p.P81S mutation presents with a milder degree of HIF 1/2 stabilization and activation of HIF target genes, providing a degree of pseudohypoxia that can still be modulated by actual hypoxia in the surrounding environment. The report also demonstrates that the VHL p.P81S and p.R167Q mutations result in the loss of interaction with Elongin C. A recent publication highlighted the mutation of this protein’s gene (TCEB1) in a small number of ccRCCs that notably lack VHL gene mutations, suggesting these could be seen as equivalent events (3).

Interestingly, another recent report identified proline 81 as part of a binding motif (PXVXL) for a novel VHL binding partner, heterochromatin protein 1, whose association is disrupted by the p.P81S mutation (10). This new association recruits VHL to chromatin where it could affect gene expression via ubiquitination of chromatin-associated proteins, or perhaps by serving as an adaptor between heterochromatin protein 1 and other proteins. This is particularly relevant considering the recent discovery of the mutation of numerous chromatin remodeling genes such as PBRM1, SETD2, BAP1, and ARID1A, largely in conjunction with pVHL loss, and the potential for mutation of selected genes, such as BAP1, to be predictive of poorer survival rates (3,11–14). Investigation of the functional significance of the VHL–HP1 interaction and potential chromatin remodeling effects could provide important mechanistic insight into the specific tumor-promoting activity of TCE–associated VHL p.P81S mutation while also identifying potential therapeutic approaches for patients affected by this disease.

References

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Inflammatory Breast Cancer: Yet Another Risk of the Obesity Epidemic?
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Two of the most perplexing problems in breast cancer, inflammatory breast cancer (IBC) and obesity, are linked in the report by Schairer and colleagues in this issue of the Journal (1). In particular, these results show a striking fourfold increased risk of IBC in obese women compared with normal weight individuals (body mass index [BMI] < 25 kg/m²).

IBC constitutes approximately 1–6% of all breast cancers (2,3), which makes studies of its risk factors somewhat difficult. IBC has an aggressive clinical course, with a 5-year disease-free survival of only 34% (4). Although IBC has been recognized as a separate entity (5), we know surprisingly little about both its etiology and pathophysiology.
IBC is a clinical diagnosis made when at least a third of the breast is involved with erythema or peau d’orange (6). In spite of its name, inflammatory cells are not characteristically seen. A pathologic finding associated with IBC is dermal lymphatic invasion by tumor cells; however, this finding is not necessary for the diagnosis. Some studies have noted an increase in microvessel density in IBC, suggesting that these tumors are angiogenic (7). Gene expression profiling studies have shown that although all subtypes of IBC exist, basal and human epidermal growth factor receptor 2 overexpressed types are the most common (8–12).

The rarity of this diagnosis makes studies of its risk factors challenging. The first report to evaluate the effect of body size on IBC was published in 1998 by Chang et al (13). In this small single-institution case-comparison study, women in the highest BMI tertile relative to the lowest tertile had increased IBC risk (IBC vs non-IBC odds ratio = 2.45; 95% confidence interval [CI] = 1.05 to 5.73). In the study reported here (1), Schairer and colleagues have taken advantage of data collected by the Breast Cancer Surveillance Consortium that includes 617 IBC case subjects and multiple comparison groups, including noninflammatory locally advanced breast cancers with chest wall/breast skin involvement, noninflammatory invasive cancers with no chest wall/breast skin involvement, and sex- and age-matched controls without breast cancer. This design offers two distinct advantages over previously conducted studies. It is by far the largest study conducted to date, and the multiple reference groups allow for comparison with both healthy individuals and with other breast cancers.

Similar to previous reported studies, most IBC case subjects were estrogen receptor negative and occurred at an earlier age at diagnosis. However, BMI was a risk factor of IBC irrespective of menopausal status and estrogen receptor status. Rate ratios for obesity (BMI ≥30 vs BMI <25) were 3.90 (95% CI = 1.50 to 10.14) in premenopausal women, 3.70 (95% CI = 1.98 to 6.94) in postmenopausal women not on hormones, and 2.94 (95% CI = 1.10 to 7.90) in postmenopausal women on hormones. These findings show conclusively that obesity is a strong risk factor for IBC, and they are in stark contrast with the far lower rate ratios for the association of obesity with other breast cancer types, which ranged from 1.02 to 1.36. This finding supports the idea that IBC is a distinct epidemiologic entity, in addition to being a distinct clinicopathologic entity.

This study illustrates both the power and weaknesses of data from consortia to conduct clinical and epidemiologic studies. On the one hand, such large numbers of case subjects are unlikely to be obtained from single-institutions studies. On the other hand, nonuniform collection of data has led to the exclusion of many case subjects and substantial missing data in the remaining case subjects. Of the 1221 IBC case subjects initially identified within the Breast Cancer Surveillance Consortium, only nearly half (617 case subjects) were enrolled in this analysis, and of those nearly half (283) did not have data on BMI. Schairer and colleagues have used sophisticated statistical techniques, including multiple imputations, to overcome the problem of missing data. However, such techniques are at best only partially able to compensate for the lack of data. These findings emphasize the need for well-thought-out and well-designed uniform collection of at least basic data across studies. In the age of big science and consortia, this is a must.

Several hypotheses have been proposed to explain the role of obesity in breast cancer carcinogenesis (14). Epidemiologic studies associating obesity with postmenopausal breast cancer contributed to the hypothesis that the peripheral conversion of androgen precursors to estradiol by aromatase in adipose tissue was a major contributing factor (15,16). The proliferative effect of estrogen on breast epithelial tissue is well established. However, this is a rather simple explanation for a very complex process. Obesity is associated with insulin resistance, and the insulinlike growth factor (IGF)-1 system may partially explain the link between obesity and breast cancer. Both insulin and IGF-1 are believed to play a role in cancer development through binding to the insulin receptor (IR) and IGF-1 receptor (IGF-1R). IGF-1 can inhibit apoptosis and stimulate cell proliferation through several downstream signaling networks, including the phosphatidylinositol 3-kinase-AKT system and the Ras/Raf mitogen-activated protein kinase systems (17).

Obesity is thought to induce a state of chronic low-grade inflammation [18]. The etiology of this inflammatory response is not known but may be hypoxia. It is proposed that as adipose tissue enlarges, individual cells are further from blood vessels and become poorly oxygenated. This state of relative hypoxia activates hypoxia-inducible factor 1α, which has been implicated in the development, growth, and metastasis of cancer type [19]. Hypoxia in adipocytes increases the expression of matrix metalloproteinases and vascular endothelial growth factor, suggesting that hypoxia in adipose tissue might be a modulator of the angiogenic process. These findings are consistent with both the increased microvessel density observed in IBC [7] and the strong association of obesity and the risk of IBC reported in this issue of the Journal [1].

Understanding the mechanism by which obesity contributes to the risk of breast cancer is important and may lead to identification of some biologic targets. However, the greatest need is to modify behavior and stop the obesity epidemic in the first place. Understanding human behavior is even more complex than understanding the pathophysiology of disease. Efforts to change behavior and reduce obesity on a public health level are one of the greatest health care challenges of our time.

References


### Hormone Replacement Therapy and Breast Cancer Risk: More Evidence for Risk Stratification?

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In this issue of the Journal, Hou and colleagues provide further evidence that the increased breast cancer risk from hormone replacement therapy (HRT) may not be present for all postmenopausal women, and they suggest that risk stratification by body mass index (BMI), race/ethnicity, and breast density could inform the prescription of HRT (1). Although other observational studies have also reported subgroup differences by these factors (eg, references 2–7), this is the largest study to date to investigate all three factors combined. In contrast, the largest randomized clinical trial (RCT) of HRT use and breast cancer, the Women's Health Initiative (WHI), reported no statistically significant differences in the HRT and breast cancer association by BMI and race when the trial was stopped (8). Inconsistent results between RCTs and observational studies increase complexity for clinical interpretations based on risk stratification.

Discrepant results from RCTs and observational studies are frequently attributed to confounding and other biases. However, subgroup results from RCTs and observational studies may also disagree because RCTs may lack statistical power for specific subgroups. For example, the size of relative risk of breast cancer from HRT use for women with BMI under 25 kg/m² was 1.35 in both the Hou et al. and WHI trial studies, even though the interaction was not statistically significant in the latter (1,8). A lack of association was also observed in both studies in women with a BMI greater than 30 kg/m² (1,8). Unlike the Hou et al. study, the WHI trial did not report any differences by race/ethnicity, but this lack of association may have been because of the smaller numbers of non-white women in the WHI trial (8). Of the two other large observational studies with sufficient numbers of black women, one did not observe an increased risk with current HRT use in postmenopausal women (4), but the other study found an increased risk from HRT when considering the duration of HRT (3). Results from studies such as that by Hou et al. that lack details of HRT use, including type and duration, should be interpreted cautiously before drawing conclusions about risk stratification by race/ethnicity.

Beyond single stratifications by BMI and race, however, the Hou et al. study advances the literature by examining breast density in combination with these factors. Even this large study, though, is underpowered for examining race/ethnicity interactions with both BMI and breast density. Previous observational studies have supported a higher risk from HRT in women with low BMI or women with high breast density (2,3,5–7), but they have not addressed whether these factors operate synergistically. The results from the interaction between BMI and breast density provide added clarity on how to interpret risk for women with a BMI between 25 and 30, a group representing approximately a third of US adult women (9). The overall modest effect of 1.15 seen for women with a BMI of 25 to less than 30 is only elevated in the Hou et al. study.

### Note

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