OXFORD UNIVERSITY PRESS | American Journal Of Epidemiology

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Journal:	*American Journal of Epidemiology*
Manuscript ID	AJE-00784-2018.R2
Manuscript Type:	Original Contribution
Key Words:	chromosome disorders; genetics; cytogenetics; cohort studies; epidemiology; mortality; neoplasms; haematological malignancies

Mortality and Cancer Incidence in Carriers of Balanced Robertsonian Translocations: a National Cohort Study

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Funding: This work was funded by Medical Research Council and Breast Cancer Now.

Conflicts of interest: None declared

Running head: Mortality and cancer risks in carriers

List of abbreviations: ALL, Acute Lymphoblastic Lymphoma; CI, Confidence Interval; SIR, Standardised Incidence Ratio; SMR, Standardised mortality ratio; UK, United Kingdom

Abstract

A balanced Robertsonian translocation results from fusion of two acrocentric chromosomes. Carriers are phenotypically normal, and are often diagnosed because of recurrent miscarriages, infertility or aneuploid offspring. Mortality and site-specific cancer risks in carriers have not been prospectively investigated. We followed 1987 carriers diagnosed in Great Britain for deaths and cancer risk, over an average of 24.1 years. Standardised mortality (SMR) and incidence (SIR) ratios were calculated comparing the number of observed events against population rates. Overall mortality was raised for carriers diagnosed aged <15 (SMR=2.00, 95% confidence interval (CI): 1.09, 3.35), not raised for those diagnosed aged 15-44 (SMR=1.06, 95% CI: 0.86-1.28) and reduced for those diagnosed aged 45-84 (SMR=0.81, 95% CI: 0.68, 0.95). Cancer incidence was increased for non-Hodgkin lymphoma (SIR=1.90, 95% CI: 1.01, 3.24) and childhood leukaemia (SIR=14.5, 95% CI: 1.75, 52.2), the latter particularly in rob(15;21) carriers (SIR=447.8, 95% CI: 11.3, 2495). Rob(13;14) carriers had a raised breast cancer risk (SIR=1.58, 95% CI: 1.12, 2.15). Mortality risks relative to the population in diagnosed carriers depend on age at cytogenetic diagnosis, possibly reflecting age-specific cytogenetic referral reasons. Carriers might be at greater risk of childhood leukaemia and non-Hodgkin lymphoma and those diagnosed with rob(13;14) of breast cancer.

Introduction

A balanced Robertsonian translocation involves fusion of two acrocentric chromosomes (chromosomes 13, 14, 15, 21, 22) with subsequent loss of the short arms. They have been found to form predominantly during female meiosis (1, 2). Individuals are phenotypically normal but are at increased risk of miscarriages, infertility and aneuploid offspring because of production of unbalanced gametes. Depending on which chromosomes are involved, carriers are at increased risk of offspring with trisomy 21 (Down syndrome) or trisomy 13 (Patau syndrome) (3, 4).

Balanced Robertsonian translocations represent the most common chromosomal rearrangements in humans. Newborn surveys estimated they occur in 1 in 1000 individuals (5-8) with higher estimates (1 in 800) obtained from surveys of children referred for neurodevelopmental disease and congenital abnormalities (9). Translocations are disproportionally common between chromosomes 13 and 14 (rob(13;14)) and 14 and 21 (rob(14;21)), with other combinations being rare (10, 11). Carriers of these translocations have 45 chromosomes, but the resulting loss of the short arms is presumed inconsequential because the short arms mainly contain repetitive ribosomal DNA (12, 13). However, mortality and site-specific cancer incidence have not been systematically investigated in carriers.

A predisposition to haematological disorders in carriers of balanced Robertsonian translocations has been suggested (14), but evidence for this, and for pre-malignant conditions is, however, derived from case reports (14-19). Recently, carriers of rob(15;21) have been estimated to be at greatly increased risk of a rare form of acute lymphoblastic leukaemia (ALL) with intrachromosomal amplification (iAMP) of chromosome 21 (20). This was based

on the finding that constitutional rob(15;21) in iAMP-ALL patients was more common than might be expected based on newborn surveys. Risk of leukaemia has, however, not been prospectively investigated in Robertsonian translocation carriers overall or by subtype.

To assess risks in individuals with balanced Robertsonian translocations, one needs a cohort design, in which large numbers of patients are followed over a long period of time for mortality and cancer risk. We therefore investigated long-term risk of mortality and cancer in a cohort of patients diagnosed as carriers at cytogenetic centres in Great Britain.

Methods

Information on patients diagnosed with balanced Robertsonian translocations was obtained from all cytogenetic centres in Great Britain (n=27), except one small centre. Records were collected as far back in time as records had been maintained at each centre (in most centres from the 1960s or 1970s). The last year that records were abstracted ranged between 1994 and 2006, depending on when data extraction was conducted at the centre, mostly in the late 1990s. Prenatal records were not retrieved.

Patient information was matched to the National Health Service Central Register (NHSCR) for England and Wales and for Scotland. These registers hold information on deaths, emigrations and other exits from the NHS for everyone who is registered with a general practitioner, and are effectively population registers of these countries. Individuals who could be uniquely identified ('flagged') on the NHSCR formed the cohort and were followed-up for cancer incidence, death, and loss to follow-up such as through emigration. The underlying cause of death, from death certificates, was coded to the revision of the International Statistical Classification of Diseases and Related Health Problems (ICD) in use at the time of death, and was subsequently bridge-coded to the ninth revision of the classification (21) to give the categories shown in the Results. Patients were excluded if they were known to have been cytogenetically examined as a consequence of a cancer diagnosis. Permission for this study was obtained from appropriate ethics committees in the United Kingdom (UK) and the national personal information advisory group.

Statistical methods

For each cohort member, we calculated person-years at risk of death by sex, 5-year age group, calendar year and country (England & Wales combined vs. Scotland). Follow-up started at the date of cytogenetic diagnosis and ended on 31 December 2016 or the eighty-fifth birthday, date of death or other loss to follow-up, whichever was earliest. Follow-up was censored at age 85 because at older ages the certified cause of death is often inaccurate and national rates are not available for 5-year age group. Expected cause-specific mortality in the cohort was calculated by multiplying the sex-, age-, calendar year-, and country-specific person-years at risk in the cohort by the corresponding national mortality rates. Standardised mortality ratios (SMRs) were derived as the ratio of observed to expected deaths, and their 95% confidence intervals (CIs) calculated using exact methods (22). We calculated absolute excess rates by subtracting the expected from the observed numbers of deaths, dividing by person-years at risk and multiplying by 100,000. Analyses were conducted with STATA 14.2 (23). All significance tests were two-sided.

Analyses of cancer incidence were conducted similarly, except that follow-up started on 1 January 1971 (the date from which national cancer registrations became available) or from the date of the cytogenetic test, whichever was later and follow-up ended on 31 December 2015, the patient's 85th birthday, date of death or date of other loss to follow-up, whichever was earliest. Standardised incidence ratios (SIRs) were obtained based on expected numbers from national cancer incidence rates. Analyses of all malignancies combined included only neoplasms classified as malignant according to the International Statistical Classification of Diseases and Related Health Problems (21), and excluded non-melanoma skin cancer because it is under-ascertained by the cancer registries (24). Likewise, analyses by cancer site included

only those coded to malignant, with the exception of central nervous system tumours for which non-malignant tumours were also included.

SMRs and SIRs were calculated for the entire cohort, by sex, by most common type of specific translocations, and by age at and calendar period of cytogenetic diagnosis and attained age. In order to investigate the possibility that mortality or cancer incidence might have been biased because some subjects were cytogenetically tested as a consequence of a prior illness, analyses were repeated after excluding from follow-up the first 36 months after cytogenetic diagnosis, because effects of such bias, if present, would be expected to 'wear off' over time.

Results

We ascertained 2590 patients with balanced Robertsonian translocations. Among these, for 574 subjects insufficient identifying information was available for flagging at NHSCR. A further 12 subjects were excluded because they could not be followed up, and 17 subjects because they were cytogenetically tested as a consequence of a diagnosis of cancer. A total of 1,987 subjects were therefore included in the cohort.

A preponderance of the cohort overall were female (59.4%) (Table 1). The greatest female excess was among those diagnosed aged 15-44 (63.0%), whereas there was no appreciable female excess among those diagnosed in childhood (50.4% female) (not in table). Nearly one third of carriers (30.8%) were diagnosed at ages 25-34 years and the majority of carriers (62.4%) were diagnosed during 1990-2006. Robertsonian translocations most frequently involved chromosomes 13 and 14 (62.8%) or chromosomes 14 and 21 (19.6%), with other combinations being much less common.

During mortality follow-up, 257 subjects died, 86 subjects exited the study when they reached age 85, 92 exited because of emigration or other reasons, and 1,552 were followed until the end of the study. The average follow-up was 24.1 (ranging from 0.01 to 55.0) years per subject.

Overall mortality in the cohort relative to the general population was non-significantly reduced (SMR=0.92, 95% CI: 0.81, 1.04), corresponding to 44.5 fewer cases per 100,000 population (Table 2). Mortality ratios were somewhat lower for males (SMR=0.87, 95% CI: 0.73, 1.03) than for females (SMR=0.98, 95% CI: 0.82, 1.17) and lower for subjects

diagnosed since 1980 compared with earlier (not shown). Mortality from congenital anomalies was significantly raised (SMR=4.72, 95% CI: 1.53, 11.0), with the five deaths being from heterogeneous anomalies and four occurring within 3 years of cytogenetic diagnosis.

Analyses of SMRs by age at cytogenetic diagnosis showed raised mortality in patients diagnosed in childhood (SMR=2.00, 95% CI: 1.09, 3.35, age 0-14 years) (Table 3). Cause-specific mortality was significantly raised for nervous system disease (SMR=11.9, 95% CI: 3.25, 30.5) and congenital anomalies (SMR=14.6, 95% CI: 4.74, 34.1). When we repeated the analyses excluding follow-up <36 months after cytogenetic diagnosis, the SMRs for mortality from all causes (SMR=0.71, 95% CI: 0.19, 1.83) and from congenital abnormalities or nervous system disease were no longer significantly raised (not shown).

Mortality among subjects diagnosed at ages 15-44 was similar to that in the general population (SMR=1.06, 95% CI: 0.86, 1.28). In those diagnosed at age ≥45, mortality was significantly reduced (SMR=0.81, 95% CI: 0.68, 0.95) (Table 3), to a similar extent in males and females (SMR 0.82 and 0.80, respectively, not in table). Risk was decreased in particular for circulatory disease (SMR=0.76, 95% CI: 0.58, 0.99), including ischaemic heart disease (SMR=0.57, 95% CI: 0.36, 0.85) and cardiac disease (SMR=0.59, 95% CI: 0.35, 0.94) (not in table). Analyses of mortality from cancer showed a decreased risk for colorectal cancer in carriers overall, but no association for other cancer sites (Table 4).

Mortality for the two main types of translocations, rob(13;21) and rob(14;21), separately were not materially different from the overall results except for raised mortality of diseases of the nervous system in rob(14;21) carriers (Table S1) and that all deaths from myeloma occurred

in rob(13;14) carriers (SMR=5.02, 95% CI: 1.37, 12.9 for overall follow-up and SMR=2.44, 95% CI: 0.50, 7.14 for ≥36 months of follow-up) (not in table).

The analyses of cancer incidence included 1981 subjects (Table 4). During follow-up, 202 malignant neoplasms and four non-malignant nervous system tumours occurred (Table 4). Risk was raised for non-Hodgkin lymphoma (SIR=1.90, 95% CI: 1.01, 3.24). The cases occurred 5-31 years after cytogenetic diagnosis and the SIR remained significant after excluding the first 36 months of follow-up. Twelve of the 13 cases involved chromosome 14 including 9 with rob(13;14) (SIR=2.12, 95% CI: 0.97, 4.03 for rob(13;14) carriers) (table S2). Risks for other types of haematological cancer in the patients overall were not raised (Table 4).

Risk of breast cancer incidence not significantly raised overall (SIR=1.27, 95% CI: 0.94, 1.67) (Table 4) and by age at cytogenetic diagnosis (SIR=0 for age <15, 1.26 for age 15-44 and 1.39 for age 45-84 years) (not in table). Risk was significantly raised, however, in rob(13;14) (SIR=1.58, 95% CI: 1.12, 2.15), but not rob(14;21) (SIR=0.73, 95% CI: 0.27, 1.59) carriers (Table S2). After excluding follow-up in the first 36 months after cytogenetic diagnosis, the SIR for breast cancer in rob(13;14) carriers remained significantly raised (not shown). Risk of colorectal cancer was borderline significantly reduced in rob(13;14) carriers (SIR=0.45, 95% CI: 0.17, 0.99) (Table S2).

In analyses of haematological disorders by attained age, carriers were at increased risk of leukaemia diagnosed in childhood (age 0-14 years) (SIR=14.5, 95% CI: 1.75, 52.2) (Table 5). The 2 cases were diagnosed with acute lymphoblastic leukaemia 2 and 10 years after cytogenetic diagnosis, respectively. One patient had a constitutional translocation rob(15;21)

(SIR=447.8, 95% CI: 11.3, 2495 for leukaemia of any type at ages 0-14 years among rob(15;21) carriers) and the other rob(13;14) (SIR=11.74, 95% CI: 0.30, 65.4 among rob(13;14) carriers) (not in table). Among the 13 cases with non-Hodgkin lymphoma, 11 were diagnosed at age 45 and over (SIR=1.89, 95% CI: 0.95, 3.38). In analyses by age at cytogenetic diagnosis, SIRs were not significantly raised for haematological disorders (Table S3).

We ascertained reasons for referral for cytogenetic testing among 250 patients postnatally diagnosed at the Wessex Regional Genetics Laboratory. Among subjects cytogenetically tested under age 20 years, the main reasons were a family history of Robertsonian translocation or other abnormality (48%), or abnormalities and developmental delay (34%). Among those diagnosed at ages 20-44, the main reasons were offspring with a Robertsonian translocation or Down's (40%), other family history of such abnormalities (28%) or fertility-related problems (24%). Subjects diagnosed at older ages were predominantly referred because they were parents (62%) or other relatives (24%) of individuals with cytogenetic abnormalities.

Discussion

Our study is the first to report on mortality and site-specific cancer risks in carriers of balanced Robertsonian translocations. It has the strength that it was prospective, based on carriers from a large population over a long period of follow-up, and that mortality and cancer outcome data were collected in an unbiased manner and could be compared against population rates. Overall mortality rates were similar to those expected based on general population rates, but we observed differences in age-specific mortality. Cancer risks overall were also similar, consistent with the only other, much smaller, cohort study of 730 carriers from Denmark, which only reported on overall cancer incidence (25). Site-specific analyses in our study showed, however, significant increased risks of non-Hodgkin lymphoma and childhood leukaemia in carriers overall, and of breast cancer in rob(13;14) carriers.

The years for which we extracted records varied by cytogenetic centre depending on the years the centre was operational, availability of historical records and the calendar period of extraction. We estimate that we extracted information for 55% of all individuals diagnosed in Great Britain during 1962-2006. This is unlikely to lead to bias, however, as the availability of records for operational reasons is expected to be unrelated to later cancer incidence and mortality. Most carriers are not detected unless they get referred for cytogenetic testing for experiencing problems with reproductive problems or abnormalities in offspring. We estimate, for the years we have the greatest numbers of carriers (1988-1998), that 20% of carriers are eventually diagnosed, based on a newborn prevalence of 1 in 1000 and the number of births in Great Britain during this period. Our study is therefore of patients with Robertsonian translocations who are diagnosed, but from a clinical and counselling perspective this is the group of cases of relevance. However, the selective forces that lead to diagnosis are then important in the interpretation of our results. Information from the Wessex

centre showed that in subjects diagnosed in childhood, referral for cytogenetic testing and hence diagnosis of a balanced Robertsonian translocation was often a consequence of existing morbidity. The effect of such referral bias would be expected to be greatest in the early years after cytogenetic diagnosis and diminish with time. The observation that SMRs for patients diagnosed with balanced Robertsonian translocation in childhood were not raised after excluding the first 36 months of follow-up suggests that the raised SMRs for these patients were due to such bias.

The majority of carriers were diagnosed at ages 15-44, with their referral reasons related to infertility or having offspring with cytogenetic abnormalities. We observed that mortality in this group was comparable to that of the general population but that mortality was reduced among carriers diagnosed at ages 45 and over, in particular from circulatory disease. The age-specificity of this finding suggests a role of referral bias rather than a genetic effect. Data on referral reasons in Wessex suggest that older subjects are usually referred for testing because of cytogenetic abnormality in their own children or other relatives. Reduced mortality in subjects diagnosed later in life might therefore be due to a selective referral of subjects who are physically well enough to have had children of their own and willing and well enough to be cytogenetically tested (26). Additionally, although the national health system of Great Britain provides access to cytogenetic testing free-of-charge to those who are referred, it is possible that carriers who are diagnosed at later ages have a higher socioeconomic status than the general population, which is associated with lower overall and cardiovascular mortality (27).

The reason for referral for cytogenetic testing, and hence degree of referral bias, may also depend on karyotype or sex (4, 28). We observed a strong preponderance of female carriers

overall, which was most pronounced at female reproductive ages, whereas there was no female excess among carriers diagnosed in childhood. The reason for the disparity in numbers by sex is therefore likely to be related to reproduction-related reasons for referral. We found, however, no evidence that mortality rates were different between rob(13;14) and rob(14;21), or between males and females.

Rob(13;14) and rob(14;21) constituted 82.4% of all translocations in our cohort, in range with previous estimates of 74-85% (10, 11). The preferential formation of these karyotypes is thought to be consequence of recombination between inverted homologous sequences shared by these chromosomes (11, 29). Breakpoints in these translocations have been reported to be very consistent and localized to specific regions in the proximal acrocentric short arms, preferentially in satellite III DNA, resulting in a dicentric chromosome (12, 29). Translocations involving other combinations of chromosomes are much less common, in particular between homologous chromosomes. For these translocations, breakpoints are variable and it is thought that they might be formed through a different mechanism (2, 11-13).

The risk of non-Hodgkin lymphoma in balanced Robertsonian translocation carriers does not appear to have been investigated before and while acquired reciprocal translocations are common in lymphoma and leukaemia (30), the mechanism by which carriers might be predisposed is not clear. Pathak proposed in 1986 that constitutional translocations, specifically rob(13;14), may predispose to T- or B-cell malignancies, depending on the breakpoint in chromosome 14 (14). This author postulated that predisposition to T-cell malignancy might result due to a break in 14q11 (T-cell alpha-receptor locus), whereas predisposition to a B-cell malignancy, which includes most non-Hodgkin lymphomas, could be due to a tandem t(13;14) translocation with a breakpoint at 14q32. It is not clear, however,

how the breakpoints involved in balanced Robertsonian translocations could affect predisposition to malignancy. Welborn reported that acquired Robertsonian translocations occur in haematological malignancies in 1 in 300-400 patients and that 60% of these translocations are isochromosomes 13, 14 or 21 (31).

Li et al (2014) recently estimated that constitutional rob(15;21) carriers are at >2700-fold increased risk of iAMP21-ALL, an rare form of ALL involving amplification of chromosome 21, and proposed a novel mechanism for cancer predisposition (20). However, their risk estimate was based on the number of constitutional rob(15;21) carriers in a series of iAMP-ALL cases and the estimated frequency of rob(15;21) from newborn surveys. Our study is the first prospective investigation of this hypothesis. Rob(15;21) is very rare, with our cohort including only 35 carriers, including five karyotyped aged <15 years. One carrier developed ALL aged <15 years, corresponding to a significant ~450-fold increased risk, albeit with a wide confidence interval. We estimate that, if this association were causal, the cumulative risk of leukaemia (of all subtypes) to the age of 15 in t(15;21) carriers is 28% (between 0.8-83% based on the confidence interval of the SIR). Among the 500-600 new childhood cases of leukaemia in Great Britain annually, about 4 might be t(15;21) carriers, but our estimates are uncertain because they are based on one case only. We have no information on tumour profile and therefore do not know whether our case had iAMP-ALL, given that IAMP constitutes only 2.1% of all ALL cases (32), but iAMP-ALL patients have been reported to be somewhat older than ALL patients overall (20), consistent with our patient. Our study therefore supports the hypothesis of increased susceptibility of rob(15;21) carriers to acute lymphoblastic leukaemia.

There are no previous data on breast cancer risk in balanced Robertsonian translocation carriers. The observed significantly raised risk in rob(13;14) carriers could be a result of chance or because nulliparity and delayed child birth are risk factors for breast cancer. However, given the age-specific differences in referral reasons, the similar SIRs for women cytogenetically diagnosed aged 15-44 and 45-84 argues somewhat against the latter. Raised breast cancer rates could also arise if our cohort is of higher socioeconomic profile than the general population overall, breast cancer rates being greater in higher socioeconomic strata (33). However, alternatively, it might be that the finding reflects a previously undiscovered genetic cause.

We also observed decreased mortality from colorectal cancer in carriers overall and decreased incidence of this cancer in rob(13;14) carriers, but not in carriers overall. Mortality, but not incidence, of myeloma in rob(13;14) carriers was raised. Given that the relative risks were not consistent between analyses, we regard these results as inconclusive and the findings would need re-examination in other studies.

In conclusion, our study suggests that subjects diagnosed with balanced Robertsonian translocations may be at increased risk of childhood leukaemia and non-Hodgkin lymphoma and those diagnosed with rob(13;14) might have a raised breast cancer risk, but that their mortality is not raised compared with that in the general population. These findings might be related to genetic factors as well as to factors associated with reasons for referral for cytogenetic testing.

Acknowledgement section

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Grants and financial support

We thank the Medical Research Council for funding this study. Minouk Schoemaker and Michael Jones ares funded by Breast Cancer Now. The Institute of Cancer Research acknowledges National Health Service funding to the Royal Marsden/Institute of Cancer Research National Institute for Health Research Biomedical Research Centre.

Acknowledgements

We are extremely grateful to Professor Patricia Jacobs for her valuable input over the years. We thank D Allen, F Barber, C Maguire, P Murnaghan, M Pelerin and M Swanwick for data collection; E Boyd, D Couzin, J Delhanty, P Ellis, M Faed, J Fennell, A Kessling, A McDermott, A Parkin, A Potter and D Ravine for access to data, N Mudie & A Hart for help in coding, H Nguyen, A Butlin and S Drummond for data entry, J Hemming, J Palmer and Z Qiao for computer programming, M Collinson, N Dennis, the NHSCRs and cancer registries of England, Wales and Scotland for follow-up data.

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Wales, Cardiff, UK (Peter Thompson); Wessex Regional Genetics Laboratory, Salisbury NHS Foundation Trust, Salisbury, UK (Christine Waterman); North West Thames Regional Genetics Service, Northwick Park & St Marks NHS Trust, Middlesex, UK (Catherine Waters). We additionally thank the following centres for providing data: West of Scotland Regional Genetics Service, Yorkhill NHS Trust, Glasgow, UK; East Anglia Regional Genetics Service, Addenbrookes Hospital, Cambridge, UK.

Conflict of interest: none declared

Table 1: Characteristics of the cohort of subjects cytogenetically diagnosed with balanced Robertsonian translocations during 1962-2006 (varying by centre) in Great Britain

Characteristic	No.	%	Person-years
Sex			
Male	807	40.6	19,355
Female	1180	59.4	28,543
Age at diagnosis (years)			
0-4	240	12.1	6,306
5-14	110	5.5	3,283
15-24	318	16.0	8,488
25-34	612	30.8	15,033
35-44	333	16.8	7,831
45-64	289	14.5	6038
65-84	85	4.3	918
Year of diagnosis			
1962-1969	121	6.1	4,064
1970-1979	181	9.1	6,351
1980-1989	445	22.4	12,315
1990-2006	1,240	62.4	25,169
Year of birth			
<1950	544	27.4	12,926
1950-1969	935	47.1	23,079
1970-1989	378	19.0	9,302
1990-2005	130	6.5	2,592
Chromosomes involved			
13;13	2	0.1	58
13;14	1,248	62.8	29,967
13;15	55	2.8	1,225
13;21	20	1.0	490
13;22	20	1.0	483
14;14	5	0.3	100
14;15	52	2.6	1,129
14;21	390	19.6	9,438
14;22	57	2.9	1,303
15;15	2	0.1	35
15;21	35	1.8	816
15;22	35	1.8	942
21;21	6	0.3	179
21;22	38	1.9	1,101
22;22	10	0.5	277
Other[a]	12	0.6	356
Total	1,987	100.0	47,899

a) Including 7 Robertsonian translocations between two D group chromosomes, 4 between a D and G group chromosome, and 1 patient mosaic for two different Robertsonian translocations

Table 2: Cause-specific mortality in 1,987 subjects with balanced Robertsonian translocations cytogenetically diagnosed during 1962-2006 in Great Britain

ICD-9 Code	Cause	No. of deaths	SMR	95% CI	AER
140-208	All malignant neoplasms	81	0.88	0.70, 1.10	-22.5
240-279	Endocrine, nutritional, metabolic, immunity	3	0.71	0.15, 2.07	-2.6
290-319	Mental disorders	4	0.70	0.19, 1.80	-3.5
320-389	Diseases of the nervous system	12	1.57	0.81, 2.75	9.1
390-459	Diseases of the circulatory system	83	0.86	0.69, 1.07	-28.4
410-414	Ischaemic heart disease	42	0.77	0.55, 1.04	-26.4
410	Acute myocardial infarction	29	0.91	0.61, 1.30	-6.3
420-429	Other heart disease	8	1.01	0.44, 1.99	0.20
430-437	Cerebrovascular disease	20	0.93	0.57, 1.43	-3.2
460-519	Diseases of the respiratory system	30	1.01	0.68, 1.44	0.70
480-486	Pneumonia	11	1.11	0.55, 1.98	2.2
490-494, 496	Chronic lower respiratory disease	10	0.67	0.32, 1.24	-10.2
520-579	Diseases of the digestive system	13	0.90	0.48, 1.53	-3.1
570-572, 573.0, 573.3-573.9	Liver disease	7	1.05	0.42, 2.17	0.71
580-629	Diseases of the genitourinary system	3	0.89	0.18, 2.59	-0.80
710-739	Musculoskeletal system and connective tissue	1	0.63	0.02, 3.48	-1.30
740-759	Congenital anomalies	5	4.72[a]	1.53, 11.0	8.2
800-999	Accidents and violence	14	0.96	0.52, 1.60	-1.33
001-999	All causes[b]	257	0.92	0.81, 1.04	-44.5

Abbreviations: AER, absolute excess rate, number of excess deaths per 100,000 population per annum; CI, confidence interval; ICD, International Statistical Classification of Diseases, 9th revision (21); SMR, standardised mortality ratio

a) two-sided P-value based on exact method $p<0.01$

b) Includes 8 deaths from causes not listed individually in the table (4 unknown, 2 senility, 1 infarction of spleen, 1 myelodysplastic syndrome)

Table 3: Cause-specific mortality in 1,987 subjects cytogenetically diagnosed with balanced Robertsonian translocations during 1962-2006 in Great Britain, by age at cytogenetic diagnosis

		Age at cytogenetic diagnosis (years)								
		0-14			15-44			45-84		
ICD-9 code	Cause	No.	SMR	95% CI	No.	SMR	95% CI	No.	SMR	95% CI
140-208	All malignant neoplasms	0	0.00	0.0, 3.08	34	0.96	0.67, 1.34	47	0.85	0.63, 1.13
240-279	Endocrine, nutritional, metabolic, immunity	0	0.0	0.0, 22.5	1	0.63	0.02, 3.52	2	0.80	0.10, 2.90
290-319	Mental disorders	0	0.0	0.0, 13.5	2	1.06	0.13, 3.82	2	0.57	0.07, 2.05
320-389	Diseases of the nervous system	4	11.9[a]	3.25, 30.5	4	1.31	0.36, 3.34	4	0.95	0.26, 2.43
390-459	Diseases of the circulatory system	0	0.0	0.0, 5.03	28	1.18	0.78, 1.70	55	0.76[b]	0.58, 0.99
460-519	Diseases of the respiratory system	1	2.83	0.07, 15.8	9	1.25	0.57, 2.37	20	0.91	0.56, 1.40
520-579	Diseases of the digestive system	1	2.50	0.06, 13.9	6	0.84	0.31, 1.83	6	0.86	0.32, 1.88
580-629	Diseases of the genitourinary system	0	0.0	0.0, 103.9	1	1.19	0.03, 6.64	2	0.80	0.10, 2.88
710-739	Musculoskeletal system and connective tissue	0	0.0	0.0, 141.0	1	1.97	0.05, 11.0	0	0.0	0.0, 3.46
740-759	Congenital anomalies	5	14.6[a]	4.74, 34.1	0	0.0	0.0, 6.93	0	0.0	0.0, 19.9
800-999	Accidents and violence	1	0.48	0.01, 2.65	10	1.11	0.53, 2.05	3	0.84	0.17, 2.47
001-999	All causes[c]	14	2.00[b]	1.09, 3.35	99	1.06	0.86, 1.28	144	0.81[b]	0.68, 0.95

Abbreviations: CI, confidence interval; ICD, International Statistical Classification of Diseases, 9th revision (21); SMR, standardised mortality ratio
a) two-sided P-value based on exact method $p<0.001$
b) two-sided P-value based on exact method $p<0.05$
c) Includes 8 deaths from causes not listed individually in the table (4 unknown, 2 senility, 1 infarction of spleen, 1 myelodysplastic syndrome)

Table 4: Cancer incidence and mortality in subjects cytogenetically diagnosed with balanced Robertsonian translocations during 1962-2006 in Great Britain

		Incidence (carriers n=1981)			Mortality (carriers n=1987)		
ICD-9 code	Cancer site	No.	SIR	95% CI	No.	SMR	95% CI
140-171, 173-208	All malignant neoplasms[a]	202	1.05	0.91, 1.20	81	0.88	0.70, 1.10
141-149	Tongue, mouth, pharynx	6	1.41	0.52, 3.07	1	0.68	0.02, 3.79
150	Oesophagus	3	0.69	0.14, 2.02	5	1.24	0.40, 2.88
151	Stomach	6	1.21	0.45, 2.62	2	0.55	0.07, 1.99
153, 154	Colon and rectum	14	0.65	0.35, 1.09	3	0.33[b]	0.07, 0.97
155	Liver	1	0.52	0.01, 2.91	1	0.55	0.01, 3.09
157	Pancreas	4	0.92	0.25, 2.35	5	1.18	0.38, 2.75
162	Lung	23	0.88	0.56, 1.32	18	0.79	0.47, 1.26
163	Pleura	2	1.93	0.23, 6.97	0	0.0	0.0, 10.3
170	Bone	1	2.76	0.07, 15.4	0	0.0	0.0, 18.5
172	Cutaneous melanoma	8	1.08	0.47, 2.14	1	0.82	0.02, 4.57
174, 175	Breast	50	1.27	0.94, 1.67	13	1.42	0.76, 2.44
179,182	Corpus uteri	5	0.95	0.31, 2.21	0	0.0	0.0, 3.51
180	Cervix	2	0.55	0.07, 2.00	0	0.0	0.0, 3.18
183	Ovary	6	1.09	0.40, 2.36	1	0.32	0.01, 1.81
184.0-184.4	Vagina & vulva	2	2.20	0.27, 7.95	1	4.12	0.10, 22.9
185	Prostate	23	1.42	0.91, 2.14	6	1.53	0.56, 3.34
186	Testis	1	0.67	0.02, 3.72	0	0.0	0.0, 44.0
187.1-187.4	Penis	2	7.01	0.85, 25.3	0	0.0	0.0, 56.7
188	Bladder and urethra	5	0.85	0.28, 1.98	4	1.66	0.45, 4.26
189	Kidney and ureter	1	0.20	0.01, 1.13	1	0.49	0.01, 2.71
190	Eye	1	2.46	0.06, 13.7	0	0.0	0.0, 50.0
191, 192, 225, 237.5, 237.6, 237.9, 239.6	Nervous system tumours, including benign[c]	8	1.47	0.64, 2.90	3	0.95	0.20, 2.78
193	Thyroid	2	1.13	0.14, 4.06	0	0.0	0.0, 18.8
196.0-199.1	Unknown primary site	5	0.81	0.26, 1.88	6	0.88	0.32, 1.91
200, 202	Non-Hodgkin lymphoma	13	1.90[b]	1.01, 3.24	4	1.57	0.43, 3.24
201	Hodgkin disease	1	0.79	0.02, 4.39	1	3.68	0.09, 20.5
203	Myeloma	4	1.76	0.48, 4.48	4	3.06	0.83, 7.81
204-208	Leukaemia	6	1.39	0.51, 3.02	0	0.0	0.0, 1.61

Abbreviations: ; CI, confidence interval; ICD, International Statistical Classification of Diseases, 9th revision (21); SIR, standardised incidence ratio; SMR, standardised mortality ratio

a) All malignant neoplasms except non-melanoma skin cancer. 1 death (from malignancy of 'other' part of digestive system) and 1 incident cancer (maxillary sinus) were not listed individually.

b) two-sided P-value based on exact method $p<0.01$

c) The 8 observed incident tumours included comprise 4 malignant cancers of the brain and 4 benign neoplasms of the meninges. For England and Wales, benign nervous system neoplasms were included from the year 1971, for Scotland from the year 2000. The three deaths for nervous system tumours were all malignant.

Table 5: Incidence of malignancies overall and of haematological malignancies in subjects cytogenetically diagnosed with balanced Robertsonian translocations during 1962-2006 in Great Britain, by attained age

		Attained age (years)								
		0-14			15-44			45-84		
ICD-9 code	Cause	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI
140-171, 173-208	All malignant neoplasms[a]	3	6.86[b]	1.41, 20.1	23	1.02	0.65, 1.53	176	1.04	0.89, 1.20
200, 202	Non-Hodgkin lymphoma	1	32.1	0.81, 179	1	0.99	0.03, 5.53	11	1.89	0.94, 3.38
201	Hodgkin disease	0	0.0	0.0, 151	1	1.43	0.04, 7.96	0	0.0	0.0, 6.77
203	Myeloma	0	0.0	0.0, 30122	0	0.0	0.0, 37.6	4	1.83	0.50, 4.69
204-208	Leukaemia	2	14.5[b]	1.75, 52.2	0	0.0	0.0, 6.14	4	1.12	0.31, 2.86

Abbreviations: CI, confidence interval; ICD, International Statistical Classification of Diseases, 9th revision (21); SIR, standardised incidence ratio

a) All malignant neoplasms except non-melanoma skin cancer.

b) two-sided P-value based on exact method $p<0.05$

Table S1: Cause-specific mortality in subjects cytogenetically diagnosed with balanced Robertsonian translocations during 1962-2006 in Great Britain, for translocations involving chromosomes 13 and 14 and chromosomes 14 and 21

		Chromosomes involved							
		rob(13;14)				rob(14;21)			
ICD-9	Cause	No.	SMR	95% CI	AER	No.	SMR	95% CI	AER
140-208	All malignant neoplasms	55	0.97	0.73, 1.27	-4.80	14	0.74	0.40, 1.24	-52.2
240-279	Endocrine, nutritional, metabolic, immunity	2	0.77	0.09, 2.78	-2.00	1	1.15	0.03, 6.41	1.40
290-319	Mental disorders	3	0.87	0.18, 2.55	-1.50	1	0.83	0.02, 4.60	-2.20
320-389	Diseases of the nervous system	2	0.43	0.05, 1.55	-8.90	6	3.68[a]	1.35, 8.01	46.3
390-459	Diseases of the circulatory system	54	0.90	0.68, 1.17	-20.3	14	0.75	0.41, 1.26	-48.9
460-519	Diseases of the respiratory system	17	0.93	0.54, 1.49	-4.10	6	0.99	0.36, 2.15	-0.70
520-579	Diseases of the digestive system	7	0.78	0.31, 1.60	-6.70	4	1.38	0.38, 3.54	11.7
580-629	Diseases of the genitourinary system	2	0.96	0.12, 3.46	-0.30	0	0.0	0.0, 5.38	-7.30
710-739	Musculoskeletal system and connective tissue	0	0.0	0.0, 3.77	-3.30	1	2.81	0.07, 15.6	6.82
740-759	Congenital anomalies	2	3.12	0.38, 11.3	4.50	1	4.79	0.12, 26.5	8.40
800-999	Accidents and violence	11	1.18	0.59, 2.11	5.60	2	0.74	0.09, 2.65	-7.70
001-999	All causes[b]	160	0.93	0.79, 1.09	-40.5	50	0.90	0.67, 1.18	-60.8

Abbreviations: AER, absolute excess rate, number of excess deaths per 100,000 population per annum; CI, confidence interval; ICD, International Statistical Classification of diseases, 9th revision (21); SMR, standardised mortality ratio

a) two-sided P-value based on exact method $p<0.05$

b) The causes of five deaths in subjects diagnosed with rob(13;14) are not listed separately (2 not known, 1 senility, 1 myelodysplastic syndrome, 1 infarction of spleen)

Table S2: Cancer incidence in subjects cytogenetically diagnosed with balanced Robertsonian translocations during 1962-2006 in Great Britain, for translocations involving chromosomes 13 and 14 and chromosomes 14 and 21

		rob(13;14)			rob(14;21)		
ICD-9 code	Cancer site	No.	SIR	95% CI	No.	SIR	95% CI
140-171, 173-208	All malignant neoplasms[a]	131	1.10	0.92, 1.31	39	0.98	0.70, 1.34
141-149	Tongue, mouth, pharynx	4	1.51	0.41, 3.88	1	1.22	0.03, 6.77
150	Oesophagus	2	0.76	0.09, 2.74	1	1.14	0.03, 6.34
151	Stomach	5	1.64	0.53, 3.82	1	1.01	0.03, 5.63
153, 154	Colon and rectum	6	0.45[b]	0.17, 0.99	6	1.34	0.49, 2.91
155	Liver	1	0.85	0.02, 4.76	0	0.0	0.00, 9.45
157	Pancreas	1	0.37	0.01, 2.08	1	1.09	0.03, 6.05
162	Lung	15	0.93	0.52, 1.54	4	0.78	0.21, 1.98
163	Pleura	1	1.62	0.04, 9.00	0	0.0	0.0, 16.9
170	Bone	1	4.43	0.11, 24.7	0	0.0	0.0, 52.3
172	Cutaneous melanoma	4	0.88	0.24, 2.24	3	1.98	0.41, 5.77
174, 175	Breast	39	1.58[c]	1.12, 2.15	6	0.73	0.27, 1.59
179,182	Corpus uteri	4	1.21	0.33, 3.09	0	0.0	0.0, 3.21
180	Cervix	2	0.89	0.11, 3.23	0	0.0	0.0, 4.94
183	Ovary	3	0.87	0.18, 2.54	1	0.83	0.02, 4.65
184.0-184.4	Vagina & vulva	1	1.76	0.04, 9.80	0	0.0	0.0, 18.8
185	Prostate	14	1.47	0.80, 2.47	4	1.18	0.32, 3.02
186	Testis	0	0.0	0.0, 3.75	1	3.77	0.10, 21.0
187.1-187.4	Penis	1	5.73	0.14, 31.9	1	18.4	0.47, 103
188	Bladder and urethra	3	0.83	0.17, 2.44	0	0.0	0.0, 3.08
189	Kidney and ureter	0	0.00	0.00, 1.23	0	0.0	0.0, 3.65
190	Eye	0	0.00	0.00, 14.7	1	12.6	0.32, 69.4
191, 192, 225, 237.5, 237.6, 237.9, 239.6	Nervous system tumours, including benign[b]	6	1.78	0.65, 3.87	2	1.78	0.22, 6.45
193	Thyroid	0	0.0	0.0, 3.35	1	2.71	0.07, 15.1
196.0-199.1	Unknown primary site	3	0.79	0.16, 2.31	1	0.77	0.02, 4.27
200, 202	Non-Hodgkin lymphoma	9	2.12	0.97, 4.03	3	2.10	0.43, 6.14
201	Hodgkin disease	0	0.00	0.00, 4.66	1	3.96	0.10, 22.1
203	Myeloma	4	2.87	0.78, 7.34	0	0.0	0.0, 7.60
204-208	Leukaemia	4	1.51	0.41, 3.86	1	1.12	0.03, 6.27

Abbreviations: CI, confidence interval; ICD, International Statistical Classification of Diseases, 9th revision (21); SIR, standardised incidence ratio

a)All malignant neoplasms except non-melanoma skin cancer. 1 cancer (maxillary sinus) is not listed separately under the rob(13;14).
b) two-sided P-value based on exact method $p<0.05$
c) two-sided P-value based on exact method $p<0.01$
d) The 8 observed tumours included comprise 4 malignant cancers of the brain and 4 benign neoplasms of the meninges. For England and Wales, benign nervous system neoplasms were included from the year 1971 for Scotland, from the year 2000.

Table S3: Incidence of cancer overall and of haematological malignancies in subjects cytogenetically diagnosed with balanced Robertsonian translocations during 1962-2006 in Great Britain, by age at cytogenetic diagnosis

		Age at cytogenetic diagnosis (years)								
		0-14			15-44			45-84		
ICD-9 code	Cause	No.	SIR	95% CI	No.	SIR	95% CI	No.	SIR	95% CI
140-171, 173-208	All malignant neoplasms[a]	5	1.07	0.35, 2.50	104	1.09	0.89, 1.32	93	1.01	0.82, 1.24
200, 202	Non-Hodgkin lymphoma	1	4.24	0.11, 23.6	7	1.93	0.78, 3.98	5	1.66	0.54, 3.88
201	Hodgkin disease	1	4.51	0.11, 25.1	0	0.0	0.0, 4.43	0	0.0	0.0, 17.2
203	Myeloma	0	0.0	0.0, 162	3	3.16	0.65, 9.23	1	0.76	0.02, 4.25
204-208	Leukaemia	2	6.99	0.85, 25.2	3	1.53	0.32, 4.47	1	0.48	0.01, 2.69

Abbreviations: CI, confidence interval; ICD, International Statistical Classification of diseases, 9th revision (21); SIR, standardised incidence ratio

a) All malignant neoplasms except non-melanoma skin cancer

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