Overweight, Obesity, Diabetes, and Risk of Breast Cancer: Interlocking Pieces of the Puzzle

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ABSTRACT

We considered epidemiological data on overweight, diabetes, insulin, and breast cancer. Overweight is inversely related to premenopausal breast cancer, but there is definite evidence that, as compared with normal weight women, the relative risk (RR) for postmenopausal breast cancer is around 1.5 for overweight women and >2 for obese women, and that the association is stronger in elderly women. Overweight and obesity are strongly related to diabetes. Diabetes is associated with postmenopausal breast cancer, too, with

summary RRs from meta-analyses of 1.15–1.20, but not with premenopausal breast cancer (RR, 0.9). There is no consistent evidence that fasting insulin is related to breast cancer risk. Thus, although overweight and obesity are strongly related to postmenopausal breast cancer, diabetes is only moderately related to it. Given the extent of the association, and the likely residual confounding by overweight, inference on causality for the diabetes–breast cancer relation remains open to discussion. *The Oncologist* 2011;16:726–729

INTRODUCTION

There is currently great interest in the relationship between altered metabolism and cancer and in the role of insulin and

insulin-like growth factor-1 (IGF-1) pathways in the etiology and progression of human cancers [1, 2]. Overexpression of the IGF-1 receptor (IGFR) and mutations in genes

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encoding enzymes at multiple steps in the downstream components of the IGF-1 pathway are found in colon, breast, and prostate cancers, and have become targets for new therapeutic interventions [3]. In addition, epidemiological evidence suggests a relationship between obesity and cancer, type II diabetes and cancer, and possibly insulin levels and cancer [2, 4]. This review summarizes the epidemiological evidence that implicates overweight status, diabetes, and insulin levels as risk factors for breast cancer.

OBESITY, DIABETES, AND BREAST CANCER

An elevated body mass index (BMI) in the overweight ($25.0\text{--}29.9\text{ kg/m}^2$) and obesity ($\text{BMI} \geq 30\text{ kg/m}^2$) ranges has been consistently associated with postmenopausal breast cancer, although it is inversely related to premenopausal breast cancer [5–7]. Whereas the inverse association between BMI and premenopausal breast cancer has been attributed to more frequent anovulation in obese women [8–10], the direct relation for postmenopausal breast cancer has generally been attributed to elevated levels and bioavailability of circulating estrogens in overweight postmenopausal women. Elevated circulating estrogen levels result from aromatase-mediated conversion of androgens to estrogens in peripheral adipose tissue, lower levels of sex hormone-binding globulin in overweight women [5, 9, 11, 12], as well as, possibly, altered regulation of aromatase expression [13]. Obesity is also associated with high levels of circulating insulin, and insulin resistance is a possible factor in the relationship between obesity and breast cancer risk. However, the few studies providing data on fasting levels of insulin and breast cancer found no consistent association [14].

A direct trend in risk between measures of BMI and postmenopausal breast cancer has long been observed, and the risk appears strongest in older women [5, 6, 9, 15]. Thus, in a pooled analysis of three Italian case-control studies including 3,108 postmenopausal breast cancer cases and 2,604 controls [16], the relative risk (RR) for the highest quintile of BMI ($>28.4\text{ kg/m}^2$) was around 1.3 for women aged 50–69 years and rose to 2.1 (95% confidence interval [CI], 1.4–3.2) for those aged ≥ 70 years. This age-related pattern of risk is similar to that observed for menopausal hormone replacement therapy and is consistent with a duration-risk relationship in exposure to high estrogen levels, and with a greater excess in estrogen levels among overweight elderly women [8]. In the New York University Women's Health cohort study [17], including 109 premenopausal and 150 postmenopausal women with breast cancer, the RR for the highest quintile of BMI was 0.8 (95% CI, 0.5–1.5) in premenopause ($\text{BMI} > 26.4\text{ kg/m}^2$) but 2.4 (95% CI, 1.4–4.1) in postmenopause ($\text{BMI} > 27.5\text{ kg/m}^2$).

In the Women's Health Initiative (WHI) Observational study [18], including 1,030 women with invasive breast cancer, the association between BMI and breast cancer risk was analyzed. Obese women ($\text{BMI} > 31.1\text{ kg/m}^2$) had a RR of 2.5 (95% CI, 1.6–3.3) compared with women with a $\text{BMI} < 22.6\text{ kg/m}^2$. In the National Institutes of Health American Association of Retired Persons Diet and Health Study, which included 2,111 postmenopausal women with breast cancer, the RR for breast cancer was around 1.5 for women with a BMI of $27.5\text{--}35\text{ kg/m}^2$ and rose to 2.1 (95% CI, 1.4–3.0) for women with a $\text{BMI} > 40\text{ kg/m}^2$, when compared with women with a BMI of $18.5\text{--}22.4\text{ kg/m}^2$. The same study as well as several other case-control [6, 19] and cohort [20] investigations reported a direct association between adult weight gain and postmenopausal breast cancer risk. The contralateral breast cancer risk is also higher in obese postmenopausal women [21]. There is, therefore, convincing evidence that, as compared with normal weight women, the RR for postmenopausal breast cancer is around 1.5 for overweight women ($\text{BMI}, 25\text{ kg/m}^2$ to $30\text{--}32\text{ kg/m}^2$) and >2 for obese women, and that the association is stronger in elderly women.

Overweight and obesity are also strongly related to diabetes. Thus, a key question is to disentangle the independent effects of overweight and of diabetes on postmenopausal breast cancer risk.

DIABETES AND BREAST CANCER RISK

Data on diabetes and (postmenopausal) breast cancer are available from at least nine case-control and 15 cohort studies. Their results indicate a modest association between diabetes and breast cancer, and have been summarized in two meta-analyses [14, 22]. These gave summary RRs of breast cancer in diabetic women of 1.15–1.20, similar in case-control and cohort studies, with CIs in the range of 1.1–1.3.

Diabetes has also been associated with excess mortality in women with breast cancer [23–25], but the extent of the excess risk has not been satisfactorily quantified.

One of the above-mentioned meta-analyses [14] also considered fasting insulin in relation to breast cancer risk. Among five studies providing data, two [26, 27] found a direct relationship and three [28–30] found no consistent association between fasting insulin and breast cancer risk in postmenopausal women. Further, in the WHI 6% random sample of women with a baseline measurement for glucose and insulin, the RR for the highest tertile of insulin was about 2, but this was based on only 190 cases of breast cancer, of which only 75 were invasive [31]. Furthermore, there was no consistent evidence of an association between plasma levels of IGF-1 and breast cancer. Similarly, plasma

levels of C-peptide, a cleavage product of endogenous insulin, are not associated with breast cancer risk [14].

The limited information available on diabetes and premenopausal breast cancer (which is unrelated to overweight [5–8]) does not support a causal role for diabetes in breast cancer. Data on diabetes and premenopausal breast cancer were considered from only three studies in a meta-analysis [22] that gave a RR of 0.91, with, however, a wide CI (0.62–1.34). No distinction, moreover, was made in that study between type I and type II diabetes. The other meta-analysis [14] considered data from two case–control [32, 33] and three cohort [34–36] studies, from a total of 4,714 premenopausal women with breast cancer and provided a summary RR of 0.94 (95% CI, 0.80–1.10).

Available data indicate, therefore, that the risk for premenopausal breast cancer is not higher in diabetic subjects. Because at least a fraction of diabetes in premenopausal women is type II, an RR below unity (summary RR, ~0.9) does not support a relevant role of insulin, insulin resistance, and IGF-1 on breast cancer risk, and rather indicates that the modest association between diabetes and postmenopausal breast cancer is partly or largely a result of residual confounding by BMI. Considering the appreciably stronger association between overweight and obesity (RR, 1.5 to >2) and breast cancer risk, compared with that of diabetes (RR, 1.15–1.2), as well as the problems of reliability and validity of information on body mass and the difficulty

of accurate allowance for BMI, residual confounding by BMI remains a likely explanation for the association between diabetes and postmenopausal breast cancer.

CONCLUSIONS

Overweight and obesity are important determinants of postmenopausal breast cancer risk. It appears, therefore, that excess estrogen availability in overweight postmenopausal women is the key pathogenic mechanism for their excess breast cancer risk [8, 11]. Whether insulin and insulin-related factors have an independent additional role is unclear from the scanty available data.

Diabetes is consistently and strongly related to the risk of colorectal, liver, pancreas, and endometrial cancer [37–40]. It is only moderately associated with breast cancer risk in epidemiological data. Given such a moderate association, and the likely presence of residual confounding by overweight, any inference on causality for the diabetes–breast cancer relationship remains speculative and unproven.

AUTHOR CONTRIBUTIONS

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