

determine which statements described them and were related to their health. The patient could answer only yes or no to each question. An example of a question about sleep and rest is, "I spend much of the day lying down in order to rest."

TIME TRADE OFF TECHNIQUE

The time trade off technique is used to derive a "utility," a score between 0 and 1, in which 1 represents perfect health and 0 a state in which the patient is indifferent between life and death.¹¹ With the help of visual aids patients were asked how many years of their current health they would be willing to forgo to achieve perfect health. For example, if a 36 year old patient stated that she was unable to choose between four years of perfect health and 40 years of her current health the utility of her current health state was $4/40=0.10$ (she would be willing to give up 36 years of her current health to achieve four years of perfect health).

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- 1 Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. *N Engl J Med* 1987;316:73-8.
- 2 Winearls CG, Pippard MJ, Downing MR, Oliver DO, Reid C, Cotes PM. Effect of human erythropoietin derived from recombinant DNA on the anaemia of patients maintained by chronic haemodialysis. *Lancet* 1986;ii:1175-7.
- 3 Canadian Erythropoietin Study Group. A prospective, randomized, double-blind study of recombinant erythropoietin (r-Hu-EPO) in chronic hemodialysis [Abstract]. *Kidney Int* 1988;33:218A.
- 4 Eschbach JW. The anemia of chronic renal failure: pathophysiology and the effect of recombinant erythropoietin. *Kidney Int* 1989;35:134-48.
- 5 Lundin AP. Quality of life: subjective and objective improvements with recombinant human erythropoietin therapy. *Semin Nephrol* 1989;9:22-9.
- 6 Schaefer RM, Kokot F, Wernze H, Geiger H, Heidland A. Improved sexual function in hemodialysis patients on recombinant erythropoietin: a possible role for prolactin. *Clin Nephrol* 1989;31:1-5.
- 7 Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J* 1985;132:919-23.
- 8 Guyatt GH, Bombardier C, Tugwell P. Measuring disease-specific quality of life in clinical trials. *Can Med Assoc J* 1986;134:889-95.
- 9 Bergner M, Bobbitt RA, Carter WB, Gilson BS. The sickness impact profile: development and final revision of a health status measure. *Med Care* 1981;19:787-805.
- 10 Hart LG, Evans RW. The functional status of ESRD patients as measured by the sickness impact profile. *J Chronic Dis* 1987;40(suppl 1):117-30S.
- 11 Churchill DN, Torrance GW, Taylor DW, et al. Measurement of quality of life in end-stage renal disease: the time trade-off approach. *Clin Invest Med* 1987;10:14-20.
- 12 Naughton J, Sevelius G, Balke B. Physiological responses of normal and pathological subjects to a modified work capacity test. *J Sports Med Phys Fitness* 1963;3:201-7.
- 13 Schwartz D, Flamant R, Lellouch J. *Clinical trials*. New York: Academic Press, 1980:137.
- 14 Winer BS. *Statistical principles in experimental design*. New York: McGraw-Hill, 1971:518-39.
- 15 Gibbons JD. *Nonparametric statistical inference*. New York: McGraw-Hill, 1971:209-26.
- 16 Mohide EA, Torrance GW, Streiner DL, Pringle DM, Gilbert R. Measuring the wellbeing of family caregivers using the time trade-off technique. *Clinical Epidemiology* 1988;41:475-82.
- 17 Jaeschke R, Singer J, Guyatt G. Health status measurement: ascertaining the minimal clinically important difference. *Controlled Clin Trials* 1989;10:407-15.

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Short term increase in risk of breast cancer associated with full term pregnancy

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Women who have their first full term pregnancy after age 35 are at higher risk of breast cancer than nulliparous women,¹ and the proportion of young women with breast cancer who have had children is higher than expected.² These and other findings suggest that women who have full term pregnancies have a transiently increased risk of breast cancer that is followed by long term protection.^{3,4} We applied the analysis described by Bruzzi *et al*⁵ to data obtained from an investigation which explored the relation between lifestyle factors and risk of breast cancer.⁴

Patients, methods, and results

Briefly, we recruited 1996 married women aged 25-59 between 1980 and 1984 from seven hospitals. They comprised 998 patients with newly diagnosed breast cancer that had been confirmed histologically and 998 controls, who had been admitted electively with conditions not originally related to breast cancer.

Patients and controls were matched for admitting hospital and within five year age groups but not for parity. The present analysis aimed at detecting any increase in the risk of breast cancer shortly after a full term pregnancy. The interval between the date of diagnosis of breast cancer and the last term birth was studied. As this is related to age, age at first term birth, and parity these variables were adjusted for in the analysis.

Only women under 50 with two or more children were included to accord with the analysis by Bruzzi *et al*,⁵ and this resulted in the study becoming unmatched (422 cases and 447 controls). The generalised interactive modelling (GLIM) package was used to estimate the maximum likelihood of effects. Graduated levels of exposure were assessed by linear trend tests.

The two groups were comparable in terms of centre of recruitment, which was ignored in subsequent analyses. An increased risk of breast cancer was associated with decreasing interval since last term birth ($p=0.021$), increasing age at first term birth ($p=0.006$), and decreasing parity ($p=0.002$) (table). When women aged under 40 and 40-49 were considered separately the trends were broadly similar, although not all were significant.

Comment

Our results suggest that a transient increase in the risk of breast cancer occurs after full term pregnancy.

	Age <40 (120 cases, 117 controls)	Age 40-49 (302 cases, 330 controls)	All women (422 cases, 447 controls)
No of years since last term birth*:			
≥10	1.00†	1.00†	1.00†
7-	0.54 (0.21 to 1.42)	0.88 (0.47 to 1.64)	0.80 (0.48 to 1.32)
3-	1.14 (0.41 to 3.20)	1.35 (0.57 to 3.20)	1.44 (0.80 to 2.61)
<3	1.96 (0.53 to 7.27)	8.55 (1.00 to 73.40)	2.92 (1.32 to 6.49)
χ ₁ for trend	1.87 (p=0.172)	1.90 (p=0.168)	5.30 (p=0.021)
Age (years) at first term birth‡:			
<20	1.00†	1.00†	1.00†
21-	1.58 (0.65 to 3.85)	1.01 (0.61 to 1.70)	1.10 (0.70 to 1.71)
23-	2.43 (0.99 to 6.00)	1.34 (0.80 to 2.25)	1.52 (0.93 to 2.36)
25-	1.87 (0.71 to 4.95)	1.51 (0.91 to 2.50)	1.54 (1.00 to 2.39)
28-	1.95 (0.50 to 7.58)	1.74 (0.94 to 3.21)	1.74 (1.00 to 3.03)
≥32	4.59 (0.38 to 55.09)	2.39 (0.85 to 6.69)	2.70 (1.06 to 6.86)
χ ₁ for trend	2.08 (p=0.149)	5.90 (p=0.015)	7.40 (p=0.006)
No of term births§:			
2	1.00†	1.00†	1.00†
3	0.84 (0.43 to 1.65)	0.53 (0.36 to 0.79)	0.60 (0.43 to 0.84)
≥4	0.66 (0.19 to 2.34)	0.53 (0.33 to 0.86)	0.57 (0.36 to 0.89)
χ ₁ for trend	0.51 (p=0.475)	9.40 (p=0.002)	9.20 (p=0.002)

*Adjusted for age (two year intervals), age at first term birth, and parity.

†Reference value for calculating relative risk.

‡Adjusted for age (two year intervals), years since last term birth, and parity.

§Adjusted for age (two year intervals), years since last term birth, and age at first term birth.

Bruzzi *et al* reported a similar relative risk (2.66; 95% confidence interval 1.31 to 5.39) to our own (2.92; 1.32 to 6.49) during the three years after the last full term pregnancy.³ They did not, however, provide data on the risk during the first year after such a pregnancy or details of the adjustments for age.

We found a significantly increased risk with decreasing interval since last term birth when adjustment for age was within five or two year bands but not when

there was no adjustment for age. Although confidence intervals were wide, much of this risk occurred during the first year after the birth (2.05; 2.57 to 163.53); the risk during the second and third years was raised only slightly (1.37; 0.71 to 2.66). This finding might be attributable partly to the underrepresentation among the controls of women who had given birth within the previous year. Possibly women with new babies delay going into hospital for elective procedures; this is supported by data from our original matched study, which included nulliparous and primiparous women. Fewer controls (four) had had a full term pregnancy within the year before admission than was estimated from the national birth rate adjusted for age (nine) whereas 25 women with breast cancer had had such a pregnancy.⁵

In conclusion, our results suggest that a modest, transient increase in the risk of breast cancer is associated with full term pregnancy, although the results may have been influenced by bias in the control group. Such a bias could also have affected the results of Bruzzi *et al*.³

- 1 Miller AB, Bulbrook RD. The epidemiology and etiology of breast cancer. *N Engl J Med* 1980;303:1246-8.
- 2 Miller AB, Bulbrook RD. UICC multidisciplinary project on breast cancer: the epidemiology, etiology and prevention of breast cancer. *Int J Cancer* 1986;37:173-7.
- 3 Bruzzi P, Negri E, La Vecchia C, *et al*. Short term increase in risk of breast cancer after full term pregnancy. *Br Med J* 1988;297:1096-8.
- 4 Meara J, McPherson K, Roberts M, Jones L, Vessey M. Alcohol, cigarette smoking and breast cancer. *Br J Cancer* 1989;60:70-3.
- 5 Office of Population Censuses and Surveys. *Birth statistics*. London: HMSO, 1985. (Series FM1.)

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Proliferative retinopathy and nephropathy at presentation in young insulin dependent diabetics

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I report the occurrence of proliferative diabetic retinopathy as the presenting symptom of type I diabetes in two young patients who also had polyneuropathy and early nephropathy. Such a presentation is extremely rare.

Case reports

Case 1—A 23 year old woman who had had polyuria for three months presented to her optician with blurring of vision. She had neovascularisation of the left optic disc and haemorrhages and exudates typical of diabetic retinopathy affecting both eyes. Her visual acuity was reduced to 6/18 in the right eye and 6/12 in the left eye. Fluorescein angiography showed extensive vascular exudation in both retinas, and she was given argon laser treatment. She weighed 52 kg and had not lost weight recently. She had a blood glucose

concentration of 18 nmol/l, ketonuria, and a blood pressure of 124/80 mm Hg. Her sense of vibration and light touch in her feet was diminished, and deep tendon reflexes in her ankles were absent. She required 42 units of insulin daily in a conventional regimen of two injections, and her diabetes was easy to stabilise. Her glycated haemoglobin concentration was 15% (normal 5.3-7.2%), and urinary excretion of protein after her diabetes had been stabilised was 120 mg/24 h (normal <80 mg/24 h). Special investigations showed typical type I diabetes (table).

Case 2—A 29 year old white man presented with a one month history of blurring of vision and a two month history of nocturia. He had a blood glucose concentration of 22 mmol/l and trace ketonuria. He weighed 65 kg, having weighed 102 kg 10 years previously. His blood pressure was 140/108 mm Hg, and examination of the cardiovascular system showed no abnormalities. Perception of vibration and temperature in his toes and the deep tendon reflexes in his ankles were diminished. His visual acuity was 6/12 in the right eye and 6/6 in the left. There was neovascularisation of both retinas and of the disc in the right eye with typical features of background diabetic retinopathy. Extensive laser treatment was given bilaterally. Visual acuity deteriorated, and he developed vitreous haemorrhages. His glycated haemoglobin concentration was 16.5%. An overnight (first morning) sample of urine had an albumin concentration of 55 mmol/l (normal <20 mmol/l). His diabetes was stabilised with 48 units of insulin given as two injections daily (table).

Characteristics of two patients presenting with proliferative diabetic retinopathy

	Case 1	Case 2
Islet cell antibody	Positive	Negative
Serum C peptide after stimulation with glucagon (pmol/l)*	<77	520
Daily insulin requirement (units/kg body weight)	0.81	0.74
Tissue type	HLA-A2, A11, B8, Bw55, DR3, DR4	HLA-A1, A29, B8, B44, DR3, DR4

*Normal >1000 pmol/l.

Comment

Both patients had proliferative diabetic retinopathy, diabetic polyneuropathy, and early nephropathy. Proliferative diabetic retinopathy in type I diabetes rarely develops until the diabetes has been present for