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good summary but obviously influenced by big pharma, especially the recommendations at the end (don't do anything!)



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# Intermittent Fasting in the Prevention and Treatment of Cancer

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**Abstract:** Chronic caloric restriction (CR) has powerful anticarcinogenic actions in both preclinical and clinical studies but may be difficult to sustain. As an alternative to CR, there has been growing interest in intermittent fasting (IF) in both the scientific and lay community as a result of promising study results, mainly in experimental animal models. According to a survey by the International Food Information Council Foundation, IF has become the most popular diet in the last year, and patients with cancer are seeking advice from oncologists about its beneficial effects for cancer prevention and treatment. However, as discussed in this review, results from IF studies in rodents are controversial and suggest potential detrimental effects in certain oncologic conditions. The effects of IF on human cancer incidence and prognosis remain unknown because of a lack of high-quality randomized clinical trials. Preliminary studies suggest that prolonged fasting in some patients who have cancer is safe and potentially capable of decreasing chemotherapy-related toxicity and tumor growth. However, because additional trials are needed to elucidate the risks and benefits of fasting for patients with cancer, the authors would not currently recommend patients undergoing active cancer treatment partake in IF outside the context of a clinical trial. IF may be considered in adults seeking cancer-prevention benefits through means of weight management, but whether IF itself affects cancer-related metabolic and molecular pathways remains unanswered. **CA Cancer J Clin 2021;71:527-546. © 2021 The Authors. CA: A Cancer Journal for Clinicians published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.**

**Keywords:** caloric restriction, fasting, obesity, neoplasms

## Introduction

Despite significant advances in the field of oncology, cancer remains the second leading cause of mortality and morbidity in the United States,[1] accounting for an estimated 608,570 deaths in 2021 alone.[2] The incidence rate is expected to increase with a rapidly aging population. The current estimated lifetime risk of being diagnosed with cancer is 40.14% for males and 38.70% for females,[3] with a projected 22 million cancer survivors in the United States by 2030.[4] Furthermore, even with a marked improvement in overall survival at 5 years, cellular and organ damage from chemotherapy and/or radiation therapy frequently results in decreased quality of life for survivors, with common residual physical symptoms such as neuropathy, fatigue, cognitive problems, and pain.[5] Such physical and psychosocial symptoms often persist well beyond 5 years,[6] with survivors reporting unmet needs even 10 years after treatment.[7] Furthermore, approximately 8% of survivors develop a second cancer, one-half of whom are likely to die from the second malignancy[8,9]

Fortunately, studies of monozygotic twins suggest that hereditary factors exert a small contribution to the risk of most neoplasms and that environmental factors play

a principal role in this regard.[10] In particular, it has been estimated that about 42% of all cancers and 45% of cancer deaths are attributed to modifiable lifestyle risk factors, including tobacco, physical inactivity, excessive adiposity, and dietary factors such as consumption of ultra-processed food and red and processed meat and low intake of plant foods rich in dietary fiber, antioxidant vitamins, and phytochemicals.[11] Overweight and obesity alone are associated with an increased risk for at least 13 different cancers,[12] and excess adiposity at the time of a cancer diagnosis is associated with poorer outcomes in most cancers.[13] Thus there is an opportunity for both prevention efforts and improved cancer outcomes through healthful lifestyle.

Calorie restriction (CR) without malnutrition remains the most robust intervention to date for cancer prevention in rodents and monkeys, and, in humans, it promotes anticarcinogenic adaptations such as decreased production of growth factors, inflammatory cytokines, and anabolic hormones as well as decreased oxidative stress and free-radical–induced DNA damage.[14] Despite a wealth of literature on the mechanisms and impact of CR, its clinical applicability remains limited because of challenges in long-term sustainability. Intermittent fasting (IF) is becoming a popular alternative to daily CR, with IF being the most frequently cited diet pattern in 2020 among Americans aged 18 to 80 years according to the International Food Information Council survey.[15] It can occur in various forms, including fasting for 24 hours on alternate days, fasting 2 days per week on nonconsecutive days, or time-restricted feeding (TRF) (Table 1). In this review, we examine the data for different forms of fasting in rodents and humans, focusing our attention on the biologic adaptations that may reduce cancer incidence and improve cancer outcomes. We also highlight new emerging scientific trends on the role of prolonged fasting and fasting-mimicking diets (FMDs) as a potential new adjunctive therapy for patients undergoing chemotherapy.

**TABLE 1. Key Definitions**

| | |
|---|---|
| Intermittent fasting (IF) | Episodic periods of little or no calorie consumption |
| Time-restricted feeding (TRF) | A form of intermittent fasting that requires limiting the consumption of calories to a window of time, typically between 4 and 12 h daily |
| Prolonged fasting | Prolonged, periodic fasting that lasts >24 h |
| Fasting-mimicking diet (FMD) | Generalized term for low-calorie diet that is low in protein and carbohydrates but high in unsaturated fat and provides between 10% and 50% of calories of normal ad libitum intake |

## Obesity, Adiposity, and Cancer Risk and Prognosis

Cohort studies suggest a strong link between excess body weight and multiple types of malignancies, including postmenopausal breast, endometrial, ovarian, colorectal, liver, pancreatic, gallbladder, gastric cardia, esophageal adenocarcinoma, renal cell, meningioma, thyroid, and multiple myeloma.[12] Accumulating data also suggest that obesity is associated with higher rates of cancer progression, recurrence, and mortality, especially for breast, prostate, and colon cancer.[13,16-20] Furthermore, cancer survivors are at higher risk of becoming obese,[21] likely because of various factors, including the use of chemotherapy, steroids, and hormonal therapy, which can accelerate weight gain.[22] Although the *obesity paradox* refers to studies demonstrating that obesity is associated with improved overall survival, this is more likely secondary to flaws in methodological mechanisms, such as using body mass index as an obesity measure, confounding and reverse causality.[23-26] However, there are studies that postulate a biologic rational for the improved survival seen in obese patients with renal cell carcinoma.[13,27,28] In those studies, the authors found that patients with renal cell carcinoma and obesity had longer overall survival than patients without obesity. One hypothesis based on transcriptomic signature differences in the primary tumor and the peritumoral adipose tissue is that increased tumor angiogenesis and increased peritumoral inflammation in the perirenal white adipose tissue of obese patients contribute to their survival advantage. Another study found that the perinephric fat contains increased numbers of activated immune cells.[28]

The mechanisms by which excessive adiposity affects cancer risk and prognosis are complex and continue to be elucidated. Chronic inflammation, insulin resistance, and altered sex hormone metabolism appear to be key factors.[29] Weight gain results in adipose tissue hypertrophy and immune infiltration, increased production and decreased clearance of free fatty acids,[30] and changes in proinflammatory cytokines and adipokine signaling, which lead to systemic insulin resistance.[31,32] Multiple mechanisms linking insulin dysregulation and cancer have been proposed. For example, compensatory hyperinsulinemia promotes cell proliferation and protects mutated cells from apoptosis through activation of the PI3K/AKT pathway and has been associated with increased risk of cancer recurrence and death.[33-35] Insulin resistance also increases levels of bioavailable sex hormones and insulin-like growth factor 1 (IGF-1) by reducing liver production of SHBG,[36,37] IGF-binding protein 1 (IGFBP-1), and IGFBP-2.[38] In addition, excessive adiposity raises circulating estrogens through increased aromatase expression.[39] Altered plasma concentrations of estrogen-related and androgen-related hormones and IGF-1 are linked to breast, endometrial, prostate, and colon cancer risk in humans.[40-43] In preclinical models, elevated estrogen, testosterone, and IGF-1 promote tumorigenesis by inducing genetic instability,

PI3K/AKT pathway

free radical–mediated DNA damage, and an impaired DNA repair response.[44,45] In addition, systemic inflammation can promote cancer development[46] and limit antitumor responses by means of immune dysregulation of natural killer cells and stromal tumor-infiltrating lymphocytes.[47,48]

Obese cancer survivors are not only at risk for poorer cancer prognosis, but they also have increased risk of diabetes and cardiovascular, liver, and kidney disease, among many other adiposity-related clinical conditions.[49-51] Therefore, there is an urgent need to improve cancer care beyond novel therapeutics by elucidating the effects of diet, exercise, and weight management in cancer prevention and treatment.

## Diet and Cancer Prognosis: Randomized Clinical Trials

Whether weight loss, without a significant change in diet composition, has a casual role in reducing cancer risk and improving prognosis remains an important but unanswered question. Much of the data regarding diet and cancer survival are in the breast cancer population, although there are data in colorectal and other cancers as well. The Women's Health Initiative Dietary Modification Trial randomized 48,835 postmenopausal women to a control arm (usual American diet) or an intervention arm of a low-fat diet rich in fruit and vegetables. There was a small but sustained 3% weight loss in the intervention arm.[52] Although these women did not experience a reduction in the risk of breast or colorectal cancer, post-hoc analysis suggests that death as a result of breast cancer was significantly lower in women who developed breast cancer after randomization to the dietary intervention compared with controls (hazard ratio, 0.78; 95% CI, 0.65-0.94; $P = .01$), with no change in clinical outcomes after adjusting for weight loss.[52] Similarly, in the Women's Intervention Nutrition Study of early stage breast cancer survivors, a low-fat dietary pattern resulted in a small but significant 2.7-kg weight loss and was associated with a 24% higher relapse-free survival rate.[53,54] In contrast, results of the Women's Healthy Eating and Living Study showed that an isocaloric high-vegetable, low-fat diet did not result in any difference in body weight or breast cancer outcomes in patients with early stage breast cancer.[55] The findings of these large, randomized trials led to the hypothesis that a negative energy balance is necessary for improving breast cancer outcomes.

The ongoing Breast Cancer Weight Loss Study (ClinicalTrials.gov identifier NCT02750826) will help to determine whether weight loss after breast cancer treatment can improve prognosis. However, additional questions will remain, including how such changes may impact treatment efficacy if implemented earlier and whether macronutrient and/or micronutrient dietary modifications can potentiate the effects of weight loss on cancer prognosis, not only for breast cancer but for many other common cancers.

## Calorie Restriction and Cancer Prevention

Chronic daily CR without malnutrition has a powerful effect in preventing spontaneous and chemically induced tumors in animal models.[56] This cancer-protective effect was first discovered in 1942 by Tannenbaum, who demonstrated that CR could markedly reduce the development of mammary tumors in rodents.[57] As reviewed elsewhere,[14] this finding has been consistently replicated in hundreds of CR studies on various tumors, including lymphomas, breast cancers, and skin cancers.[58-61] Tumor xenografts in mice are also sensitive to dietary restriction, with the exception of tumors that have PI3K pathway activations.[62] More recently, CR has been evaluated in rhesus monkeys, animals that share a strikingly similar genome to that of humans.[63] Both the University of Wisconsin and National Institute on Aging CR primate trials have shown a 50% decrease in the incidence of spontaneous cancer, most commonly gastrointestinal adenocarcinoma, in monkeys consuming a 30% CR diet compared with ad libitum-fed animals.[64,65]

Data on the effects of daily CR in humans are slowly accumulating and suggest a beneficial effect, even when started in older adults with obesity who most likely already harbor acquired mutations and even microscopic in situ tumors.[66] One study from Sweden compared patients who underwent bariatric surgery with a control group and found a 29% reduction in cancer incidence and 23% lower cancer mortality after a median 20 years of follow-up.[67] The reduction of cancer incidence was associated with a reduced risk of overall female-specific cancers, including breast and gynecologic cancers, with greater benefit in patients who had higher baseline serum insulin levels.[68] The Look AHEAD trial (ClinicalTrials.gov identifier NCT00017953) was a randomized trial of 4859 overweight, diabetic patients without a baseline cancer diagnosis who were randomized to an intensive lifestyle intervention that included a calorie goal of 1200 to 1800 kilocalories (kcal) daily (<30% of calories from fat and >15% from protein).[69] Differences in weight loss were most pronounced after 1 year, with an average weight loss of 8.7 kg compared with 0.75 kg in the intervention group.[69] With a median follow-up of 11 years, patients in the intensive lifestyle intervention group had a 16% lower incidence of obesity-related cancers (including esophagus, colon, rectum, kidney, pancreas, stomach, liver, gallbladder, thyroid, uterine, ovarian, postmenopausal breast, and multiple myeloma), which the authors proposed was secondary to weight loss, but there was no difference in the incidence of cancers not associated with obesity.[69]

Multiple intersecting mechanisms are responsible for the protective effects of chronic daily CR on cancer development and progression.[14] Animal and human studies have shown that energy restriction results in major sustained metabolic and hormonal adaptations associated with reduced

cancer risk, including reduced insulin levels and improved insulin sensitivity,[70,71] increased IGFBP-1 and SHBG,[72] reduced bioavailable testosterone and estrogen,[73] and reduced inflammation[74] and oxidative stress.[75-77] These adaptations support the mechanistic data by which adiposity increases cancer risk. At the molecular level, long-term CR in rodents and humans activates DNA repair, autophagy, and antioxidant and heat-shock protein chaperone pathways while inhibiting cell proliferation and cell senescence biomarkers.[78-80] Additional mechanisms include decreased production of growth factors and reactive oxygen species and enhanced anticancer immunity.[14]

## Intermittent Fasting

Although studies of CR in cancer prevention are favorable, many individuals find CR difficult to sustain for prolonged periods. IF is being proposed as an alternative to chronic CR (in which daily food intake is reduced by 10%-25% but meal frequency is unchanged) because it may prove to be more sustainable. Fasting has a rich history rooted in religious traditions and has been practiced for thousands of years.[81] Christianity, Judaism, Buddhism, and Islam have advocated various forms of fasting, although Islamic fasts, such as Ramadan, are most similar to secular IF regimens.[82] Fasting has been studied by the medical community since the early 1900s for various conditions, including obesity,[81] and has recently grown in popularity across many regions of the world.

IF refers to episodic periods of little to no calorie consumption. Variations of IF include every-other-day complete 24-hour fasting[83,84] or fasting on 1 or 2 nonconsecutive days per week, typically referred to as the 6:1 and 5:2 diets, respectively.[85,86] Many fasting programs advise no or small caloric intake (eg, 500 kcal daily) during the fasting period[87] with an unlimited amount of calorie-free beverages such as water, coffee (without sugar or milk), bone broth, and diet soft drinks.[88] A third method, TRF, requires limiting the consumption of calories to a window of time, typically between 4 and 12 hours daily.[89] TRF may or may not include CR during the nonfasting period, which may have additional positive effects, including on circadian rhythm.[90] Disruptions in circadian rhythm have been linked to increases in metabolic disorders associated with cancer risk, such as diabetes and obesity, as well as to breast, liver, colon, lung, skin, and prostate cancers.[91,92] A meta-analysis found that 5 years of night shift work increased the risk of breast cancer in women by 3.3%.[93] Disruptions to the circadian rhythm are hypothesized to be involved in tumorigenesis through disruption of the expression in genes involved metabolism, autophagy, and DNA damage repair.[91] Mouse models have shown that IF can reset circadian rhythms, although this depends on feeding time.[94]

is there an optimal feeding time? certainly not near sleep

## Fasting in Preclinical Models

### Intermittent Fasting and Cancer Development and Growth in Rodent Models

IF has been extensively studied in preclinical mouse models of cancer with promising yet mixed results (see Table 2).[95-117] For example, IF did not inhibit spontaneous mammary cancer development and failed to slow tumor growth in DBA mice[95]; however, in xenograft mouse models of breast cancer, melanoma, and neuroblastoma, 2 cycles of 48-hour fasting alone were as effective as 2 cycles of chemotherapy at reducing tumor progression.[101] In a small study of a xenograft LAPC-4 human prostate cancer model, an IF regimen composed of 2 separate 24-hour fasting periods showed trends (hazard ratio, 0.59-0.65; $P > .05$) toward delayed tumor growth and improved survival despite no differences in body weight.[118] However, in the larger follow-up study, there was no difference in mouse survival or tumor volumes between mice in the IF cohort and the control groups.[96] In cancer-prone, p53-deficient mice (mimicking the Li-Fraumeni syndrome in humans), a 1 day per week fasting regimen significantly delayed tumor onset ($P = .001$), reduced tumor metastasis (61% in the fasting group developed metastasis vs 75% in the ad libitum group), and increased overall survival ($P = .039$) compared with mice fed ad libitum, although to a lesser extent than chronic CR.[119] In that study, feeding was controlled on nonfasting days to prevent overfeeding, resulting in a significant reduction in weight in the fasting group. Similarly, human lung, liver, and ovarian tumor-bearing mice undergoing periodic 1-day or 2-day per week fasting protocols experienced decreased tumor growth and metastases and improved survival compared with control mice.[100] In a notable study with no weight change between groups, alternate-day fasting (ADF) for 2 weeks reduced tumor growth in a mouse model of colon cancer ($P < .05$).[99] This was associated with increased expression of *Atg5* and LC3II/I, which are markers of autophagy, suggesting one potential mechanism for the effect of ADF independent of weight loss in mice.

In hematologic malignancies, IF decreased the rate of development of both B-cell and T-cell acute lymphoblastic leukemia, with the fasting mice having 0.48% ± 0.1% of leukemic GFP-positive cells in the peripheral blood 7 weeks posttransplantation compared with 67.7% ± 8.4% in the control mice.[97] However, IF did not decrease the rate of acute myeloid leukemia in mouse models with these tumors.[97] In OF1 mice, 4 months of ADF caused a significant 33% reduction in the incidence of lymphoma.[98] In that study, similar to the colon cancer study,[99] there was no difference in body weight between the fasting and control mice, because fasting mice consumed almost twice the daily amount as control mice on their feast days, suggesting that alternative mechanisms

**TABLE 2. Selected Studies of Intermittent Fasting in Mouse Models of Cancer**

| STUDY | MOUSE STRAIN | TUMOR MODEL | FASTING SCHEDULE | OUTCOME | MECHANISMS |
|---|---|---|---|---|---|
| Intermittent fasting in cancer prevention and treatment | | | | | |
| Tannenbaum 1950[95] | Female DBA inbred strain | Spontaneous mammary tumors | 24-h fasting every Mon and Thurs compared with ad libitum (ad lib) (n = 104) | No difference in the % of mice forming mammary carcinoma and the mean time of appearance of the tumors | Neg results likely due to insufficient weight loss per author |
| Thomas 2010[96] | Male CB-17 SCID | LAPC-4 prostate cancer | 24-h fasting every Mon and Thurs compared with ad lib (n = 100) | No difference in tumor volume at any time point; serum insulin and IGFBP-3 similar; IGF-1 and IGF-1/IGFBP-3 higher in the fasting arm | Neg results likely due to insufficient weight loss per author; higher urine ketone levels in fasting mice gradually declined later on |
| Lu 2017[97] | Irradiated SCID mice | N-Myc B-ALL, Notch1 T-ALL, MLL-AF9 AML | Six cycles of 1-d fasting followed by 1-d feeding; alternative, 2-d fasting followed by 2-d feeding | Completely inhibited B-ALL or T-ALL development, at both early and late stage, prolonged survival, but no effect on AML model; fasting decreased circulating glucose and insulin levels, IGF-1, and leptin and increased IGFBP-1 | Effects of fasting on leukemia development are cancer type-dependent; fasting-attenuated LEPR signaling in ALL development and maintenance |
| Descamps 2005[98] | Aged OF1 mice | Spontaneous lymphoma | Alternate-d fasting (ADF) compared with ad lib | Fasting significantly reduced the incidence of lymphoma (0% vs 33% for controls) | Fasting exerted a beneficial antioxidant effect, absence of weight loss |
| Sun 2017[99] | Female BALB/c | CT26 colon | ADF for 2 wk | Fasting inhibited tumor growth | Fasting altered cancer immune microenvironment without weight loss |
| Chen 2012[100] | Female athymic BALB/c and Beige-nude mice | Human A549 lung, HepG-2 liver, SKOV-3 ovarian | 4 wk of periodic 1-d fasting or 2-d fasting per wk | Fasting led to tumor growth arrest, regression, reduced metastasis, and improved survival | Fasting led to NK cell reactivity and IGFBP-3 increase |
| Lee 2012[101] | BALB/c, C57BL/6 for mouse tumor, nude mice for human tumor | 4T1 breast, B16 melanoma, GL26 glioma, neuroblastoma NXS2, MDA-231, neuroblastoma ACN, OVCAR3 | 48-h fasting every wk × 2 | Fasting was as effective as chemotherapy in delaying progression of different tumors and increased the effectiveness of these drugs against melanoma, glioma, and breast cancer cells | There is tumor growth upon refeeding; fasting differentially regulated translation and proliferation genes and increased oxidative stress, caspase-3 cleavage, DNA damage, and apoptosis |
| Prolonged fasting before and during chemotherapy | | | | | |
| Raffaghello 2008[102] | A/J, CD-1, Nude/nude mice | Neuroblastoma NXS2 | 48-h to 60-h fasting then etoposide | Fasting protects host more than protecting tumor | Fasting causes differential stress resistance in normal and cancer cells |
| Shi 2012[103] | CD-1 female nude mice | Lung adenocarcinoma A549, mesothelioma ZL55 | Fasting started 32 h before and 16 h after CDDP once weekly × 3 | Fasting protects normal cells but not cancer cells from cisplatin | Activation of ATM/Chk2p53 |
| Pietrocola 2016[104] | Female C57Bl/6, BALB/c, and nude athymic mice | MCA205 fibrosarcoma | Fasting 48 h followed by chemotherapy (MTX, oxaliplatin, CDDP) | Improved chemotherapy antitumor effect in immunocompetent mice but not in athymic mice | Fasting induced autophagy, inhibition of regulatory T cells; fasting can be replaced with caloric restriction mimetics such as hydroxycitrate |
| Safdie 2012[105] | C57BL/6N | SC or intracranial murine GL26 glioma, rat C6, human U251 LN229 and A172 glioma | Fasting 48 h before temozolomide or radiation | Sensitized glioma but not glia cells to chemotherapy and radiation efficacy | Fasting reduced glucose and IGF-1 |

**TABLE 2. (Continued)**

| STUDY | MOUSE STRAIN | TUMOR MODEL | FASTING SCHEDULE | OUTCOME | MECHANISMS |
|---|---|---|---|---|---|
| Saleh 2013[106] | Female Balb/c | Orthotopic 4T1, 67NR | ADF and radiation | ADF added to radiotherapy, reduced tumor growth; greater effect if involved caloric restriction | Downregulation of the IGF-1R pathway |
| Bianchi 2015[107] | Balb/c | CT26 colon | 48-h fasting followed by oxaliplatin | Fasting potentiated the effects of oxaliplatin | Fasting downregulated aerobic glycolysis, and glutaminolysis while increasing oxidative phosphorylation; fasting promoted anti-Warburg effect by increased oxygen consumption but failed to generate ATP, resulting in oxidative damage and apoptosis |
| Huisman 2016[108] | Male Balb/c | CT26 colon | 3 d of fasting followed by irinotecan | Fasting prevented toxicities but did not enhance the efficacy of chemotherapy | Fasting induced a lower systemic exposure to SN-38, which may explain the absence of adverse side effects, while tumor levels of SN-38 were unchanged |
| Jongbloed 2019[109] | Male Balb/c | CT26 colon | 3 d of fasting followed by irinotecan | Fasting reduced chemotherapy-induced side effects | Fasting activated a protective stress response in normal tissue but not in cancer |
| Tinkum 2015[110] | B6(Cg)-Tyr$^{c\text{-}2J}$/J | | Fasting for 24 h followed by etoposide | Fasting preserved small intestinal (SI) architecture, improved survival | Fasting maintained SI stem cell viability and SI barrier function; DNA repair and DNA damage response genes were elevated, with DNA damage more efficiently repaired |
| Fasting-mimicking diets (FMDs) as adjuvant cancer treatment | | | | | |
| Di Biase 2016[111] | Female Balb/c, female C57BL/6 | 4T1 breast in Balb/c, B16 melanoma in C57BL/6 | FMD or fasting and chemotherapy (doxorubicin, or cyclophosphamide) | FMD is as effective as fasting alone or in combination with chemotherapy in reducing tumor progression but is not effective in nude mice | FMD reduces IGF-1, increases the levels of bone marrow common lymphoid progenitor cells and cytotoxic CD8-positive tumor-infiltrating lymphocytes; this effect is partially mediated by downregulating HO-1 |
| Caffa 2020[112] | NOD/SCIDγ | MCF7 xenograft | FMD in combination with hormonal therapy (tamoxifen or fulvestrant) and CDK4/6 inhibitor (palbociclib) | FMD improved efficacy of tamoxifen and fulvestrant and CDK4/6 inhibitor; FMD prevented tamoxifen-induced endometrial hyperplasia | FMD lowered circulating IGF-1, insulin, and leptin and inhibits AKT-mTOR signaling by upregulation of EGR1 and PTEN |
| Time-restricted feeding (TRF) in cancer development and treatment | | | | | |
| Das 2021[113] | Female C57BL/6 J, ovariectomized, or chemically induced ovotoxicity; transgenic PyMT female mice | Orthotopic Py230 and E0771 breast cancer cells, tail vein injection of E0771 cells, MMTV-PyMT spontaneous breast cancer | TRF from 10 PM to 6 AM daily with high-fat diet (HFD) | TRF abrogates obesity-enhanced postmenopausal mammary tumor growth in the absence of calorie restriction or weight loss and reduces metastasis in the lung; inhibition of insulin with diazoxide mimics TRF, but insulin pump reverses the effect of TRF | TRF increases insulin sensitivity, reduces hyperinsulinemia, restores diurnal gene expression rhythms in the tumor, and attenuates tumor growth and insulin signaling |
| Sundaram & Yan 2018[114] | MMTV-PyMT mice (FVB) | MMTV-PyMT spontaneous breast cancer | TRF of HFD at dark phase (12 h) between 12 and 24 h | TRF mitigates HFD-enhanced mammary tumorigenesis | TRF reduced the HFD-induced parameters, including plasma leptin, MCP-1, PAI-1, hepatocyte growth factor, and angiogenic factors |

**TABLE 2. (Continued)**

| STUDY | MOUSE STRAIN | TUMOR MODEL | FASTING SCHEDULE | OUTCOME | MECHANISMS |
|---|---|---|---|---|---|
| Yan 2019[115] | Male C57BL/6 mice | Subcutaneous Lewis lung carcinoma xenograft | TRF of HFD at dark phase (12 h) between 12 and 24 h | TRF prevented HFD-enhanced lung metastasis | TRF prevented HFD-induced increase in plasma glucose, insulin, cytokines, and angiogenic factors |
| Turbitt 2020[116] | Balb/c mice | Orthotopic renal tumor cells | TRF of HFD at dark phase for 12 h | TRF did not alter tumor weight, lung, or metastasis and failed to improve anti–CTLA-4 efficacy | TRF did not alter excised renal tumor weights or intratumoral immune response |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CDDP, cisplatin; CDK4/6, cyclin-dependent kinase 4/6; HO-1, heme oxygenase-1; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; IGFBP-3, insulin-like growth factor binding protein 3; LEPR, leptin receptor; MLL, mixed lineage leukemia; MTX, methotrexate; Neg, negative; NK, natural killer; NOD, nonobese diabetic; SCID, severe combined immunodeficiency; T-ALL, T-cell acute lymphoblastic leukemia.

TABLE 2. (Continued)

| STUDY | MOUSE STRAIN | TUMOR MODEL | FASTING SCHEDULE | OUTCOME | MECHANISMS |
|---|---|---|---|---|---|
| Yan 2019[115] | Male C57BL/6 mice | Subcutaneous Lewis lung carcinoma xenograft | TRF of HFD at dark phase (12 h) between 12 and 24 h | TRF prevented HFD-induced metastasis | TRF prevented HFD-induced inc glucose, insulin, cytokines, and factors |
| Turbitt 2020[116] | Balb/c mice | Orthotopic renal tumor cells | TRF of HFD at dark phase for 12 h | TRF did not alter tumor weight, lung, or metastasis and failed to improve anti–CTLA-4 efficacy | TRF did not alter excised renal t intratumoral immune response |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-cell acute lymphoblastic leukemia; CDDP, cisplatin; CDK4/6, cyclin-dependent kinase 4/6; HO-1, heme oxygenase-1; HFD, high-fat diet; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor 1 receptor; IGFBP-3, insulin-like growth factor binding protein 3; LEPR, leptin receptor; MLL, mixed lineage leukemia; MTX, methotrexate; Neg, negative; NK, natural killer; NOD, nonobese diabetic; SCID, severe combined immunodeficiency; T-ALL, T-cell acute lymphoblastic leukemia.

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beyond weight change may play a role in the effects of fasting.[98] On the basis of studies in mice and rats, these mechanisms may include changes in fasting glucose, insulin, and IGF-1.[84,120]

Rats can sustain longer fasting periods than mice, and results in these rodents are mostly negative, with few exceptions (Table 3).[121-126] An early study conducted in 1988 did find that rats who were initiated on ADF 1 week before intraperitoneal injection of mammary ascites tumor cells had longer survival than those fed ad libitum (50% vs 12.5% survival at 10 days, respectively).[121] In another positive study, rats exposed to a liver chemical carcinogenesis process were randomized to usual diet, fasting for 48 hours before the carcinogenesis process, or fasting for 48 hours each week for 1 month after the exposure to carcinogenic chemicals.[122] Fasting was successful in decreasing the number and size of liver nodules, but only when implemented after the induction of the carcinogenesis process.[122] In contrast, refeeding after fasting has been associated with promotion of carcinogenesis in several rat studies.[123,124] In an experiment evaluating the effect of fasting/refeeding on promotion of hepatocarcinogenesis, the percentage of liver volume occupied by altered hepatic foci was greater at 140 days in animals who underwent 2 cycles of prolonged fasting for 5 days after carcinogenesis induction (days 16-21 and days 23-28) than in ad libitum-fed controls (2.446% ± 1.1700 in the fasting group vs 1.201% ± 0.3595 in the control group).[123] Similarly, rats who underwent 3 cycles of 3 consecutive days of fasting followed by refeeding (11 days) 1 week after carcinogenesis exposure had a statistically significant 50% higher incidence of hepatocellular carcinoma than control animals at 1 year.[124] Moreover, cancers in the group that underwent the fasting/refeeding cycles were found to be larger and more aggressive.[124] A sharp increase in hepatocyte proliferation was observed on day 2 of refeeding.[124] In a rat model of colon carcinogenesis, animals who underwent 5 cycles of 4-day fasting followed by 7 to 10 days of refeeding, which consisted of resuming an ad libitum protein-containing chow diet after exposure to carcinogens, experienced higher rates of crypt multiplicity (preneoplastic lesions) at the end of the experiments (70 and 92 days).[125,127] In addition, the cell proliferation rate was higher (mitotic index, 1.9 ± 0.5 in the refed group vs 1.3 ± 0.4 in the control group after 70 days), and the apoptotic index was lower in the aberrant crypt foci (apoptotic index, 2.2 ± 0.1 in the refed group vs 4.0 ± 0.3 in the control group after 70 days) in rats undergoing fasting/refeeding.[125] Finally, rats that fasted for 4 days followed by refeeding with a subnecrotizing diethylnitrosamine carcinogenesis exposure (started after 1 day of refeeding) were found to have liver carcinomas, whereas no preneoplastic or neoplastic lesions were detected in the regularly fed mice.[126]

TABLE 3. Selected Studies of Intermittent Fasting in Rat Models of Cancer

| STUDY | RAT STRAIN | TUMOR MODEL | FASTING SCHEDULE | OUTCOME |
|---|---|---|---|---|
| Siegel 1988[121] | Fisher rat | Intraperitoneal Mat 13762 | Alternate d of fasting initiated 1 wk before seeding tumor cells | Alternate d of fasting led to longer survival of tumor-bearing rat, with minimum weight loss |
| Rocha 2002[122] | Wistar rat | Diethylnitrosamine (DEN)-induced hepatocarcinogenesis | Group 1, ad libitum (ad lib); group 2, 48-h fasting before DEN treatment, then ad lib; group 3, after DEN treatment, start 48-h fasting weekly × 48 cycles | Fasting before DEN initiation did not influence the development of preneoplastic lesions (group 2 vs group 1); however, long-term intermittent fasting during postinitiation stage decreased the number and size of premalignant liver nodules (group 3 vs group 1) |
| Hikita 1997[123] | Female Sprague-Dawley rat | DEN-induced hepatocarcinogenesis | DEN treatment followed by 2 periods of 5 d of fasting separated by 2 d (fasting on d 16-20, then on d 24-28), then fed ad lib | The initial transient inhibition of hepatic preneoplastic lesions associated with fasting period promoted hepatocarcinogenesis during subsequent refeeding period (more liver lesions developed at 140 d for mice fasted early on) |
| Tomasi 1999[124] | Male Fischer 344 rat | DEN-induced hepatocarcinogenesis | DEN injection; 1 wk later, started 3 cycles of 3-d fasting followed by 11-d refeeding, then fed ad lib | Fasting/refeeding early after carcinogen initiation led to 2-fold increase in the incidence of hepatocellular carcinoma compared with those fed ad lib (72% vs 36%) at 1 y; in addition, there was a sharp increase in hepatocyte proliferation on d 2 of refeeding. |
| Caderni 2002[125] | Male Fischer 344 rat | Azoxymethane (AOM)-induced colorectal carcinogenesis | AOM injection; 1 wk later, started 5 cycles of 4-d fasting followed by 7-d to 10-d refeeding, then fed ad lib | Fasting/refeeding caused a dramatic increase in transcript multiplicity 70 and 92 d after AOM; fasting/refeeding increased mitotic and labeling index in the aberrant crypt foci, with associated decrease in p21 and increase in TGFβ1 |
| Tessitore 1998[126] | Fischer 344 rat | DENA-induced hepatocarcinogenesis | Fast × 4 d, then refeed with DENA at subnecrogenic dose given after 1 d of refeeding | Fasting/refeeding made the subnecrogenic dose of DENA able to initiate hepatocyte and development of cancer |

TABLE 3. Selected Studies of Intermittent Fasting in Rat Models of Cancer

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| Tomasi 1999[124] | Male Fischer 344 rat | DEN-induced hepatocarcinogenesis | DEN injection; 1 wk later, started 3 cycles of 3-d fasting fol- lowed by 11-d refeeding, then fed ad lib | Fasting/refeeding early after carcinogen initiation led to 2-fol incidence of hepatocellular carcinoma compared with those 36%) at 1 y; in addition, there was a sharp increase in hepa d 2 of refeeding. |
| Caderni 2002[125] | Male Fischer 344 rat | Azoxymethane (AOM)-induced colorectal carcinogenesis | AOM injection; 1 wk later, started 5 cycles of 4-d fasting fol- lowed by 7-d to 10-d refeeding, then fed ad lib | Fasting/refeeding caused a dramatic increase in transcript mu after AOM; fasting/refeeding increased mitotic and labeling crypt foci, with associated decrease in p21 and increase in |
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## Time-Restricted Feeding and Cancer in Rodent Models

Very few rodent studies and no human studies have evaluated the independent effects of TRF in modulating cancer risk through synchronization of circadian rhythms. In a recent study of high-fat–driven, postmenopausal breast cancer mouse models, TRF markedly inhibited tumor initiation, progression, and metastasis compared with mice fed ad libitum in the absence of CR or weight loss. This beneficial effect of TRF was probably mediated, at least in part, by reduced insulin signaling because systemic insulin infusion through implanted pumps reversed the TRF-mediated cancer protective actions.[113] Similarly, Sundaram and Yan found that TRF prevented the procarcinogenic effects of a high-fat diet in a transgenic MMTV-PyMT model of spontaneous breast cancer.[114] This group also demonstrated that TRF prevented high-fat diet–enhanced metastasis in a subcutaneously injected Lewis lung cancer mouse model.[115] In contrast, TRF failed to demonstrate reductions of tumor growth, weight, or metastasis in a high-fat diet mouse model of renal cancer.[116]

## Summary of Fasting and Cancer Development and Growth in Rodent Models

Overall, the data regarding the effects of fasting on cancer development and growth in rodent models are inconsistent. The negative or even potentially harmful effects of fasting seen in some animal models of cancer may be secondary to the timing and length of the fasting schedules or to other unknown factors, such as a detrimental impact on insulin regulation and maladaptive molecular responses to refeeding. Nonetheless, these findings strongly suggest that more IF preclinical studies are needed to better understand the underlying mechanisms and differences in outcomes before clinicians may start to consider safely and confidently prescribing fasting for the treatment of cancer in humans.

## Intermittent Fasting and Cancer in Humans

Although there have been no reported studies of IF in nonhuman primates, given the feasibility and favorable weight loss effect of different forms of IF in overweight and obese men and women, clinical trials have been conducted to test its impact on metabolic and hormonal end points that are linked with cancer development or prognosis, mostly in patients without cancer.[128,129]

Several short-term (2-6 months) randomized clinical trials have shown favorable effects of ADF or a 5:2 diet in improving some cancer risk factors, including decreased fasting glucose, insulin, and leptin levels and increased adiponectin,[130] all of which have been implicated in cancer pathogenesis.[131] However, several long-term (12-month) trials of IF failed to demonstrate any significant improvement in insulin sensitivity or C-reactive protein at month 6 or 12,[132-134] especially when more sophisticated indexes

of insulin sensitivity (eg, the Quantitative Insulin Sensitivity Check Index and the Matsuda index) were used.[135] Small and underpowered studies of TRF have found significant changes in weight-associated metabolic parameters such as insulin sensitivity and oxidative stress.[136-138] However, in a large, randomized controlled trial of TRF in 116 overweight/obese men and women, despite high adherence to the TRF protocol (8-hour feeding window), there was no statistically significant change in weight compared with the control group, nor were there any significant differences in fasting insulin or fasting glucose levels.[139] Moreover, accumulating data suggest that, unlike in rodents, in which metabolic adaptations of IF are independent of weight change, in humans, weight loss is required to improve metabolic health.

Few studies have been conducted in cancer populations themselves (Table 4),[140-147] but many are underway to examine the role of IF in cancer biology and recurrence. A small nonrandomized study of 23 women at increased risk for breast cancer found that 1 month of IF (2 days per week of 65% energy restriction) led to a 4.8% reduction in body weight, a 8.0% reduction in body fat, and an improvement in the Homeostatic Model Assessment (HOMA) for Insulin Resistance Index on both fasting and nonfasting days.[148] Changes in breast tissue gene expression from matched preintervention and postintervention biopsies were variable, with no clear change in cancer-associated pathways.[148] Currently, there are several ongoing trials in the advanced cancer setting, with one trial examining the role of IF in reducing tumor progression in patients treated for metastatic prostate cancer (ClinicalTrials.gov identifier NCT02710721) and another in patients with metastatic breast cancer on endocrine therapy (ClinicalTrials.gov identifier NCT04708860). Additional IF trials among survivors of breast cancer (ClinicalTrials.gov identifier NCT04330339), prostate cancer (ClinicalTrials.gov identifier NCT04288336), colon cancer (ClinicalTrials.gov identifier NCT04345978), chronic lymphocytic leukemia/small lymphocytic lymphoma (ClinicalTrials.gov identifier NCT04626843), gliomas (ClinicalTrials.gov identifier NCT04461938), and childhood cancers (ClinicalTrials.gov identifier NCT03523377) are ongoing, although the breast and prostate trials have a primary outcome of feasibility, and most studies have secondary outcomes focused on either weight-associated metabolic parameters (breast cancers, gliomas, childhood cancers) or biomarker recurrence (prostate cancers, chronic lymphocytic leukemia). Only the colon cancer trial has a survival-based outcome, with the primary outcome of disease-free survival and the secondary outcome of overall survival.

## Mechanisms of Intermittent Fasting in Cancer: Rodents Are Not Humans

Evidence of the role of IF in cancer prevention is mainly from preclinical data derived from cell lines and animal models and lacks uniformity in its conclusions. Moreover, important caveats when extrapolating data from animal models to humans are the remarkable differences in biologic adaptations to fasting between rodents and humans. For example, because of their high metabolic rate, most strains of mice die of starvation after a 48-hour to 60-hour fast. In contrast, even lean humans can undergo 57 to 73 days of total fasting before death occurs.[149] This suggests that a 24-hour fast-feed cycle in mice most likely equates approximately to recurrent 5-day fast-feed cycles in humans. There may also be notable gender differences because levels of ketone bodies after fasting have been found to be lower in men than in women, potentially because of differences in glucose requirements.[150] In addition, rodent models undergoing IF are fed nutritionally balanced chow during nonfasting periods, whereas humans consuming a typical Western diet are likely to ingest additional empty calories from a range of ultra-processed, nutrient-poor foods. Although preclinical models have added value because they to attempt to elucidate the underlying mechanisms of IF, translation into humans is imperfect. Therefore, future studies focused on clinical testing of IF in humans have the greatest potential to provide meaningful results for patients with cancer.

### *Intermittent fasting and IGF-1*

Rodent models undergoing IF have noted decreased leptin and IGF-1 levels.[119] IF in mice markedly increases FGF21, which plays a major role in reducing IGF-1 levels through hepatic inhibition of phosphorylated STAT5.[151] IGF-1 promotes cancer development through the inhibition of apoptosis while increasing cell proliferation and genomic instability,[152] and higher levels of IGF-1 have been associated with breast, colon, and prostate cancer.[40-43] However, some studies have shown that IF does not reduce serum IGF-1 concentrations in humans.[72,153] IF also increases IGFBP-1 in rodents,[151] which reduces IGF-1 bioavailability and has been shown to decrease cell motility in a breast cancer cell line.[154] Decreased expression of IGFBP-1 has also been associated with metastasis and worse survival in hepatocellular carcinoma.[155] Interestingly, daily CR causes a sustained increase in circulating IGFBP-1 levels in humans,[72] but nothing is known on the effects of IF.

### *Intermittent fasting and ketone formation*

Although some mechanisms of fasting and chronic CR may overlap, the formation of ketone bodies is unique to fasting. Under fasting conditions, ketone bodies are produced in the liver from fatty acids as the main source of brain energy.[156,157] Ketone bodies have been shown to inhibit histone deacetylases and may decrease tumor growth.[158,159] In addition, the ketone body β-hydroxybutyrate acts as an endogenous histone deacetylase inhibitor, resulting in downstream signaling that protects against oxidative stress.[160] However, in mice, plasma concentrations of ketones increase after just

**TABLE 4. Clinical Studies**

| STUDY | STUDY TYPE | TUMOR TYPE | PATIENT POPULATION | FASTING SCHEDULE | OUTCOME |
|---|---|---|---|---|---|
| de Groot 2015[140] | Randomized pilot study | HER2-negative breast cancer, stage II/III | 13 patients receiving (neo)-adjuvant chemotherapy | Randomized to fast 24 h before and after chemotherapy vs diet compatible with guidelines for healthy nutrition | • Fasting well tolerated<br>• Fasting reduced hematologic toxicity<br>• Fasting may promote the recovery of chemotherapy-induced DNA damage |
| Dorff 2016[141] | Feasibility study | Breast, ovarian, and uterine cancers, any stage | 20 patients receiving platinum-based chemotherapy | Fasting before chemotherapy for 24, 48, or 72 h | • Fasting feasible and safe<br>• Trend toward decreased rates of neutropenia and neuropathy in fasting cohorts<br>• Less DNA damage in fasting cohorts |
| Zorn 2020[142] | Pilot study | Gynecologic cancers, any stage | 30 patients undergoing (neo)-adjuvant chemotherapy with a minimum of 4 cycles of the same chemotherapy protocol | Short-term fasting for 96 h during one-half of planned chemotherapy cycles and a regular diet during the remaining cycles | • Fasting associated with higher ketone bodies and lower circulating insulin and IGF-1 levels<br>• Decreased frequency and severity of stomatitis, headaches, and weakness;, decreased total toxicity score, fewer chemotherapy delays during fasting<br>• No improvement in patient reported quality of life, chemotherapy induced neuropathy or fatigue |
| Badar 2014[143] | Feasibility study | Various cancers (breast, non-Hodgkin lymphoma, acute myeloid leukemia, nasopharynx, ovarian, and colon) | 11 patients receiving chemotherapy | Patients received chemotherapy during Ramadan fasting | • Fasting safe and well tolerated |
| Safdie 2009[144] | Case series | Various cancers (breast, prostate, ovarian, uterine, nonsmall cell lung, and esophageal) | 10 patients receiving chemotherapy | Patients underwent fasting before (48-140 h) and/or after (5-56 h) chemotherapy | • Fasting safe and well tolerated<br>• Reduced fatigue, weakness, and gastrointestinal adverse events reported while fasting |
| Bauersfeld 2018[145] | Randomized pilot study | Breast and ovarian cancer, any stage | 34 patients receiving chemotherapy | Patients randomized to a short-term fasting diet in the first one-half of chemotherapy, followed by a normocaloric diet or randomized to the normocaloric diet, followed by the short-term fasting diet | • Patients undergoing the fasting diet had improved quality of life and fatigue within 8 d of chemotherapy |
| de Groot 2020[146] | Randomized phase 2 study | HER2-negative breast cancer, stage II/III | 131 patients receiving neoadjuvant chemotherapy | Fasting-mimicking diet (FMD) (4-d plant-based low amino-acid substitution diet with soups, broths, liquids, and tea) 3 d before and during neoadjuvant chemotherapy | • No difference between grade 3/4 toxicity during chemotherapy between patients in the fasting cohort and the usual care cohort<br>• FMD cohort more likely to have Miller-Payne 4/5 pathologic response<br>• Patients with greater adherence to the FMD had a higher percentage of Miller- Payne scores of 4/5 |
| Marinac 2016[147] | Prospective | Breast cancer, early stage | 2413 patients completed 24-h dietary recalls collected at baseline, y 1, and y 4 | Dietary recalls used to estimate nightly fasting duration | • Fasting <13 h per night associated with a 36% increased risk of breast cancer recurrence compared with those fasting for ≥13 h per night |

4 to 7 hours of fasting and peak after 24 hours,[161] whereas, in humans, ketone bodies do not start to increase until 18 to 24 hours and do not peak until 2 weeks of fasting.[141,162,163] This is an example of the unique physiologic differences that must be considered when determining how studies from mouse models should inform human studies.

### *Autophagy*

Another potential mechanism by which IF may affect cancer cells is through autophagy, a lysosomal-degradation pathway that allows for homeostasis within the cell by recycling molecules and clearing damaged proteins and organelles.[164-166] As a result of autophagy, sugars, nucleosides/nucleotides, amino acids, and fatty acids are produced that can then be reused by the cell.[167] However, the association between autophagy and cancer is complex. Autophagy has been linked to both procarcinogenic and anticarcinogenic processes, regulating both oncogenes and tumor-suppressor genes.[168-170] It has been hypothesized that dysregulation of autophagy may contribute to tumorigenesis[171-174] through a complex series of mechanisms that allow tumor cells to survive periods of stress, including nutrient deprivation.[175] Fasting in mammals has been shown to induce autophagy,[176] and this starvation-induced autophagy may protect normal cells against malignant transformation.[173] Furthermore, fasting-related autophagy may affect cancer therapies because it has been shown to sensitize cancer cells to chemotherapy.[177,178] Nevertheless, enhanced autophagy may also play a role in resistance to certain cancer therapies.[179,180] Whether or not IF increases autophagic processes in humans is unknown, and more research is needed to better understand the possible benefits and harms of fasting-related autophagy in patients with cancer.

## Periodic, Prolonged Fasting as a Potential Cancer Treatment

In contrast to IF, which consists of frequent 18-hour to 24-hour periods without or with limited amounts of food, prolonged periodic fasting that lasts >24 hours may have important therapeutic roles in protecting normal tissues against chemotherapy and radiotherapy toxicity.[181] Unlike normal cells, cancer cells are capable of uncontrolled growth because of genomic alterations such as mutations in oncogenes, including *RAS*, *AKT*, and *mTOR*.[182] These mutated oncogenes may prevent cancer cells, but not normal cells, from switching into a stress-resistance mode during fasting.[183] This mechanism has been termed the *differential stress response* and could explain why fasting may protect healthy cells from toxic effects of chemotherapy while improving treatment efficacy on cancer cells.[184] In addition, cancer cells are known to have an altered metabolism that relies primarily on glycolysis and results in increased glucose uptake and fermentation of glucose to lactate, known as the Warburg effect.[185] Therefore, glucose starvation, as seen in prolonged fasting and in ketogenic diets, may sensitize cancer cells to the damaging effects of chemotherapy (which have increased reliance on glucose uptake) and promote apoptosis.[181] Moreover, marked reductions of IGF-1 induced by prolonged fasting in rodents and humans also have the potential to preferentially sensitize cancer cells to chemotherapy.[186] Indeed, circulating IGF-1 levels are 80% lower in liver IGF-1–deficient mice, which are protected against chemotherapy-related toxicity.[186] Decreased levels of IGF-1 as a result of fasting have also been shown to increase hematopoietic stem cell–based regeneration and reverse immunosuppression in mice undergoing prolonged fasting.[187]

## Rodent Studies of Prolonged Fasting Before and During Cancer Therapy

Prolonged fasting has been studied in mice undergoing treatment for malignancy as an adjuvant therapy. As with the prevention data, the results have been mixed with regard to the impact of prolonged fasting on both treatment-related toxicity and tumor growth. In metastatic neuroblastoma mouse models, mice that underwent 48 to 60 hours of fasting before intravenous injection of high-dose etoposide had reduced chemotherapy toxicity but experienced a diminished etoposide-induced effect on metastases and cancer-dependent death because of partial protection of NXS2 cancer cells.[102] In mesothelioma and lung cancer xenograft models, mice undergoing 48 hours of fasting per week timed concurrently with cisplatin chemotherapy were found to have significantly decreased tumor progression and, in some cases (60% of mesothelioma xenografts and 40% of lung carcinoma xenografts), complete remission.[103] No complete remissions were observed in the chemotherapy-alone cohort of mice in that study.[103] A study of fibrosarcoma mouse models found that a 48-hour fast before chemotherapy improved the efficacy of chemotherapy,[104] but this effect was not observed in autophagy-deficient mice that harbored knockdown of the autophagy-related gene *Atg5*, which is consistent with the notion that intact autophagy is required for a response to immunogenic chemotherapy.[104] In subcutaneous allografts of breast cancer (4T1), melanoma (b16), and neuroblastoma (NXS2, Neuro-2a), 2 cycles of fasting alone (48 hours each) were as effective as 2 cycles of chemotherapy (cyclophosphamide for breast cancer and doxorubicin for melanoma and neuroblastoma) at reducing tumor progression 20 days after the final treatment.[101] In the melanoma models, however, cancer progression was not affected after the first cycle of fasting, which potentially suggests a concerning acquired cancer resistance to fasting alone.[101] In the same study, fasting combined with chemotherapy was superior in terms of cancer-free survival at 300 days compared with chemotherapy alone in breast cancer, melanoma, and glioma mouse models.[101] In a separate study of glioma

models, fasting for 48 hours before the administration of temozolomide sensitized mice to the treatment and improved survival.[105] A study of 2 murine models of triple-negative breast cancers showed that ADF provided an additive effect to radiation therapy, resulting in reduced tumor growth, with an even greater effect when ADF involved CR.[106]

In contrast, in a colon cancer model, 48 hours per week of fasting concurrently with oxaliplatin chemotherapy resulted only in a transient reduction of cancer growth, mostly during the fasting period, but not in the postfasting period.[107] Similarly, subcutaneous human breast cancer and ovarian cancer xenograft models were noted to have reductions in tumor growth initially, but this effect was reversed after refeeding.[101] In a colorectal cancer model, mice treated with irinotecan were randomized to fasting or nonfasting before chemotherapy.[108] Those randomized to fasting experienced fewer side effects (diarrhea and neutropenia), but there was no difference in tumor response over the nonfasting group.[108] A potential protective mechanism of fasting against irinotecan toxicity might be mediated by transcriptional changes leading to decreased hepatic cell injury and improved stress resistance.[109] In addition, fasting has been suggested to reduce chemotherapy-related toxicity by promoting small intestinal epithelial stem cell survival, in turn preserving small intestine architecture and barrier function.[110]

### Rodent Studies of Fasting-Mimicking Diets Before and During Cancer Therapy

Because water-only fasting for >48 to 60 hours is deadly in most strains of laboratory mice, FMDs that can be administered over many days have been developed and tested, with promising results in both mice and humans. These diets are low in protein and carbohydrates, high in unsaturated fat, and provide between 10% and 50% of calories of normal ad libitum intake. In mouse breast cancer and melanoma models, mice underwent 48 to 60 hours of fasting or a 96-hour FMD. The FMD consisted of 1 day of low-calorie broth, vegetable medley powder, olive oil, and essential fatty acids followed by 2 to 4 days of low-calorie broth powders and glycerol.[188] The FMD alone or in combination with chemotherapy was shown to decrease tumor progression as effectively as short-term starvation.[111] The FMD in combination with doxorubicin was found to promote CD3-positive/CD8-positive tumor-infiltrating lymphocytes, a marker of favorable therapeutic response.[111,189]

In addition to combining fasting with chemotherapy in rodent models, a recent study examined fasting and endocrine therapy. In several mouse models of hormone receptor-positive breast cancer, an FMD increased the efficacy of endocrine therapy by increasing antitumor activity and preventing acquired resistance,[112] and it lowered circulating levels of IGF-1, insulin, and leptin, which have important implications for estrogen-independent estrogen receptor activity and promote the growth of hormone receptor-positive breast cancer.[112] Fasting upregulated EGR1 and PTEN, which have been associated with an improved prognosis in breast cancer as a result of the downregulation of AKT-mTOR signaling, a pathway that is associated with tumor growth and endocrine resistance in breast cancer.[112] Finally, in mice receiving endocrine therapy and a cyclin-dependent kinase 4/6 inhibitor, an FMD enhanced tumor regression and reversed acquired resistance to endocrine therapy treatment compared with pharmacotherapy alone.[112]

### Impact of Prolonged Fasting and Fasting-Mimicking Diets on Cancer Treatment Toxicity in Humans

Currently, there are limited chemoprotective therapies available: these include 1) mesna, which detoxifies metabolites of cyclophosphamide in the kidney and reduces bladder hemorrhage, although this chemoprotective effect is relatively narrow; and 2) amifostine, which reduces the incidence of neutropenia-related fever and infection induced by DNA-binding chemotherapeutic agents but has several common and serious side effects.[190] However, a few small preliminary clinical studies suggest that markedly reducing calorie and/or protein intake before and during chemotherapy might reduce the acute and chronic detrimental effects of chemotherapy and improve quality of life.

In one study, 13 patients with HER2-negative, stage II/III breast cancer receiving standard-of-care chemotherapy with docetaxel, doxorubicin, and cyclophosphamide were randomized to fast for 24 hours before and after chemotherapy (n = 7) or to a nonfasting diet (n = 6) following standard guidelines for healthy nutrition.[140] This fasting regimen was well tolerated, and only 2 patients withdrew from the study secondary to side effects (pyrosis and recurrent febrile neutropenia), which were unlikely related to fasting. Short-term fasting was also found to reduce hematologic toxicity in women receiving chemotherapy, with significantly higher erythrocyte and thrombocyte counts after chemotherapy in the fasting arm. Patients in the control cohort were found to have increased markers of DNA damage after chemotherapy compared with those who had fasted and had lower circulating IGF-1 levels.[140] The authors hypothesized that fasting might promote the recovery of chemotherapy-induced DNA damage.

In a feasibility study, 20 patients with multiple tumor types (including mainly breast, ovarian, and uterine cancers) received various platinum-based chemotherapy regimens and underwent fasting before chemotherapy for either 24, 48, or 72 hours.[141] The study found that fasting was feasible and safe, with minimal side effects, comprising fatigue, headache, and dizziness. Thirteen of the 20 patients reported calorie consumption within the complaint range,

but 2 experienced grade 1 weight loss (from 5% to <10%) in this trial.[141] Compared with those who fasted for 24 hours before chemotherapy, patients who fasted for 48 to 72 hours before chemotherapy experienced a nonsignificant trend toward decreased rates of neutropenia as well as lower rates of neuropathy.[141] Markers of DNA damage in peripheral blood mononuclear cells were increased in all cohorts but less so in the longer fasting cohort.[141]

A recently published pilot study examined short-term fasting in 30 patients with gynecologic cancers who were undergoing chemotherapy.[142] Patients underwent modified short-term fasting for 96 hours during one-half of planned chemotherapy cycles and a regular diet during the remaining cycles, resulting in mild weight loss (<5%) with apparent preservation of lean mass. Physiologic blood ketosis (blood ketone level ≥ 0.6 mmol/L) was measured as an indicator of patient compliance and was observed in 40 of the 56 (71.4%) chemotherapy cycles. As expected, this prolonged fasting was associated with lower circulating insulin and IGF-1 levels, and patients reported significantly decreased frequency and severity of headaches, weakness, and stomatitis. The latter may be secondary to less oral trauma during fasting. In addition, the total toxicity score was significantly reduced during the fasting periods, and there were significantly fewer chemotherapy delays as well. There was no improvement in patient-reported quality of life, chemotherapy-induced neuropathy, or fatigue.[142]

Although there was initial concern regarding weight loss in patients with cancer who were undergoing chemotherapy, no trials have reported severe weight loss or malnutrition as a result of fasting.[191] In a small uncontrolled study of 11 patients with various malignancies who were receiving chemotherapy during the Ramadan fast, fasting was found to be safe and well tolerated.[143] In a small case series, 10 patients with multiple types of cancer, including breast, prostate, ovarian, uterine, nonsmall cell lung, and esophageal cancers, underwent fasting before (48-140 hours) and/or after (5-56 hours) chemotherapy.[144] Patients were treated with an average of 4 cycles of chemotherapy. That case series found that fasting was safe and well tolerated, with the only significant side effects reported as hunger and light-headedness.[144] In addition, patients reported reduced fatigue, weakness, and gastrointestinal adverse events while fasting.[144] As a case series, that report was limited by patient and tumor heterogeneity as well as a lack of standardized fasting protocols. In a small study of 34 patients with breast and ovarian cancer undergoing chemotherapy, patients were randomized to a short-term fasting diet in the first one-half of chemotherapy followed by a normocaloric diet or to the normocaloric diet followed by the short-term fasting diet.[145] Patients began the fast 36 hours before chemotherapy and ended fasting 24 hours after chemotherapy, consuming only water, tea, vegetable broth, and vegetable juice for a maximum 350 kcal per day. No significant weight loss was reported; however, 8 of the 15 patients discontinued the study because of poor adherence. Those patients who successfully completed the fasting diet reported improved quality of life and fatigue within 8 days of chemotherapy. These improvements were not observed during the normocaloric diet.

As discussed above, FMDs may be more attractive than true fasting diets in patients with cancer because these low-sugar, low-protein diets are supposed to mimic the effects of fasting with less restriction on food intake.[188] In the DIRECT trial of 131 women with HER2-negative, stage II/III breast cancer (ClinicalTrials.gov identifier NCT02126449), chemotherapy-induced DNA damage in T lymphocytes was significantly reduced in patients who consumed an FMD 3 days before and during neoadjuvant chemotherapy.[146] The FMD in that study comprised a 4-day plant-based, low-amino-acid substitution diet with soups, broths, liquids, and tea; 81.5% patients completed the FMD during the first cycle, but only 33.8% tolerated the FMD with all cycles of chemotherapy, citing dislike of the diet as the main reason for noncompliance. The study found no difference in grade 3 and 4 toxicity during chemotherapy between the fasting and usual care cohorts, although patients on the FMD did not receive dexamethasone (typically used to reduce toxicity),[146] suggesting a potential role of fasting in reducing chemotherapy-related toxicity.

### Prolonged Fasting and Fasting-Mimicking Diets as Adjunctive Therapies to Cancer Treatment in Humans

As part of the prospective Women's Healthy Eating and Living Study, 24-hour dietary recall data were collected on >2400 women with a history of breast cancer but without a history of diabetes.[147] In a secondary analysis, fasting for <13 hours per night was associated with a 36% increased risk of breast cancer recurrence compared with fasting for ≥13 hours per night (hazard ratio, 1.36; 95% CI, 1.05-1.76).[147] In the above discussed DIRECT trial, patients in the FMD cohort were more likely to have Miller-Payne pathologic response scores of 4 or 5, indicating from 90% to 100% tumor cell loss after neoadjuvant chemotherapy.[146] In addition, patients with greater adherence to the FMD (as assessed by lower glucose, insulin, and IGF-1 levels and higher ketone bodies) had a higher percentage of Miller and Payne scores of 4 or 5 in the surgical specimen.[146] To our knowledge, this is the only reported study of fasting with a pathologic outcome related to prognosis. There is one study ongoing in patients with localized prostate cancer to determine whether long-term IF can prevent recurrence, with no results reported to date (ClinicalTrials.gov identifier NCT04288336). Another trial ongoing in patients with multiple tumor types to receive

monthly cycles of an FMD also includes progression-free survival and overall survival as secondary end points, but the primary end point is feasibility and safety (ClinicalTrials.gov identifier NCT03595540). Several other trials are in progress to assess the impact of different dietary manipulations on the response to various therapeutic agents but, clearly, more well designed and appropriately powered randomized clinical trials are needed to assess the effects of fasting or FMDs on recurrence risk and survival outcomes before recommending the practice of fasting or FMD in patients with cancer. Moreover, many overweight and obese men and women with cancer take a range of drugs (eg, antidiabetic and antihypertensive agents), which could have serious negative, and potentially fatal, consequences when coupled with fasting, including hypotension and severe hypoglycemia.

## Future Directions

Data regarding IF and radiation are limited.[192] A preclinical study in a mouse model of pancreatic cancer examined fasting for 24 hours before abdominal radiation.[193] Fasting reduced toxicity, allowing for increasing doses of radiation, but it did not impair tumor cell death from radiation. Fasting was also found to enhance the effects of concurrent chemotherapy and radiation in murine glioma models.[105] Clinical trials in humans have been limited. The CAREFOR trial is an ongoing feasibility trial involving CR in patients with early stage breast cancer undergoing radiation therapy (ClinicalTrials.gov identifier NCT01819233). Data regarding fasting and radiation are largely limited to the preclinical setting; therefore, further clinical trials are needed before fasting during radiation therapy can be recommended to patients.

Over the past 10 years, immunotherapy has increasingly changed the landscape of cancer care and is included in the frontline standard-of-care treatment for multiple advanced malignancies, including melanoma, nonsmall cell cancer, renal cell cancer, and some breast, bladder, and colon cancers. Although more studies are needed, nutrition likely has effects on leukocytes and thus may have important implications for immune responses in cancer.[194] Obesity has been associated with fewer cytotoxic T cells and natural killer cells.[195,196] As described above, fasting and CR decrease IGF-1 levels and activate autophagy. This, in turn, may promote an increase in precursors of CD8-positive T lymphocytes and enhance the immune response.[194,197] Preclinical models studying the combination of immunotherapy, chemotherapy, and fasting showed improved tumor responses in mouse models of mammary tumors and fibrosarcomas, with a 90% cure rate (9 of 10 mice had complete tumor regression) compared with a 40% cure rate using chemotherapy and immunotherapy alone.[198] Clinical data are sparse; however, 2 ongoing clinical trials are examining the feasibility of IF and immunotherapy in melanoma (ClinicalTrials.gov identifier NCT04387084) and nonsmall cell lung cancer (ClinicalTrials.gov identifier NCT03700437).

## Conclusions

Substantial evidence demonstrates that obesity, with its associated metabolic, molecular, and immunologic alterations, increases the risk and worsens the prognosis of many common cancers. Thus weight management is crucial to patients with cancer and cancer survivors. Research is ongoing to evaluate the role of IF in cancer prevention and cancer-related outcomes because it is effective in reducing body weight and may have indirect and direct effects on tumor biology as well. However, human studies evaluating the effects of IF on growth signaling from insulin and other pertinent hormonal and inflammatory markers of carcinogenesis appear to be clinically insignificant, at least with the current data, which often lack statistical power and long-term follow-up. The effects of IF on clinically relevant cancer outcomes such as cancer incidence and prognosis after a diagnosis of cancer are unknown because there is a lack of human studies. Moreover, data in rodents are inconsistent and suggest potential detrimental effects of IF in certain oncologic conditions. Despite the knowledge gaps and challenges surrounding changing human dietary patterns, IF remains an attractive modality to explore in a research setting, especially when combined with a healthy diet and regular physical activity,[199] because it is associated with minimal side effects, is affordable, and likely exerts its effects in a tumor-agnostic fashion.

suck-up section: ACS, no recs!

## Recommendations for Clinicians

For overweight and obese patients seeking weight loss or weight management as means of primary cancer prevention, IF may be an option, especially when coupled during nonfasting days with the dietary and exercise recommendations of the American Cancer Society Guideline for Diet and Physical Activity.[199] Several observational studies and a few small clinical trials suggest that prolonged fasting in selected patients with cancer who receive chemotherapy may be safe, feasible, and potentially capable of decreasing chemotherapy-related toxicity and tumor growth. However, preclinical data are inconsistent with minimal data from human clinical trials. Therefore, additional studies are warranted to determine whether patients will ultimately benefit from fasting, and, if so, in what ways, before recommending IF in the management of patients with cancer. In conclusion, we would recommend against IF for patients undergoing active cancer treatment unless doing so as part of a clinical trial. We would also advise patients who previously used IF as a weight-loss strategy before a cancer diagnoses not to continue it during treatment unless doing so as part of a clinical trial. In long-term cancer survivors no longer on active cancer therapy, such as chemotherapy or radiation

therapy, we would recommend clinicians discuss IF with patients who are interested in pursuing it and clarify their goals of IF. As a weight-loss strategy, this may be an option for patients, but there are currently no data to suggest that IF in the absence of weight loss and/or changes in diet quality and physical activity patterns will have a positive impact on cancer outcomes, including either recurrence or the development of secondary cancers. However, there may be potential benefits for other cardiometabolic conditions common in cancer survivors such as obesity, diabetes mellitus, and cardiovascular disease. As with any potential therapeutic strategy, the risks and benefits of fasting must be discussed with patients. In the case of IF and cancer, the benefits are not well defined, and the risks have to be ruled out. ■

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