

RESEARCH LETTER

Protective Effect of Diabetes Against Metastasis in Patients With Non-Small Cell Lung Cancer

Cancer can spread by both lymphatic and hematogenous routes, and metastases are found most commonly in organs fed by the downstream lymphatic and blood flow.¹ The tumor cells secrete proteinases or induce proteinase secretion by stromal cells that lead to degradation of the architecture of vascular basal membranes, creating local access through which to migrate into vasculature. In patients with long-standing diabetes mellitus, diabetic microangiopathy renders the vascular basal membrane less digestible by tumor cells, which may play a role in impeding neoplastic cell spread and metastasis.^{2,3} There has been debate in the literature concerning the protective effect of diabetes on patients with cancer in terms of improving their mortality. In reference to the 2 letters published in the ARCHIVES,^{4,5} we undertook a larger database review to investigate the possible hypothesis that diabetes has a protective effect in patients with coexisting cancers.

The objective of the study was to determine whether patients with both cancer and diabetes mellitus have less risk of metastasis and subsequently decreased mortality compared with nondiabetic patients with cancer.

A total of 566 patients with non-small cell lung cancer diagnosed between 1996 and 2000 were identified using the Henry Ford Hospital tumor registry. Medical records were reviewed to confirm study eligibility and to obtain data on diabetic status and progression to metastatic disease. Our results showed that stage and diabetes are significant predictors of metastasis. As expected, a higher stage is associated with a greater risk of metastatic progression (risk ratio [RR], 1.70; 95% confidence interval [CI], 1.40-2.07; $P < .001$). However, diabetes is associated with a lower risk (RR, 0.51; 95% CI, 0.31-0.85; $P = .01$). When a multivariable model is used to estimate adjusted risks, both stage and diabetes have RR estimates that are virtually unchanged (RR, 0.53 [95% CI, 0.32-0.89, and RR, 1.69 [95% CI, 1.38-2.07], respectively) and which remain statistically significant. Stage and age are the only significant predictors for death (RR, 1.56 [95% CI, 1.38-1.76] and RR, 1.03 [95% CI, 1.02-1.04], respectively). Diabetes does not have a significant association with death. Although the RR is less than 1.00, the P value is .41 and the 95% CI goes from 0.68 to 1.17. As with metastasis, the RRs in the multivariable model are

very similar to the unadjusted estimates. Stage and age are still strong predictors of death, and diabetes still has little association with mortality in this model.

The results of our study add new information concerning the effect of diabetes in cancer, since all other studies did not look specifically at the rate of metastasis. The results from this study are suggestive that diabetes is associated with a lower risk of metastasis in patients with non-small cell cancer of the lung but is not associated with lower mortality rate. These data provide the basis for future research aimed at understanding whether diabetes-related microvessel changes play a protective role against metastasis in patients with cancer.

Also, these findings may prompt further investigation on the molecular level for other methods of improving mortality in patients with cancer.

Amr Hanbali, MD
Khaled Al-Khasawneh, MD
Christine Cole-Johnson, PhD
George Divine, PhD
Haytham Ali, MD

Correspondence: Dr Hanbali, Henry Ford Health Systems, Hematology/Oncology Department, 2799 W Grand Blvd, Clara Ford Pavilion, Fifth Floor, Detroit, MI 48202 (ahanbal1@hfhs.org).

1. Nerlich AG, Hagedorn HG, Boheim M, Schleicher ED. Patient with diabetes-induced microangiopathy show a reduced frequency of carcinomas. *In Vivo*. 1998;12:667-670.
2. Spranger J, Kroke A, Mohlig M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes. *Diabetes*. 2003;52:812-817.
3. Tomiyama R, Kinjo F, Hokama A, Saito A. Relationship between diabetes mellitus and the site of colorectal cancer. *Am J Gastroenterol*. 2003;98:944-945.
4. De Giorgio R, Barbara G, Cecconi A, et al. Diabetes is associated with longer survival rates in patients with malignant tumors [letter]. *Arch Intern Med*. 2000;160:2217.
5. Hiroaki S, Ishikawa I, Kurishima K, et al. Diabetes is not associated with longer survival in patients with lung cancer [letter]. *Arch Intern Med*. 2001;161:485.

COMMENTS & OPINIONS

Risedronate for the Prevention of Hip Fractures: Concern About Validity of Trials

With concern, we read the trials conducted by Sato and colleagues comparing risedronate sodium with placebo in male patients with stroke¹ and female patients with Alzheimer disease (AD).²

Both trials were conducted in a single center. Yet, patients (500 women with AD and 280 men with stroke)

were recruited in only 3 months: the patients with AD in March and April 2003 and the patients with stroke in April and May 2003. Related to a third single-center trial with risedronate in 374 female patients with stroke at the same hospital that was published by the group in 2005,³ a correspondence letter⁴ expressed concern about the high frequency of recruitment, which was performed in only 4 months (between April and July 2003).³ In their reply, Sato and colleagues⁵ stated that their hospital is a specialized center for stroke and that they treat about 2800 patients with stroke per year. Even if these circumstances are taken into account, recruiting 280 male patients with stroke who meet all eligibility criteria in a single center in only 2 months appears implausible. This applies to an even greater extent to the 500 female patients with AD. Of note, Sato et al⁵ stated that only 1 physician (ie, Sato himself) did all AD diagnoses as well as the follow-up assessments of all 780 patients every 4 weeks.

Baseline data indicate that the study groups are strikingly well matched.^{1,2} Given the relatively small study sizes, the high frequency of identical baseline variables appears unusual.

The third trial by Sato et al^{3(p812)} included a comparison group of healthy volunteers. Whereas the 2 patient groups were followed up every 4 weeks, members of the comparison group “visited the clinic 6 and 12 months after enrolment, and 16 dropped out.” An almost identical sentence is found in the trial with male patients with stroke: “Members of the comparison group visited the clinic 6, 12, and 18 months after enrollment; 6 members dropped out.”^{1(p1744)} Yet, the statement makes no sense in this context, since, in the latter study,¹ there was no comparison group described, the frequency of follow-up of patients was stated to be every 4 weeks, and the number of patients excluded from the placebo group was 7.

In the population of patients with AD, only 8% did not complete the trial. Is it possible that 92% of this seriously ill but community-dwelling patients should have been able to attend all dates of follow-up every 4 weeks? Were there no admissions to nursing homes?

The effects of the intervention were exceptionally large: relative risk of having a hip fracture was reduced in the risedronate groups by 81%¹ and by 74%.² The effects on hip fracture risk in large outcome trials with bisphosphonates are much lower; for example, in a trial in 9331 elderly women, risedronate reduced the risk by 30%.⁶

In a MEDLINE search (Sato Y AND random* AND fractures), we found 11 further randomized controlled trials of fracture prevention of at least 6 months' duration by Sato et al, in which folate and mecobalamin, sunlight exposition, ipriflavone, vitamin D, vitamin K, alendronate, and etidronate were compared with placebo or no drug. Extremely large effects with significant results were described in all but 2 of these studies despite their small size.

Two of these trials found in our MEDLINE search and a further study by Sato et al are included in a meta-analysis of randomized controlled trials on the effects of vitamin K in the prevention of fractures.⁷ The authors

state that the effect is particularly striking, with an approximate 80% reduction in hip fractures. However, they advise caution on these findings, considering that such a large effect could be due to chance or “some other unidentified reason.”^{7(p1259)}

We are deeply concerned whether the data provided by Sato et al^{1,2} are valid.

Jutta Martha Halbekath
Stefanie Schenk
Andreas von Maxen, MD
Gabriele Meyer, PhD
Ingrid Mühlhauser, MD

Correspondence: Ms Halbekath, Arznei-Telegramm, Bergstrasse 38 A/Wasserturm, Berlin 12169, Germany (redaktion@arznei-telegramm.de).

1. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med.* 2005;165:1743-1748.
2. Sato Y, Kanoko T, Satoh K, Iwamoto J. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. *Arch Intern Med.* 2005;165:1737-1742.
3. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate therapy for prevention of hip fracture after stroke in elderly women. *Neurology.* 2005;64:811-816.
4. Poole KES, Warburton EA, Reeve J. Risedronate therapy for prevention of hip fracture after stroke in elderly women [letter]. *Neurology.* 2005;65:1513.
5. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate therapy for prevention of hip fracture after stroke in elderly women [reply]. *Neurology.* 2005;64:1514.
6. McClung MR, Geusens P, Miller PD, et al; Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med.* 2001;344:333-340.
7. Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166:1256-1261.

In reply

Although it was described that the study was done in a single hospital, I requested my physician colleagues of other nearby hospitals to participate in the 2 studies. Therefore, regarding the study on AD,¹ we actually had 2 collaborating hospitals, and each of them followed 195 and 93 patients. The remaining 212 patients were followed at Mitate Hospital, Tagawa, Japan. Similarly, in the stroke study,² the 2 collaborating hospitals followed 123 and 81 patients, and the remaining 76 patients were from Mitate Hospital. I apologize for confusing the readers of the ARCHIVES by not providing the numbers of patients in other hospitals involved in the studies. The authors did not describe this fact, the reason being that these hospitals were reluctant to have their names in the article. Diagnosis of AD was performed by myself and another neurologist who was not an active member of the study. I saw many neurological patients 6 days a week and performed follow-up assessment of patients with AD or stroke. However, 3 clinical psychologists performed the Mini-Mental State Examination on each patient with AD, and the Barthel index was assessed by 2 occupational therapists. This fact was not described in the article. The average number of the study subjects who visited each of the 3 hospitals ranged from 8 to 14 patients per day.

The high frequency of identical baseline variables was not by design but by chance. The group of neurological pa-

tients consist of homogeneous geriatric subjects, and their background characteristics fell into a relatively small range of variation.

We included the comparison group in the trial of fracture prevention in male patients with stroke,² but the data and explanation about this group was deleted during the review process, and the sentence about the comparison group was an error in the revised manuscript.

Most of the patients with AD followed at the Mitate Hospital were under the care of nursing homes, and they visited the hospitals with the assistance of nursing home employees. Regarding the patients at home, many of them received regular visits and care by home helpers and visiting nurses, and they sometimes came to the hospitals on such occasions. Relatively high Barthel indexes and Mini-Mental State Examination scores may also contribute to the low dropout rate.¹

We believe there are 2 potential causes of the reduced bone mineral density (BMD) in patients with stroke. One is immobilization-induced bone resorption, which develops shortly after stroke.³ This, in turn, induces hypercalcemia with resultant inhibition of parathyroid hormone secretion and 1,25-dihydroxyvitamin D production.⁴ Severe 25-hydroxyvitamin D deficiency due to sunlight deprivation with compensatory hyperparathyroidism leads to enhanced bone resorption in patients with AD.⁵ In patients with AD, decrease in bone turnover variables was more pronounced in the risedronate sodium group, indicating that greater inhibition of bone resorption may have brought about significant improvement in BMD in the risedronate group.¹ Indeed, estrogen deficiency is a key factor in the pathogenesis of postmenopausal osteoporosis. Thus, reduced BMD in patients with stroke or AD is different from postmenopausal osteoporosis, and patients are likely to benefit highly from the inhibition of bone resorption with risedronate therapy.^{1,2}

In neurological diseases, nutritional vitamin K deficiency also contributed to reduced BMD.⁶⁻⁸ An osteoblastic effect of vitamin K treatment was evident and reflected in the decreased plasma levels of Glu-osteocalcin. Menatetrenone may exert an inhibitory effect on bone resorption, since it brought about decreases in levels of ionized calcium and urinary deoxypyridinoline.⁹ These 2 mechanisms may be related to the high effectiveness on fracture prevention in our series.¹⁰ Other studies of fracture prevention with vitamin K (phytonadione and menaquinone) were carried out in patients with postmenopausal osteoporosis without nutritional vitamin K deficiency and immobilization.¹⁰

Yoshihiro Sato, MD

Correspondence: Dr Sato, Department of Neurology, Mitate Hospital, 3237 Yugeta, Tagawa 826-0041, Japan (y-sato@ktarn.or.jp).

1. Sato Y, Iwamoto J, Kanoko T, Satoh K. The prevention of hip fracture with risedronate and ergocalciferol plus calcium supplementation in elderly women with Alzheimer disease: a randomized controlled trial. *Arch Intern Med.* 2005;165:1737-1742.
2. Sato Y, Iwamoto J, Kanoko T, Satoh K. Risedronate sodium therapy for prevention of hip fracture in men 65 years or older after stroke. *Arch Intern Med.* 2005;165:1743-1748.
3. Sato Y, Kuno H, Kaji M, Ohshima Y, Asoh T, Oizumi K. Increased bone resorption during the first year after stroke. *Stroke.* 1998;29:1373-1377.

4. Sato Y, Oizumi K, Kuno H, Kaji M. Effect of immobilization upon renal synthesis of 1, 25-dihydroxyvitamin D in disabled elderly stroke patients. *Bone.* 1999;24:271-275.
5. Sato Y, Kanoko T, Satoh K, Iwamoto J. Risk factors for hip fracture among elderly patients with Alzheimer's disease. *J Neurol Sci.* 2004;223:107-112.
6. Sato Y, Tsuru T, Oizumi K, Kaji M. Vitamin K deficiency and osteopenia in disuse-affected limbs of vitamin D-deficient patients with long-standing stroke. *Am J Phys Med Rehabil.* 1999;78:317-322.
7. Sato Y, Kaji M, Kuno H, Tsuru T, Satoh K, Kondo I. Vitamin K deficiency and osteopenia in vitamin D-deficient elderly female patients with Parkinson's disease. *Arch Phys Med Rehabil.* 2002;83:86-91.
8. Sato Y, Honda Y, Hayashida N, Iwamoto J, Kanoko T, Satoh K. Vitamin K deficiency and osteopenia in elderly women with Alzheimer's disease. *Arch Phys Med Rehabil.* 2005;86:576-581.
9. Sato Y, Honda Y, Kuno H, Oizumi K. Menatetrenone ameliorates osteopenia in disuse-affected limbs of vitamin D- and K- deficient stroke patients. *Bone.* 1998;23:291-296.
10. Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166:1256-1261.

Alternatives for Menopause

The "systematic" review by Nedrow et al¹ seems less than reliable. The authors claim that they included all relevant randomized controlled trials and meta-analyses published in English. However, the exclusion of non-English articles seems not very systematic, particularly in areas that are dominated by investigators from non-English-speaking countries. Even accounting for this factor, we fail to understand why the authors only included 4 randomized controlled trials of black cohosh. Our systematic review published in 2002 (not mentioned by Nedrow et al¹) already included 4 randomized controlled trials.² It is now outdated, since several new studies have emerged. To make matters worse, the "Adverse Effects" subsection in the article by Nedrow et al¹ is woefully incomplete. Virtually none of the numerous treatments reviewed by Nedrow et al¹ is free of adverse effects.³ Yet the authors only mention those of soy, black cohosh, and kava. When Nedrow et al¹ conclude that "data are insufficient," we should perhaps take this with a pinch of salt.

Edzard Ernst, MD, PhD
Francesca Borrelli, PhD

Correspondence: Dr Ernst, Complementary Medicine, 25 Victoria Park Rd, Exeter EX2 4NT, England (Edzard.Ernst@pms.ac.uk).

1. Nedrow A, Miller J, Walker M, Nygren P, Hoyt Huffman L, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms. *Arch Intern Med.* 2006;166:1453-1465.
2. Borrelli F, Ernst E. *Cimicifuga racemosa*: a systematic review of its clinical efficacy. *Eur J Clin Pharmacol.* 2002;58:235-241.
3. Ernst E, Pittler MH, Wider B, Boddy K. *The Desktop Guide to Complementary and Alternative Medicine.* 2nd ed. Edinburgh, Scotland: Mosby/Elsevier; 2006.

In reply

We acknowledge the substantial contributions of Ernst and Borelli in the field of complementary and alternative medicine over the past decades. We concur that inclusion of non-English literature is desirable, and applaud Borelli and Ernst¹ for inclusion of such in their review of black cohosh