Cancer Anorexia Cachexia Syndrome

Cancer Cachexia - Definitions

- Derives from the Greek ‘kakos’ meaning bad & ‘hexis’ meaning condition
- A physical fading of wholeness
- Syndrome of decreased appetite, weight loss, metabolic alterations & inflammatory state

Cancer Cachexia - What it is?

- An extreme progressive weight loss in cancer patients
- Occurs also in other chronic diseases (cardiac disease & chronic infection but not neurological disease)
- Due to a systemic inflammatory response
- Mediated through cytokines & other factors such as proteolysis inducing factor (PIF) & lipid mobilising factor (LMF)

(Regnard, 2004)

Cancer Cachexia - Features

- Some or all of the following features are exhibited in varying degrees:
  - Hypophagia / anorexia
  - Early satiety
  - Anemia
  - Weight loss with depletion & alteration of body compartments
  - Edema
  - Asthenia (weakness)

(Freeman & Donnelly, 2004)

Theories of Nutrition & Cachexia in Cancer

It is NOT:

- Due to starvation
- Due to malnutrition
- Due to competition by the tumor
- Restricted to cancer
- Reversed by nutritional support

(Regnard, 2004)

Cancer Cachexia - Prevalence

- Occurs in ~ 70% of patients during the terminal course of disease
- Weight loss > 10% pre illness weight occurs in up to 45% of hospitalised cancer patients
- Cancer of the Upper GI & lung have the highest prevalence of weight loss
- Lung cancer patients with 30% weight loss show 75% depletion of skeletal muscle
- Breast cancer, sarcomas & NHL show the least weight loss

(Payne-James *et al.*, 2001)

Cancer Cachexia - Etiology

- Understanding is limited & based upon the knowledge of abnormalities in nutrition behaviour & metabolic patterns
- Appears as a classic case of malnutrition
- 3 theories have been suggested:
- Metabolic competition
- Malnutrition
- Alterations of metabolic pathways

(Payne-James *et al*., 2001)

Cancer Cachexia - Metabolic Competition

- Neoplastic cells compete with host tissues for protein, functioning as a 'nitrogen trap'
- In experiments where tumor is a high % of animal weight this theory holds, but in human tumors – even patients with a very small tumour can have severe cachexia

(Morrison, 1976)

Cancer Cachexia – Malnutrition

- Upper aerodigestive disease is an obvious cause of malnutrition
- Regardless of tumor location, anorexia is the most common cause of hypophagia & usually consists of a loss of appetite &/or feelings of early satiety
- Hypophagia has been related to the presence of dysgeusia
- Diminished ability to perceive sweet flavors leads to anorexia

(Payne-James *et al*., 2001)

Cancer Cachexia – Malnutrition

- Reduced threshold for bitter flavors linked to an aversion to meat
- Dysosmia is also related to an aversion to food
- Malnutrition leads to secondary changes in the GI tract which may be responsible for the feeling of fullness, delayed emptying, defective digestion & the poor absorption of nutrients
- However, malnutrition alone is not thought to be the main cause of cachexia

(Payne-James *et al*., 2001)

Metabolic Alterations in Starvation v Cancer Cachexia – CHO Metabolism

Metabolic Alteration	Starvation	Cancer Cachexia
Glucose tolerance	Decreased	Decreased
Insulin sensitivity	Decreased	Decreased
Glucose turnover	Decreased	Increased
Serum glucose level	Decreased	Unchanged
Serum insulin level	Decreased	Unchanged
Hepatic gluconeogenesis	Increased	Increased
Serum lactate level	Unchanged	Increased
Cori cycle activity	Unchanged	Increased

Adapted from Rivadeneira *et al*.,1998

Metabolic Alterations in Starvation v Cancer Cachexia – Fat Metabolism

Metabolic Alteration	Starvation	Cancer Cachexia
Lipolysis	Increased	Increased
Lipoprotein lipase activity	Unchanged	Decreased
Serum triglyceride level	Unchanged	Increased

Adapted from Rivadeneira *et al.*,1998

Metabolic Alterations in Starvation v Cancer Cachexia – Protein Metabolism

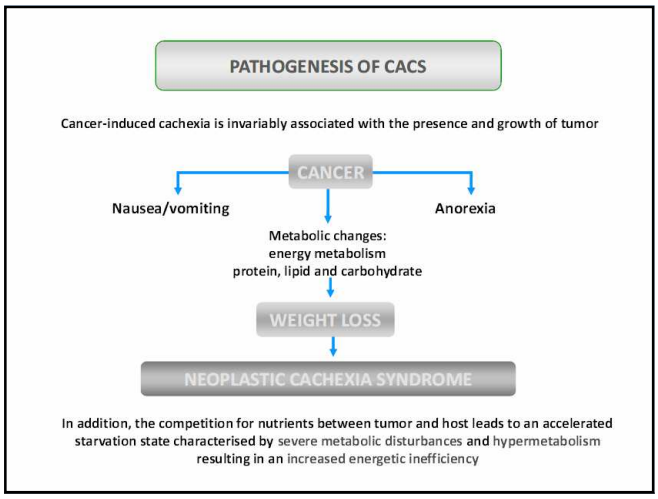
Metabolic Alteration	Starvation	Cancer Cachexia
Protein turnover	Decreased	Increased
Skeletal muscle catabolism	Decreased	Increased
Nitrogen balance	Negative	Negative
Urinary nitrogen excretion	Decreased	Unchanged

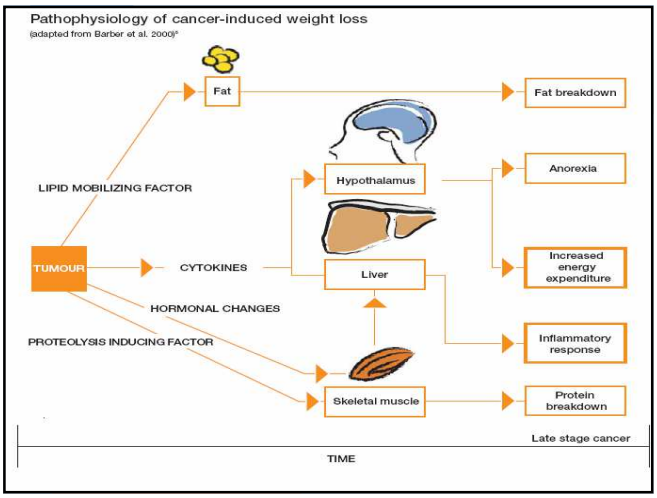
Adapted from Rivadeneira *et al.*, 1998

Cancer Cachexia - Cytokines

- Produced by host in response to tumor
- Cytokines regulate many of the nutritional & metabolic disturbances in the cancer patient leading to:
  - Decreased appetite
  - Increase in BMR
  - Increased glucose uptake
  - Increased mobilization of fat & protein stores
  - Increased muscle protein release

(Tisdale, 2004)





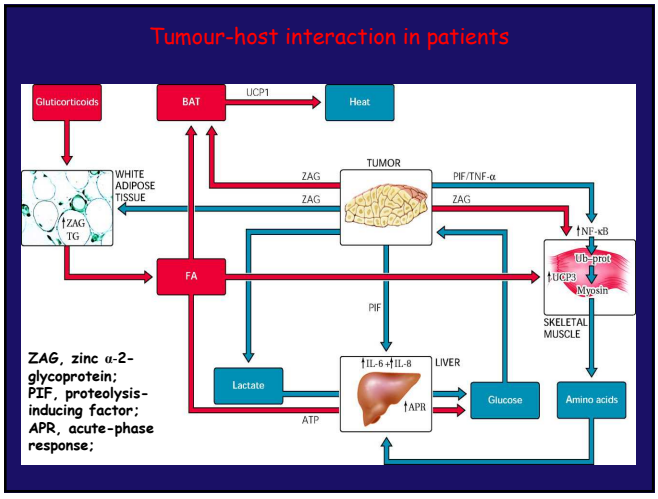
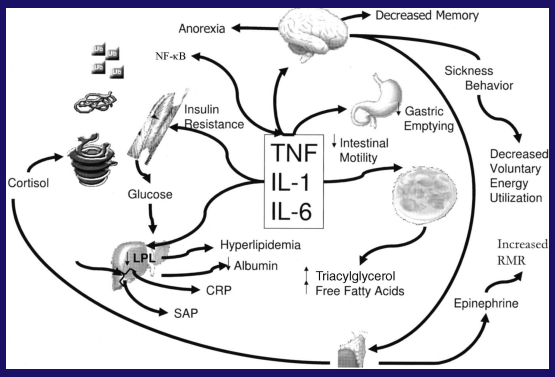


Table 1 | **Potential mediators of cachexia**

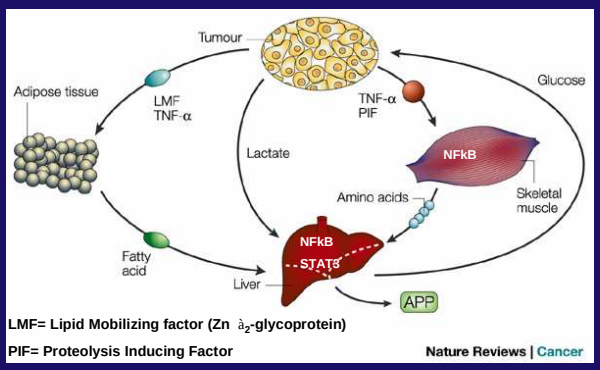
Host/tumour products	Effect on appetite	Effect on cachexia in animal models	Effect on cachexia in humans
Tumour necrosis factor (TNF)-α	↓[51]	+[57]	+[62] −[63]
Interleukin (IL)-6	↓[52]	+[52]	+[64] −[65]
IL-1	?	+[58]	−[63,65]
Ciliary neurotrophic factor (CNTF)	↓[53]	+[59]	?
Interferon (IFN)-γ	↓[54]	+[60]	−[63,92]
Lipid-mobilizing factor (LMF)	NC	+[61]	+[93]
Proteolysis-inducing factor (PIF)	NC	+[61]	+[67]

↓, decrease; NC, no change; +, positive association; –, no association; ?, not known.

ROLE OF CYTOKINES IN CACHEXIA

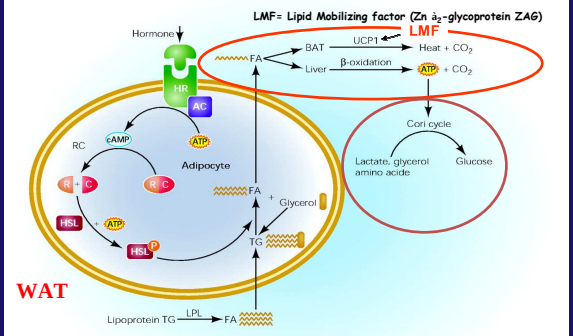


PIF and PROTEOLYSIS in CANCER PATIENTS



Pif 24 KDa PROMOTES proteasome proteolysis in muscle and synthesis of IL-6 and IL-8 in liver.

ALTERED METABOLISM OF FAT TISSUES IN CANCER



HR, Hormone receptor; AC, adenylate cyclase; FA, fatty acid; BAT, brown adipose tissue; RC, regulatory and catalytic subunits of cAMP-dependent protein kinase; HSL, hormone-sensitive lipase; P, phosphorylation; TG, triglycerides; LPL, lipoprotein lipase