various established interventions, risks of treatment-related complications, potential risks and benefits of investigational therapies. The risk of contralateral breast cancer and its management are already part of many discussions at initial diagnosis and should be emphasized, but not overemphasized. As Graeser et al[12] have shown, knowledge of *BRCA1/2* mutation status may inform this aspect of the discussion, providing reassurance to women whose genetic testing is negative and stratified information to mutation carriers on which to base some difficult decisions. While the data should further impel us to find better nonsurgical ways of preventing breast cancer in women at risk—including breast cancer survivors and women with and without inherited susceptibilities—for the moment, at least, we can provide ever more reliable and refined information with which to personalize our patients' care.

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Recognition and Treatment of Sleep Disturbances in Cancer

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See accompanying article on page 6033

Fatigue is recognized by oncologists as one of the most frequent complaints of patients with cancer. More importantly, fatigue is among the symptoms about which patients express the most concern. What is less recognized is that there are many components of fatigue, including physiologic factors (such as pain, anemia or menopause), psychological factors (such as depression or anxiety), and chronobiologic factors (such as circadian rhythms disorders and sleep).[1] In particular, the relationship between fatigue and sleep is becoming more clear, with data suggesting that sleep problems are significantly correlated with increased fatigue.[2] Yet, patients with cancer are not always asked about their sleep nor treated appropriately for their sleep problems.

Insomnia is defined as difficulty falling asleep, difficulty staying asleep, and/or nonrestorative sleep, resulting in daytime dysfunction.[3] The most common sleep-related complaints of patients with cancer are difficulty falling asleep, difficulty staying asleep, and frequent and prolonged nighttime awakenings.[4,5] In other words, patients with cancer are complaining of insomnia.

The risk factors for insomnia in cancer include the cancer itself (eg, tumors that increase steroid production, symptoms of tumor invasion resulting in pain, dyspnea, nausea, pruritus), treatment factors (eg, corticosteroids, hormonal fluctuations), medications (eg, narcotics, chemotherapy, neuroleptics, sympathomimetics, steroids, sedative hypnotics), environmental factors (eg, temperature extremes or too much light or noise in the bedroom), psychosocial disturbances (eg, depression, anxiety, stress), and comorbid medical disorders (eg, headaches, other primary sleep disorders).[6] In a study of cancer survivors, 52% reported sleeping difficulties, and although two thirds reported their insomnia began before their cancer diagnosis, 58% reported that having cancer aggravated their sleep problem.[7] This suggests a negative feedback loop where the challenges faced by patients with cancer may contribute to insomnia, which in turn may feed

back to exacerbate medical conditions comorbid with cancer.[4] Treatment of the sleep problem at any time point might therefore break that cycle.

An important aspect of treatment is, of course, identifying the problem. Sleep needs to be thought of as part of the symptom cluster often associated with cancer. The concept of symptom clusters is not new in the field of cancer.[8,9] In a study by Liu et al,[10] which examined a symptom cluster of poor sleep, fatigue and depression, results suggested that the more symptoms within that symptom cluster the patients experienced before the start of chemotherapy, the worse the symptoms they experienced during chemotherapy. In addition, those patients with more frequent and more severe symptoms pretreatment experienced the most severe symptoms during treatment.

However, several studies have shown that many patients with cancer do not mention their sleep problems, with close to 80% assuming it is caused by the treatment, 60% wrongly assuming that the symptoms will not last, and almost half believing that their physicians cannot do anything to help them.[11,12] What this means is that clinicians need to include sleep as part of the symptom cluster already recognized, and to ask all patients about their sleep. Without asking the question, "How are you sleeping?" this important problem might never be identified and addressed.

The importance of treatment rises from the knowledge that insomnia results in more severe fatigue, leads to mood disturbances, contributes to immunosuppression, affects quality of life, and potentially affects the course of the cancer.[6,13] The question for every clinician then becomes, "How do I best treat insomnia in my patients with cancer?"

Insomnia in this patient population may be due to a variety of causes; therefore, treatment may need to be multimodal and include both pharmacologic treatment (eg, benzodiazepine receptor agonists or melatonin receptor agonists) and nonpharmacologic therapies.[6,13] The 2005 National Institutes of Health State-of-the-Science Conference statement on insomnia concluded that behavioral therapies are the most effective treatments for insomnia,[3] and there have now been several studies showing that cognitive behavioral therapy for insomnia is effective in treating this sleep problem in cancer survivors.[14-17] These studies all confirmed that cognitive behavioral therapy for insomnia improved sleep efficiency (the percent of time spent sleeping out of time in bed), increased total sleep time, improved fatigue and mood (ie, decreased depression and anxiety), and improved quality of life, with therapeutic effects maintained at 3-, 6- and 12-month follow-up.

One of the innovative features of the Berger et al study[18] in this issue of *Journal of Clinical Oncology* is that intervention was initiated before the patients with cancer developed sleep disturbances and severe fatigue. Results suggested that although sleep improved at 90 days postchemotherapy in the group administered behavioral therapy for insomnia, unlike the studies that initiated treatment postchemotherapy to patients with insomnia, at 1 year there were no longer any differences between the groups. Whereas Berger et al[18] concluded that clinicians need to identify and intervene with behavioral therapy at the point that patients with cancer report moderate/severe insomnia, the other take-home message should be that treatment initiated during chemotherapy may have short-term benefits, and additional treatment might be needed postchemotherapy. Berger et al[18] are correct that clinicians need to ask their patients about their sleep and initiate treatment when the problem is identified.

In summary, sleep disorders, particularly insomnia, are common in patients with cancer. Sleep needs to be assessed carefully in patients with cancer to improve quality of life and possibly to help improve the course of the disease. There are a variety of effective pharmacologic and nonpharmacologic therapies available for the management of cancer-related insomnia. But for those therapies to work, the clinician must first identify the problem by communicating with the patient and then be willing to initiate the appropriate treatment. Only then will we be able to improve the quality of life for our patients with cancer during and after their cancer treatment.

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The Forest and the Trees: Pathways and Proteins As Colorectal Cancer Biomarkers

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See accompanying articles on pages 5924 and 5931

In a 1990 review, Fearon and Vogelstein[1] presented a model for the genetic basis of colorectal neoplasia, stating that colorectal cancer (CRC) development requires the accumulation of mutations in multiple genes that regulate cell growth and differentiation. They proposed that "identification of the genetic alterations present in tumors may provide a molecular tool for improved estimation of prognosis in patients with CRC . . . multiple pathways exist in which new chemotherapeutic agents might achieve a therapeutic advantage."[1(p764)] The molecular characteristics described in the 1990 Fearon and Vogelstein review included mutational activation of the oncogenes *c-myc* and *KRAS* and tumor suppressor loss by mutation of TP53 or allelic loss at chromosome 18q. These events occur at a relatively high frequency in CRC; yet, almost two decades later, we still have much to learn concerning the prognostic or predictive value of these four markers, and that of the many other tumor-associated characteristics subsequently identified.

This issue of *Journal of Clinical Oncology* includes two articles concerning K-Ras,[2,3] a protein whose inactivation in CRC was first observed in 1987 but has only recently been identified as a significant clinical biomarker.[4,5] K-Ras activation occurs downstream of epidermal growth factor receptor (EGFR), and studies of CRCs from patients treated with the anti-EGFR antibodies panitumumab or cetuximab showed that mutational activation of *KRAS* predicts lack of treatment response. These studies involved both retrospective tissue collections from non–randomly assigned patients and correlative studies from prospectively randomized clinical trials of anti-EGFR therapy. The results were striking, showing that responses to anti-EGFR–containing regimens were equal to controls for patients with *K-Ras* mutant tumors. Differences in progression-free survival for antibody-treated patients whose tumors were with or without *KRAS* mutations were on the order of 2 to 5 months, in favor of the wild-type cases (reviewed in Walther et al[6]).

Laurent-Puig et al[2] retrospectively studied 173 advanced CRC cases collected from six hospitals, of which all but one received a cetuximab-containing regimen as second-line or greater therapy. They examined additional members of the EGFR signaling pathway, predicting that *KRAS* wild-type tumors would fail to respond to cetuximab if signaling was driven by other mechanisms of constitutive pathway activation. Consistent with known regulatory mechanisms of EGFR signaling, they found that EGFR amplification predicted improved cetuximab response. In addition, activation of pathway members K-Ras or BRAF, or loss of the phosptastase and tensin homolog tumor suppressor, correlated with lack of clinical response. If these results are confirmed in additional studies, then as many as 70% of patients with metastatic CRC may reasonably be excluded from EGFR-directed therapies. In addition, analysis of other pathway members, such as PI3K (PIK3CA), may further improve the ability to predict anti-EGFR response. It is anticipated that these results will also hold for use of anti-EGFR agents in the adjuvant setting. Collectively, the clinical correlation of tumor EGFR pathway activation status and targeted agent response represents a major advance, sparing the majority of patients with advanced CRC therapies that are both costly and ineffective.

It is still not clear whether constitutive activation of EGFR pathway is in itself a negative prognostic factor for CRC. One crude way of assessing this is to examine the prevalence of these signaling changes across the different clinical stages of CRC. Microsatellite instability (MSI), the best understood colon cancer molecular prognostic factor, is present in roughly 25% to 30% of stage II, 15% to 20% of stage III, and less than 10% of stage IV disease, consistent with its characterization in many clinical biomarker analyses as a predictor of less aggressive behavior. This same approach suggests that the presence of a *KRAS* mutation is probably not prognostic, as the prevalence of K-Ras activation is approximately 35% to 55% across all cancer stages, with the higher value achieved by testing for multiple uncommon *KRAS* mutations. The existing prognostic data concerning K-Ras involve small studies indicating that K-*Ras*-mutant tumors carry a worse prognosis, and a few larger studies reporting no association with outcome (reviewed in ref 6). A second report in this issue, from Richman et al, provides data using prospectively collected tissues from the Medical Research Council Fluorouracil, Oxaliplatin and Irinotecan: Use and Sequencing (FOCUS) trial, a large study of advanced CRC patients that was conducted from 2000 to 2003. Patients included in this biomarker analysis were randomly assigned to receive either first-line fluorouracil (FU), followed by either FU/irinotecan or FU/oxaliplatin on progression, or FU/irinotecan or FU/oxaliplatin as first-line therapy, with no protocol-specified second-line treatment. This group tested tumors from 711 patients for mutations in *KRAS* and *BRAF*. They found that the presence of these mutations predicted poor overall survival, but no difference in disease-free survival. Unfortunately, despite the high quality of this study, anti-EGFR therapy was available for CRC clinical trials in Europe during the enrollment period of the MRC FOCUS trial, raising the possibility that second line treatment could have biased this result.

