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Abstract

Objective: Malignant pleural mesothelioma (MPM) is a rare malignancy associated with exposure to asbestos. The protracted latent period of MPM means that its incidence has continued to rise across Europe after the introduction of restrictions on asbestos use. In order to obtain a clearer indication of trends in the Republic of Ireland (ROI), incidence and survival were assessed based on all MPM cases reported since the establishment of the National Cancer Registry of Ireland (NCR).

Methods NCR recorded 337 MPM diagnoses in the ROI during 1994-2009. Survival was assessed for all cases diagnosed with adequate follow-up (n=330). Crude and European age-standardized incidence rates were calculated for all cases and for 4-year periods. A Cox model of observed (all-cause) survival was used to generate hazard ratios for the effect of: gender; age at diagnosis; diagnosis cohort; region of residence; histological type; and tumour stage. Single p-values for the variables indicated were calculated using either a stratified log-rank test or stratified trend test.

Results: Over the study period the age-standardized MPM incidence in the ROI rose from 4.98 cases per million (cpm) to 7.24 cpm. The 1-yr survival rate for all MPM cases was 29.6% (CI 24.7-34.6%). Excess mortality risk was associated with age at diagnosis (75-89 yrs vs. 55-64 yrs, HR 1.88, 95% CI 1.35-2.63, P<0.001) and tumour stage (III vs. I HR 1.57, 95% CI 1.00-2.48, P<0.05; IV vs. I HR 1.55, 95% CI 1.08-2.21, P<0.05). Age showed a significant survival trend (P<0.001) but tumour stage did not (P=0.150). There was significant heterogeneity between the survival of patients resident in different regions (P=0.027).

Conclusion: MPM incidence and mortality continued to rise in the ROI after the restrictions on asbestos use and the predictors of survival detected in this study are broadly consistent with those identified for other countries.

1. Introduction

Exposure to the asbestos group of silicate minerals is the greatest risk factor for the development of malignant pleural mesothelioma (MPM) (1). The six minerals categorised as 'asbestos' are divided into two structural types: amphibole and serpentine, with amphibole minerals having the greatest carcinogenicity. Legislation enacted since the mid 1980s has progressively limited the use of asbestos in the Republic of Ireland (ROI), and the importation and use of all asbestos was banned in 2000 following the introduction of legislation by the European Union. Despite the widespread use of asbestos over past decades and its continued presence in existing buildings, few studies have been carried out on MPM incidence or survival in the ROI.

Most cases of MPM diagnosed in the ROI between 1994 and 1998 were in individuals involved in construction-related trades (2). That study showed an annual increase of 14.4% in MPM incidence (P=0.08) and predicted a large increase in incidence over coming decades. A geographical comparison study on the incidence of MPM and other mesotheliomas in patients diagnosed between 1978 and 2002, across five European regions, grouped the UK and ROI together as one region (3). That study concluded that the European age-standardized incidence of pleural and pericardial mesothelioma was highest in the UK and ROI, at 18.2 cases per million (cpm) per year, compared with 10 in Northern Europe, 12.1 in Central Europe, 3.3 in Eastern Europe and 11.4 in Southern Europe. Patients diagnosed with MPM in the UK and ROI also had a lower 1-yr survival (31%) compared with patients in other regions (34%-48%) (3). Gender differences in MPM survival have been observed in multiple studies from various parts of the World. (4) (5). The gender dichotomy has variously been attributed to the greater burden of asbestos fibres in the lungs of male patients compared to females (5) or the tumour suppressive actions of oestrogen receptor beta activation by circulating oestrogens, so attenuating tumour cell growth and MPM progression (6, 7).

We performed analysis on all MPM cases diagnosed in the ROI between 1994 and 2009, to provide more comprehensive figures on MPM incidence here and to assess factors influencing survival.

2. Methods

The data source for this study was the National Cancer Registry, Ireland (NCR). The NCR was established in 1991 and has recorded all cancer diagnoses made in the ROI for the years 1994 onwards. The data collated by the NCR have been used in many epidemiological studies and include age at diagnosis, gender, post-diagnosis survival, histological type, tumour stage, occupation and geographical region of residence. Data were analysed for all cases of MPM recorded by the NCR between 1994 and 2009. The age-standardized incidence rates were calculated for the time periods shown and for the whole study period using the European standard population distribution (8). Observed (all-cause) and relative survival estimates to five years after diagnosis were calculated actuarially using STATA-11 software (StataCorp LP, Texas). Follow-up intervals used were three months in the first year after diagnosis, six months in the second and third years, and annually thereafter. Follow-up was based on linkage of cases to national death certificate data held by the Central Statistics Office, Ireland, covering deaths up to the end of 2010, supplemented by clinical information for some patients. Deaths after 31st December 2010 were excluded.

A total of 337 MPM cases were diagnosed over the study period (1994-2009) (Table 1). Of 16 patients without a recorded death up to the end of 2010, 6 were known to have died after 2010 and, along with 3 patients diagnosed in 2008 or 2009, were assumed to be still alive at the end of 2010. For the seven remaining patients (diagnosed 1995-2003) without recorded death data, follow-up was censored on the most recently available treatment or hospital in-patient date. Adequate follow-up ($\geq$1 day) was available for 330 patients (Table 1). A Cox model of observed (all-cause) survival, adjusted for age, gender, region and stage, and stratified for histological subtype (epithelioid, sarcomatoid, biphasic and undetermined) and

diagnosis period to allow for non-proportional hazards shown by these variables, was used to generate hazard ratios for the effect of patient and tumour factors (Table 1). For comparison, a less optimal model was also applied, adjusted but not stratified for subtype and region. Equivalent models of relative survival were also applied, giving very similar results (not reported here). The heterogeneity of each survival by gender, diagnosis cohort, HSE region and histological sub-type was assessed using a stratified log-rank test for equality of survivor function. Trends in survival by age and tumour stage (I-IV) at diagnosis were assessed by stratified trend tests. Cause-specific survival was not assessed in this study because of the high proportion of unknown or undisclosed causes of death for this patient group. Restriction of statistical analysis to 1-yr or 3-yr follow-up did not appreciably change the findings compared to models based on 5-yr follow-up presented here.

3. Results

Incidence

There were 337 MPM diagnoses in the ROI over the period 1994-2009. Survival data were available for 330 patients - 289 male (87.6%) and 41 female (12.4%) (Table 1). There was an upward trend in the number of MPM diagnoses made over the study period, from 58 MPM diagnoses during the four-year period 1994-1997 to 114 during 2006-2009 (Table 1). This represents a mean rise in annual incidence from 4.98 cases per million (cpm) 1994-1997 to 7.24 cpm 2006-2009. Of those cases with adequate post diagnosis follow-up for survival analysis, only a small number of cases 43 (13%) were diagnosed in individuals <55 years of age; this is consistent with the model of MPM disease progression where malignancy develops often decades after exposure to the carcinogen. Incidence rates were also calculated for all primary pleural malignancies diagnosed over the study period (n=438), sub-categorised into MPM and non-MPM (NM), and the age-standardized incidence was compared for each of the four-year periods (Table 3). NM incidence among females was 0.56 cpm and 0.64 cpm for periods 1994-1997 and 2006-2009 respectively, while in males

the rate declined from 3.45 cpm to 2.11 cpm. Over the same period the incidence of MPM among males rose from 9.08 cpm to 13.11 cpm.

Gender

The observed one-yr post-diagnosis survival for male patients was 28.6% (95% CI 23.5-33.9%), and 36.6% (95% CI 22.2–50.9%) for females (Table 2, Fig. 1A). Median survival was 197 days in males, 253 days in females. Survival was significantly better among female patients in an adjusted but un-stratified model of observed survival with a hazard ratio (HR) 0.68 (95% CI 0.47-0.98, P=0.036) compared to males, but was not significant in a fully stratified model (Table 1 and footnote).

Age at Diagnosis

At diagnosis, 43 (13%) of the patients in this cohort were aged 18-54 years, 113 (34.2%) 55-64 years, 107 (32.4%) 65-74 years and 67 (20.3%) were aged 75-89 years (Table 2). In total 287 (87%) of the patients were aged over 55 years at the time of MPM diagnosis. Compared with age-group 55-64, observed survival was significantly poorer in age-group 75-89 (HR 1.88, 1.35–2.63, P<0.001) (Table 1, Fig. 1B). There was a significant overall trend in survival by age (P<0.001). The proportion of patients diagnosed below age 55 fell from 22% (13 cases) during 1994-1997 to 7% (8) during 2006-2009, while diagnoses at 75 years or over rose from 17% (10) to 28% (33) over the same timescale.

Diagnosis Cohort

The cases included for survival analysis spanned a 16-year diagnosis period (Table 2), and possible variation in survival over time was examined and adjusted for using four-year cohorts (Fig. 1D). The 1-yr survival rate for the whole study population was 29.6% (95% CI 24.7-34.6%). The 1-yr survival rate for each of the study cohorts was: 1994-1997, 27.0% (95% CI 16.1-38.9%); 1998-2001, 20.6% (CI 11.7-31.3%); 2002-2005, 36.8% (27.2-46.4%); and 2006-2009, 29.8% (CI 21.7-38.3%). Definitive hazard ratios for cohort could not be

computed, because of non-proportional hazards. An unstratified model indicated significantly poorer survival for the 1998-2001 cohort (Table 1 and footnote), but a stratified log-rank test did not identify significant heterogeneity between the diagnosis cohorts (P= 0.184).

Histological Subtype

Malignant mesothelioma can be classified by the histological morphology of tumour cells during haematoxylin-eosin staining as epithelioid, sarcomatoid or mixed (biphasic). Epithelioid MPM is characterized by polygonal, oval, or cuboidal cells that often mimic non-neoplastic reactive mesothelial cells. Sarcomatoid MPM tumours consist of spindle-shaped cells, and biphasic MPM contains both epithelioid areas and sarcomatoid areas within the same tumour (9). The histological subtype was available for only 81 (24.5%) of the 330 Irish MPM cases included in the survival analysis, of which 63 (77.8%) were diagnosed as epithelioid, 14 (17.3%) biphasic and 4 (4.9%) as sarcomatoid (Table 1), which is consistent with previous studies showing epithelioid is the most common histological subtype followed by biphasic and sarcomatoid MPM (10, 11). The final Cox model was stratified for subtype because of non-proportional hazards, but an equivalent but unstratified model failed to confirm any statistically significant survival variation by subtype.

Tumour Stage at Diagnosis

TNM staging information was available for only 153 (46.4%) of the MPM cases in the survival cohort (Table 1, Fig. 1F), on the assumption that the N category was N0 and M category was M0 unless there was an explicit statement of node-positive or distant metastatic disease. Most cases were either un-staged (lacking a T-category) or were assigned to stage I, III or IV, with few assigned to stage II (possibly an artefact of the TNM staging criteria and data incompleteness). In the Cox model examined, survival of stage III and IV patients was significantly poorer, compared with stage I (Table 1): HR for stage III 1.58 (95% CI 1.00-2.48, P<0.05), HR for stage IV 1.67 (95% CI 1.09-2.55, P<0.05).

Region of Residence

The provision of public hospital healthcare in the ROI is administered through four HSE administrative areas (Table 1). HSE region of residence is associated with survival for some other cancers in Ireland, and was thus included in analyses here. There was some suggestion of higher survival for Dublin / North-East region, and lower survival for the Western region, compared with Dublin / Mid-Leinster (Table 1), but neither was statistical significantly. However, a stratified log-rank test indicated significant heterogeneity between the regions (P=0.027).

Therapeutic Intervention

In the Irish cohort 140 patients (44% of the total) did not receive radiotherapy, chemotherapy or surgical intervention, and the median survival for these patients was only 2.8 months, compared with 9.0 months for patients who did receive some kind of therapeutic intervention (not tabulated). The decision on whether chemotherapy is administered is based on multiple factors including predicted response and current health status, and it is probable that those who received chemotherapeutic intervention had other positive indicators which also contributed to their improved survival. Of patients diagnosed during 1994-1997, 21 (36%) received some form of tumour-directed therapy; this increased to 91 patients (69%) for 2006-2009. Survival seemed to be poorest in the 1998-2001 diagnosis group, where multimodal therapy was used at lowest frequency to treat only 5 patients (8%). For those patients where tumour stage was known (n=153), 14 (30%) of stage III patients did not receive treatment compared to 23 (41%) of stage IV patients.

Occupation

The last occupation of 223 of 362 MPM patients diagnosed between 1994 and 2010 was known. The occupations most highly represented were: construction (28 cases); woodworking (22 cases); managers working in agriculture or forestry (18 cases); plant and

machine operators (13 cases); road transport workers (13 cases) and mining/ manufacturing workers (13 cases).

4. Discussion

The average incidence of MPM in the Republic of Ireland over the period 1994-2009 (European population age-standardized rate [EASR] 6.02 cases per million and crude rate 5.34 cpm) is comparable with the crude rates of MPM observed in some European countries such as Austria (5.6 cpm), Poland (4 cpm) and Spain (4 cpm), but lower than reported in others such as Norway (16 cpm), Sweden (12 cpm), France (10-13 cpm), over a similar period (12). That review also quoted a crude rate of 30 cpm for Great Britain, derived from mortality data. European data from the RARECARE project for 1995-2002 indicated a higher EASR of pleural or pericardial mesothelioma for the UK and ROI combined (18.2 cpm) than for four other regions of Europe (range 3.3-12.1 cpm) (3). More recent figures indicate an EASR for all mesothelioma averaging 31 cpm for the whole of the UK and 17 cpm for Northern Ireland in 2009 (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/Mesothelioma/incidence/#In), compared with a total mesothelioma EASR for the ROI of 7.24 cpm during 2006-2009 (6.02 1994-2009).

Differences in the scale of asbestos use possibly contribute to the apparent differences in MPM incidence between the UK and ROI. The peak in asbestos importation here occurred in 1980 at 8,413 tonnes compared to the 1975 peak for the UK at 139,185 tonnes (13), and overall asbestos use in the ROI has been much less intensive than in the UK. However, the implementation of the ban occurred later, and in 1996 asbestos importation into the ROI was 4,638 tonnes (67.7% of peak) compared to 7,099 tonnes (5.1% of peak) in the UK. Most cases of MPM arising today in the UK are assumed to be the result of exposure to fire retardant amosite (brown asbestos) that was incorporated into building materials (14). The contribution of serpentine white asbestos (chrysotile) to malignancy remains controversial, and most malignancies arising from chrysotile exposure are believed to be the result of

natural contamination with amphibole asbestos sub-types, or the mixing of chrysotile with amphiboles in the manufacture of some building materials (15). Precise data on the quantities of individual asbestos subtypes imported into the ROI are not available. MPM is a disease of extremely long latency where 40 years may lapse between exposure to asbestos and the diagnosis of malignancy. Since low-level but sustained importation of asbestos containing materials continued into the 1990s, it is not surprising that there has been a progressive increase in age-adjusted incidence of MPM in each of the study cohorts from 1994 to 2009. This increase is consistent with data from other European countries where MPM incidence has continued to rise even after the asbestos ban. We noted that the percentage of cases diagnosed in patients over the age of 75 years in ROI over the study period rose from 17% to 28%, while the number diagnoses under the age of 55 years declined. The shift in the MPM burden to a more elderly demographic group has implications for future healthcare planning. It is likely that the incidence in Ireland will peak over the next decade, with the increasing age of diagnosis for the most highly exposed sub-set of the population

To investigate whether diagnostic improvements in distinguishing MPM from other (or unspecified) pleural malignancies could account for the apparent change in incidence over the study period, the incidence for MPM and non-mesothelioma or unspecified pleural neoplasms (NM) were compared. The latter can arise from metastatic invasion of the pleura by other malignancies such as lung or breast carcinoma (16, 17), but cases registered by the NCR should be primary pleural neoplasms only and may include some unconfirmed mesothelioma. Cases registered as mesothelioma under current NCR rules must be microscopically verified (except for death-certificate-only cases), and purely clinical or radiological diagnoses of mesothelioma are coded as ‘unknown cancer morphology.’ Total numbers of NM cases declined from 21 during 1994-1997 to 17 during 2009-2009, and rates of NM showed no clear trend, in contrast to the marked rise in MPM diagnoses. The incidence of all pleural malignancies rose from 6.98 to 7.77 cpm over the study period, most

of this increase attributable to the increase in MPM incidence. However, the more marked increase in MPM incidence over time, compared with all pleural malignancies, suggests that some of the MPM trend may be accounted for by improved specificity of diagnoses.

A number of factors may contribute to survival differences between diagnosis periods or patient groups. Survival appeared to be poorest in the second-earliest diagnosis cohort, and to improve more recently, although a log-rank test (stratified for other factors) did not confirm significant heterogeneity (P=0.184), and chance effects could not be rule out. Lead time-bias is significant consideration in interpreting survival data, and may have contributed to some of the survival differences between subgroups in this study. Different patient cohorts may be separated by a significant period of time when diagnostic practices may have changed, and age group or gender may influence an individual's motivation for seeking timely medical advice (18). In 1996 a National Cancer Strategy to improve infrastructure and service provision was implemented in ROI (19). This provided a national framework for the development and funding of cancer care after inconsistencies in treatment were found at different centres and may have contributed to improvements in care in recent years. Nevertheless, we found significant heterogeneity in survival by region of residence.

Therapeutic practices in ROI have changed over the study period with the percentage of patients receiving some intervention rising from 36% to 69%. The more extensive use of single mode and multimodal interventions (most often chemotherapy in combination with surgery or radiotherapy) after 2002 may contribute to apparent survival differences over the different diagnosis periods. Progressively these limited therapeutic improvements may come to be confounded by the increasing age of patients at diagnosis, which affects their suitability for particular interventions and so may restrict future use of some therapies, particularly surgery.

The histological subtype is one of the most important prognostic indicators influencing MPM survival. Patients diagnosed with epithelioid MPM have longer post-diagnosis survival times, patients with sarcomatoid MPM shorter survival and patients with biphasic MPM, intermediate survival (20). Histological subtype influences the selection of specific therapeutic regimes, with sarcomatoid patients not being appropriate for surgery. Data presented in this study refers to the histological sub-type at diagnosis, but sub-type plasticity and progression to a sarcomatoid tumour cell phenotype over time would adversely affect survival. Such an epithelial-mesenchymal transition in MPM has been linked to a loss of PTEN activity in tumour cells (21). Higher Butchart (22) or TNM (23) tumour stage classification at diagnosis for MPM correlates with worse survival. Data from this present study is based on tumour stage at diagnosis and indicates that patients diagnosed at tumour stages III and IV have a worse survival than those who are diagnosed at stage I. However, no further conclusion could be drawn on the contribution of histological type or tumour stage in this cohort of patients due to the limited tumour classification data available. We also have no information on tumour stage progression, or on possible changes over time in the thoroughness of stage investigations (which might lead to 'stage migration').

The male/female ratio of patients diagnosed with MPM in Ireland during 1994-2009 was 7.0 which is somewhat higher than that reported in England (1997-2007) at 5.7 (24) and Australia at 5.4 (25), but much higher than that reported for some other countries such as France at 3.8 (26) and Italy at 2.4 (25). Differences in occupational versus environmental asbestos exposure might possibly explain differences in the male/female incidence ratio between countries. The (probably) over-represented occupations of patients diagnosed with MPM in the ROI (Table 4) include construction trades, metal working, electrical trades and mining which are associated with greater asbestos exposure and which have a largely male workforce (27, 28). However, without the availability of complete information on occupation (and occupational exposures over time), including comparative information for other cancers,

caution is required in drawing any conclusions from the limited occupational data presented here.

The median survival for MPM patients in the ROI was 6.5 months for males and 8.3 months for females. This is comparable with MPM survival reported for England at 8.9 months (29), the US at 7 months (30) and Japan at 5-6 months (31). A significantly improved survival for female patients has been described in other studies and has been attributed to reduced asbestos fibre load (5) or the tumour suppressive action of circulating oestrogens (6, 7). Female gender was a positive predictor of survival in this study in a non-stratified Cox model. It has been proposed that circulating oestrogens attenuate the progression from epithelioid to sarcomatoid MPM in females (7), thus gender and histological subtype may not be independent variables. However, the lack of fuller (including post-diagnosis) information on histological subtype for this cohort prevents further investigation.

Even though the majority of MPM cases occur later in life, it is clear that there is a percentage of MPM cases that are diagnosed in younger patients (27, 31). It is possible that such cases occur due to asbestos exposure in the urban environment rather than occupational exposure; however a genetic predisposition to developing MPM may also account for younger cases (32).

5. Conclusion

MPM is a rare malignancy, but the number of MPM diagnoses made in the Republic of Ireland has continued to rise over the period 1994-2009, consistent with observations made in other industrialised countries. The impact of survival predictors such as gender, histological type, tumour stage and age at diagnosis measured in this group of subjects is comparable with data from other studies.

Figure Legends

Figure 1.

Observed survival of pleural mesothelioma cases recorded in the Republic of Ireland between 1994 and 2009 with follow-up to December 31st 2010 (N=330). Individual survival curves are plotted by gender (A); age at diagnosis (B); age at diagnosis above or below 55 years for each gender (C); diagnosis cohort (D); histological subtype (E); tumour grade (F); and region of diagnosis (G).

Conflicts of Interest.

None of the Authors have any conflicts of interest to disclose.

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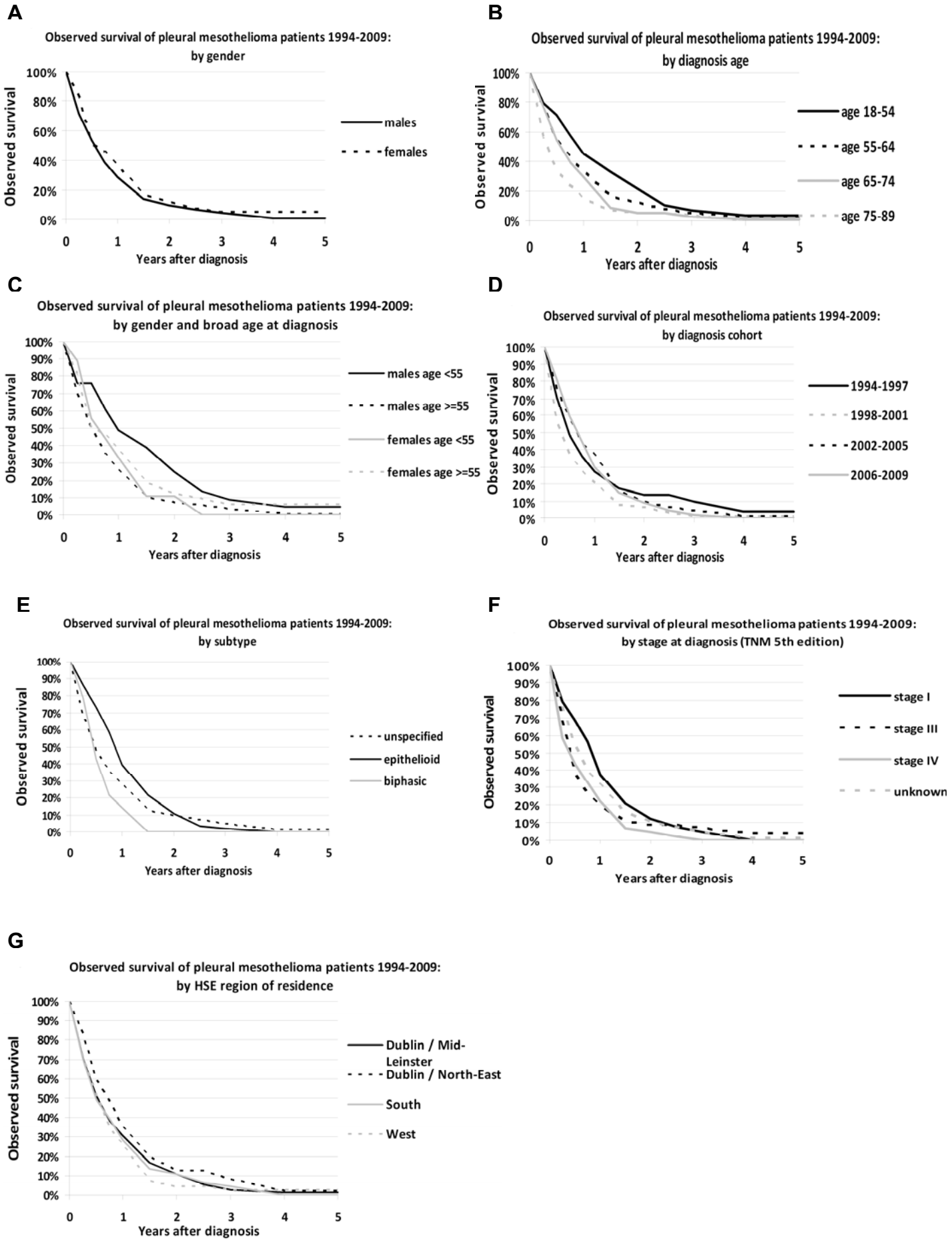
A
Observed survival of pleural mesothelioma patients 1994-2009: by gender
Observed survival
100%
80%
60%
40%
20%
0%
0
1
2
3
4
5
Years after diagnosis
males
females
B
Observed survival of pleural mesothelioma patients 1994-2009: by diagnosis age
Observed survival
Years after diagnosis
age 18-54
age 55-64
age 65-74
age 75-89
C
Observed survival of pleural mesothelioma patients 1994-2009: by gender and broad age at diagnosis
Observed survival
Years after diagnosis
males age <55
males age >=55
females age <55
females age >=55
D
Observed survival of pleural mesothelioma patients 1994-2009: by diagnosis cohort
Observed survival
Years after diagnosis
1994-1997
1998-2001
2002-2005
2006-2009
E
Observed survival of pleural mesothelioma patients 1994-2009: by subtype
Observed survival
Years after diagnosis
unspecified
epithelioid
biphasic
F
Observed survival of pleural mesothelioma patients 1994-2009: by stage at diagnosis (TNM 5th edition)
Observed survival
Years after diagnosis
stage I
stage III
stage IV
unknown
G
Observed survival of pleural mesothelioma patients 1994-2009: by HSE region of residence
Observed survival
Years after diagnosis
Dublin / Mid-Leinster
Dublin / North-East
South
West

Figure 1

Table 1. Case numbers, and influence of gender and other factors on observed survival of pleural mesothelioma patients diagnosed 1994-2009 (based on follow-up to 31/12/2010.

	n (%)	HR[b]	95% CI	P[c]	age-adjusted (& crude) rate per million[a]	n (for survival analysis)
Diagnosis cohort				P=0.184		
1994-1997	59 (16.3)	-	-		4.98 (4.08)	58
1998-2001	64 (17.7)	-	-		5.04 (4.24)	63
2002-2005	97 (26.8)	-	-		6.85 (6.03)	95
2006-2009	117 (32.3)	-	-		7.24 (6.70)	114
1994-2009	337 (100)	-	-		6.02 (5.34)	330
HSE region of residence				P=0.027		
Dublin/Mid-Leinster	105 (31.8)	1.00	-			
Dublin/North-East	60 (18.2)	0.77	0.54-1.10			
South	87 (26.4)	0.98	0.70-1.35			
West	78 (23.6)	1.24	0.90-1.72			
Age (years) at diagnosis				P<0.001		
18-54	43 (13.0)	0.78	0.53-1.16			
55-64	113 (34.2)	1.00	-			
65-74	107 (32.4)	1.18	0.87-1.58			
75-89	67 (20.3)	***1.88	1.35-2.63			
Gender				P=0.778		
Male	289 (87.6)	1.00	-			
Female	41 (12.4)	0.80	0.55-1.16			
Histology type	**n (% of 81 known)**			P=0.762		
Epithelioid	63 (77.8)	-	-			
Biphasic	14 (17.3)	-	-			
Sarcomatoid	4 (4.9)	-	-			
Unspecified	249	-	-			
Tumour stage	**n (% of 153 known)**			P=0.150		
I	48 (31.4)	1.00	-			
II	3 (2.0)	1.26	0.37-4.22			
III	46 (30.0)	*1.58	1.00-2.48			
IV	56 (36.6)	*1.67	1.09-2.55			
Unknown	177	1.08	-			

[a]Age-standardized rates per million per year using the European standard population (crude rates in parentheses)). Age-standardized rate is calculated as the mean (or midpoint) of the age-standardized rates for males and females separately, crude rate as sum of male and female cases/sum of male and female populations. The age-standardized (and crude) rates for mesothelioma of all sites combined (not just pleura) were 5.39 (4.49) cpm for 1994-1997, 5.14 (4.51) 1998-2001, 7.78 (7.15) 2002-2005, 7.83 (7.22) 2006-2009 and 6.62 (5.93) 1994-2009.

[b]Cox model of observed survival, stratified by subtype and diagnosis cohort to allow for non-proportional hazards, also adjusted for gender, age, region, and stage. In an equivalent but less optimal model, adjusted for but not stratified by subtype and diagnosis cohort, the HR for female gender was 0.68 (95% CI 0.47-0.98, P=0.036); HRs for subtype, relative to unspecified subtype, were 0.59 (0.20-1.72, P=0.332) for epithelioid, 0.79 (0.58-1.06, P=0.118) for sarcomatoid and 1.31 (0.75-2.28, P=0.347) for biphasic; HR for 1998-2001 relative to 1994-1997 cohort was 1.73 (1.18-2.55, P=0.005), otherwise no significant variation by cohort; HRs for age and stage showed little change.

[c]P-value from log-rank test for equality of survivor functions or (for age and stages I-IV) from trend test, all adjusted for (stratified by) the other variables listed.

*P<0.05, ** P<0.01, *** P<0.001.

Table 2. Observed (all-cause) survival of pleural mesothelioma patients diagnosed in Ireland, 1994-2009 (based on follow-up to 31/12/2010).

		1-yr		3-yr		5-yr	
	n	**survival**	**95% CI**	**survival**	**95% CI**	**survival**	**95% CI**
1994-2009	330	29.6%	24.7-34.6%	4.3%	2.3-7.1%	1.6%	0.5-3.7%
males	289	28.6%	23.5-33.9%	4.2%	2.2-7.3%	0.9%	0.2-3.1%
females	41	36.6%	22.2-50.9%	4.9%	0.9-14.5%	4.9%	0.9-14.5%
age 18-54	43	45.4%	30.0-59.5%	6.8%	1.4-18.5%	3.4%	0.3-14.3%
55-64	113	32.7%	24.3-41.4%	5.4%	2.1-11.1%	2.2%	0.4-6.8%
65-74	107	29.3%	20.9-38.1%	2.5%	0.5-7.5%	1.3%	0.1-5.9%
75-89	67	14.9%	7.7-24.4%	3.5%	0.7-10.5%	-	
55-89	287	27.3%	22.2-32.5%	3.9%	2.0-6.9%	1.3%	0.4-3.5%
epithelioid	63	39.7%	27.6-51.4%	1.8%	0.2-8.3%		
sarcomatoid	4	-		-		-	
biphasic	14	14.3%	2.3-36.5%				
unspecified	249	28.0%	22.5-33.6%	4.9%	2.5-8.4%	1.6%	0.5-4.3%
Dublin / Mid-Leinster	105	30.5%	21.9-39.3%	2.6%	0.5-7.9%	1.3%	0.1-6.1%
Dublin / North-East	60	35.0%	23.2-46.9%	8.3%	2.9-17.5%	2.1%	0.2-9.4%
South	87	28.4%	19.2-38.1%	4.6%	1.3-11.3%	-	
West	78	25.6%	16.5-35.6%	2.9%	0.6-8.8%	2.9%	0.6-8.8%
Stage I	48	37.5%	24.0-50.8%	4.8%	0.9-14.1%	-	
Stage II	3	-		-		-	
Stage III	46	19.6%	9.7-32.0%	6.5%	1.7-16.0%	4.4%	0.8-13.0%
Stage IV	56	22.0%	12.1-33.6%	0.0%		-	
Stage unknown	177	31.9%	25.1-38.7%	4.8%	2.1-9.3%	1.6%	0.3-5.1%
1994-1997	58	27.0%	16.1-38.9%	9.8%	3.7-19.5%	3.9%	0.7-11.8%
1998-2001	63	20.6%	11.7-31.3%	1.6%	0.1-7.5%	1.6%	0.1-7.5%
2002-2005	95	36.8%	27.2-46.4%	4.4%	1.5-10.0%	1.1%	0.1-5.4%
2006-2009	114	29.8%	21.7-38.3%	2.2%	0.3-8.8%	-	

Table 3. All cases of pleural malignancy (excluding lymphoma) diagnosed in the Republic of Ireland 1994-2009 to December 31st 2009 (n=438) divided into malignant pleural mesothelioma (MPM) and non-mesothelioma (NM). The incidence and age-adjusted rate are categorised by gender and diagnosis cohort.

Cohort	Gender	n			Age-adjusted rate per million [a]		
		MPM	NM	All	MPM	NM	All
1994-1997	M	54	21	75	9.08	3.45	12.53
	F	5	4	9	0.89	0.56	1.44
	total	59	25	84	4.98	2.00	6.98
1998-2001	M	51	20	71	8.02	3.16	11.19
	F	13	9	22	2.05	0.95	3.0
	total	64	29	93	5.04	2.05	7.09
2002-2005	M	87	15	102	12.35	2.33	14.67
	F	10	7	17	1.33	0.83	2.16
	total	97	22	119	6.85	3.16	8.41
2006-2009	M	104	17	121	13.11	2.11	15.23
	F	13	8	21	1.36	0.64	2.00
	total	117	25	142	7.24	1.37	8.61
1994-2009	M	296	73	369	10.64	2.76	13.40
	F	41	28	69	1.41	0.74	2.15
	total	337	101	438	6.02	1.75	7.77

[a] European population age-standardized rates.

Table 4. Occupational distribution of pleural mesothelioma cases diagnosed in the Republic of Ireland 1994-2010.

Occupation	Number of Diagnoses
Construction Trades	28
Woodworking Trades	22
Managers in Farming, Horticulture, Forestry and Fishing	18
Plant and Machine Operatives NEC	13
Road Transport Operatives	13
Other Occupations in Mining and Manufacturing	13
Metal Forming, Welding and Related Trades	11
Electrical/Electronic Trades	10
Managers and Proprietors in Service Industries	7
Sales Assistants and Check-Out Operators	5
Not Classified	6
Occupation groups with <5 members	77
Unknown	139
N=362	