HHS Public Access

Author manuscript

Recent Results Cancer Res. Author manuscript; available in PMC 2020 September 07.

Published in final edited form as:

Recent Results Cancer Res. 2016 ; 207: 241–266. doi:10.1007/978-3-319-42118-6_12.

Fasting and Caloric Restriction in Cancer Prevention and Treatment

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Keywords

Cancer; Caloric restriction; Dietary restriction; Fasting; Chemotherapy; Stress resistance; Sensitization

Abstract

Cancer is the second leading cause of death in the USA and among the leading major diseases in the world. It is anticipated to continue to increase because of the growth of the aging population and prevalence of risk factors such as obesity, smoking, and/or poor dietary habits. Cancer treatment has remained relatively similar during the past 30 years with chemotherapy and/or radiotherapy in combination with surgery remaining the standard therapies although novel therapies are slowly replacing or complementing the standard ones. According to the American Cancer Society, the dietary recommendation for cancer patients receiving chemotherapy is to increase calorie and protein intake. In addition, there are no clear guidelines on the type of nutrition that could have a major impact on cancer incidence. Yet, various forms of reduced caloric intake such as calorie restriction (CR) or fasting demonstrate a wide range of beneficial effects able to help prevent malignancies and increase the efficacy of cancer therapies. Whereas chronic CR provides both beneficial and detrimental effects as well as major compliance challenges, periodic fasting (PF), fasting-mimicking diets (FMDs), and dietary restriction (DR) without a reduction in calories are emerging as interventions with the potential to be widely used to prevent and treat cancer. Here, we review preclinical and preliminary clinical studies on dietary restriction and fasting and their role in inducing cellular protection and chemotherapy resistance.

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1 Introduction

In 2012, an estimated 14.1 million new cases of cancer occurred and approximately 8.2 million people died of cancer worldwide (Torre et al. 2015), although the exact number can only be estimated because incidence rates and treatment modalities for some parts of the world are not fully established. In the USA, one out of every four deaths was estimated to be due to cancer in 2012 (Siegel et al. 2012). The worldwide number of deaths is projected to increase to 13.2 million by 2030 due to the expected increase in the elderly population, as well as the adoption to cancer-causing behaviors (e.g., cigarette smoking) (Brawley 2011). Notably up to 35 % of all cancer deaths worldwide have been reported to be avoidable through adjustments to lifestyle and environmental factors, such as physical activity and dietary habits (Danaei et al. 2005). However, this estimate does not take into account the more recent advances in dietary interventions to affect aging and age-related diseases, which are likely to cause a major increase in the percentage of preventable cancers (Levine et al. 2014).

Compared to the improvements in the prevention and treatment of heart disease, cancer treatment and mortality have remained relatively unchanged over the past 30 years (Jemal et al. 2008). Chemotherapy and/or radiotherapy in combination with surgical removal of the tumor mass remain the standard therapies. Chemotherapy improves the survival rates of cancer patients but causes damage to normal tissues and leads to significant side effects such as emotional distress, myelo-suppression, fatigue, vomiting, diarrhea, and even death (Love et al. 1989; Partridge et al. 2001). Despite newly designed drugs that target specific cancer markers, cytotoxic drugs will have accompanying side effects unless novel and complimentary interventions or strategies are adopted. In the following sections, we discuss preclinical and preliminary clinical results on how specific forms of dietary restriction (DR) and periodic fasting (PF; 24 h or more) can have significant impact on the prevention and treatment of cancer while minimizing the adverse effects and limitations associated with chronic calorie restriction (CR).

The effects of CR on cancer prevention were first described more than 100 years ago (Moreschi 1909) and was followed by a large body of work demonstrating its tumor preventive effects in various animal models. However, recent studies in both mice and monkeys indicate that the effects of CR on longevity are either limited or absent and, in mice, CR can even reduce longevity (Colman et al. 2009; Mattison et al. 2012; Goodrick et al. 1990; Liao et al. 2010). The role of CR in cancer treatment is even more problematic considering that it would be extremely difficult to chronically restrict calorie intake in cancer patients. PF instead has been demonstrated to be effective in reducing pre-neoplastic lesions (Grasl-Kraupp et al. 1994) and in both cancer prevention and treatment, particularly in combination with cytotoxic drugs (Grasl-Kraupp et al. 1994; Brandhorst et al. 2015; Lee et al. 2012). PF protects normal cells/tissues from chemotherapy-induced toxicity (Lee et al. 2010; Raffaghello et al. 2008) while simultaneously increasing its therapeutic efficacy on a wide variety of malignant cells (Lee et al. 2012; Safdie et al. 2012). Newly designed dietary compositions aimed at inducing fasting-like effects that allow nourishment are slowly emerging as potential therapies to delay aging-associated diseases such as cancer (Brandhorst et al. 2015). These fasting-mimicking diets (FMD) and PF also promote

multisystem regeneration and rejuvenation by promoting the self-renewal of stem cells and the generation of white blood cells (Brandhorst et al. 2015; Cheng et al. 2014). Thus, novel and periodic forms of extreme DR as well as targeted reductions in specific macronutrients, and a combination of both, are likely to replace the original balanced and chronic restriction of all calorie sources.

2 Conserved Role of Nutrient-Sensing Signaling Pathways in Life span and Stress Resistance

Fluctuations in food availability force most organisms into periods of drastically reduced caloric intake or even starvation. Whereas a sufficient nutrient supply enables growth and proliferation, periods of very low food availability, or the lack of specific macromolecules, activate alternative metabolic modes allowing organisms to remain protected against damage that could negatively affect fitness (Madia et al. 2009; Harrison and Archer 1989). High cellular growth rates and high stress protection rarely coexist, indicating that cells invest energy in either one or the other. In fact, when nutrients are abundant, the activation of nutrient-sensing signaling cascades promotes cellular growth while when they are scarce the down-regulation of these signaling pathways blocks cellular proliferation and activates stress resistance transcription factors which negatively regulate these pro-aging pathways (Fontana et al. 2010; Longo 1999; Guarente and Kenyon 2000; Kenyon 2001; Longo and Finch 2003). Over the last 20 years, diet-based approaches have been combined with genetic approaches to identify the genes and pathways that mediate nutrient-dependent effects on longevity and health span.

The most studied form of diet-based antiaging interventions is CR, which commonly describes a 20–40 % reduction in calorie intake. DR instead can also refer to restrictions of particular macromolecular components of the diet, without affecting daily calorie intake (e.g., low protein compensated with high fat). Alternate-day fasting (ADF), also often described as intermittent fasting (IF), is another well-studied and beneficial form of DR discussed in detail elsewhere. Finally, PF is distinct from ADF/IF as meal frequency is interrupted and caloric intake drastically reduced for periods generally ranging from 48 h to 3 weeks. In addition to CR, some forms of IF and PF have been shown to promote stress resistance and longevity in model organisms ranging from unicellular yeast to mammals, indicating that the molecular mechanisms responsible for the protective effects of CR have likely evolved billions of years ago and are partially conserved in many species (Fontana et al. 2010; Longo and Mattson 2014).

In the prokaryote *E. coli*, lack of glucose or nitrogen (comparable to protein restriction in mammals) increases the resistance to high levels of hydrogen peroxide (Jenkins et al. 1988). The complete lack of nutrients also extends the longevity of bacteria, which can be reversed by adding to the medium various nutrients except for acetate, a carbon source associated with starvation conditions (Gonidakis et al. 2010). In the yeast *S. cerevisiae*, cells switched from standard growth medium to water display a twofold increase in chronological life span and a major increase in resistance against oxidative insults and heat stress (Lee et al. 2012; Fabrizio and Longo 2003). Reducing the concentration of glucose from 2 to 0.5 % in the

growth media can have similar, although less efficient effects on stress resistance (Longo et al. 1997; Wei et al. 2008). PF in yeast, which is implemented by switching yeast cells back and forth from nutrient-rich medium to water every 48 h, extends both medium and maximum longevity and increases the number of yeast cells surviving hydrogen peroxide treatment by more than 100-fold (Brandhorst et al. 2015). Although the precise mechanisms of DR-dependent life span extension in yeast are not yet fully understood, they include the down-regulation of the amino acid response Tor-S6K (Sch9) pathway and of the glucose-responsive Ras/adenylate cyclase(AC)/PKA pathway, and the activation of the serine threonine kinase Rim15 which increases stress resistance against oxidants, genotoxins, and heat shock through genes including superoxide dismutases and heat-shock proteins controlled by the transcription factors Msn2, Msn4, and Gis1 (Madia et al. 2009; Longo and Finch 2003; Fabrizio et al. 2003; Fabrizio et al. 2001). Deletion of these transcription factors reverses the protective effects of glucose restriction, demonstrating their requirement for maximum protection (Wei et al. 2008). Surprisingly, the deletion of Rim15, or of its downstream stress response transcription factors Msn2/4 and Gis1, does not prevent the life span effects of PF (Brandhorst et al. 2015). These results indicate that PF can protect simple organisms from toxins and aging by mechanisms that are in part independent of conserved pro-longevity transcription factors.

The protective effects of food restriction/starvation on the unicellular *E. coli* and *S. cerevisiae* are also observed in multicellular organisms. In the fruit fly *D. melanogaster*, dilution or reduction of food have been shown to extend life span, although intermittent food deprivation does not (Grandison et al. 2009; Piper and Partridge 2007). The fasting-induced protection against oxidative stress in flies is mediated by the repression of translation (consistent with energy diversion from cellular growth to protection) through increased expression of d4E-BP downstream of the PI3K/Akt/dFOXO3 pathway (Tettweiler et al. 2005; Villa-Cuesta et al. 2010). Of note is that moderate DR does not protect flies against the oxidative damage caused by re-oxygenation injury whereas a more stringent DR does (Vigne and Frelin 2007). Mutations in the insulin receptor substrate *chico* extend life span in *D. melanogaster* although its role in stress resistance remains unclear (Clancy et al. 2001; Giannakou and Partridge 2007). In the nematode *C. elegans*, CR and fasting, achieved by feeding either reduced amounts or no bacteria, also increase life span (Smith et al. 2008). Life span extension in *C. elegans* requires AMPK, a regulator of cellular glucose uptake and β-oxidation of fatty acids, as well as the stress resistance transcription factor DAF-16, analogous to Msn2/4 and Gis1 in yeast and FOXOs in *D. melanogaster* and mammals (Greer et al. 2007). Fasting every other day also increases oxidative stress resistance in *C. elegans* and increases life span by up to 56 % via modulation of the RHEB-1 and TOR signaling pathway, which are linked to DAF-16 (Weinkove et al. 2006; Honjoh et al. 2009). Conversely, excessive glucose shortens the life span of *C. elegans*, in part by decreasing DAF-16 activity (Lee et al. 2009). In adult *C. elegans*, mutations in age-1 (PI3K homolog) and daf-2 (insulin/IGF-1 receptor homolog) result in a 65–100 % life span extension by decreasing AKT-1/AKT-2 signaling, and by activating DAF-16, which is also associated with resistance to oxidative and ER stress (Johnson 1990; Paradis et al. 1999; Hsu et al. 2003; Henis-Korenblit et al. 2010).

Orthologues of the genes regulating life span and stress resistance in *S. cerevisiae* and *C. elegans* downstream of the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis regulate stress resistance and/or life span in mice (Coschigano et al. 2003; Holzenberger et al. 2003; Bonkowski et al. 2009; Selman et al. 2009; Brown-Borg 2009). In laboratory mice, mutations in the insulin-GH/IGF-1 axis increase life span by up to 150 % and conversely, mice that overexpress GH have a shortened life span (Brown-Borg et al. 1996; Murakami 2006; Bartke et al. 2002). In agreement with the findings in lower eukaryotes, cultured cells derived from long-lived mice with deficiencies in the GH/IGF-1 axis have higher resistance against H_2O_2-induced oxidative stress, UV, genotoxins, as well as heat- and cadmium-induced stress (Murakami 2006; Salmon et al. 2005). Vice versa, activities of the antioxidant enzymes superoxide dismutases and catalase decrease in murine hepatocytes exposed to GH or IGF-1 and in transgenic mice overexpressing GH (Brown-Borg and Rakoczy 2000; Brown-Borg et al. 2002). IGF-1 sensitizes primary neurons to oxidative stress through Ras/Erk-dependent mechanisms (Li et al. 2008), and experiments in rat primary glia and mouse fibroblasts suggest that IGF-1 exposure sensitizes these cell types against oxidative damage and chemotherapeutic drugs (Lee et al. 2010). In addition, IGF-1 attenuates the cellular stress response and the expression of stress response proteins HSP72 and heme-oxygenase in rats (Sharma et al. 2000).

In mammals, various forms of partial or complete food deprivation have been investigated that range from daily 20–40 % CR, intermittent fasting (IF, including alternate-day fasting, ADF), and PF. The multisystemic benefits of CR on rodent life span have been extensively studied and are beyond the scope of this review. Generally, CR increases rodent life span by up to 60 % and delays the occurrence of many chronic diseases including cancer and improves stress resistance (Koubova and Guarente 2003; Mattson 2005; Mattson and Wan 2005). However, there is variability in the effects of CR and some genetic backgrounds do not experience a life span extension and can even display reduced longevity (Liao et al. 2010; Sohal and Forster 2014), likely because of trade-offs between effects on aging and effects on systems which may benefit from a higher calorie intake and/or fat level (Rikke et al. 2010). In mice, the longevity effects of CR involve reduced activity of the GHR/IGF-1 pathways since CR does not further extend the life span of GH signaling-deficient mice (Bonkowski et al. 2009; Arum et al. 2009). CR is associated with reduced oxidative stress and cellular proliferation (Youngman 1993; Sohal and Weindruch 1996) while enhancing DNA repair processes and autophagy (Weraarchakul et al. 1989; Cuervo et al. 2005; Wohlgemuth et al. 2007). CR effectively reduces the levels of plasma insulin, cholesterol, triglycerides, growth factors such as IGF-1, and inflammatory cytokines (Mahoney et al. 2006; Matsuzaki et al. 2001). CR also elevates plasma high-density lipoprotein levels, resulting in a reduced risk for atherosclerosis, diabetes, and obesity (Paoletti et al. 2006; Larson-Meyer et al. 2008). In a mouse model of DR-induced stress resistance, restriction of sulfur amino acids increased hydrogen sulfide production and the protection from oxidative damage induced by hepatic reperfusion injury (Hine et al. 2015). Of note, a severe restriction of dietary protein can extend the life span of rodents by up to 20 %, independently of the caloric intake (Pamplona and Barja 2006). Reduced levels of serum IGF-1 in rats and mice fed with protein-restricted diets might explain the beneficial effects on longevity (Sonntag et al. 1999; Brandhorst et al. 2013). Reducing protein intake and

IGF-1 signaling also significantly reduces the incidence and progression of breast cancer and melanoma in murine models of tumor progression (Levine et al. 2014).

In rodents, the most studied fasting method has been IF which promotes protection against multiple diseases and causes a major reduction in the incidence of lymphomas (Goodrick et al. 1990; Mattson and Wan 2005; Descamps et al. 2005; Mattson 2012). The effects of alternate-day fasting on longevity in rodents depend on the species and age at diet initiation and can range from negative effects to as much as an 80 % life span extension (Goodrick et al. 1990; Arum et al. 2009; Goodrick et al. 1982). Similar to CR, IF increases the survivorship and improves insulin sensitivity of male wild-type mice, but fails to affect either parameter in GHR-KO mice (Arum et al. 2009). The major differences between IF and PF in mice are the duration and frequency of the fast. IF cycles usually last 24 h and are separated by one day of normal food intake (alternate-day fasting), whereas PF cycles last 2 or more days and are at least 1 week apart to allow for regaining of normal weight (Longo and Mattson 2014). Additional differences include the molecular changes caused by these fasting regimes on a variety of growth factors and metabolic markers, since IF causes more frequent but less pronounced changes than PF. Although less studied than IF, PF has been shown to have potent effects on cellular protection. PF for 48–60 h prior to etoposide induced lethal oxidative stress causes a significant increase in survival in three different mouse strains (Raffaghello et al. 2008). Similarly, 72 h of food deprivation before exposure to lethal doses of the chemotherapeutic drug doxorubicin, which causes oxidative stress-induced cardiotoxicity, protects CD-1 mice (Lee et al. 2010). Following ischemic reperfusion, which is associated with the production of reactive oxygen species in the affected tissue, fasting demonstrates protective effects in the mouse kidney and liver, rat brain as well as human liver against reperfusion injury (Mitchell et al. 2009; van Ginhoven et al. 2009; Verweij et al. 2011). Traumatic brain injury followed by fasting has neuroprotective effects, reduces oxidative damage, and improves cognitive function (Davis et al. 2008).

Despite its advantages, the extreme nature of prolonged water-only fasting could cause adverse effects, such as the exacerbation of previous malnourishments and dysfunctions. These concerns are now being addressed through the implementation of newly designed dietary interventions aimed to induce PF-like effects while minimizing the risk of adverse effects and the burden of complete food restriction. In C57Bl/6 mice, a 4-day-long diet that mimics the effects offasting (fasting-mimicking diet, FMD) has been shown to lower blood glucose levels by 40 % and IGF-1 by 45 %, while increasing ketone bodies ninefold and IGFBP-1, which inhibits IGF-1, eightfold by the end of the FMD. The FMD extends health span and longevity, promotes hippocampal neurogenesis, lowers visceral fat, reduces skin lesions, rejuvenates the immune system, and retards bone mineral density loss in old mice (Brandhorst et al. 2015). The FMD started at middle age reduces tumor incidence, delays cancer onset, and causes a major reduction in the number of lesions, which may reflect a general switch from malignant to benign tumors.

Together, results from the range of studies and organisms described above indicate that enhanced stress resistance is a highly conserved phenotype of starved and long-lived organisms, which is in part mediated by reduced signaling through the GH and IGF-1 axis.

3 The Physiological Response to Fasting in Mammals

Mammals undergo distinct metabolic changes when deprived of food that are different from that of CR (Wang et al. 2006; Lee and Longo 2011). The post-absorptive phase, lasting for 10 or more hours after food ingestion involves the utilization of glycogen as the main stored energy source. Following the depletion of the hepatic glycogen storage, amino acids serve as gluconeogenic substrates while the brain consumes most of the remaining glucose. After about 72 h of fasting, serum glucose levels can reach 50–60 mg/dL in a healthy person, but return to normal levels within 30 min after oral administration of 100 g glucose (Unger et al. 1963). Glycerol and fatty acids are released from the adipose tissue and as a result, acetoacetate, β-hydroxybutyrate and acetone become the main carbon sources within a few days of fasting. During the last phase of prolonged food deprivation, the fat storage is eventually exhausted and muscles are being degraded to allow gluconeogenesis. In rats, this occurs after 4–5 days but does not result in a major increase in glucose levels (Wang et al. 2006). For humans, it is estimated that a 70-kg person can obtain basal caloric requirements from fat reserves for up to 2–3 months of fasting (Cahill and Owen 1968; Cahill et al. 1968), leading to an initially rapid weight loss that subsequently tapers off. During the first week of fasting, an average of 0.9 kg/day is lost, followed by a 0.3-kg/day weight loss by the third week of fasting, resulting in an approximately 20 % body weight loss after 30–35 days of fasting (Kerndt et al. 1982). Thus, PF is generally feasible and tolerable, but may be accompanied by side effects, such as headaches, light-headedness, nausea, weakness, edema, anemia, and amenorrhea (Bloom 1959; Runcie and Thomson 1970; Drenick and Smith 1964).

In accordance with the systemic effects of fasting, a plethora of extrinsic and intrinsic growth factors is affected, including mediators of evolutionarily conserved pathways that promote stress sensitivity and aging, such as IGF-1 (Fontana et al. 2010; Longo and Mattson 2014). IGF-1 levels decrease by up to 65 % following 120 h of PF in humans despite increased GH secretion (Ketelslegers et al. 1995; Underwood et al. 1994; Moller and Jorgensen 2009; Maccario et al. 2001) due to the increase in IGFBP-1, which decreases IGF-1 bioavailability and prevents the feedback inhibition of GH secretion by IGF-1 (Zapf et al. 1995). In humans, GH levels eventually decrease after 3–10 days of fasting and level off (Merimee and Fineberg 1974; Palmblad et al. 1977). In mice, PF (24–72 h) decreases IGF-1 level by 70 % and is associated with a 11-fold increase in IGFBP-1 (Lee et al. 2010; Tannenbaum et al. 1979; Frystyk et al. 1999), reduced protein synthesis, reduced AKT activity, reduced mTOR/S6K, increased 4E-BP1 activity, and increased FOXO-1, FOXO-3, and FOXO-4 (Sans et al. 2004; Imae et al. 2003).

Starving mice or mammalian cells triggers autophagy in various tissues, which is regulated by several genes that also regulate aging and stress resistance, such as AMPK, mTOR, and sirtuins (Kroemer et al. 2010; Marino et al. 2010; Morselli et al. 2009). Oncogenic signaling, e.g., through PI3K and Akt, has been shown to inhibit autophagy, whereas tumor suppressors such as PTEN and TSC2 can trigger autophagy (Morselli et al. 2009). Autophagy is elevated in many cancer cells and increases the resistance of cancer cells to chemotherapy (Morselli et al. 2009). Increased autophagy has been hypothesized to be mediated by ammonia as a by-product of glutaminolysis occurring in the mitochondria of

malignant cells undergoing the Warburg effect to supply biosynthetic precursors required for their high proliferation rate (Vander Heiden et al. 2009). Therefore, autophagy triggered by fasting may be beneficial to normal cells but detrimental to malignant cells.

4 DR, Fasting and Cancer Treatment

Tumors arise over time from the combination of DNA damage and mutations associated with changes in the environmental niche surrounding precancerous cells (Hanahan and Weinberg 2011). Not surprisingly, aging is the major risk factor for the development of many cancer types (DePinho 2000; Campisi et al. 2011). Studies on caloric intake that delay organismal aging emphasize the preventive role of CR in cancer establishment. Over a century ago, the first direct relationship between chronic CR and the prevention of tumor transplantation in mice was demonstrated (Moreschi 1909). Subsequently, a multitude of studies has established that CR reduces the progression of spontaneous or induced tumors in various animal models (Tannenbaum 1996; Tannenbaum 1940; Berrigan et al. 2002; Hursting et al. 1994). Further, CR has also been shown to reduce the cancer incidence in rodents. Roy Walford and Richard Weindruch reported that CR beginning either at the time of weaning or at 12 months of age increased life span, delayed immunologic aging in laboratory mice, and reduced spontaneous cancer incidence by more than 50 % (Weindruch and Walford 1982; Weindruch et al. 1986). In a multitude of auto- and xenograft tumor models, CR causes potent antigrowth effects, although some cell lines remain resistant. Resistance to CR has been associated with mutations that cause the constitutive activation of the phosphatidylinositol-3-kinase (PI3K) pathway; substitution of the mutant allele of PI3K with wild-type PI3K reestablishes a DR-sensitive cancer cell (Kalaany and Sabatini 2009).

Support for the potential application of CR in humans arose from a 20-year longitudinal adult-onset 30 % CR study in rhesus monkeys which decreased cancer incidence by 50 % and reduced mortality (Colman et al. 2009). These findings, however, have to be analyzed carefully as a CR regimen implemented in young and older age rhesus monkeys at the National Institute on Aging (NIA) has not improved survival outcomes (Mattison et al. 2012). Whether or not CR has the potential to reduce cancer incidence in humans remains largely unclear, although CR can reduce clinical markers associated with cancer if it also involves protein restriction (Longo and Fontana 2010). Despite data indicating benefits in cancer prevention at least in certain mouse genetic backgrounds, the use of CR in therapy is problematic in part because it would be extremely difficult to chronically restrict cancer patients even if a benefit was demonstrated. Further, chronic CR merely delays the progression of the disease (Mukherjee et al. 2004; Bonorden et al. 2009), and its effectiveness might be reduced to a subset of CR-responsive cancers (Kalaany and Sabatini 2009). In addition, in mice chronic CR is associated with weight loss, delayed wound healing, and impaired immune function, all of which may impose a significant risk to cancer patients receiving chemotherapy, surgery or immunity-based treatments, or who are at risk for losing weight and becoming frail and cachectic (Fontana et al. 2010; Kristan 2008; Reed et al. 1996; Kim and Demetri 1996).

Data suggest that PF (mice for 48–72 h, humans 4–5 days) may induce metabolic changes which delay the growth of damaged cells, without the negative side effects and limitations

associated with chronic CR. In rats, fasting for 8 days or 40 % CR for 3 months, reduces pre-neoplastic liver masses by 20–30 %. Putative pre-neoplastic liver foci have significantly lowered DNA replications but increased apoptosis during PF, resulting in the reduced number and volume of putative pre-neoplastic liver foci by 85 % throughout the following 17 months (Grasl-Kraupp et al. 1994). However, in contrast to the protective effect of chronic CR on carcinogenesis (Tagliaferro et al. 1996), fasting followed by refeeding sustained tumor initiation in the rat liver enhances the growth of aberrant crypt foci in the colorectal mucosa and mammary tumors even by otherwise non-initiating carcinogen doses (Premoselli et al. 1998; Sesca et al. 1998; Tessitore et al. 1999). Given that the refeeding phase is associated with increased cellular proliferation in the liver and colorectal epithelium (Brandhorst et al. 2015; Cuervo et al. 2005), exposure to carcinogens during this period might explain these effects. Therefore, it is of importance to consider that normal food intake following PF should be initiated once the half-life of potential carcinogens indicates its expiration. Despite these caveats, PF has been shown to have potent protective effects in cancer treatment, in part due its impact on host metabolism. PF decreases blood glucose in mice by up to 75 % whereas long-term CR or IF cause a 15 % reduction (Longo and Mattson 2014; Lee and Longo 2011); this seems of particular importance given the glucose dependent phenotype of many cancer cells (Vander Heiden et al. 2009; Warburg 1956). PF reduces the pro-proliferative growth factor IGF-1 by up to 75 % (Lee et al. 2010; Underwood et al. 1994), while chronic CR causes a 25 % IGF-1 reduction in mice (Barger et al. 2008) and has no impact on IGF-1 levels in humans unless combined with protein restriction (Fontana et al. 2008). Furthermore, chronic DR with protein restriction only causes a 30 % reduction in IGF-1 for humans (Fontana et al. 2008).

5 Differential Stress Resistance by Fasting

As described above, PF inactivates partially conserved pro-proliferative pathways and increases resistance to oxidative and other stresses in lower eukaryotes, whereas the constitutive activation of analogous pathways play central roles in promoting cancer. Ras and Akt function in signal transduction pathways that are frequently found in a constitutively activated form in cancer cells (Kinzler and Vogelstein 1996; Hanahan and Weinberg 2000; Medema and Bos 1993). The connection between (de-regulated) cellular proliferation and stress resistance provides the theoretical foundation for a fasting-induced differential protection of normal cells from chemotoxicity (differential stress resistance, DSR). DSR is based on the hypothesis that in response to fasting, normal cells enter a stress-resistant state (Raffaghello et al. 2008; Longo et al. 1997) characterized by reduced/lack of cell divisions and the utilization of metabolites generated from the breakdown of fats, proteins and organelles. Self-sufficiency in growth signals enabled by gain-of-function mutations in oncogenes (e.g., Ras, Akt, mTOR) grants constitutive activation of proliferation pathways and together with loss-of-function mutations in tumor-suppressor genes (e.g., Rb, p53, PTEN) allows cancer cells to disregard antiproliferative signals such as those occurring during fasting, thereby prohibiting malignant cells to enter a nondividing and protected state (Hanahan and Weinberg 2000). The inability of cancer cells to respond to antigrowth signals or to grow in the absence of growth factors, a well-established hallmark of cancer, prevents the protective effect of fasting regardless of the type of cancer or oncogene mutations (Lee

and Longo 2011). DSR therefore presents a method to preferentially target malignant cells with chemotherapy and other drugs (Raffaghello et al. 2008) while increasing the resistance against cytotoxic stressors through cell detoxification systems in normal dividing and/or nondividing cells. In fact, fasting induces the protection against lethal doses of the chemotherapeutic drug etoposide in A/J, CD-1, and athymic nude mice (Raffaghello et al. 2008). In a different set of experiments, CD-1 mice were protected from high-dose doxorubicin, known to cause cardiotoxicity (Lee et al. 2010). Analogously, transgenic mice with a conditional liver-specific IGF-1 gene deletion (LID), which results in a 70–80 % reduction in circulating IGF-1 levels, show enhanced protection to cytotoxic chemotherapy drugs including cyclophosphamide, doxorubicin, and 5-FU, although they are not protected against the topoisomerase inhibitor etoposide (Lee et al. 2010). Studies in mice demonstrate that restoring IGF-1 to normal levels during fasting reverses the protection against lethal doses of doxorubicin (Lee et al. 2010). Similarly, three days of fasting protects FabplCre;$Apc^{15lox/+}$ mice, which spontaneously develop intestinal tumors, against the side effects of a high dose of irinotecan whereas ad libitum-fed mice experience weight loss, reduced activity, ruffled coat, hunched-back posture, diarrhea, and leukopenia (Huisman et al. 2015). Fasting reduces the delayed-type chemotherapy-induced nausea and vomiting in cancer-bearing dogs receiving doxorubicin (Withers et al. 2014). The protective effect of fasting can promote potent changes even to the stem cell population: PF represses the immunosuppression and mortality caused by cyclophosphamide through signal transduction changes in long-term hematopoietic stem cells and niche cells that promote stress resistance, self-renewal, and lineage-balanced regeneration (Cheng et al. 2014), in agreement with preliminary data on the protection of lymphocytes from chemotoxicity in fasting patients (Safdie et al. 2009). Fasting has been shown to also promote regenerative effects in both the blood and other systems including the nervous system, muscle and liver indicating that, in addition to protecting against the toxicity of cancer drugs, it can stimulate the generation of healthy cells and tissue damaged by the therapy (Brandhorst et al. 2015; Cheng et al. 2014).

6 Differential Stress Sensitization of Cancer Cells by Fasting

Malignant cells are generated in a high nourishment environment and, therefore, thrive in environments resembling those in which they have evolved. Cancer cells generally prefer high levels of glucose to rely on glycolysis more than on oxidative phosphorylation (Warburg effect), which provides energy and biosynthetic precursors essential for proliferation (Vander Heiden et al. 2009). Glycolysis allows the metabolism of glucose-6-phosphate in the pentose shunt pathway, which provides substrates essential for nucleotide synthesis and NADPH production. The Warburg effect may restrict cytochrome c-mediated apoptosis, thereby favoring tumor cell survival and apoptosis evasion through decreased respiration (Vaughn and Deshmukh 2008; Ruckenstuhl et al. 2009). However, glucose alone does not supply all the building blocks required for cellular proliferation and cancer cells therefore depend on amino acids, particularly glutamine, as a nitrogen source (Vander Heiden et al. 2009). Glutamine, the circulating amino acid with the highest concentration in humans, plays a crucial part in the uptake of essential amino acids and can support NADPH production, making it necessary for lipid and nucleotide biosynthesis (Nicklin et al. 2009). Similarly to the effects of CR, protein/amino acid restriction have been demonstrated to

increase longevity and to delay the onset of many aging-related diseases, including cancer (Mirzaei et al. 2014). The major reduction in circulating glucose and amino acids during fasting is a significant disadvantage to tumor cells that usually experience an almost unlimited supply through the bloodstream.

The same mutations that cause tumor cells to remain locked in a pro-growth mode render them also sensitive to alterations in the cellular environment. In evolutionary biology, it is well established that most acquired mutations become disadvantageous. The mutations generated in cancer cells are also mostly deleterious although such negative effects may not be observable until the cancer cells are in an environment that exposes that detrimental effect. For example, a mutation that requires high levels of glutamine would not be problematic to cancer cells until the concentration of glutamine becomes limited. In *S. cerevisiae*, expression of the oncogene-like RAS2val19 not only reverses the (water-) starvation induced protection against hydrogen peroxide and menadione, the constitutive activation of Ras sensitizes yeast cells compared to wild-type cells, a phenomenon called differential stress sensitization (DSS) (Lee et al. 2012).

In vitro models of fasting (by reducing glucose and/or serum availability in the growth medium) sensitize murine, rat and human glioblastoma multiforme cells, but not primary mixed glia, to temozolomide chemotherapy (Safdie et al. 2012). Similarly, fasting sensitizes 15 of 17 human and rodent cancer cell lines to the chemotherapeutic agents' doxorubicin and/or cyclophosphamide (Lee et al. 2012), while serum starvation alone is sufficient to induce sensitization to cisplatin in human mesothelioma and lung carcinoma cells (Shi et al. 2012). In a metastatic mouse neuroblastoma model, fasting for 48 h followed by a single administration of high-dose chemotherapy, but not either treatment alone, successfully improves survival limited by both drug toxicity and metastases and results in long-term cancer-free survival (Lee et al. 2012). In subcutaneous mouse models of melanoma and breast cancer, fasting cycles are as effective as chemotherapy alone while the combination of both treatment modalities significantly improves treatment efficacy (Lee et al. 2012). Similarly, fasting prior to gemcitabine injection significant decreases the progression of pancreatic cancer tumors by more than 40 %, in part through increased gemcitabine uptake of malignant cells (D'Aronzo et al. 2015). PF in combination with cisplatin for three weeks reduces the progression of mesothelioma by more than 60 % compared to the untreated control and a complete remission was observed in 60 % of the combination-treated mice (Shi et al. 2012). 48 h of PF also sensitizes both subcutaneous and intracranial glioma models to radio- and chemotherapy (Safdie et al. 2012), an effect not mimicked by dietary protein restriction alone (Brandhorst et al. 2013). 48 h of starvation, with or without oxaliplatin, reduces the progression of CT26 colorectal tumors through the down-regulation of aerobic glycolysis and glutaminolysis, while increasing oxidative phosphorylation in complex I and II of the mitochondrial electron transport chain, thereby resulting in reduced ATP production, increased oxidative stress, and apoptosis (Bianchi et al. 2015). In murine 4T1 breast cancer cells, PF increases the phosphorylation of the stress-sensitizing Akt and S6 kinases and is associated with increased oxidative stress, caspase-3 cleavage, DNA damage, and subsequent apoptosis (Lee et al. 2012), whereas the PF-induced activation of the ATM/Chk2/p53 signaling cascade is AMPK dependent and sensitizes mesothelioma cells to cisplatin (Shi et al. 2012). In breast cancer and melanoma cells fasting causes the

sumoylation of the specialized DNA polymerase REV1 by SUMO2/3, resulting in the relief of REV1's inhibition of p53 and enhancing p53's effects on pro-apoptotic gene expression and apoptosis (Shim et al. 2015).

Many oncogenes are tyrosine kinases and thus provide a target for cancer treatment. PF potentiates the growth inhibiting efficacy of commonly administered tyrosine kinase inhibitors, such as erlotinib, gefitinib, lapatinib, crizotinib, and regorafenib, in in vitro and xenograft models by inhibiting the MAPK signaling and E2F-dependent inhibition of transcription (Caffa et al. 2015). In a non-small cell lung cancer xenograft model, subcutaneous tumor growth was effectively reduced by crizotinib or fasting whereas the combination of fasting with crizotinib was the most efficient treatment option. Similar results have been demonstrated in a colorectal cancer xenograft model for the combination of fasting with regorafenib (Caffa et al. 2015). These results demonstrate the dependence of malignant cells on steady levels of glucose, amino acids, and growth factors and indicate that reducing these factors may protect the organism while reducing tumor progression, particularly in combination with chemotherapy, by generating a challenging environment for the survival of the cancer cell.

Different molecule classes, including antisense RNA, monoclonal antibodies, and dominant negative IGF-1R gene variants have been employed toward this aim (Bahr and Groner 2004), and at least 12 different IGF-1R targeting compounds, including small antagonistic molecules and antibodies, have entered clinical trials (Gualberto and Pollak 2009). These agents have been able to reverse the transformed phenotype in several rodent and human cancer cell lines and, in analogy to fasting, sensitized cancer cells to conventional chemotherapeutic treatment and irradiation (Bahr and Groner 2004). However, IGF-1R blockade did not yield positive results in human trials, possibly because it also interferes with the positive function of IGF-1 in the proliferation of normal cells including stem and immune cells. In contrast, fasting promotes reduced levels of glucose and IGF-1 which return to the normal range after refeeding therefore generating an ideal environment to negatively affect the growth and survival of cancer cells but not that of normal cells.

7 Clinical Efficacy of Fasting

Several studies indicate that fasting has the potential to prevent and treat diseases and promote health in humans. For example, a water-only fast lasting 10–14 days followed by a low-fat, low-sodium vegan-based refeeding period (approximately 6–7 days on average) reduces systolic blood pressure points more than twofold compared to a combined vegan low-fat, low-salt diet and exercise (Goldhamer et al. 2001; Goldhamer 2002). Consuming a very-low-calorie diet of 350 kcal/day (an almost fasting-like approach) has been considered safe in a large cohort with over 2000 participants with chronic diseases, providing evidence that the very-low-calorie diet may protect against several diseases (Michalsen et al. 2005). Additionally, in a randomized clinical trial to evaluate the effects of 2 days of IF (500 kcal/day) a week on weight loss and metabolic disease risk markers in young overweight women found that both chronic CR and IF are equally efficient in reducing biomarkers associated with disease risk (Harvie et al. 2011). Fasting has also been proposed to protect patients

from ischemic reperfusion damage following surgery, in which oxidative stress is largely responsible for the damage (Mitchell et al. 2009; van Ginhoven et al. 2009).

Although no randomized clinical trials are (yet) available to evaluate the effect of CR, IF or PF in cancer prevention, preclinical and clinical research supports the potential application in prevention and treatment of human cancers. PF, or fasting-like dietary regimen, can have pronounced effects on IGF-1, insulin, glucose, IGFBP1, and ketone body levels, thereby generating a protective environment for normal cells while creating a metabolic environment that does not favor precancerous and/or cancer cells (Barger et al. 2008; Mercken et al. 2013). In a pilot clinical trial, three monthly FMD cycles decreased risk factors/biomarkers for aging, diabetes, cardiovascular disease, and cancer without major adverse effects, providing support for the use of FMDs to promote health span (Brandhorst et al. 2015). Although not significant, the percentage of mesenchymal stem and progenitor cells in the peripheral blood mono-nucleated cell population showed a trend to increase at the end of FMD, in line with the results obtained in mice (Brandhorst et al. 2015). In these study participants, fasting blood glucose and IGF-1 levels were significantly reduced and remained lower than baseline levels even after resuming their normal diet following the final FMD cycle. Elevated circulating IGF-1 is associated with increased risk of developing certain malignancies (Giovannucci et al. 2003; Smith et al. 2000). In a population-based study of over 6000 American adults, respondents of 50–65 years that reported high protein intake had the highest circulating IGF-1 levels and experienced a 75 % increase in overall mortality and a fourfold increase in cancer death risk during the following 18 years compared to the low-protein/low-IGF-1 cohort (Levine et al. 2014). However, it is important to note that high protein intake was associated with reduced cancer and overall mortality in respondents over 65, indicating that high protein intake may be beneficial in older adults or at least that older adults reporting a low-protein diet are malnourished, frail, and sick (Levine et al. 2014; Dickinson et al. 2014). Although severe IGF-1 deficiency caused by growth hormone receptor deficiency (GHRD) known as Laron’s syndrome leads to growth defects in humans, individuals with GHRD rarely develop cancer (Guevara-Aguirre et al. 2011; Steuerman et al. 2011).

In cancer treatment, preliminary studies of 10 patients with a variety of malignancies that voluntarily fasted for up to 180 h in combination with their prescribed chemotherapy indicate a reduction in common chemotherapy-associated side effects such as vomiting, diarrhea, fatigue and weakness, and in the cases where cancer progression could be followed, there was no evidence that fasting protected tumors or interfered with chemotherapy efficacy (Safdie et al. 2009). Analogous to the effects of fasting on the immune system in mice, the results from a phase I clinical trial indicate that 72 but not 24 h of PF in combination with chemotherapy were associated with normal lymphocyte counts and maintenance of a normal lineage balance in white blood cells (Cheng et al. 2014; Safdie et al. 2009). In a pilot study, 7 out of 13 women diagnosed with HER2-negative stage II/III breast cancer were randomized to fast 24 h before and 24 h after receiving neo-adjuvant (docetaxel/doxorubicin/cyclophosphamide) chemotherapy (de Groot et al. 2015). Fasting was well tolerated and protected from the chemotherapy-dependent reduction in erythrocyte and thrombocyte counts and possibly DNA damage in healthy cells compared to the non-fasted group. The study observed no changes in leukocyte or neutrophil counts which may

be associated with a pegfilgrastim-induced production of white blood cells. Notably, the use of the antiemetic drug dexamethasone may explain the observed glucose increase despite 24 h of starvation and likely attenuated some metabolic benefits of starvation, e.g., a more prominent reduction in IGF-1 (de Groot et al. 2015). However, 48 h of fasting may not be sufficient to optimize the differential stress resistance or sensitization of normal and malignant cells. A number of clinical trials are now addressing the effects of fasting or fasting-mimicking diets on humans and the diet-induced protection of patients from the side effects of chemotherapy while sensitizing cancer cells to the treatment (Table 1).

8 Conclusions

CR has been known to have major health benefits in the vast majority of laboratory animal models. However, chronic CR is not feasible for the great majority of subjects and it often causes detrimental effects, possibly by negatively affecting the immune system, wound healing, and other important functions. PF but particularly higher calorie fasting-mimicking diets have the potential to promote the beneficial effects of CR, while reducing or eliminating adverse effects, and minimizing the burden of chronic restriction or of diets requiring drastic changes several times a week or every other day. The constitutive activation of nutrient signaling pathways which promotes the growth of cancerous cells might also be their Achilles' heel since they allow the use of fasting to promote the protection of normal cells and organs and sensitization of cancer cells, thus generating a wide-acting, consistent, and inexpensive strategy to increase therapeutic index.

Taken together, these results indicate that PF and FMD have the potential to play an important complementary role in medicine by promoting disease prevention, enhancing disease treatment, delaying the aging process, and stimulating stem cell-based regeneration.

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Table 1

Clinical trials using dietary restriction and fasting in patients with cancer

Identifier	Title	Purpose	Intervention	Location
NCT01175837	"Short-term fasting before chemotherapy in treating patients with cancer"	Assess the safety and feasibility of short-term fasting prior to administration of chemotherapy	Short-term fasting, 24–48 h	Mayo Clinic, Rochester, Minnesota, USA
NCT00936364	"Short-term fasting: impact on toxicity"	Reducing side effects in patients receiving gemcitabine hydrochloride and cisplatin for advanced solid tumors	Short-term fasting, 24–72 h	University of Southern California, Los Angeles, California, USA
NCT01304251	"Effects of short-term fasting on tolerance to chemotherapy"	Determine the effect of short-term fasting on tolerance to adjuvant chemotherapy in breast cancer patients	Short-term fasting, 24 h before and after chemotherapy	Leiden University Hospital, Leiden, Netherlands
NCT01954836	"Short-term fasting during chemotherapy in patients with gynecological cancer—a randomized controlled cross-over trial"	Assessments of adverse effects, quality of life and laboratory values	Short-term fasting, 60–72 h	Charite University, Berlin, Germany
NCT01802346	"Controlled low calorie diet in reducing side effects and increasing response to chemotherapy in patients with breast or prostate cancer"	Assessments of a low-calorie diet in reducing side effects and increasing response to chemotherapy in patients with breast or prostate cancer	Low-calorie diet 3 days prior to and 1 day after chemotherapy	University of Southern California, Los Angeles, California, USA
NCT02126449	"Dietary restriction as an adjunct to neoadjuvant chemotherapy for HER2 negative breast cancer"	Evaluate the impact of a FMD on tolerance to and efficacy of neoadjuvant chemotherapy in women with stage II or III breast cancer	FMD 3 days prior to and 1 day after chemotherapy	Leiden University Hospital, Leiden, Netherlands

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