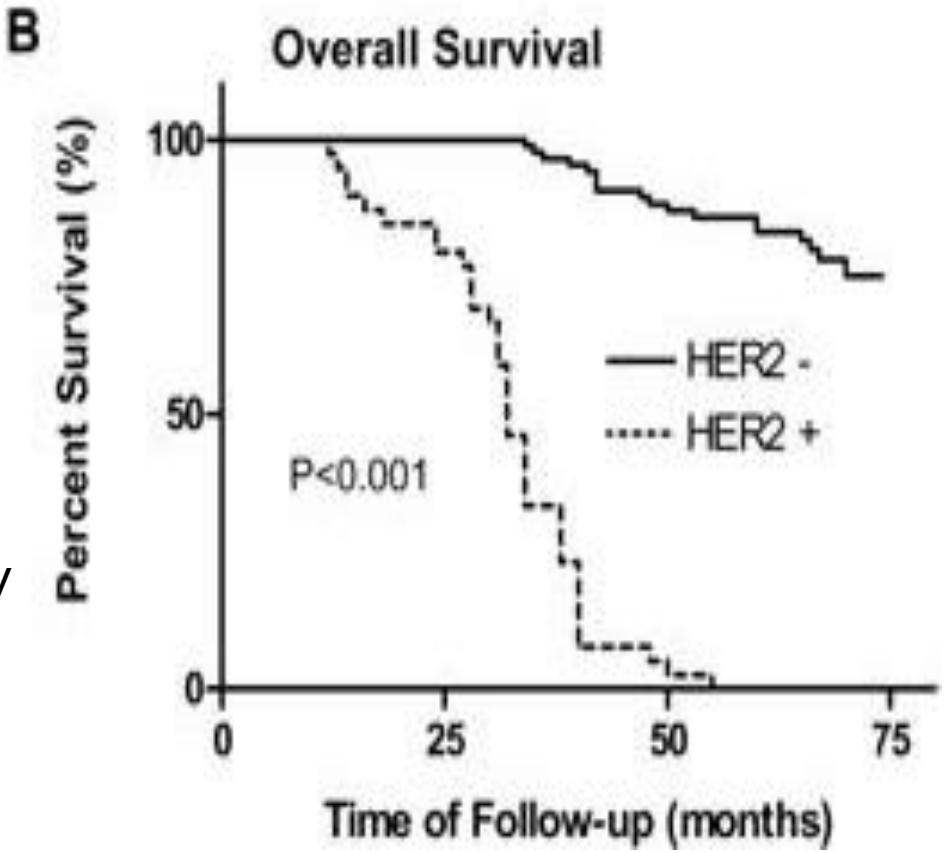
1. Treatment
2. Stage
3. ER/PR status (breast cancer)
4. Emergency treatment (in colorectal cancer)
5. Histological sub-types (Gleeson, Bokhman, serous v. others)

Key prognostic factors: stage & histological subtypes

AJCC staging



Breast cancer



Key prognostic factors: emergency presentation

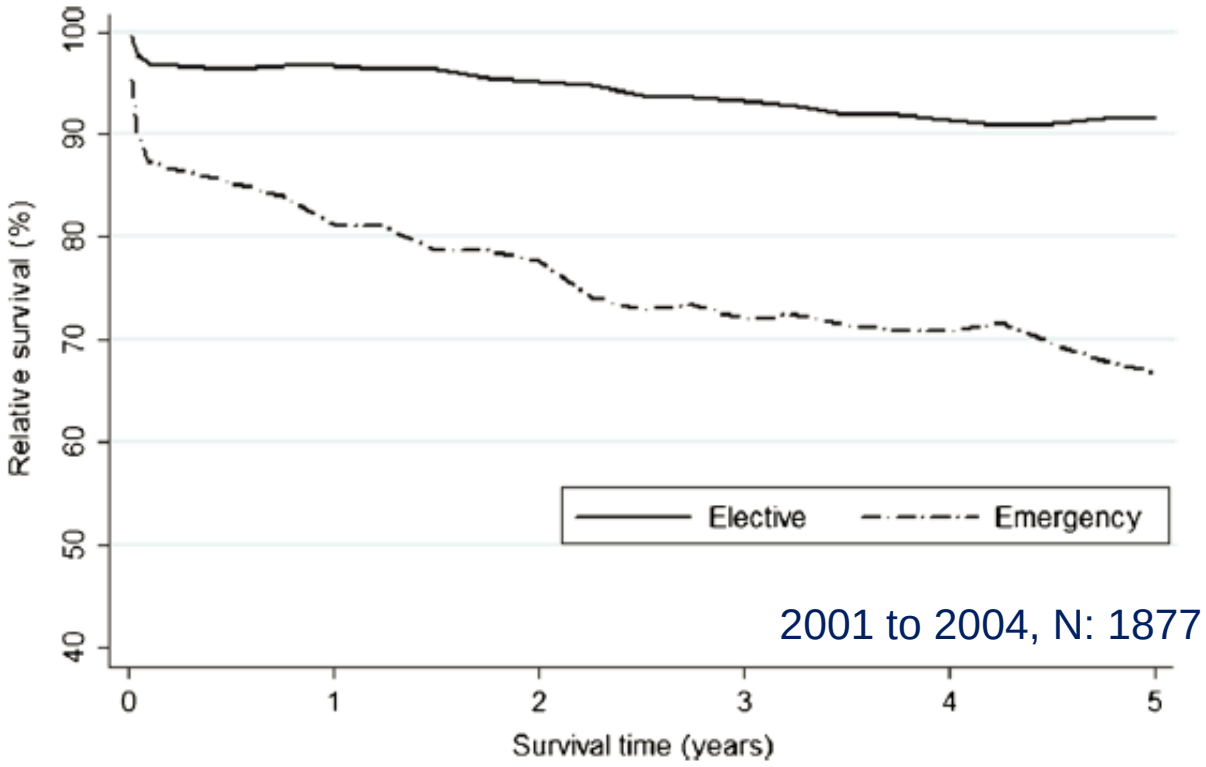
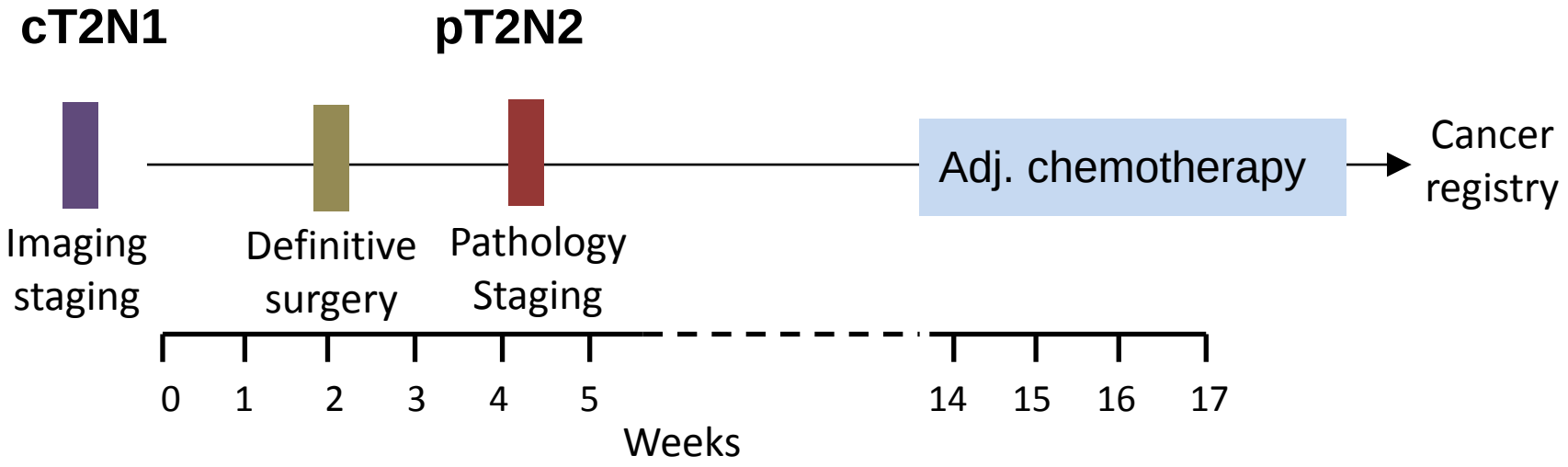
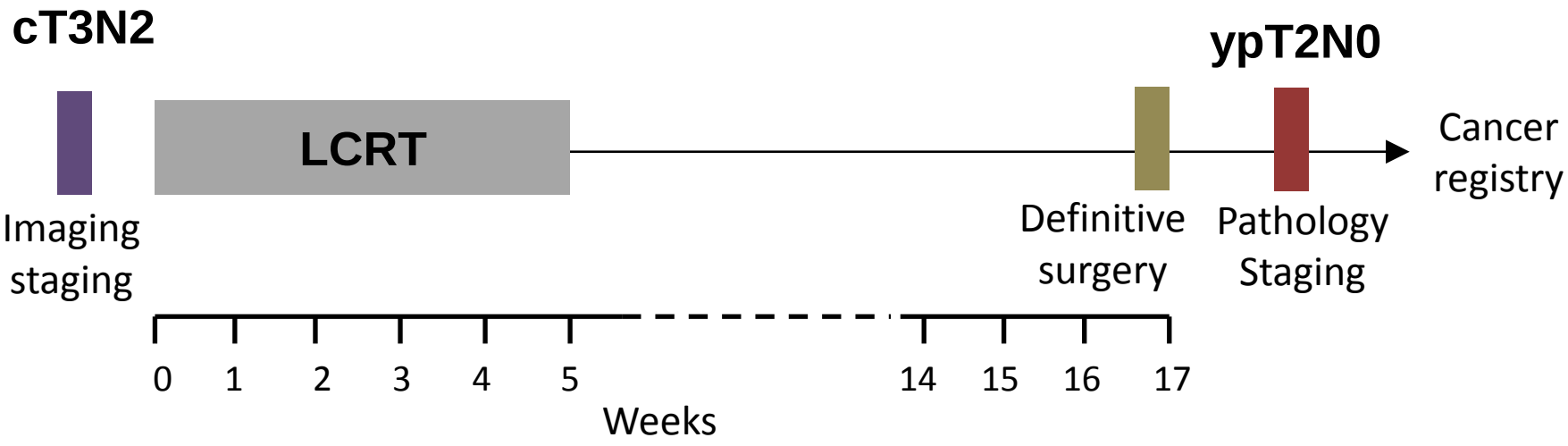


Fig. 1 Relative survival curves after surgery with curative intent in patients with node-negative colorectal cancer by mode of presentation

West of Scotland Colorectal Cancer Managed Clinical Network
Int J Colorectal Diseases 2014

Complexity of modern staging & treatment
Example: rectal cancer

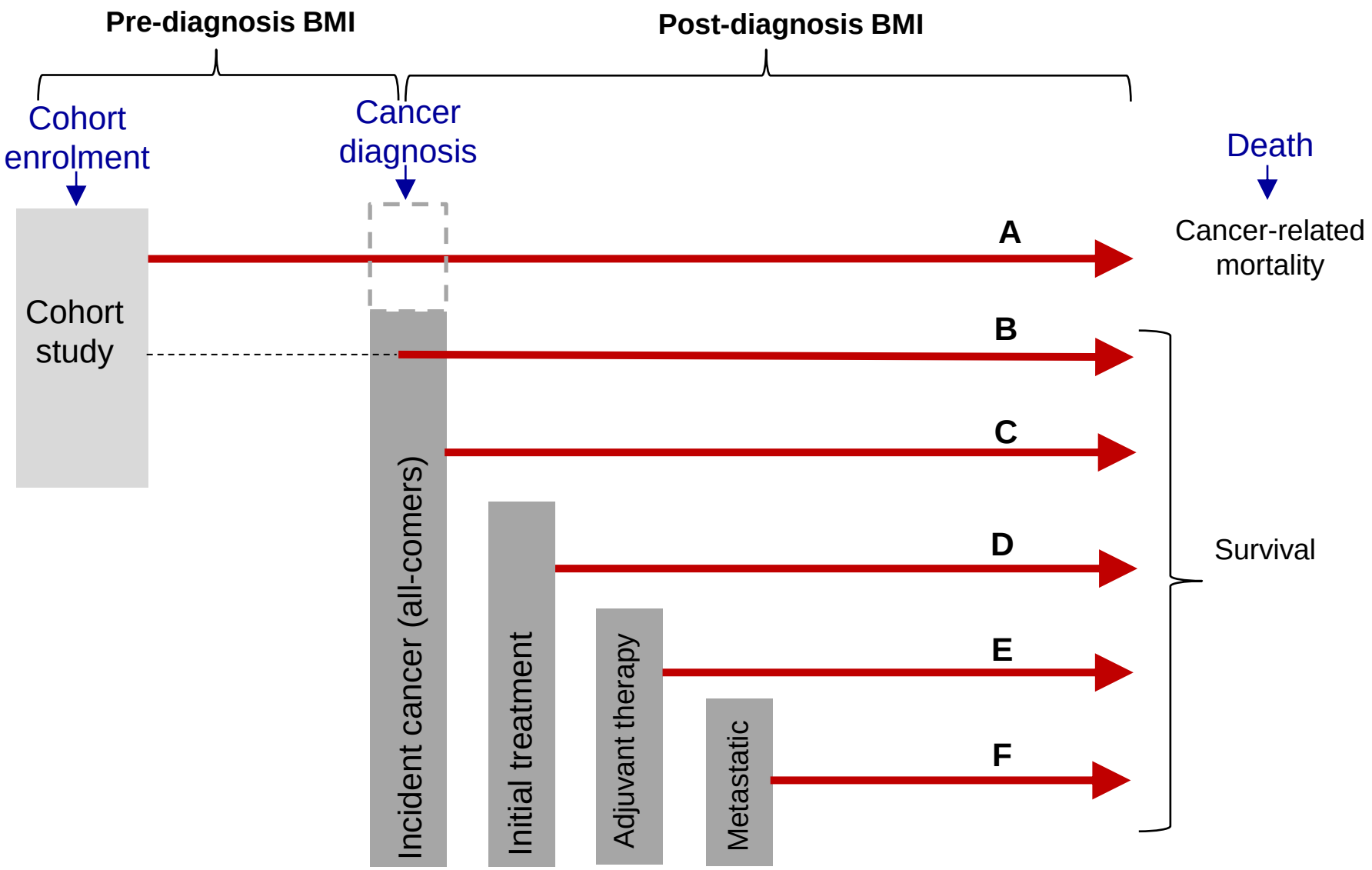




Findings: types of studies in systematic reviews

1. Population-based (registries)
2. Cancer cases within inception cohorts
3. Post-diagnosis survival (treatment series)
4. Secondary analyses in RCTs

Timing of BMI determination



Meta-analyses in breast cancer

	No. of studies	Cancer-specific survival (obese versus normal weight)
Protani et al. 2010	45 (mixed study types)	1.33 (1.19 – 1.50)
Azrad & Demark-Wahnefried 2014	Added 11	BMI influences outcome in ER positive but not triple negative
Niraula et al. 2012	21 (receptor status: menopausal status)	ER positive: 1.31 (1.17 – 1.46) ER negative: 1.18 (1.06 - 1.31) No difference by meno. status
Chan et al. 2014	82 (mixed study types)	Pre-diagnosis: 1.35 (1.24 – 1.47) < 12 months: 1.25 (1.10 – 1.42) ≥ 12 months: 1.68 (0.90 – 3.15)
Kwan et al. 2012	4 cohorts: IPD	Obese III: 1.40 (1.00 – 1.93)
Cecchini et al. 2016	4 adjuvant RCTs: B-30, B-34, B-38, B-31	B-30 ER positive: 1.30 (1.09 – 1.56) B-34, B-38, B31: no associations

Meta-analyses in Colorectal cancer

	No. of studies	Cancer-specific survival (obese versus normal weight)
Wu et al. 2014	29 (mixed study types)	Pre-diagnosis: 1.30 (1.17 – 1.44) Peri-diagnosis: 1.08 (1.03 – 1.13) Post-treatment: 0.89 (0.75 – 1.05)
Parkin et al. 2014	35 (6 categories)	Similar findings expressed: 5 kg/m^2
Sinicrope et al. 2014	21 (adjuvant RCTs)	Overweight: 0.95 (0.89 – 1.02) Obese I: 1.11 (1.02 – 1.21) Obese II/III: 1.10 (1.00 – 1.20)
Lee et al. 2015	16 prospective cohorts	Pre-diagnosis: 1.22 (1.00 – 1.35) Post-diagnosis: 0.95 (0.80 – 1.30)

Meta-analyses in other cancers

	No. of studies	Cancer-specific survival (obese versus normal weight)
Prostate cancer		
Cao & Ma 2011	12 (mixed study types)	Pre-diagnosis: 1.15 (1.06 – 1.25)* 6 months post dx: 1.20 (0.99 – 1.46)*
Hu et al. 2014	26 Treatment series	Biochemical recurrence All studies: 1.16 (1.08 – 1.24)*
Endometrial cancer		
Arem & Irwin 2013	12 (mixed study types)	4 studies reported significant association; 8 found no association
Ovarian cancer		
Protani et al. 2012	14 (mixed study types)	Pre-diagnosis: 1.13 (0.95 – 1.35) At diagnosis: 1.13 (0.81 – 1.57)
Bae et al. 2016	17 (mixed study types)	Pre-diagnosis: 1.35 (1.03 – 1.76) At diagnosis: 1.07 (0.951 – 1.21)

*per 5 kg/m^2

Confounders: meta-analyses in breast cancer

	Treatment	Stage	ER/PR
Protani et al. 2010			
Azrad Demark-Wahnefried 2014			
Niraula et al. 2012			
Chan et al. 2014			
Kwan et al. 2012			
Cecchini et al. 2016			

Proportion of studies adjusting for confounder

80 – 100%

60 – 79%

< 60%

Confounders: meta-analyses in colorectal cancer

	Treatment	Stage	Emergency
Wu et al. 2014			
Parkin et al. 2014			
Sinicrope et al. 2014			
Lee et al. 2015			

Proportion of studies adjusting for confounder

80 – 100%

60 – 79%

< 60%

Confounders: meta-analyses in other cancers

		Treatment	Stage	Hist. sub-type
Prostate cancer	Cao & Ma 2011			
Prostate cancer	Hu et al. 2014			
Endometrial cancer	Arem & Irwin 2013			
Ovarian cancer	Protani et al. 2012			
Ovarian cancer	Bae et al. 2016			

Proportion of studies adjusting for confounder

80 – 100%

60 – 79%

< 60%

Appropriate adjustment for key confounding factors

We concluded that:

“Much of the evidence underpinning the (oncological) rationale for weight management after cancer diagnosis is WCRF grade ‘limited suggestive’.

This interpretation challenges many contemporary commentaries.

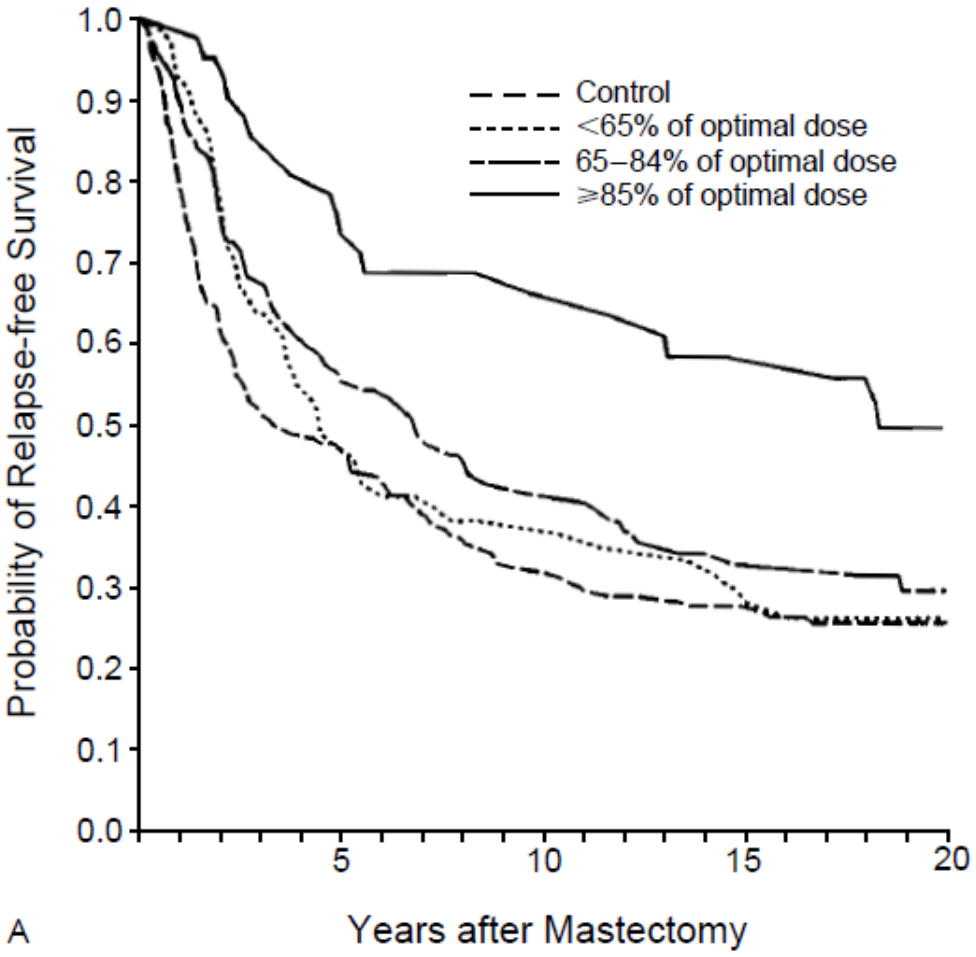
Long-term oncological outcomes are awaited from a small number of cancer-specific trials assessing the impact of weight management.”

Chemotherapy dose-capping

			Percentages				
Authors, country	Cancer type	Study name/ type	Normal weight	Over-weight	Obese	Severely obese	P value
			1st cycle dose reduction (< 0.9 standard dose)				
Griggs et al. 2005, USA	Breast	Retrospective cohort study, Pittsburgh	9.0	11.0	20.0	37.0	< 0.0001
			dose reduction (not specified)				
Gennari et al. 2016, Italy	Breast	Phase III trial	3.0	3.0	8.0		0.03
			dose reduction (< 0.95 standard dose)				
Dignam et al. 2006, USA	Colon	NSABP C-04 and C-05	7.0		55.0	73.0	
Chambers et al. 2012, UK	Colorectal	FOCUS trial	4.0	9.0	32.0		< 0.0001
Chambers et al. 2012, UK	Colorectal	FOCUS2 trial	12.0	21.0	60.0		< 0.0001
Chambers et al. 2012, UK	Colorectal	COIN trial	4.0	16.0	54.0		< 0.0001
			Dose reduction (any course)				
Wright et al. 2008, USA	Ovarian	Gynecologic Oncology Group (GOG) protocol 158	34.0	14.8	21.1		0.004
			Relative dose intensity < 85%				
Au-Yeung et al. 2014, Australia	Ovarian	Australian Ovarian Cancer Study (AOCS)	39.0	39.0	67.0		< 0.001

Effect of dose-reduction

Node positive breast cancer trial: CMF versus control
Relapse-free survival



Bonadonna et al. NEJM 1995 April 6

Chemotherapy dose-capping

We concluded that:

"…….. the implication of this (dose capping) is that the observed adverse prognosis associated with obesity in many cancer types may reflect confounding due to sub-optimal chemotherapy dosing and reduced therapeutic effect relative to normal weight cancer patients"

Summary

- Key prognostic factors are often inadequately adjusted for in studies
- Secondary analysis of RCTs offer better capture of treatment, stage & other prognostic factors
- Caveat: secondary analysis of RCTs tend to be in adjuvant trials, and susceptible to dose-capping confounding

Implications

- While, we await long-term FU in weight intervention trials, we have to be honest with our patients
- Research: large-scale IPD secondary analysis of RCTs, which also capture chemotherapy details
- Smaller pooled analyses might be better that large heterogeneous meta-analyses

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