

Intermittent Fasting in the Prevention and Treatment of Cancer

Katherine K. Clifton, MD ¹; Cynthia X. Ma, MD, PhD¹; Luigi Fontana, MD, PhD, FRACP^{2,3,4}; Lindsay L. Peterson, MD, MSCR ¹

¹School of Medicine, Division of Medical Oncology, Washington University in St Louis, St Louis, Missouri; ²Charles Perkins Center, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales Australia; ³Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, New South Wales Australia; ⁴Department of Clinical and Experimental Sciences, Brescia University, Brescia, Italy.

Corresponding Authors: Luigi Fontana MD, PhD, FRACP, Charles Perkins Centre, John Hopkins Drive, The University of Sydney, NSW 2006, Australia (luigi.fontana@sydney.edu.au); Lindsay L. Peterson, MD, MSCR, Washington University, 660 South Euclid Avenue, Campus Box 8056, St Louis, MO 63110 (llpeterson@wustl.edu).

The last 2 authors contributed equally to this article.

DISCLOSURES: Luigi Fontana is supported by grants from the Australian National Health and Medical Research Council (Investigator Grant APP1177797), the Australian Youth and Health Foundation, and the Philip Bushell Foundation). Cynthia X. Ma reports grants and personal fees from Puma and Pfizer and personal fees from Eli Lilly, Novartis, Seattle Genetics, Agendia, AstraZeneca, Phillips Electronics, Tempus, Biovica, Bayer, and Sanofi outside the submitted work. Luigi Fontana reports book royalties from Hardie for his book *The Path to Longevity* (2020) outside the submitted work. Lindsay L. Peterson reports a Mentored Research Scholar Grant (MRSG1819901NEC) from the American Cancer Society paid to the Washington University School of Medicine outside the submitted work. Katherine K. Clifton reports a grant from the Cancer and Aging Research Group outside the submitted work.

doi: 10.3322/caac.21694. Available online at cancerjournal.com

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.

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

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

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 rationale 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,

free radical–mediated DNA damage, and an impaired DNA repair response.^{44,45} In addition, systemic inflammation can promote cancer development⁴⁶ 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 inflammation⁷⁴ 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 period⁸⁷ 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

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 mice⁹⁵; 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 $0.48\% \pm 0.1\%$ of leukemic GFP-positive cells in the peripheral blood 7 weeks posttransplantation compared with $67.7\% \pm 8.4\%$ 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-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
Caiffa 2020 ¹¹²	NOD/SCIDy	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 ovariotoxicity; 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.

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 refeed 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 refeed 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

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 non-human 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 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	<ul style="list-style-type: none"> Fasting well tolerated Fasting reduced hematologic toxicity 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	<ul style="list-style-type: none"> Fasting feasible and safe Trend toward decreased rates of neutropenia and neuropathy 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	<ul style="list-style-type: none"> Less DNA damage in fasting cohorts Fasting associated with higher ketone bodies and lower circulating insulin and IGF-1 levels Decreased frequency and severity of stomatitis, headaches, and weakness; decreased total toxicity score, fewer chemotherapy delays during fasting
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	<ul style="list-style-type: none"> No improvement in patient reported quality of life, chemotherapy induced neuropathy or fatigue Fasting safe and well tolerated
Safdie 2009 ¹⁴⁴	Case series	Various cancers (breast, prostate, ovarian, uterine, non-small cell lung, and esophageal)	10 patients receiving chemotherapy	Patients underwent fasting before (48-140 h) and/or after (5-56 h) chemotherapy	<ul style="list-style-type: none"> Fasting safe and well tolerated 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> No difference between grade 3/4 toxicity during chemotherapy between patients in the fasting cohort and the usual care cohort FMD cohort more likely to have Miller-Payne 4/5 pathologic response 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	<ul style="list-style-type: none"> 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 tumorigenesis¹⁷¹⁻¹⁷⁴ 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 re-feeding.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.

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. ■

References

- Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2018. *NCHS Data Brief*. 2020;355:1-8.
- Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71:7-33.
- Howlander N, Noone AM, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2016. National Cancer Institute; 2019.
- Miller KD, Nogueira L, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2019. *CA Cancer J Clin*. 2019;69:363-385.
- Beckjord EB, Reynolds KA, van Londen GJ, et al. Population-level trends in post-treatment cancer survivors' concerns and associated receipt of care: results from the 2006 and 2010 LIVESTRONG surveys. *J Psychosoc Oncol*. 2014;32:125-151.
- Foster C, Wright D, Hill H, Hopkinson J, Roffe L. Psychosocial implications of living 5 years or more following a cancer diagnosis: a systematic review of the research evidence. *Eur J Cancer Care*. 2009;18:223-247.
- Burg MA, Adorno G, Lopez EDS, et al. Current unmet needs of cancer survivors: analysis of open-ended responses to the American Cancer Society Study of Cancer Survivors II. *Cancer*. 2015;121:623-630.
- Donin N, Filson C, Drakaki A, et al. Risk of second primary malignancies among cancer survivors in the United States, 1992 through 2008. *Cancer*. 2016;122:3075-3086.
- Mariotto AB, Rowland JH, Ries LA, Scoppa S, Feuer EJ. Multiple cancer prevalence: a growing challenge in long-term survivorship. *Cancer Epidemiol Biomarkers Prev*. 2007;16:566-571.
- Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000;343:78-85.
- Islami F, Goding Sauer A, Miller KD, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. *CA Cancer J Clin*. 2018;68:31-54.
- Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375:794-798.
- Petrelli F, Cortellini A, Indini A, et al. Association of obesity with survival outcomes in patients with cancer: a systematic review and meta-analysis. *JAMA Network Open*. 2021;4:e213520.
- Longo VD, Fontana L. Calorie restriction and cancer prevention: metabolic and molecular mechanisms. *Trends Pharmacol Sci*. 2010;31:89-98.
- International Food Information Council (IFIC). 2020 Food & Health Survey [press release]. IFIC; 2020. Accessed June 15, 2021. [ific.org/media-information/press-releases/2020-food-and-health-survey/](https://www.ific.org/media-information/press-releases/2020-food-and-health-survey/)
- Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. *Breast Cancer Res Treat*. 2010;123:627-635.
- Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. *Cancer Prev Res*. 2011;4:486-501.
- Sinicrope FA, Foster NR, Sargent DJ, O'Connell MJ, Rankin C. Obesity is an independent prognostic variable in colon cancer survivors. *Clin Cancer Res*. 2010;16:1884-1893.
- Troeschel AN, Hartman TJ, Jacobs EJ, et al. Postdiagnosis body mass index, weight change, and mortality from prostate cancer, cardiovascular disease, and all causes among survivors of nonmetastatic prostate cancer. *J Clin Oncol*. 2020;38:2018-2027.
- Di Bella CM, Howard LE, Oyekunle T, et al. Abdominal and pelvic adipose tissue distribution and risk of prostate cancer recurrence after radiation therapy. *Prostate*. 2020;80:1244-1252.
- Greenlee H, Shi Z, Molmenti CLS, Rundle A, Tsai WY. Trends in obesity prevalence in adults with a history of cancer: results from the US National Health Interview Survey, 1997 to 2014. *J Clin Oncol*. 2016;34:3133-3140.
- Goodwin PJ, Ennis M, Pritchard KI, et al. Adjuvant treatment and onset of menopause predict weight gain after breast cancer diagnosis. *J Clin Oncol*. 1999;17:120.
- Lennon H, Sperrin M, Badrick E, Renehan AG. The obesity paradox in cancer: a review. *Curr Oncol Rep*. 2016;18:56.
- Lee DH, Giovannucci EL. The obesity paradox in cancer: epidemiologic insights and perspectives. *Curr Nutr Rep*. 2019;8:175-181.
- Park Y, Peterson LL, Colditz GA. The plausibility of obesity paradox in cancer—point. *Cancer Res*. 2018;78:1898-1903.
- Zhou Z, Macpherson J, Gray SR, et al. Are people with metabolically healthy obesity really healthy? A prospective cohort study of 381,363 UK Biobank participants. *Diabetologia*. Published online June 10, 2021. doi:10.1007/S00125-021-05484-6
- Sanchez A, Furberg H, Kuo F, et al. Transcriptomic signatures related to the obesity paradox in patients with clear cell renal cell carcinoma: a cohort study. *Lancet Oncol*. 2020;21:283-293.
- Santoni M, Cortellini A, Buti S. Unlocking the secret of the obesity paradox in renal tumours. *Lancet Oncol*. 2020;21:194-196.
- Lohmann AE, Goodwin PJ, Chlebowski RT, Pan K, Stambolic V, Dowling RJ. Association of obesity-related metabolic disruptions with cancer risk and outcome. *J Clin Oncol*. 2016;34:4249-4255.
- Boden G. Obesity and free fatty acids. *Endocrinol Metab Clin North Am*. 2008;37:635-646, viii-ix.
- Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab*. 2004;89:2548-2556.

32. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes*. 2007;56:1010-1013.
33. Goodwin PJ, Ennis M, Pritchard KI, et al. Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic associations. *J Clin Oncol*. 2012;30:164-171.
34. Duggan C, Irwin ML, Xiao L, et al. Associations of insulin resistance and adiponectin with mortality in women with breast cancer. *J Clin Oncol*. 2011;29:32-39.
35. Prisco M, Romano G, Peruzzi F, Valentini B, Baserga R. Insulin and IGF-I receptors signaling in protection from apoptosis. *Horm Metab Res*. 1999;31(2-3):80-89.
36. Pugeat M, Crave JC, Elmidani M, et al. Pathophysiology of sex hormone binding globulin (SHBG): relation to insulin. *J Steroid Biochem Mol Biol*. 1991;40(4-6):841-849.
37. Poretsky L, Kalin MF. The gonadotropic function of insulin. *Endocr Rev*. 1987;8:132-141.
38. Powell DR, Suwanichkul A, Cabbage ML, DePaolis LA, Snuggs MB, Lee PD. Insulin inhibits transcription of the human gene for insulin-like growth factor-binding protein-1. *J Biol Chem*. 1991;266:18868-18876.
39. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. *JAMA*. 1997;278:1407-1411.
40. Shanmugalingam T, Bosco C, Ridley AJ, Van Hemelrijck M. Is there a role for IGF-1 in the development of second primary cancers? *Cancer Med*. 2016;5:3353-3367.
41. Peyrat JP, Bonnetterre J, Hecquet B, et al. Plasma insulin-like growth factor-1 (IGF-1) concentrations in human breast cancer. *Eur J Cancer*. 1993;29A:492-497.
42. Chen C, Zhang Q, Liu S, et al. IL-17 and insulin/IGF1 enhance adhesion of prostate cancer cells to vascular endothelial cells through CD44-VCAM-1 interaction. *Prostate*. 2015;75:883-895.
43. Nomura AMY, Stemmermann GN, Lee J, Pollak MN. Serum insulin-like growth factor I and subsequent risk of colorectal cancer among Japanese-American men. *Am J Epidemiol*. 2003;158:424-431.
44. Sachdev D, Yee D. The IGF system and breast cancer. *Endocr Relat Cancer*. 2001;8:197-209.
45. Flototto T, Djahansouzi S, Glaeser M, et al. Hormones and hormone antagonists: mechanisms of action in carcinogenesis of endometrial and breast cancer. *Horm Metab Res*. 2001;33:451-457.
46. Galdiero MR, Marone G, Mantovani A. Cancer inflammation and cytokines. *Cold Spring Harbor Perspect Biol*. 2018;10:a028662.
47. Michelet X, Dyck L, Hogan A, et al. Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. *Nat Immunol*. 2018;19:1330-1340.
48. Floris G, Richard F, Hamy AS, et al. Body mass index and tumor-infiltrating lymphocytes in triple-negative breast cancer. *J Natl Cancer Inst*. 2021;113:146-153.
49. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. *Ann Transl Med*. 2017;5:161.
50. Bray GA. Medical consequences of obesity. *J Clin Endocrinol Metab*. 2004;89:2583-2589.
51. Vucenik I, Stains JP. Obesity and cancer risk: evidence, mechanisms, and recommendations. *Annals N Y Acad Sci*. 2012;1271:37-43.
52. Chlebowski RT, Aragaki AK, Anderson GL, et al. Association of low-fat dietary pattern with breast cancer overall survival: a secondary analysis of the Women's Health Initiative randomized clinical trial. *JAMA Oncol*. 2018;4:e181212.
53. Hoy MK, Winters BL, Chlebowski RT, et al. Implementing a low-fat eating plan in the Women's Intervention Nutrition Study. *J Am Diet Assoc*. 2009;109:688-696.
54. Blackburn GL, Wang KA. Dietary fat reduction and breast cancer outcome: results from the Women's Intervention Nutrition Study (WINS). *Am J Clin Nutr*. 2007;86:s878-s881.
55. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: the Women's Healthy Eating and Living (WHEL) randomized trial. *JAMA*. 2007;298:289-298.
56. Redman LM, Ravussin E. Caloric restriction in humans: impact on physiological, psychological, and behavioral outcomes. *Antioxid Redox Signal*. 2011;14:275-287.
57. Tannenbaum A. The genesis and growth of tumors. III. Effects of a high-fat diet. *Cancer Res*. 1942;2:468.
58. Weindruch R, Walford RL. Dietary restriction in mice beginning at 1 year of age: effect on life-span and spontaneous cancer incidence. *Science*. 1982;215:1415-1418.
59. Birt DF, Kris ES, Choe M, Pelling JC. Dietary energy and fat effects on tumor promotion. *Cancer Res*. 1992;52(7 suppl):2035s-2039s.
60. Albanes D. Total calories, body weight, and tumor incidence in mice. *Cancer Res*. 1987;47:1987-1992.
61. Boissonneault GA, Elson CE, Pariza MW. Net energy effects of dietary fat on chemically induced mammary carcinogenesis in F344 rats. *J Natl Cancer Inst*. 1986;76:335-338.
62. Kalaany NY, Sabatini DM. Tumours with PI3K activation are resistant to dietary restriction. *Nature*. 2009;458:725-731.
63. Gibbs RA, Rogers J, Katze MG, et al. Evolutionary and biomedical insights from the rhesus macaque genome. *Science*. 2007;316:222-234.
64. Colman RJ, Anderson RM, Johnson SC, et al. Caloric restriction delays disease onset and mortality in rhesus monkeys. *Science*. 2009;325:201-204.
65. Mattison JA, Roth GS, Beasley TM, et al. Impact of caloric restriction on health and survival in rhesus monkeys from the NIA study. *Nature*. 2012;489:318-321.
66. Folkman J, Kalluri R. Cancer without disease. *Nature*. 2004;427:787.
67. Carlsson LMS, Sjöholm K, Jacobson P, et al. Life expectancy after bariatric surgery in the Swedish Obese Subjects Study. *N Engl J Med*. 2020;383:1535-1543.
68. Anveden A, Taube M, Peltonen M, et al. Long-term incidence of female-specific cancer after bariatric surgery or usual care in the Swedish Obese Subjects Study. *Gynecol Oncol*. 2017;145:224-229.
69. Yeh HC, Bantle JP, Cassidy-Begay M, et al. Intensive weight loss intervention and cancer risk in adults with type 2 diabetes: analysis of the Look AHEAD randomized clinical trial. *Obesity (Silver Spring)*. 2020;28:1678-1686.
70. Kraus WE, Bhapkar M, Huffman KM, et al. Two years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2019;7:673-683.
71. Weiss EP, Racette SB, Villareal DT, et al. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. *Am J Clin Nutr*. 2006;84:1033-1042.
72. Fontana L, Villareal DT, Das SK, et al. Effects of 2-year calorie restriction on circulating levels of IGF-1, IGF-binding proteins and cortisol in nonobese men

- and women: a randomized clinical trial. *Aging Cell*. 2016;15:22-27.
73. Cangemi R, Friedmann AJ, Holloszy JO, Fontana L. Long-term effects of calorie restriction on serum sex-hormone concentrations in men. *Aging Cell*. 2010;9:236-242.
 74. Meydani SN, Das SK, Pieper CF, et al. Long-term moderate calorie restriction inhibits inflammation without impairing cell-mediated immunity: a randomized controlled trial in non-obese humans. *Aging*. 2016;8:1416-1431.
 75. Il'yasova D, Fontana L, Bhopkar M, et al. Effects of 2 years of caloric restriction on oxidative status assessed by urinary F2-isoprostanes: the CALERIE 2 randomized clinical trial. *Aging Cell*. 2018;17:e12719.
 76. Hofer T, Fontana L, Anton SD, et al. Long-term effects of caloric restriction or exercise on DNA and RNA oxidation levels in white blood cells and urine in humans. *Rejuvenation Res*. 2008;11:793-799.
 77. Heilbronn LK, de Jonge L, Frisard MI, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. *JAMA*. 2006;295:1539-1548.
 78. Mercken EM, Crosby SD, Lamming DW, et al. Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile. *Aging Cell*. 2013;12:645-651.
 79. Yang L, Licastro D, Cava E, et al. Long-term calorie restriction enhances cellular quality-control processes in human skeletal muscle. *Cell Rep*. 2016;14:422-428.
 80. Fontana L, Mitchell SE, Wang B, et al. The effects of graded caloric restriction: XII. Comparison of mouse to human impact on cellular senescence in the colon. *Aging Cell*. 2018;17:e12746.
 81. Kerndt PR, Naughton JL, Driscoll CE, Loxterkamp DA. Fasting: the history, pathophysiology and complications. *West J Med*. 1982;137:379-399.
 82. Hoddy KK, Marlatt KL, Cetinkaya H, Ravussin E. Intermittent fasting and metabolic health: from religious fast to time-restricted feeding. *Obesity (Silver Spring)*. 2020;28(suppl 1):S29-S37.
 83. Bruce-Keller AJ, Umberger G, McFall R, Mattson MP. Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. *Ann Neurol*. 1999;45:8-15.
 84. Anson RM, Guo Z, de Cabo R, et al. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. *Proc Natl Acad Sci U S A*. 2003;100:6216-6220.
 85. Fung J. *The Obesity Code: Unlocking the Secrets of Weight Loss*. Greystone Books; 2016.
 86. Harvie MN, Pegington M, Mattson MP, et al. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. *Int J Obes (Lond)*. 2011;35:714-727.
 87. Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. *Nutr Rev*. 2015;73:661-674.
 88. Stote KS, Baer DJ, Spears K, et al. A controlled trial of reduced meal frequency without caloric restriction in healthy, normal-weight, middle-aged adults. *Am J Clin Nutr*. 2007;85:981-988.
 89. Rothschild J, Hoddy KK, Jambazian P, Varady KA. Time-restricted feeding and risk of metabolic disease: a review of human and animal studies. *Nutr Rev*. 2014;72:308-318.
 90. Panda S. Circadian physiology of metabolism. *Science*. 2016;354:1008-1015.
 91. Sulli G, Lam MTY, Panda S. Interplay between circadian clock and cancer: new frontiers for cancer treatment. *Trends Cancer*. 2019;5:475-494.
 92. Sulli G, Manoogian ENC, Taub PR, Panda S. Training the circadian clock, clocking the drugs, and drugging the clock to prevent, manage, and treat chronic diseases. *Trends Pharmacol Sci*. 2018;39:812-827.
 93. Yuan X, Zhu C, Wang M, Mo F, Du W, Ma X. Night shift work increases the risks of multiple primary cancers in women: a systematic review and meta-analysis of 61 articles. *Cancer Epidemiol Biomarkers Prev*. 2018;27:25-40.
 94. Froy O, Chapnik N, Miskin R. Effect of intermittent fasting on circadian rhythms in mice depends on feeding time. *Mech Ageing Dev*. 2009;130:154-160.
 95. Tannenbaum A, Silverstone H. Failure to inhibit the formation of mammary carcinoma in mice by intermittent fasting. *Cancer Res*. 1950;10:577-579.
 96. Thomas JA 2nd, Antonelli JA, Lloyd JC, et al. Effect of intermittent fasting on prostate cancer tumor growth in a mouse model. *Prostate Cancer Prostatic Dis*. 2010;13:350-355.
 97. Lu Z, Xie J, Wu G, et al. Fasting selectively blocks development of acute lymphoblastic leukemia via leptin-receptor upregulation. *Nat Med*. 2017;23:79-90.
 98. Descamps O, Riondel J, Ducros V, Roussel AM. Mitochondrial production of reactive oxygen species and incidence of age-associated lymphoma in OF1 mice: effect of alternate-day fasting. *Mech Ageing Dev*. 2005;126:1185-1191.
 99. Sun P, Wang H, He Z, et al. Fasting inhibits colorectal cancer growth by reducing M2 polarization of tumor-associated macrophages. *Oncotarget*. 2017;8:74649-74660.
 100. Chen X, Lin X, Li M. Comprehensive modulation of tumor progression and regression with periodic fasting and refeeding circles via boosting IGF1R-3 loops and NK responses. *Endocrinology*. 2012;153:4622-4632.
 101. Lee C, Raffaghello L, Brandhorst S, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med*. 2012;4:124ra127.
 102. Raffaghello L, Lee C, Safdie FM, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. *Proc Natl Acad Sci U S A*. 2008;105:8215-8220.
 103. Shi Y, Felley-Bosco E, Marti TM, Orłowski K, Pruschy M, Stahel RA. Starvation-induced activation of ATM/Chk2/p53 signaling sensitizes cancer cells to cisplatin. *BMC Cancer*. 2012;12:571.
 104. Pietrocola F, Pol J, Vacchelli E, et al. Caloric restriction mimetics enhance anticancer immunosurveillance. *Cancer Cell*. 2016;30:147-160.
 105. Safdie F, Brandhorst S, Wei M, et al. Fasting enhances the response of glioma to chemo- and radiotherapy. *PLoS One*. 2012;7:e44603.
 106. Saleh AD, Simone BA, Palazzo J, et al. Caloric restriction augments radiation efficacy in breast cancer. *Cell Cycle*. 2013;12:1955-1963.
 107. Bianchi G, Martella R, Ravera S, et al. Fasting induces anti-Warburg effect that increases respiration but reduces ATP-synthesis to promote apoptosis in colon cancer models. *Oncotarget*. 2015;6:11806-11819.
 108. Huisman SA, de Bruijn P, Ghobadi Moghaddam-Helmantel IM, et al. Fasting protects against the side effects of irinotecan treatment but does not affect anti-tumour activity in mice. *Br J Pharmacol*. 2016;173:804-814.
 109. Jongbloed F, Huisman SA, van Steeg H, et al. The transcriptomic response to irinotecan in colon carcinoma bearing mice preconditioned by fasting. *Oncotarget*. 2019;10:2224-2234.

110. Tinkum KL, Stemler KM, White LS, et al. Fasting protects mice from lethal DNA damage by promoting small intestinal epithelial stem cell survival. *Proc Natl Acad Sci U S A*. 2015;112:E7148-E7154.
111. Di Biase S, Lee C, Brandhorst S, et al. Fasting-mimicking diet reduces HO-1 to promote T cell-mediated tumor cytotoxicity. *Cancer Cell*. 2016;30:136-146.
112. Caffa I, Spagnolo V, Vernieri C, et al. Fasting-mimicking diet and hormone therapy induce breast cancer regression. *Nature*. 2020;583:620-624.
113. Das M, Ellies LG, Kumar D, et al. Time-restricted feeding normalizes hyperinsulinemia to inhibit breast cancer in obese postmenopausal mouse models. *Nat Commun*. 2021;12:565.
114. Sundaram S, Yan L. Time-restricted feeding mitigates high-fat diet-enhanced mammary tumorigenesis in MMTV-PyMT mice. *Nutr Res*. 2018;59:72-79.
115. Yan L, Sundaram S, Mehus AA, Picklo MJ. Time-restricted feeding attenuates high-fat diet-enhanced spontaneous metastasis of Lewis lung carcinoma in mice. *Anticancer Res*. 2019;39:1739-1748.
116. Turbitt WJ, Orlandella RM, Gibson JT, Peterson CM, Norian LA. Therapeutic time-restricted feeding reduces renal tumor bioluminescence in mice but fails to improve anti-CTLA-4 efficacy. *Anticancer Res*. 2020;40:5445-5456.
117. Thompson HJ, McTiernan A. Weight cycling and cancer: weighing the evidence of intermittent caloric restriction and cancer risk. *Cancer Prev Res (Phila)*. 2011;4:1736-1742.
118. Buschemeyer WC 3rd, Klink JC, Mavropoulos JC, et al. Effect of intermittent fasting with or without caloric restriction on prostate cancer growth and survival in SCID mice. *Prostate*. 2010;70:1037-1043.
119. Berrigan D, Perkins SN, Haines DC, Hursting SD. Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice. *Carcinogenesis*. 2002;23:817-822.
120. Wan R, Camandola S, Mattson MP. Intermittent fasting and dietary supplementation with 2-deoxy-D-glucose improve functional and metabolic cardiovascular risk factors in rats. *FASEB J*. 2003;17:1133-1134.
121. Siegel I, Liu TL, Nepomuceno N, Gleicher N. Effects of short-term dietary restriction on survival of mammary ascites tumor-bearing rats. *Cancer Invest*. 1988;6:677-680.
122. Rocha NS, Barbisan LF, de Oliveira MLC, de Camargo JLV. Effects of fasting and intermittent fasting on rat hepatocarcinogenesis induced by diethylnitrosamine. *Teratog Carcinog Mutagen*. 2002;22:129-138.
123. Hikita H, Vaughan J, Pitot HC. The effect of two periods of short-term fasting during the promotion stage of hepatocarcinogenesis in rats: the role of apoptosis and cell proliferation. *Carcinogenesis*. 1997;18:159-166.
124. Tomasi C, Laconi E, Laconi S, Greco M, Sarma DS, Pani P. Effect of fasting/refeeding on the incidence of chemically induced hepatocellular carcinoma in the rat. *Carcinogenesis*. 1999;20:1979-1983.
125. Caderni G, Perrelli MG, Cecchini F, Tessitore L. Enhanced growth of colorectal aberrant crypt foci in fasted/refed rats involves changes in TGFbeta1 and p21CIP expressions. *Carcinogenesis*. 2002;23:323-327.
126. Tessitore L. Hepatocellular carcinoma is induced by a subnecrogenic dose of diethylnitrosamine in previously fasted-refed rats. *Nutr Cancer*. 1998;32:49-54.
127. McLellan EA, Medline A, Bird RP. Sequential analyses of the growth and morphological characteristics of aberrant crypt foci: putative preneoplastic lesions. *Cancer Res*. 1991;51:5270-5274.
128. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. *N Engl J Med*. 2019;381:2541-2551.
129. Patterson RE, Laughlin GA, LaCroix AZ, et al. Intermittent fasting and human metabolic health. *J Acad Nutr Diet*. 2015;115:1203-1212.
130. Cho Y, Hong N, Kim KW, et al. The effectiveness of intermittent fasting to reduce body mass index and glucose metabolism: a systematic review and meta-analysis. *J Clin Med*. 2019;8:1645.
131. Grossmann ME, Cleary MP. The balance between leptin and adiponectin in the control of carcinogenesis—focus on mammary tumorigenesis. *Biochimie*. 2012;94:2164-2171.
132. Sundfor TM, Svendsen M, Tonstad S. Effect of intermittent versus continuous energy restriction on weight loss, maintenance and cardiometabolic risk: a randomized 1-year trial. *Nutr Metab Cardiovasc Dis*. 2018;28:698-706.
133. Schubel R, Nattenmuller J, Sookthai D, et al. Effects of intermittent and continuous calorie restriction on body weight and metabolism over 50 wk: a randomized controlled trial. *Am J Clin Nutr*. 2018;108:933-945.
134. Trepanowski JF, Kroeger CM, Barnosky A, et al. Effect of alternate-day fasting on weight loss, weight maintenance, and cardioprotection among metabolically healthy obese adults: a randomized clinical trial. *JAMA Intern Med*. 2017;177:930-938.
135. Stekovic S, Hofer SJ, Tripolt N, et al. Alternate day fasting improves physiological and molecular markers of aging in healthy, non-obese humans. *Cell Metab*. 2020;31:878-881.
136. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab*. 2018;27:1212-1221.e3.
137. Jamshed H, Beyl RA, Della Manna DL, Yang ES, Ravussin E, Peterson CM. Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, aging, and autophagy in humans. *Nutrients*. 2019;11:1234.
138. Hutchison AT, Regmi P, Manoogian ENC, et al. Time-restricted feeding improves glucose tolerance in men at risk for type 2 diabetes: a randomized crossover trial. *Obesity (Silver Spring)*. 2019;27:724-732.
139. Lowe DA, Wu N, Rohdin-Bibby L, et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: the TREAT randomized clinical trial. *JAMA Intern Med*. 2020;180:1491-1499.
140. de Groot S, Vreeswijk MP, Welters MJ, et al. The effects of short-term fasting on tolerance to (neo)adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study. *BMC Cancer*. 2015;15:652.
141. Dorff TB, Groshen S, Garcia A, et al. Safety and feasibility of fasting in combination with platinum-based chemotherapy. *BMC Cancer*. 2016;16:360.
142. Zorn S, Ehret J, Schauble R, et al. Impact of modified short-term fasting and its combination with a fasting supportive diet during chemotherapy on the incidence and severity of chemotherapy-induced toxicities in cancer patients—a controlled cross-over pilot study. *BMC Cancer*. 2020;20:578.
143. Badar T, Ismail A, AlShanqeeti A. Safety and feasibility of Muslim fasting while receiving chemotherapy. *IOSR J Pharm*. 2014;4:15-20.
144. Safdie FM, Dorff T, Quinn D, et al. Fasting and cancer treatment in humans: a case series report. *Aging (Albany NY)*. 2009;1:988-1007.
145. Bauersfeld SP, Kessler CS, Wischnewsky M, et al. The effects of short-term fasting

- on quality of life and tolerance to chemotherapy in patients with breast and ovarian cancer: a randomized cross-over pilot study. *BMC Cancer*. 2018;18:476.
146. de Groot S, Lugtenberg RT, Cohen D, et al. Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial. *Nat Commun*. 2020;11:3083.
 147. Marinac CR, Nelson SH, Breen CI, et al. Prolonged nightly fasting and breast cancer prognosis. *JAMA Oncol*. 2016;2:1049-1055.
 148. Harvie MN, Sims AH, Pegington M, et al. Intermittent energy restriction induces changes in breast gene expression and systemic metabolism. *Breast Cancer Res*. 2016;18:57.
 149. Leiter LA, Marliss EB. Survival during fasting may depend on fat as well as protein stores. *JAMA*. 1982;248:2306-2307.
 150. Haymond MW, Karl IE, Clarke WL, Pagliara AS, Santiago JV. Differences in circulating gluconeogenic substrates during short-term fasting in men, women, and children. *Metabolism*. 1982;31:33-42.
 151. Inagaki T, Lin VY, Goetz R, Mohammadi M, Mangelsdorf DJ, Kliewer SA. Inhibition of growth hormone signaling by the fasting-induced hormone FGF21. *Cell Metab*. 2008;8:77-83.
 152. Yu H, Rohan T. Role of the insulin-like growth factor family in cancer development and progression. *J Natl Cancer Inst*. 2000;92:1472-1489.
 153. Fontana L, Weiss EP, Villareal DT, Klein S, Holloszy JO. Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans. *Aging Cell*. 2008;7:681-687.
 154. Zhang X, Yee D. Insulin-like growth factor binding protein-1 (IGFBP-1) inhibits breast cancer cell motility. *Cancer Res*. 2002;62:4369-4375.
 155. Dai B, Ruan B, Wu J, et al. Insulin-like growth factor binding protein-1 inhibits cancer cell invasion and is associated with poor prognosis in hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2014;7:5645-5654.
 156. Kimura I, Inoue D, Maeda T, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proc Natl Acad Sci U S A*. 2011;108:8030-8035.
 157. Gano LB, Patel M, Rho JM. Ketogenic diets, mitochondria, and neurological diseases. *J Lipid Res*. 2014;55:2211-2228.
 158. Newman JC, Verdin E. Ketone bodies as signaling metabolites. *Trends Endocrinol Metab*. 2014;25:42-52.
 159. Zimmermann S, Kiefer F, Prudenziati M, et al. Reduced body size and decreased intestinal tumor rates in HDAC2-mutant mice. *Cancer Res*. 2007;67:9047-9054.
 160. Shimazu T, Hirschey MD, Newman J, et al. Suppression of oxidative stress by β -hydroxybutyrate, an endogenous histone deacetylase inhibitor. *Science*. 2013;339:211-214.
 161. Schreiber RA, Yeh YY. Temporal changes in plasma levels and metabolism of ketone bodies by liver and brain after ethanol and/or starvation in C57BL/6J mice. *Drug Alcohol Depend*. 1984;13:151-160.
 162. Cahill GF Jr, Herrera MG, Morgan AP, et al. Hormone-fuel interrelationships during fasting. *J Clin Invest*. 1966;45:1751-1769.
 163. Haller W, Bines JE. Starvation and fasting: biochemical aspects. In: Caballero B, ed. *Encyclopedia of Human Nutrition*. 3rd ed. Academic Press; 2013:209-218.
 164. Antunes F, Erustes AG, Costa AJ, et al. Autophagy and intermittent fasting: the connection for cancer therapy? *Clinics (Sao Paulo)*. 2018;73 (suppl 1):e814s.
 165. Levine B, Klionsky DJ. Development by self-digestion: molecular mechanisms and biological functions of autophagy. *Dev Cell*. 2004;6:463-477.
 166. Bagherniya M, Butler AE, Barreto GE, Sahebkar A. The effect of fasting or calorie restriction on autophagy induction: a review of the literature. *Ageing Res Rev*. 2018;47:183-197.
 167. Kimmelman AC, White E. Autophagy and tumor metabolism. *Cell Metab*. 2017;25:1037-1043.
 168. Yun CW, Lee SH. The roles of autophagy in cancer. *Int J Med Sci*. 2018;19:3466.
 169. Mrakovcic M, Frohlich LF. p53-mediated molecular control of autophagy in tumor cells. *Biomolecules*. 2018;8:14.
 170. Botti J, Djavaheri-Mergny M, Pilatte Y, Codogno P. Autophagy signaling and the cogwheels of cancer. *Autophagy*. 2006;2:67-73.
 171. Amaravadi R, Kimmelman AC, White E. Recent insights into the function of autophagy in cancer. *Genes Dev*. 2016;30:1913-1930.
 172. Galluzzi L, Pietrocola F, Bravo-San Pedro JM, et al. Autophagy in malignant transformation and cancer progression. *EMBO J*. 2015;34:856-880.
 173. White E, Mehnert JM, Chan CS. Autophagy, metabolism, and cancer. *Clin Cancer Res*. 2015;21:5037-5046.
 174. Liu J, Debnath J. Chapter 1. The evolving, multifaceted roles of autophagy in cancer. In: Tew KD, Fisher PB, eds. *Advances in Cancer Research*. Vol 130. Academic Press; 2016:1-53.
 175. Degenhardt K, Mathew R, Beaudoin B, et al. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. *Cancer Cell*. 2006;10:51-64.
 176. Kroemer G, Marino G, Levine B. Autophagy and the integrated stress response. *Mol Cell*. 2010;40:280-293.
 177. Marino G, Kroemer G. Ammonia: a diffusible factor released by proliferating cells that induces autophagy. *Sci Signal*. 2010;3:pe19. doi:10.1126/scisignal.3124pe19
 178. Chi KH, Wang YS, Huang YC, et al. Simultaneous activation and inhibition of autophagy sensitizes cancer cells to chemotherapy. *Oncotarget*. 2016;7:58075-58088.
 179. Chen Z, Jiang Q, Zhu P, et al. NPRL2 enhances autophagy and the resistance to everolimus in castration-resistant prostate cancer. *Prostate*. 2019;79:44-53.
 180. Xiao X, Wang W, Li Y, et al. HSP90AA1-mediated autophagy promotes drug resistance in osteosarcoma. *J Exp Clin Cancer Res*. 2018;37:201.
 181. Naveed S, Aslam M, Ahmad A. Starvation based differential chemotherapy: a novel approach for cancer treatment. *Oman Med J*. 2014;29:391-398.
 182. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100:57-70.
 183. Raffaghello L, Safdie F, Bianchi G, Dorff T, Fontana L, Longo VD. Fasting and differential chemotherapy protection in patients. *Cell Cycle*. 2010;9:4474-4476.
 184. de Groot S, Pijl H, van der Hoeven JJM, Kroep JR. Effects of short-term fasting on cancer treatment. *J Exp Clin Cancer Res*. 2019;38:209.
 185. Liberti MV, Locasale JW. The Warburg effect: how does it benefit cancer cells? *Trends Biochem Sci*. 2016;41:211-218.
 186. Lee C, Safdie FM, Raffaghello L, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res*. 2010;70:1564-1572.
 187. Cheng CW, Adams GB, Perin L, et al. Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression. *Cell Stem Cell*. 2014;14:810-823.
 188. Brandhorst S, Choi IY, Wei M, et al. A periodic diet that mimics fasting promotes multi-system regeneration, enhanced

- cognitive performance, and healthspan. *Cell Metab.* 2015;22:86-99.
189. Andre F, Dieci MV, Dubsky P, et al. Molecular pathways: involvement of immune pathways in the therapeutic response and outcome in breast cancer. *Clin Cancer Res.* 2013;19:28-33.
190. Kouvaris JR, Kouloulis VE, Vlahos LJ. Amifostine: the first selective-target and broad-spectrum radioprotector. *Oncologist.* 2007;12:738-747.
191. Nencioni A, Caffa I, Cortellino S, Longo VD. Fasting and cancer: molecular mechanisms and clinical application. *Nat Rev Cancer.* 2018;18:707-719.
192. Valayer S, Kim D, Fogtman A, et al. The potential of fasting and caloric restriction to mitigate radiation damage—a systematic review. *Front Nutr.* 2020;7:584543.
193. de la Cruz Bonilla M, Stemler KM, Jeter-Jones S, et al. Fasting reduces intestinal radiotoxicity, enabling dose-escalated radiation therapy for pancreatic cancer. *Int J Radiat Oncol Biol Phys.* 2019;105:537-547.
194. Zitvogel L, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. *Nat Immunol.* 2017;18:843-850.
195. Lamas O, Marti A, Martinez JA. Obesity and immunocompetence. *Eur J Clin Nutr.* 2002;56(suppl 3):S42-S45.
196. Conroy MJ, Dunne MR, Donohoe CL, Reynolds JV. Obesity-associated cancer: an immunological perspective. *Proc Nutr Soc.* 2016;75:125-138.
197. Eriau E, Paillet J, Kroemer G, Pol JG. Metabolic reprogramming by reduced calorie intake or pharmacological caloric restriction mimetics for improved cancer immunotherapy. *Cancers.* 2021;13:1260.
198. Levesque S, Le Naour J, Pietrocola F, et al. A synergistic triad of chemotherapy, immune checkpoint inhibitors, and caloric restriction mimetics eradicates tumors in mice. *Oncoimmunology.* 2019;8:e1657375.
199. Rock CL, Thomson C, Gansler T, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. *CA Cancer J Clin.* 2020;70:245-271.