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Variation in the TNF Gene Promoter and Risk of Osteolysis After Total Hip Arthroplasty

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ABSTRACT

Genetic factors may influence implant failure caused by osteolysis after THA. In an association study of 481 subjects after THA, we found that carriage of the *TNF−238A* allele was associated with an increased incidence of osteolysis versus noncarriage (odds ratio, 1.7) and was independent of other risk factors. Genetic and environmental factors influence implant survival after THA.

Introduction: Tumor necrosis factor (TNF) is thought to play a role in osteolysis, the major cause of implant failure after total hip arthroplasty (THA). Natural sequence variations at −238 and −308 in the TNF gene promoter are associated with differences in susceptibility to several TNF-mediated diseases. We tested whether these polymorphisms are associated with osteolysis after THA.

Materials and Methods: A total of 481 whites (214 with failed versus 267 with intact implants) were recruited 11.7 ± 4 years after cemented THA. Genomic DNA was extracted from peripheral blood and genotyped for the −238 and −308 polymorphisms using the Taqman 5′ nuclease method. Healthy controls ($n = 500$) from the background population were also genotyped to establish the local prevalence of these alleles.

Results: The carriage of *−238A* was 8.8% in the background population and 10.9% in the THA controls ($p > 0.05$). Carriage of *−238A* in the osteolysis group was 17.3% (odds ratio, 1.7; 95% CI, 1.0–2.9). Carriage was highest (20.5%) in patients with more widespread osteolysis (OR, 2.1; 1.2–3.8). The association of *−238A* with osteolysis was independent of other risk factors for osteolysis (logistic regression analysis: OR, 1.8; 1.0–3.2). Carriage of *−308A* was not associated with osteolysis.

Conclusion: Genetic, as well as environmental factors, influence implant failure after THA. Whether the *TNF−238* polymorphism causes a biological change that predisposes to loosening or is in linkage disequilibrium with such a locus is not yet known.

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Key words: tumor necrosis factor, polymorphism, total hip arthroplasty, osteolysis, cytokines, polymorphisms, implants, association, population studies

INTRODUCTION

OSTEOARTHRITIS IS A LEADING cause of chronic disability at older ages. The prevalence of symptomatic hip osteoarthritis in subjects over 55 years of age is approximately 2.5–5%,[1] and the development of total hip arthroplasty (THA) as a cost-effective treatment represents one of the major surgical advances of the 20th century.

Despite the success of THA, approximately 5% of implants inserted for osteoarthritis will fail within 10 years because of aseptic loosening, resulting in pain and disability.[2] Presently, approximately 17% of THA procedures performed in the United States each year are revision pro-

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cedures for failed implants.[3] Revision THA, which involves replacing the failed implant with a new one, is associated with higher cost, mortality, and poorer functional outcome than primary surgery.[4]

One important mechanism of loosening is thought to be because of a host response to particulate wear debris generated from the implant materials.[5] In this process, debris at the interface between implant and host stimulates a foreign body reaction characterized by macrophage-mediated osteoclast activation and local bone resorption, termed "osteolysis."[5] Loss of periprosthetic bone undermines implant support and leads to mechanical failure, termed "aseptic loosening." Risk factors for aseptic loosening include young age, male sex, and high levels of implant wear.[4,6] However, much of the observed differences in osteolytic response to particulate debris and wide variation in implant survival between individuals remain unexplained.[7]

Tumor necrosis factor (TNF) is a major pro-inflammatory cytokine that is thought to play a role in osteolysis. Elevated levels of TNF are found in osteolytic lesions and synovial fluid taken from patients with failed implants.[8,9] Particulate debris of clinically relevant size stimulates macrophage activation, TNF production, and osteolysis in cell and organ cultures.[10–12] Transgenic mice that fail to express 55 and p75 TNF receptors or are deficient in NFκB signaling (NFκB1$^{-/-}$), in contrast to their wildtype counterparts, do not develop osteolysis when challenged with particulate debris.[13,14] Also, addition of wear particles to mouse calvaria in vivo results in osteolysis that is inhibited by intraperitoneal injection of the TNF antagonist, Etanercept (0.2 mg, alternate days).[15]

The gene coding for TNF is on chromosome 6p21.3 in the class III region of the major histocompatibility complex.[16] Single nucleotide polymorphisms at the −238 and −308 positions in the promoter region, both guanine to adenine (G to A) transitions, are the most extensively investigated sequence variations of the *TNF* gene in white populations.[17] Carriage of the (less common) *A* allele at these sites has been associated with increased severity of a number of infective and inflammatory conditions including malaria,[18] chronic active hepatitis,[19] and psoriasis.[20] In this study, we tested whether carriage of the *A* allele at the −238 and −308 sites of the *TNF* gene is a risk factor for osteolysis after THA.

MATERIALS AND METHODS

Study population

Between February 2000 and February 2001, men and women who had previously undergone THA for idiopathic osteoarthritis of the hip were recruited. All were white and of North European descent and had received a cemented implant with a polyethylene acetabular-bearing surface. Subjects were excluded if they had any history of inflammatory arthropathy or known secondary causes of hip arthritis such as trauma, avascular necrosis, or developmental or childhood hip disease. Subjects were also excluded if they had taken courses of immunosuppressant agents or bisphosphonates for a continuous period of greater than 6 months since THA or if there was clinical suspicion of implant infection. All subjects provided written informed consent before participation. The study was approved by the North Sheffield, North Derbyshire, and St James's University Hospital Research Ethics Committees and conducted in accordance with the ethical principals stated in the Declaration of Helsinki.

The osteolysis group consisted of subjects with aseptic loosening diagnosed on plain radiographs of the hip taken before revision surgery and had loosening confirmed surgically, and subjects who had osteolytic lesions or established aseptic loosening on plain radiographs taken on the day of genotyping. Loosening of the prosthetic stem and cup were defined according to the criteria of Harris and McGann[21] and Harris and Penenberg,[22] respectively, and included those implants classified as definitely or probably loose. The control group was comprised of subjects with no evidence of aseptic loosening or osteolytic lesions on plain anteroposterior and lateral radiographs of the hip taken on the day of genotyping. The radiographs were digitized using a Lumisys laser digitizer (Lumisys Inc., Sunnyvale, CA, USA). Acetabular cup polyethylene linear wear was measured using the Ein-Bild-Roentgen-Analyse (EBRA) method according to a protocol previously described[23] and expressed as total linear wear. Wear measurements using the EBRA software were based on the difference in centering of the femoral head and the center of the cup using a supine AP radiograph of the pelvis. For the THA control subjects, the measured radiograph was that taken on the day of genotyping. In the case of the osteolysis subjects, the last radiograph taken before revision surgery was used.

Peripheral whole blood was taken from the THA subjects, and genomic DNA was extracted using chloroform and alcohol. Extracted DNA was stored at +4°C before genotyping. Genomic DNA was also extracted from the peripheral blood of a random anonymous sample of 500 healthy blood-donor subjects from the same geographical region to determine the prevalence of the genotypes in the local background population. The −238 and −308 polymorphisms were genotyped using the Taqman 5′ nuclease method (PE Applied Biosystems, Foster City, CA, USA). This assay uses the 5′-3′ nuclease activity of *Taq*DNA polymerase to cleave a fluorogenic probe that is specific for one of two alleles at the target polymorphism site and is described in detail elsewhere.[24] The primer sequences for *TNF−238* were as follows: forward primer 5′-GCATCAAGGATACCCCTCACA-3′; reverse primer 5′-ATCAGTCAGTGGCCCAGAAGA-3′. The Taqman probes for *TNF−238* were as follows: TET label 5′-CCTCCCTGCTCCGATTCCG-3′; FAM label 5′-TCCTCCCTGCTCTGATTCCGA-3′ (Scandinavian Gene Synthesis AB, Koping, Sweden). The primer sequences for TNF−308 were as follows: forward primer 5′-GGCCACTGACTGATTTGTGTGT-3′; reverse primer 5′-CAAAAGAAATGGAGGCAATAGGTT-3′ (Scandinavian Gene Synthesis AB). The Taqman probes for TNF−308 were as follows: TET label 5′-ACCCCGTCCCCATGCCC-3′; FAM label 5′-AACCCCGTCCTCATGCCC C-3′. The polymerase chain reaction (PCR) conditions were heating to 95°C for 10 minutes followed by 40 cycles at 95°C for 15 s and 58°C for 1 minute using a PTC-200 thermal cycler (MJ Research, Inc.,

Table 1. Characteristics of Study Subjects

Characteristic	*THA control* (n = *267*)	*THA osteolysis* (n = *214*)	p *Value*
Age at primary THA (years)*	64 ± 8	59 ± 9	<0.001
Age < 55 years at primary THA (yes/no)†	37/230	72/142	<0.001
Sex (male/female)†	118/149	120/94	0.012
Body mass index (kg/m^2)*	28 ± 5	28 ± 4	>0.05
Primary THA before 1988 (yes/no)†	91/176	141/73	<0.001
Osteolysis-free survival (years)*	12 ± 4	10 ± 4	<0.001

Values are mean ± SD.

* Student's *t*-test.

† χ^2 test with Yates' correction.

Osteolysis-free survival for THA control, time from primary THA surgery to date of clinical review and genotyping; for THA osteolysis, time from primary THA surgery to date of diagnosis of osteolysis.

Watertown, MA, USA). Fluorescence detection and genotyping were performed using an ABI Prism 7200 sequence detector (PE Applied Biosystems).

Statistical analysis

Between-group comparisons were analyzed using Student's unpaired *t*-test for continuous variables and the χ^2 test with Yates' correction for categorical variables. The independence of the effect of TNF genotype from other factors associated with osteolysis was examined using logistic regression analysis, with backward-stepwise exclusion of nonsignificant covariates using the Wald statistic. All statistical analyses were two-tailed, using a critical *p* value of 0.05. All were made using SPSS statistical software (version 11.5; SPSS UK, Chertsey, UK), with the exception of odds ratios for osteolysis associated with allele carriage (the ratio of the odds of osteolysis in subjects carrying the allele of interest versus those not carrying the allele), which were calculated using Medcalc statistical software version 5.00 (Medcalc, Mariakerke, Belgium).

RESULTS

Characteristics of patients

Four hundred eighty-one subjects were recruited, of whom 214 formed the osteolysis group. The distribution of primary cemented THA designs in the THA control subjects were 229 (86%) Charnley, 24 (9%) Stanmore, 11 (4%) Howse, and 3 (1%) McKee-Arden implants. The distribution of primary cemented THA designs in the THA osteolysis subjects were 173 (81%) Charnley, 8 (4%) Stanmore, 13 (8%) Howse, 16 (8%) McKee-Arden, and 4 (2%) other implant designs.

In 117 subjects (55%), osteolysis around the femoral and pelvic implant components had occurred, 47 (22%) had only femoral osteolysis, and 50 (23%) had only pelvic osteolysis. Revision THA for aseptic loosening had been performed in 170 (79%) of the osteolysis subjects, 9 (4%) were awaiting revision, and in the remainder, revision was not indicated on clinical grounds or had been declined. In 127 (75%) of the revisions, microbiological cultures had been taken from the hip joint, and all were free from infection. All subjects in the control group ($n = 267$) were free from osteolysis and aseptic loosening using radiographs taken on the day of genotyping. One hundred twenty (45%) of the THA controls and 129 (60%) of the osteolysis subjects had bilateral THA. In the osteolysis group, 47 (36%) subjects had bilateral aseptic loosening, of whom 28 (22%) had had bilateral revision procedures.

Subjects in the osteolysis group were younger, and a greater proportion was of male sex versus those in the THA control group (Table 1). A greater proportion of osteolysis subjects underwent primary THA before the year 1988 versus those in the THA control group, although the osteolysis-free follow-up time was greater in the THA control group versus the osteolysis group (Table 1). Implant wear measurements were possible in 441 (90%) subjects. In the remainder, measurement was not technically possible because of lack of suitable measurement landmarks in 38 subjects and because no suitable prerevision radiograph was available in 12 subjects. The median cup polyethylene linear wear in the THA controls was 0.75 mm (interquartile range [IQR], 0.48–1.19) and in the osteolysis group was 1.22 mm (0.77–1.97; Mann-Whitney $p < 0.001$). The mean annual linear wear rate, after log transformation to normalize the data distribution, was 0.07 mm in the THA control group and 0.13 mm in the osteolysis group (Student's *t*-test, $t = -10.76$, $p < 0.001$).

Allele frequency

The distribution of genotypes for the −238 and −308 polymorphisms within each subject group were in Hardy-Weinberg equilibrium (Table 2, χ^2 test, $p > 0.05$, all groups). There was no evidence of significant linkage disequilibrium between the −238 and −308 loci in the local background population (PM-plus analysis software,[25] $\chi^2 = 1.2$, $p = 0.3$).

The frequency of *−238A* in the THA controls was similar to that in the local background population (Table 2, χ^2 test, $p > 0.05$). The frequency of *−238A* was higher in the osteolysis group versus both the THA controls (χ^2 3.84, $p = 0.05$) and the local background population (χ^2 10.3, $p = 0.001$). The frequency of the −238A allele was highest in those subjects with both femoral and pelvic osteolysis versus both the THA controls (χ^2 6.09, $p = 0.01$) and the

TABLE 2. GENOTYPE DISTRIBUTION, ALLELE FREQUENCY, AND CARRIAGE RATE OF *TNF−238A* AND *−308A* IN STUDY SAMPLE

	TNF−238 *polymorphism*					TNF−308 *polymorphism*				
	Genotype distribution			A *allele frequency*	A *allele carriage rate*	*Genotype distribution*			A *allele frequency*	A *allele carriage rate*
Population	*GG*	*GA*	*AA*	*(%)*	*(%)*	*GG*	*GA*	*AA*	*(%)*	*(%)*
Background population ($n = 500$)	456	44	0	4.4	8.8	331	153	14	18.2	33.5
THA controls ($n = 267$)	238	29	0	5.4	10.9	178	77	12	18.9	33.3
THA osteolysis ($n = 214$)	177	36	1	8.9*	17.3§	134	71	9	20.8	37.4
Osteolysis subgroups										
Femoral and pelvic osteolysis ($n = 117$)	93	23	1	10.7†	20.5¶	76	34	7	21.1	35.0
Femoral osteolysis ($n = 47$)	38	9	0	9.6‡	19.1**	29	17	1	20.2	38.3
Pelvic osteolysis ($n = 50$)	46	4	0	4.0‡	8.0††	29	20	1	22.0	42.0

The genotype distribution within each group was in Hardy-Weinberg equilibrium (χ^2, $p > 0.05$).
* Allele frequency vs. THA controls χ^2 3.84, $p = 0.05$, and vs. local background population χ^2 10.3, $p = 0.001$.
† Allele frequency vs. THA controls χ^2 6.09, $p = 0.01$, and vs. local background population χ^2 13.0, $p = 0.0003$.
‡ Allele frequency vs. both THA controls and local background population χ^2 test $p > 0.05$.
§ Carriage rate vs. THA controls χ^2 3.62, $p = 0.06$, and vs. local background population χ^2 9.91, $p = 0.002$.
¶ Carriage rate vs. THA controls χ^2 5.58, $p = 0.02$, and vs. local background population χ^2 12.1, $p = 0.0005$.
** Carriage rate vs. THA controls χ^2 1.74, $p = 0.19$, and vs. local background population χ^2 4.14, $p = 0.04$.
†† Carriage rate vs. both THA controls and local background population χ^2 test $p > 0.05$.

background population (χ^2 13.0, $p = 0.0003$). No difference in allele frequency was found between those subjects who had unilateral osteolysis versus bilateral osteolysis ($p > 0.05$). The frequency of the *TNF−308A* allele did not differ between the THA subjects (Table 2, $p > 0.05$ all comparisons) or between the THA subjects and the local background population ($p > 0.05$).

Allele carriage rate and odds ratios

The carriage rate of *−238A* in the THA controls was 8.8% and was similar to the local background population (Table 2). The odds ratio (OR) for carriage of *−238A* in the osteolysis subjects was significantly higher than in the THA controls (Fig. 1; OR, 1.7; 95% CI, 1.0–2.9). The OR for *−238A* carriage in those with both femoral and pelvic osteolysis ($n = 117$) was 2.1 (1.2–3.8). Subjects with only femoral osteolysis ($n = 47$) had a similar OR, but the 95% CI was not significant. Subjects with only pelvic osteolysis ($n = 50$) had a *−238A* carriage rate that was similar to the THA controls and background population. The *TNF−308A* allele carriage rate was 33% in the THA controls and 34% in the local background population (Table 2). No differences in *−308A* carriage rate or ORs were observed between the THA groups (Table 2; Fig. 1).

Relationships between risk factors and osteolysis

The independence of *TNF−238A* carriage from other known risk factors associated with osteolysis was examined using logistic regression analysis. Covariates included in the initial model were carriage of *TNF−238A* versus *−238G*, age at surgery (<55 versus ≥55 years), sex, year of THA (<1988 versus ≥1988), and implant polyethylene wear. The value for polyethylene wear in the 9.4% of subjects in whom it could not be measured was estimated using interpolation by multiplying the mean annual wear rate for that subject's group by the osteolysis-free survival time for that individual. Logistic regression analysis results are presented both with and without polyethylene wear as an analysis covariate. The OR for osteolysis associated with *TNF−238A* carriage was 1.8 (1.0–3.2, $p = 0.05$) after correction for significant covariates (Table 3). When cup polyethylene wear was excluded from the analysis, the OR was 1.8 (1.0–3.2; $p = 0.04$). In subjects with osteolysis around both implant components, the OR was 2.3 (1.1–4.5, $p = 0.02$). When cup polyethylene wear was excluded from this analysis, the OR was 2.3 (1.2–4.4; $p = 0.02$).

DISCUSSION

In this study, we aimed to determine whether natural variance within the promoter region of the *TNF* gene contributes to the risk of osteolysis after cemented THA. The frequencies of *−238A* and *−308A* in our background population were similar to those previously found in other European populations.[26,27] The allele frequency and OR for carriage of *−238A* in subjects with osteolysis was approximately twice that in subjects with successful implants and the background population. The relationship between carriage of *−238A* and osteolysis was strongest in those subjects with both femoral and pelvic osteolysis (observed power 70%, calculated using the Altman method).[28] Subjects with only femoral osteolysis had similar carriage rates to those with osteolysis around both implant components, although the sample size for this analysis was smaller (observed power 30%), and the OR was not significant. The carriage rate for those with only pelvic osteolysis was similar to the controls. The reason for this is unclear but may also be the result of small sample size in this subgroup. We were unable to determine whether there was any gene-dose effect associated with *−238A* because of the relatively low frequency of this allele in the study population. However, the single *−238A/A* homozygous subject in the osteolysis group had undergone revision of both the femoral and pelvic implants for osteolysis at 12.5 years and has subse-

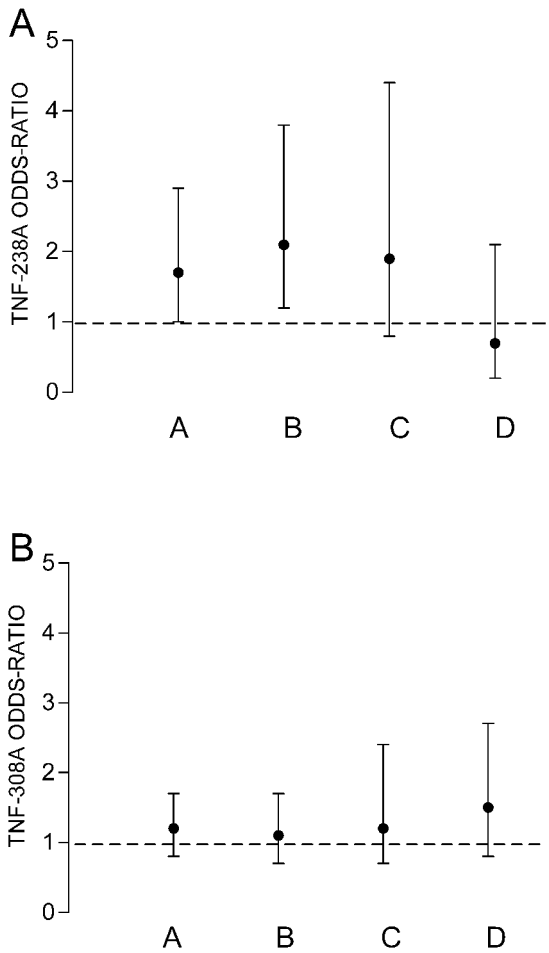

FIG. 1. ORs and 95% CIs for osteolysis after THA associated with carriage of (A) *TNF−238A* and (B) *TNF−308A* polymorphisms. Broken line indicates carriage rate of *A* allele in THA controls ($n = 267$). A, THA osteolysis group ($n = 214$); B, subjects with both femoral and pelvic osteolysis ($n = 117$); C, subjects with femoral osteolysis only ($n = 47$); D, subjects with pelvic osteolysis only ($n = 50$).

quently undergone another exchange of both revision implant components for further aseptic loosening.

The population in our study reflected the findings of other studies that young age, male sex, and amount of implant wear, but not body mass index (BMI), were associated with osteolysis.[4,6] The polyethylene annual linear wear rate in the THA control subjects was also similar to that previously measured by other investigators for successful implants of similar design using the EBRA software.[29] Data from the Swedish hip register, a national audit of the results of THA, shows a secular trend toward better survival rates in recent years associated with improvements in implant design and surgical technique.[30] This trend was also present in our population. After adjustment for these risk factors using logistic regression analysis, carriage of the *−238A* allele remained an independent risk factor for osteolysis, although the magnitude of its effect was only moderate. The osteolysis-free survival in the THA controls was longer than that of the osteolysis subjects. This may have contributed a conservative bias to the estimation of the effects of the *TNF−238A* allele and the amount of implant wear that are not corrected for in the logistic regression model. Using an alternate survival analysis approach of the Cox proportional hazards model to determine the independence of the *−238A* allele from other risk factors, the hazards ratio for osteolysis associated with *TNF−238A* carriage was 1.5 ($p = 0.03$).

We did observe a small consistent trend toward a higher carriage rate of the *−308A* allele in the osteolysis subjects, and a possible weak association of this genotype with loosening has not been excluded by this study. However, it is unlikely that this small increase in *−308A* allele frequency is caused by linkage disequilibrium between the −308A and *−238A* alleles because we could find no evidence of linkage between these loci in our local population using PM-plus analysis software.[25] This finding is consistent with previous observations that the *−238A* allele is associated with the HLA B18, F1C30, DR3, and the B57, SC61, DR7 extended haplotypes,[31] whereas the *−308A* allele is strongly associated with the HLA A1, B8, DR3 extended haplotype,[32] and suggests that the two polymorphisms arise from different genetic lineages.

Although association studies provide a powerful method for exploring the relationship between genotype and disease, they have a number of limitations. Two reasons for false results are small sample size (resulting in low powered studies that are unable to consistently detect susceptibility loci of only moderate effect) and genetic admixture. In this study, we examined a large population of subjects many years after THA and included a high proportion of subjects with failed implants. We also controlled for genetic admixture by selecting a single ethnic group for study and included only THA subjects with primary idiopathic osteoarthritis. Subjects with other causes for arthritis, including inflammatory arthropathies, were excluded. All subjects were also exposed to the same type of particulate stimuli, because all had had cemented implants with a polyethylene acetabular bearing surface. The distribution of the implant types observed in this study was similar between the osteolysis and control groups, and most of the implants studied in this report (95.2%) have been identified by the United Kingdom National Health Service Health Technologies Assessment Program as having good recorded outcomes at 10 years or more.[33,34]

Although these data represent the first report of a genetic contribution to osteolysis, the genetic component to this condition is likely to be complex, with many polymorphisms making a modest contribution to the total observed variability. Candidate genes would include those coding for interleukin (IL)-1 and IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), prostaglandin E2, and several proteinases that are involved in osteolysis.[8] Regulation of osteoclast activity is also governed by interaction with osteoblasts through the RANK/RANK ligand system that, in turn, is mediated by other factors such as osteoprotegerin and the pro-inflammatory cytokines.[35] Polymorphisms within the genes that code for many of these mediators and their receptors influence bone resorption in conditions such as osteoporosis and periodontitis[36,37] and

TABLE 3. ORS FOR OSTEOLYSIS AFTER THA ASSOCIATED WITH VARIOUS RISK FACTORS

Analysis covariate	*Coefficient (β)*	*SE*	p *Value*	*OR*	*95% CI lower*	*95% CI upper*
Age < 55 years at THA	0.68	0.26	0.008	2.0	1.2	3.3
Sex (male)	0.35	0.20	0.09	1.4	1.0	2.1
THA before 1988	0.92	0.22	<0.001	2.5	1.6	3.8
Polyethylene wear (mm)	0.70	0.16	<0.001	2.0	1.5	2.7
TNF−238A	0.57	0.30	0.05	1.8	1.0	3.2
Constant	−1.87	0.23	<0.001			

Logistic regression analysis including all study subjects ($n = 267$ THA controls and 214 THA osteolysis subjects); only the final step in the analysis is shown after backwards-stepwise exclusion of nonsignificant covariates using the Wald statistic (criteria for retention in model $p < 0.1$).

may also contribute to the phenotypic variation in periprosthetic osteolysis.

TNF is thought to stimulate osteoclastogenesis by both RANK/RANK ligand-dependent and -independent mechanisms.[38] The finding that polymorphism in the TNF promoter region is associated with increased risk of osteolysis supports the current view that TNF plays a role in the development of aseptic loosening after THA and may help explain the wide differences in implant survival observed between individuals. These findings, if replicated in other adequately powered studies, have implications for developing therapies to inhibit progression of osteolysis, and in the identification of at-risk populations to target such therapies.

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