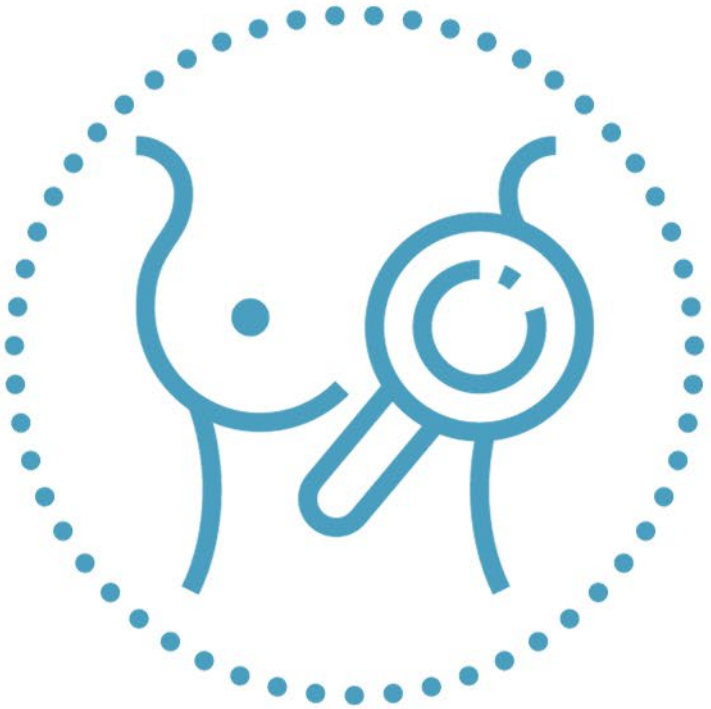
National Cancer Registry Ireland

METASTATIC BREAST CANCER IN IRELAND:

A NATIONAL CANCER REGISTRY ANALYSIS 2024



THE NATIONAL CANCER REGISTRY

www.ncri.ie

About the National Cancer Registry of Ireland

The National Cancer Registry was established by the Minister for Health in 1991. It has been collecting comprehensive cancer information for the population of the Republic of Ireland since 1994. This information is used in research into the causes of cancer, in education and information programmes, and in the planning and management of cancer services to deliver the best cancer care to the whole population.

The mission of the National Cancer Registry of Ireland (NCRI) is to capture data and communicate information on cancer patients nationally to support the improvement of cancer outcomes in Ireland.

We collect information from all hospitals in Ireland on the number of persons diagnosed with cancer and the types of cancer they have. We also follow up the numbers dying from their cancer or from other causes. All the patient's personal and private details are removed before summaries of this information are made available to the public and health professionals through our annual cancer report and other reports on our website.

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Report at a glance

Who are we, and what do we do?

The National Cancer Registry of Ireland (NCRI) works on behalf of the Department of Health and collects information from all hospitals in Ireland on the number of persons diagnosed with cancer and the types of cancer they have.

NCRI also follows up the numbers of people dying from their cancer or from other causes. Patient personal and private details are removed before summaries of this information are made available to the public and health professionals through our annual cancer report and other reports on our website (www.ncri.ie)

How are the numbers reported?

Collecting and checking all of this information is performed by a combination of manual and electronic processes. Our staff collect cancer diagnosis information and then use an agreed system of coding (The International Classification of Diseases) to group the cancers into different types.

After a process of collating diverse information from Irish hospitals and validating the accuracy, cancer reports are published following analysis of de-identified data.

Supporting information

The Irish Cancer Society provides simple explanations for many of the medical terms used to describe breast cancer.

These explanations can be found by clicking on the links opposite.

They are also included in the 'Glossary & Definitions' section below.

These explanations will help lay readers to better understand this report.

Links to supporting information

Metastatic Breast Cancer

Staging and grading of breast cancer

What is in this report?

The information presented is a description of the data extracted and collated from the NCRI databases to broadly describe metastatic breast cancer (MBC) pattern from 1994 to 2018 in Ireland, with particular reference to the years 2005-2018. The overall focus of the study is to estimate the levels of distant metastatic disease in patients diagnosed with invasive breast cancer.
Findings are presented for:

- Metastatic site distribution
- The cumulative risk of developing distant metastases after diagnosis
- Overall risk of distant metastasis, at diagnosis or subsequently.
- The cumulative risk of breast cancer deaths

What is the purpose of this report?

At the population level accurate recording of cancer progression and recurrence are important measures. They might contribute to a greater understanding of cancer outcomes.

The main focus of this study is to use available cancer registry data to estimate the overall risk and prevalence of distant metastatic disease in breast cancer patients. Metastases at diagnosis or subsequently are considered.

This work also evaluates the quality of NCRI data on metastatic breast cancer. Based on this, we recommend changes to improve collection of progression and recurrence data for breast and other cancers.

What was found?

Metastatic sites

Metastatic sites

Five sites accounted for just under 83% of all metastases recorded for breast cancers diagnosed between 1994 and 2018. These were

- Bone - 37%
- Liver - 17%
- Lung - 14%
- Brain - 8%
- Lymph nodes - 7%

Figures for lymph nodes may include some regional (non-distant) metastases.

What was found?

Distant metastasis: diagnosis period 2005-2018

Distant metastasis: diagnosis period 2005-2018

The risk of developing distant metastases (among patients without distant metastases at the time of original diagnosis) increased with follow-up time.

It was highest in those diagnosed before 45 years of age, (cumulative risk 16% at 10 years post-diagnosis). The lowest risk at 10 years post diagnosis was in those aged 55-64 at 9%.

The risk of distant metastatic disease at 10 years post-diagnosis

- was two to three times greater in those diagnosed with stage III (cumulative risk 30%) cancer compared to those diagnosed with stage II (12%) or stage I (4%).
- was higher for patients with grade 3-4 tumour at diagnosis (cumulative risk 16%), compared with 3% for grade 1 (3%) and grade 2 tumours (10%).
- was slightly higher in patients who have HER2+ receptor compared to those who are HER2- at diagnosis (13% v 11%)
- was higher for patients who were ER/PR- at diagnosis compared to those who were ER/PR+ at diagnosis (cumulative risk 16% versus 10% respectively).

Similar patterns were evident for comparisons based on cumulative risk of distant metastatic disease up to 14 years post-diagnosis

What was found?

Breast cancer deaths in patients with no distant metastases at diagnosis.

Breast cancer deaths in patients with no distant metastases at diagnosis.

The number of breast cancer deaths have decreased over time in cancer patients who did not have distant metastases at diagnosis. Just over 17% of those diagnosed between 2005 and 2018 died of their cancer within 10 years. For the diagnosis period 1994 to 2004, 29% died within 10 years.

- At 5, 10 and 14 years post-diagnosis the 15-44 age group have a higher risk of dying of their breast cancer relative to those aged 45-54 and 55-65, but lower than those age 65 and over. Mortality risk from breast cancer is highest among patients in the oldest age-group.

- The risk of dying of breast cancer is lowest in those diagnosed with early-stage disease and highest in those with more advanced stage at diagnosis.

Glossary and Definitions	
Breast cancer	All patients diagnosed with invasive breast cancer (ICD-10 C50) 1994 – 2018 inclusive), counting only the first breast cancer per patient for analyses in this report.
Cause specific survival	The National Cancer Institute (NCI) defines cause-specific survival (CSS) as '*The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, to the date of death from the disease. Patients who die from causes unrelated to the disease are not counted in this measurement.'*
Cumulative risk	A measure of the total risk that a certain event will happen during a given period of time – for example, the likelihood that a person who is free of a certain type of cancer will develop that cancer by a specific age.
MBC	Metastatic breast cancer (MBC) is cancer that has spread from the first (primary) tumour in the breast to another part of the body. It is also known as secondary breast cancer, advanced breast cancer or stage 4 breast cancer. Source: Irish Cancer Society
Metastasis	Metastasis is cancer that has spread (other than by direct extension) from the primary site. Metastases can be • regional (for example, spread to lymph nodes draining a primary site) • distant (for example, to other organs or to more distant lymph nodes). Distant metastases may be present at diagnosis but may be not detected until after initial diagnosis and treatment. • Metastases detected after surgery do not form part of staging at the time of diagnosis. • Metastases recorded at diagnosis indicate a cancer is more advanced than cases where metastases are not detected at the time of diagnosis. • Cancer that has already spread, or metastasized, to distant parts of the body by the time of diagnosis is called 'de novo' cancer. The National Cancer Registry codes distant metastases diagnosed within four months of diagnosis (up to and including time of surgery). If planned surgery happens later than four months after diagnosis, the date of surgery is used as the cut-off date.
ICD10	International Classification of Diseases 10th Revision.
ICD-O-3	The International Classification of Diseases for Oncology, Third Edition.

NOS	Not otherwise specified.
Recurrence	Recurrence is reappearance of a disease after a period when there was no evidence of disease following reductive treatment. • Breast cancer that recurs at the original site is called a local recurrence. • Breast cancer that returns and spreads to (or is subsequently detected in), other parts of the body is called a regional or distant recurrence. Regional recurrence may be by direct extension from the primary site, or by regional metastasis.

TNM	Tumour, node, metastasis, (TNM stage).
	
	• Tumour (T): How big is the tumour?
	• Node (N): Is there cancer in the lymph nodes?
	  ○ N0 means no lymph nodes are affected
	  ○ If the cancer has spread to the lymph nodes (positive lymph nodes) the N will have a number to describe how many lymph nodes are affected.
	• Metastasis (M): Has the cancer has spread to other parts of the body?
	  ○ M1 means the cancer has spread (metastasised) to other organs
	  ○ M0 means it has not spread.
	
	Source: Irish Cancer Society.

Stage	Cancer stage defined using TNM staging system is used to give a newly diagnosed cancer a number stage – from I to IV. For breast cancer these are • Stage 0: Non-invasive breast cancer • Stage I: The cancer is found only in the breast • Stage II: The cancer is found in the breast and nearby lymph nodes • Stage III: The cancer has spread to more lymph nodes • Stage IV: The cancer has spread to other organs in the body. This is called metastatic breast cancer. Source: Irish Cancer Society.

Introduction

Population-based cancer registries routinely monitor cancer incidence and prevalence to measure the cancer burden in a defined area. Cancer registries generally focus their efforts on collecting information on new diagnoses of cancer and the characteristics of the patients and tumours at the time of initial diagnosis. Patients are also followed up passively using death registration data to assess cancer outcomes such as survival. However, as survival has improved thanks to advances in early detection and available treatments, there is an increasing demand for information on a broader range of outcomes, including quality of life. Disease progression is one important prognostic factor that affects quality of life (Müller et al., 2018; Park et al., 2021). Currently standardised definitions and protocols for recording information on recurrence or progression of disease after the initial diagnosis period are lacking and this affects the quality of metastatic cancer data routinely collected.

The need for internationally approved guidance on what qualifies as a recurrence has been identified (Izci et al., 2020). The European Network of Cancer Registries has established a working group to address this issue (*Working Groups | European Network of Cancer Registries*, 2023). Also efforts to determine the 'true' burden of distant metastatic breast cancer are ongoing. The NCRI is a contributor to an international project that aims to examine how cancer registries in five high income countries collect information about new and recurrent metastatic breast cancer (International Agency for Research on Cancer, 2020). The five countries are Canada - British Columbia, Ireland, The Netherlands, Norway and the USA - Connecticut. The UNCOV_MBC project is focused on invasive female breast cancer cases diagnosed from 2005 onwards with follow-up to 2019.

As the numbers of cancer survivors increase in Ireland (National Cancer Registry Ireland, 2022), health services will come under increasing pressure with increased need/requirement for services (medical and psycho-social) for survivors. Improved monitoring of cancer progression and recurrence can inform both service provision and survivorship care. Epidemiological and clinical research to identify treatments associated with lower levels of recurrence and longer time to progression will improve patient outcomes. Follow-up protocols underpinned by more robust data might allow for better outcomes for patients and allow health services to allocate resources more efficiently. Moreover, the information could help identify patient groups who require additional support.

It has been reported that 90% of deaths in patients with solid tumours are as a result of metastasis (Riggio et al., 2021). In Norway using cancer registry data, Dillekås et al reported that 66.7% of cancer deaths from solid tumours in 2015 were caused by metastases, while the proportion of all breast cancer deaths caused by metastatic disease was 75.6% (Dillekås et al., 2019). The authors report that these figures may be an underestimation since (unlike metastases diagnosed at the same time as the primary tumour), metastases discovered at some later time point are often known to be underreported (Dillekås et al., 2019).

In Ireland, the National Cancer Registry (NCRI) does not yet routinely capture the number of patients living with late-stage cancer or the number of cancer patients whose disease has returned after a period of time when the cancer could not be detected (cancer recurrence). However, much relevant information is already collected on an incidental basis, and analysis of these existing data will, at the very least, assist planning for improvements in data collection.

The information presented here uses NCRI data to broadly describe the metastatic breast cancer (MBC) disease pattern from 1994 to 2018 in Ireland, with particular reference to the years 2005-2018. The latter period aligns with the UNCOV_MBC project timeframe. The overall focus of the report is to estimate the levels of distant metastatic disease in patients diagnosed with invasive breast cancer, both at diagnosis and subsequently. However, we recognise from the outset that the data currently available are likely to underestimate the true burden of distant metastatic breast cancer, and we make some recommendations aimed at improving the completeness of the data required.

Methods and patient characteristics

Current NCRI registration and recording of recurrence and distant metastasis data

The primary focus of NCRI data collection is on the patient, tumour and treatment data associated with new diagnoses of primary cancer. Limited data on metastases (if identified either at the time of diagnosis of the primary tumour, or subsequently) have been recorded since 1994. Data related to the occurrence of metastases that are captured include the specific data items date of diagnosis of the metastatic tumour and its site (using ICD-O3 topography codes). A primary cancer may have multiple associated metastases.

In 2002 a "recurrence date" field was added to the database. In general only one date, (that is the first recurrence date), is recorded per tumour. On discussion with the data collection team, it was decided that this field is currently unsuitable for use in analysis of cancer recurrence as we cannot be fully confident in the accuracy of the data recorded.

Data preparation and analysis

Individuals diagnosed with invasive breast cancer (C50 ICD10) between 1994 and 2018 were included in the study. Male breast cancer which accounts for less than one percent of new cases each year in Ireland are included in this analysis. Table (m1) below shows the criteria used to identify the study population.

Data on the date of diagnosis and site of all metastatic tumours associated with a primary invasive breast cancer were extracted. Metastases identified up to 90 days prior to the date of diagnosis of the primary breast cancer were included. The date of the earliest metastatic tumour was used as the date of first metastasis for calculation of cumulative risk of metastases in patients who did not have metastatic disease at the time of diagnosis (i.e., M0 at diagnosis).

While the sites/locations of all metastases are routinely captured, it is not explicitly recorded whether a metastasis site is local, regional or distant. For some sites this distinction is implicit, by comparison with the primary site; for example brain and lung are always distant metastatic sites, while lymph nodes or thorax (not otherwise specified, NOS**)** may be local, regional or distant. Reported metastatic sites that could have been regional or local to the primary breast cancer were excluded when calculating distant metastatic cancer risk, for example metastasis site thorax NOS was recorded for some breast cancer patients but was excluded in the cumulative risk analyses.

Cause-of-death information was derived from death certificate data provided by the Central Statistics Office, (Central Statistics Office, 2019).

Table m1 Criteria used to identify the study dataset

Step	Inclusion/exclusion criteria	n
A	Invasive breast cancers (ICD-10 C50) diagnosed 1994 – 2018 inclusive	61,552
B	Exclude second or subsequent primary breast cancers in the same patient	61,155
C	Distant metastases present at diagnosis (M1)	4,056[#1]
D	Distant metastases recorded at > 4 months in patients without metastases at diagnosis (not M1)	5,565
E	Other metastases recorded in patients without metastases at diagnosis (not M1) (These patients had a regional/distant metastasis recorded within 4 months of diagnosis that did not contribute to staging at diagnosis)	401[#2]
F	Distant metastases present at diagnosis (M1) or subsequently (C+ D+ E)	10,013[#1]

#1 n= 9 patients classified M1 at diagnosis included in C above were not counted in F
#2 n= 401 patients are counted in F above, of these n= 16 were regional/distant and n=385 were distant.

Statistical analysis

Demographic and clinical characteristics

For the purpose of this report the main outcome measure was distant metastases in breast cancer patients who were not M1 at diagnosis. This was based on D above (table m1) because of some uncertainty as to whether cases in E might better be combined with C. However, overall figures (sum of C + D + E) are tabulated in addition to D only.

Demographic and clinical characteristics of patients diagnosed with invasive breast cancer are presented separately by diagnosis periods 1994-2004 and 2005-2018. Further subgroup analysis is provided of distant metastases stratified by demographic and clinical characteristics.

Sites of metastases

For this report descriptive statistics are provided for all metastases recorded between 1994-2018, but with the main focus on patients originally diagnosed during 2005-2018. Metastases records were not deduplicated, so that there may be >1 record of a given site-category

relating to a specific primary breast cancer. Also, not all records are confirmed distant metastases, that is some may relate to local recurrences or to regional/locoregional spread (at diagnosis or subsequently). In particular, metastases in lymph nodes may include a mix of regional and distant metastasis

Cumulative risk of mortality and distant metastases

Kaplan-Meier cumulative risk curves for cause specific mortality and distant metastasis in patients not M1 at diagnosis were calculated, for two diagnosis periods, 1994-2004 and 2005-2018. A more detailed analysis by patient demographics and clinical characteristics for the later diagnosis period (2005-2018), is provided. These analyses provide further context to the information on the risk of developing distant metastatic disease post-diagnosis, as the majority of deaths attributed to breast cancer should involve distant metastasis – thus a risk of cause-specific death substantially higher than the risk of distant metastatic disease, over an equivalent follow-up period, would be a likely indicator of substantial under-recording of distant metastatic disease.

All analyses used Stata/IC 15.1 software package, (*Stata/IC*, 2020).

Results

Demographic and clinical characteristics

In total, 61,155 patients were included in the analyses. The characteristics of the included patients and their first primary breast cancers can be seen in Table 1.0.

Patients M0 at diagnosis

Of the 57,099 patients who did not have metastatic breast cancer at diagnosis, 5,565 patients subsequently had a distant metastatic tumour recorded (Table 2.0).

Table 1.0 Demographic and clinical characteristics (at diagnosis) of all patients diagnosed with invasive breast cancer 1994-2018						
	1994-2004 (n=20643)		**2005-2018 (n=40512)**		**Total (n=61155)**	
Subgroup	**M0**	**M1**	**M0**	**M1**	**M0**	**M1**
Sex						
Female	19051 (99.4%)	1456 (99.2%)	37602 (99.2%)	2567 (99.2%)	56653 (99.2%)	4023 (99.2%)
Male	124 (0.6%)	12 (0.8%)	322 (0.8%)	21 (0.8%)	446 (0.8%)	33 (0.8%)
Age group						
15-44 years	2774 (14.5%)	146 (9.9%)	5155 (13.6%)	312 (12.1%)	7929 (13.9%)	458 (11.3%)
45-54 years	4696 (24.5%)	265 (18.1%)	9697 (25.6%)	469 (18.1%)	14393 (25.2%)	734 (18.1%)
55-64 years	4709 (24.6%)	351 (23.9%)	9797 (25.8%)	521 (20.1%)	14506 (25.4%)	872 (21.5%)
65-74 years	3510 (18.3%)	380 (25.9%)	6757 (17.8%)	622 (24%)	10267 (18%)	1002 (24.7%)
75+ years	3486 (18.2%)	326 (22.2%)	6518 (17.2%)	664 (25.7%)	10004 (17.5%)	990 (24.4%)
Stage at diagnosis						
Stage I	5010 (26.3%)	-	13037 (34.6%)	-	18047 (31.8%)	-
Stage II	9959 (52.3%)	-	16595 (44.1%)	-	26554 (46.8%)	-
Stage III	2644 (13.9%)	-	5097 (13.5%)	-	7741 (13.7%)	-
Stage IV	-	1463 (100%)	-	2586 (100%)	-	4049 (100%)
Unknown	1439 (7.6%)	(0%)	2926 (7.8%)	-	4365 (7.7%)	-
T category						
T1	6848 (35.8%)	128 (8.7%)	16418 (43.6%)	262 (10.2%)	23266 (41%)	390 (9.7%)
T2	7962 (41.7%)	375 (25.5%)	14202 (37.7%)	842 (32.8%)	22164 (39.1%)	1217 (30.2%)
T3	1635 (8.6%)	166 (11.3%)	2687 (7.1%)	304 (11.8%)	4322 (7.6%)	470 (11.6%)
T4	1220 (6.4%)	565 (38.5%)	1330 (3.5%)	801 (31.2%)	2550 (4.5%)	1366 (33.8%)
TX	1451 (7.6%)	234 (15.9%)	3002 (8%)	359 (14%)	4453 (7.8%)	593 (14.7%)
N Category						
N0	8853 (46.3%)	187 (12.7%)	19884 (52.5%)	303 (11.7%)	28737 (50.4%)	490 (12.1%)
N1	6833 (35.7%)	543 (37%)	10809 (28.5%)	1204 (46.6%)	17642 (30.9%)	1747 (43.1%)
N2	554 (2.9%)	208 (14.2%)	1776 (4.7%)	350 (13.5%)	2330 (4.1%)	558 (13.8%)
N3	184 (1%)	46 (3.1%)	1098 (2.9%)	233 (9%)	1282 (2.2%)	279 (6.9%)
NX	2712 (14.2%)	483 (32.9%)	4321 (11.4%)	496 (19.2%)	7033 (12.3%)	979 (24.2%)
Grade						
Grade 1	1785 (9.3%)	32 (2.2%)	3925 (10.3%)	80 (3.1%)	5710 (10%)	112 (2.8%)
Grade 2	5910 (30.8%)	316 (21.5%)	19275 (50.8%)	1221 (47.2%)	25185 (44.1%)	1537 (37.9%)
Grade 3-4	5709 (29.8%)	456 (31.1%)	12265 (32.3%)	961 (37.1%)	17974 (31.5%)	1417 (34.9%)
Unknown	5771 (30.1%)	664 (45.2%)	2459 (6.5%)	326 (12.6%)	8230 (14.4%)	990 (24.4%)
HER2						
Negative	2685 (75.4%)	194 (69.5%)	28016 (83.9%)	1633 (74.2%)	30701 (83.1%)	1827 (73.6%)
Positive	878 (24.6%)	85 (30.5%)	5360 (16.1%)	569 (25.8%)	6238 (16.9%)	654 (26.4%)
ER/PR						
Negative	1321 (20.2%)	98 (23.6%)	5312 (15.2%)	470 (20.3%)	6633 (16%)	568 (20.8%)
Positive	5208 (79.8%)	317 (76.4%)	29555 (84.8%)	1849 (79.7%)	34763 (84%)	2166 (79.2%)

Table 2.0 Demographic and clinical characteristics of patients with invasive non metastatic (M0) breast cancer at diagnosis, who subsequently developed distant metastatic cancer 1994-2018						
	1994-2004 (n=19168)		2005-2018 (n=37915)		[#]Total (n=57083)	
Subgroup	Developed Metastases	No Metastases	Developed Metastases	No Metastases	Developed Metastases	No Metastases
Median months of follow-up	**67**	**171**	**33**	**56**	**45**	**68**
Sex						
Female	2885 (99.4%)	16159 (99.3%)	2641 (99.2%)	34952 (99.1%)	5526 (99.3%)	51111 (99.2%)
Male	17 (0.6%)	107 (0.7%)	22 (0.8%)	300 (0.9%)	39 (0.7%)	407 (0.8%)
Age group						
15-44 years	627 (21.6%)	2144 (13.2%)	575 (21.6%)	4577 (13%)	1202 (21.6%)	6721 (13%)
45-54 years	804 (27.7%)	3891 (23.9%)	679 (25.5%)	9014 (25.6%)	1483 (26.6%)	12905 (25%)
55-64 years	793 (27.3%)	3916 (24.1%)	586 (22%)	9210 (26.1%)	1379 (24.8%)	13126 (25.5%)
65-74 years	471 (16.2%)	3037 (18.7%)	467 (17.5%)	6289 (17.8%)	938 (16.9%)	9326 (18.1%)
75+ years	207 (7.1%)	3278 (20.2%)	356 (13.4%)	6162 (17.5%)	563 (10.1%)	9440 (18.3%)
Stage at diagnosis						
Stage I	384 (13.3%)	4626 (28.6%)	298 (11.2%)	12739 (36.4%)	682 (12.3%)	17365 (33.9%)
Stage II	1790 (61.9%)	8167 (50.6%)	1297 (48.9%)	15293 (43.7%)	3087 (55.7%)	23460 (45.9%)
Stage III	617 (21.3%)	2024 (12.5%)	947 (35.7%)	4147 (11.8%)	1564 (28.2%)	6171 (12.1%)
Unknown	100 (3.5%)	1337 (8.3%)	108 (4.1%)	2817 (8%)	208 (3.8%)	4154 (8.1%)
T category						
T1	740 (25.5%)	6106 (37.7%)	538 (20.3%)	15879 (45.4%)	1278 (23%)	21985 (43%)
T2	1458 (50.3%)	6503 (40.1%)	1313 (49.4%)	12885 (36.8%)	2771 (49.9%)	19388 (37.9%)
T3	375 (12.9%)	1260 (7.8%)	436 (16.4%)	2248 (6.4%)	811 (14.6%)	3508 (6.9%)
T4	221 (7.6%)	997 (6.2%)	250 (9.4%)	1080 (3.1%)	471 (8.5%)	2077 (4.1%)
TX	105 (3.6%)	1344 (8.3%)	119 (4.5%)	2882 (8.2%)	224 (4%)	4226 (8.3%)
N category						
N0	897 (31%)	7956 (49%)	708 (26.6%)	19176 (54.4%)	1605 (28.9%)	27132 (52.7%)
N1	1585 (54.7%)	5245 (32.3%)	1179 (44.4%)	9623 (27.3%)	2764 (49.7%)	14868 (28.9%)
N2	152 (5.2%)	402 (2.5%)	313 (11.8%)	1463 (4.2%)	465 (8.4%)	1865 (3.6%)
N3	49 (1.7%)	134 (0.8%)	254 (9.6%)	843 (2.4%)	303 (5.5%)	977 (1.9%)
NX	215 (7.4%)	2494 (15.4%)	204 (7.7%)	4116 (11.7%)	419 (7.5%)	6610 (12.8%)
Grade						
Grade 1	164 (5.7%)	1621 (10%)	70 (2.6%)	3855 (10.9%)	234 (4.2%)	5476 (10.6%)
Grade 2	968 (33.4%)	4940 (30.4%)	1100 (41.3%)	18172 (51.5%)	2068 (37.2%)	23112 (44.9%)
Grade 3-4	1047 (36.1%)	4659 (28.6%)	1387 (52.1%)	10873 (30.8%)	2434 (43.7%)	15532 (30.1%)
Unknown	723 (24.9%)	5046 (31%)	106 (4%)	2352 (6.7%)	829 (14.9%)	7398 (14.4%)
HER 2						
Negative	530 (70.8%)	2153 (76.6%)	1974 (80.7%)	26039 (84.2%)	2504 (78.3%)	28192 (83.6%)
Positive	219 (29.2%)	658 (23.4%)	473 (19.3%)	4884 (15.8%)	692 (21.7%)	5542 (16.4%)
ER/PR						
Negative	276 (23.7%)	1044 (19.5%)	656 (25.7%)	4653 (14.4%)	932 (25.1%)	5697 (15.1%)
Positive	888 (76.3%)	4318 (80.5%)	1897 (74.3%)	27655 (85.6%)	2785 (74.9%)	31973 (84.9%)

[#] n= 16 patients whose first metastasis within four months of diagnosis was regional/distant were excluded from this dataset.

Cumulative risk of metastasis and cause specific mortality

Tables A.1 to A.5 in Appendix 1 show the cumulative risk of breast cancer mortality and distant metastatic disease at 1, 5, 10, 14 and 25 years post-diagnosis by demographic and clinical characteristics at diagnosis. These tabulations summarise (at selected intervals) the fuller survival risk curves presented below.

Cumulative recorded risk of distant metastatic disease, M0 at diagnosis

It is important to note that the estimates presented here of the risk of distant metastatic recurrence (based on time-to-event analysis taking account of the follow-up time available for each patient) should be considered minima i.e. the absolute values quoted are likely to be underestimates. Nevertheless, relative comparisons between subgroups should broadly be valid, though it is also important to emphasise that these comparisons are univariate and do not, for example, take account of possible differences in stage distribution between different age-groups or vice versa.

Diagnosis period

Cumulative risk curves for distant metastases in patients M0 at diagnosis are shown (Figure 1-a) with up to either 14 or 25 years follow-up, depending on diagnosis period. Relative to patients diagnosed between 1994 and 2004 with no distant metastases at diagnosis, patients diagnosed between 2005 and 2018 had a small increased risk of a distant metastatic disease in the first year post-diagnosis, (1.0% versus 0.7%). Thereafter the risk remained lower, at 5, 10 and 14 years post-diagnosis.

Subsequent statistics are based on diagnosis period 2005-2018 only.

Age

In breast cancer patients who had no distant metastases at diagnosis, the cumulative risk of distant metastatic disease differed based on age at diagnosis, (Figure 1-b). At one year post diagnosis, the estimated cumulative risk of distant metastatic disease was highest (≥ 1.5%) in those who were diagnosed with breast cancer before 45 years of age (relative to older age-groups), (Figure 1-b). The risk remained highest for this age-group at 5 (≥12%), 10 (≥16%) and 14 (≥19%) years post diagnosis. Within each survival period, the risk then decreases by age-group before increasing again in those diagnosed after 64 years of age. Among the age groups, the risk of distant metastatic disease was consistently lowest for those who were diagnosed between ages 55 and 64 years, at 5 (≥6%), 10 (≥9%) and 14 (≥11%) years post diagnosis.

Stage at diagnosis

In breast cancer patients who had no distant metastases at diagnosis, the cumulative risk of distant metastatic disease was seen to increase with higher stage at diagnosis, (Figure 1-c). This was true at 1, 5, 10 and 14 years post-diagnosis. The risk of distant metastatic disease was at least two to three times greater in those diagnosed with stage III cancer compared to those diagnosed at stage II (Figure 1-c). At 5 years post-diagnosis the estimated cumulative risk of distant metastases was ≥ 7% (stage II at diagnosis) versus ≥ 22% (stage III at diagnosis), ≥12% versus ≥ 30% respectively at 10 years and ≥ 15% versus ≥ 34% respectively at 14 years post-diagnosis. Patients with stage I breast cancer at diagnosis had the lowest recorded (≥4.6%) risk of distant metastatic disease 14 years post diagnosis. Irrespective of stage at

diagnosis, the highest proportions of recorded recurrences were detected in the first 5 years post-diagnosis.

Grade

In breast cancer patients who had no distant metastases at diagnosis, the cumulative risk of distant metastatic disease was seen to increase with higher grade at diagnosis, (Figure 1-d). The cumulative risk of distant metastatic disease was highest in the first 5 years following diagnosis for patients diagnosed with grade 3-4 tumour relative to patients diagnosed with lower grade tumours (grade 1 and 2). For patients diagnosed with grade 3-4 tumours the cumulative risk was ≥ 13%, (Figure 1-d). The risk of developing metastases increased gradually over time for patients diagnosed with grade 1 and grade 2 tumours. The general pattern of a large increase in risk of up to the fifth year post-diagnosis followed by a substantial levelling thereafter suggest metastatic disease is more likely to be recorded in the first 5 years following diagnosis.

Receptor status (HER2 and ER/PR)

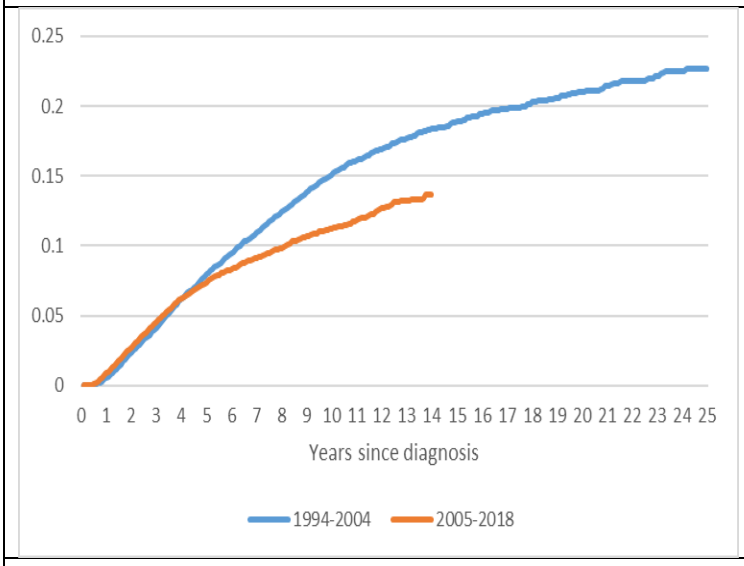
In breast cancer patients who had no distant metastases at diagnosis, the cumulative risk of distant metastatic disease differed based on receptor status at diagnosis, (Figure 1-e).

Overall patients who were HER2+ at diagnosis had a higher risk of developing distant metastatic disease at 5, 10 and 14 years post-diagnosis compared to those who were HER2- at diagnosis, (≥ 10% versus ≥7%, ≥13% v ≥11%, and ≥15% v ≥14% respectively), (Figure 1-e). Similar to grade, distant metastatic disease was more likely to be recorded in the first 5 years following diagnosis and cumulative risk levelled off thereafter. More detailed follow-up in the 5 year post-diagnosis period might possibly explain this. The risk of distant metastases among HER2+ patients was seen to rise more rapidly in the first 5 years post diagnosis, while the risk with HER2- was more gradual, though cumulative risks for both converge by 10 to 14 years post-diagnosis.

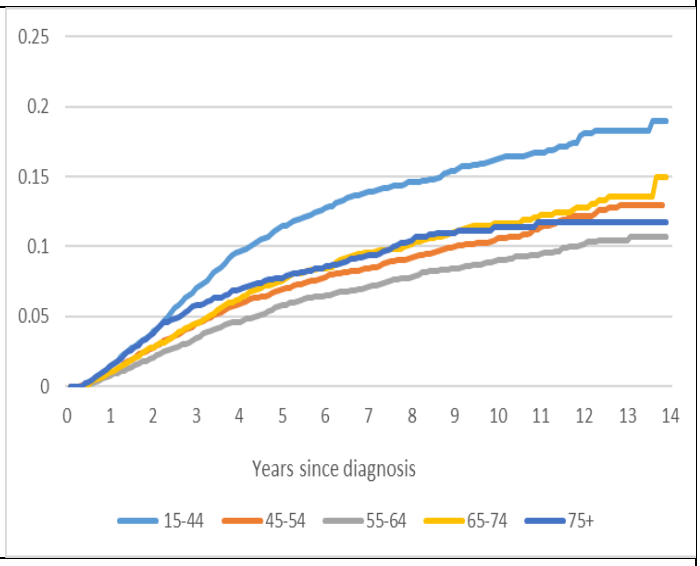
Breast cancer patients who were ER/PR- at diagnosis had a significantly higher risk of distant metastatic disease than those who were ER/PR + at diagnosis, (Figure 1-f). The increased risk was evident at 1, 5, 10 and 14 years post-diagnosis (≥2.8% v ≥0.7%, ≥15% v ≥6%, ≥17% v ≥10%, ≥17% v ≥13%) respectively. Similar to the patterns seen previously for tumour grade and HER2 status, the recorded risk of developing metastases for ER/PR- patients appeared highest in the first 5 years post-diagnosis. The risk of distant metastatic disease for these patients increased rapidly in the 5 years post-diagnosis and then gradually levelled off. The risk of developing metastases for ER/PR+ tumours at diagnosis increased more gradually over the entire 14 year follow-up period.

Figure 1 Cumulative risk of distant metastases in breast cancer patients who had no distant metastases (M0) at diagnosis by:

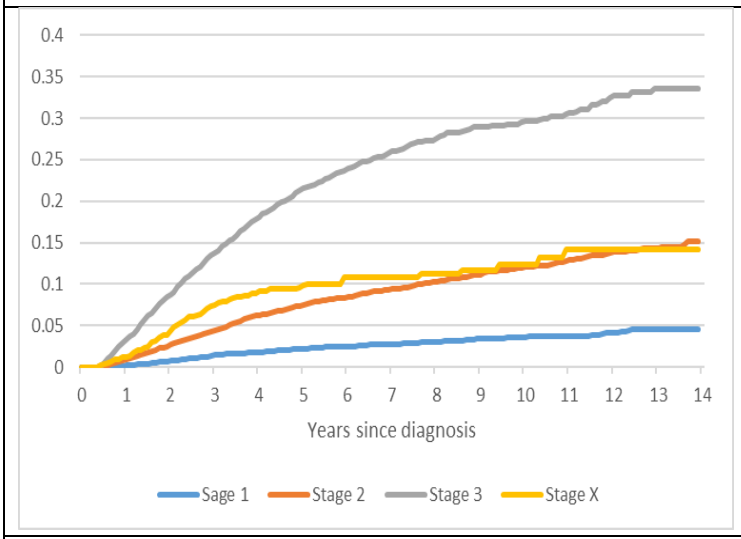
(A) Diagnosis period



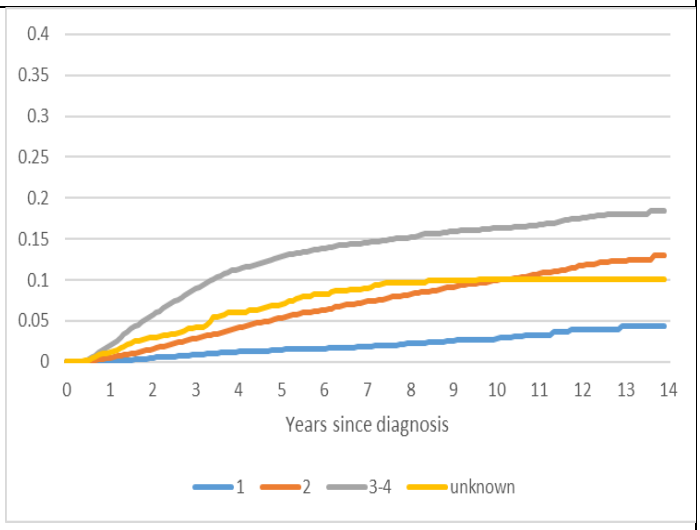
(B) Age 2005-2018



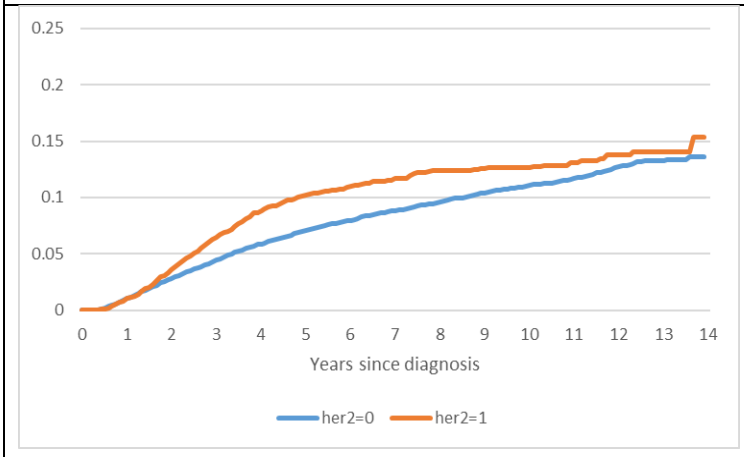
(C) Stage 2005-2018



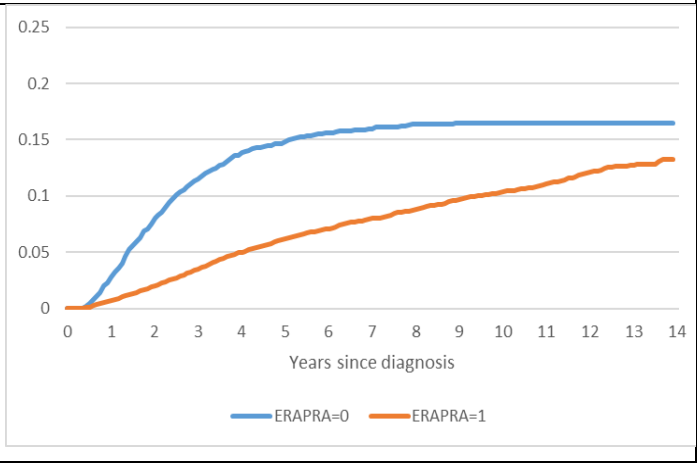
(D) Grade 2005-2018



(E) HER2 2005-2018



(F) ER/PR 2005-2018



Cumulative risk of mortality, M0 at diagnosis

Diagnosis period

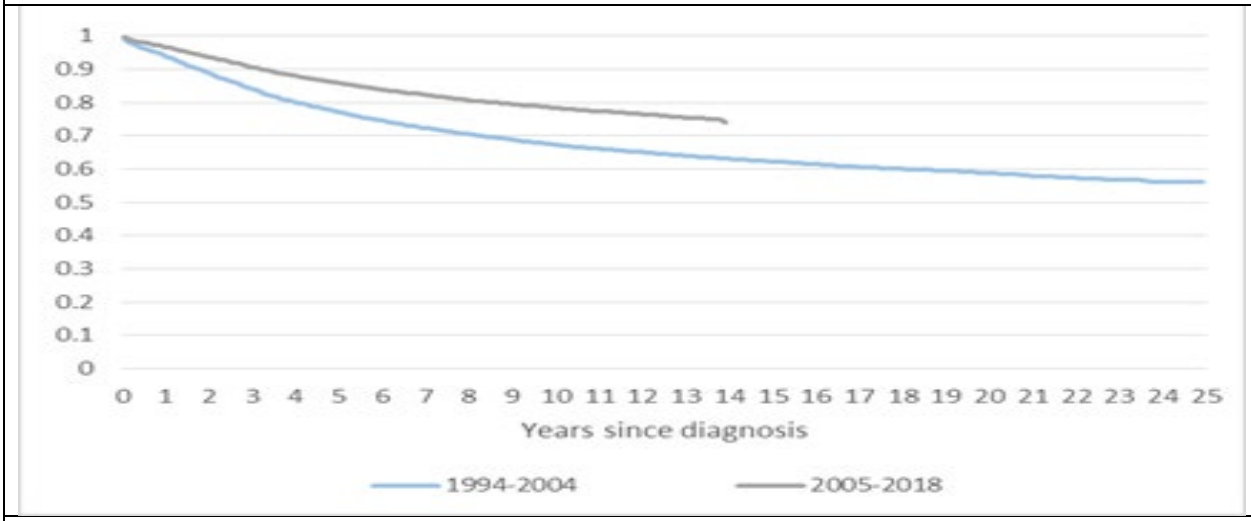
For breast cancer patients who did not have distant metastases at diagnosis, cause-specific mortality has improved over time, (Figure 2-a). On average 29% of breast cancer patients diagnosed between 1994 and 2004 died as a result of their breast cancer within 10 years following diagnosis. For those diagnosed in the later time period (2005-2018), 17% of patients died as a result of their cancer within 10 years after diagnosis.

Age

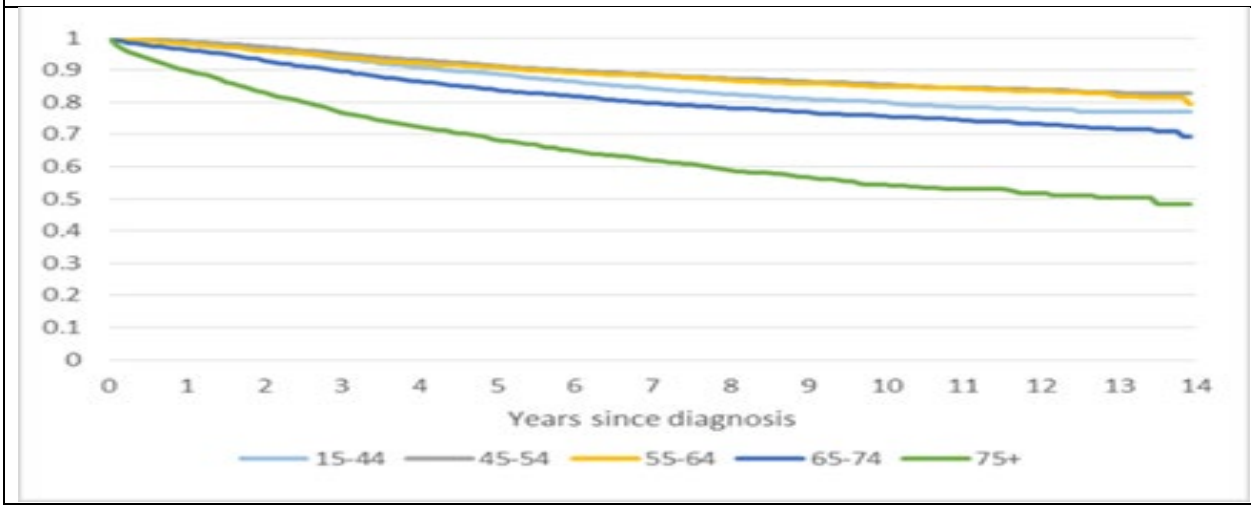
Figure 2-b shows the cumulative risk of cause-specific mortality among breast cancer patients diagnosed in Ireland, 2005-2018, by age at diagnosis. At one year post diagnosis, cause specific survival ranged from 99.5% in the youngest age-group (15-44 years) to 93.9% in the oldest age-group (75+ years). That is, 0.5% of those aged 15-44 years at diagnosis died as a result of their breast cancer within one year compared to 7% of those aged 75 years or older at diagnosis. At 5, 10 and 14 years the 15-44 year age-group had a higher risk of dying of their breast cancer than those aged 45-54 years and 55-64 years , but lower than those age 65 and over. This pattern across age-groups is consistent within each of the survival timeframes (5, 10 and 14 year survival).

Figure 2 Cause-specific survival in breast cancer patients who had no distant metastases (M0) at diagnosis by:

(A) Diagnosis period



(B) Age at diagnosis



Overall cumulative risk of distant metastases at diagnosis and subsequently

The cumulative overall risk of distant metastasis (that is present at diagnosis or at > 4 months in patients without metastases at diagnosis) among breast cancer patients diagnosed in Ireland is presented here, for different patient subgroups, to provide a minimum measure of the overall burden of MBC.

Diagnosis period

The cumulative overall risk of distant metastases (at diagnosis or subsequently) among breast cancer patients was broadly similar in the two time periods at 1 and 5 years post-diagnosis, (figure 3-a). There was a lower risk of distant metastases recorded by 10 (≥18% versus ≥22%) and 14 years (≥21% versus ≥25%) post-diagnosis in the 2005-2018 time period relative to 1994-2004 time period.

The following statistics are based on diagnosis period 2005-2018 only.

Age

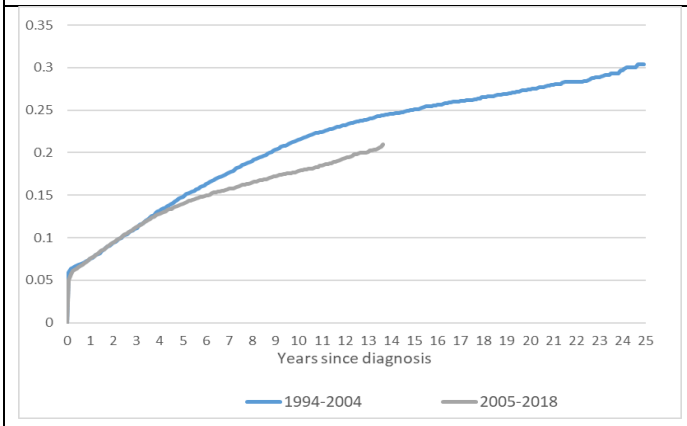
The two oldest age-groups at diagnosis (65-74 years and 75+ years) had the highest recorded risk of distant metastasis in the year following diagnosis at ≥11% and ≥10% respectively, (Figure 3-b). The cumulative risk of distant metastases recorded in the youngest age-group increased from ≥7% in the year following diagnosis to ≥17% by 5 years post-diagnosis, (Figure 3b). By 5, 10 and 14 years post-diagnosis, the youngest and oldest age-groups were most likely to have distant metastases. Those aged 45-64 years at diagnosis were least likely to have had distant metastases. The pattern of a consistently lower risk in this age group was also seen when distant metastases at diagnosis were excluded (Figure 1-b). In this analysis, the inclusion of distant metastases at diagnosis resulted in an overall increased cumulative risk for the oldest age-group.

Stage, grade, receptor status

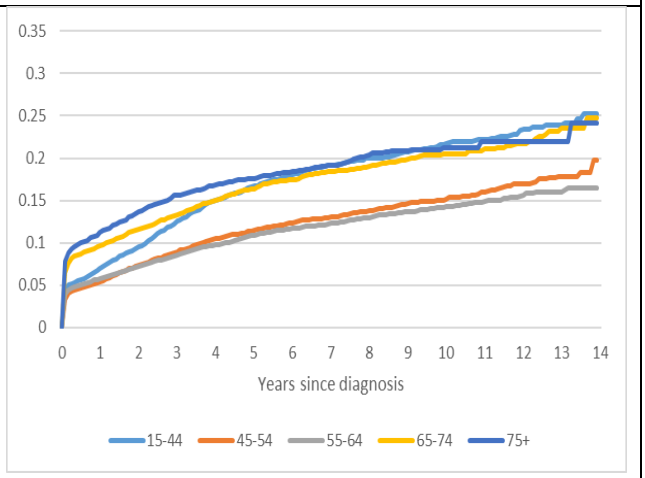
Overall risks of distant metastatic breast cancer are not graphed or described here in relation to these variables, but details are shown in Tables A.1 to A.4.

Figure 3 Cumulative risk of distant metastases at diagnosis (M1) and subsequently in breast cancer patients by:

(A) Diagnosis period



(B) Age 2005-2018



Sites of metastases

17172 site-specific metastases were recorded in 10,013 patients (at diagnosis or subsequently). Based on topographic codes, 15,715 (91%) were deemed likely to have been distant metastases. Of all patients who died from their breast cancer, 56% had recorded distant metastases (at diagnosis or subsequently).

Table 3 below shows the breakdown of breast cancer metastases by site and by time from primary breast cancer diagnosis. For cancers diagnosed between 1994 and 2018, 37% of all metastases occurred in bone, 17% in liver, 14% in lung, 8% in brain and 7% in lymph nodes.

These five sites accounted for just under 83% of all metastases recorded. In the 4 months following a breast cancer diagnosis, just over 45% of all recorded breast metastases were found in bone, 17% in liver, 15% in lung and 7% in lymph nodes. Between four months and one year after diagnosis, bone (32%) followed by liver (16%), brain (15%) and lung (15%) accounted for 78% of all recorded metastases. The proportion of metastases found in the brain increased from 3% to 15% in the first year post-diagnosis. Brain accounted for 13% of all metastases at 1-5 years post-diagnosis and 9% at 5-10 years post-diagnosis.

Table 3.0 Proportional breakdown of metastasis site recorded 1994 to 2018, by time from primary breast cancer diagnosis

Metastasis[1] Site	4 months following primary diagnosis	>4 <=12 months after diagnosis	>1 <=5 years after diagnosis	>5 <=10 years after diagnosis	>10 years after diagnosis	Totals
Bone	2976 (45.2%)	357 (32.4%)	1686 (31.3%)	941 (33.6%)	427 (32.7%)	6387 (37.2%)
Liver	1114 16.9)	176 (16%)	976 (18.1%)	473 (16.9%)	151 (11.6%)	2890 (16.8%)
Lung	956 14.5%)	164 (14.9%)	737 (3.7%)	368 (13.1%)	180 (13.8%)	2405 (14%)
Brain	199 (3.0%)	167 (15.2%)	687 (12.8%)	242 (8.6%)	88 (6.7%)	1383 (8.1%)
Lymph nodes	467 (7.1%)	69 (6.3%)	358 (6.7%)	176 (6.3%)	88 (6.7%)	1158 (6.7%)
Pleura (mainly)	190 (2.9%)	47 (4.3%)	334 (6.2%)	224 (8%)	130 (10%)	925 (5.4%)
Skin	62 (0.9%)	26 (2.4%)	123 (2.3%)	50 (1.8%)	41 (3.1%)	302 (1.8%)
Connective/soft tissue	71 (1.1%)	14 (1.3%)	74 (1.4%)	36 (1.3%)	31 (2.4%)	226 (1.3%)
Retroperitoneum /peritoneum	99 (1.5%)	6 (0.5%)	84 (1.6%)	67 (2.4%)	47 (3.6%)	303 (1.8) %
Adrenal gland	68 (1.0%)	13 (1.2%)	38 (0.7%)	16 (0.6%)	4 (0.3%)	139 (0.8%)
Ovary	28 (0.4%)	11 (1%)	35 (0.7%)	27 (1%)	14 (1.1%)	115 (0.7%)
Other sites	352 (5.3%)	51 (4.6%)	250 (4.6%)	183 (6.5%)	103 (7.9%)	939 (5.5%)
Total	6582	1101	5382	2803	1304	17172

*Based on categories recommended by American Joint Committee on Cancer, (Edge & American Joint Committee on Cancer, 2010)

Prevalence / survivorship

In total, of the 61,155 breast cancer patients diagnosed during 1994-2018, 10,013 had distant metastases recorded either at diagnosis or subsequently, based on NCRI data for the first invasive breast cancer in each patient. Of these, 1,717 patients were still alive at 31/12/2018, providing a minimum estimate of the number of survivors, at that date, of distant metastasis from breast cancer. Of the 1,717 survivors, 762 (44%) had distant metastases recorded as part of stage at diagnosis and 955 (56%) had distant metastases subsequently recorded, that is a later progression of disease, (Table 4).

Table 4.0 Demographic and clinical characteristics of patients diagnosed with distant metastatic breast cancer at diagnosis or subsequently, (1994-2018), who were alive at the end of follow-up 31/12/2018.	
Subgroup	Survivors n =1717
Sex	
Female	1704 (99.2%)
Male	13 (0.8%)
Age group at diagnosis	
15-44 years	385 (22.4%)
45-54 years	515 (30%)
55-64 years	370 (21.5%)
65-74 years	293 (17.1%)
75+ years	154 (9%)
Stage at diagnosis	
Stage I	145 (8.4%)
Stage II	488 (28.4%)
Stage III	263 (15.3%)
Stage IV	762 (44.4%)
Unknown	59 (3.5%)
T category	
T1	357 (20.8%)
T2	729 (42.5%)
T3	244 (14.2%)
T4	225 (13.1%)
TX	162 (9.4%)
N Category	
N0	433 (25.2%)
N1	800 (46.6%)
N2	178 (10.4%)
N3	121 (7%)
NX	185 (10.8%)
Grade	
Grade 1	79 (4.6%)
Grade 2	837 (48.7%)
Grade 3-4	634 (36.9%)
Unknown	167 (9.7%)
HER2	
Negative	992 (57.8%)
Positive	346 (20.2%)
Unknown	379 (22.1%)
ER/PR	
Negative	196 (11.4%)
Positive	1231 (71.7%)
Unknown	290 (16.9%)

Discussion

Metastases

Using NCRI data, the minimum proportion initially diagnosed with non-metastatic invasive breast cancer between 2005-2018 who later developed distant metastases was 8% after 5 years. It was 11% after 10 years follow-up and 14% after 14 years follow-up. For 1994-2004 the proportions were 8%, 15% and 18% after 5, 10 and 14 years respectively. As might be expected, given advances in cancer treatment and care, the proportion of patients who developed metastatic disease following initial diagnosis were lower in the most recent period (2005-2018) than in the earlier period. The minimum proportion of cases who developed distant metastases after 25 years of follow-up was available for cases diagnosed 1994-2004 only and was estimated to be 23%.

The estimates presented in this report are at the lower end of what has been reported in the literature: 7%-14% at 5-years (Holleczek et al., 2019; Lord et al., 2022; Minicozzi et al., 2013; van Roozendaal et al., 2016); 11%-19% at 10 years (Geurts et al., 2017; Holleczek et al., 2019; Lord et al., 2022; Lyngholm et al., 2016) and approximately 20-22% after 15-20 years (Hölzel et al., 2017; Lord et al., 2022; Lyngholm et al., 2016). Five of these studies were European based and used cancer registry data. These were Germany - (Holleczek et al., 2019; Hölzel et al., 2017), The Netherlands - (Geurts et al., 2017; van Roozendaal et al., 2016) and Italy - (Minicozzi et al., 2013). The sixth study used data from the New South Wales cancer registry in Australia, (Lord et al., 2022). The populations included, the time periods under study and the study aims and methodologies varied across the studies so that it is difficult to interpret variations across studies.

In Ireland, developments such as improvements in early detection through the introduction of the national screening programme, improved imaging and diagnostic techniques as well as improved treatment options may have reduced the risk of progression and recurrence. Also, the pattern of recurrence over time might have changed, for example, if recurrence risk, among medium/long-term survivors, was pushed further out from diagnosis.

Two broad patterns emerged from the main findings of this report. Firstly, the highest proportion of metastatic disease (in patients without distant metastases at diagnosis) was recorded in the first 5 years post-diagnosis. This finding may be due to in part to more targeted follow-up in the first 5 years following diagnosis, though it might also reflect the natural history or course of the disease. The highest risk of developing metastases in the first 5 years post-diagnosis was observed in ER- patients. The continued gradual increase in the risk of metastases for ER+ breast cancer patients over time seen in this analysis have been described elsewhere (Colleoni et al., 2016). A number of other studies have reported the highest risk of recurrence in the first few years following diagnosis varies depending on a number of factors. These include time period of diagnosis, age, receptor status etc: (Geurts et al., 2017; Holleczek et al., 2019; Hölzel et al., 2017; Lord et al., 2022; Lyngholm et al., 2016)

The second broad pattern seen was an expected increased risk of subsequently developing metastases in those recorded as having advanced and/or aggressive disease at diagnosis, based on higher stage, grade or a particular hormone receptor profile (e.g., ER/PR-). The risk of developing distant metastatic cancer after diagnosis was higher in younger patients (aged 45 years or less) throughout follow-up. This is consistent with what has been reported previously in the literature (Holleczek et al., 2019; Lord et al., 2022), and with other studies

noting the increased risk of recurrence coupled with higher mortality linked to more aggressive disease in younger patients (Azim & Partridge, 2014; Radecka & Litwiniuk, 2016).

The associations seen from Irish cancer registry data are based on descriptive univariate comparisons, and a more detailed (multivariable) analysis might further clarify which (combinations of) factors contribute to the risk of developing metastatic disease in patients without distant metastases at diagnosis.

Where patients with distant metastases at diagnosis are included, the oldest age-groups at diagnosis had the highest cumulative risk of distant metastasis post-diagnosis. Until 2015 patients over 64 years of age were not eligible for routine population based screening so this may be a contributing factor (Fitzpatrick et al., 2018).

Bone, liver and lung in that order were consistently the three most common sites for breast cancer metastases for all the time periods examined up to 10 years post-diagnosis. Bone, liver and lung have been reported to be the most common metastatic sites internationally (Calip et al., 2022; Hölzel et al., 2017; Lord et al., 2022; Malmgren et al., 2018) and in Ireland (Courtney et al., 2022). While lymph nodes are also a common site for metastases, it is not always possible to distinguish between regional and distant nodal metastasis in our data.

Cause-specific mortality

Comparisons between the recorded risk of distant metastases and the cumulative risk of cause specific survival for a given period of follow-up might give an indication of the degree to which distant metastases are under recorded.

Cause-specific mortality from breast cancer has improved over time, as also noted for net (relative) survival from breast cancer in Ireland (NCRI annual report 2022 reference). Across both survival periods (at 1, 5, 10 and 14 years post-diagnosis) patients diagnosed in the later time period (2005-2018) were less likely to die as a result of their breast cancer than for those diagnosed in the earlier time period (1994-2004).

For patients diagnosed in the interval 2005-2018 and excluding those with distant metastases at diagnosis, patients aged 15-44 years at diagnosis had a higher risk of dying of their breast cancer relative to those aged 45-54 years or 55-64 years at 5, 10 and 14 years post-diagnosis but lower relative to those aged 65 years and over. Patients who are diagnosed later in life and who survive 5 or more years are likely to have more comorbidities than younger patients. This might impact treatment decisions for older patients who may be treated less aggressively than younger patients (Ferrigni et al., 2019; Wyld et al., 2021). In this context the increased mortality risk shown here in the youngest age-group may be underestimated.

Excluding patients with distant metastases at diagnosis, cause-specific mortality increases with later stage at diagnosis, across all survival periods. Patients ‘stage unknown’ at diagnosis had survival comparable with stage III survival. This might reflect incomplete follow-up and less complete staging workups in those with more severe disease.

Overall, based on Irish patients diagnosed during 2005-2018 with breast cancer that was not initially staged as distant metastatic, we estimated cumulative cause-specific mortality risk as 17% by 10 years after diagnosis, compared with a minimum estimate of 11% of distant metastatic disease over the same interval (Table A.3). By 14 years after diagnosis, our

equivalent estimates were 22% (cause-specific mortality) and 14% (distant metastatic disease) (Table A.4). At face value, given that the majority of cause-specific breast cancer deaths result from distant metastasis (Dillekås et al., 2019; Riggio et al., 2021) and that not all patients developing distant metastases will die within the same follow-up period, it would seem that our figures underestimate the true risk of developing distant metastatic breast cancer after diagnosis. Figures in tables A.3 and A.4 suggest that the degree of underestimation is highest for older patients. There may be age-related differences in the reliability of cause-of-death coding or in average length of follow-up data, so these findings should be interpreted with caution.

Quality of NCRI recurrence / distant metastasis recording

The overall focus of this report is to estimate the levels of distant metastatic disease in patients diagnosed with invasive breast cancer. We have shown that more metastases were captured in the first 5 years after diagnosis than subsequently. Comparing cause specific mortality to the risk of developing metastatic disease, the numbers of metastases recorded stabilize from 5 years onwards while mortality continues to increase. This, and the quantitative comparisons noted above, suggest the data collected currently by NCRI substantially underestimate the number of people who develop metastatic disease, particularly those which are occurring more than 5 years after diagnosis. Under reporting of metastases discovered after diagnosis is a known issue (Dillekås et al., 2019), including (or perhaps especially) in those who die of other causes. Alternatively, there may be a time lag (which is hopefully increasing over time) between developing MBC and death.

While the data analysed and presented in this report are informative, a number of limitations have been identified. These are described below.

Limitations

The NCRI has been collecting data on metastases at diagnosis comprehensively, and on subsequent metastatic tumours opportunistically, since 1994. Date of recurrence has been collected, if available, from 2002, but limited to a single recurrence per patient. The level of detail available in the NCRI database for distant metastases, is more substantial than the basic 'date of recurrence' field, and includes multiple dates.

The main focus of this report is on distant metastatic breast cancer which develops after the initial diagnosis period, that is, a record of subsequent distant disease (M1) in someone who did not have a distant metastasis at diagnosis (M0), with particular reference to the period 2005 to 2008. Staging at diagnosis is collected by the NCRI. A patient who is staged M1 at diagnosis has, by definition, a distant metastasis while those not M1 at diagnosis may never go on to develop metastases or can develop regional, local or distant metastases at some later point. We identified a small number of cases where a recorded distant metastasis within four months of diagnosis has not contributed to staging. This can occur if the distant metastasis is recorded subsequent to definitive surgery, as such information does not contribute to clinical or pathological stage at diagnosis based on international staging rules. On occasion it may result from coding/registration error.

Similarly, where the first metastases recorded within four months of diagnosis cannot be accurately classified as regional or distant, a tumour may be misclassified as M0 at diagnosis. Even where standard staging rules are followed, it is not always clear whether a distant metastatic tumour identified within four months of initial diagnosis genuinely reflects i.)

progression or worsening of the disease or ii.) more advanced disease missed at the time of initial diagnosis/treatment. Older patients, in particular, may be less likely to be comprehensively investigated and so they are more likely to have metastases missed at diagnosis. Because of these considerations, figures presented in this report for 'distant metastatic disease' count only records of distant metastasis that were first recorded more than four months after diagnosis (and only in patients originally staged as not having distant metastatic disease). We also present figures on 'overall' distant metastatic risk, which include apparent distant metastases within four months post-diagnosis along with distant metastases captured as part of stage at diagnosis.

Underestimation of the risk of distant metastatic disease is likely to occur based on the routine data collected by NCRI and, indeed, probably most population-based cancer registries. In this study, the methodological decision to exclude metastatic sites that could have been local or regional to the primary breast cancer will have compounded the underestimation. On the other hand, ongoing development of the cancer registration systems as well as more general improvements in health services information infrastructures (e.g., electronic data capture, greater storage and processing power) will have facilitated more timely and complete data capture so that data quality will have improved over the timescale of the study.

This study uses death certificate cause-of-death as a benchmark against which MBC is measured. It assumes underlying cause of death is accurately determined. A Swiss study of women diagnosed with breast cancer found cause of death was less accurately recorded in specific subgroups, in particular older age-groups (80 years and over) and those with more advanced disease. (Schaffar et al., 2013). Similar biases may affect this study and cannot be ruled out.

Survival data post-2018 is limited in this dataset, therefore follow-up data for the second time-period, 2005-2018, is truncated at 14 years (last follow-up date 31/12/2018). For those diagnosed in 2005 there are 14 years follow-up data up to and including 2018, for those diagnosed in 2006 there are 13 years follow-up data etc.

Conclusions

Using existing registry data, we present patterns of MBC over time, and how it varies by patient and tumour characteristics at diagnosis. The Irish experience mirrors that seen internationally, although the proportion of cases developing metastatic disease seems lower than that cited in the international literature, pointing to data ascertainment issues. The ongoing efforts of the ENCR working group clarifying cancer recurrence, progression and transformation data items to be collected by population based cancer registries will improve data collection. The work of the UNCOV-MBC (Uncovering Disparities in Metastatic Breast Cancer Outcomes) collaborative group will also contribute to efforts to improve data quality.

Improving early detection and treatments have led to better survival. Using cancer registry data to accurately identify patients who have had recurrence and quantifying the true risk of distant metastatic breast cancer remains an ongoing challenge.

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Appendices

The following tables show estimates of the cumulative risk of breast cancer mortality and cumulative minimum risk of breast cancer metastasis for Irish breast cancer patients at 1, 5, 10, 14 and 25 years post-diagnosis, based on National Cancer Registry Ireland data. Unless specified otherwise, figures relate to patients diagnosed 2005-2018, with follow-up to the end of 2018.

A1 Cumulative risk tables

Table A.1 Cumulative risk of mortality and minimum cumulative risk of distant metastasis (recurrence and/or at diagnosis) by 1 year after diagnosis			
	Excluding M1 at diagnosis[1]		**Including M1 at diagnosis[2]**
Subgroup	**Cause-specific mortality**	**Distant metastatic recurrence**	**Distant metastasis (at diagnosis or recurrence)**
1994-2004	3.5%	0.7%	7.5%
2005-2018	1.7%	1.0%	7.5%
2005-2018:			
Female	1.7%	1.0%	7.5%
Male	2.4%	0.3%	7.5%
Age 15-44	0.5%	1.5%	7.0%
Age 45-54	0.5%	0.7%	5.4%
Age 55-64	0.6%	0.8%	5.8%
Age 65-74	1.6%	1.0%	9.7%
Age 75+	6.7%	1.5%	11.2%
Stage I	0.4%	0.2%	0.3%
Stage II	1.2%	0.9%	1.4%
Stage III	4.3%	3.2%	5.1%
Unknown	7.3%	1.3%	4.4%
T1	0.5%	0.3%	1.8%
T2	1.3%	1.2%	6.7%
T3	2.0%	2.7%	12.7%
T4	11.5%	4.3%	39.9%
TX	7.2%	1.2%	14.8%
N0	0.7%	0.5%	2.0%
N1	1.6%	1.4%	11.2%
N2	2.5%	3.1%	18.8%
N3	3.1%	3.2%	19.5%
NX	6.9%	1.1%	13.4%
Grade 1	0.8%	0.2%	2.2%
Grade 2	1.1%	0.5%	6.3%
Grade 3-4	2.2%	2.0%	9.4%
Unknown	7.0%	1.2%	15.0%
HER2-	1.3%	1.0%	6.5%
HER2+	1.5%	1.0%	10.5%
ER/PR-	3.3%	2.8%	10.9%
ER/PR+	1.2%	0.7%	6.5%

[1]Excluding cases with distant metastasis at diagnosis. [2]Including cases with distant metastasis at diagnosis

Table A.2 Cumulative risk of mortality and minimum cumulative risk of distant metastasis (recurrence and/or at diagnosis) by 5 years after diagnosis			
	Excluding M1 at diagnosis[1]		**Including M1 at a diagnosis[2]**
Subgroup	**Cause-specific mortality**	**Distant metastatic recurrence**	**Distant metastasis (at diagnosis or recurrence)**
1994-2004	18.8%	8.1%	14.8%
2005-2018	10.2%	7.5%	14.0%
2005-2018:			
Female	10.2%	7.5%	14.0%
Male	10.4%	9.5%	16.5%
Age 15-44	8.3%	11.5%	16.7%
Age 45-54	6.2%	6.9%	11.5%
Age 55-64	5.8%	5.8%	10.9%
Age 65-74	10.7%	7.5%	16.4%
Age 75+	26.1%	7.7%	17.6%
Stage I	2.8%	2.2%	2.4%
Stage II	9.3%	7.4%	7.8%
Stage III	26.6%	21.6%	23.4%
Unknown	27.2%	9.8%	12.8%
T1	3.7%	3.2%	4.8%
T2	11.1%	9.1%	14.6%
T3	19.4%	18.2%	27.5%
T4	42.9%	23.8%	54.7%
TX	26.9%	10.9%	24.1%
N0	4.8%	3.5%	5.0%
N1	12.3%	10.4%	19.9%
N2	20.6%	20.7%	34.7%
N3	30.6%	27.9%	42.2%
NX	23.6%	9.1%	21.1%
Grade 1	2.6%	1.4%	3.7%
Grade 2	7.1%	5.4%	11.4%
Grade 3-4	15.8%	12.9%	19.9%
Unknown	20.2%	7.0%	20.5%
HER2-	9.2%	7.1%	12.6%
HER2+	11.8%	10.2%	19.6%
ER/PR-	20.0%	14.8%	22.4%
ER/PR+	7.9%	6.2%	12.2%

[1]Excluding cases with distant metastasis at diagnosis. [2]Including cases with distant metastasis at diagnosis

Table A.3 Cumulative risk of mortality and minimum cumulative risk of distant metastasis (recurrence and/or at diagnosis) by 10 years after diagnosis			
	Excluding M1 at a diagnosis[1]		**Including M1 at a diagnosis[2]**
Subgroup	**Cause-specific mortality**	**Distant metastatic recurrence[1]**	**Distant metastasis (at diagnosis or recurrence)**
1994-2004	28.6%	15.2%	21.5%
2005-2018	17.1%	11.3%	17.9%
2005-2018:			
Female	17.1%	11.2%	17.8%
Male	19.3%	13.6%	21.7%
Age 15-44	16.5%	16.3%	21.7%
Age 45-54	11.3%	10.4%	15.2%
Age 55-64	11.2%	9.0%	14.2%
Age 65-74	18.5%	11.6%	20.5%
Age 75+	40.0%	11.4%	21.2%
Stage I	5.7%	3.6%	3.8%
Stage II	17.0%	12.0%	12.4%
Stage III	40.2%	29.6%	31.3%
Unknown	40.3%	12.3%	15.3%
T1	7.3%	4.9%	6.7%
T2	20.0%	14.5%	20.1%
T3	31.5%	25.7%	34.5%
T4	56.8%	32.9%	61.0%
TX	41.5%	13.8%	27.1%
N0	8.9%	5.7%	7.4%
N1	21.5%	16.1%	25.5%
N2	33.2%	27.5%	41.1%
N3	46.4%	38.0%	51.8%
NX	34.0%	11.5%	23.5%
Grade 1	5.6%	2.8%	5.4%
Grade 2	14.7%	10.0%	16.0%
Grade 3-4	23.2%	16.3%	23.4%
Unknown	25.8%	10.1%	23.4%
HER2-	16.2%	11.1%	16.8%
HER2+	18.0%	12.6%	22.2%
ER/PR-	25.4%	16.5%	22.4%
ER/PR+	15.2%	10.4%	12.2%

[1]Excluding cases with distant metastasis at diagnosis. [2]Including cases with distant metastasis at diagnosis

Table A.4 Cumulative risk of mortality and minimum cumulative risk of distant metastasis (recurrence and/or at diagnosis) by 14 years after diagnosis			
	Excluding M1 at a diagnosis[1]		**Including M1 at a diagnosis[2]**
Subgroup	**Cause-specific mortality**	**Distant metastatic recurrence**	**Distant metastasis (at diagnosis or recurrence)**
1994-2004	32.9%	18.3%	24.5%
2005-2018	21.5%	13.6%	21.4%
2005-2018:			
Female	21.5%	13.6%	21.4%
Male	-	-	-
Age 15-44	19.7%	19.0%	25.3%
Age 45-54	13.8%	13.0%	19.7%
Age 55-64	16.7%	10.7%	16.4%
Age 65-74	25.2%	14.9%	24.7%
Age 75+	46.9%	11.8%	24.2%
Stage I	7.6%	4.6%	4.7%
Stage II	22.7%	15.1%	5.5%
Stage III	46.5%	33.6%	35.2%
Unknown	43.0%	14.2%	17.1%
T1	7.3%	6.4%	9.5%
T2	20.0%	18.0%	24.2%
T3	31.5%	28.5%	39.4%
T4	56.8%	-	-
TX	41.5%	15.6%	37.6%
N0	11.3%	7.0%	9.9%
N1	27.7%	19.8%	29.9%
N2	42.0%	34.6%	50.3%
N3	51.1%	39.5%	54.6%
NX	40.8%	12.8%	27.8%
Grade 1	9.9%	4.4%	6.9%
Grade 2	19.0%	12.9%	20.7%
Grade 3-4	26.4%	18.5%	26.5%
Unknown	34.1%	10.1%	24.5%
HER2-	21.0%	13.6%	19.8%
HER2+	23.5%	15.4%	27.7%
ER/PR-	25.4%	16.5%	24.8%
ER/PR+	15.2%	13.3%	20.7%

[1]Excluding cases with distant metastasis at diagnosis. [2]Including cases with distant metastasis at diagnosis

Table A.5 Cumulative risk of mortality and minimum cumulative risk of distant metastasis (recurrence and/or at diagnosis) by 25 years after diagnosis			
	M0 at a diagnosis[1]		**M1 at a diagnosis[2]**
Subgroup	**Cause-specific mortality**	**Distant metastatic recurrence**	**Distant metastasis (at diagnosis or recurrence)**
1994-2004	40.4%	22.6%	30.4%

[1]Excluding cases with distant metastasis at diagnosis. [2]Including cases with distant metastasis at diagnosis

A2. Recommendations to improve routine recording of breast cancer recurrence

The European Network of Cancer Registries (ENCR) has established a working group which is in the process of developing guidelines on the collection of recurrence data for cancer registries. Pending the recommendations of that working group and based on the data preparation, analyses and discussions involved in producing the present report, some recommendations have been compiled. These reference the NCRI and broader Irish data collections, to facilitate more thorough yet routine recording of cancer recurrence data. In summary, these include:

- Recording of all recurrence dates for a given patient/tumour and including the first recurrence (ideally separately for local, regional and distant).
- More explicit coding of which metastatic events contribute to stage at diagnosis and which are considered to involve recurrence or progression.
- More explicit coding of metastases regional or distant, to minimise (as far as possible) ambiguity in subsequent interpretation or analysis, which may not always be clear from the context.
- Explore/discuss with the wider hospital coding and cancer registration community opportunities for improving the routine coding, or availability of such routine coding, of cancer recurrence and metastasis data. For example, developing protocols to more accurately record and categorise recurrences/metastases related to second or subsequent primary cancers.