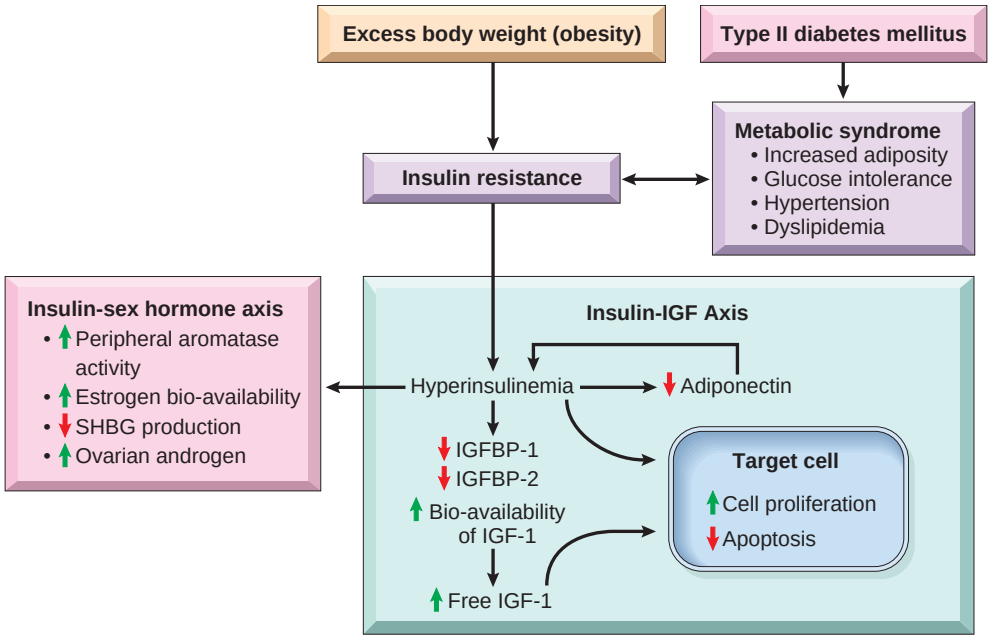

Figure 9-32 Obesity, metabolic syndrome, and cancer. Obesity and excessive weight are precursors of the metabolic syndrome, which is associated with insulin resistance, type 2 diabetes, and hormonal changes. Increases in insulin and IGF-1 (insulin-like growth factor-1) stimulate cell proliferation and inhibit apoptosis and may contribute to tumor development. IGF, Insulin-like growth factor; IGFBP, insulin-like growth factor-binding protein; SHBG, sex hormone-binding globulin. (Modified from Renehan AG, et al: Obesity and cancer risk: the role of the insulin-IGF axis. Trends Endocrinol Metab 17:328, 2006.)

increased production of cytokines and chemokines by adipose tissue in obese patients creates a chronic proinflammatory state marked by high levels of circulating C-reactive protein. This relationship may be more than a one-way street, as emerging evidence suggests that immune cells, particularly tissue macrophages, have important roles in regulating adipocyte function. Through this panoply of mediators, adipose tissue participates in the control of energy balance and energy metabolism, functioning as a link between lipid metabolism, nutrition, and inflammatory responses. Thus, the adipocyte, which was relegated to an obscure and passive role as the "Cinderella of cells of metabolism," is now "the Belle of the Ball" at the forefront of metabolic research.

Regulation of adipocyte numbers. The total number of adipocytes is established during childhood and adolescence (yet another reason to be concerned about childhood obesity), and is higher in obese than in lean individuals. In adults, it is estimated that approximately 10% of adipocytes are renewed annually, regardless of the level of the individual's body mass, but the number of adipocytes remains constant. Thus, adipocyte numbers are tightly controlled, and loss of fat mass in an adult person occurs through shrinkage of existing adipocytes. The well-known difficulty in maintaining weight losses from dieting is not well understood but appears to be related to homeostatic mechanisms that keep body fat constant over time. Thus, unless lowered caloric intake and/or increase energy expenditure is sustained, body weight inexorably returns to prediet levels. In a sense, therefore, the number of adipocytes create a set point for body weight.

Other emerging factors associated with obesity: role of the gut microbiome. A surprising and potentially important new explanation for the development of obesity has focused on alterations in the gut microbiome. Diet has marked effects on the bacterial makeup of the colon, and the bacterial flora in turn can have large effects on the ability of the host to break down certain dietary constituents (e.g., fiber) and absorb nutrients, as well as on epithelial integrity and inflammation. In response to these changes, expression of gut factors such as PYY that feedback on central appetite centers may also be altered. The data showing that gut flora can influence obesity are strong in certain mouse models, but the relevance of these models to human obesity, although tantalizing, remain to be proven.

General Consequences of Obesity

Obesity, particularly *central obesity,* increases the risk for a number of conditions, including type 2 diabetes and cardiovascular disease (Fig. 9-32). Obesity is the main driver of a cluster of alterations known as the *metabolic syndrome* characterized by visceral or intra-abdominal adiposity, insulin resistance, hyperinsulinemia, glucose intolerance, hypertension, hypertriglyceridemia, and low HDL cholesterol (Chapter 11).

- Obesity is associated with *insulin resistance* and *hyperinsulinemia,* important features of type 2 diabetes (Chapter 24), and weight loss is associated with improvements in these abnormalities. Excess insulin, in turn, may play a role in the retention of sodium, expansion of blood volume, production of excess norepinephrine, and smooth muscle proliferation that are the hallmarks of hypertension. Regardless of the nature of the pathogenic mechanisms, the risk of developing *hypertension* among previously normotensive persons increases proportionately with weight.