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Abstract

Cancer is one of the most frequent causes of worldwide death and morbidity and is a major public health problem. Although, there are several widely used treatment methods including chemo-, immune- and radiotherapies, these mostly lack sufficient efficiency and induce toxicities in normal surrounding tissues. Thus, finding new approaches to mitigate side effects and potentially accelerate treatment is paramount. In line with this, increasing preclinical evidence indicates that caloric restriction (CR) and fasting might have anticancer effects by reducing tumor progression, enhancing death of cancer cells, and elevating the effectiveness and tolerability of chemo- and radiotherapies. Nonetheless, clinical studies assessing the potential of CR and fasting in cancer are scarce and inconsistent, and more investigations are still required to clarify their effect in different aspects of cancer treatment. In this review, we have summarized the findings of preclinical and clinical studies of CR and fasting with respect to efficacy and on the adverse effects of standard cancer treatments.

Keywords: cancer, caloric restriction, CR, fasting, chemotherapy, efficacy, adverse effects

1. Introduction

Non-communicable diseases such as cardiovascular disease and cancers account for the majority of deaths in the world [**1**]. In 2018, estimates indicated that 18.1 million new cases of cancer occurred, and almost 9.6 million people died from cancer worldwide [**1**]. To compound this, the incidence of cancer and related mortality is growing, and projections indicate that the mortality rate will reach 13.2 million per year by 2030[**2**]. Cancer is a multifactorial disease which can arise by non-modifiable (e.g., genetic susceptibility, age, race, and gender) and modifiable (e.g., cigarette smoking, unhealthy diet, physical inactivity, obesity, alcohol consumption, high fat diet, and radiation exposure) risk factors [**2-4**]. According to Daniel et al., 35% of the cancer-related mortality in 2001 was linked to modifiable risk factors, including obesity, and unhealthy or sedentary lifestyles [**5**]. There are many types of cancer therapeutics, although the combination of surgery for removal of the tumor mass with chemo- and/or radiation therapy is the standard and the most frequent method [**6, 7**]. Although chemotherapy enhances lifespan, this comes with considerable severe side effects due to destructive effects on normal tissues, such as myelosuppression, *alopecia totalis*, gastrointestinal mucosal injury, nausea, fatigue, vomiting, diarrhea, severe muscle wasting, excessive unbearable body pain, infertility and emotional distress, as well as death [**8-10**].

The beneficial effects of caloric restriction (CR) on life extension, disease prevention, and acceleration of treatment, have attracted the attention of researchers and clinicians [**11**]. In addition, a growing body of evidence has shown that fasting stimulates similar biological pathways as seen with CR [**12**]. CR is defined as a reduction in energy intake of usually between 20–40 %, without malnutrition, and fasting refers to complete deprivation of food except for water [**7, 13, 14**]. Fasting can be classified as intermittent or periodic, based on the duration. Intermittent fasting can be alternate-day (≥16 h) or 48 h fasting per week, and periodic fasting is typically a minimum of 3 days fasting every 2 or more weeks [**13, 14**]. The efficacy of CR and fasting in cancer may occur via indirect effects on body mass and metabolism. In the USA, estimates indicate that overweight and obesity are responsible for 14 and 20% of cancer-related mortality in males and females, respectively [**15**]. CR and fasting have effects on hormone and growth factor signaling pathways, inflammation, energy homeostasis, and vascular disturbances, in amelioration of the tumor microenvironment. In addition, fasting and CR may help to improve the efficiency and tolerability of antitumor agents [**16**]. This occurs

via a decrease in mitogenic stimuli in healthy cells and inhibitory effects on the cell cycle in cancer cells [**17, 18**]. Here, we review the evidence showing the effect of CR and fasting as a cancer treatment and on the reduction of treatment-related adverse events.

2. Systemic response to CR and fasting

2.1. Oxidative stress

The oxidative damage hypothesis of aging suggests that increased metabolism from high nutrient levels leads to generation of reactive oxygen species (ROS) that can damage cellular lipids, proteins and DNA molecules, leading to impaired cellular functions, increased genomic instability and, ultimately, cancer and decreased lifespan [**19-21**]. Conversely, lowering nutrient levels by CR or starvation is thought to retard or prevent ROS-related damage, thereby preserving cellular functions and genome stability, staving off cancer and extending health span and lifespan (**Figure 1**) [**22-25**]. These findings are consistent with those of studies which showed that premature aging diseases, such as Werner syndrome and Hutchinson Gilford Progeria syndrome, have high levels of DNA damage and corresponding low rates of DNA repair [**26, 27**]. In these conditions, the accumulation of genomic damage drives their cells into a premature senescence state, which leads to an earlier onset of age-related diseases like cancer [**28**].

Although results in the scientific literature have been mixed, it has been proposed that CR may increase health span and lifespan by causing an increase in the expression of enzymes that protect against damaging ROS [**29, 30**]. A comprehensive review found that dietary restriction in rodents had little effect on mitochondrial ROS production or antioxidant enzyme activity, but it generally led to decreased oxidative damage and increased glutathione levels [**31**]. Support for the hypothesis comes from studies which found that over-expression of antioxidant enzymes retarded age-related accumulation of oxidative damage and extended the maximum life-span of Drosophila melanogaster, and from results showing that CR lowered the levels of oxidative stress and age-associated damages, and extended the maximum life-span of some mammalian species [**29**]. However, some studies which exposed Drosophilia melanogaster to CR, found no relationship between lifespan extension and increased resistance to oxidative stress [**32**].

2.2. Hormones and metabolism

The systemic response to fasting involves changes in circulating levels of glucose and several hormones and growth factors such as insulin, insulin-like growth factor 1(IGF-1) and leptin[**33, 34**]. In the early response to fasting, insulin levels begin to decline, and glucagon levels increase, leading to increased glycogen utilization and hepatic glucose release. This also leads to breakdown of triglycerides into glycerol and free fatty acids (**Fig. 1**) [**7, 16**]. Under starvation conditions, most tissues can derive their energy requirements from fatty acids, apart from the brain which depends on glucose and ketone bodies produced from acetyl-CoA in hepatocytes [**35, 36**]. Under fasting conditions, IGF-1 levels diminish due to the elevation in IGF-binding protein-1 (IGFBP-1) levels which binds to circulating IGF-1 and thereby blocks its interaction with cell surface receptors [**37**]. In addition, fasting lowers the circulating levels of leptin, a hormone mainly produced by adipocytes that regulates energy balance and represses appetite, and heightens the levels of adiponectin, an adipokine that stimulates fatty acid breakdown and contributes to regulation of glucose levels [**38, 39**]. This highlights the complex effects of fasting and CR on the production of growth factors and hormones and the regulation of cellular energy levels.

3. Cellular responses to CR and fasting

Many studies have now demonstrated that CR and fasting increases lifespan and healthspan, and the IGF-1 signaling cascade is a crucial pathway involved in these effects (**Figure 2**) [**37, 40, 41**]. As mentioned previously, glucose is the preferential fuel of cancer cells, which have adjusted their metabolism to promote proliferation, growth and survival, and this feature is known as the Warburg effect (**Figure 3**) [**42**]. Following binding of insulin and IGF-1 to their receptors, glycolysis increases and leads to promotion of tumor cell proliferation and reduced apoptosis, and these effects can be counteracted by CR and fasting [**43**].

Under normal situations, insulin and IGF-1 activate the signaling pathways associated with proliferation including the phosphatidylinositol 3-kinase / protein kinase B / mammalian target of rapamycin (PI3K/Akt/mTORC1) and Ras/Raf/mitogen-activated protein kinase (MAPK) cascades [**44, 45**]. The PI3K/AKT/mTORC1 pathway is a master regulator of protein synthesis,

cell proliferation, and survival in response to a variety of extracellular signals. However, hyperactivation of this pathway has been observed in many types of cancers such as glioblastoma, ovarian and colon cancer [**46-49**].

CR and the resulting low levels of glucose lead to a decrease in the intracellular ATP/AMP ratio. This leads to activation of the AMP-dependent kinase (AMPK), which acts as a tumor suppressor via activation of p53 and cyclin-dependent kinase (CDK) inhibitor protein p27 [**50**]. Additionally, AMPK inhibits the mTORC1 pathway by phosphorylation of mTOR inhibitors, which decreases the proliferative activity of cells and boosts catabolic processes that repress the metabolism of fast-growing cancer cells [**50, 51**]. Also, CR up-regulates NAD^+-dependent deacetylase sirtuin-1 (SIRT1) activity, which plays an important role in energy homeostasis, muscle adaptation to nutrient deficiency and lifespan extension by deacetylation of target genes such as those encoding transcription factors Ku70, p53, and forkhead box protein O1 (FOXO1) [**52-54**]. SIRT1 also deacetylates genes encoding glycolytic enzymes, which leads to a reduction in glycolysis and elevation of hepatic glucose production [**55-57**]. Moreover, SIRT1 and AMPK positively regulate each other [**58, 59**].

CR also induces peroxisome proliferator-activated receptor-gamma (PPARγ), and expression of NF-E2-related factor 2 (Nrf2), which predominantly acts as a trigger of an anti-stress response which defends the cells against exogenous and endogenous insults via up-regulation of certain antioxidant enzymes like heme oxygenase 1, superoxide dismutase (SOD) and catalase (CAT)[**60-62**].Conversely, it has been demonstrated that lack of Nrf2 induces spontaneous tumors and promotes tumor development and metastasis[**63, 64**].Therefore, development of Nrf2 inducers may be an effective approach in anti-cancer therapeutics.

The CR-induced increase in adiponectin levels results inactivation of liver kinase B1 (LKB1) and AMPK, and reductions in PI3K/AKT, MAPK and NF-κB signaling pathways which, in turn, leads to inhibition of tumor cell adhesion, migration, and proliferation [**65-68**]. This is important as over-activation of the NF-κB-signaling pathway in tumor cells has been demonstrated to promote proliferation and angiogenesis, inhibit apoptosis and facilitate local and distant metastases [**69, 70**].

In many cancers, dysregulation of leptin and/or the leptin receptor has been found to drive cancer processes such as angiogenesis, metastasis, tumorigenesis and survival or resistance to

apoptosis [**71, 72**]. This occurs mainly via the JAK/STAT pathway which modulates PI3K/AKT3 signaling, and expression of anti-apoptotic proteins, angiogenic factors (vascular endothelial growth factor, VEGF) and hypoxia-inducible factor-1α (HIF-1α).

4. Preclinical studies of CR in cancer models

Different in vitro and in vivo studies have investigated the effects of a CR diet on various aspects of cancer. Most of these have been carried out in models of breast cancer.

4.1 Effects of CR in models of breast cancer

In a mouse model of breast cancer, the incidence of breast tumors was found to be significantly lower after chronic CR and intermittent CR, compared to a control ad libitum diet (71.0, 35.4 and 9.1%, respectively) [**73**]. Also, the intermittent CR protocolled to increased expression of the adiponectin receptor (ADIPO-R) in mammary tissue, and the levels of leptin and the leptin receptor complex were decreased. This same study suggested that the findings of the increased adiponectin/leptin ratio and reduced leptin levels were consistent with the protective effects of intermittent CR against cancer.

Similarly, another study found that chronic and intermittent CR led to significantly decreased incidence of breast tumors, with the former being more effective [**74**]. Also, the numbers and masses of the tumors were lower in both CR groups. However, mammary tumor DNA breaks were significantly higher in the intermittent CR group during a re-feeding stage of the study, compared to re-feeding in the chronic CR and control groups.

In another study, rats on normal or CR diet were given either 17β-estradiol, to induce mammary tumorigenesis, or no hormonal treatment [**75**]. The CR-treated group showed reduced mammary cancer incidence and tumor burden and elevated latency to appearance of the first palpable mammary cancer. This inhibitory effect was tissue-specific and did not affect prolactin-producing pituitary tumors, and was negatively associated with the level of circulating progesterone. In another study, a 30% reduction in calorie intake repressed mammary epithelial cell density, the proliferative index, and estrogen receptor (ER) and ErbB2 signaling in a mouse mammary tumour model [**76**]. In another model of breast cancer, neither

chronic or intermittent CR had a significant effect on levels of the oxidative stress biomarker malondialdehyde (MDA), although the chronic CR group had lower MDA levels at different time points of the study [**77**]. In addition, the chronic CR group showed increased activities of the antioxidant enzymes, SOD and CAT, compared to the other groups. In a mouse mammary tumor virus-transforming growth factor alpha (MMTV-TGF-α) breast cancer mouse model, 15% chronic and intermittent CR led to a significant elevation in serum concentrations of adropin, an energy homeostasis regulatory molecule [**78**]. The study also found that adropin treatment (50 ng/mL) for 24 h caused the initial phases of apoptosis in the Michigan Cancer Foundation-7 (MCF-7) breast cancer cell line. In an aggressive model of hormone-independent breast cancer, CR led to a significant reduction in tumor growth and lung metastasis, and the levels of blood glucose, insulin, and IGF-1 were lower than in the control group [**79**].

Other studies of CR in breast cancer models have shown effects on the expression of microRNAs (miRNAs), suggesting effects on RNA silencing and/or post-transcriptional regulation of gene expression. In a model of breast cancer liver metastasis, CR led to increased expression of miR-29b, miR-29c, and miR-30b in liver tissue and increased levels of miR-29c, miR-30a and miR-30b expression in tumor tissue [**80**]. These miRNAs are known to reduce IGF-1 expression and other members of the miR-30 class target the IGF-1 receptor. Also, CR regulated the expression of miR-200a in a model of luminal mammary cancer, and this was positively associated with tumor development with no effect on body weight [**81**]. In addition, the CR group showed a significantly reduced tumor size and increased tumor-free survival. In another mouse model of a triple-negative breast cancer tumor, CR and radiation therapy significantly downregulated the expression of both miR-17 and miR-20a, which have a regulatory role in many varieties of cancers [**82**].

It has been shown that adiponectin has a protective effect against tumor cell growth and migration [**83, 84**]. Cicekdal *et al.* showed that chronic CR in MMTV-TGF-α female mice led to a significant increase in the methylation level of *ADIPOR1*, the gene encoding ADIPO-R, compared to control group [**85**].

4.2 Effects of CR in animal models of other cancers

In a mouse model of intestinal tumorigenesis, both the CR group and a group administered a diet high in olive fruit and vegetable (OFV) showed a significantly lower frequency of

intestinal polyps than the control diet group [**86**]. In addition, both CR and OFV diets led to decreased lean and fat mass, and the levels of leptin and IGF-1 were reduced significantly in the CR group. In another trial, Ploeger *et al.* reported that exercise did not influence liver oncogenesis, whereas a CR diet protocol led to blockade of tumor formation and reduced steatosis, hepatocyte ballooning, inflammation, and immune cell infiltration, which are hallmarks of non-alcoholic fatty liver disease (NAFLD) progression to liver tumorigenesis [**87**].

Another study assessed the effects of 30% CR versus a high fat/low calcium (HFLC) diet in a mouse model of lymphoma and intestinal adenoma and carcinoma [**88**]. This revealed that the incidence of adenocarcinoma or lymphoma did not differ between two groups, but the incidence of adenomas was significantly higher in the HFLC group. Moreover, the lifespan of mice in the CR group was markedly longer compared to that of mice in the HFLC-treated group. Yoshida et al. assessed the effects of CR on radiation-induced myeloid leukaemia in two analyses [**89**]. In the first analysis, administration of a CR diet over the lifetime and post-irradiation led to a significant reduction in the spontaneous incidence of myeloid leukaemia, number of hematopoietic stem cells (HSCs), target cells for radiation-induced leukemogenesis, and the size of the cycling fraction of HSCs. In the second analysis, they found that the latency periods of myeloid leukaemia were significantly prolonged following lifetime- and post-irradiation CR treatment. Also, the survival rate was significantly higher in both groups [**90**]. In another study, CR treatment of mice with or without knockout of the antioxidant enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1) led to increased survival and decreased skin tumorigenesis [**91**], This suggested that the effect of CR on lifespan extension and tumorigenesis may occur through a pathway independent of NQO1 expression. Also, a study testing Nrf2-KO and WT mice indicated that the lifespan extension and increased insulin sensitivity induced by CR treatment was not completely a consequence of Nrf2 pathway up-regulation [**92**].

Another study found that a 60% reduction in calorie intake resulted in a decrease in the percentage of Ki-67-positive tumor cells as well as the size and density of blood vessels in a pancreatic ductal adenocarcinoma (PDA) mouse model [**93**]. Also, the progression of cancer cells from the implanted ipsilateral hemisphere into the contralateral hemisphere was lower in the CR group.

In a murine model of pancreatic cancer, intermittent CR and 25% chronic CR led to a substantial lag in the progression of pancreatic intraepithelial neoplasia to PDA which was associated with reduced levels of glucose transporter 1(GLUT1), increased expression of SIRT1, increased serum adiponectin, and decreased serum leptin [**94**]. In addition, chronic CR significantly decreased phosphorylation of mTOR compared with intermittent CR and control groups, while phosphorylation of AMPK and AKT was unaffected. In agreement with these findings, a 30% reduction in calorie intake led to a significant decrease in body weight, tumor volume, and phosphorylation of mTOR and AKT in another model of pancreatic cancer [**95**]. The same study also found that CR led to reduced levels of glucose, IGF-1 and leptin, although insulin and IGF-1 receptor levels were not altered.

In two mouse models of ovarian cancer, CR caused a significant activation of AMPK and SIRT1, and a reduction in the AKT/mTOR pathway [**96, 97**]. In addition, CR limited tumor growth and metastatic spread, and improved the levels ofcertain plasma biomarkers [i.e., IGF-1, leptin,monocyte chemoattractant protein 1(MCP-1), VEGF, interleukin 6 (IL-6), and adiponectin].

In a mouse model of prostate cancer, CR led to a reduction in final tumor weight, plasma insulin, and IGF-1 levels, although IGF-1 receptor expression did not change [**98**]. In addition, apoptosis was significantly higher in the CR group. In another prostate cancer model, CR treatment led to reduced levels of circulating insulin, IGF-1, and leptin, increased levels of adiponectin, and decreased activation of AKT, mTORC1, STAT3 and NF-κB (p65) signalling [**99**].

Aministration of CR in a murine cancer cachexia model showed higher grip strength and a trend towards higher levels of myogenin (a transcription factor involved in regulation of skeletal muscle development or repair) compared to the observation of significant wasting in the control group [**100**].

5 Effects of CRduring chemo- and radiotherapy

To investigate the protective effect of CR against chemotherapy-induced ovarian damage, rats treated with cyclophosphamide were administered a diet containing a 35% reduction in calories compared with standard chow [**101**]. In the case of the rats on standard chow, 83.3% lost their

oestrous cycle, while in the CR group this value was 41.7%. In addition, CR significantly enhanced primordial follicle reserve, induced ovarian SIRT-1, and repressed P53 expression, but had no effect on FOXO3a expression.

In a model of triple negative breast cancer, CR ameliorated the chemotherapy-induced inflammation makers TNF-α and IL-1β, and reduced insulin and IGF-1 receptor signalling pathways compared to the control diet [**102**]. Also, the CR diet led to increased overall survival and fewer lung metastases than the control diet. These findings were consistent with those of another study in mice with triple negative breast cancer which showed that CR alone and combined with radiation therapy led to down-regulation of IGF1 receptor signalling, a significant reduction in overall number and volume of lung metastases [**103**]. The CR diet also increased survival and the time to metastases progression. In a similar model, CR treatment alone and combined with radiation delayed tumor growth by 56 and 82%, respectively [**104**]. Also, tumor cell apoptosis increased following CR and radiation therapies and this was found to occur via modulation of the IGF-1 receptor signalling pathway. Liu et al. showed that following CR, chemotherapy-induced mucositis was markedly reduced with lower intestinal permeability, reduced epithelial injury, lower bacterial translocation, and higher numbers of epithelial stem cells [**105**]. The same study showed that CR regulated gut microbiota composition, particularly *Lactobacillus* and *Lachnospiraceae*, which play an important role in relieving inflammation and promotion of gut barrier function.

6 Preclinical studies of fasting in cancer models

The efficacy of fasting on cancer has been evaluated in several animal model studies. In one study which used CR and intermittent fasting in male $p53^{+/-}$ mice, the appearance of tumors was delayed compared to the control group [**106**]. In addition, plasma leptin and IGF-1 levels were substantially lower in the CR and intermittent fasting groups, although CR was more effective. In a model of colon carcinoma, tumor volume was significantly decreased and survival increased by fasting and these effects were greater following fasting and rapamycin combination therapy [**107**]. Also, the expression levels of farnesyl-diphosphate farnesyltransferase 1 (FDFT1) were increased in both fasting and combination therapy groups, suggestive of effects on increased cholesterol synthesis, and this involved down-regulation of

AKT/mTOR/HIF1α signalling. Similarly, Sun *et al.* reported that alternate day fasting for 2 weeks substantially reduced colon tumor growth in BALB/c mice without any significant reduction in body weight [**108**].

In contrast with the above studies, Buschemeyer *et al.* reported no significant improvement in survival in a mouse model of prostate cancer following 15% and 28% chronic CR or intermittent fasting with/without CR [**109**].Similarly, intermittent fasting (2 days per week) did not influence body weight, survival, serum insulin, IGF-BP3, and tumor phospho-AKT levels in a murine model of prostate cancer [**110**]. Thus, further studies are required to resolve these discrepancies.

7 Effects of fasting during chemo- and radiotherapy

In mouse subcutaneous or intracranial models of GL26 glioma, 48 h fasting prior to radiotherapy and chemotherapy increased survival and tumor sensitivity to treatment [**111**]. Fasting for 24 h prior to radiation in mouse models of pancreatic tumors delayed tumor growth and subsequently increased survival [**112**]. The same study also showed that fasting substantially protected small intestinal stem cells from radiation-induced toxicity. Another study showed that fasting treatment alone or in combination with doxorubicin or cyclophosphamide chemotherapy retarded the growth of subcutaneously tumors, and increased survival in metastatic models of breast cancer, melanoma, and neuroblastoma, with the combination therapy being more effective [**113**]. Di Biase *et al.* reported that fasting prior to chemotherapy significantly reduced doxorubicin-induced cardiotoxicity, including prevention of the reduction in left ventricle diastolic and/or systolic volumes, and modulation of left ventricle wall thinning [**114**]. In another phase of the investigation, the authors demonstrated that concomitant treatment of doxorubicin chemotherapy with insulin and fasting significantly lowered glucose levels and increased survival, and the effects of fasting were greater than those of insulin. An in vitro phase of this same study showed that fasting and glucose restriction regulated epidermal growth factor receptor 1 (EGR1) levels through increased AMPK activity, and protected against glucose-dependent sensitization to chemotherapy. In another investigation, fasting combined with chemotherapy effectively reduced tumor progression, down-regulated cancer cell heme oxygenase-1 expression, expanded lymphoid progenitors in

bone marrow, and increased anticancer immune response [**115**]. These findings suggest that immunological components may be involved in the fasting-mediated chemotherapy enhancement. In a model of lung carcinoma, tumor growth was inhibited by fasting, methotrexate, and a fasting + methotrexate combination therapy by 34, 27, and 46%, respectively [**116**]. The tumor growth index was 0.7 in fasted groups, while it was 0.81 in the methotrexate treatment.

8 Clinical studies of CR and fasting

Although many in vivo studies have revealed the potential role of CR and fasting in cancer therapeutics, only a small number of clinical studies have been carried out to evaluate these alternative treatment approaches. The results of these trials are summarized below.

In a case series study, fasting 48 to 140 h pre- and/or 5 to 56 h post-chemotherapy in 10 patients with a variety of malignancies had no serious side effects from the fasting, apart from hunger and light headedness, while assessment of the chemotherapy-induced side effects in fasted patients showed a reduction in fatigue, weakness, and gastrointestinal side effects [**117**]. In addition, fasting did not prevent the chemotherapy-induced reduction of tumor volume or tumor markers in the patients assessed for cancer progression.

A controlled trial of 19 obese and overweight males with new diagnoses of prostate cancer tested the effects of a 6-week CR diet compared to continuation of their current diets [**118**]. The study found that serum IGF-BP3levels were significantly elevated in the CR compared to control group, although the levels of insulin, IGF-1, IGF-1:IGFBP-3 ratio, and adiponectin were not affected. Also, in comparison to control group, a significant reduction in body weight was detected, although body mass indices (BMIs) were not significantly altered. In another randomized-controlled trial, HER2-negative breast cancer patients were randomly assigned to either fasting or a control diet group for 24 h pre- and post-chemotherapy [**119**]. The fasting group showed a marked elevation in erythrocyte- and thrombocyte counts 7 days after chemotherapy, compared to the control diet group. Also, the fasting group showed a reduced rise in the DNA damage marker H2A histone family member X (γ-H2AX) in CD45+ CD3- cells, compared to the control diet group. In a randomized cross-over pilot study, the effects of

fasting during 4-6 chemotherapy cycles on quality of life were assessed in gynaecological cancer patients [**120**]. Fasting was well-tolerated and quality of life and fatigue during chemotherapy were improved. Finally, a trial which assessed the effects of pre-chemotherapy fasting for 24, 48 and 72 h in cancer patients found that serum levels of IGFBP1, insulin, and glucose did not change after two cycles of chemotherapy but DNA damage in peripheral blood mononuclear cells was reduced following the 48 and 72 h fasting periods [**121**].

9 Conclusions

Although the underlying molecular mechanisms have not yet been completely elucidated, the findings presented in this review provide preclinical evidence demonstrating that CR and fasting have the potential to play an important complementary role in medicine by promoting disease prevention, delaying tumor progression, enhancing sensitization of tumor cells to chemotherapy agents and protecting host tissues against chemotherapy-induced damage to healthy cells. Also, limited evidence from clinical trials suggests that CR and fasting may improve responses and/or reduce adverse effects of chemotherapy or radiotherapy. We conclude that more clinical studies consisting of larger sample sizes with careful design of the diet components and follow-up, and standardized treatment protocols are needed to fully evaluate the benefits and risks of these dietary interventions as standalone treatments or as an adjunct to standard chemo- and radiotherapies. The other critically important issue that needs to be further investigated is whether such a dietary approach might be beneficial for all types of cancers, and what should be the duration of such interventions to carefully balance between the expected benefits and risks.

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Table 1. List of in vivo studies reporting effects of fasting/calorie restriction on various aspects of cancer treatment

Author, Year	Treatments	Model	Type of cancer	Finding
Pearson et al., 2008 [**64**]	1. Ad libitum (AL) 2. 40% calorie restriction (CR)	1. Nrf2- KO mice 2. WT mice	Papilloma	Lifespan extension and insulin sensitivity induced by CR not completely a consequence of Nrf2 pathway upregulation. Liver levels of NQO1 mRNA markedly higher in WT-CR group. In KO mice tumor incidence was 100% by 30 weeks. In both CR-treated groups, glucose and insulin levels decreased
Rogozina et al., 2011 [**73**]	1. Ad libitum (AL) 2. 25% chronic calorie restriction (CCR) 3. Intermittent calorie restriction(ICR)	MMTV-TGF-α mice	Breast cancer	Calorie restriction significantly decreased breast tumor incidence. Leptin level was significantly higher in AL group In ICR group, mammary tissue AdipoR1 expression increased and leptin and ObRb expression decreased compared to AL group
Cleary et al., 2007 [**74**]	1. Ad libitum (AL) 2. Chronic calorie restriction (CCR) 3. Intermittent calorie restriction(ICR)	MMTV-TGF-α mice	Breast cancer	Calorie restriction significantly decreased breast tumor incidence.The number and weight of the tumors were lower in CCR and ICR groups.Mammary tumor DNA breaks significantly higher in ICR group
Harvell et al., 2002 [**75**]	1. Ad libitum (AL) 2. AL+ 17β-estradiol (AL+E2) 3. 40% calorie restriction(CR) 4. CR+E2	ACI rats	Breast cancer	AL+E2 group exhibited palpable mammary tumors. CR reduced E2-induced mammary tumorigenesis. CR had no effect on E2-induced prolactin-producing pituitary tumors
Ma et al., 2018 [**76**]	1. Ad lib fed (AL) 2. 30% calorie restriction (CR)	MMTV-ErbB2 mice	Breast cancer	Estrogen receptor (ER) and ErbB2 signaling suppressed and proliferative index decreased by CR intervention
Cicekdal et al., 2019 [**77**]	1. Ad libitum (AL) 2. Chronic calorie restriction (CCR, 15%) 3. Intermittent CR	MMTV-TGF-α (C57BL6) mice	Breast cancer	No significant differences in MDA levels between groups. CCR group showed higher CAT and SOD activity compared to other groups
Tuna et al., 2017 [**78**]	1. Ad libitum (AL) 2. 15% chronic calorie restriction (CCR) 3. Intermittent calorie-restricted(ICR)	MMTV-TGFα mice	Breast cancer	Calorie restriction maintained serum levels of adropin
Phoenix et al., 2010 [**79**]	1. Ad libitum (AL) 2. 35% calorie restriction (CR)	Balb/c mice	Triple negative breast cancer	There were a marked reduction in blood glucose, insulin and IGF-1 levels. CR treatment limited tumor growth and secondary metastases to the lung.
Shastri et al., 2020 [**80**]	1. Ad libitum 2. 30% calorie restriction	BALB/c mice	Breast cancer liver metastasis	Expression of miR-29b, miR-29c and miR-30b in liver tissue and miR-29c, miR-30a and miR-30b in tumor tissue significantly increased

Devlin et al., 2016 [**81**]	1. Ad-libitum diet 2. Calorie restriction (30%)	Sprague Dawley rats	Luminal breast cancer	Bodyweight did not change by CR treatment. Expression of miR-200a was substantially lower in CR group. CR group had smaller tumors and higher tumor-free survival vs. controls
Jinet al., 2014 [**82**]	1. Ad libitum (AL) 2. AL+ radiation therapy(IR) 3. 30% calorie restriction (CR) 4. CR+ IR	Balb/c mice	Triple negative breast cancer	CR and IR decreased the expression of miR-17 and miR-20a
Cicekdal et al., 2020 [**85**]	1. Ad-libitum 2. 15% chronic calorie restriction 3. Intermittentcalorie restriction (60%)	MMTV-TGF-α (C57/BL6) mice	Breast Cancer	Levels of AdipoR1 methylation in chronic calorie restriction group higher than ad-libitum group
Mai et al., 2003 [**86**]	1. Ad libitum (AL) 2. Calorie restriction (CR) 3. High in olive fruit + vegetable (OFV) 4. High fat diet(HF)	*Apc*^{Min} mice	Intestinal tumorigenesis	The number of polyps significantly decreased in CR and OFV compared to AL group. Compared to AL, OFV and HF groups, leptin and IGF-1 substantially decreased in CR group
Ploeger et al., 2017 [**87**]	1. 30% calorie restriction (CR) 2. Exercise	C57Bl/6 mice	Liver tumorigenesis	CR prevented hepatic tumor formation and reduced steatosis, hepatocyte ballooning, inflammation and immune cell infiltration
Tsao et al., 2002 [**88**]	1. High fat/low calcium (HFLC) 2. 30% calorie restriction (CR) 3. Ad libitum (AL)	Mlh1 deficient mice	Lymphomas, and intestinal adenoma carcinoma	Incidence of adenocarcinoma or lymphoma not different between CR and HFLC groups. Incidence of adenomas significantly higher in HFLC group. Lifespan of the CR group was markedly higher than HFLC
Yoshida et al., 2002 [**89**]	1. Non-restricted diet + irradiation (CAL-) 2. Postirradiation calorie restriction (POST) 3. Preirradiation calorie restriction (PRE) 4. Lifetime calorie restriction(T)	C3H/He mice	Myeloid leukemia	POST and T groups showed significant reduction in spontaneous incidence of myeloid leukemia, number of hematopoietic stem cells (HSC), and size of cycling fraction of HSC compared to CAL- group
Yoshida et al., 2006 [**90**]	1. Non-restricted diet + irradiation (CAL-) 2. Postirradiation calorie restriction (POST) 3. Preirradiation calorie restriction(PRE) 4. Lifetime calorie restriction(T)	C3H/He mice	Myeloid leukemia	Incidence of myeloid leukemia:CAL-> PRE> POST> T Latency periods of myeloid leukemia in POST and T groups significantly prolonged compared with that in the CAL- group. CAL- had lesser survival than POST and T groups
Diaz-Ruiz et al., 2019 [**91**]	1. Ad lib fed (AL) 2. 40% reduction in calorie intake (CR)	1. NQO1-KO male mice 2. littermate (LM) mice	Skin carcinogenesis	In CR- treated groups, tumorigenesis suppressed and longevity increased, which suggests that effects of CR are independent of NQO1 expression
Shelton et al., 2010 [**93**]	1. Ad libitum (AL) 2. 60% calorie restriction (CR)	VM mice	Glioblastoma multiforme	% Ki-67-positive tumor cells and blood vessel size/density markedly lower in CR group. Tumor progression significantly lower in CR group

Lanza-Jacoby et al., 2013 [**94**]	1. Ad libitum (AL) 2. Intermittent calorie reduction(ICR) 3. 25% chronic calorie reduction (CCR)	LSL-Kras^{G12D}/; Pdx-1/Cre mice	Pancreatic cancer	Both CR groups significantly delayed progression of pancreatic intraepithelial neoplasias to PDA. CR increased protein expression of SIRT1 and decreased that of Glut1. Serum adiponectin increased and leptin decreased in CR groups.CCR significantly decreasedmTOR phosphorylation compared with ICR and AL groups (P<0.01). No significant changes in phosphorylation of AMPK and Akt following CR
Lashinger et al., 2011 [**95**]	1. Ad libitum 2. 30% calorie restriction	C57BL/6 mice	Pancreatic cancer	Calorie restriction significantly reduced body weight, tumor volume, phosphorylation of mTOR and Akt, and levels of IGF-1, glucose, and leptn .Insulin and IGF-1R did not change
Al-Wahab et al., 2015 [**96**]	1. Regular diet (RD) 2. High energy diet (HED) 3. 30% calorie restriction (CR)	C57B6 mice	Ovarian cancer	CR group had higher activation of AMPK and SIRT1 and lower activation of Akt and mTOR than RD and HED. Tumor growth and spread of ovarian tumors significantly restricted in CR group. In CR group, plasma levels of IGF-1, leptin, MCP-1, VEGF, and IL-6 decreased and adiponectin significantly increased
Al-Wahab et al., 2014**[97**]	1. Regular diet (RD) 2. High energy diet (HED) 3. Calorie-restricted diet (30%, CR)	C57B6 mice	Epithelial ovarian cancer	CR group had higher activation of AMPK and SIRT1 and lower activation of Akt and mTOR than RD and HED. Tumor burden lower in CR group. Compared to RD group, plasma levels of insulin, IGF-1, MCP-1, and IL-6 decreased and adiponectin levels increased in CR group
Galet et al., 2013 [**98**]	1. Ad libitum (AL) 2. AL+ ganitumab(GA) 3. 40% calorie restriction (CR) 4. CR+ GA	CB17 severe combined immunodeficient mice	Prostate cancer	In CR group, apoptosis significantly increased and final tumor weight, plasma insulin, and IGF-1 levels reduced, but the expression of IGF-1R unaffected.In CR+ GA group, greater reduction in final tumor weight was seen. Also, tumor proliferation and plasma insulin decreased and tumor cells apoptosis increased
Blando et al., 2011 [**99**]	1. Diet induced overweight (DIV) 2. Diet induced obesity (DIO) 3. 30% calorie reduction (CR)	Hi-Myc mice	Prostate cancer	Compared with DIV group, activation of Akt, mTORC1, STAT3, and NF-κB (p65) significantly decreased by CR, and increased in DIO group.In DIO group, mRNA levels for IL 1α, 1β, 6, 7, 23, 27, NF-κB1 (p50), TNF-α, and VEGF family members increased compared to the other groups
Levolger et al., 2018 [**100**]	1. Ad lib fed (AL) 2. 30% calorie restriction (CR)	CD2F1 mice	Colon-26 adenocarcinoma	Wasting observed in AL group. In CR group, grip-strength change was less severe and myogenin expression was higher
Xiang et al., 2012 [**101**]	1. Ad libitum (AL) 2. 35% calorie restriction (CR) 3. cyclophosphamide+ AL (CTX) 4. CR+CTX	Sprague–Dawley rats	---------	CR did not disrupt estrous cycling and maintained it in CR+CTX group. CR+CTX and CR significantly increased ovary SIRT-1 expression and led to decreased follicle apoptosis by reduction in P53 expression

Simone et al., 2018 [**102**]	1. Ad lib fed (AL) 2. 30% calorie restriction (CR) 3. Cisplatin 4. Docetaxel 5. CR+ docetaxel (CR+DOX) 6. CR+ cisplatin (CR+ CIS)	Balb/c mice	Triple negative breast cancer	CR increased serum levels of adiponectin CR+DOX and CR+ CIS showed significant reduction in leptin IGF-1R and IRS signaling pathways more significantly decreased in combination therapie. Chemotherapy+ CR showed longer overall survival and fewer lung metastases than the AL group CR modulated chemotherapy-induced inflammation
Simone et al., 2016 [**103**]	1. Ad libitum (AL) 2. AL+ radiation therapy(IR) 3. 30% calorie restriction (CR) 4. CR+ IR	BALB/c mice	Triple negative breast cancer	CR substantially reduced overall number and volume of lung metastases, and increased survival and time to metastases progression CR downregulated IGF-1R signaling pathway
Saleh et al., 2013 [**104**]	1. Ad libitum (AL) 2. AL+ radiation therapy(IR) 3. 30% calorie restriction (CR) 4. CR+ IR	Balb/c mice	Triple negative breast cancer	CR-treated groups resulted in substantial tumor regression. CR and IR treatment caused more apoptosis and less proliferation of tumors IGF-1R, IRS, PIK3ca and mTO R downregulated by CR
Liu et al., 2019 [**105**]	1. Ad-libitum diet+ normal saline 2. Ad-libitum diet+CTX 3. Calorie restriction +normal saline 4. Calorie restriction +CTX	C57BL/6 mice	---------	Pretreatment with calorie restriction significantly decreased CTX-induced mucositis. Calorie restriction modulated gut microbiota, especially Lactobacillus and Lachnospiraceae
Berrigan et al., 2002 [**106**]	1. Ad libitum (AL) 2. Calorie restriction (CR) 3. Intermittent fasting (1 day/week)	p53+/– mice	Spontaneous tumorigenesis	CR and fasting significantly delayed appearance of tumors. IGF-1 and leptin significantly decreased with CR and fasting
Weng et al., 2020 [**107**]	1. ad lib fed (AL) 2. AL+ Rapamycin (RAP) 3. Fasting mimic diet (FMD) 4. FMD+ RAP	BALB/c mice	Colon carcinoma	FMD and RAP treatments led to decreased tumor volume and increased survival and FDFT1 expression compared to AL group
Sun et al., 2017 [**108**]	1. Alternate day fasting and ad libitum diet on non-fasting days 2. Control group with standard condition	Wild-type BALB/c mice	Colorectal cancer	Cancer cell growth blocked with fasting without significant weight loss
Buschemeyer et al., 2010 [**109**]	1. Ad libitum (AL) 2. 15% caloric restriction (CR) 3. 28% CR 4. Intermittent fasting with CR 5. Intermittent fasting without CR	SCID mice	Prostate cancer	No significant difference in survival observed
Thomas et al., 2010 [**110**]	1. Ad libitum 2. Intermittent fasting	CB17 severe combined immunodeficient mice	Prostate cancer	Intermittent fasting did not influence bodyweight, survival, serum insulin, IGFBP-3 or tumor phospho-Akt levels compared to control group

Safdie et al., 2012 [**111**]	1. Control (untreated) 2. Fasting (48 hours) 3. Temozolomide(TZ) 4. Fasting+ TZ 5. Radiotherapy(RT) 6. Fasting+ RT	C57BL/6N mice	Glioma	Fasting increased survival and tumor sensitivity to radiotherapy and chemotherapy
de la Cruz et al., 2019 [**112**]	1. Fed unirradiated 2. Fed-irradiated 3. Fasted unirradiated 4. Fasted-irradiated	C57BL/6J mice	Pancreatic cancer	Pre-radiation fasting caused lag in tumor growth and increased survival. Fasting enhanced regeneration of intestinal stem cells after high-dose radiation
Lee et al., 2012 [**113**]	1. Ad libitum (AL) 2. Fasting 3. Fasting+ chemotherapy 4. Chemotherapy	BALB/c mice C57Bl/6 mice nude mice	Subcutaneous and metastatic tumor models: Breast cancer Melanoma Neuroblastoma	Fasting cycles (between 1 and 4 times) in combination with chemotherapy was more effective than each treatment alone in retarding growth of subcutaneously growing tumors and increasing survival in metastatic models of breast cancer, melanoma, and neuroblastoma
Di Biase et al., 2017 [**114**]	1. Rapamycin(Rapa) 2. Dexamethasone (Dexa) 3. Insulin 4. Insulin+ Rapa 5. Insulin+ Dexa 6. Fasting 7. Fasting+ Rapa 8. Fasting+ Dexa 9. Control	C57BL/6 mice	---------	Administration of Rapa and Dexa 2 weeks before chemotherapy significantly induced hyperglycemia and reduced survival. Insulin, fasting and their combinations significantly decreased glucose levels and enhanced survival. Also fasting was significantly more effective. In the other phase of this study, fasting significantly decreased doxorubicin -induced cardiotoxicity
Korshunov et al., 2018 [**116**]	1. Control 2. Methotrexate (MTX) 3. Intermittent fasting 4. MTX + intermittent fasting	C57BL/6j mice	Lewis lung carcinoma	Rate of tumor growth inhibition was 34, 27, and 46 % in fasting, MTX, and combination therapy, respectively. Kinetic tumor growth index was 0.7 in fasted groups, and 0.81 in MTX alone.Combination therapy mitigated MTX anti-metastatic activity by 20 % but alleviated side effects

Table 2. List of clinical studies reporting the effects of fasting/calorie restriction on various aspects of cancer treatment.

Author, Year	Study design	Intervention	Control group	Duration	Population	Number of participants	Main finding
Safdie, F. M, et al., 2009 [**117**]	case series report	Fasting	------	48 to 140 h prior to and/or 5 to 56 h following chemotherapy	Variety of malignancies (breast, lung, ovary, prostate, esophagus, and uterus)	10	Patient self-reports of side effects induced by chemotherapy (fatigue, weakness, and gastrointestinal) reduced by fasting. Weight loss induced by fasting rapidly recovered in most patients. Fasting did not alter tumor growth of subjects in which cancer progression was detectable
Wright, J. L, et al. 2013 [**118**]	Randomized controlled	Calorie restriction	Current diet	6-week	Obese and overweight men with newly diagnosed prostate cancer	19	Serum IGF-BP3 levels significantly increased in CR compared to control group. No significant differences in serum levels of insulin, IGF-1, IGF-1/IGFBP-3, and adiponectin between groups
de Groot S, et al. 2015 [**119**]	Randomized -controlled	Fasting	Healthy nutrition according to guidelines	48 hours (24 h pre- and post-chemotherapy) In 6 chemotherapy cycles	HER2-negative breast cancer patients	13	A week after chemotherapy, erythrocyte- and thrombocyte counts elevated significantly compared to control group. Levels of γ-H2AX significantly raised in CD45 + CD3- cells in controls. Fasting well tolerated
Bauersfeld S. P, et al. 2018 [**120**]	Randomized cross-over	Fasting	Normocaloric nutrition	60 h (36 h before and 24 h after chemotherapy) In 2-3 chemotherapy cycles	Patients with gynecological cancer	34	Fasting improved quality of life and fatigue induced by chemotherapy. Fasting was well tolerated
Dorff T. B, et al. 2016 [**121**]	---------	Fasting	---------	24 and 48 h pre-chemotherapy 72 h (divided as 48 pre-chemo and 24 post-chemotherapy) In 2 chemotherapy cycle	Cancer patients	20	IGFBP1, insulin and glucose levels did not differ. DNA damage reduced following 48 and 72 h fasting

Table 3. List of ongoing clinical studies evaluate the effects of fasting/calorie restriction on cancer treatment.

Identifier	Study design	Intervention	Control group	Duration	Population	Number of participants	Primary endpoint
ISRCTN17994717 [**122**]	Randomized controlled	Fasting	Standard dietary	36 h prior to chemotherapy During 3 chemotherapy cycles	Stage 2/3 colorectal cancer	30	Feasibility of the trial
NCT03709147 [**123**]	Open-label, randomized	1. Metformin 2. Metformin + FMD	---------	5-days FMD every 3 weeks During up to 4 cycles of chemotherapy	Lung adenocarcinoma with inactive LKB1	88	Progression-free survival
NCT03131024 [**124**]	Randomized controlled	1. Calorie restriction (50%) 2. 30-min vigorous-intensity aerobic exercise (24 h prior to chemotherapy)	Usual cancer care	48 h prior to chemotherapy During 3 chemotherapy cycles	Women with early stage breast cancer	56	Left ventricular ejection fraction (LVEF) reserve
NCT03700437	Randomized controlled	FMD	Regular diet	96 hours (72 h prior to and 24 h after chemotherapy) During 4 chemotherapy cycles	Patients with non-small cell lung cancer	40	Count of circulating tumor cells and DNA damage
NCT03595540	Single-arm, open label	FMD	---------	5 days every month for 6 months During cancer treatment	Patients with solid or hematologic tumors	60	Feasibility and safety
NCT03162289	Randomize, open label	Modified fasting	Vegan diet	60-72 h (36-48 h prior to and 24 h after chemotherapy) During 4 chemotherapy cycles	Women with ovarian or breast cancer	150	Quality of life
NCT03340935	Single-arm, open label	FMD	---------	5 days (up to 8 consecutive FMD cycles) During cancer treatment	Patients with any malignancy (except for small cell neuroendocrine tumors)	85	Safety of FMD

NCT02710721	Randomized controlled	Modified fasting or FMD	Individual nutrition training	60 hours (36h prior to and 24h after chemotherapy) During 6 chemotherapy cycles	Men with advanced metastatic prostate cancer	60	Quality of life
NCT01802346	Randomized controlled	Restricted diet	A normal diet with receiving dietary advice	4 days (3 days prior to and 1 day after chemotherapy) During 12 weeks	Patients with breast or prostate cancer	120	Side effects and efficacy of chemotherapy and changes in plasma insulin, glucose, IGF1 and IGFBP levels