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Online Supplementary Material

Cardiovascular sequelae in long term survivors of young people's cancer – a linked cohort study

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eTable 1: Diagnosis and Operations codes used to identify cardiovascular late effects

| Category | ICD-10 Code | Description |
|----------------------------------|--|--|
| Hypertension | I10 | Essential (primary) hypertension |
| | I11 | Hypertensive heart disease |
| | I12 | Hypertensive renal disease |
| | I13 | Hypertensive heart and renal disease |
| | I15 | Secondary hypertension |
| Cardiomyopathy and Heart Failure | I42 | Cardiomyopathy |
| | I43 | Cardiomyopathy in diseases classified elsewhere |
| | I50 | Heart Failure |
| | I51 | Complications and ill-defined descriptions of heart disease |
| | I52 | Other heart disorders in diseases classified elsewhere |
| Coronary Artery Disease | I20 | Angina pectoris |
| | I21 | Acute myocardial infarction |
| | I22 | Subsequent myocardial infarction |
| | I23 | Certain current complications following acute myocardial infarction |
| | I24 | Other acute ischaemic heart diseases |
| | I25 | Chronic ischaemic heart disease |
| Pulmonary Heart Disease | I26 | Pulmonary embolism |
| | I27 | Other pulmonary heart diseases |
| | I28 | Other diseases of pulmonary vessels |
| Pericardial disease | I30 | Acute pericarditis |
| | I31 | Other diseases of pericardium |
| | I32 | Pericarditis in diseases classified elsewhere |
| Valvular Heart Disease | I08 | Multiple valve diseases |
| | I34 | Nonrheumatic mitral valve disorders |
| | I35 | Nonrheumatic aortic valve disorders |
| | I36 | Nonrheumatic tricuspid valve disorders |
| | I37 | Pulmonary valve disorders |
| | I33 | Acute and subacute endocarditis |
| | I38 | Endocarditis, valve unspecified |
| | I39 | Endocarditis and heart valve disorders in diseases classified elsewhere |
| Conduction Disorders | I44 | Atrioventricular and left bundle-branch block |
| | I45 | Other conduction disorders |
| | I46 | Cardiac arrest |
| | I47 | Paroxysmal tachycardia |
| | I48 | Atrial fibrillation and flutter |
| | I49 | Other cardiac arrhythmias |
| Cerebrovascular Disease | I60 | Subarachnoid haemorrhage |
| | I61 | Intracerebral haemorrhage |
| | I62 | Other non traumatic intracranial haemorrhage |
| | I63 | Cerebral Infarction |
| | I64 | Stroke, not specified as haemorrhage or infarction |
| | I65 | Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction |
| | I66 | Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction |
| | I67 | Other cerebrovascular diseases |
| | I68 | Cerebrovascular disorders in diseases classified elsewhere |
| | I69 | Sequelae of cerebrovascular disease |
| G45 | Transient cerebral ischaemic attacks and related syndromes | |

Table continued on next page

| Category | OPCS - 4.5 | Description |
|---------------------------|------------|---|
| | K02 | Other Transplantation of heart |
| | K13 | Transluminal repair of defect of septum |
| | K14 | Other open operations on septum of heart |
| | K16 | Other therapeutic transluminal operations on septum of heart |
| | K23 | Other operations of wall of heart |
| | K25 | Plastic repair of mitral valve |
| | K26 | Plastic repair of aortic valve |
| | K27 | Plastic repair of tricuspid valve |
| | K28 | Plastic repair of pulmonary valve |
| | K29 | Plastic repair of unspecified valve of hear |
| | K30 | Revision of plastic repair of valve of heart |
| | K31 | Open incision of valve of heart |
| | K32 | Closed incision of valve of heart |
| | K33 | Operations on aortic root |
| | K34 | Other open operations on valve of heart |
| | K35 | Therapeutic transluminal operations on valve of heart |
| | K36 | Excision of valve of heart |
| | K38 | Other operations on structure adjacent to valve of heart |
| | K40 | Saphenous vein graft replacement of coronary artery |
| | K41 | Other autograft replacement of coronary artery |
| | K42 | Allograft replacement of coronary artery |
| | K43 | Prosthetic replacement of coronary artery |
| | K44 | Other replacement of coronary artery |
| | K45 | Connection of thoracic artery to coronary artery |
| Operations and Procedures | K46 | Other bypass of coronary artery |
| | K47 | Repair of coronary artery |
| | K48 | Other open operations on coronary artery |
| | K49 | Transluminal balloon angioplasty of coronary artery |
| | K50 | Other therapeutic transluminal operations on coronary artery |
| | K51 | Diagnostic transluminal operations on coronary artery |
| | K52 | Open operations on conducting system of heart |
| | K53 | Other incision of heart |
| | K54 | Open heart assist operations |
| | K55 | Other open operations on heart |
| | K56 | Transluminal heart assist operations |
| | K57 | Other therapeutic transluminal operations on heart |
| | K58 | Diagnostic transluminal operations on heart |
| | K59 | Cardioverter defibrillator introduced through vein |
| | K60 | Cardiac pacemaker system introduced through vein |
| | K61 | Other cardiac pacemaker system |
| | K62 | Therapeutic transluminal operations on heart |
| | K63 | Contrast radiology of heart |
| | K65 | Catherisation of heart |
| | K67 | Excision of pericardium |
| | K68 | Drainage of pericardium |
| | K69 | Incision of pericardium |
| | K71 | Other operations on pericardium |
| | K75 | Percutaneous transluminal ballon angioplasty and insertion of stent into coronary |
| | K77 | Transluminal drainage of pericardium |
| | K78 | Transluminal operations on internal mammary artery side branch |

eTable 2: Number of cases and unadjusted hazard ratios (HRs) for cardiovascular late effects

| | Late Effect N | No Late Effect N | Total (N) | HR (95% CI) | P value |
|---|------------------|---------------------|-------------|------------------|-------------|
| Gender | | | | | |
| Male | 69 | 1857 | 1926 | 1 | |
| Female | 50 | 1271 | 1321 | 1.02 (0.71-1.46) | 0.933 |
| Age at cancer diagnosis | | | | | |
| 0–14 years | 40 | 1327 | 1367 | 1 | |
| 15–29 years | 79 | 1801 | 1880 | 1.69 (1.16-2.48) | 0.007 |
| Diagnostic Group^a | | | | | |
| I: Leukaemia | 23 | 564 | 587 | 1 | |
| II: Lymphoma | 32 | 681 | 713 | 1.10 (0.65-1.89) | 0.719 |
| III: CNS tumours | 16 | 474 | 490 | 0.83 (0.44-1.57) | 0.567 |
| IV – XII: Other solid tumours | 48 | 1409 | 1457 | 0.87 (0.53-1.43) | 0.583 |
| Treatment | | | | | |
| Cx (+/- Sx) | 41 | 1201 | 1242 | 1 | |
| Rt (+/- Sx) | 9 | 312 | 321 | 0.70 (0.34-1.45) | 0.340 |
| Cx & Rt (+/- Sx) | 27 | 464 | 491 | 0.86 (0.52-1.41) | 0.543 |
| Sx alone or no known treatment | 42 | 1151 | 1193 | 0.87 (0.57-1.34) | 0.532 |
| Number of Anthracyclines | | | | | |
| Zero | 88 | 2089 | 2177 | 1 | |
| One | 21 | 835 | 856 | 0.70 (0.43-1.12) | 0.137 |
| Two | 10 | 199 | 209 | 1.52 (0.79-2.93) | 0.209 |
| Three | 0 | 5 | 5 | - | - |
| Radiation to the Chest | | | | | |
| No | 112 | 3026 | 3138 | 1 | |
| Yes | 7 | 102 | 109 | 1.64 (0.76-3.52) | 0.204 |
| Cranial Radiation | | | | | |
| No | 108 | 2905 | 3013 | 1 | |
| Yes | 11 | 223 | 234 | 0.98 (0.53-1.83) | 0.956 |
| Radiation to the Neck | | | | | |
| No | 111 | 2951 | 3062 | 1 | |
| Yes | 8 | 177 | 185 | 1.00 (0.49-2.06) | 0.994 |
| Deprivation quintile^b | | | | | |
| Most Deprived (5) | 45 | 1062 | 1104 | 1 | |
| 4 | 19 | 653 | 672 | 0.72 (0.42-1.24) | 0.230 |
| 3 | 24 | 587 | 611 | 1.02 (0.62-1.69) | 0.484 |
| 2 | 25 | 500 | 525 | 1.19 (0.73-1.96) | 0.927 |
| Least Deprived (1) | 9 | 326 | 335 | 0.64 (0.31-1.33) | 0.235 |
| Total | 119 | 3128 | 3247 | 3128 | 3247 |

^aInternational classification of childhood cancer; ^bIndex of Multiple Deprivation 2007

eTable 3: Use of Anthracyclines – Excess hazard ratios (HR) and 95% confidence intervals (CI) obtained from a Royston-Parma relative survival model, modelling the risk of a cardiovascular late event for long term survivors of childhood and young adult cancer diagnosed between 1991 and 2006

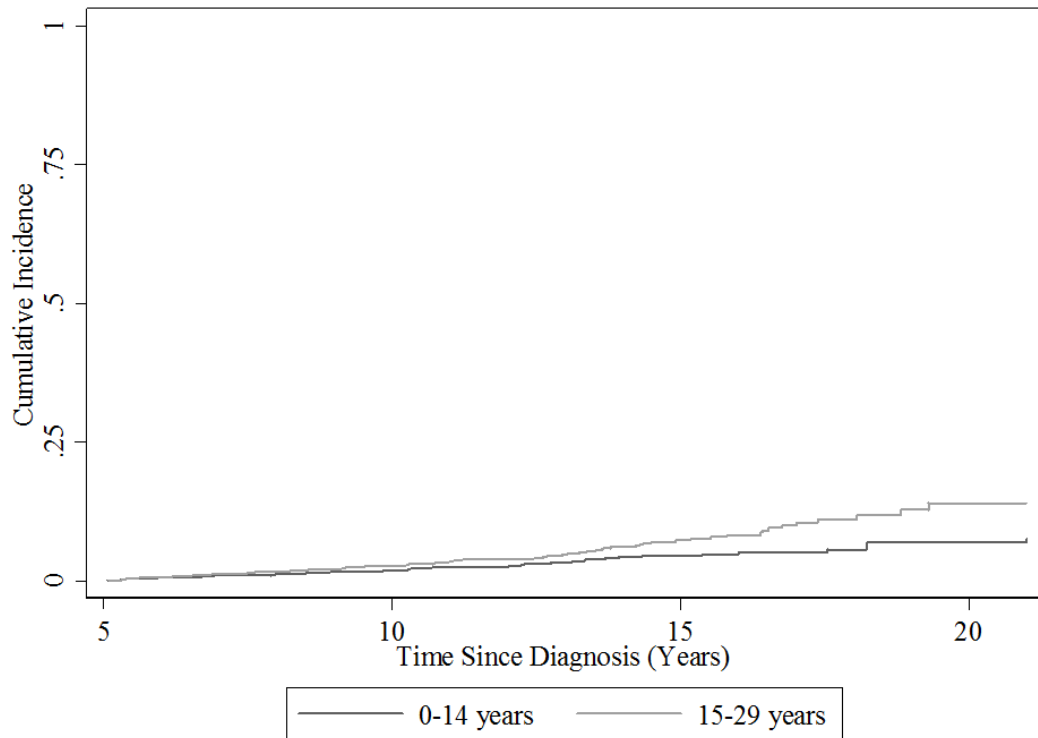
| Variable | HR | 95% CI | | P value |
|---|------|--------|-------|---------|
| | | lower | upper | |
| Sex | | | | |
| <i>Male</i> | 1 | | | |
| <i>Female</i> | 1.86 | 0.84 | 4.11 | 0.124 |
| Age Group | | | | |
| <i>0–14</i> | 1 | | | |
| <i>15–29</i> | 1.04 | 0.44 | 2.49 | 0.922 |
| Year of Diagnosis | 1.01 | 0.88 | 1.15 | 0.927 |
| Diagnostic Group | | | | |
| <i>Non-Haematological Tumours</i> | 1 | | | |
| <i>Haematological Tumours</i> | 0.90 | 0.41 | 1.99 | 0.800 |
| Treatment Group | | | | |
| <i>Cx+RT (+/- Sx)</i> | 1 | | | |
| <i>Cx</i> | 0.85 | 0.33 | 2.17 | 0.736 |
| Number of Anthracyclines[†] | 0.56 | 0.23 | 1.37 | 0.204 |
| Deprivation^a | 1.00 | 0.99 | 1.00 | 0.896 |

[†]Number of distinct anthracycline drugs administered, ^{††}Index of Multiple Deprivation 2007

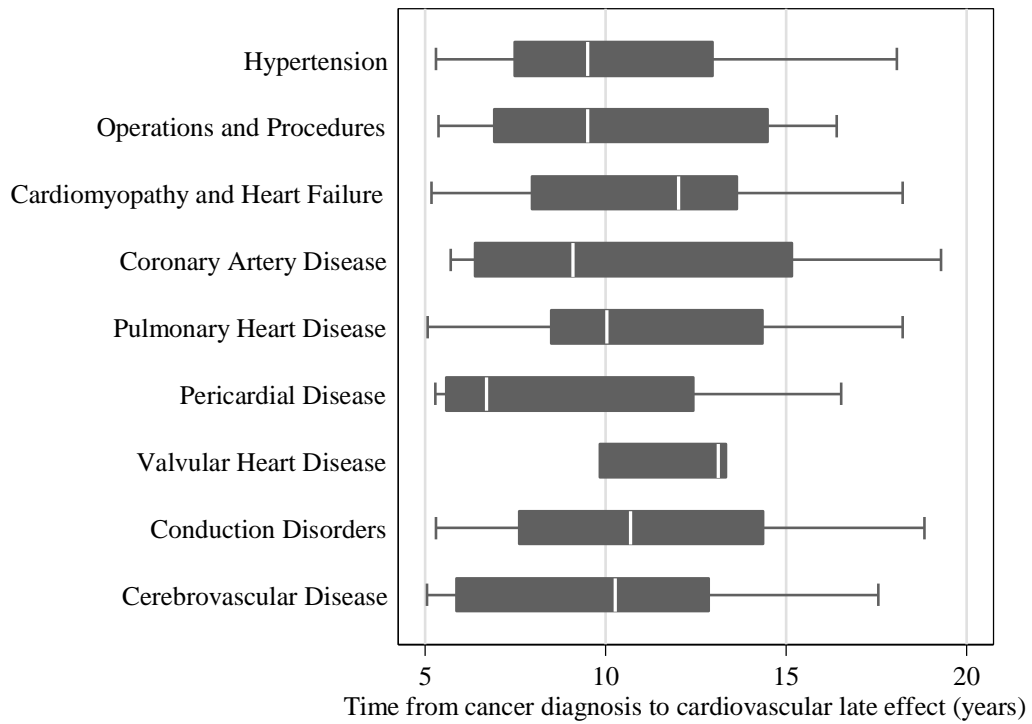
eTable 4: Chest Radiation – Excess hazard ratios (HR) and 95% confidence intervals (CI) obtained from a Royston-Parmar relative survival model, modelling the risk of a cardiovascular late event (excluding Cerebralvascular Disease) for long term survivors of childhood and young adult cancer diagnosed between 1991 and 2006

| Variable | HR | 95% CI | | P-value |
|-------------------------------------|------|--------|--------|---------|
| | | lower | upper | |
| Sex | | | | |
| <i>Male</i> | 1 | | | |
| <i>Female</i> | 50.4 | 0.003 | 815900 | 0.428 |
| Age Group | | | | |
| <i>0-14</i> | 1 | | | |
| <i>15-29</i> | 0.82 | 0.13 | 5.04 | 0.832 |
| Year of Diagnosis | 0.95 | 0.79 | 1.15 | 0.594 |
| Diagnostic Group | | | | |
| <i>Other solid tumours</i> | 1 | | | |
| <i>Leukaemia</i> | 0.52 | 0.12 | 2.26 | 0.382 |
| <i>Lymphoma</i> | 0.10 | 0.01 | 2.90 | 0.180 |
| <i>CNS tumours</i> | 0.62 | 0.09 | 4.26 | 0.626 |
| Chest Radiation | | | | |
| <i>No</i> | 1 | | | |
| <i>Yes</i> | 7.36 | 0.97 | 55.7 | 0.053 |
| †Index of Multiple Deprivation 2007 | | | | |

eFigure 1: Cumulative incidence of cardiovascular late effects amongst cancer survivors by age group



eFigure 2: Box and Whisker plots of time to first cardiovascular late effect



eFigure 3: Hospitalisation rate ratios and 95% confidence intervals comparing cardiovascular late effects amongst cancer survivors to the general population

