Dietary Intake and Energy Expenditure in Breast Cancer

Subjects: Endocrinology & Metabolism

Contributor: Sarah A. Purcell

Many breast cancer survivors (BCS) gain fat mass and lose fat-free mass during treatment (chemotherapy, radiation, surgery) and estrogen suppression therapy, which increases the risk of developing comorbidities. Whether these body composition alterations are a result of changes in dietary intake, energy expenditure, or both is unclear. Thus, we reviewed studies that have measured components of energy balance in BCS who have completed treatment. Longitudinal studies suggest that BCS reduce self-reported energy intake and increase fruit and vegetable consumption. Although some evidence suggests that resting metabolic rate is higher in BCS than in age-matched controls, no study has measured total daily energy expenditure (TDEE) in this population. Whether physical activity levels are altered in BCS is unclear, but evidence suggests that light-intensity physical activity is lower in BCS compared to age-matched controls. We also discuss the mechanisms through which estrogen suppression may impact energy balance and develop a theoretical framework of dietary intake and TDEE interactions in BCS. Preclinical and human experimental studies indicate that estrogen suppression likely elicits increased energy intake and decreased TDEE, although this has not been systematically investigated in BCS specifically. Estrogen suppression may modulate energy balance via alterations in appetite, fat-free mass, resting metabolic rate, and physical activity. There are several potential areas for future mechanistic energetic research in BCS (e.g., characterizing predictors of intervention response, appetite, dynamic changes in energy balance, and differences in cancer sub-types) that would ultimately support the development of more targeted and personalized behavioral interventions.

Keywords: metabolism ; obesity ; nutrition ; exercise ; oncology

1. Introduction

Breast cancer prevention, screening practices, and effective treatment modalities confer favorable long-term survival in breast cancer survivors (BCS). In fact, 62% of cases are diagnosed at a localized stage (no spread to locations outside the breast), for which the 5-year survival is 99% [1]. Despite high success rates of breast cancer treatment, many cancer survivors have increased risk of developing comorbidities such as cardiovascular disease, diabetes, and chronic pain compared to age-matched women without previous cancer [2][3]. Unfavorable body composition profiles (i.e., reduced fat-free mass [FFM], increased fat mass [FM]) may contribute to the development of comorbidities and poorer survival. In fact, over one-third of women with nonmetastatic breast cancer may have low FFM at diagnosis, which is associated with higher overall mortality, especially when this occurs with high FM, or ‘sarcopenic obesity’ [4]. Changes in body composition may also worsen during chemotherapy, radiation, and surgery or long-term estrogen suppression therapy [5][6][7]. The effects on body composition may persist years after completion of treatment and negatively impacts long-term prognosis and risk of developing comorbidities [4][8][9][10][11]. In fact, up to 28% of metastatic [12] and 6% of non-metastatic [13] BCS with obesity have low FFM. Characterizing the mechanisms that contribute to changes in body composition in BCS would guide intervention strategies to improve overall health of this population.

Fundamentally, alterations in body composition are indicative of long-term energy balance induced by changes in dietary intake (e.g., energy intake [EI], macronutrient intake), and/or total daily energy expenditure (TDEE; primarily resting metabolic rate [RMR] and physical activity energy expenditure). However, mechanisms contributing to changes in energy balance in BCS are largely uncharacterized. Premenopausal BCS often undergo long-term therapeutic estrogen suppression; this treatment modality may increase the likelihood of elevated EI and/or decreased TDEE. However, our understanding of estrogen in energy balance arises from experimental estrogen suppression studies in women without previous breast cancer. Therefore, characterizing energy balance components is particularly relevant in this population as this could support the generation of targeted interventions that prevent adverse alterations in body composition.

Understanding how dietary intake and energy expenditure changes independently of behavioral interventions and whether components of energy balance in BCS differ compared to healthy controls would help support the generation of personalized behavioral weight management programs and dietary and physical activity guidelines. Therefore, the objective of this review is to summarize studies that have characterized changes in dietary intake and energy expenditure in BCS after completion of treatment (i.e., chemotherapy, radiation, and surgery). Because estrogen suppression therapy may have independent effects on dietary intake and energy expenditure, we also review evidence from studies that have performed experimental suppression of ovarian function to provide insight into potential mechanisms contributing to energy imbalance in BCS.

2. Estrogen Suppression in the Regulation of Energy Balance

Approximately 75% of premenopausal women with breast cancer have estrogen- and/or progesterone-receptor positive tumors (ER+, PR+) and undergo 5–10 years of estrogen suppression via gonadotropin-releasing hormone (GnRH) agonists (i.e., leuprolide or goserelin), selective estrogen receptor modulators (i.e., tamoxifen), or aromatase inhibitor therapy [14]. These therapy regimens are highly effective for reducing the risk of cancer recurrence but may also contribute to increased FM [15], especially in younger, premenopausal women. Interestingly, weight gain occurs more often in female BCS compared to male BCS [16][17], suggesting that the more pronounced reduction in estrogen that occurs in female BCS may be detrimental for weight management. To our knowledge, there are no human data on how estrogen suppression impacts components of energy balance in BCS or whether energy balance alterations occur independently of previous chemotherapy or radiation. Our understanding of the impact of sex hormones and energy balance is derived from data in women without previous breast cancer which show that estrogen impacts dietary intake through the modulation of appetite and TDEE through modulation of physical activity and RMR, **Figure 1**. Although other sex hormones (e.g., progesterone, testosterone) may impact specific energy balance parameters this review will focus on estrogen for brevity and relevancy, given the impact of estrogen on body composition regulation [18]; the reader is referred to previous reviews in this area for more mechanistic perspectives [19][20][21].

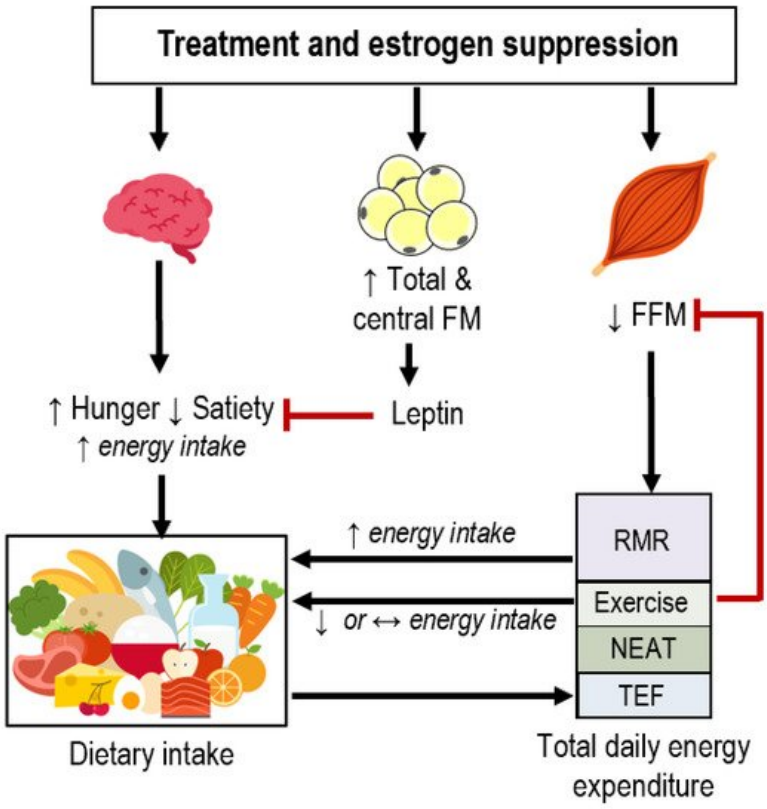

Figure 1. Theoretical interaction of dietary intake and components of energy expenditure after treatment and during estrogen suppression therapy. Estrogen suppression initiates changes in appetitive hormones (e.g., ghrelin, cholecystokinin, peptide-YY) that interact with hypothalamic nuclei and neuronal circuits; this, in turn may alter subjective appetite in a manner favoring increased energy intake. Changes in specific components of energy balance likely underpin the propensity for fat mass (FM) gain and fat-free mass (FFM) loss in breast cancer survivors. Experimental estrogen suppression results in increased total and central FM. This in turn will increase leptin which may alter appetite in a manner favoring decreased energy intake. Experimental estrogen suppression also decreases FFM (represented as skeletal muscle, although FFM also consists of organs and non-adipose tissues); exercise helps prevent decreased skeletal muscle and assumed FFM. There is also evidence that resting metabolic rate (RMR) positively correlates to hunger and

energy intake. Exercise often results in reduced or maintained energy intake in people with obesity through alterations in appetitive hormones and subjective perceptions of appetite. Dietary intake determines the thermic effect of feeding (TEF). NEAT: non-exercise activity thermogenesis.

2.1. Estrogen and Appetite

While the physiological mechanisms causing altered dietary intake have not been described in BCS, experimental animal models and observational human studies of estrogen suppression indicate that estrogen is an important regulator of appetite. Animal models have shown that estrogen regulates dietary intake through peripheral appetite signals by decreasing orexigenic (e.g., neuropeptide-Y, ghrelin, and melanin-concentrating hormone) and increasing anorectic (e.g., leptin, cholecystokinin) peptides [20]. These peptides interact with the hypothalamus—and in particular the arcuate nucleus—to coordinate energy balance. Estradiol (the most potent and prevalent form of circulating estrogen)stimulates anorexigenic pro-opiomelanocortin and cocaine-amphetamine-regulated transcript neuronal populations and inhibits orexigenic neuropeptide-Y and Agouti-related peptide neurons [22][23]. These mechanisms are apparent in animal models, wherein ovariectomy results in marked increases in food intake and body weight, which are reversed with exogenous estrogen [24][25].

In humans, dietary intake varies according to menstrual cycle. Specifically, EI is lowest during the periovulatory phase of the menstrual cycle when estradiol levels are high, and greatest during the premenstrual period when progesterone levels are high [19][26]. During menopause, the production of female sex hormones drops dramatically. Hunger and prospective food consumption increases during the menopausal transition and remains elevated in the early postmenopausal years [27]. However, these changes in appetite may not cause alterations in dietary intake. In a sample of 106 healthy women, EI, protein, carbohydrate, and fiber were higher in the 3–4 years before the onset of menopause [28]. However, these changes in dietary intake were self-reported, which may introduce error. Given our understanding of the role of female sex hormones in the regulation of dietary intake during the menstrual cycle and menopausal transition, it is likely that gonadal function loss due to treatment, estrogen suppression therapy, or both contribute to the development of obesity in BCS. However, the mechanisms underpinning this phenomenon have not been systematically investigated in BCS.

2.2. Estrogen and Total Daily Energy Expenditure

Estrogen also modulates physical activity, RMR and TDEE, as supported by both animal and experimental human studies. For example, ovariectomized rats exhibit drastic reductions in TDEE as a result of diminished physical activity and RMR [29], which are reversed by exogenous estradiol administration.

There are also human data wherein premenopausal females undergo experimental ovarian hormone suppression. Short-term (6 day) GnRH antagonist administration resulted in reduced RMR (mean ± standard error: 1334 ± 36 kcal/day) compared to RMR measured in the mid-luteal phase (1405 ± 42 kcal/day) and early follicular phase (1376 ± 43 kcal/day) [30]. Longer studies of experimental estrogen suppression utilized a GnRH agonist which supresses anterior pituitary gonadotropins and gonadal sex hormones via a negative feedback loop. Using this model, 70 premenopausal women were randomized to 20 weeks of either GnRH agonist + estradiol addback or GnRH agonist + placebo (N = 35 each group) [31][32]. Estrogen suppression resulted in increased visceral FM and decreased FFM, which was prevented with estradiol addback [31]. There was also a decrease in RMR in the placebo group (~−50 kcal/day) that was not observed in the group that received estradiol addback. Furthermore, 24 h EE measured via whole room indirect calorimetry was also reduced by estrogen suppression (~100–110 kcal/day), but was not prevented by estradiol addback [32]. A similar follow-up study was conducted in which premenopausal women were randomized to 24 weeks of GnRH agonist (N = 14), GnRH agonist + aerobic exercise (N = 11), or placebo (N = 9) [33]. Although free-living TDEE (as measured by doubly labeled water) decreased 93 kcal/day and RMR decreased 59 kcal/day in the GnRH agonist group, these differences were nonsignificant within or between groups. There were also no significant alterations in physical activity energy expenditure, although these results may be due to large variability in energy expenditure components observed in this study [33]. In sum, it appears that reduced estrogen may decrease RMR and TDEE in confined settings; however, these changes may not translate to free-living settings as evidenced by results from doubly labeled water. Because data from experimental estrogen suppression are conflicting and are an imperfect memetic of sex hormone alterations due to cancer treatment and therapy, trials of energy expenditure in BCS are greatly needed to understand energy balance.

2.3. Relationships between Dietary Intake and Energy Expenditure in Breast Cancer Survivors

Emerging evidence in people without previous cancer have provided consistent evidence to support the notion that body composition, RMR, and physical activity predict EI and several parameters of appetite [34][35]. Adipose tissue (the largest component of FM) relates to appetite through the release of leptin. Leptin serves as a feedback mechanism that acts

through hypothalamic neuropeptide and neurons to inhibit dietary intake [36]. ‘Leptin resistance’ (a decrease in sensitivity to circulating leptin) often occurs in people with obesity and would negate the relationship between leptin and appetite. More recent investigations show modest but consistent evidence that FFM also relates to appetite and dietary intake, likely as a result of the energetic demand from metabolically active tissues that make up FFM. Specifically, the FFM-EI relationship is mediated by RMR, which positively relates to meal size and EI [37]. The correlation between RMR and EI occurs independently of FM and BMI [38], although it may be less apparent in people with obesity [39]. It is believed that EI is also driven by habitual TDEE; that is, individuals with increased physical activity and RMR would be expected to have a higher EI to compensate for their higher energy requirements. For example, free-living physical activity as measured by heart rate monitors was directly and positively related to EI as measured by 7-day weighted food records in healthy adults (BMI range: 16.7–49.3 kg/m^2) [40]. There was also an indirect positive association between physical activity and RMR, mediated by FFM [40].

Whether these relationships exist in populations that are susceptible to aberrant appetite, body composition, and/or energy expenditure—such as BCS—has not been studied. As previously discussed in this review and others [41], BCS often experience reduced FFM, which may relate to reduced RMR. In this model, it would be expected that a reduced RMR would lead to a lower drive to eat. However, there is little research investigating how dynamic changes in body composition, RMR, and physical activity affect EI in BCS. Among males in conditions of extreme negative energy balance, both FM and FFM independently and inversely associated with EI during refeeding after severe caloric restriction. The hyperphagic response after weight loss ceased only when participants had recovered 100% of their pre-weight loss FFM, at which point FM values exceeded baseline values by 74% [42][43]. In more moderate negative energy balance over a 26-week weight loss diet, there were positive associations between the proportion of FFM lost and changes in hunger and desire to eat and negative associations between change in fullness in men, but not women [44]. These sex differences may be due in part to lower levels of FFM (expressed as a percent of total body weight) in women at baseline. While the data are limited, it is conceivable that altered body composition and RMR may relate to changes in appetite and dietary intake in BCS (**Figure 1**), although the existence and potential magnitude of these relationships in cancer survivors are currently theoretical.

As previously discussed in this review, BCS may decrease physical activity after treatment. Low physical activity likely contributes to FM gain directly through decreased TDEE and indirectly through downstream effects on appetite and EI. Energy balance and negative energy balance are more attainable at higher levels of physical activity (i.e., “high energy flux”). In other words, increased physical activity in sedentary adults would presumably increase TDEE, resulting in a greater buffer for high EI that is inevitable in pervasive obesogenic environments. For a comprehensive review of “energy flux”, the reader is referred to Melby et al. [45]. Higher physical activity may also relate to dietary intake via the effects of exercise on appetite. Exercise interventions decrease hunger, increase satiety, reduce neuronal responses to food, and alter appetite hormones in a manner that would support lower EI [46][47][48][49][50][51]. These concepts lend credence to the notion that low physical activity in BCS may contribute to dysregulation of energy balance through low energy flux and appetite perceptions that enhance EI.

Dietary intake and TDEE are also inherently related through TEF. The magnitude of TEF is proportionate to the energy and macronutrient content of dietary intake, with protein and alcohol eliciting a greater energetic response than fat or carbohydrate [52]. Weight loss, weight gain, obesity, insulin resistance, advanced age, physical fitness, and genetic factors also contribute to TEF variability between individuals [53]. As described above, many BCS report decreased EI after treatment and diagnosis with or without changes in macronutrient distributions, which would impact TEF. However, measuring TEF is burdensome; as a result, there are limited data on TEF in cancer patients. To date, only one study has measured TEF in breast cancer patients (*N* = 18) actively undergoing chemotherapy. TEF was defined as the increase in energy expenditure above RMR after consumption of a nutritional supplement (5 mL/kg body weight) [54]. TEF trended towards decreasing during chemotherapy and rebounded to pre-treatment levels after chemotherapy [54]. While TEF might be lower than expected during treatment, the specific interactions between nutrient digestion, absorption and metabolism and the impact on the TEF in BCS after treatment has not been explored.

3. Psychological Alterations and Energy Balance after Breast Cancer

Breast cancer diagnosis and treatment may serve as a “teachable moment” and catalyst for altering energy balance through positive health behavior changes [55]. Concerns of cancer recurrence or mortality are common among BCS, and many report feelings of fear, depression and anxiety towards their cancer prognosis, body image concerns, sexual dysfunction, work and family life problems during the transition from active treatment to long-term survivorship [56]. These psychological alterations may serve as the impetus for behavior change in sub-groups of survivors. Specifically, BCS who believe that unhealthy dietary intake, lack of physical activity, and smoking contributed to their cancer or are related to

recurrence are more apt to positively modify behavior [57]. In a sample of 250 women with non-metastatic breast cancer, those who made positive changes in their dietary intake in the year after diagnosis were more likely to be younger, have lymph node involvement, be receiving adjuvant therapy, and to be more distressed at diagnosis [58]. The latter finding suggests that those with greater amounts worry about their disease and recurrence are more likely to make lifestyle changes. Qualitative data in breast, prostate, and colon cancer survivors support this notion; beliefs that behavior influences recurrence are associated with implementing positive health changes [59]. However, other data in BCS have not reported changes in other health behaviors such as tobacco or alcohol use [60], casting doubt on the applicability of the "teachable moment" for other health behavior changes. It is possible that cancer diagnosis and treatment may indeed serve as a motivator for altering dietary intake and physical activity in certain groups of BCS; however, whether these behavior changes are indelible or explain the findings presented in this review is not clear.

4. Areas for Future Research and Conclusions

There are compelling and numerous data that describe body composition alterations in BCS and there is growing consensus that diet and/or exercise interventions can prevent unfavorable changes in body composition. However, the behavioral and physiological mechanisms of energy balance in BCS are largely uncharacterized. There are several knowledge gaps that future research should address, such as:

- Expanded use of more accurate techniques such as doubly labeled water ($^{2}H_2$ and ^{18}O), accelerometers and whole-room indirect calorimetry would help promote further understanding of TDEE and its components in different clinical populations. While these techniques are not practical in large sample sizes, they could provide useful insight on the mechanistic underpinnings of energy balance in BCS (and cancer survivors in general) in smaller samples. Other techniques that include repeated measures of body composition and energy expenditure [61][62] or mathematical models [63] may also help quantify energy balance in this population.

- Use of stable isotopes to measure intake of food groups could be used to complement recall or record-based methods of dietary intake. For example, $^{13}C/^{12}C$ can be used describe intake of C_4 plants (e.g., corn, cane sugars) and C_3 plants (e.g., fruits and vegetables, wheat, nuts, seeds); similarly, $^{15}N/^{14}N$ can be used to characterize fish and meat intake [64][65]. Use of isotopes paired with repeated measures of dietary recall and TDEE would provide valuable insight of energy balance in BCS.

- Inter-individual variability in body composition responses to exercise suggests that individuals compensate more or less to the same intervention. In other words, some individuals may increase EI, decrease physical activity, or both in response to exercise training. Elucidating the predictors of response and whether such predictors differ in BCS will help facilitate the design of more efficacious, personalized interventions for weight management.

- Weight loss can be achieved through alterations in physical activity and dietary intake, but most individuals regain the weight they lost [66]. Physiological and psychological changes in appetite and energy expenditure in the context of an obesogenic environment underpin weight regain [67][68]. Characterization of energy balance during weight loss and maintenance in BCS—and whether this differs from individuals without previous cancer—would help generate more durable strategies for body weight management.

- Eating behavior and appetite parameters are important determinants of dietary intake. As discussed in this review, there is modest evidence that appetite fluctuates across the menstrual cycle and menopausal transition due to altered sex hormones. Elucidation of the effects of sex hormones on appetite in estrogen-suppressed BCS may support the development of more targeted nutrition interventions.

- There is increasing cross-sectional evidence that components of dietary intake and TDEE are related. Whether specific components of TDEE predict dietary intake and appetite in instances of energy imbalance is unclear in the general population and in people with chronic disease. Elucidating the complex interrelations among energy balance parameters in the context of different conditions may help better predict intervention response and devise better solutions for weight management.

- Differentiation of outcomes according to tumor pathology (i.e., ER, PR, and human epidermal growth factor-2 status), patient age, and treatment modalities may also promote personalized intervention strategies. As previously reviewed [15][69], women who are premenopausal at diagnosis have a higher risk of FM gain compared to women who were postmenopausal at diagnosis. This is likely a direct result different treatment modalities and estrogen status; how these factors impact behavior and physiology related to energy balance is unknown.Finally, characterizing energy balance components in other cancer populations is warranted, especially in those that often undergo rigorous chemotherapy or

hormonal treatments or are at risk for developing obesity (e.g., colorectal, prostate, ovarian cancers). This review focused on BCS because of the risk of weight gain, effect of hormonal therapies, and the availability of enough evidence to form conservative conclusions regarding dietary intake and energy expenditure. However, there is limited data on how various cancer types and treatment modalities may impact specific components of energy balance after treatment in other cancer types; it is also unclear if energy balance differs among cancer types or compared to individuals without previous cancer.

References

1. American Cancer Society. Cancer Facts & Figures 2019; American Cancer Society: Atlanta, GA, USA, 2019.
2. Ng, H.S.; Koczwara, B.; Roder, D.; Niyonsenga, T.; Vitry, A. Incidence of Comorbidities in Women with Breast Cancer Treated with Tamoxifen or an Aromatase Inhibitor: An Australian Population-Based Cohort Study. J. Comorbidity 2018, 8, 16–24.
3. Bradshaw, P.T.; Stevens, J.; Khankari, N.; Teitelbaum, S.L.; Neugut, A.I.; Gammon, M.D. Cardiovascular Disease Mortality Among Breast Cancer Survivors. Epidemiology 2016, 27, 6–13.
4. Caan, B.J.; Cespedes, F.E.M.; Prado, C.M.; Alexeeff, S.; Kroenke, C.H.; Bradshaw, P.; Quesenberry, C.P.; Weltzien, E.K.; Castillo, A.L.; Olobatuyi, T.A.; et al. Association of Muscle and Adiposity Measured by Computed Tomography with Survival in Patients with Nonmetastatic Breast Cancer. JAMA Oncol. 2018, 4, 798–804.
5. Godinho-Mota, J.C.M.; Mota, J.F.; Goncalves, L.V.; Soares, L.R.; Schincaglia, R.M.; Prado, C.M.; Martins, K.A.; Freitas-Junior, R. Chemotherapy negatively impacts body composition, physical function and metabolic profile in patients with breast cancer. Clin. Nutr. 2021, 40, 3421–3428.
6. Demark-Wahnefried, W.; Peterson, B.L.; Winer, E.P.; Marks, L.; Aziz, N.; Marcom, P.K.; Blackwell, K.; Rimer, B.K. Changes in weight, body composition, and factors influencing energy balance among premenopausal breast cancer patients receiving adjuvant chemotherapy. J. Clin. Oncol. 2001, 19, 2381–2389.
7. Makari-Judson, G.; Braun, B.; Jerry, D.J.; Mertens, W.C. Weight gain following breast cancer diagnosis: Implication and proposed mechanisms. World J. Clin. Oncol. 2014, 5, 272–282.
8. Ewertz, M.; Jensen, M.-B.; Gunnarsdóttir, K.Á.; Højris, I.; Jakobsen, E.H.; Nielsen, D.; Stenbygaard, L.E.; Tange, U.B.; Cold, S. Effect of Obesity on Prognosis after Early-Stage Breast Cancer. J. Clin. Oncol. 2010, 29, 25–31.
9. Protani, M.; Coory, M.; Martin, J.H. Effect of obesity on survival of women with breast cancer: Systematic review and meta-analysis. Breast Cancer Res. Treat. 2010, 123, 627–635.
10. Goodwin, P.J.; Ennis, M.; Pritchard, K.I.; Trudeau, M.E.; Koo, J.; Taylor, S.K.; Hood, N. Insulin- and obesity-related variables in early-stage breast cancer: Correlations and time course of prognostic associations. J. Clin. Oncol. 2012, 30, 164–171.
11. Prado, C.M.; Purcell, S.A.; Alish, C.; Pereira, S.L.; Deutz, N.E.; Heyland, D.K.; Goodpaster, B.H.; Tappenden, K.A.; Heymsfield, S.B. Implications of low muscle mass across the continuum of care: A narrative review. Ann. Med. 2018, 50, 675–693.
12. Rier, H.N.; Jager, A.; Sleijfer, S.; van Rosmalen, J.; Kock, M.C.J.M.; Levin, M.-D. Low muscle attenuation is a prognostic factor for survival in metastatic breast cancer patients treated with first line palliative chemotherapy. Breast 2017, 31, 9–15.
13. Del Fabbro, E.; Parsons, H.; Warneke, C.L.; Pulivarthi, K.; Litton, J.K.; Dev, R.; Palla, S.L.; Brewster, A.; Bruera, E. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. Oncologist 2012, 17, 1240–1245.
14. Francis, P.A.; Pagani, O.; Fleming, G.F.; Walley, B.A.; Colleoni, M.; Láng, I.; Gómez, H.L.; Tondini, C.; Ciruelos, E.; Burstein, H.J.; et al. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N. Engl. J. Med. 2018, 379, 122–137.
15. Sheean, P.M.; Hoskins, K.; Stolley, M. Body composition changes in females treated for breast cancer: A review of the evidence. Breast Cancer Res. Treat 2012, 135, 663–680.
16. Gross, A.L.; May, B.J.; Axilbund, J.E.; Armstrong, D.K.; Roden, R.B.S.; Visvanathan, K. Weight change in breast cancer survivors compared to cancer-free women: A prospective study in women at familial risk of breast cancer. Cancer Epidemiol. Prev. Biomark. 2015, 24, 1262–1269.
17. Visram, H.; Kanji, F.; Dent, S.F. Endocrine therapy for male breast cancer: Rates of toxicity and adherence. Curr. Oncol. 2010, 17, 17–21.

18. Finkelstein, J.S.; Lee, H.; Burnett-Bowie, S.-A.M.; Pallais, J.C.; Yu, E.W.; Borges, L.F.; Jones, B.F.; Barry, C.V.; Wulczyn, K.E.; Thomas, B.J.; et al. Gonadal steroids and body composition, strength, and sexual function in men. N. Engl. J. Med. 2013, 369, 1011–1022.
19. Hirschberg, A.L. Sex hormones, appetite and eating behaviour in women. Maturitas 2012, 71, 248–256.
20. Brown, L.M.; Clegg, D.J. Central effects of estradiol in the regulation of food intake, body weight, and adiposity. J. Steroid Biochem. Mol. Biol. 2010, 122, 65–73.
21. Butera, P.C. Estradiol and the control of food intake. Physiol. Behav. 2010, 99, 175–180.
22. Sotonyi, P.; Gao, Q.; Bechmann, I.; Horvath, T.L. Estrogen promotes parvalbumin expression in arcuate nucleus POMC neurons. Reprod. Sci. 2010, 17, 1077–1080.
23. Olofsson, L.E.; Pierce, A.A.; Xu, A.W. Functional requirement of AgRP and NPY neurons in ovarian cycle-dependent regulation of food intake. Proc. Natl. Acad. Sci. USA 2009, 106, 15932–15937.
24. Belsito, K.; Vester, B.; Keel, T.; Graves, T.; Swanson, K. Impact of ovariohysterectomy and food intake on body composition, physical activity, and adipose gene expression in cats. J. Anim. Sci. 2009, 87, 594–602.
25. Gorzek, J.F.; Hendrickson, K.C.; Forstner, J.P.; Rixen, J.L.; Moran, A.L.; Lowe, D.A. Estradiol and tamoxifen reverse ovariectomy-induced physical inactivity in mice. Med. Sci. Sports Exerc. 2007, 39, 248–256.
26. Buffenstein, R.; Poppitt, S.D.; McDevitt, R.M.; Prentice, A.M. Food intake and the menstrual cycle: A retrospective analysis, with implications for appetite research. Physiol. Behav. 1995, 58, 1067–1077.
27. Duval, K.; Prud'homme, D.; Rabasa-Lhoret, R.; Strychar, I.; Brochu, M.; Lavoie, J.-M.; Doucet, E. Effects of the menopausal transition on dietary intake and appetite: A MONET Group Study. Eur. J. Clin. Nutr. 2014, 68, 271–276.
28. Lovejoy, J.C.; Champagne, C.M.; de Jonge, L.; Xie, H.; Smith, S.R. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int. J. Obes. 2008, 32, 949–958.
29. Camporez, J.P.G.; Jornayvaz, F.R.; Lee, H.-Y.; Kanda, S.; Guigni, B.A.; Kahn, M.; Samuel, V.T.; Carvalho, C.R.O.; Petersen, K.F.; Jurczak, M.J.; et al. Cellular Mechanism by Which Estradiol Protects Female Ovariectomized Mice From High-Fat Diet-Induced Hepatic and Muscle Insulin Resistance. Endocrinology 2013, 154, 1021–1028.
30. Day, D.S.; Gozansky, W.S.; Van Pelt, R.E.; Schwartz, R.S.; Kohrt, W.M. Sex hormone suppression reduces resting energy expenditure and -adrenergic support of resting energy expenditure. J. Clin. Endocrinol. Metab. 2005, 90, 3312–3317.
31. Shea, K.L.; Gavin, K.M.; Melanson, E.L.; Gibbons, E.; Stavros, A.; Wolfe, P.; Kittelson, J.M.; Vondracek, S.F.; Schwartz, R.S.; Wierman, M.E.; et al. Body composition and bone mineral density after ovarian hormone suppression with or without estradiol treatment. Menopause 2015, 22, 1045–1052.
32. Melanson, E.L.; Gavin, K.M.; Shea, K.L.; Wolfe, P.; Wierman, M.E.; Schwartz, R.S.; Kohrt, W.M. Regulation of energy expenditure by estradiol in premenopausal women. J. Appl. Physiol. 2015, 119, 975–981.
33. Gavin, K.M.; Melanson, E.L.; Hildreth, K.L.; Gibbons, E.; Bessesen, D.H.; Kohrt, W.M. A Randomized Controlled Trial of Ovarian Suppression in Premenopausal Women: No Change in Free-Living Energy Expenditure. Obesity 2020, 28, 2125–2133.
34. Hopkins, M.; Finlayson, G.; Duarte, C.; Gibbons, C.; Johnstone, A.M.; Whybrow, S.; Horgan, G.W.; Blundell, J.E.; Stubbs, R.J. Biological and psychological mediators of the relationships between fat mass, fat-free mass and energy intake. Int. J. Obes. 2018, 43, 233–242.
35. McNeil, J.; Lamothe, G.; Cameron, J.D.; Riou, M.E.; Cadieux, S.; Lafreniere, J.; Goldfield, G.; Willbond, S.; Prud'homme, D.; Doucet, E. Investigating predictors of eating: Is resting metabolic rate really the strongest proxy of energy intake? Am. J. Clin. Nutr. 2017, 106, 1206–1212.
36. Klok, M.D.; Jakobsdottir, S.; Drent, M.L. The role of leptin and ghrelin in the regulation of food intake and body weight in humans: A review. Obes. Rev. Off. J. Int. Assoc. Study Obes. 2007, 8, 21–34.
37. Hopkins, M.; Finlayson, G.; Duarte, C.; Whybrow, S.; Ritz, P.; Horgan, G.W.; Blundell, J.E.; Stubbs, R.J. Modelling the associations between fat-free mass, resting metabolic rate and energy intake in the context of total energy balance. Int. J. Obes. 2016, 40, 312–318.
38. Blundell, J.E.; Caudwell, P.; Gibbons, C.; Hopkins, M.; Naslund, E.; King, N.A.; Finlayson, G. Body composition and appetite: Fat-free mass (but not fat mass or BMI) is positively associated with self-determined meal size and daily energy intake in humans. Br. J. Nutr. 2012, 107, 445–449.
39. Casanova, N.; Beaulieu, K.; Oustric, P.; O'Connor, D.; Gibbons, C.; Duarte, C.; Blundell, J.; Stubbs, R.J.; Finlayson, G.; Hopkins, M. Body Fatness Influences Associations of Body Composition and Energy Expenditure with Energy Intake in Healthy Women. Obesity 2021, 29, 125–132.

40. Hopkins, M.; Duarte, C.; Beaulieu, K.; Finlayson, G.; Gibbons, C.; Johnstone, A.M.; Whybrow, S.; Horgan, G.W.; Blundell, J.E.; Stubbs, R.J. Activity energy expenditure is an independent predictor of energy intake in humans. Int. J. Obes. 2019, 43, 1466–1474.

41. Brown, J.C.; Cespedes Feliciano, E.M.; Caan, B.J. The evolution of body composition in oncology-epidemiology, clinical trials, and the future of patient care: Facts and numbers. J. Cachexia. Sarcopenia Muscle 2018, 9, 1200–1208.

42. Dulloo, A.G.; Jacquet, J.; Girardier, L. Poststarvation hyperphagia and body fat overshooting in humans: A role for feedback signals from lean and fat tissues. Am. J. Clin. Nutr. 1997, 65, 717–723.

43. Muller, M.J.; Enderle, J.; Pourhassan, M.; Braun, W.; Eggeling, B.; Lagerpusch, M.; Gluer, C.C.; Kehayias, J.J.; Kiosz, D.; Bosy-Westphal, A. Metabolic adaptation to caloric restriction and subsequent refeeding: The Minnesota Starvation Experiment revisited. Am. J. Clin. Nutr. 2015, 102, 807–819.

44. Turicchi, J.; O'Driscoll, R.; Finlayson, G.; Duarte, C.; Hopkins, M.; Martins, N.; Michalowska, J.; Larsen, T.M.; van Baak, M.A.; Astrup, A.; et al. Associations between the proportion of fat-free mass loss during weight loss, changes in appetite, and subsequent weight change: Results from a randomized 2-stage dietary intervention trial. Am. J. Clin. Nutr. 2020, 111, 536–544.

45. Melby, C.L.; Paris, H.L.; Sayer, R.D.; Bell, C.; Hill, J.O. Increasing Energy Flux to Maintain Diet-Induced Weight Loss. Nutrients 2019, 11, 2533.

46. King, N.A.; Burley, V.J.; Blundell, J.E. Exercise-induced suppression of appetite: Effects on food intake and implications for energy balance. Eur. J. Clin. Nutr. 1994, 48, 715–724.

47. Broom, D.R.; Stensel, D.J.; Bishop, N.C.; Burns, S.F.; Miyashita, M. Exercise-induced suppression of acylated ghrelin in humans. J. Appl. Physiol. 2007, 102, 2165–2171.

48. Cornier, M.-A.; Melanson, E.L.; Salzberg, A.K.; Bechtell, J.L.; Tregellas, J.R. The effects of exercise on the neuronal response to food cues. Physiol. Behav. 2012, 105, 1028–1034.

49. Bales, C.W.; Hawk, V.H.; Granville, E.O.; Rose, S.B.; Shields, T.; Bateman, L.; Willis, L.; Piner, L.W.; Slentz, C.A.; Houmard, J.A.; et al. Aerobic and resistance training effects on energy intake: The STRRIDE-AT/RT study. Med. Sci. Sport. Exerc. 2012, 44, 2033–2039.

50. Legget, K.T.; Wylie, K.P.; Cornier, M.-A.; Melanson, E.L.; Paschall, C.J.; Tregellas, J.R. Exercise-related changes in between-network connectivity in overweight/obese adults. Physiol. Behav. 2016, 158, 60–67.

51. Dorling, J.; Broom, D.R.; Burns, S.F.; Clayton, D.J.; Deighton, K.; James, L.J.; King, J.A.; Miyashita, M.; Thackray, A.E.; Batterham, R.L.; et al. Acute and Chronic Effects of Exercise on Appetite, Energy Intake, and Appetite-Related Hormones: The Modulating Effect of Adiposity, Sex, and Habitual Physical Activity. Nutrients 2018, 10, 1140.

52. Westerterp, K.R. Diet induced thermogenesis. Nutr. Metab. 2004, 1, 1–5.

53. Donahoo, W.T.; Levine, J.A.; Melanson, E.L. Variability in energy expenditure and its components. Curr. Opin. Clin. Nutr. Metab. Care 2004, 7, 599–605.

54. Demark-Wahnefried, W.; Hars, V.; Conaway, M.R.; Havlin, K.; Rimer, B.K.; McElveen, G.; Winer, E.P. Reduced rates of metabolism and decreased physical activity in breast cancer patients receiving adjuvant chemotherapy. Am. J. Clin. Nutr. 1997, 65, 1495–1501.

55. Demark-Wahnefried, W.; Aziz, N.M.; Rowland, J.H.; Pinto, B.M. Riding the crest of the teachable moment: Promoting long-term health after the diagnosis of cancer. J. Clin. Oncol. 2005, 23, 5814–5830.

56. Hodgkinson, K.; Butow, P.; Hunt, G.E.; Pendlebury, S.; Hobbs, K.M.; Wain, G. Breast cancer survivors' supportive care needs 2–10 years after diagnosis. Support. Care Cancer Off. J. Multinatl. Assoc. Support. Care Cancer 2007, 15, 515–523.

57. Rabin, C.; Pinto, B. Cancer-related beliefs and health behavior change among breast cancer survivors and their first-degree relatives. Psychooncology 2006, 15, 701–712.

58. Maunsell, E.; Drolet, M.; Brisson, J.; Robert, J.; Deschênes, L. Dietary change after breast cancer: Extent, predictors, and relation with psychological distress. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2002, 20, 1017–1025.

59. Corbett, T.; Cheetham, T.; Müller, A.M.; Slodkowska-Barabasz, J.; Wilde, L.; Krusche, A.; Richardson, A.; Foster, C.; Watson, E.; Little, P.; et al. Exploring cancer survivors' views of health behaviour change: "Where do you start, where do you stop with everything?". Psychooncology 2018, 27, 1816–1824.

60. Bidstrup, P.E.; Dalton, S.O.; Christensen, J.; Tjonneland, A.; Larsen, S.B.; Karlsen, R.; Brewster, A.; Bondy, M.; Johansen, C. Changes in body mass index and alcohol and tobacco consumption among breast cancer survivors and cancer-free women: A prospective study in the Danish Diet, Cancer and Health Cohort. Acta Oncol. 2013, 52, 327–335.

61. de Jonge, L.; DeLany, J.P.; Nguyen, T.; Howard, J.; Hadley, E.C.; Redman, L.M.; Ravussin, E. Validation study of energy expenditure and intake during calorie restriction using doubly labeled water and changes in body composition. Am. J. Clin. Nutr. 2007, 85, 73–79.
62. Racette, S.B.; Das, S.K.; Bhapkar, M.; Hadley, E.C.; Roberts, S.B.; Ravussin, E.; Pieper, C.; DeLany, J.P.; Kraus, W.E.; Rochon, J.; et al. Approaches for quantifying energy intake and %calorie restriction during calorie restriction interventions in humans: The multicenter CALERIE study. Am. J. Physiol. Endocrinol. Metab. 2012, 302, E441–E448.
63. Thomas, D.M.; Scioletti, M.; Heymsfield, S.B. Predictive Mathematical Models of Weight Loss. Curr. Diab. Rep. 2019, 19, 93.
64. Owino, V.O.; Slater, C.; Loechl, C.U. Using stable isotope techniques in nutrition assessments and tracking of global targets post-2015. Proc. Nutr. Soc. 2017, 76, 495–503.
65. Patel, P.S.; Cooper, A.J.M.; O'Connell, T.C.; Kuhnle, G.G.C.; Kneale, C.K.; Mulligan, A.M.; Luben, R.N.; Brage, S.; Khaw, K.-T.; Wareham, N.J.; et al. Serum carbon and nitrogen stable isotopes as potential biomarkers of dietary intake and their relation with incident type 2 diabetes: The EPIC-Norfolk study. Am. J. Clin. Nutr. 2014, 100, 708–718.
66. Franz, M.J.; VanWormer, J.J.; Crain, A.L.; Boucher, J.L.; Histon, T.; Caplan, W.; Bowman, J.D.; Pronk, N.P. Weight-loss outcomes: A systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J. Am. Diet. Assoc. 2007, 107, 1755–1767.
67. Greenway, F.L. Physiological adaptations to weight loss and factors favouring weight regain. Int. J. Obes. 2015, 39, 1188–1196.
68. Maclean, P.S.; Bergouignan, A.; Cornier, M.A.; Jackman, M.R. Biology's response to dieting: The impetus for weight regain. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2011, 301, 581–600.
69. Pedersen, B.; Delmar, C.; Lörincz, T.; Falkmer, U.; Grønkjær, M. Investigating Changes in Weight and Body Composition Among Women in Adjuvant Treatment for Breast Cancer: A Scoping Review. Cancer Nurs. 2019, 42, 91–105.