Weight and breast cancer

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1. Summary

Excess weight can influence quality of life and impair health by leading to an increased risk of diseases such as type 2 diabetes, heart disease and certain cancers. With breast cancer, the risk association between excess weight is dependent on menopausal status for women; weight increases the risk of breast cancer in postmenopausal women but there is no evidence that being overweight when pre-menopausal is associated with an increased risk of breast cancer. Being overweight or obese is also a risk factor for breast cancer in men. Three main mechanisms have been proposed to explain the association between weight and breast cancer, including insulin resistance, chronic low-grade inflammation, and sex hormone bioavailability.

2. Introduction

Breast cancer is the most common cancer in the UK, with around 56,000 women and 400 men receiving a new breast cancer diagnosis each year [1]. Many factors can influence a person's risk of developing breast cancer, including age, genetics, hormones, diet, lifestyle [1], exposure to some types of chemicals and the environment [2]. Breast Cancer UK estimates that at least 30% of all breast cancers are attributable to preventable causes.

The World Health Organisation reports that in 2022, 2.5 billion people worldwide, over 18 years old, were considered overweight, and 890 million adults were living with obesity [3]. The number of adults who are overweight has increased from 25% to 43% between

Glossary box:

Adipose tissue: connective tissue mainly made of fat cells (adipocytes).

Body mass index (BMI): a medical screening tool using the ratio of an adult's height to their weight (i.e. 'body mass'), expressed in units of kg/m², to categorise their weight for their height.

Central adiposity: accumulation of fat around the abdomen.

Subcutaneous fat: fat that sits under the skin.

Visceral fat: fat found deep within the abdominal cavity and surrounds internal organs.

Waist-to-height ratio: a measure of central adiposity comparing a person's waist size (waist circumference) to their height, to diagnose obesity in conjunction with the BMI.

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1990 and 2022, while adult obesity has more than doubled, from 7% to 16%, in that time frame [3,4]. In the UK, in 2022, 64% of adults were overweight or living with obesity, and 29% were living with obesity [5]. Excess weight is one of the leading lifestyle-related risk factors of death worldwide [6].

Excess weight, which includes being overweight or obese, has been linked with an increased risk of developing at least 13 different types of cancers, including female breast cancer, and is the second biggest cause of cancer in the UK, causing over 1 in 20 cases [7]. The risk of cancer is higher the more weight is gained and the longer the weight is held [7].

In this review, we explore the latest evidence on the association between weight and breast cancer, separating the pre- and post-menopause phases for women, and exploring the different mechanisms through which excess weight can impact breast cancer risk.

3. Overweight and obesity

Overweight and obesity occur when energy intake (diet) exceeds energy requirements for activities of daily living and energy expenditure (physical activity) [3], resulting in an accumulation of fat [8]. Both are now considered complex and multifactorial chronic diseases resulting from an interplay between a person's genetic pre-disposition to weight gain and environmental factors, such as obesogenic factors (e.g. food availability and access, physical activity levels) and psycho-social factors (e.g. socio-economic status, and psychological and social support) [3,8,9]. It is estimated that 1 in 8 people worldwide [3] and 1 in 4 people in the UK, were living with obesity in 2022 [10].

The screening and diagnosis of overweight and obesity are most commonly assessed by anthropometric measures, such as the body mass index (BMI), a surrogate marker (estimate) of an individual's body fatness [3]. BMI is

Table 1: BMI score categorisation based on ethnic background (adapted from [3,11]).

European background		Asian, Chinese, Middle Eastern, Black African or African-Caribbean background*	
BMI Score (kg/m2)	Category	BMI Score (kg/m2)	Category
<18.5	Underweight	<18.5	Underweight
18.5 – 24.9	Normal weight	18.5 – 22.9	Normal weight
25 – 29.9	Overweight	23 – 27.4	Overweight
30 – 34.9	Obesity class 1	27.5 – 32.4	Obesity class 1
35 - 39.9	Obesity class 2	32.5-37.4	Obesity class 2
40 or above	Obesity class 3	37.5 or above	Obesity class 3

* Research shows people from some Black, Asian and minority ethnic groups are more prone to central adiposity and have an increased cardiometabolic health risk at lower BMI thresholds [12].

calculated by dividing a person's body weight in kilograms by height in meters squared: BMI = weight (kg)/height² (m²). BMI score is expressed in units of kg/m² and categorised into underweight, healthy weight, overweight, obese and severely obese (see table 1).

Although the BMI score is a useful indicator easily obtained in an array of settings, there are some limitations. BMI does not account for differences in body types between men and women, does not distinguish between fat mass and muscular mass (it measures whether an individual carries excess weight and not specifically excess fat), and does not consider fat distribution [5,13]. In cases where an individual is very muscular, such as high-performance athletes or bodybuilders, they may have a high BMI although their body fat content may be low [10]. BMI is also limited in evaluating bodyweight health of individuals of short stature [13].

Additional measurements, such as the waist-to-height ratio which compares an individual's waist size (waist circumference) to their height, can help diagnose obesity in conjunction with the BMI [3,10]. This measure provides an estimate of central adiposity, the fat accumulated around the abdomen which contains both subcutaneous fat (found under the skin) and visceral fat (found deep within the abdominal cavity and surrounds internal organs) [14], to help assess and predict weight-related health risks, in all sexes and ethnicities [12]. The waist-to-height ratio is calculated by dividing a person's waist circumference by their height, measured in the same units (e.g. centimetres or inches). A waist-to-height ratio of 0.5 or higher means there may be increased health risks (see Table 2) [10].

Obesity can influence quality of life, such as moving or sleeping, and can increase the risk of many other health conditions and adverse health outcomes, including type 2 diabetes, heart disease, and some types of cancers [3,10].

4. Weight and breast cancer

Weight gain and body fatness (being overweight or living with obesity) are linked with a higher incidence and progression of at least 13 different types of cancers [7,15,16]. However, the underlying mechanisms linking cancer

Table 2: Classification of waist-to-height ratios (adapted from [5,11]).

Waist-to-height ratio		
Waist-to-height ratio	**Category**	**Health risk**
0.4 - 0.49	Normal central adiposity	No increase
0.5 - 0.59	Increased central adiposity	Increase
0.6 or above	High central adiposity	Higher increase

risk and adiposity are complex and not yet fully understood, and different mechanisms may lead to the development of different cancers [17].

Three main mechanisms have been proposed through which adiposity could promote cancer development: insulin resistance, inflammation, and sex hormone bioavailability [17–19].

The first proposed mechanism relates to insulin and insulin-like growth factor-1 (IGF-1), hormones with key roles in glucose metabolism, cell proliferation, angiogenesis (development of new blood vessels) and inhibiting cell death. Excess body fat, particularly abdominal fat, is associated with insulin resistance and hyperinsulinemia (excess insulin is secreted resulting in high levels of insulin circulating in the blood), which leads to increased levels and prolonged action of IGF-1 [17,18]. Overstimulation of insulin and IGF-1 promotes cell proliferation, including cancer cells [7] and therefore is thought to increase the risk of several cancers, including breast cancer [17,18].

The second suggested mechanism is that obesity is associated with a chronic, low-grade inflammatory state [15,19]. This mechanism relates to the concept that adipose tissue is a metabolic "organ" that releases an array of bioactive signalling molecules. Obesity leads to adipocyte (cells that form adipose tissue) dysfunction through hypertrophy (increase in cell size) causing cell death and the release of inflammatory signals, which recruit macrophages and induce a chronic state of inflammation in adipose tissue [20].

This inflammation is characterised by the secretion of pro-inflammatory cytokines (such as interleukin-1-beta (IL-1β) interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α)) and the dysregulation of adipokines like leptin and adiponectin [20].

As part of its normal function, leptin is a hormone that plays a key role in body weight by sending signals to inform the brain of the metabolic status of the body to help reduce appetite and enhance energy expenditure when fat accumulates [18]. Leptin is also pro-inflammatory, promotes cell proliferation, and prevents cell apoptosis [17]. In contrast, adiponectin is an anti-inflammatory, apoptosis-inducing and insulin-sensitising hormone. Adiponectin also promotes glucose uptake and reduces triglyceride (fat) storage [18]. In obese individuals, circulating leptin levels tend to be consistently elevated, while adiponectin tends to be low, maintaining the adipose tissue-related state of inflammation [20,21] which has been linked to the development and progression of several cancers [17–19,22] including breast cancer [15,17,18].

The altered levels of proinflammatory cytokines in overweight and obese individuals regulate C-reactive protein (CRP), a marker of inflammation, which may also contribute to carcinogenesis by increasing cell proliferation [18–20]. Additionally, obesity and inflammation are drivers of immune dysfunction [16]. The obesity-associated inflammation exacerbates immunosenescence (the ageing of the immune system), impairing the immune detection and elimination of

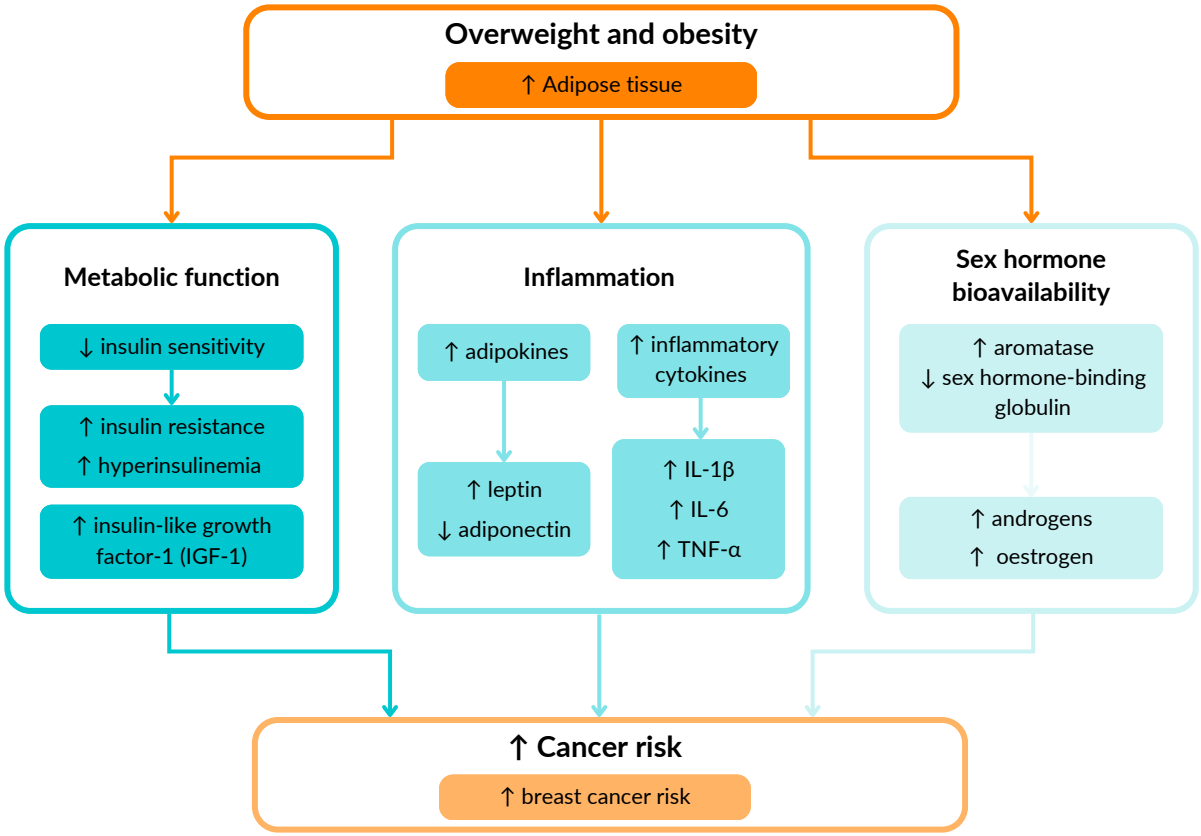

Figure 1: Three main proposed mechanisms that may contribute to the development of cancer, including breast cancer (adapted from [18,19]).

tumour cells, which increases the risk of cancer developing [23,24].

Finally, the third proposed mechanism pertains to the bioavailability of sex hormones and continues with the concept that adipose tissue is a metabolic "organ". For both men and postmenopausal women, adipose tissue is the main source of circulating oestrogen [17]. The level of circulating oestrogen is a risk factor for hormone-sensitive cancers, particularly breast cancer, mainly because oestrogen can drive rates of cell division and promote the growth of oestrogen-responsive tumours [25]. Aromatase, an enzyme found in adipose tissue, which is highly expressed in obese individuals, facilitates and increases the conversion of androgens to oestrogen [17,21]. Aromatase production and oestrogen production are both increased in the context of breast cancer [26], and in various settings, aromatase inhibitors are indicated in the treatment of postmenopausal hormone-receptive breast cancers [27]. While, sex hormone-binding globulin, which modulates the bioavailability of free sex hormones by binding with them and limiting their diffusion, is reduced in people with higher adiposity [18,19].

With breast cancer, it seems the risk association between excess weight and breast cancer is dependent on menopausal status for women; weight increases the risk of breast cancer in postmenopausal women but does not appear to increase breast cancer risk for pre-menopausal women [28]. Adiposity is also a risk factor for breast cancer in men [29].

4.1 Premenopausal women breast cancer

In premenopausal women, being overweight or obese does not appear to be associated with an increase in breast cancer risk [30].

Studies, including multiple meta-analyses, have reported a negative correlation between obesity and the risk of premenopausal breast cancer [28,30]. There is evidence that being overweight or obese in young adulthood (between the ages of about 18 and 30 years) and in adulthood before menopause decreases the risk of premenopausal breast cancer [31]. The Premenopausal Breast Cancer Collaborative Group found an estimated 12-23% reduction in the risk of premenopausal breast cancer per 5kg/m2 increase in BMI [32]. A recent 2023 meta-analysis reported that in both case-control studies and cross-sectional studies, obese women had a 6% lower risk of pre-menopausal breast cancer compared to women of a normal weight [30].

The mechanisms by which excess weight does not increase the risk of premenopausal breast cancer are challenging and still not fully understood. Currently, there is no single well-established mechanism [33]. A possible mechanism relates to oestrogen production, which is mainly produced by the ovaries in premenopausal women. Data suggests that overweight and obese women have significantly lower oestradiol levels compared to women with a normal body weight [28]. Body fatness in premenopausal women can affect the functioning of the ovaries, resulting in anovulation or amenorrhea, and consequently abnormal hormone profiles and reduced exposure to sex hormones, including oestrogen [28,30,33]. Additionally, obese pre-menopausal women tend to have longer menstruation than women of a normal weight range, which also reduces the duration of oestrogen exposure and could contribute to the reduced risk of premenopausal breast cancer [30].

It is important to note that premenopausal women should not aim to gain weight in order to reduce their risk of premenopausal breast cancer. Weight gain and excess weight are also associated with a variety of other health risks, including cardiovascular diseases, diabetes, and other cancers [3]. Evidence suggests that obese premenopausal women who get breast cancer tend to have more aggressive subtypes (e.g. triple-negative breast cancer) [34], there is strong evidence that weight gain throughout adulthood increases the risk of developing breast cancer postmenopause [33,35]. Fat distribution may also play a role in the risk of premenopausal breast cancer; a higher waist circumference (a higher level of abdominal adiposity) seems to be associated with an increased risk of premenopausal breast cancer after accounting for BMI, which may be explained through chronic inflammation and insulin resistance [33]. It should also be noted that some endocrine-disrupting chemicals (EDCs) and other harmful chemicals, which may increase breast cancer risk, are highly fat-soluble leading to their bioaccumulation in adipose tissue [36,37] and their concentrations tend to be higher in

people living with obesity compared to people of normal weight [38].

4.2 Postmenopausal women breast cancer

When women have reached menopause, there is strong evidence that being overweight or obese throughout adulthood and greater weight gain in adulthood becomes a significant risk factor for developing breast cancer [31].

The Million Women Study in the UK found there was around a 30% higher risk of breast cancer in postmenopausal women who were obese compared to those of a healthy weight [39]. A recent systematic review and meta-analysis looking at obesity and breast cancer risk in women according to menstruation status showed that obese postmenopausal women have a higher chance of developing breast cancer by up to 26%, compared to normal-weight women [30].

The increased risk of breast cancer in overweight and obese postmenopausal women is mainly explained by the fact that body fatness increases concentrations of circulating sex hormones, in particular, oestrogen, a known risk factor for the development of breast cancer [33,39]. Although the production of oestrogen decreases with age and postmenopausal women have lower blood levels of oestrogen compared to premenopausal women, after menopause, the production of oestrogen (which was localised mainly in the ovaries during premenopause) becomes noncyclical and shifts to being mostly localised in adipose tissue [16,28]. Therefore, excess adipose tissue in postmenopausal women exacerbates oestrogen biosynthesis [30]. Excess body fatness not only increases oestrogen production, it also can increase the bioavailability of oestrogen through the insulin and IGF-1 pathways which inhibits the synthesis of sex-hormone binding globulin and consequently keeps oestrogens in circulation [16,30,40]. Additionally, excess body fat can also promote the secretion of pro-inflammatory cytokines, such as TNFα and IL-6, which also enables oestrogen synthesis by inducing aromatase expression [16,20]. There is also evidence that obesity is associated with breast adipose inflammation and elevated leptin levels both of which could be attributed to the increased obesity-associated postmenopausal breast cancer risk [17,20].

4.3 Male breast cancer

Breast cancer in men is less common than breast cancer in women, however, in the UK, around 400 men receive a new breast cancer diagnosis each year [1]. Although the link to breast cancer in women is stronger, data suggests that being overweight or obese is also linked to the risk of breast cancer in men [41].

Since the 1990s, rising levels of obesity have paralleled with rising numbers of men receiving a breast cancer diagnosis [42,43]. Results from the Male Breast Cancer Pooling Project found that obesity increased the risk of breast cancer in men by approximately 30%, a similar risk increase to postmenopausal breast cancer risk in women [44].

Men produce small amounts of

oestrogen, however, high levels or prolonged exposure to oestrogen in men has been linked to an increased risk of male breast cancer [41]. Excess body fat and changes to the adipose microenvironment may lead to a hormonal imbalance, characterised by low testosterone and excess oestrogen, which contributes to an increasing risk of male breast cancer [43,45]. Additionally, adipose tissue contains aromatase, which converts testosterone to oestrogen, altering the bioavailable ratio of oestrogen to testosterone [42,46]. Obesity in men is also associated with low sex hormone-binding globulin levels, which also increases circulating oestrogen [44}. Furthermore, inflammation related to obesity and subsequent immune dysregulation may also be contributing mechanisms for male breast cancer [23,43].

5. Weight loss and breast cancer risk

Very few studies have looked at weight loss and breast cancer risk in premenopausal women, however, some data suggests that weight loss in premenopausal women does not change premenopausal breast cancer risk [47].

Given the evidence associating excess weight and postmenopausal breast cancer risk, it can be assumed that weight loss may help prevent or reduce the risk of postmenopausal breast cancer [18]. Studies show that sustained weight loss was associated with lower breast cancer risk among post-menopausal women [16,48–50]. Weight loss, more specifically fat mass loss, in postmenopausal women with excess fat showed improved sex hormone levels, metabolic and inflammatory markers (insulin, adiponectin, leptin, and CRP), all of which are markers of breast cancer in serum or breast tissue, suggesting a link to a reduction in breast cancer risk [16,51]. Furthermore, several studies have reported that weight loss can also improve health-related quality of life in breast cancer patients, with longer multimodal weight loss interventions including diet, physical activity (aerobic/aerobic exercises and resistance training) and psychosocial (lifestyle advice or counselling) support having a greater impact [20,52].

In men with obesity, evidence indicates that sufficient weight loss can decrease circulating levels of oestrogen [46] and may return the ratio of sex hormones to normal physiological levels [42], which may in turn reduce male breast cancer risk.

Despite these findings, more studies are needed to further support which types of weight loss interventions may be beneficial for breast cancer prevention [20], and the impact of weight regain following weight loss on breast cancer incidence [18]. It has been suggested that avoiding weight gain may be a better breast cancer prevention target than weight loss, due to the physiological alterations associated with weight gain that can persist despite weight loss [18].

6. Conclusion

The risk relationship between excess weight gain, defined by body mass index, and breast cancer seems to be

dependent on menopausal status in women; obesity does not appear to increase the risk of breast cancer in premenopausal women, and conversely, it increases the risk of breast cancer in postmenopausal women by up to 30%. Being overweight or obese is also linked to the risk of breast cancer in men.

There are three main proposed mechanisms for excess weight increasing breast cancer risk in men and postmenopausal women which include insulin resistance, chronic inflammation, and increased oestrogen bioavailability and circulation. Sustained weight loss, more specifically the loss of fat mass, seems to reduce the risk of breast cancer among postmenopausal women. However, further research is needed to support which types of weight loss interventions may be the most beneficial for breast cancer prevention, and whether avoiding weight gain may be a better breast cancer prevention tool than weight loss.

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About Breast Cancer UK

Who we are?

Breast Cancer UK aims to prevent breast cancer through scientific research, collaboration, education and policy change. We educate and raise awareness of the risk factors for breast cancer and provide practical information to help people reduce these risks. We campaign to ensure government policies support the prevention of breast cancer. And we fund scientific research that helps to better understand what risk factors contribute to breast cancer, and how to address them For further information on breast cancer risk factors please visit our website www.breastcanceruk.org.uk

To view this information in a more accessible format or to provide feedback, please contact us.

This review is for information purposes only and does not cover all breast cancer risks. Nor does it constitute medical advice and should not be used as an alternative to professional care. If you detect a lump or have any concerns, seek advice from your GP. Breast Cancer UK has made every effort to ensure the content of this leaflet is correct at the time of publishing but no warranty is given to that effect nor any liability accepted for any loss or damage arising from its use.

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We welcome your feedback, if you have any comments or suggestions about this review please contact us at info@breastcanceruk.org.uk or on 0208 1327088.

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