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Review

Metabolism in Cancer Patients

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Abstract. *Today still only 50% of newly diagnosed cancers can be cured. While molecular mechanisms of cell proliferation are being studied intensively, comparably little research energy, however, has been spent on unravelling metabolic interactions of cancer and host tissues. Evidence is accumulating that systemic as well as local metabolic patterns have considerable impact on tumour growth, as well as on body composition and organ functions. This may lead to new treatments in oncology. Cancer development - and recurrence - may be inhibited by physical activity, as well as by avoiding obesity, the metabolic syndrome and insulin resistance. Antineoplastic treatments induce reductions in nutritional intake and require individually tailored nutritional support. New concepts are being considered to metabolically starve or reprogram cancer cells. During palliative treatment of progressive tumours, it should be good clinical practice to avoid or treat malnutrition and chronic inflammatory states. At late stages, the primary goal should be symptomatic relief and attention to subjective individual needs.*

Cancer treatment has improved considerably during the last 50 years; the disease, however, has not lost its frightening impact and still only about 50% of patients will be cured (1-4). Classical oncology has concentrated almost exclusively on directly destroying or quieting the malignant tumour cells. New evidence, however, puts this mono-conceptual framework into question (5-7). An increasing number of studies suggest that similar attention should be paid to the tumour microenvironment, *i.e.* the tumour stroma (8), as well as to the tumour macroenvironment, *i.e.* the systemic metabolic pattern (9). Virchow cited by Ewing (10) stated that "no man, even under torture, can say exactly what a tumour is", but today there is a growing understanding that cancer is more than just the sum of malignant cells (11-13).

Cancer is a potentially fatal disease and, due to the incomplete success of standard medical therapies, many patients are susceptible to promises of unconventional and mystic treatment offers (14-16). Strengthening or guiding the body to eliminate cancer is an appealing concept. Thus, there is a diverse spectrum of nutritional diets, suggestions and therapies that are being offered as protection from or as a cure for cancer (17-20). The aim of this review is to consider the scientific basis of this general approach.

Cancer progresses through several phases and it is important to understand that metabolic patterns and requirements are not constant during these periods. Before onset and after curative treatment, the metabolic situation is undisturbed by interactions with cancer tissues or by direct antineoplastic treatments; but patterns such as the metabolic syndrome may favour tumour growth and recurrence (21, 22). Aggressive anticancer therapies strain body resources and this may compromise their completion or effectivity (23). Palliative treatment of advanced tumours is often complicated by chronic inflammation which may favour tumour growth and development or worsening of cachexia at the same time (24, 25). It is relevant to look for specific metabolic patterns, since this may translate into specific supportive treatments.

Cancer Prevention – Importance of Body Weight and Physical Activity

Available epidemiological data on nutrition and cancer incidence were scrutinized and the findings published in a detailed report in 1997 by the World Cancer Research Fund (WCRF). The expert group concluded that plant foods were of major importance when considering cancer prevention with respect to most tumour entities (26). The following decade saw the arrival of results from several large and well-designed international epidemiological studies, many of them reporting only small or no protection from cancer by plant foods or other nutritional

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ingredients (27). At the same time, however, an increasing number of articles reported findings that appear to underline the potential importance of metabolic patterns as opposed to the combination of nutrients consumed (28-33).

Obese individuals are at a substantially higher risk of being diagnosed with and die from cancer (29). Diabetes (30) and high fasting glucose levels (31) are associated with an increase in cancer mortality. Insulin treatment, as opposed to dietary treatment, in diabetes is associated with a two-fold increase in the incidence of colon cancer (32). It has been proposed that components of the 'metabolic syndrome', *e.g.* hyperglycaemia, hyperinsulinaemia, insulin resistance and increased levels of growth factors, may be responsible for generating a tumour promoting environment (21, 22, 33-41). Avoiding and treating insulin resistance and the metabolic syndrome may thus become a new paradigm of cancer prevention. Accordingly, the second report of the WCRF expert panel on cancer prevention was renamed to include the term 'physical activity' (28). These most recent suggestions stress the primary importance of maintaining a healthy body weight as well as a high level of bodily activity throughout life, but they still maintain the preference for plant origin when choosing foods (28).

Cancer Treatment with Curative Intent: Counteracting Catabolic Challenges

Malnutrition diminishes treatment options and efficacy as well as prognosis (42), and therefore, should be screened for, avoided and treated (43). Treatment-induced anorexia, mucositis, gastrointestinal motility disorders, infections, and immobilization are expected to contribute to loss of weight and tissue mass, loss of organ function and loss of subjective quality of life; data specifying these interactions, however, are scarce (44-47). It is a primary goal in patients undergoing anticancer therapies to secure nutritional needs, which are similar to those of healthy weight-matched controls (43). Prior to major surgery, patients benefit from oral nutritional support for 5-7 days and patients with weight loss greater than 10% of pre-cancer body weight should receive nutritional support for 10-14 days (48). During radiotherapy, outcome is improved by dedicated nutritional counselling (49); when oral intake remains insufficient, sip feeds or tube feeding are advised (43). Patients undergoing chemotherapy should be monitored for nutritional deficits and should be counselled regularly by dieticians specialised in oncological problems (43). Routine artificial nutritional support, however, is not indicated, but should be initiated when sufficient oral intake cannot be maintained (43, 50, 51).

Post-treatment Phase: Preventing Recurrence by Avoiding Insulin Resistance

Conventional oncological wisdom assumes recurrences of treated cancer to result from either the continuous proliferation at some intrinsic rate of left-over malignant cells or from some additional growth-promoting genetic defect acquired by hidden pre-malignant cells stemming from the precursor of the treated cancer. New evidence points to the relevance of systemic metabolic patterns which may regulate growth potential and growth rates of premalignant or malignant cells and tissues. It is possible that these metabolic patterns are similar or identical to those relevant to primary cancer prevention (52-55).

A review of 159 papers led Chlebowski *et al.* (56) to conclude that overweight or post-treatment weight gain were associated with increases in the risks of recurrence and death in postmenopausal women with breast cancer. It was postulated that endocrine factors such as high oestrogen, insulin or insulin-like growth factor (IGF levels in obese) patients contributed to risk increase. Similarly, it has been reported that obesity increases the risk of recurrence in patients after curative therapy of prostate cancer (57).

In a prospective randomised controlled multicentre study, it was shown that repeated nutritional counselling to reduce fat intake lowered body weight and decreased recurrence rates in postmenopausal breast cancer by 24% from 12%-10% during a mean follow-up period of 60 months (58). This reduction is similar in size to the effects of adjuvant endocrine treatments.

Whole-body metabolism is strongly influenced by muscular activity, resulting in increased peripheral insulin sensitivity and decreases in circulating levels of glucose, insulin and other growth factors. In early-stage breast cancer, fasting insulin levels were shown to be associated with distant recurrence and death (53). Several studies have reported decreased recurrence and death rates in patients with stage I to III breast and colon cancer who were physically active (52, 54, 59). These decreases were significant and relevant and amounted to about 40-50% benefit in those reporting more than 9 (breast cancer) or more than 18 (colon cancer) metabolic equivalent tasks (METs) per week when compared to sedentary subjects. 9 METs are achieved by 2 to 3 hours of vigorous exercise. Again, the size of these effects is similar to or greater than the effects of adjuvant endocrine or chemotherapy treatments.

Pierce and co-workers (60) compared recurrence-free survival after breast cancer treatment in post-menopausal women consuming small or larger amounts of plant foods and reporting little or much physical activity. Recurrence-free survival was best in physically active patients consuming large amounts of vegetables and fruits. Neither

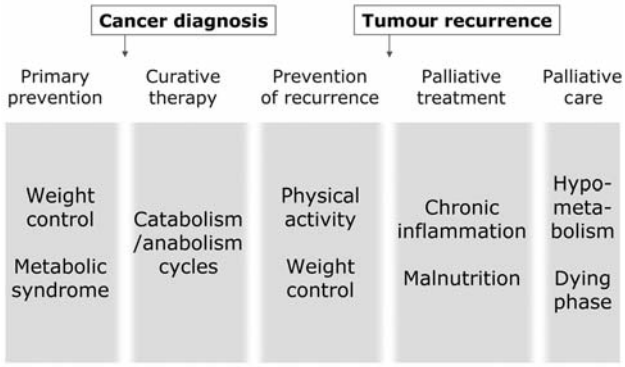

Figure 1. *Phases of cancer progress and typical associated metabolic challenges.*

activity in low-plant food consumers nor high vegetable/fruit intake in inactive individuals conferred a benefit *versus* inactive individuals consuming little plant foods.

Palliative Cancer Treatment – Targeting Inflammation and Malnutrition

It has been known since ancient times that in any disease, malnutrition has a negative impact on prognosis (61). Weight loss in cancer is associated with dramatically reduced survival rates and, therefore, it is a marker and a reliable predictor of poor prognosis (42, 62, 63). Unlike in true starvation, patients in many disease states cannot conserve muscle and rapidly lose body cell mass (64, 65), thus depleting vital tissues, including those of the immunological defence system (66). Several groups observed infection as the single most important cause of death in cancer patients, amounting to 30-68% of deaths (67-69).

Unfortunately, weight loss in cancer is very frequent, being reported in 50% of gastrointestinal cancer patients even before tumour diagnosis (42) and occurring in up to 80% of patients in the palliative setting (63). The causes are multi-factorial and include fear, despair, loneliness, and pain, changes in smell and taste, as well as defects in gastrointestinal functions (70). A frequently observed and potentially severely aggravating condition is the development of a systemic inflammatory response syndrome leading to anorexia and fatigue (9). The syndrome arises as the clinical equivalent of a genetically programmed metabolic switch responsible for orchestrating the demarcation and resolution of any injury or attack on the integrity of the body (8, 71). This inflammatory syndrome needs to be distinguished from starvation and the associated metabolic ketosis (72).

Metabolic treatment should concentrate on anti-inflammatory attempts as well as on supplying sufficient energy and protein to avoid further loss of cell mass (8, 43). When choosing energy substrates, glucose is poorly utilised due to inflammation-induced insulin resistance, while fat utilisation is conserved (73).

The nutritional state is at risk in individuals with advanced cancer since providing nutrients is often associated with the fear of feeding the tumour (74). While this argument cannot be dismissed completely, it has been demonstrated that intravenous infusion of glucose does not increase the high basal metabolic activity of tumour tissues (75). Fat is not well used by malignant tissues (76), while it is well used by host tissues (73).

An elusive goal of alternative medicine for a long time has been to diminish tumour growth by changing nutritional patterns. Many of these attempts may be traced to Nobel prize laureate Otto Warburg, who in 1924 detected aerobic glycolysis as a metabolic curiosity of malignant cells (77). He later suggested killing cancer cells by depriving them of glucose or glycolytic activity (78).

More recently, these ideas have resurfaced (6) and gained credibility when it was demonstrated that during the course of their development and in response to hypoxia, malignant cells activate a metabolic network favouring the loss of oxidative capacity and increasing reliance on glucose utilisation (5, 79-81). Activation of the hypoxia-inducible factor (HIF) (82) and serine-threonine kinase pAkt (83), among other factors, are involved in these changes of the intracellular milieu. Vital reliance on glucose was demonstrated by synergistic effects of glycolytic antagonists such as 2-deoxy-D-glucose and cytostatic agents such as adriamycin (84). Similarly, transfecting malignant cells with myrAkt generates cells that display high levels of phosphorylated Akt and no longer tolerate cultivation in glucose-free medium (83). Relying on new data, it has been proposed that malignant cells utilise an ATP-generating transketolase variant TKTL1 to shunt glucose through the pentose phosphate pathway and thus avoid the dangers of radical oxygen species associated with oxidative energy transfer (85). Thus, it may be assumed that glucose-deprivation may have growth-inhibiting effects on human tumours (86). It may be speculated, however, that metabolic modulation may not be possible by dietary interventions alone, but may require additional pharmaceutical means (7, 87, 88). This is supported by the observation that cancer cells frequently overexpress glucose transporter GLUT1, which operates efficiently at very low glucose concentrations (89-91).

Based on the above arguments, it has been suggested to prefer fat over glucose when supplying energy substrates to cancer patients (76). Unfortunately, this has not yet been addressed conclusively in clinical studies.

Terminal Phase

During the last weeks and days of life, all previously considered metabolic strategies lose their relevance, except when offered to relieve acute suffering. The primary task of terminal care is to relieve hunger and thirst and organ-specific symptoms and to concentrate on the suffering individual and his or her most urgent needs (43).

Conclusion

The metabolic milieu has relevant effects on tumour growth and should be shifted into the focus of anticancer strategies. Malnutrition, insulin resistance and inflammation all affect outcome negatively and should be avoided or treated. When considering nutritional choices for those with active cancer, fat should probably be preferred over glucose. Dying patients should not be fed unless required to alleviate hunger or thirst.

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