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Original Contribution

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

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A balanced robertsonian translocation (rob) results from fusion of 2 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 1,987 carriers diagnosed in Great Britain for deaths and cancer risk, over an average of 24.1 years. Standardized mortality and incidence ratios were calculated comparing the number of observed events against population rates. Overall mortality was higher for carriers diagnosed before age 15 years (standardized mortality ratio (SMR) = 2.00, 95% confidence interval (CI): 1.09, 3.35), similar for those diagnosed aged 15–44 years (SMR = 1.06, 95% CI: 0.86–1.28), and lower for those diagnosed aged 45–84 years (SMR = 0.81, 95% CI: 0.68, 0.95). Cancer incidence was higher for non-Hodgkin lymphoma (standardized incidence ratio (SIR) = 1.90, 95% CI: 1.01, 3.24) and childhood leukemia (SIR = 14.5, 95% CI: 1.75, 52.2), the latter particularly in rob(15;21) carriers (SIR = 447.8, 95% CI: 11.3, 2,495). Rob(13;14) carriers had a higher 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 leukemia and non-Hodgkin lymphoma and those diagnosed with rob(13;14) of breast cancer.

chromosome disorders; cohort studies; cytogenetics; epidemiology; genetics; hematological malignancies; mortality; neoplasms

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; iAMP, intrachromosomal amplification; rob, robertsonian translocation; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

A balanced robertsonian translocation (rob) involves fusion of 2 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 higher risk of miscarriages, infertility, and aneuploid offspring because of the production of unbalanced gametes. Depending on which chromosomes are involved, carriers are at higher risk of offspring with trisomy 21 (Down syndrome) or trisomy 13 (Patau syndrome) (3, 4).

Balanced robertsonian translocations represent the most common chromosomal rearrangement in humans. Newborn surveys have estimated that they occur in 1 in 1,000 individuals (5–8), with higher estimates (1 in 800) obtained from surveys of children referred for neurodevelopmental disease and congenital abnormalities (9). Translocations are disproportionately 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 hematological disorders in carriers of balanced robertsonian translocations has been suggested (14); evidence for this and for premalignant conditions is, however, derived from case reports (14–19). Recently, carriers of rob(15;21) have been estimated to be at much higher risk of a rare form of acute lymphoblastic leukemia (ALL) with intrachromosomal

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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 leukemia has, however, not been prospectively investigated in robertsonian translocation carriers overall or according to subtype.

To assess risks in individuals with balanced robertsonian translocations, one needs a cohort design in which large numbers of carriers 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 persons diagnosed as carriers at cytogenetic centers in Great Britain.

METHODS

Information on patients diagnosed with balanced robertsonian translocations was obtained from all cytogenetic centers in Great Britain ($n = 27$), except for one small center. Records were collected as far back in time as records had been maintained at each center (in most centers 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 center, 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 National Health Service 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 National Health Service Central Register 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 below in 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 and the national personal information advisory group.

For each cohort member, we calculated person-years at risk of death according to sex, 5-year age group, calendar year, and country (England and Wales combined vs. Scotland). Follow-up started at the date of cytogenetic diagnosis and ended on December 31, 2016, or the 85th birthday, date of death, or date of other loss to follow-up, whichever was earliest. Follow-up was censored at age 85 years 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. Standardized mortality ratios were derived as the ratio of observed to expected deaths, and their 95% confidence intervals were 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 performed with STATA, version 14.2 (StataCorp LLC, College Station, Texas) (23). All significance tests were 2-sided.

Analyses of cancer incidence were conducted similarly, except that follow-up started on January 1, 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 December 31, 2015, the patient's 85th birthday, date of death, or date of other loss to follow-up, whichever was earliest. Standardized incidence ratios 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 Classification of Diseases, Ninth Revision* (21), and excluded nonmelanoma skin cancer because it is underascertained by the cancer registries (24). Likewise, analyses according to cancer site included only those coded to malignant, with the exception of central nervous system tumors, for which nonmalignant tumors were also included.

Standardized mortality ratios and standardized incidence ratios were calculated for the entire cohort, according to sex, most common type of specific translocations, 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 2,590 patients with balanced robertsonian translocations. Among these, insufficient identifying information was available for flagging at the National Health Service Central Register for 574 subjects. 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 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) (data not shown). 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 years, 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 years per subject (ranging from 0.01 to 55.0 years).

Overall mortality in the cohort relative to the general population was nonsignificantly lower (standardized mortality ratio

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Table 1. Characteristics of the Cohort of Persons Cytogenetically Diagnosed With Balanced Robertsonian Translocations, Great Britain, 1962–2006

Characteristic	No. of Persons	%	Person-Years
Sex			
Male	807	40.6	19,355
Female	1,180	59.4	28,544
Age at diagnosis, years			
0–4	240	12.1	6,306
5–14	110	5.5	3,284
15–24	318	16.0	8,489
25–34	612	30.8	15,033
35–44	333	16.8	7,831
45–64	289	14.5	6,038
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			
Before 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 2 D-group chromosomes, 4 between a D- and G-group chromosome, and 1 patient mosaic for 2 different robertsonian translocations.

(SMR) = 0.92, 95% confidence interval (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 (data not shown). Mortality from congenital anomalies was significantly higher (SMR = 4.72, 95% CI: 1.53, 11.0), with the 5 deaths being from heterogeneous anomalies and 4 occurring within 3 years of cytogenetic diagnosis.

Analyses of standardized mortality ratios according to age at cytogenetic diagnosis showed higher mortality in patients diagnosed in childhood (for ages 0–14 years, SMR = 2.00, 95% CI: 1.09, 3.35) (Table 3). Cause-specific mortality was significantly higher 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 standardized mortality ratios 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 higher (data not shown).

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

Mortality for the 2 main types of translocations, rob(13;21) and rob(14;21), separately were not materially different from the overall results except for higher mortality of diseases of the nervous system in rob(14;21) carriers (Web Table 1), and all deaths from myeloma occurred in rob(13;14) carriers (for overall follow-up, SMR = 5.02, 95% CI: 1.37, 12.9; and for ≥36 months of follow-up, SMR = 2.44, 95% CI: 0.50, 7.14) (data not shown).

The analyses of cancer incidence included 1,981 subjects (Table 4). During follow-up, 202 malignant neoplasms and 4 nonmalignant nervous system tumors occurred. Risk was higher for non-Hodgkin lymphoma (standardized incidence ratio (SIR) = 1.90, 95% CI: 1.01, 3.24). The cases occurred 5–31 years after cytogenetic diagnosis, and the standardized incidence ratio 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) (for rob(13;14) carriers, SIR = 2.12, 95% CI: 0.97, 4.03) (Web Table 2). Risks for other types of hematological cancer in the patients overall were not higher (Table 4).

Risk of breast cancer incidence was not significantly higher overall (SIR = 1.27, 95% CI: 0.94, 1.67) (Table 4) or according to age at cytogenetic diagnosis (SIR = 0 for ages <15 years, 1.26 for ages 15–44 years, and 1.39 for ages 45–84 years) (data not shown). Risk was significantly higher, however, in rob(13;14) carriers (SIR = 1.58, 95% CI: 1.12, 2.15), but not rob(14;21) carriers (SIR = 0.73, 95% CI: 0.27, 1.59) (Web Table 2). After excluding follow-up in the first 36 months after cytogenetic diagnosis, the standardized incidence ratio for breast cancer in rob(13;14) carriers remained significantly

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Table 2. Cause-Specific Mortality Among 1,987 Persons Cytogenetically Diagnosed With Balanced Robertsonian Translocations, Great Britain, 1962–2006

ICD-9 Code	Cause	No. of Deaths	SMR	95% CI	AER[a]
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	Ischemic 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[b]	1.53, 11.0	8.2
800–999	Accidents and violence	14	0.96	0.52, 1.60	−1.33
001–999	All causes[c]	257	0.92	0.81, 1.04	−44.5

Abbreviations: AER, absolute excess rate; CI, confidence interval; ICD-9, *International Classification of Diseases, Ninth Revision*; SMR, standardized mortality ratio.

[a] Number of excess deaths per 100,000 population per annum.

[b] Two-sided P value based on exact method; $P < 0.01$.

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

higher (data not shown). Risk of colorectal cancer was borderline significantly lower in rob(13;14) carriers (SIR = 0.45, 95% CI: 0.17, 0.99) (Web Table 2).

In analyses of hematological disorders according to attained age, carriers were at higher risk of leukemia diagnosed in childhood (for ages 0–14 years, SIR = 14.5, 95% CI: 1.75, 52.2) (Table 5). The 2 cases were diagnosed with acute lymphoblastic leukemia 2 and 10 years after cytogenetic diagnosis, respectively. One patient had a constitutional translocation rob(15;21) (for leukemia of any type at ages 0–14 years among rob(15;21) carriers, SIR = 447.8, 95% CI: 11.3, 2,495) and the other rob (13;14) (among rob(13;14) carriers, SIR = 11.74, 95% CI: 0.30, 65.4) (data not shown). Among the 13 cases with non-Hodgkin lymphoma, 11 were diagnosed at age 45 years or older (SIR = 1.89, 95% CI: 0.95, 3.38). In analyses according to age at cytogenetic diagnosis, standardized incidence ratios were not significantly higher for hematological disorders (Web Table 3).

We ascertained reasons for referral for cytogenetic testing among 250 patients postnatally diagnosed at the Wessex Regional Genetics Laboratory. Among subjects cytogenetically tested younger than 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 years, the main reasons were offspring with a robertsonian translocation or Down syndrome (40%), other family history of such abnormalities (28%), or fertility-related problems (24%). Subjects diagnosed at older ages were referred predominantly because they were parents (62%) or other relatives (24%) of individuals with cytogenetic abnormalities.

DISCUSSION

Our study is, to our knowledge, 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 reported only on overall cancer incidence (25). However, site-specific analyses in our study showed significant, higher risks of non-Hodgkin lymphoma and childhood leukemia in carriers overall and of breast cancer in rob(13;14) carriers.

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Table 3. Cause-Specific Mortality Among 1,987 Persons Cytogenetically Diagnosed With Balanced Robertsonian Translocations, According to Age at Cytogenetic Diagnosis, Great Britain, 1962–2006

ICD-9 Code	Cause	Age at Cytogenetic Diagnosis, years								
		0–14			15–44			45–84		
		No. of Deaths	SMR	95% CI	No. of Deaths	SMR	95% CI	No. of Deaths	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-9, *International Classification of Diseases, Ninth Revision*; SMR, standardized 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, and 1 myelodysplastic syndrome).

The years for which we extracted records varied according to cytogenetic center depending on the years the center 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 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 1,000 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 led to diagnosis are then important in the interpretation of our results. Information from the Wessex center 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 standardized mortality ratios for patients diagnosed with balanced robertsonian translocation in childhood were not higher after excluding the first 36 months of follow-up suggests that the higher standardized mortality ratios for these patients were due to such bias.

The majority of carriers were diagnosed at ages 15–44 years, 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 lower among carriers diagnosed at ages 45 or older, 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. Lower 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, which is associated with lower overall and cardiovascular mortality, than the general population (27).

The reason for referral for cytogenetic testing, and hence degree of referral bias, might 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

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Table 4. Cancer Incidence and Mortality in Persons Cytogenetically Diagnosed With Balanced Robertsonian Translocations, Great Britain, 1962–2006

ICD-9 Code	Cancer Site	Incidence (n = 1,981)			Mortality (n = 1,987)		
		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	Esophagus	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 and 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 tumors, including benign tumors[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	Leukemia	6	1.39	0.51, 3.02	0	0.0	0.0, 1.61

Abbreviations: CI, confidence interval; ICD-9, *International Classification of Diseases, Ninth Revision*; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

[a] All malignant neoplasms except nonmelanoma 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 tumors 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 and for Scotland from the year 2000. The tumors of the 3 persons who died with nervous system tumors were all malignant.

by sex is therefore likely to be connected to reproduction-related reasons for referral. We found, however, no evidence that mortality rates were different between rob(13;14) and rob(14;21) carriers 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 a 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).

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Table 5. Incidence of Malignancies Overall and of Hematological Malignancies Among Persons Cytogenetically Diagnosed With Balanced Robertsonian Translocations, by Attained Age, Great Britain, 1962–2006

ICD-9 Code	Cause	Attained Age, Years								
		0–14			15–44			45–84		
		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	Leukemia	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-9, *International Classification of Diseases, Ninth Revision*; SIR, standardized incidence ratio.
[a] All malignant neoplasms except nonmelanoma skin cancer.
[b] Two-sided *P* value based on exact method; $P < 0.05$.

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 leukemia (30), the mechanism by which carriers might be predisposed is not clear. Pathak (14) proposed in 1986 that constitutional translocations, specifically t(13;14), might predispose to T- or B-cell malignancies, depending on the breakpoint in chromosome 14. Pathak 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 (31) reported that acquired robertsonian translocations occur in hematological malignancies in 1 in 300–400 patients and that 60% of these translocations are isochromosomes 13, 14, or 21.

Li et al. (20) recently estimated that constitutional rob(15;21) carriers are at >2,700-fold increased risk of iAMP21-ALL, a rare form of ALL involving amplification of chromosome 21, and proposed a novel mechanism for cancer predisposition. 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 5 karyotyped when aged <15 years. One carrier developed ALL when 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 leukemia (of all subtypes) to the age of 15 years in t(15;21) carriers is 28% (between 0.8% and 83% based on the confidence interval of the SIR). Among the 500–600 new childhood cases of leukemia in Great Britain annually, about 4 might be t(15;21) carriers, but our estimates are uncertain because they are based on 1 case only. We have no information on tumor 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 leukemia.

There are no previous data on breast cancer risk in balanced robertsonian translocation carriers. The observed significantly higher 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 standardized incidence ratios for women cytogenetically diagnosed at ages 15–44 and 45–84 years argues somewhat against the latter. Higher breast cancer rates could also arise if our cohort is of higher socioeconomic profile than the general population overall, breast cancer rates being higher in higher socioeconomic strata (33). However, alternatively, it might be that the finding reflects a previously undiscovered genetic cause.

We also observed lower mortality from colorectal cancer in carriers overall and lower 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 higher. Given that the relative risks were not consistent between analyses, we regard these results as inconclusive, and the findings would need reexamination in other studies.

In conclusion, our study suggests that subjects diagnosed with balanced robertsonian translocations might be at increased risk of childhood leukemia and non-Hodgkin lymphoma, and those diagnosed with rob(13;14) might have a higher breast cancer risk, but that their mortality is not higher 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.

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