A Prospective Study on Habitual Duration of Sleep and Incidence of Breast Cancer in a Large Cohort of Women

Simone P. Pinheiro,[1,2] Eva S. Schernhammer,[2,4] Shelley S. Tworoger,[1,2] and Karin B. Michels[1,2,3]

[1]Department of Epidemiology, Harvard School of Public Health; [2]Channing Laboratory, Departments of Medicine and [3]Obstetrics, Gynecology, and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and [4]LBI-ACR VIEnna and ACR-ITR VIEnna, Vienna, Austria

Abstract

Mounting evidence suggests habitual sleep duration is associated with various health outcomes; both short and long sleep duration have been implicated in increased risk of cardiovascular disease, diabetes, and all-cause mortality. However, data on the relation between sleep duration and cancer risk are sparse and inconclusive. A link between low levels of melatonin, a hormone closely related to sleep, and increased risk of breast cancer has recently been suggested but it is unclear whether duration of sleep may affect breast cancer risk. We explored the association between habitual sleep duration reported in 1986 and subsequent risk of breast cancer in the Nurses' Health Study using Cox proportional hazards models. During 16 years of follow-up, 4,223 incident cases of breast cancer occurred among 77,418 women in this cohort. Compared with women sleeping 7 hours, covariate-adjusted hazard ratios and 95% confidence intervals for those sleeping ≤5, 6, 8, and ≥9 hours were 0.93 (0.79-1.09), 0.98 (0.91-1.06), 1.05 (0.97-1.13), and 0.95 (0.82-1.11), respectively. A moderate trend in risk increase towards longer sleep duration was observed when analyses were restricted to participants who reported same sleep duration in 1986 and 2000 (P_{trend} = 0.05). In this prospective study, we found no convincing evidence for an association between sleep duration and the incidence of breast cancer. (Cancer Res 2006; 66(10): 5521-5)

Introduction

Both long and short habitual sleep may be associated with increased risk of coronary heart disease (1) and symptomatic diabetes (2). Duration of sleep has also been associated with increased all-cause mortality in several studies (3–5), although only among men in one study (5). There is some evidence indicating that sleep duration may affect women and men differently. In a study by Amagai et al. (6), short sleep was associated with increased all-cause mortality only among men whereas long sleep was associated with increased all-cause mortality only among women. Data on sleep duration and cancer risk are sparse and inconclusive. An association between melatonin, a hormone closely related to sleep (7), and breast cancer has been suggested (8), raising the question of whether sleep duration may also affect breast cancer risk.

Sleep pattern disruptions related to night-shift work, a surrogate for light exposure at night, may increase breast cancer risk (9), possibly through decreased levels of melatonin (8). Melatonin is a hormone secreted primarily by the pineal gland during the dark phase of the light-dark cycle (10); exposure to light suppresses melatonin production (11). Melatonin may inhibit breast tumorigenesis directly by inhibiting breast cell proliferation and invasiveness, and indirectly by suppressing the mitotic activity of endogenous hormones such as 17β-estradiol (8). Decreased first morning urine levels of 6-sulfatoxymelatonin were recently associated with increased premenopausal breast cancer risk (12). First morning measurements of 6-sulfatoxymelatonin, the major metabolite of melatonin (7), seem to closely reflect nighttime melatonin levels (13).

Melatonin levels may be closely related to sleep duration. Serum melatonin concentrations have shown to be lower in habitual short sleepers (<6 h/night) than in long sleepers (>9 h/night; ref. 14), and in elderly insomniacs than in age-matched controls (15). Under experimental conditions, increasing the length of the night (participants were confined to a dark environment 14 hours per day for four weeks) was associated with both longer sleep duration and increased nocturnal secretion of melatonin (16). Sleep duration may influence melatonin levels by determining length of light exposure, thereby affecting breast cancer risk.

Sleep duration may also influence breast cancer risk by affecting immune functioning (17). Although it is unclear whether decreased immune function plays direct role in breast cancer, the importance of immune responses in antineoplastic activities is established (18). In this study, we evaluated whether self-reported habitual sleep duration influences breast cancer incidence in a large cohort of women.

Materials and Methods

We prospectively examined the relation between self-reported habitual sleep duration and breast cancer incidence among participants of the Nurses' Health Study. The Nurses' Health Study is composed of 121,700 U.S. female registered nurses, ages 30 to 55 years at entry, who responded to a mailed questionnaire in 1976 (19). Self-reported information on several covariates including weight, reproductive events, physical activity, and smoking has been updated every 2 years via mailed questionnaires; information on diet and family history of breast cancer has been updated every 4 years. Information on height, age at menarche, and age at first birth was obtained in 1976. Information on sleep duration was obtained in 1986 and again in 2000. In 1986, participants were asked to specify the total hours of sleep in a 24-hour period; possible choices included ≤5, 6, 7, 8, 9, 10, and ≥11 hours. Information on timing and quality of sleep was not collected from participants.

In 1986, 83,027 participants provided information on habitual sleep duration. We excluded participants with a diagnosis of cancer (except non-melanoma skin cancer) before baseline, leaving 77,418 women for this analysis. Incident invasive breast cancer cases, diagnosed between

June 1, 1986 and May 31, 2002, were identified through self-report and confirmed by blinded medical chart review or by the participants. Most breast cancer deaths were identified by the next of kin or through National Death Index searches.

We used Cox proportional regression models to estimate breast cancer hazard ratios (HR) and 95% confidence intervals (95% CI) by sleep duration [≤5, 6, 7 (reference), 8, and ≥9 hours per 24 hours] adjusting for established risk factors for breast cancer (most updated biennially), and likelihood ratio tests to evaluate whether the association between sleep duration and breast cancer was modified by menopause status, history of night-shift work, or smoking status. Only sleep information obtained in 1986 was used in our main analyses. Additional analyses restricted to participants who consistently reported same sleep duration in both 1986 and 2000 questionnaires were conducted.

Results

Participants sleeping ≤5 hours were more likely to be postmenopausal, nulliparous, and to have worked rotating night shift, and less likely to be married or to report current postmenopausal hormone use or history of benign breast disease. Alcohol intake was lowest among short sleepers and highest among long sleepers. Both groups were more likely than normal sleepers to report depressive symptoms (Table 1).

Our analysis included 4,223 incident cases of invasive breast cancer newly diagnosed during 1,153,077 person-years of follow-up between 1986 and 2002. We did not find any significant difference in breast cancer incidence across categories of sleep length in age-adjusted analyses (Table 2). Additional adjustments for potential confounding variables including caffeine consumption, depression, and stress did not alter our results. We did not adjust for night-shift work because the effects of shift work on breast cancer may be mediated through changes in sleep duration; however, adjusting for shift work in our main analyses did not affect our results. Secondary analyses restricted to participants who reported the same number of hours of sleep in 1986 and in 2000 ($n = 26,346$) provided similar results although there was a moderate trend in risk increase in breast cancer among women sleeping >7 hours (Table 3).

We also conducted analyses in the entire cohort stratifying on menopause status or night-shift work; results were essentially unchanged from our main analyses (Table 4). Additional analyses excluding breast cancer cases diagnosed within 4 years after baseline in 1986 (to minimize the possibility of undiagnosed breast cancer affecting sleep duration in 1986) did not alter results [multivariate-adjusted HR and 95% CI for those sleeping ≤5, 6, 8, and ≥9 hours compared with 7 hours were 0.94 (0.79-1.12), 0.94 (0.86-1.03), 1.04 (0.95-1.14), and 0.90 (0.76-1.08), respectively]. Secondary analyses including both *in situ* and invasive breast tumors were also conducted but results were essentially unchanged (data not shown).

Although plasma melatonin may be inversely related to tumor estrogen receptor concentrations (20), habitual sleep duration was not associated with estrogen-positive or estrogen-negative tumors. Moreover, in spite of recent evidence suggesting that plasma melatonin levels may be affected by smoking (21), stratifying our analyses by smoking status produced essentially unaltered results (data not shown).

Discussion

The effect of sleep duration on health has only begun to be elucidated. Sleep restriction has been associated with detrimental physiologic effects, including impairment of glucose tolerance (22) and inflammatory responses (23). Both long and short habitual sleep have been implicated in various health outcomes. Long sleep was associated with increased risk of coronary heart disease (1) and symptomatic diabetes (2). Short sleep was also associated with

Table 1. Mean age and age-adjusted baseline characteristics by sleep category					
	≤5 h (n = 3,553)	6 h (n = 19,834)	7 h (n = 32,041)	8 h (n = 18,333)	≥9 h (n = 3,657)
Age (y)	53.6	53.0	52.6	53.2	53.6
Body mass index (kg/m^2)	26.4	25.7	25.1	25.2	25.6
Age at menarche (y)	12.4	12.5	12.5	12.6	12.6
Nulliparous (%)	7.9	6.9	6.2	6.9	7.0
No. births*	3.2	3.3	3.2	3.2	3.2
Age at first birth (y)*	25.0	24.8	24.8	24.8	24.8
No alcohol consumption (%)	37.1	32.4	30.1	31.4	34.0
Alcohol intake (g/d)[†]	8.5	9.0	9.3	10.3	12.6
Postmenopausal (%)	58.6	57.7	56.8	56.1	55.1
Currently taking hormone replacement therapy (%)[‡]	13.1	16.2	17.2	16.5	16.3
Family history of breast cancer (%)	7.5	8.0	8.1	8.2	7.8
History of benign breast disease (%)	32.6	33.6	35.3	33.8	34.1
Never worked rotating shifts (%)	27.8	33.2	37.5	38.6	38.0
Married (%)	60.9	69.5	75.2	75.5	73.8
Depressive symptoms (%)[§]	9.4	6.6	5.5	6.1	8.6

NOTE: Age-adjusted means unless otherwise noted.
*Among parous women ($n = 72,234$).
[†]Among those who drink alcohol ($n = 53,024$).
[‡]Among postmenopausal women only ($n = 44,038$).
[§]Reported in 1992 and in 1996.

Table 2. Breast cancer HRs and 95% CIs by sleep duration category as reported in 1986

	Person-years	No. incident cases of breast cancer	Age-adjusted HR (95% CI)	Multivariate HR* (95% CI)
≤5 h	52,422	174	0.88 (0.75-1.03)	0.93 (0.79-1.09)
6 h	295,731	1,051	0.96 (0.89-1.04)	0.98 (0.91-1.06)
7 h[†]	479,130	1,752	1.00	1.00
8 h	272,345	1,057	1.05 (0.97-1.13)	1.05 (0.97-1.13)
≥9 h	53,449	189	0.95 (0.82-1.10)	0.95 (0.82-1.11)
P_{trend}[‡]			0.07	0.18

*Adjusted for age (months), body mass index (<20, 20-22, 23-24, 25-26,27-29, 30-34, 35-39, ≥39 kg/m^2), height (<58, 58-61, 61-63, 63-66, 66-68, ≥68 inches), history of benign breast disease (yes/no), family history of breast cancer (yes/no), parity and age at first birth (nulliparous; 1-2 births and <25, 25-30, or ≥30 years at first birth; 2-3 births and <25, 25-30, or ≥30 years at first birth; >4 births and <25 or ≥25 years at first birth), age at menarche (<11, 11-13, 13-16, ≥16 years), age at menopause (premenopausal, dubious menopause, <45, 45-49, 50-54, or >54 years at menopause), postmenopausal hormone use (premenopausal, dubious menopause, never hormone replacement therapy user, past hormone replacement therapy user <5 or ≥5 years, current hormone replacement therapy user <5 or ≥5 years), physical activity (<2, 2-6, 7-17, or >17 METs/week), alcohol and caloric intake (quintiles), and smoking (never smoker, past <45, 45-99, or ≥99; current <45, 45-99, or ≥99 pack-years).
[†]Reference category.
[‡]Test for trend modeling sleep as continuous categories and calculating Wald statistic.

increased risk of coronary heart disease (1) and diabetes, although the association with the latter was not statistically significant after adjustment for body mass index in one study (24), perhaps suggesting that sleep restriction may increase diabetes risk through changes in body mall index. Duration of sleep has also been associated with increased all-cause mortality in several studies although their findings are not entirely consistent. Both short and long sleep duration were associated with increased all-cause mortality among participants of the Nurses' Health Study (3) and among participants of the Japanese Collaborative Cohort Study (4). Kojima et al. (5) reported an association between both short and long sleep duration and increased all-cause mortality among men but not among women. Indeed, there is some evidence indicating that sleep duration may affect men and women differently. In a study by Amagai et al. (6), short sleep was associated with increased all-cause mortality among men, but not among women, whereas long sleep was associated with increased all-cause mortality only among women. In our study, sleep duration was not associated with breast cancer incidence although a moderate trend in risk increase towards those sleeping >7 hours

was suggested when analyses were restricted to participants who consistently reported same sleep duration in 1986 and 2000.

To our knowledge, only one other recent study (also prospective in nature) has explored the association between sleep duration and breast cancer risk, in which a protective effect of long sleep duration was suggested (25). However, in the Finish study, sleep duration reported in 1975 and 1981 were used to predict breast cancer from 1976 to 1981 and from 1982 to 1996, respectively. Thus, undiagnosed breast cancer may have affected duration of sleep, as it is possible that those who reported longer sleep hours were less likely to have had breast cancer. Moreover, the proportion of short (≤6 hours) and long sleepers (≥9 hours) in the study by Verkasalo et al. (~10% and 16%, respectively) varied considerably from the proportion of short and long sleepers in our study (~30% and 5%, respectively); intrinsic differences between the two populations may explain, at least in part, the differences in findings. Finally, because their findings were based on a limited number of breast cancer cases [14 (≤6 hours), 125 (7-8 hours), and 7 (≥9 hours) cases], their results may be associated with greater uncertainty.

Table 3. Breast cancer HRs and 95% CIs among participants who consistently reported the same number of hours of sleep in 1986 and 2000

	Person-years	No. incident cases of breast cancer	Age-adjusted HR (95% CI)	Multivariate HR* (95% CI)
≤5 h	12,812	41	0.98 (0.71-1.34)	1.06 (0.77-1.46)
6 h	93,753	295	1.01 (0.88-1.17)	1.04 (0.90-1.20)
7 h[†]	188,890	581	1.00	1.00
8 h	99,032	373	1.21 (1.06-1.38)	1.22 (1.07-1.39)
≥9 h	11,296	43	1.19 (0.87-1.63)	1.17 (0.85-1.60)
P_{trend}[‡]			0.01	0.05

*Adjusted for age, body mass index, height, history of benign breast disease, family history of breast cancer, parity and age at first birth, age at menarche, age at menopause, postmenopausal hormone use, physical activity, alcohol and caloric intake, and smoking.
[†]Reference category.
[‡]Test for trend modeling sleep as continuous categories and calculating Wald statistic.

Table 4. Multivariate-adjusted breast cancer HRs and 95% CIs by sleep category stratifying by menopause status (premenopausal/postmenopausal) and shift work (never/ever)

	≤5 h	6 h	7 h*	8 h	≥9 h
Menopause status [†]					
Premenopausal (*n* = 28,045)	0.74 (0.39-1.41)	1.05 (0.82-1.33)	1.00	0.93 (0.73-1.19)	0.92 (0.57-1.47)
Person-years (no. cases)	6,205 (11)	43,381 (106)	79,660 (192)	44,204 (102)	8,574 (20)
Postmenopausal (*n* = 44,038)	0.97 (0.82-1.14)	0.97 (0.89-1.06)	1.00	1.07 (0.99-1.16)	0.96 (0.81-1.13)
Person-years (no. cases)	42,425 (157)	233,801 (893)	371,575 (1-487)	213,286 (921)	42,088 (162)
Rotating night-shift work [†,‡]					
Never (*n* = 28,066)	0.83 (0.60-1.13)	0.99 (0.87-1.13)	1.00	0.96 (0.85-1.10)	0.85 (0.65-1.11)
Person-years (no. cases)	21,661 (65)	131,891 (447)	225,181 (805)	131,408 (455)	26,015 (84)
Ever (*n* = 41,308)	0.98 (0.80-1.20)	1.00 (0.90-1.11)	1.00	1.13 (1.02-1.25)	0.99 (0.81-1.23)
Person-years (no. cases)	30,761 (109)	163,840 (604)	253,949 (947)	140,936 (602)	27,434 (105)

NOTE: All models adjusted for age, body mass index, height, history of benign breast disease, family history of breast cancer, parity and age at first birth, age at menarche, age at menopause, postmenopausal hormone use, physical activity, alcohol and caloric intake, and smoking.
*Reference category.
[†]Likelihood ratio tests for interaction between menopause status and sleep duration, *P* = 0.72; between shift work and sleep duration, *P* = 0.22.
[‡]Models additionally adjusted for menopause status.

Exposure to light at night may be associated with decreased melatonin production (26), which is implicated in increased breast cancer risk (12, 27, 28). Melatonin production may be closely related to sleep duration (14–16). Short sleepers are probably more exposed to light by staying up later or by waking up earlier, potentially lowering melatonin production. Our results, however, are not compatible with the hypothesized detrimental effects of decreased sleep duration on breast cancer incidence through decreased melatonin levels.

We were unable to capture whether most of the reported sleep occurred at night, which is of particular importance to our cohort of nurses, as many have worked night shifts. Because melatonin is produced mainly at night, the effects of sleep duration on breast cancer may be attenuated among participants who sleep mostly during daytime. However, analyses restricted to those who never worked night shift produced results similar to our main analyses. Urine concentrations of melatonin have been associated with premenopausal breast cancer risk (12) and decreased melatonin levels may primarily affect breast cancer diagnosed before menopause. However, our results were unaltered by excluding postmenopausal women from analyses.

Our study has some limitations. Although its prospective nature eliminates recall bias, nondifferential misclassification of exposure cannot be ruled out, as we relied on self-reported data. Because our exposure has multiple categories, even random misclassification could have biased our results in any direction (29). However, self-reporting of habitual sleep duration was strongly correlated to 1-week sleep diaries in our population (3). Moreover, in light of the association between melatonin levels and breast cancer risk, it might have been interesting to consider timing of sleep in our analyses. However, we accounted for rotating shift work, which is likely to affect sleeping pattern and the times that sleep occurred. Additionally, information on quality of sleep was not obtained from our participants. Though it is possible that quality of sleep is affected among women working rotating shifts, this is likely to affect women regardless of duration of sleep. Although we used information on sleep duration obtained only at baseline in our main analyses, restricting our analyses to those who consistently reported same amount of sleep hours in 1986 and 2000 (thus minimizing misclassification of exposure) produced similar results, though a moderate trend in risk increase towards those sleeping >7 hours was suggested. We cannot rule out residual confounding by characteristics such as healthy lifestyle, although we controlled for closely related covariates (e.g., diet and physical activity). Short and long sleepers may differ from each other in many ways, thus confounding by unmeasured factors cannot be discarded.

Our study has several strengths, foremost its large size, prospective nature, and long duration of follow-up. Information on most of covariates was updated every 2 years. Although measurement error is inevitable, particularly in studies using self-reporting instruments, using repeated measurements over the follow-up period may reduce within-person random error. The detailed nature of our questionnaires allowed for control of many potential confounders, including most established breast cancer risk factors.

To our knowledge, this is one of the first studies to explore the effects of sleep duration in breast cancer. Our study provides no convincing evidence for an association between sleep duration and breast cancer. Our findings suggest that unknown sleep-related factors may counterbalance the effects of melatonin on breast cancer, and raise the possibility of mechanisms beyond decreased melatonin levels to explain the relation between shift work and breast cancer risk.

Acknowledgments

References

1. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med 2003;163:205–9.

2. Schultes B, Schmid S, Peters A, Born J, Fehm HL. Sleep loss and the development of diabetes: a review of current evidence. Exp Clin Endocrinol Diabetes 2005; 113:563–7.

3. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. Sleep 2004;27:440–4.

4. Tamakoshi A, Ohno Y. Self-reported sleep duration as a predictor of all-cause mortality: results from the JACC study, Japan. Sleep 2004;27:51–4.

5. Kojima M, Wakai K, Kawamura T, et al. Sleep patterns and total mortality: a 12-year follow-up study in Japan. J Epidemiol 2000;10:87–93.

6. Amagai Y, Ishikawa S, Gotoh T, et al. Sleep duration and mortality in Japan: the Jichi Medical School Cohort Study. J Epidemiol 2004;14:124–8.

7. Brzezinski A. Melatonin in humans. N Engl J Med 1997; 336:186–95.

8. Anisimov VN. The role of pineal gland in breast cancer development. Crit Rev Oncol Hematol 2003;46: 221–34.

9. Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. Night work and breast cancer risk: a systematic review and meta-analysis. Eur J Cancer 2005;41:2023–32.

10. Arendt J. Melatonin and the pineal gland: influence on mammalian seasonal and circadian physiology. Rev Reprod 1998;3:13–22.

11. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol 2000;526 Pt 3:695–702.

12. Schernhammer ES, Hankinson SE. Urinary melatonin levels and breast cancer risk. J Natl Cancer Inst 2005;97: 1084–7.

13. Graham C, Cook MR, Kavet R, Sastre A, Smith DK. Prediction of nocturnal plasma melatonin from morning urinary measures. J Pineal Res 1998;24: 230–8.

14. Aeschbach D, Sher L, Postolache TT, et al. A longer biological night in long sleepers than in short sleepers. J Clin Endocrinol Metab 2003;88:26–30.

15. Haimov I, Laudon M, Zisapel N, et al. Sleep disorders and melatonin rhythms in elderly people. Bmj 1994;309:167.

16. Wehr TA. In short photoperiods, human sleep is biphasic. J Sleep Res 1992;1:103–7.

17. Malik SW, Kaplan J. Sleep deprivation. Prim Care 2005;32:475–90.

18. Foss FM. Immunologic mechanisms of antitumor activity. Semin Oncol 2002;29:5–11.

19. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6: 49–62.

20. Tamarkin L, Danforth D, Lichter A, et al. Decreased nocturnal plasma melatonin peak in patients with estrogen receptor positive breast cancer. Science 1982; 216:1003–5.

21. Ozguner F, Koyu A, Cesur G. Active smoking causes oxidative stress and decreases blood melatonin levels. Toxicol Ind Health 2005;21:21–6.

22. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet 1999; 354:1435–9.

23. Vgontzas AN, Zoumakis E, Bixler EO, et al. Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. J Clin Endocrinol Metab 2004;89:2119–26.

24. Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care 2003;26: 380–4.

25. Verkasalo PK, Lillberg K, Stevens RG, et al. Sleep duration and breast cancer: a prospective cohort study. Cancer Res 2005;65:9595–600.

26. Lewy AJ, Wehr TA, Goodwin FK, Newsome DA, Markey SP. Light suppresses melatonin secretion in humans. Science 1980;210:1267–9.

27. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. J Natl Cancer Inst 2001;93:1563–8.

28. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst 2001;93:1557–62.

29. Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia (PA): Lippincott-Raven; 1998. p. xiii.

A Prospective Study on Habitual Duration of Sleep and Incidence of Breast Cancer in a Large Cohort of Women

Simone P. Pinheiro, Eva S. Schernhammer, Shelley S. Tworoger, et al.

Updated version	Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/66/10/5521

Cited articles	This article cites 28 articles, 6 of which you can access for free at: http://cancerres.aacrjournals.org/content/66/10/5521.full#ref-list-1
Citing articles	This article has been cited by 3 HighWire-hosted articles. Access the articles at: http://cancerres.aacrjournals.org/content/66/10/5521.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/66/10/5521. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.