

Chapter 2

The Link Between Obesity and Breast Cancer Risk: Epidemiological Evidence

2.1 BMI and Breast Cancer Risk

BMI is routinely used to qualify an individual's adiposity, yet it is simply a measure of an individual's mass (kg) divided by their height² (m²). According to the WHO international classification, individuals with a BMI between 18.5 and 24.99 are considered healthy, whereas those with a BMI between 25 and 29.99 or of 30 and above are considered overweight or obese, respectively. Recently and due to the growing number of individuals with BMI values above 30, it has also become necessary to further subdivide the obese category into three classes; obese class I (BMI 30–34.99), obese class II (BMI 35–39.99) and obese class III (BMI \geq 40) [16].

Obesity rates have doubled since 1980 and in 2008, were estimated at 300 million for adult women [17]. A BMI above 25 increases the risk of a number of diseases, including heart disease and stroke, diabetes, musculoskeletal disorders, as well as cancers of the endometrium, colon and breast. An exponential increase in the number of publications examining the association between BMI and breast cancer has occurred over the last two decades (Fig. 2.1). As of July 1st, 2013, using the search terms “body mass index” and “breast cancer” in Pubmed returned 2221 publications, 232 were published in 2012 alone. This highlights the burden of these co-morbidities as well as the advances made in recent years, in particular with regards to understanding the epidemiological link and effect of obesity on breast cancer management.

Obesity is associated with an increased risk of breast cancer, and is also positively associated with tumor size and a higher probability of having positive axillary lymph nodes and faster growing tumors [18–20]. Interestingly, higher energy intake also increases the risk of breast cancer [21]. It is well accepted that obesity increases the risk of developing breast cancer after menopause, and it has even been suggested that up to 50 % of postmenopausal breast cancers are attributable to obesity [22]. However, the degree of increased relative risk and whether or not this also holds true for premenopausal women is contentious. A number of meta-analyses have been performed in recent years examining the

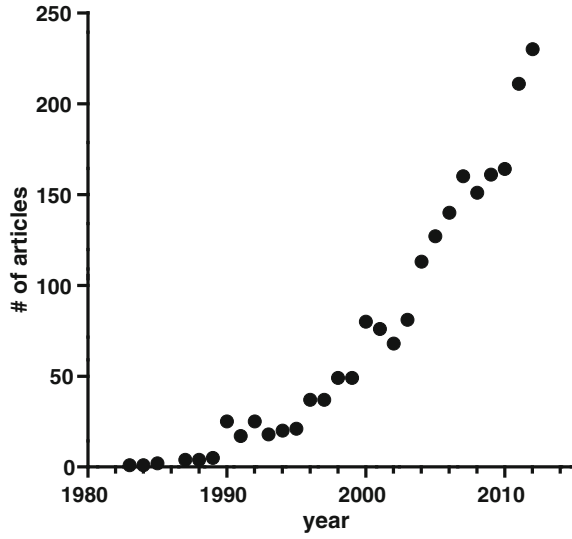


Fig. 2.1 Number of publications on BMI and breast cancer over the last 3 decades. A Pubmed search was performed using search terms “body mass index” and “breast cancer” and plotted as number of articles per year

Table 2.1 Effect of high BMI on breast cancer risk with respect to menopausal status

Type of study	Menopausal status	RR (95 % CI)	Reference
Meta-analysis	Premenopausal	0.93 (0.86–1.02)	Cheraghi et al. [23]
	Postmenopausal	1.15 (1.07–1.24)	
Meta-analysis	Premenopausal	0.98 (0.97–0.99) ^a	Bergström et al. [24]
	Postmenopausal	1.02 (1.02–1.03) ^a	
Meta-analysis (Triple negative)	Premenopausal	1.43 (1.23–1.65)	Pierobon et al. [29]
	Postmenopausal	0.99 (0.79–1.24)	
Meta-analysis	Postmenopausal	1.19 (1.05–1.34)	Key et al. [31]

^a per unit increase in BMI

effect of BMI on breast cancer with age (Table 2.1). In 2012, Cheraghi et al. performed a meta-analysis of 50 studies, 15 cohort studies and 35 case-control studies involving 2,104,203 and 71,216 participants, respectively [23]. There was no significant effect of BMI on breast cancer risk in premenopausal women, but a direct and significant correlation was observed between BMI and breast cancer risk in postmenopausal women. This was consistent with findings from Bergstrom et al. who demonstrated that a one unit increase in BMI was associated with a 2 % increased risk of developing breast cancer in postmenopausal women [24], a relationship that was not found in the premenopausal group. A number of studies have also described obesity as strongly protective against breast cancer in premenopausal women [25–28]. This has been attributed, at least in part, to a greater number of anovulatory menstrual cycles and hence, decreased lifetime exposure to estrogens. Nevertheless, a study Biglia et al. demonstrated that high BMI was significantly associated with larger sized tumors in both pre- and postmenopausal women [20]. In this case, obese premenopausal women displayed more vascular infiltration and metastasis to axillary lymph nodes compared to healthy weight women. Moreover, a meta-analysis by Pierobon et al. revealed that obesity is a significant risk factor for triple negative breast cancers in pre- but not postmenopausal women [29]. Interestingly, there is also evidence for an association of BRCA1 mutations and BMI with breast cancer risk in premenopausal women ($P = 0.045$) [30].

2.2 BMI and Breast Tumor Hormone Receptor Status

The types of tumors which occur in obese pre- and postmenopausal women have also been examined. In Japanese women, and consistent with the study of Pierobon et al., obesity is associated with an increased risk of triple negative tumors prior to menopause [32]. Conversely, the majority of luminal B breast cancers tended to occur in obese postmenopausal women. In the study by Biglia et al., BMI was not associated with tumor type in premenopausal women, however, there was a significant association between BMI and estrogen receptor (ER)/progesterone

receptor (PgR)-positive tumors in postmenopausal women [20]. A recent case-control study by John et al. demonstrated that weight gain of ≥ 30 kg between early adulthood and menopause was associated with a 1.53-fold increased risk of developing hormone receptor-positive breast cancer amongst all women studied, while non-hispanic white women were 3.82-fold more likely to develop breast cancer compared to women who's weight remained stable [33]. A similar study was undertaken by Krishnan et al. who demonstrated that while weight at 18–21 years was not associated with risk of breast cancer after menopause, an increase in weight during adulthood was positively associated with the increased risk of PgR-positive breast cancers after menopause (HR per 5 kg/m² gain in BMI: 1.43; 95 % CI: 1.23–1.66) [34]. Taken together, these studies demonstrate that obesity-related postmenopausal tumors are largely dependent on steroid hormones for growth. Conversely, obese premenopausal women tend to develop triple negative tumors, suggesting that other obesity-associated factors may play pivotal roles in tumor development.

2.3 Obesity and Mammographic Density

Mammographic density is one of the strongest predictors of breast cancer risk and reflects the relationship between dense epithelial and non-epithelial cell abundance, as well as acellular components including collagen [reviewed in 35]. The relationship between obesity, mammographic density and breast cancer, however, is still unresolved. This is largely due to the fact that obese women tend to have less dense breasts, as measured by percentage breast volume and absolute dense breast volume [36]. There are some key findings, however, that suggest that the relationship is more complex [37]. There is considerable heterogeneity of dense and non-dense areas within the breast and this reflects important differences in tissue composition, including the presence of estrogen-producing stromal cells. Indeed, aromatase expression [38] and the ratio of parent estrogen compounds (estrone and estradiol) to estrogen metabolites [39] are higher in dense areas of the breast compared to non-dense areas. Therefore, additional studies examining the differences in these areas are warranted in order to elucidate whether a relationship between obesity, mammographic density and breast cancer risk exists.

2.4 Waist-to-Hip Ratio and Breast Cancer

The often reported inverse association between BMI and breast cancer risk in premenopausal women has caused much controversy. This is largely due to the fact that BMI reflects overall adiposity rather than specific sites of adipose depots. More recently, waist-to-hip ratio has gained popularity as a measure of unhealthy weight

gain and a study by Amadou et al. demonstrated that each 0.1 unit increase in waist-to-hip ratio was associated with an increased relative risk of 1.19 (95 % CI: 1.15–1.24) of premenopausal breast cancer irrespective of ethnicity [40]. Additional studies, however, are required in order to determine whether waist-to-hip ratio should be used in assessing a premenopausal woman's risk of breast cancer.

2.5 The Metabolic Syndrome, Diabetes Mellitus and Breast Cancer

Overweight and obesity significantly increases the risk of developing type 2 diabetes mellitus (T2DM). Namely, an overweight individual carries a threefold increased risk of T2DM whereas obese individuals are seven times more likely to develop T2DM [41]. With increased obesity rates has come an increase in the prevalence of T2DM. It is now estimated that approximately 7 % of Americans have T2DM as a consequence of the development of insulin resistance (reviewed in [42]). This figure is not only characteristic of US populations but also represents a growing trend in other developed and developing countries. The risk of death in individuals with T2DM is twofold [43] and occurs as a result of a number of diabetes-related complications including heart disease and stroke, as well as infectious diseases, degenerative disorders and several types of cancers [44].

Several studies have examined the association between diabetes and breast cancer risk and a meta-analysis was recently performed [45]. From observational studies, the summary relative risk of developing breast cancer in women with T2DM compared to those without was 1.17 (95 % CI: 1.13–1.63), whereas prospective and retrospective studies had a summary relative risk of 1.23 (95 % CI: 1.12–1.35) and 1.36 (95 % CI: 1.13–1.63), respectively. Of interest, studies that adjusted for BMI had a lower summary relative risk than those that didn't (1.16 vs. 1.33, respectively). This suggests that BMI itself is a risk factor for breast cancer, but the remaining increased risk also supports a role for diabetes independent of BMI. Indeed, a study of women in Eastern China demonstrated that women with a history of diabetes were 3.5 times more likely to develop breast cancer than women who didn't (odds ratio: 3.556; 95 % CI: 0.904–13.994), whereas having a high BMI index was associated with a 1.5-fold increased risk of developing the disease (odds ratio: 1.528; 95 % CI: 1.083–2.155) [46].

The relationship between the metabolic syndrome and breast cancer risk has also been examined in a recent meta-analysis [47]. Nine studies were included in the meta-analysis and overall metabolic syndrome was shown to be associated with a 52 % increase in breast cancer risk. This study also examined associations between BMI, hyperglycemia, blood pressure, triglycerides and cholesterol in relation to breast cancer risk.

2.6 Breast Size and Breast Cancer

Few studies have examined whether or not an association exists between breast size and breast cancer risk. In 2006, a prospective study examining breast size and premenopausal breast cancer incidence demonstrated that healthy weight women with a bra cup size of “D or larger” had a significantly higher incidence of breast cancer than women who reported “A or smaller” [48]. The association was lost in women with a higher BMI. In a study by Markkula et al., a prospective breast cancer cohort study ($n = 772$) examined the characteristics of women with breast cancer who had a larger breast size [49]. Findings demonstrate that breast that were larger than 850 ml in volume tended to have larger tumor size, more advanced histological grade and more axillary node involvement. Much debate relating to whether increased risk of breast cancer in larger breasted women is in fact due to most women with larger breasts having a higher BMI. Nevertheless, after adjusting for BMI, this study demonstrated that in patients with ER-positive tumors, breast size was an independent predictor of disease-free and distant metastasis-free survival.

2.7 Effect of Obesity on Disease-Free Survival

A number of studies have examined the impact of BMI on breast cancer recurrence and death. A retrospective cohort study by Kamineni et al. demonstrated that obese women with early-stage breast cancer had a significantly increased risk of recurrence (HR 2.42; 95 % CI: 1.34–4.41) and breast cancer-related death (HR 2.41; 95 % CI: 1.00–5.81) within 10 years of diagnosis compared to healthy-weight women [19].

Druesne-Pecollo et al. performed a meta-analysis of clinical studies whereby they examined the impact of excess body weight on second primary cancer risk after breast cancer across thirteen prospective, five cohort and eight nested case-control studies [50]. Findings demonstrate that obesity increases the relative risk of developing breast, contralateral breast, endometrial and colon second primary cancers. Elevated serum total cholesterol, triglycerides, low-density lipoprotein cholesterol and the ratio between low-density and high density lipoprotein cholesterol, known to occur in obesity and the metabolic syndrome, have also been shown to be associated with a significantly higher distant metastasis rate [51]. A study by Forsythe et al. demonstrated that breast cancer survivors who were overweight or obese also had higher pain compared to healthy weight women and when examined longitudinally, weight gain above 5 % was positively associated with above-average pain [52]. Finally, diabetes has also been shown to be positively associated with risk of breast cancer-associated death after controlling for BMI (relative risk: 1.16; 95 % CI: 1.03–1.29) [53].

Obesity and Breast Cancer

The Role of Dysregulated Estrogen Metabolism

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