9. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21:1431–1439.
10. Hudis C, Citron M, Berry D, et al. Five year follow-up of INT C9741: dose-dense chemotherapy is safe and effective. *Breast Cancer Res Treat*. 2005; 94(Suppl 1):S20.
11. Fisher B, Anderson S, Wickerham DL, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. *J Clin Oncol*. 1997;15: 1858–1869.
12. Fisher B, Anderson S, DeCillis A, et al. Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-25. *J Clin Oncol*. 1999;17:3374–3388.

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An Organismic View of Cancer

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There is an association between glucose intolerance and pancreatic cancer (1), but the nature of the relationship remains unclear. In this issue of the Journal, Wolpin et al. (2) report the results of a nested case–control study. They found that in a multivariable model with mutual adjustment for HbA1c, insulin, and proinsulin, their biomarker for hyperglycemia, HbA1c, and their biomarker for impaired pancreatic beta-cell function, the plasma proinsulin/insulin ratio, were not associated with pancreatic cancer, whereas their biomarker for peripheral insulin resistance, plasma proinsulin, was related with pancreatic cancer. Wolpin et al. (2) go on to say that their biomarker for peripheral insulin resistance was elevated before the detection of the pancreatic cancer, which suggests that peripheral insulin resistance preceded the clinical detection of pancreatic cancer and was involved in its etiology. In other words, peripheral insulin resistance may predispose patients to pancreatic cancer, and correcting insulin resistance may prevent pancreatic cancer.

Causal factors, factors directly related to the etiology of the disease, should be accurate predictors of the disease they cause (3). Although Wolpin et al. (2) demonstrate a statistically significant relationship between pancreatic cancer and proinsulin, the fact that a relationship exists between the parameter/variance estimates of the independent variable and the dependent variable and that the relationship is unlikely to have occurred by chance does not entitle us to conclude that the independent variable is an accurate predictor of the dependent variable. In other words, statistical significance is not predictive accuracy. What was the discriminative accuracy of proinsulin? Wolpin et al.'s marker of peripheral insulin resistance added only 0.04 to the baseline model receiver operating characteristic of 0.59 (see Supplementary Table 3 for the article). This result was not statistically significant and is not clinically important. Furthermore, the baseline accuracy was only slightly better than flipping a coin at predicting pancreatic cancer. Therefore, in terms of predictive accuracy, it is unlikely that peripheral insulin resistance caused pancreatic cancer.

More interestingly, Wolpin et al. (2) claim that the physiology of the body is involved in the etiology of the disease. This contrasts with a tumor-centric model of cancer, which states that we should focus on the tumor. Regardless of whether peripheral insulin resistance is a cause of pancreatic cancer, an organism-centric perspective is important.

The tumor-centric model of sporadic solid cancers asserts that risk factors affect tissue by their action on cells' transcriptomes and once we know that effect we can reduce the risk of incident disease. Further, when the genomics of a tumor are known, we may be able control and defeat the cancer. Clearly, the immune system and other systems affect and are affected by the cancer—but they are usually viewed from the perspective of the cancer. This perspective is similar to a geocentric model of the solar system, where the sun revolves around the earth, or in this case, the tumor.

Another cancer model can be called "organismic." In this view, the body is a unitary system. The solid tumor arises within and is a functional component of the body. In the organismic model, the body is the proper unit of analysis. This is similar to a heliocentric model where a planet is part of a larger, integrated system and its motion cannot be properly understood apart from the larger system.

The body can be viewed as an organism that is composed of integrated, mutually interdependent, functional components, all of which must operate properly if the body is to maintain physiologic homeostasis. The body gives rise to the tumor, and the body uses its regulatory systems to maintain homeostasis in the face of the disequilibriums caused by the tumor. In other words, the tumor is not an isolated entity; it is an integral part of a larger system. The organismic view is interactional. The maturing tumor perturbs the system, and the system attempts to adapt to it, which includes ameliorating its effects, and the body tries to control it, which involves trying to stop it from gaining biological and physiological dominance. The body and tumor interact with

each other in a coordinated manner using many of the same systems in an attempt to achieve their goals; both the body and the tumor can be viewed as exhibiting goal-directed behaviors. It is almost teleological—the tumor wants to control the body and the body wants to control the tumor. It is literally a struggle to the death. Sometimes the body wins and the premalignant tissue is suppressed or the tumor regresses; other times the tumor progresses past the point where the body can control it and it begins to take over the body. In other words, once a solid tumor is a functional part of a larger system and its genomics are a combination of the cancer and of its action on and reaction to the body, then, because the cancer is now an inextricable part of the body, it may be that the only way for us to totally destroy the cancer is to destroy the body.

As a practical matter, we should look for the effects of organ-expressed factors on tumor function (4); we should explore the effects of tumor-expressed factors on the body (5,6) and on metastases (7); and we should investigate how the body maintains it functioning in response to tumor-expressed factors.

Why is the organismic model of cancer important? The tumor-centric model assumes once we know the cancer and its effects we know everything we need to know to understand and destroy it. Therefore, all we have to do is study tumors and their local and distant effects. The organismic model suggests that we need to understand the body as an integrated system that gives rise to the tumor and that tries to adapt to it, tries to control it, and tries to destroy it. The key insight is that the tumor is a part of the body; it is born in the body, it lives within the milieu of the body, and it uses the body's systems to establish itself, to maintain its existence, and to grow and dominate. In this view, our primary goal should not be to directly attack the cancer; rather, it should be to assist the body in defeating the cancer.

References

1. Habib SL, Rojna MJ. Diabetes and risk of cancer [published online ahead of print February 7, 2013]. *ISRN Oncol*. 2013. doi:10.1155/2013/583786.
2. Wolpin BM, Bai Y, Qian ZR, et al. Hyperglycemia, insulin resistance, impaired pancreatic β-cell function, and risk of pancreatic cancer. *J Natl Cancer Inst*. 2013;105(14):1027–1035.
3. Burke HB, Goodman PH, Rosen DB, et al. Artificial neural networks improve the accuracy of cancer survival prediction. *Cancer*. 1997;79:857–862.
4. Deng ZB, Zhuang X, Ju S, et al. Exosome-like nanoparticles form intestinal mucosal cells carry prostaglandin E2 and suppress activation of liver NKT cells. *J Immunol*. 2013;190(7):3579–3589.
5. Xiang X, Poliakov A, Lui Y, et al. Induction of myeloid-derived suppressor cells by tumor exosomes. *Int J Cancer*. 2009;124(11):2621–2633.
6. Xiang X, Liu Y, Zhang S, et al. TLR2-mediated expansion of MDSCs is dependent on the source of tumor exosomes. *Am J Pathol*. 2010;177(4):1606–1610.
7. Liu Y, Xiang X, Zhuang X, et al. Contribution of MyD88 to the tumor exosome-mediated induction of myeloid derived suppressor cells. *Am J Pathol*. 2010;176(5):2490–2499.

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