



## Conference on ‘Diet, nutrition and the changing face of cancer survivorship’ Symposium 1: Nutrition during diagnosis and treatment

### Early breast cancer: why does obesity affect prognosis?

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High BMI is associated with an increased risk of breast cancer in post-menopausal women but poorer outcomes in all age groups. The underlying mechanism is likely to be multifactorial. Patients with a high BMI may present later due to body habitus. Some studies have also indicated an increased incidence of biologically adverse features, including a higher frequency of oestrogen receptor (ER negative) tumours, in obese patients. Obese patients have a higher frequency of surgical complications, potentially delaying systemic therapies, and reports suggest that chemotherapy and endocrine therapy are less effective in patients with BMI  $\geq 30$  kg/m<sup>2</sup>.

High BMI is generally interpreted as excess adiposity and a World Cancer Research Fund report judged that the associations between BMI and incidence of breast cancer were due to body fatness. However, BMI cannot distinguish lean mass from fat mass, or characterise body fat distribution. Most chemotherapy drugs are dosed according to calculated body surface area (BSA). Patients with a similar BSA or BMI may have wide variations in their distribution of adipose tissue and skeletal muscle (body composition); however, few studies have looked at the effect of this on chemotherapy tolerance or effectiveness. Finally, adjuvant treatments for breast cancer can themselves result in body composition changes.

Research is required to fully understand the biological mechanisms by which obesity influences cancer behaviour and the impact of obesity on treatment effectiveness and tolerance so that specific management strategies can be developed to improve the prognosis of this patient group.

#### Early breast cancer: Obesity: BMI: Cytotoxic dosing: Toxicity: Surgical complications

Breast cancer remains a significant health burden in both developed and developing countries, with over 1.68 million cases diagnosed globally in 2012<sup>(1)</sup>. Although, in many countries, the number of breast cancer survivors is growing due to earlier diagnosis and advances in treatment, this diagnosis is still the most common cause of cancer death worldwide for females, accounting for 522 000 deaths in 2012<sup>(1)</sup>. In the UK, there are over 55 000 new breast cancer diagnoses and over 12 000 deaths due to this disease per year<sup>(2)</sup>. A number of associations with the development of breast cancer have been identified such as age, early menarche, late menopause, family history and hereditary breast cancer susceptibility syndromes<sup>(3)</sup>. More recently, attention has focused on

modifiable risk factors, which describe a range of behavioural and lifestyle factors. The most significant modifiable risk factor for developing breast cancer is obesity, but only convincingly for post-menopausal women<sup>(4,5)</sup>.

There is now evidence to suggest that obesity at diagnosis of early (curable) breast cancer is associated with reduced breast cancer survival in both pre- and post-menopausal women<sup>(6,7)</sup> (Table 1). Here we review the evidence that body mass has implications both for the intrinsic pathology of breast cancer and the effectiveness of treatments, as well as the limitations of the current evidence base. All data presented in this review refer to patients with early breast cancer and not to patients with metastatic disease.

Abbreviations: AI, aromatase inhibitor; BSA, body surface area; ER, oestrogen receptor; WCRF, World Cancer Research Fund.

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### Obesity: the scale of the problem

Obesity is defined as an excess accumulation of adipose tissue and occurs when energetic intake exceeds energy expenditure. The WHO specifically defines obesity as BMI  $>30$  kg/m<sup>2</sup>, with BMI  $25 \leq \text{BMI} < 30$  kg/m<sup>2</sup>, categorised as overweight<sup>(8)</sup>. Storing excess energy served a valuable evolutionary purpose to allow our ancestors to store energy in times of nutritional deprivation. However, obesity is now a pandemic health concern in both developed and developing countries, with over 600 million adults worldwide estimated to be obese<sup>(9)</sup>. In the UK, 27% of British women are obese and this figure is predicted to increase to 43% by 2030<sup>(10,11)</sup>. The links with type 2 diabetes and CVD have long been established, but it has also become increasingly clear that there is a substantial link between obesity and an increased frequency of a number of cancers<sup>(12)</sup>. The International Agency for Research on Cancer has identified thirteen obesity-related cancers, which include oesophageal adenocarcinoma, stomach, colorectal, liver, gallbladder, pancreas, post-menopausal breast, endometrium, ovary, renal cell, thyroid, meningioma and multiple myeloma<sup>(13)</sup>. Therefore, for these types of cancer, the proportion of patients with obesity is likely to be significant. These associations are further worrying given the increasing prevalence of childhood obesity, potentially increasing the incidence of cancer as these obese children reach adulthood<sup>(14)</sup>.

### Obesity and risk of breast cancer

The World Cancer Research Fund (WCRF) review has classified the evidence that body fatness increases the relative risk of post-menopausal breast cancer as convincing<sup>(5)</sup>. This risk is of the order of 12% higher for women who are overweight (BMI 25–29.9 kg/m<sup>2</sup>) and 16% higher who are obese (BMI  $\geq 30$  kg/m<sup>2</sup>), compared with women of healthy body mass (BMI 20–24.9 kg/m<sup>2</sup>)<sup>(15)</sup>. For every 5 kg/m<sup>2</sup> increase in BMI, there is a 12% increased relative risk of post-menopausal breast cancer<sup>(12)</sup>. Obese post-menopausal women have an increased risk of hormone receptor-positive breast cancer compared with women of healthy BMI; however, obesity is not associated with an increased risk of hormone receptor-negative breast cancer in post-menopausal women<sup>(16)</sup>.

Post-menopausal hormone replacement therapy may modify the relationship between obesity and post-menopausal breast cancer. The Nurses' Health Study found that BMI and adult weight gain were associated with 60% to 2-fold increased relative risk, respectively, of post-menopausal breast cancer among women who had never used hormone replacement therapy, whereas there was an attenuation of this relationship among women who used hormones<sup>(17)</sup>. In terms of women who used hormone therapy, results from the Women's Health Initiative showed an increased risk of post-menopausal breast cancer for oestrogen–progestogen preparations compared with oestrogen alone<sup>(18)</sup>. The attenuation of the risk seen in women who use hormone

replacement therapy may be due to the fact that circulating oestrogen levels are elevated among women using hormone replacement therapy, minimising the impact of the adipose tissue oestrogen production, which is the primary source of oestrogen production via the aromatase enzyme in post-menopausal women.

In contrast, studies indicate that obesity does not increase the risk of developing premenopausal breast cancer with some meta-analyses even suggesting that the risk is slightly lower in pre-menopausal women who are overweight and obese compared with healthy weight individuals<sup>(5,12,15,19)</sup>. However, weight gain during adulthood is associated with a significant increased risk of post-menopausal breast cancer<sup>(20)</sup>.

### Mechanisms of cancer development in obesity

The molecular mechanisms promoting cancer development in obesity are not fully understood; however, it is clear that a number of different biological pathways are involved<sup>(21)</sup>. In addition to storing excess energy in the form of lipid, adipose tissue has an active role in endocrine signalling to the rest of the body. Increased adipose tissue is associated directly with increased levels of many circulating hormones, including insulin, insulin-like growth factors and sex hormones, creating an environment that encourages carcinogenesis<sup>(22)</sup>. Abdominal fatness is also associated with insulin resistance, further increasing the pancreatic production of insulin<sup>(23)</sup>. In addition, extensive data suggest that adipose tissue secretes specific molecules into the bloodstream, which signal to other organs to coordinate responses to an altered metabolic state<sup>(21)</sup>. One example is leptin, an adipocyte-derived hormone that is the central mediator of a feedback loop that regulates appetite and energy homeostasis<sup>(24)</sup>. There is an up-regulation of the leptin receptor in breast cancer, and leptin also stimulates the expression and activity of aromatase and the transactivation of the oestrogen receptor (ER) in breast cancer cells, both of which stimulate tumour growth<sup>(24–26)</sup>. Several studies indicate an anti-tumour effect of adiponectin<sup>(24)</sup>. Adiponectin levels are reduced in obesity and inversely associated with breast cancer risk in post-menopausal women<sup>(27)</sup>.

More recently, obesity has become recognised as a chronic pro-inflammatory state.

Cytokines secreted by adipose tissue can activate macrophages, and in obese individuals, adipose tissue becomes infiltrated with macrophages<sup>(28,29)</sup>. It has been demonstrated that tumour-associated macrophages have a key role in the tumour micro-environment. Increased macrophage chemoattractant protein 1 in breast tumour extracts is an early predictor of early relapse and metastasis<sup>(30,31)</sup>. Proliferating macrophages in breast tumours are also associated with a high tumour grade and poor prognosis<sup>(32)</sup>. Adipocytes are also able to produce pro-inflammatory factors such as TNF- $\alpha$ , C-reactive protein and IL-6, and higher serum levels of these cytokines are seen in obese than lean individuals suggesting that obesity has a systemic as well as local pro-inflammatory



effect<sup>(22)</sup>. It has been proposed that carcinogenesis is promoted by the activation of the inflammatory cascade<sup>(33)</sup> (Fig. 1).

Clearer elucidation of the complex molecular mechanisms that underlie tumour development in obesity is required and may unlock the potential for therapeutic interventions, notably in the modulation of inflammatory pathways as chemoprevention.

### Obesity and breast cancer outcomes

Several published meta-analyses indicate that obesity is a prognostic factor for poorer outcomes after a diagnosis of breast cancer<sup>(6,34,35)</sup>. In the largest of these, Chan *et al.* reported a meta-analysis of eighty-two clinical studies including 213 075 breast cancer survivors. A pre-diagnosis BMI  $\geq 30$  kg/m<sup>2</sup> was associated with a total mortality of relative risk 1.41 (95% CI 1.29, 1.53) compared with a reference group of healthy weight patients (BMI 20–24.9); the relative risk for BMI 25–29.9 was also significantly raised at 1.07 (95% CI 1.02, 1.12)<sup>(6)</sup>. Each additional 5 kg/m<sup>2</sup> BMI before diagnosis was associated with a 17% increase in total mortality and a 18% increase in breast cancer mortality (11% increase in total mortality and 14% increase in breast cancer mortality at <12 months from diagnosis and 8 and 29%, respectively, at >12 months from diagnosis)<sup>(6)</sup>. The long-term effects of obesity at diagnosis were highlighted by a study of just under 19 000 Danish women treated for early-stage breast cancer between 1977 and 2006, in which Ewertz *et al.* found that the risk of distant metastases separated after approximately 3 years, showing a trend of increasing risk with increasing BMI. At 10 years, the incidences were 20.1% for patients with BMI <25 kg/m<sup>2</sup>, 22.4% for patients with BMI 25–29 kg/m<sup>2</sup> and 24.3% for patients with BMI  $\geq 30$  kg/m<sup>2</sup>. At 30 years, the cumulative risks of dying of breast cancer were 46.4% for patients with BMI <25 kg/m<sup>2</sup>, 53.4% for patients with BMI 25–29 kg/m<sup>2</sup> and 57.2% for patients with BMI  $\geq 30$  kg/m<sup>2</sup><sup>(34)</sup>.

Despite the significant quantity of generally consistent data linking obesity at diagnosis of early breast cancer to poorer overall mortality and breast cancer-specific mortality, the 2014 WCRF continuous update project on breast cancer survivors report categorised the level of evidence as limited on the basis it was not clear to what extent individual studies have fully adjusted for potential confounders such as the tumour type, type of treatment, amount of treatment received and the dissemination of the disease<sup>(7)</sup> (Table 2).

Despite the absence of an association between obesity and the risk of developing breast cancer in premenopausal women, there is evidence that obesity is significantly associated with poor outcomes in premenopausal breast cancer patients. The UK Prospective Study of Sporadic and Hereditary breast cancer in young women, a cohort study of almost 3000 women aged 40 years and under at diagnosis found that obese patients have significantly lower 8-year overall survival than

healthy weight patients (58.6 v. 73.3%,  $P < 0.001$ )<sup>(36)</sup>. Multivariable analyses adjusting for tumour grade, size, nodal and human epidermal growth factor receptor 2 status indicated that obesity was a significant independent predictor of overall survival (hazard ratio 1.65,  $P < 0.001$ ) and distant disease-free survival (hazard ratio 1.44). The Chan *et al.* meta-analysis confirmed that the impact of obesity at diagnosis is greater on premenopausal women than postmenopausal women with obesity associated with summary relative risks of 1.75 (95% CI 1.26, 2.41) for premenopausal and 1.34 (95% CI 1.18, 1.53) for postmenopausal breast cancer<sup>(6)</sup>.

### Presentation and pathology

Compared with those with BMI <25 kg/m<sup>2</sup>, patients with BMI  $\geq 30$  kg/m<sup>2</sup> tend to have larger tumours and more positive axillary lymph nodes involvement<sup>(34,37)</sup>. These unfavourable pathological features could be explained by a delayed presentation in this group of patients: a larger body habitus may result in breast lumps being less palpable or obvious. More recently, the UK Prospective study of Sporadic and Hereditary breast cancer in young women reported on young breast cancer patients who were below screening age and therefore all presented symptomatically. This study showed that again, in obese and overweight patients, median tumour size was significantly higher and there were more node-positive tumours than in healthy weight patients<sup>(36)</sup>. In these cohort studies, multivariate analysis demonstrated that obesity retained an independent effect on prognosis on adjustment for disease stage.

Additionally, a number of studies have also reported increased frequency of grade 3 tumours in obese breast cancer patients, compared with those with a healthy weight<sup>(34,37)</sup>, and increased frequency of ER-negative and oestrogen/progesterone/human epidermal growth factor receptor 2 (triple) negative tumours has also been demonstrated<sup>(36)</sup>. These features are all well-established biomarkers of aggressive behaviour in early breast cancer and these associations suggest that obesity may influence the intrinsic biology of breast tumours, perhaps by affecting the tumour micro-environment. Studies which have adjusted for grade and human epidermal growth factor receptor 2 status suggest that obesity exerts an additional effect beyond these prognostic factors<sup>(34,36,37)</sup>. Data on the effect of obesity in ER-positive and ER-negative tumours are more conflicting. Although some reports have indicated an equivalent effect of obesity on the outcome of ER-positive and ER-negative tumours<sup>(38)</sup>, more recent studies have reported a stronger effect of obesity on the outcome of women with ER-positive breast tumours than ER-negative tumours<sup>(36,39,40)</sup>. Pan *et al.* demonstrated a breast cancer mortality-adjusted relative risk of 1.34 (95% CI 1.22, 1.47) associated with obesity in peri/premenopausal ER-positive patients but no association between BMI and breast cancer mortality in ER-negative patients<sup>(39,40)</sup>. However, it should be noted that many data sets contained relatively small numbers of ER-negative

patients and analyses may have been underpowered in this patient group.

### Local treatment issues

#### *Surgery*

Obese patients with breast cancer have a higher risk of post-surgical complications and this is most clearly seen with post-mastectomy skin flap necrosis where obesity is a recognised risk factor<sup>(41,42)</sup>. Data from the 2007–2012 American College of Surgeons National Surgical Quality Improvement Program<sup>®</sup> database of 7207 women who had undergone unilateral mastectomy showed a clear increase in both major complications ( $P=0.005$ ) and minor complications ( $P<0.001$ ) as BMI increased<sup>(43)</sup>. The authors concluded that these findings highlight the need for personalised pre-operative risk assessment and counselling of obese patients<sup>(43)</sup>.

In a series of 718 surgical breast reconstructions including 64 (9%) obese patients, a number of complications were seen more frequently in obese patients than normal-weight patients including flap complications (39 v. 20%), overall donor site complications (23 v. 11%), infection (5 v. 1%), seroma (9 v. 1%) and hernia (6 v. 2%)<sup>(44)</sup>. A prospective, multi-centred cohort study of 15 937 patients undergoing breast reconstruction procedures additionally reported that obese patients had greater lengths of hospital stay and longer operating times as well as higher rates of complications (wound, medical, infections, return to theatre, graft loss and major surgical complications). All these factors reached statistical significance<sup>(45)</sup>. Furthermore, obesity may negatively influence the decision for immediate breast reconstruction after mastectomy<sup>(45)</sup>.

With breast-conserving treatment, there is also increased risk of arm lymphoedema associated with obesity; in a series of 282 patients, higher BMI was related with a greater frequency (36% of obese patients v. 12% in the non-obese group) and severity of arm oedema (9% of obese patients v. 2% in non-obese patients)<sup>(46)</sup>. These post-operative complications can all impact on adjuvant treatment, resulting in patients experiencing delays in commencing radiotherapy or chemotherapy.

An interesting observation from the STARSurgUK study, which analysed the surgical outcomes of patients with gastrointestinal cancer, was that there were no effects of increasing BMI on complications after surgery for benign disease, but clear relationships between BMI and post-surgical complications where the indication was malignancy<sup>(47)</sup>. This raises the possibility that the cancer state interacts with obesity to affect the healing process.

#### *Radiotherapy*

Use of standard radiotherapy regimens for the breast and chest wall is associated with an increased risk of skin toxicity for the overweight patient<sup>(48)</sup>. Obesity also poses significant challenges in the delivery and accuracy of radiotherapy, notably regarding technical considerations

of delivering the optimum radiation dose to the tumour bed. This may require adaptations to equipment, additional time, changes in the posture of the patient and challenges in terms of daily reproducibility<sup>(49–51)</sup>. A particular example is the use of prone breast irradiation for morbidly obese patients. In a study of 110 patients with BMI 34 kg/m<sup>2</sup> treated with breast conserving surgery followed by three-dimensional-conformal whole breast irradiation in prone position showed favourable toxicity profiles and good cosmesis<sup>(52)</sup>. However, as the standard treatment involves a supine position, there is a clearly a need to prospectively assess tumour dose delivery in obese women<sup>(53)</sup>.

### Systemic treatment issues

#### *Cytotoxic therapy*

In adult patients with cancer, chemotherapy dosing has traditionally been based on a patient's estimated body surface area (BSA), calculated from their height and weight<sup>(54)</sup>. Chemotherapy is given either before (neoadjuvant) or after (adjuvant) surgery to selected patients with early breast cancer in order to reduce the risk of future metastatic disease. It is well established that administering adjuvant chemotherapy on time and at the optimal dose is vital to achieve maximal risk reduction with the classic publication by Belladonna indicating that a chemotherapy dose intensity <85% of the intended dose intensity was equivalent to not giving any chemotherapy at all<sup>(55)</sup>. However, concerns about the potential toxicity of cytotoxic doses associated with high calculated BSA have led to many oncologists routinely capping chemotherapy doses at a maximum BSA of 2.0 or using either ideal body weight or adjusted ideal body weight to calculate drug doses. Reviews of routine practice indicate that up to 40% of obese patients receive limited doses that are not based on actual body weight and it has been postulated that this use of sub-optimal chemotherapy doses results in a reduced therapeutic effect, which could potentially explain the observed adverse prognosis of obese patients<sup>(56–60)</sup>.

An expert panel review of the literature found no evidence that short- or long-term toxicity is increased in obese patients receiving full weight-based chemotherapy doses and the resultant American Society of Clinical Oncology clinical practice guideline recommends that full weight-based cytotoxic chemotherapy doses be used to treat obese patients with cancer<sup>(61)</sup> (Table 3). However, it should be noted that the data presented were taken largely from clinical trial patients and it is possible that patients in trials have been selected for a certain level of medical fitness; therefore, these data may not fully represent the real-world situation. In addition, the data collected largely looked only at haematological toxicity criteria. The need for more research in this area was therefore highlighted by American Society of Clinical Oncology<sup>(61)</sup>. A subsequent meta-analysis of 9134 chemotherapy patients treated on the basis of actual body weight found similar or lower rates of toxic effects compared with normal-weight patients<sup>(62)</sup>. However, a more recent



study of data from 3023 patients with breast cancer published after this did demonstrate an increase in significant toxicity in obese patients given dose-intense anthracycline and taxane chemotherapy regimens dosed according to actual body weight<sup>(63)</sup>.

The consequences of a high proportion of obese patients being treated with reduced doses are that survival advantages are lost and outcomes are potentially similar to those of the untreated cohorts. This is seen in trials (of different cancer types including breast) where participants received reduced doses of adjuvant chemotherapy, and where the adjuvant chemotherapy is known to improve survival<sup>(64,65)</sup>. It may also be the case that the observed adverse prognosis of obese patients may be the result of the sub-therapeutic chemotherapy doses and reduced therapeutic effect rather than obesity as a stand-alone factor<sup>(66)</sup>.

Studies of pathological response rates in the neoadjuvant treatment setting offer to provide a further insight into the effect of obesity on the effectiveness of systemic therapies; however, currently the available data are conflicting. Although a number of studies have reported higher BMI associated with poorer pathological complete response rates and inferior overall survival<sup>(67–69)</sup>, other studies have not found this association<sup>(70)</sup>. This may also be explained by variations in chemotherapy prescribing habits as Farr *et al.*<sup>(70)</sup> confirmed that all obese patients analysed had received full uncapped doses of anthracycline–taxane-based chemotherapy whilst prescribing data were not available in all the other publications.

#### Biological therapies

Unlike traditional cytotoxic drugs, most biological anti-cancer agents (including monoclonal antibodies and small molecule inhibitors) are prescribed by weight or as absolute doses. The most commonly used biological agent in early breast cancer treatment is trastuzumab (Herceptin). This is currently prescribed as either a flat dose (600 mg) for the subcutaneous formulation, or at a maintenance dose (6 mg/kg) for the intravenous preparations; there is no specific guidance for the dosing of obese patients, although in some but not all studies, obesity was found to be a risk factor for trastuzumab-induced cardiac toxicity<sup>(71,72)</sup>.

#### Hormonal therapies

The observation that obesity has a greater impact on the prognosis of ER-positive than ER-negative patients<sup>(36,39,40)</sup> could indicate that obesity influences the effectiveness of adjuvant hormonal therapy effectiveness. Concerns have been reported that aromatase inhibitors (AI; used commonly as adjuvant treatment in post-menopausal breast cancer patients) may be less effective in obese than healthy weight patients as obesity is associated with increased levels of peripheral aromatase activity, which is the therapeutic target for AI. An analysis of the ABCSG-12 trial reported that BMI significantly influenced the efficacy of (the AI) anastrozole plus goserelin in premenopausal patients but did not influence the prognosis of

patients treated with tamoxifen plus goserelin<sup>(73)</sup>. However, analyses of interactions between AI and BMI in other breast cancer trials have been inconsistent in terms of long-term outcomes<sup>(74)</sup>. Goodwin and co-workers concluded that, overall, the findings did not support the use of BMI as a prediction biomarker of treatment with AI in the adjuvant setting in post-menopausal women with breast cancer<sup>(74–76)</sup>. Associations between non-adherence and BMI have been reported for other medications but data on tamoxifen adherence and BMI are lacking<sup>(77)</sup>.

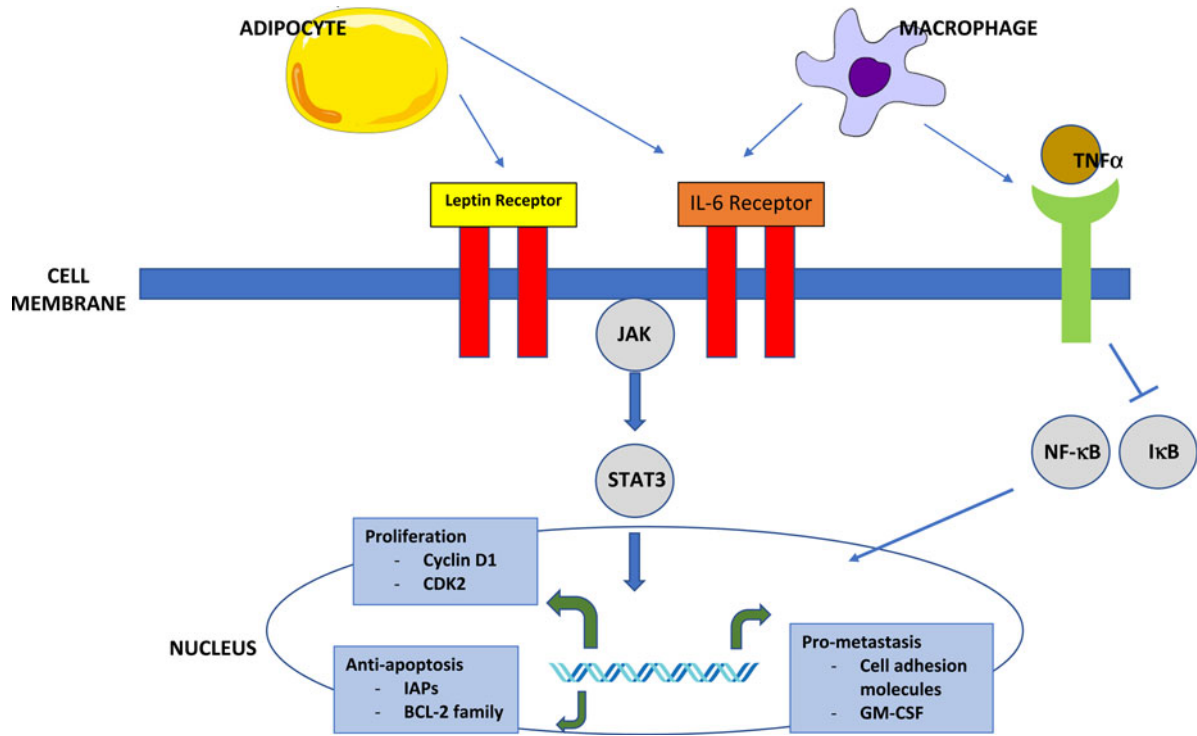
#### Weight changes during treatment for breast cancer

Weight gain during chemotherapy is a common feature of treatment with contemporary regimens of 4–6 months of anthracycline and taxane chemotherapy, which are the standard regimens for early breast cancer. European, American and Asian studies report that 30–50 % of women gain more than 5 % of body weight, with a mean weight change of 2–3 kg in the first year after diagnosis<sup>(77–88)</sup>. There is a persistence of weight gain when measured at 3 and 6 years after diagnosis<sup>(78,85)</sup>. Weight is gained both during and after the chemotherapy period<sup>(83,85)</sup>. The cause of weight gain due to chemotherapy is usually multifactorial, with use of steroids, change in eating patterns, reduction in physical activity due to fatigue, oedema secondary to taxane chemotherapy and hormonal changes all playing a role. The greatest weight gain is observed in women who are premenopausal, stop smoking after the diagnosis, have a healthy weight at diagnosis or experience a chemotherapy-induced menopause<sup>(77,83,86,87)</sup>. Studies indicate changes in body composition with gain of fat mass and loss of muscle as well as alterations in fluid compartments<sup>(88)</sup>.

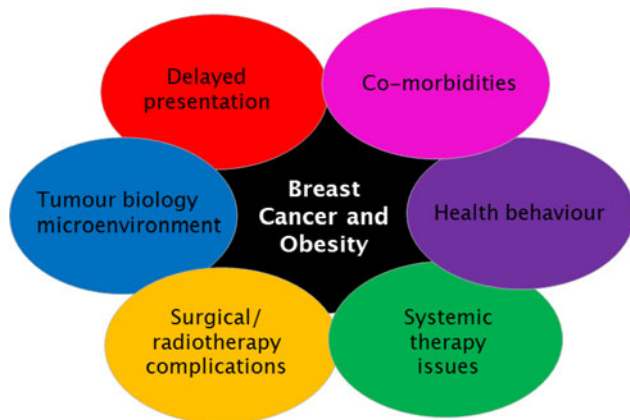
The consequences of chemotherapy-related weight gain was addressed by Playdon *et al.* in their meta-analysis of 23 832 cancer cases where they found that, compared with women who maintained their weight, those women with a >10 % weight gain after diagnosis had increased overall mortality (hazard ratio 1.23; 95 % CI 1.09, 1.39,  $P < 0.001$ ); breast cancer-specific mortality was increased but not to a statistically significant level (hazard ratio 1.17; 95 % CI 1.00, 1.38,  $P = 0.05$ )<sup>(89)</sup>. No association between weight gain and recurrence was identified. In contrast, in a pooled analysis of 6596 women with ER-positive tumours, more than 10 % weight gain was associated with an increased risk of late recurrence, defined as more than 5 years after diagnosis<sup>(90)</sup>.

#### Limitations of using BMI

BMI is a simple surrogate marker of obesity, but it is not a reliable measure of body fat for individuals as it cannot distinguish lean mass from fat mass, or characterise body fat distribution. Body fat is generally distributed viscero-ally, subcutaneously and internally (most in the liver), and the body fat distribution pattern can differ significantly between individuals with the same BMI.



**Fig. 1.** (Colour online) Inflammatory signalling in obesity. Circulating leptin produced by adipocytes can bind both to the leptin receptor and the IL-6 receptor. This leads to the activation of the JAK-signal transducer and activation of the transcription (STAT) signalling pathway through STAT3. STAT3 functions as an oncogenic transcription factor. Inflammatory cells in the adipose tissue produce IL-6 and TNF- $\alpha$ . IL-6 promotes proliferation and metastasis by activating the JAK-STAT pathway. TNF- $\alpha$  binds to the TNF receptor, activating NF- $\kappa$ B through the degradation of I $\kappa$ B. NF- $\kappa$ B is free to translocate to the nucleus, where it inhibits apoptosis and promotes proliferation and metastasis. Similarly, macrophages are also able to activate the IL-6 and TNF receptors<sup>(21)</sup>.



**Fig. 2.** (Colour online) Interacting factors in obese patient with early breast cancer, which may adversely affect prognosis.

Similarly, patients with the same BSA may have wide variations in the distribution of adipose tissue and skeletal muscle; thus, BSA fails to accurately reflect drug pharmacodynamics and pharmacokinetic variability in obese patients. In a large analysis of 1206 cancer patients, Sparreboom *et al.* showed drug-specific interactions between BMI and the pharmacokinetic clearance of cytotoxic drugs including doxorubicin, which is commonly used in the treatment of early breast cancer<sup>(91)</sup>.

Very few studies have looked at the effect of body composition patterns on chemotherapy tolerance because the gold standard ‘four-compartment model’ measurement of body composition requires complex procedures not routinely available in the clinical environment. Two small series using limited body composition data derived from comprised tomography images indicate that sarcopaenia (low muscle mass) is associated with increased chemotherapy toxicity, regardless of overall BMI<sup>(92,93)</sup>. Sarcopaenia may result in a relatively higher chemotherapy dose as lean body mass is a predictor of volume of distribution for some drugs<sup>(94)</sup>. Del Fabbro *et al.* reported a higher pathological complete response rate to neoadjuvant chemotherapy for breast cancer in healthy BMI patients with sarcopaenia<sup>(95)</sup>.

In a larger study, Iwase *et al.* retrospectively analysed 172 advanced breast cancer patients who underwent surgery after neoadjuvant chemotherapy<sup>(96)</sup>. Body composition parameters including abdominal circumference, subcutaneous fat area, visceral fat area and skeletal muscle area were calculated using comprised tomography volume-analysing software. Distant disease-free survival was significantly worse in the high visceral fat area group than in the lower visceral fat area group. Furthermore, in the high visceral fat area group, postmenopausal patients had significantly shorter distant disease-free survival than premenopausal patients<sup>(95)</sup>.



**Table 1.** Key findings of published meta-analyses and large studies ( $n > 1000$ ) reporting the effect of obesity at diagnosis on the outcome of early breast cancer

Reference	Study design	N Median follow-up	Study information and endpoints	Study findings
Berclaz <i>et al.</i> <sup>(99)</sup>	Retrospective study of patients randomised to international breast cancer study group trials studying chemo/endocrine therapy	6792 14 years	Investigated association between BMI at diagnosis and OS/DFS. Analyses adjusted for menopausal status, tumour pathology and treatment	Healthy BMI associated with significantly longer OS and DFS than patients with intermediate or obese BMI with similar effect in pre- and peri-menopausal women. BMI was independent prognostic factor for OS but not DFS
Kroenke <i>et al.</i> <sup>(100)</sup>	Retrospective cohort study of patients recruited to the nurses' health study and diagnosed with breast cancer	5204 9 years	Investigated weight prior to diagnosis and weight gain after diagnosis as predictors of breast cancer survival and mortality. Results stratified by smoking, menopausal status and adjusted for pathological prognostic factors and treatment	Weight before diagnosis was positively associated with breast cancer recurrence and death, but only in never smokers. Weight gain after diagnosis of 0.5–2.0 or >2.0 kg/m <sup>2</sup> had elevated risk of breast cancer death compared with weight maintenance. Associations stronger in pre- than post-menopausal women
Abrahamson <i>et al.</i> <sup>(101)</sup>	Prospective cohort study of breast cancer patients aged 20–54	1254 8–10 years	Investigated effect of general and abdominal obesity (measured within few months of diagnosis) on all-cause mortality in young breast cancer patients	Increased mortality observed for women who were obese at the time of recruitment compared with women of healthy weight (HR 1.48)
Tao <i>et al.</i> <sup>(102)</sup>	Population-based case-control study of breast cancer patients aged 25–64	1455 5.1 years	Investigated association between BMI at or soon after breast cancer diagnosis and OS and DFS. Results adjusted for age and disease stage	Inverse association between BMI and OS and DFS with BMI <23.0: OS 86.5 %; BMI 23.0–24.9: OS 83.8 %; BMI >25: 80.1 %. Associations between BMI and survival persisted after adjustment for known prognostic factors
Caan <i>et al.</i> <sup>(103)</sup>	Prospective cohort study of breast cancer patients aged 18–70 years	1692 5.0 years	Investigated associations between BMI before diagnosis/weight change post-diagnosis, and breast cancer recurrence/mortality/any cause mortality. Analyses adjusted for known prognostic factors	Obesity at 1 year before diagnosis was associated with increased risk of any cause mortality (HR 1.6) and breast cancer mortality (HR 1.6). Weight gain ≤4 years after diagnosis not associated with increased risk of recurrence or total mortality
Majed <i>et al.</i> <sup>(37)</sup>	Single-centre prospective cohort study of French breast cancer patients	14 709 8.0 years	Investigated association between BMI at diagnosis and metastatic recurrence, disease-free interval, OS. Analyses adjusted for known prognostic factors	In MVA obesity was an independent negative prognostic factor for metastasis recurrence (HR 1.12); disease-free interval (HR 1.10); OS (HR 1.12)
De Azambuja <i>et al.</i> <sup>(104)</sup>	Retrospective analysis of node-positive breast cancer patients enrolled in BIG 02-98 adjuvant chemotherapy study	2887 5.2 years	Investigated association between BMI at diagnosis and DFS/OS. Analyses adjusted for known prognostic factors	Obese patients had poorer 5-year OS (HR 1.34) and DFS (HR 1.20) than non-obese patients. In MVA obesity was an independent prognostic factor for OS and DFS
Emaus <i>et al.</i> <sup>(105)</sup>	Prospective survival study of breast cancer cases within the Norwegian counties study	1364 8.2 years	Investigated effect of metabolic components, including BMI on total mortality/breast cancer mortality. Analyses adjusted for age and tumour stage	Obese women had a significantly higher overall mortality (HR 1.47) and non-significantly higher breast cancer mortality (HR 1.43) than women with a healthy BMI
Keegan <i>et al.</i> <sup>(106)</sup>	Prospective cohort study of Canadian and Australian breast cancer patients	4153 7.8 years	Investigated associations between BMI at diagnosis and all-cause mortality, stratified by patient characteristics	Increased BMI positively associated with all-cause mortality (HR 1.77 for obese; HR 1.39 for overweight patients) in women age ≥50 years with ER-positive disease
Protani <i>et al.</i> <sup>(35)</sup>	Meta-analysis of forty-three studies of BMI and breast cancer outcome (study-level data)	Median 1192 4–14 years	Investigated association between BMI at diagnosis and DFS/OS. Included studies with variable adjustments for known prognostic factors	Obesity associated with poorer OS (HR 1.33) and BCSS (HR 1.33)

Table 1. (Cont.)

Reference	Study design	N Median follow-up	Study information and endpoints	Study findings
Ewertz <i>et al.</i> <sup>(34)</sup>	Retrospective cohort study of Danish breast cancer patients	18 967 7.1 years	Investigated association between BMI at diagnosis and breast cancer recurrence, breast cancer mortality and total mortality. Analyses adjusted for known prognostic factors	Obesity associated with increased risk of distant metastases (HR 1.46) and breast cancer mortality (HR 1.38). BMI not associated with locoregional recurrences
Niraula <i>et al.</i> <sup>(38)</sup>	Meta-analysis of twenty-one clinical studies of BMI and breast cancer outcome (study-level data)	177– 14 709 4–>10 years	Investigation of association of obesity with OS and BCSS in relation to hormone receptor status and menopausal status	Obesity associated with poorer OS (ER-positive cancers: HR 1.31; ER-negative: HR 1.18;) and BCSS (ER-positive: HR 1.36; ER-negative: HR 1.46). No significant differences between HR for pre and post-menopausal women
Pajares <i>et al.</i> <sup>(107)</sup>	Retrospective cohort analysis of breast cancer patients enrolled in four randomised adjuvant chemotherapy I trials	5683 7.8 years	Investigated association between BMI at diagnosis and disease recurrence, breast cancer mortality and total mortality. Analyses adjusted for age, pathological prognostic factors and treatment	Obese patients had similar outcomes to patients with a healthy BMI. Severely obese patients (BMI ≥35) had significantly increased risk of recurrence (HR 1.26, breast cancer mortality (HR 1.32) and overall mortality (HR 1.35)
Ladoire <i>et al.</i> <sup>(108)</sup>	Retrospective pooled analysis of node-positive French breast cancer patients recruited to two adjuvant chemotherapy trials	4996 5.9 years	Investigated association between BMI at diagnosis and DFS/OS. Analyses adjusted for known prognostic factors	Obesity associated with poorer DFS (HR 1.18) and poorer OS (HR 1.38). On adjustment for disease characteristics BMI had no influence on DFS or OS when appropriate dose intensity adjuvant chemotherapy delivered
Chan <i>et al.</i> <sup>(6)</sup>	Meta-analysis of eighty-two clinical studies of BMI and breast cancer outcome (study-level data)	2 13 075 >5 years	Investigated association between BMI at diagnosis and overall mortality/breast cancer mortality. Included studies with variable adjustments for known prognostic factors	Obesity associated with increased overall mortality (HR 1.33) and breast cancer mortality (HR 1.31). Overall mortality risks higher in pre-than post-menopausal obese women (HR 1.75 v. 1.34)
Copson <i>et al.</i> <sup>(36)</sup>	Prospective study of UK breast cancer patients aged <41 years at diagnosis	2843 5.9 years	Investigated association between BMI at diagnosis and DFS/OS. Analyses adjusted for known prognostic factors, age, ethnicity and treatment	Obesity associated with poorer OS (HR 1.65) and disease free interval (HR 1.47). In MVA, obesity was an independent prognostic factor in ER-positive patients
Chung <i>et al.</i> <sup>(109)</sup>	Retrospective cohort study of breast cancer patients from single Korean centre	8742 7.7 years	Investigated association between BMI at diagnosis and OS, BCSS, stratified by ER status	Obesity was associated with poorer OS (HR 1.51) and significantly poorer BCSS (HR 1.80) in ER-positive breast cancer. In ER-negative breast cancer, high BMI was associated with improved a better OS (HR 0.44) and BCSS (HR 0.53)
Guo <i>et al.</i> <sup>(110)</sup>	Mendelian randomisation analysis using individual-level data from six large BC cancer–case cohorts including individuals of European ancestry	36 210	Investigated possible causal role of BMI in BCSS using BMI genetic risk score based on genotypes at ninety-four known BMI-associated inherited genetic variants not affected by potential environmental confounding factors	BMI genetic score was associated with reduced BCSS for ER-positive cases (HR 1.1), suggesting a causal effect of increased BMI on reduced breast cancer survival for ER-positive breast cancer. No association for ER-negative cases

OS, overall survival; DFS, disease-free survival; HR, hazard ratio; MVA, multi-variable analyses; BCSS, breast cancer-specific death; ER, oestrogen receptor.



**Table 2.** World Cancer Research Fund continuous update project on diet, nutrition, physical activity and breast cancer survivors, 2014; summary of panel judgements<sup>(7)\*</sup>

2014	DIET, NUTRITION, PHYSICAL ACTIVITY AND BREAST CANCER SURVIVAL (BY OUTCOME)												
	Timing of exposure assessment	ALL CAUSE MORTALITY				BREAST CANCER MORTALITY				SECOND PRIMARY BREAST CANCER			
		DECREASES RISK		INCREASES RISK		DECREASES RISK		INCREASES RISK		DECREASES RISK		INCREASES RISK	
		Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome	Exposure	Outcome
STRONG EVIDENCE	Convincing												
	Probable												
LIMITED EVIDENCE	Limited – suggestive	Physical activity	Before diagnosis	Body fatness	Before diagnosis	Physical activity	Before diagnosis	Body fatness*	Before diagnosis			Body fatness	Before diagnosis
		Foods containing fibre	Before diagnosis	Total fat	Before diagnosis								
		Foods containing soy	Before diagnosis	Saturated fatty acids	Before diagnosis								
STRONG EVIDENCE	Substantial effect on risk unlikely												

**STRONG:** Evidence strong enough to support a judgement of a convincing or probable causal relationship and generally justify making recommendations.  
**LIMITED:** Evidence that is too limited to justify making specific recommendations.  
 \* Post-menopause only.

\* This material has been reproduced from the World Cancer Research Fund International/American Institute for cancer research continuous update project report: diet, nutrition, physical activity and breast cancer survivors (2014). Available at [www.wcrf.org/int/research-we-fund/continuous-update-project-reports/breast-cancer-survivors](http://www.wcrf.org/int/research-we-fund/continuous-update-project-reports/breast-cancer-survivors).

**Table 3.** Summary of American Society of Clinical Oncologists panel recommendations for treatment of obese patients<sup>(59)</sup>

Recommendation
1 Actual body weight to be used when selecting cytotoxic chemotherapy doses regardless of obesity status
2 Full body weight chemotherapy doses (oral and intravenous) to be used in the treatment of the obese patient with cancer, particularly when the goal of treatment is cure
3 Clinicians should follow the same guidelines for dose reductions, regardless of obesity status, for all patients, depending on the type and severity of toxicity, any comorbid conditions, and whether the intention of the treatment is cure or palliation
4 Consideration of fixed dosing only for selected cytotoxic agents (e.g. carboplatin, bleomycin, vincristine)
5 Body surface area to be calculated using any of standard formulae

The importance of visceral fat may be explained by the fact that it appears to be more hormonally active than other types of body fat; this appears to promote inflammation, insulin resistance and increases in leptin and adiponectin.

Further research is clearly required to fully assess the interactions between body composition and chemotherapy toxicity and effectiveness<sup>(97)</sup>. Techniques such as dual-energy X-ray absorptiometry, bioelectrical impedance, computerised tomography scan software and MRI analysis provide a clearer picture of body composition and may have a role in the management and treatment planning of obese patients in the future<sup>(88)</sup>. However,

clearly the risk-benefits and cost-effectiveness of such approaches will need to be addressed as currently it is not a routine practice for all early breast cancer patients to undergo cross-sectional imaging for staging purposes.

### Health behaviour

Finally, it cannot be excluded that obesity or body fatness are surrogate markers for other health behaviours in addition to dietary ones. The WCRF continuous update project on diet, nutrition, physical activity and breast cancer survivors additionally investigated the impact of physical activity both before and after a diagnosis of breast cancer on long-term survival. They concluded that there was limited but consistent evidence that physical activity prior to diagnosis was associated with a reduction in both all-cause and breast cancer mortality<sup>(7)</sup>. The same conclusion was reached regarding physical activity after breast cancer diagnosis. Similar results were reported by the After Breast Cancer Pooling Project, which reported a 27% significant decreased risk of mortality and a 25% reduction in breast cancer mortality associated with engagement in at least 10 metabolic equivalent per task hours per week compared with <10 metabolic equivalent per task hours per week<sup>(98)</sup>. The WCRF has therefore concluded that there is sufficient evidence to recommend that early breast cancer patients follow the WCRF cancer prevention recommendations,

which include being physically active in addition to eating a healthy diet and maintaining a healthy weight. However, more evidence is needed in order to make specific recommendations on lifestyle modifications for breast cancer survivors. Prospective studies to evaluate whether weight loss and lifestyle interventions will improve breast cancer outcomes are now in progress.

### Conclusions

The obesity epidemic in both developed and developing countries poses challenges in terms of both increasing cancer incidence and specific management considerations. Obesity at diagnosis is associated with reduced breast cancer-specific and overall survival. Research is required to fully understand the biological mechanisms behind this as well as the practical implications of obesity on treatment effectiveness and tolerance (Fig. 2). Work is also required to fully elucidate body composition patterns in order to define the true nature of the risk factor presented by obesity in early breast cancer. With greater understanding of the link between obesity and breast cancer outcome, specific treatment strategies, including lifestyle interventions, can be developed to improve the prognosis of this patient group.

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### Conflicts of Interest

None.

### Authorship

This paper was jointly conceived and written by the three authors. All authors have approved the submitted manuscript.

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