Obesity and breast cancer

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“I believe in the crickets that fill the night with magical crystals; I believe in the grinder who lives of manufacturing golden stars with his marvelous wheel; I believe in the air quality of human, configured on the memory of Isadora Duncan...”

Aquiles Nazoa. I pray the Creed, in Private Life of Rag Dolls.

Obesity, according to WHO, shows an alarming increase globally, especially in urban areas of countries with low and middle income; what was once considered a disease of the upper classes, is now a problem that does not distinguish socioeconomic strata. The problem lies primarily in malnutrition, a diet with excess fat and carbohydrates, and decreased physical activity. Obesity, defined as a body mass index (BMI) equal to or greater than 30 Kgr/m$^2$, is closely related to metabolic syndrome and type 2 diabetes, which increase the risk of cardiovascular diseases that are the leading cause of death worldwide$^1$.

But obesity, is not only associated with increased incidence of cardiovascular disease. According to the International Agency for Research on Cancer (IARC), there is sufficient evidence to conclude that there is a relationship between obesity and the risk of colon cancer, breast cancer in post-menopausal women, endometrial cancer, kidney cancer and esophageal adenocarcinoma. Obesity also complicates the prognosis in cancer patients due to comorbidity and increased complications from cancer treatment in obese patients.

Minicozzi et al recently published in the European Journal of Cancer, an investigation that relates metabolic indices such as BMI and fasting serum glucose with survival in breast cancer patients$^2$. According to this study, patients with estrogen and progesterone receptor positive breast cancer have a higher risk of death of the disease if they have a BMI greater than 27 kg/m2 (HR: 4.99) and fasting glucose $>$ 94 gr / dl (HR: 5.49). This does not apply to patients with receptor-negative tumors, which reveals the hormonal causal link. According to this study, not only obesity and carbohydrate metabolism disorders are a risk for developing breast cancer, but patients with these altered parameters, are more likely to die from breast cancer than thin patients with normal glycemia. According to the authors, “the consistently-observed association of post-menopausal obesity with breast cancer development is usually interpreted as due to aromatization, by adipose, of androgens into estrogens – the latter having a mitogenic effect on breast epithelium. High glucose is known to favour the selection of malignant cell clones resistant to hypoxia by shifting
energy production to anaerobic glucose metabolism. Insulin may cooperate with estrogens in stimulating the proliferation of breast epithelium and cancer cells".

Several mechanisms have been described to explain the association between obesity and cancer. These two conditions have in common an increased fatty acid synthase (FAS) that catalyzes the fatty acids into structural lipids necessary for cell division, so this enzyme is useful for cancer cells that are in permanent division; and obesity, through the enzyme, allow the growth of cancer cells. Monoacylglycerol lipase (MAGL) is also increased, which also provides lipids to structural tasks. Moreover, these lipids, being transferred to the tumor, are source of energy for the very active metabolism of cancer tissue. Adipose stromal cells also could induce tumor neoangiogenesis, which allows tumor vascularization and ensures their survival. Lipid signaling fatty acid derivatives, through autocrine and paracrine signals induce progression and invasion of tumor cells. Obesity is also a pro-inflammatory state with subsequent production of inflammatory cytokines (TNFa, interleukin 6, PAI-1), which generate an environment conducive to the development of malignant cells. Probably the most important mechanism of the association of obesity and cancer, is the alteration of the signaling cascade of insulin, as well described Minicozzi et al. with consequent cell proliferation through stimulation of the receptors related to this molecule.

It is for this reason that it has been postulated metformin as a drug that “takes away sugar from cancer” and has been proposed in the arsenal of breast cancer chemoprevention. Metformin decreases insulin levels which attenuate the stimulation of hybrid receptor insulin/insulin-like growth factor (IR/IGF-1R) that are overexpressed in cells and breast cancer, which would reduce the cell proliferation and induce apoptosis. Metformin may also act directly on mammary cancer cell increasing AMP kinase phosphorylation at the mitochondrial level which would limit cell proliferation and induce apoptosis. Metformin also impacts the activity of the enzyme aromatase which indirectly decrease estrogen levels. Well, probably more studies are needed to evaluate the possible role of this drug in cancer prevention, specifically in tumor types that are associated with obesity and impaired insulin.

It is necessary to achieve a reduction in the incidence of overweight and obesity worldwide, not only to reduce the incidence of cardiovascular disease, but also for the prevention of cancer and improve survival in oncology patients; therefore, only in Latin America there is an incidence of obesity above 30% in most countries. On this basis, treatment of the cancer patient necessarily involves metabolic management with lifestyle changes in diet and physical activity, and medication use, if necessary, to optimize metabolism of lipids and carbohydrates for better prognosis. The interdisciplinary management ensures better performance of cancer treatment. On the other hand, insisting on return to a healthy lifestyle as part of cancer prevention programs, avoiding overweight with proper eating habits and encouraging physical activity especially in children and young people to avoid the inevitable long-term outcomes generated by excesses.

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References

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