Momentous sprint at the 2156 Olympics?

Women sprinters are closing the gap on men and may one day overtake them.

The 2004 Olympic women's 100-metre sprint champion, Yuliya Nesterenko, is assured of fame and fortune. But we show here that — if current trends continue — it is the winner of the event in the 2156 Olympics whose name will be etched in sporting history forever, because this may be the first occasion on which the race is won in a faster time than the men's event.

The Athens Olympic Games could be viewed as another giant experiment in human athletic achievement. Are women narrowing the gap with men, or falling further behind? Some argue that the gains made by women in running events between the 1930s and the 1980s are decreasing as the women's achievements plateau[1]. Others contend that there is no evidence that athletes, male or female, are reaching the limits of their potential[1,2].

In a limited test, we plot the winning times of the men's and women's Olympic finals over the past 100 years (ref. 3; for data set, see supplementary information) against the competition date (Fig. 1). A range of curve-fitting procedures were tested (for methods, see supplementary information), but there was no evidence that the addition of extra parameters improved the model fit significantly from the simple linear relationships shown here. The remarkably strong linear trends that were first highlighted over ten years ago[2] persist for the Olympic 100-metre sprints. There is no indication that a plateau has been reached by either male or female athletes in the Olympic 100-metre sprint record.

Extrapolation of these trends to the 2008 Olympiad indicates that the women's 100-metre race could be won in a time of 10.57 ± 0.232 seconds and the men's event in 9.73 ± 0.144 seconds. Should these trends continue, the projections will intersect at the 2156 Olympics, when — for the first time ever — the winning women's 100-metre sprint time of 8.079 seconds will be lower than that of the men's winning time of 8.098 seconds (Fig. 1). The 95% confidence intervals, estimated through Markov chain Monte Carlo simulation[4] (see supplementary information), indicate that this could occur as early as the 2064 or as late as the 2788 Games.

This simple analysis overlooks numerous confounding influences, such as timing accuracy, environmental variations, national boycotts and the use of legal and illegal stimulants. But it is also defended by the limited amount of variance that remains unexplained by these linear relationships.

So will these trends continue and can women really close the gap on men? Those who contend that the gender gap is widening say that drug use explains why women's times were improving faster than men's, particularly as that improvement slowed after the introduction of drug testing[1]. However, no evidence for this is found here. By contrast, those who maintain that there could be a continuing decrease in gender gap point out that only a minority of the world's female population has been given the opportunity to compete (O. Anderson, www.pponline.co.uk/encyc/0151.htm).

Whether these trends will continue at the Beijing Olympics in 2008 remains to be seen. Sports, biological and medical sciences should enable athletes to continue to improve on Olympic and world records, by fair means or foul[5]. But only time will tell whether in the 66th Olympiad the fastest human on the planet will be female.

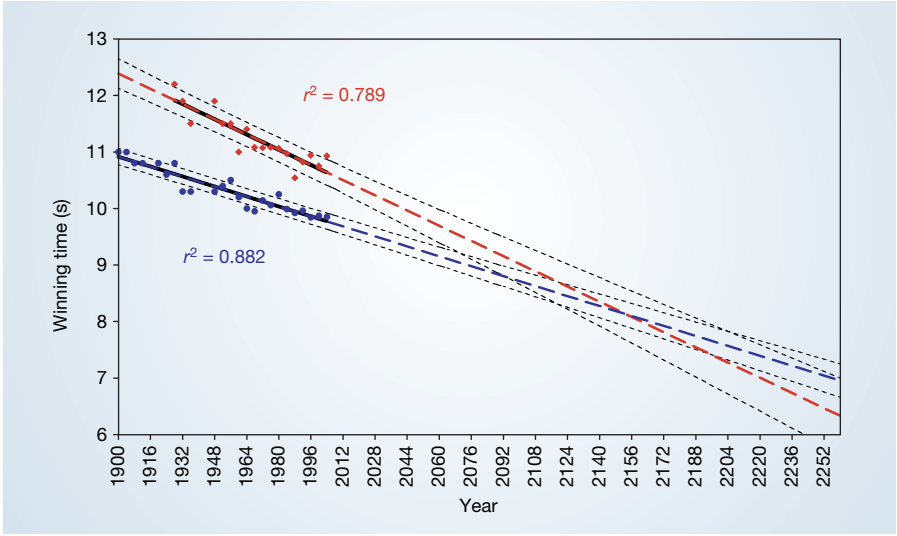

Figure 1 The winning Olympic 100-metre sprint times for men (blue points) and women (red points), with superimposed best-fit linear regression lines (solid black lines) and coefficients of determination. The regression lines are extrapolated (broken blue and red lines for men and women, respectively) and 95% confidence intervals (dotted black lines) based on the available points are superimposed. The projections intersect just before the 2156 Olympics, when the winning women's 100-metre sprint time of 8.079 s will be faster than the men's at 8.098 s.

Andrew J. Tatem*, Carlos A. Guerra*, Peter M. Atkinson†, Simon I. Hay*‡

**TALA Research Group, Department of Zoology, University of Oxford, Oxford OX1 3PS, UK*
e-mail: andy.tatem@zoology.oxford.ac.uk
†School of Geography, University of Southampton, Highfield, Southampton SO17 1BJ, UK
‡Public Health Group, KEMRI/Wellcome Trust Research Laboratories, PO Box 43640, 00100 GPO, Nairobi, Kenya

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Lung cancer

Intragenic ERBB2 kinase mutations in tumours

The protein-kinase family is the most frequently mutated gene family found in human cancer and faulty kinase enzymes are being investigated as promising targets for the design of antitumour therapies. We have sequenced the gene encoding the transmembrane protein tyrosine kinase ERBB2 (also known as HER2 or Neu) from 120 primary lung tumours and identified 4% that have mutations within the kinase domain; in the adenocarcinoma subtype of lung cancer, 10% of cases had mutations. ERBB2 inhibitors, which have so far proved to be ineffective in treating lung cancer, should now be clinically re-evaluated in the specific subset of patients with lung cancer whose tumours carry *ERBB2* mutations.

The successful treatment of chronic myelogenous leukaemia with a drug (known as imatinib, marketed as Gleevec) that inhibits a mutant protein kinase has fostered interest in the development of other kinase inhibitors[1]. Gefitinib, an inhibitor of the epidermal growth-factor receptor (EGFR), induces a marked response in a small subset of lung cancers; activating mutations have been found in the *EGFR* gene in tumours that respond to gefitinib but are rare in those that do not respond[2,3]. The response to gefitinib as a treatment for lung cancer therefore seems to be predicated upon the presence of an *EGFR* mutation in the tumour.

ERBB2 and EGFR are both members of the EGFR kinase subfamily. Receptor oligomerization triggers signalling cascades implicated in cell growth, differentiation and survival. As part of an evaluation of these and other kinase genes for their involvement in human cancer and in order to find potential targets for mutant-kinase inhibitors, we sequenced the entire coding sequence and the exon/intron boundaries of the *ERBB2* gene in 120 primary lung tumours.

We identified three unambiguous somatic mutations (which were not present in normal DNA from the same individuals), two instances of an in-frame insertion (PD1353a and PD0258a) and a missense substitution (PD0270a) (Table 1). Two additional likely somatic mutations were found in tumours for which no normal tissue was available (one of these is a further instance of the previously observed in-frame insertion; the second is a different in-frame insertion, two amino acids distal to the other insertion). All mutations were located in the kinase domain. These in-frame insertions are adjacent to, and the missense mutation overlaps with, the analogous structural region of the in-frame *EGFR* deletions that are associated with some lung tumours[2,3] (Fig. 1).

Immunocytochemical staining for ERBB2 revealed no differences between tumours with or without *ERBB2* mutations, indicating that overexpression probably does not accompany the mutation. *ERBB2* amplification was found in 1/49 adenocarcinomas and 1/14 large-cell carcinomas (neither of which had an intragenic mutation). None of the cancers associated with *ERBB2* mutation had mutations in *KRAS2*, *NRAS* or *BRAF*, genes that have also been implicated in the development of lung cancer[4].

We determined the complete *ERBB2* coding sequence in 18 breast, 20 gastric and 15 testicular tumours; the kinase domain was sequenced in 303 primary cancers, including 31 colorectal, 40 renal, 27 ovarian, 10 glioma, 9 acute lymphocytic leukaemia, 20 myeloproliferative disease, 76 sarcoma, 11 papillary thyroid, 23 bladder, 56 additional breast and 235 cancer cell lines (see supplementary information). Three further somatic mutations were found, all in the kinase domain (Table 1); a mutation was also detected in a primary gastric cancer between two in-frame insertions.

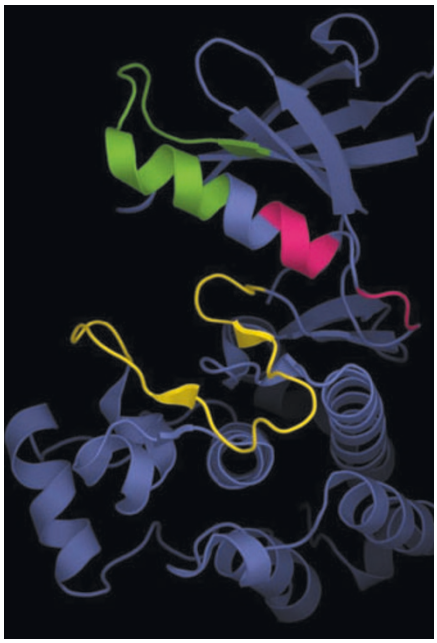

Figure 1 Similar positioning within the epidermal growth-factor receptor (EGFR) kinase domain (database accession numbers MMDB:20494/PDB:1M17) of the EGFR and ERBB2 mutations that are found in a proportion of lung tumours. The composite position of reported EGFR deletions[2,3] is indicated in green; the relative positions of the ERBB2 insertions described here are mapped onto the EGFR sequence and are shown in pink. The first third of the activation loop of the kinase domain is indicated in yellow for orientation.

In the lung tumours, all of the intragenic *ERBB2* mutations that we found were in adenocarcinomas (Table 1). The frequency was 4.2% (5/120) in non-small-cell lung carcinomas (NSCLCs) overall and 9.8% (5/51) in adenocarcinomas. By comparison, we found *EGFR* mutations in 2% (2/120) of NSCLCs and 4% (2/51) of adenocarcinomas, in agreement with a comparable series described previously[3]. None of these had an *ERBB2* mutation. Four out of five cases with *ERBB2* mutations were current or ex-smokers (*EGFR* mutation cases are predominantly found in never-smokers[2,3]).

Although amplification of *ERBB2* has been demonstrated in 20% of breast cancers[5] and occurs at a lower frequency in other cancers[6], intragenic mutations in *ERBB2* in human cancer have not previously been reported. The pattern of *ERBB2* mutations, supported by precedents from other mutated kinases implicated in cancer development, strongly indicates that these mutations activate the ERBB2 kinase.

The drug trastuzumab (marketed as Herceptin), a humanized antibody against the extracellular domain of ERBB2, has been approved for treatment of metastatic breast cancer and is most effective in breast cancers with *ERBB2* amplification[7]. The presence of a mutation appears to be a major determinant of response to therapy, as is the case with gefitinib and the EGFR mutations[2,3]. But results from phase II trials of trastuzumab as a treatment for NSCLC have not shown any advantage for most patients[7] and have provided insufficient evidence to proceed to phase III trials[8]. However, our findings, coupled with results from gefitinib inhibition of EGFR mutants, indicate that targeting of ERBB2 with antibodies or small-molecule inhibitors should be considered in cases of lung adenocarcinoma that have demonstrable *ERBB2* mutations.

Table 1 **ERBB2 mutations in primary tumours**

Sample	*Tumour/histology*	*Nucleotide**	*Amino acid**
PD1353a	NSCLC adenocarcinoma	2322 ins/dup(GCATACGTGATG)	ins774(AYVM)
PD0258a	NSCLC adenocarcinoma	2322 ins/dup(GCATACGTGATG)	ins774(AYVM)
PD0317a	NSCLC adenocarcinoma	2322 ins/dup(GCATACGTGATG)	ins774(AYVM)
PD0319a	NSCLC adenocarcinoma	2335 ins(CTGTGGGCT)	ins779(VGS)
PD0270a	NSCLC adenocarcinoma	TT2263-4CC	L755P
PD1487a	Glioblastoma	G2740A	E914K
PD1403a	Gastric tumour	G2326A	G776S
PD0888a	Ovarian tumour	A2570G	N857S

NSCLC, non-small-cell lung carcinoma; ins, insertion; dup, duplication (see supplementary information); amino-acid residues are shown in the single-letter notation and substitutions are represented as wild-type residue/position/mutant residue.
*Numbering represents the position relative to the A of the ATG codon/initiating methionine as the first nucleotide in the NCBI database (RefSeq accession NM_004448.1).

Cancer Genome Project and Collaborative Group*

e-mail: paf@sanger.ac.uk

***Philip Stephens[1], Chris Hunter[1], Graham Bignell[1], Sarah Edkins[1], Helen Davies[1], Jon Teague[1], Claire Stevens[1], Sarah O'Meara[1], Raffaella Smith[1], Adrian Parker[1], Andy Barthorpe[1], Matthew Blow[1], Lisa Brackenbury[1], Adam Butler[1], Oliver Clarke[1], Jennifer Cole[1], Ed Dicks[1], Angus Dike[1], Anja Drozd[1], Ken Edwards[1], Simon Forbes[1], Rebecca Foster[1], Kristian Gray[1], Chris Greenman[1], Kelly Halliday[1], Katy Hills[1], Vivienne Kosmidou[1], Richard Lugg[1], Andy Menzies[1], Janet Perry[1], Robert Petty[1], Keiran Raine[1], Lewis Ratford[1], Rebecca Shepherd[1], Alexandra Small[1], Yvonne Stephens[1], Calli Tofts[1], Jennifer Varian[1], Sofie West[1], Sara Widaa[1], Andrew Yates[1], Francis Brasseur[2], Colin S. Cooper[3], Adrienne M. Flanagan[4], Margaret Knowles[5], Suet Y. Leung[6], David N. Louis[7], Leendert H. J. Looijenga[8], Bruce Malkowicz[9], Marco A. Pierotti[10], Bin Teh[11], Georgia Chenevix-Trench[12], Barbara L. Weber[13], Siu T. Yuen[6], Grace Harris[14], Peter Goldstraw[14], Andrew G. Nicholson[14], P. Andrew Futreal[1], Richard Wooster[1], Michael R. Stratton[1,3]**

[1]Cancer Genome Project, Wellcome Trust Sanger Institute, Hinxton CB10 1SA, UK; [2]Ludwig Institute for Cancer Research, 1200 Brussels, Belgium; [3]Institute of Cancer Research, Sutton SM2 5NG, UK; [4]Institute of Orthopaedics, University College London, Stanmore HA7 4LP, UK; [5]Cancer Research UK Clinical Centre, St James's University Hospital, Leeds LS9 7TF, UK; [6]University of Hong Kong Department of Pathology, Queen Mary Hospital, Hong Kong; [7]Massachusetts General Hospital East, Molecular Pathology Unit, Charlestown, Massachusetts 02129, USA; [8]Laboratory of Pathology/Experimental Patho-Oncology, Erasmus MC University Medical Center Rotterdam, Daniel den Hoed Cancer Center, Josephine Nefkens Institute, 3000 DR Rotterdam, The Netherlands; [9]University of Pennsylvania Division of Urology, Philadelphia, Pennsylvania 19104, USA; [10]Instituto Nazionale Tumori and FIRC Institute of Molecular Oncology, Milan, Italy; [11]Laboratory of Cancer Genetics, Van Andel Research Institute, Grand Rapids, Michigan 49503, USA; [12]Queensland Institute of Medical Research, Royal Brisbane Hospital, Herston, Queensland 4029, Australia; [13]University of Pennsylvania Cancer Centre, Philadelphia, Pennsylvania 19104-6160, USA; [14]Royal Brompton Hospital, London SW3 6NP, UK.

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