Joint Pain with Aromatase Inhibitors: Abnormal Frequency of Sjögren's Syndrome

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ABSTRACT. ***Objective.*** Since the results of the ATAC study, women who have undergone surgery for breast cancer and who require adjuvant hormone therapy are often treated with aromatase inhibitors. With these treatments, joint pain is frequent (30% to 40%) and quite often disabling (5% to 10%). Our objective was to investigate the origin of the pain induced by the anti-aromatases.

Methods. Twenty-four women of mean age 59 years with joint pain of > 5/10 on a visual analog scale underwent a rheumatological consultation and systematic laboratory tests.

Results. In 5 patients, pain was considered to have a well defined cause: osteoarthritis, shoulder tendinitis, or paraneoplastic aponeurositis. The other 19 patients had inflammatory pain of the fingers, wrists, shoulders, forefeet, ankles, or knees, with slight synovial thickening of the PIP and MCP joints. Two had an inflammatory syndrome on laboratory tests. Nine of these patients had antinuclear antibodies (ANA > 1/160 on HEp-2 cells) and 4 had rheumatoid factors (> 20 U). Ten patients had sicca syndrome of the eyes or mouth, 7 had probable Sjögren's syndrome according to the San Diego criteria, and one had definite Sjögren's syndrome. One had rheumatoid arthritis, one had Hashimoto thyroiditis, and 2 had positive hepatitis C serology.

Conclusion. Is the almost total estrogen depletion induced by aromatase inhibitors conducive to the development of sicca syndromes with ANA? Our results should be considered in relation to the Sjögren-like syndromes occurring in aromatase knock-out mice as recently reported. (First Release Oct 15 2007; J Rheumatol 2007;34:2259–63)

Key Indexing Terms:
AROMATASE INHIBITORS WOMEN JOINT PAIN SJÖGREN'S SYNDROME ESTROGEN

The ATAC study (Arimidex, Tamoxifen, Alone or in Combination)[1] demonstrated the superiority of anastrozole over tamoxifen in adjuvant treatment of breast cancer. This molecule has since been administered frequently to women who have had a breast neoplasm. In the ATAC study, 27.8% of women treated with anastrozole presented muscular and skeletal symptoms. The first hypothesis considered to explain these symptoms is estrogen deficiency induced by the aromatase inhibitor.

To determine the origin of this pain, a rheumatological consultation, radiological examination, laboratory tests and immunological investigations were carried out in women who experienced disabling pain while treated with aromatase inhibitors.

MATERIALS AND METHODS

Over a 6-month period, patients treated with aromatase inhibitors and presenting pain greater than 5/10 on a visual analog scale (VAS) at a followup cancerology consultation were referred to a rheumatology consultation. During this visit, the number of painful joints, number of swollen joints, extraarticular signs, and history were recorded. The following laboratory tests were carried out: measurement of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), investigation for antinuclear antibodies (on sHEp-2 cells), rheumatoid factors (RF; by ELISA), anti-citrullinated protein antibodies, anti-thyroglobulin antibodies, serum tests for hepatitis B and C, and investigation for sicca syndrome by Schirmer test and the compress test[2]. Accessory salivary gland biopsy was carried out if there was dryness of the eyes or mouth. Radiographs of the forefeet, hands, and wrists (anterior views) and of the painful joints were obtained.

RESULTS

Twenty-four patients, mean age 59 years (range 47–69 yrs), were examined; 21 had neoplasia in remission and 3 presented local recurrence or metastases. These women had all been treated with surgery and radiotherapy. Eleven patients had had chemotherapy; 2 were treated with trastuzumab and 2 patients who were not menopausal at the time of diagnosis were treated with triptorelin acetate. Twenty patients were treated with anastrozole at the time of the rheumatological consultation and 4 with letrozole, and 12 patients had received tamoxifen before treatment with aromatase inhibitors. In 2 of these 12 patients, pain had appeared with tamoxifen and had worsened with aromatase inhibitors, while the 12 others had no pain with tamoxifen, but pain had started with aromatase inhibitors. Pain had begun at a mean of 2.5 months after the start of treatment (15 days to 6 months).

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Five patients were examined individually: one patient no longer had pain because she had discontinued anastrozole 6 weeks before the consultation and pain had regressed within 2 weeks of discontinuation; one patient had clear and isolated bilateral supraspinatus tendinitis; one presented probable paraneoplastic aponeurositis of both hands and progressive peritoneal metastases; and 2 had clinical and radiological signs of osteoarthritis (knees and spine).

The other 19 patients experienced pain, generally of inflammatory type, with some night-wakening, morning stiffness of 15 to 30 minutes' duration, and an impression of swollen fingers in the morning. In the majority of patients, pain improved with exercise, whereas it worsened in some. Pain affected the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints, the wrists, shoulders, forefeet, ankles and knees, and was usually symmetrical. Muscle pain of the forearms and arms was sometimes reported. In the feet, pain appeared especially with the first few steps, on start of weight-bearing, whether on waking in the morning or after some time spent in a sitting position. The mean number of painful joints was 12 (range 3 to 20). Except for one patient with a diagnosis of rheumatoid arthritis (RA), who had joint inflammation, some PIP and MCP joints appeared slightly swollen, although synovitis or effusion could not be definitely affirmed.

Laboratory test results were as follows.

Two patients had an inflammatory syndrome with ESR > 25 mm/h and CRP > 5 mg/l; these were the patient with RA and one patient with Sjögren's syndrome (SS). Mean ESR was 17 mm/h (range 3 to 48) and mean CRP 2.8 mg/l (range 0.5 to 12).

Nine patients had antinuclear antibodies > 1/160: 3 at 1/160, 3 at 1/320, and 3 at 1/640. No anti-DNA, anti-extractable nuclear antigen, anti-Sm, or anti-RNP antibodies were found. Eight of these patients had sicca symptoms. Only one of them had significant levels of anti-SSA and anti-SSB antibodies.

Four patients had RF > 20 U, at 38 U and 92 U for 2 patients with hepatitis C virus (HCV) and 150 U for the patient with RA.

Two patients had anti-citrullinated protein antibodies (one patient with SS and the patient with RA).

On radiographs, we observed no epiphyseal bone loss or juxtaarticular erosion. Some patients showed signs of common degenerative joint disease of the distal interphalangeal joints and the trapeziometacarpal or femorotibial joints.

With regard to treatment, paracetamol was generally ineffective. In 8 of the 19 patients, nonsteroidal antiinflammatory drugs reduced by 50% the degree of pain measured on VAS. In 9 of the 19 patients with inflammatory pain we proposed corticosteroid therapy with prednisone 10 mg/day for 8 days. This treatment reduced the pain by 50% in 3 patients and almost completely ameliorated it in 6.

Of these 19 patients (Table 1), one had true RA, without sicca symptoms, and had clinical arthritis of the PIP and MCP, RF, and anti-citrullinated protein antibodies. Two carried HCV, without sicca symptoms, and had RF: in one the hepatitis C had been known for 20 years, with low liver activity (score A1F0 on biopsy). The liver disease was not accompanied by joint pain; this appeared with tamoxifen and was exacerbated with anastrozole. In the second patient, the HCV was discovered in the course of the investigations of joint pain. The hepatitis was not previously identified and transaminases were normal. In one patient, Hashimoto thyroiditis (strongly positive antithyroglobulin antibodies) with hypothyroidism (thyroid-stimulating hormone 9.8) was diagnosed, with no other autoantibodies. This patient had no sicca symptoms.

Ten of our 19 patients complained of sicca syndrome affecting the mouth, the eyes, or both. The clinical sicca syndrome could not be attributed to chemotherapy, as it had persisted several months, or even years, after the latter had been discontinued. The majority of patients experienced onset or exacerbation of this disorder with aromatase inhibitors.

Sicca syndrome was confirmed by a Schirmer test and/or a compress test. Biopsy of the accessory salivary glands performed in 9 patients showed Chisholm stage IV in one case, stage II in 3, and stage I in 5. Eight of these patients had antinuclear antibodies. However, with a single exception, these patients had no biological inflammatory syndrome or hypergammaglobulinemia. One of these 10 patients had Raynaud's syndrome that developed after introduction of the aromatase inhibitor. None had the cutaneous signs suggestive of lupus. None had signs in favor of associated connective tissue disease. According to the San Diego criteria, one of these patients thus presented definite and the others probable SS[3].

DISCUSSION

Frequency and expression of pain with aromatase inhibitors. In January 2005, a study of 9366 menopausal women with localized breast cancer, in a 68-month followup, showed the superiority of anastrozole over tamoxifen in the prevention of metastases and development of contralateral cancers. That study showed that anastrozole led to fewer uterine and vascular side effects than tamoxifen. On the other hand, joint pain and osteoporotic fractures were increased in women treated with anastrozole[1].

In September 2005, Felson and Cummings[4] called attention to joint pain with aromatase inhibitors. In the ATAC study, 35.6% of women treated with anastrozole had joint pain, compared with 29.4% of women treated with tamoxifen. When letrozole was given after tamoxifen, 21.3% of women had joint pain compared with 16.6% of women receiving placebo. Comparing exemestane with placebo after 2 to 3 years of treatment with tamoxifen, 33% of women receiving the aromatase inhibitor had pain compared with 29.7% with placebo.

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Table 1. Clinical and biological data for 19 patients with arthralgia.

Patient	Age, yrs	Painful Joints	Aromatase Inhibitor	Sicca Syndrome	Chisholm Stage	CRP, mg/l	ANA	Rheumatoid Factor	Anti-TPO Antibody	HCV	Diagnosis
1	56	Hands, wrists, knees	Letro	Yes	I	2.1	0	0	0	0	Unknown
2	58	Hands, wrists, feet, knees	Anas	No	ND	4.1	0	0	0	0	Unknown
3	66	Hands, knees	Anas	No	ND	0.5	0	0	0	0	Unknown
4	62	Hands, wrists, feet	Anas	No	ND	3	0	0	0	0	Unknown
5	52	Shoulder, hands	Letro	No	ND	1.5	1/80	0	0	0	Unknown
6	50	Hands, feet	Anas	Yes	ND	1.1	0	38	0	0	Unknown
7	65	Hands, shoulders, knees	Anas	No	ND	1.4	1/160	0	0	0	Unknown
8	60	Hands, shoulders, feet	Letro	No	ND	15	0	150	0	0	RA
9	68	Hands, shoulders, knees	Anas	Yes	II	11	1/640	0	0	0	Sjögren's
10	54	Hands, feet	Letro	No	ND	2	0	0	136	0	Thyroiditis
11	50	Hands, elbows, shoulders	Anas	No	ND	2.1	0	38	0	+	C hepatitis
12	47	Hands, shoulders, feet	Anas	Yes	I	3.8	1/640	0	0	0	Sjögren's
13	53	Hands, wrists, shoulders	Anas	Yes	II	1.2	1/320	0	0	0	Sjögren's
14	65	Hands, shoulders, feet	Anas	Yes	IV	13	1/640	0	0	0	Sjögren's
15	59	Hands, wrists, feet	Anas	Yes	I	1	1/160	0	0	0	Sjögren's
16	53	Hands, wrists, knees, feet	Anas	Yes	I	1.1	1/320	0	0	0	Sjögren's
17	49	Hands, wrists, shoulders, feet	Anas	No	ND	2	1/80	92	0	+	C hepatitis
18	62	Hands, knees, feet	Anas	Yes	I	1.4	1/160	0	0	0	Sjögren's
19	59	Hands, wrists, feet	Letro	Yes	II	1	1/320	0	0	0	Sjögren's

Letro: letrozole; Anas: anastrozole; CRP: C-reactive protein; ANA: antinuclear antibodies; anti-TPO: anti-thyroperoxydase antibodies; HCV: hepatitis C virus; RA: rheumatoid arthritis; ND: not done.

Donnellan, *et al*[5] in 2001 emphasized the importance and frequency of pain: in 77 patients treated with anastrozole, 16% had joint pain and 5% had to discontinue treatment because of its severity. Ohsako, *et al*[6], reporting on 53 patients treated with anastrozole between 2001 and 2005, observed a frequency of joint symptoms of 26% with finger stiffness in 13 patients. These 13 patients discontinued treatment and the symptoms improved.

Since the results of the ATAC study, the adjuvant treatment of numerous patients has been changed and tamoxifen has been replaced by aromatase inhibitors, in particular by anastrozole[7]. In normal practice, it appears that the number of patients who experience considerable disabling pain requiring symptomatic treatment and specialized consultations is markedly higher with aromatase inhibitors than with tamoxifen. Our small series is an illustration, as in the 12 patients who received tamoxifen before aromatase inhibitors, only 2 had joint pain with tamoxifen. For 10 of the 12, pain appeared when the aromatase inhibitor was introduced.

Our study concerned women with considerable pain (VAS > 5/10) who sought rheumatological advice. First, we noted the inflammatory expression of the pain reported by the patients: frequent night-wakening, morning stiffness with an impression of sausage-like swelling of the fingers causing some women to remove their rings, and onset of pain during the day when they spent some time without moving, while in general physical activity or sports reduced rather than increased the pain. Pain affected mainly the PIP and MCP joints, wrists, shoulders, forefeet, tarsal bones, ankles, and knees. Half the patients experienced paraarticular pain and muscle pain predominating in the forearms and arms. Except for the patient with established RA, we did not observe true arthritis with synovitis or effusion. However, we had the impression that there was swelling of the PIP and MCP in about half the patients. Clinically, we observed that pain could affect the flexor tendons of the fingers, which were painful on pressure. In patients experiencing pain with anastrozole, Morales, *et al*[7] reported that magnetic resonance imaging scan revealed tenosynovial inflammation of the flexor tendons of the hand and wrist.

The pain experienced by our patients somewhat resembled the joint pain of menopause, but the latter is more diffuse and its inflammatory expression is more marked. Their pain seemed to us to be very similar to that of patients with primary SS.

It was noteworthy that the symptoms were identical in the 15 patients treated with anastrozole and the 4 patients treated with letrozole. In 3 patients who experienced pain with anastrozole, this treatment was replaced by letrozole, but there was no change in the symptoms.

Mechanism of pain with aromatase inhibitors. Aromatase inhibitors block aromatase activity, which transforms adrenal androgens to estrogens. Women receiving this treatment therefore have almost total estrogen depletion[9]. Tamoxifen has an estrogen antagonist action on specific tissues (the mammary gland in particular).

After menopause, many women have joint pain. This was observed as early as 1925 by Cecil and Archer, who called these pains "menopausal arthritis"[10]. It has been

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reported that OA becomes moderately inflammatory in the months and years following menopause. In studies of menopausal hormone replacement therapy, it has been shown that women who receive conjugated estrogen have a 32% to 38% lower chance of developing muscular and skeletal symptoms than women who are not taking this treatment[11,12]. In addition, induction of artificial menopause by administration of leuprolide has been shown to cause joint and muscle pain in about 25% of women. This pain could be related to mild joint inflammation or to preexisting joint disease that becomes inflammatory[13]. This is linked with increased secretion of proinflammatory cytokines related to estrogen deficiency [e.g., interleukin 6 (IL-6), tumor necrosis factor-α, IL-1ß, IL-10][14,15].

The other hypothesis involves exacerbation of pain through an analgesic neurological effect of estrogens. Estrogens have receptors in the central nervous system[16], and they inhibit prostaglandin E_2 synthesis in the neuroglia. The pain threshold becomes lower during pregnancy whereas it becomes higher after the menopause. Estrogen deprivation secondary to administration of aromatase inhibitors could exacerbate the perception of pain by a central neurological action.

Frequency of biological signs of autoimmunity with aromatase inhibitors. In our series of 19 patients experiencing inflammatory joint pain with aromatase inhibitors, we found an abnormal frequency of autoantibodies: 9 women had antinuclear antibody (ANA) titer > 1/160. In 1997, Tan, *et al*[17] investigated ANA on HEp2 cells in a general control population aged 20 to 60 years: ANA were found in only 13% of the population for levels at 1/80, and in 5% of controls when titers were ≥ 1/160. The frequency was identical in all age-groups studied. In a recent study, Nilsson, *et al*[18] showed that only 3.5% of women blood donors aged 20 to 68 years had ANA at titers ≥ 1/200. Only one of our patients had anti-SSA and anti-SSB antibodies. Four of 19 patients had RF and one had antithyroglobulin antibodies.

To our knowledge, no other team has assessed the frequency of autoantibodies with aromatase inhibitors. In our small series, the number of patients with biological signs of autoimmunity seems markedly greater than the expected number.

Do our patients have SS? We cannot affirm that our patients have SS. Our patients have arthralgia and myalgia similar to those of SS, and they have sicca syndrome and ANA. But they do not have biological inflammatory syndrome or typical lesions of the accessory salivary glands, and only one patient had anti-SSA and anti-SSB antibodies.

Possible links between SS and aromatase inhibitors. At high doses, estrogens are known to suppress Th1-mediated immune responses and to stimulate Th2-mediated immune responses. For this reason, diseases such as RA that are mediated by Th1 tend to improve with estrogens, whereas those mediated by Th2, such as SLE, tend to worsen[19-21].

The role of sex hormones in SS is debated[22,23]. First, the female predominance (90%) and the mean age of onset (45 yrs) are notable. In women, some investigators have sought the relationships between the activity of primary SS and sex hormone levels. Brennan, *et al* found no correlation between disease activity and estrogen levels. They did, however, find a correlation between disease activity and testosterone levels[24]. Taiym, *et al* found no significant difference between estrogen and progesterone levels in women with SS compared with a control population; however they found increased prolactin levels in these patients[25].

Recent reports from animal models are instructive; Shim, *et al*[26] found increased B lymphocytes in the hematopoietic bone marrow of genetically aromatase-deficient mice, and they observed that these mice developed autoimmune exocrinopathy with renal involvement resembling SS. When the mice were treated with phytoestrogens, B-lymphocyte infiltration was significantly decreased and glandular lesions improved. Hayashi, *et al*[27] showed that estrogen deficiency in the mouse induces cleavage of α-fodrin through upregulation of caspase 1 activity. The cleaved α-fodrin acts as an autoantigen and activates T-lymphocyte cytotoxicity via the Fas-Fas ligand system (a system described in particular in the salivary and lacrimal glands[28]).

In our 24 patients who experienced pain with aromatase inhibitors, an independent cause was found in 20% of cases: periarthritis of the shoulder, paraneoplastic aponeurositis, and degenerative joint disorder. The other patients had a homogeneous presentation, with night-time joint pain and abnormal frequency of ANA (9/19) and sicca syndrome (10/19). Low-dose corticosteroids are often very effective. In women with breast cancer, aromatase inhibitors, perhaps through the major estrogen deficiency they induce, could be conducive to development of such a syndrome associating joint pain, sicca syndrome, presence of ANA with no biological inflammatory syndrome, with moderate histopathological lesions of the accessory salivary glands. Study of a larger patient series and investigation for sicca syndrome and autoantibodies in women who have had breast cancer but who have not been treated with aromatase inhibitors is needed to confirm this hypothesis. Similarly, it is essential to follow these patients after aromatase inhibitors have been discontinued to assess the reversibility of the sicca syndrome.

REFERENCES

1. Howell A, Cuzick J, Baum M, et al; ATAC Trialists' Group. Result of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60-2.
2. Laroche M, Arlet P, Authier JP, Cantagrel A, Mazières B, Arlet J. The compress test, an easy test for diagnosing and evaluating xerostomy [French]. Presse Med 1987;16:1704.
3. Fox RI, Howell FV, Bone RC, Michelson P. Primary Sjogren syndrome: clinical and immunopathologic features. Semin Arthritis Rheum 1984;14:77-105.
4. Felson DT, Cummings SR. Aromatase inhibitors and the syndrome

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of arthralgias with estrogen deprivation. Arthritis Rheum 2005;52:2594-8.
5. Donnellan PP, Douglas SL, Cameron DA, Leonard RC. Aromatase inhibitors and arthralgia. J Clin Oncol 2001;19:2767.
6. Ohsako T, Inoue K, Nagamoto N, Yoshida Y, Nakahara O, Sakamoto N. Joint symptoms: a practical problem of anastrozole. Breast Cancer 2006;13:284-8.
7. Morales L, Pans S, Paridaens R, et al. Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging. Breast Cancer Res Treat 2007;104:87-91. Epub 2006 Oct 24.
8. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Oncol 2005;23:5138-47.
9. Lonning PE. Pharmacology of aromatase inhibitors. Breast 1996;5:206-8.
10. Cecil RL, Archer BH. Arthritis of the menopause. JAMA 1925;84:75-9.
11. Greendale GA, Reboussin BA, Hogan P, et al. Symptom relief and side effects of postmenopausal hormones: results from the Post-menopausal Estrogen/Progestin Replacement Interventions Trial. Obstet Gynecol 1998;92:982-8.
12. Nevitt MC, Felson DT, Williams EN, Grady D. The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women. Arthritis Rheum 2001;44:811-8.
13. Kurebayashi S, Miyashita Y, Hirose T, Kasayama S, Akira S, Kishimoto T. Characterization of mechanisms of interleukin-6-gene repression by estrogen receptor. J Steroid Biochem Mol Biol 1997;60:11-7.
14. Vural P, Akgul C, Canbaz M. Effects of hormone replacement therapy on plasma pro-inflammatory and anti-inflammatory cytokines and some bone turnover markers in postmenopausal women. Pharmacol Res 2006;54:298-302.
15. Friedman AJ, Juneau-Norcross M, Rein MS. Adverse effects of leuprolide acetate depot treatment. Fertil Steril 1993;59:448-50.
16. Blomqvist A. Sex hormones and pain: a new role for brain aromatase? J Comp Neurol 2000;423:549-51.
17. Tan EM, Feltkamp TE, Smolen JS, et al. Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum 1997;40:1601-11.
18. Nilsson BO, Skogh T, Ernerudh J, et al. Antinuclear antibodies in the oldest-old women and men. J Autoimmun 2006;27:281-8.
19. Shearn MA. Sjogren's syndrome. Semin Arthritis Rheum 1972;2:165-91.
20. Haddad J, Deny P, Munz-Gotheil C, et al. Lymphocytic sialadenitis of Sjogren's syndrome associated with chronic hepatitis C virus liver disease. Lancet 1992;339:321-3.
21. Cutolo M, Sulli A, Capellino S, et al. Sex hormones' influence on the immune system: basic and clinical aspects in autoimmunity. Lupus 2004;13:635-8.
22. Foster H, Stephenson A, Walker D, et al. Linkage study of HLA and primary Sjogren's syndrome in multicase families. Arthritis Rheum 1993;36:473-84.
23. Moutsopoulos HM, Manoussakis MN. Immunopathogenesis of Sjogren's syndrome: "facts and fancy". Autoimmunity 1989;5:17-24.
24. Brennan MT, Sankar V, Leakan RA, Grisius MM, et al. Sex steroid hormones in primary Sjogren's syndrome. J Rheumatol 2003;30:1267-71.
25. Taiym S, Haghighat N, Al-Hashimi I. A comparison of the hormone levels in patients with Sjogren's syndrome and healthy controls. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:579-83.
26. Shim GJ, Warner M, Kim HJ, et al. Aromatase-deficient mice spontaneously develop a lymphoproliferative autoimmune disease resembling Sjogren's syndrome. Proc Natl Acad Sci USA 2004;101:12628-33.
27. Hayashi Y, Arakaki R, Ishimaru N. Apoptosis and estrogen deficiency in primary Sjogren syndrome. Curr Opin Rheumatol 2004;16:522-6.
28. Haneji N, Nakamura T, Takio K, et al. Identification of alpha-fodrin as a candidate autoantigen in primary Sjogren's syndrome. Science 1997;276:604-7.

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