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The impact of patient comorbidity on cancer stage at diagnosis

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Background: It is known that cancer stage is affected by comorbidity, but the evidence regarding the magnitude and even direction of this effect is highly inconsistent and poorly understood. The aims of this study were to establish the impact of comorbidity on cancer stage at diagnosis, using both specific individual comorbid conditions and a global measure of comorbidity; and to assess whether this impact varied by cancer site, level of comorbidity burden and individual comorbidity type.

Methods: We examined comorbidity among 140% patients with breast, colon, rectal, liver, stomach, ovarian, uterine, bladder or kidney cancer. Patients were identified from cancer registry data, and then linked to hospitalisation data to determine the presence of comorbidity in the 5 years preceding cancer diagnosis. Individual comorbid conditions were identified using ICD-10 codes, and overall burden of comorbidity attributed using a cancer-specific measure of comorbidity (C3 Index).

Results: We observed that the presence of patient comorbidity (a) increases the odds of being diagnosed with distant metastases, (b) does not lead to earlier diagnosis and (c) increases the likelihood of a patient receiving no stage of disease at diagnosis.

Conclusions: Patient comorbidity has a substantial impact on cancer stage at diagnosis; however, this impact varies considerably by cancer type, individual comorbid condition and overall comorbidity burden.

It is known that cancer stage at diagnosis is affected by patient comorbidity, but the evidence regarding the magnitude and even direction of this effect is highly inconsistent (Terret *et al*, 2009; Corkum *et al*, 2012). This is because there are several competing mechanisms that may impact on stage at diagnosis (Fleming *et al*, 2005). Increased contact with health services may result in a 'surveillance effect' – leading to earlier diagnosis. In contrast, comorbidity may distract both the clinician and the patient from early signs and symptoms of cancer – leading to delayed diagnosis. In some cases, the patient has such severe comorbidity that their life expectancy is so limited that diagnostic investigation does not appear warranted. Furthermore, some comorbid conditions (e.g., diabetes) may have a direct effect on cancer growth (Giovannucci *et al*, 2010). The balance of these mechanisms is likely to vary by comorbidity and cancer type, as well as by health system factors.

The aims of this paper were: (a) to establish the impact of comorbidity on cancer stage at diagnosis across a wide range of cancers, using both specific individual comorbid conditions and a global measure of comorbidity; and (b) assess whether this impact varied by cancer site, level of comorbidity burden and individual comorbidity type.

MATERIALS AND METHODS

Participants. The current study is part of the wider C3 (Cancer, Comorbidity and Care) study, which investigated the impact of patient comorbidity on cancer care and outcomes. The New Zealand Cancer Registry (NZCR) was used to identify patients diagnosed with one of nine cancers (01 January 2006–31 December 2008), which were then clustered into five cancer 'groups': female breast (ICD-10-AM code: C50), colorectal (C18–C20), gynaecological (ovarian (C56) and uterine (C54)), upper gastrointestinal (liver (C22) and stomach (C16)) and urological (bladder (C67) and kidney (C64)). These cancers were included to represent a range of cancers that varied in terms of patient characteristics and underlying burden of comorbidity.

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Patients were excluded if they were diagnosed with carcinomain situ, aged <25 years at diagnosis, non-New Zealand residents, had a previous diagnosis of the same cancer or were diagnosed post mortem. Our final cohort included $n = 14\,096$ patients.

Data sources. Cancer Registry data were linked to public hospital (and reporting private hospital) discharge data (National Minimum Data Set (NMDS)) via a unique identifier, for the 5 years before the cancer diagnosis.

Variables. Sex, age at diagnosis, prioritised ethnicity, domicile code, cancer site, date of diagnosis and stage (SEER Summary Stage; categorised as local, regional, distant and unknown (Young *et al*, 2000)) were determined from the NZCR. For each patient, an index date was defined as the first admission that occurred at or within four weeks of date of cancer diagnosis, with the index cancer as the primary diagnosis. Where no such admission was identifiable, index date was the date of cancer diagnosis on the NZCR.

Level of patient deprivation was determined using the 2006 New Zealand Deprivation Index (NZDep) using domicile data (missing for 5.1%) (Salmond and Crampton, 2012).

All comorbid conditions recorded on the NMDS in the 5 years before the index hospitalisation date were identified, and used to calculate a C3 Index score for each patient (Sarfati *et al*, 2014). The C3 Index is a cancer-specific index of comorbidity, which is calculated based on the presence of 42 chronic conditions – each weighted according to its impact on non-cancer mortality among cancer patients, and then summed to arrive at a comorbidity score (Sarfati *et al*, 2014). C3 Index scores were categorised into '0' (≤ 0), '1' (≤ 1.00), '2' (≤ 2.00) and '3' (> 2.00).

Conditions that might be closely related to the primary cancer of interest or its treatment were excluded (Supplementary Material 5), while conditions that may have been complications of the primary disease or its treatment were only included if they were recorded before the index date (Supplementary Material 6).

Statistical analysis. Analysis was performed in SAS (v9.3, SAS Institute Inc., Cary, NC, USA). Key demographic, disease and comorbidity characteristics were described and standardised to the total New Zealand cancer population. Multinomial logistic regression methods were used to assess the extent to which overall level of patient comorbidity and individual comorbid conditions impacted on stage of disease adjusting for age (continuous), sex (where relevant), cancer group or site (as relevant), ethnicity (Māori/ non-Māori) and deprivation. When the impact of individual conditions was being assessed, we limited adjustment to age, sex, ethnicity and cancer group (for full cohort) because of limited numbers (methodology detailed in Supplementary Material 7).

Ethical approval was gained through the New Zealand Health and Disability Ethics Committee (reference #: MEC/10/042/EXP).

RESULTS

Table 1 shows the characteristics of the cohort in relation to their overall comorbidity status, with these data stratified by cancer type in Supplementary Material 3. Those in higher comorbidity categories tended to be older, proportionately less likely to be female, more likely to be Māori and more likely to live in more deprived areas (Table 1).

	C3 Index category												
	0		1			2			3				
	n	Crude %	Adj %ª	n	Crude %	Adj %ª	n	Crude %	Adj %ª	n	Crude %	Adj %ª	Pb
Cohort size/% total cohort	8873	63%		1891	13%		1233	9%		2099	15%		—
Age (years)													_
25–49 50–64 65–74 75 +	1874 3164 2115 1720	21% 36% 24% 19%		214 508 501 668	11% 27% 26% 35%	 	86 244 346 557	7% 20% 28% 45%		46 286 539 1228	2% 14% 26% 59%		
Median years (LQR, UQR)	62	(52, 72)		70	(59, 79)		74	(64, 81)		77	(69, 83)		
Sex													< 0.01
Female Male	6555 2318	74% 26%	72% 28%	1202 689	64% 36%	64% 36%	735 498	60% 40%	61% 39%	1150 949	55% 45%	56% 44%	
Ethnicity													< 0.01
Māori Non-Māori	739 8134	8% 92%	7% 93%	187 1704	10% 90%	12% 88%	137 1096	11% 89%	14% 86%	224 1875	11% 89%	22% 78%	
Stage of disease (SEER)													< 0.01
Local Regional Distant Unknown	3543 3026 1041 1263	40% 34% 12% 14%	39% 34% 12% 15%	640 595 322 334	34% 31% 17% 18%	35% 31% 17% 17%	220 365 380 268	18% 30% 31% 22%	34% 30% 17% 19%	361 486 578 674	17% 23% 28% 32%	27% 28% 18% 27%	
Deprivation (NZDep; $1 = \text{least}, 10 = \text{most}$)													< 0.01
1–2 3–4 5–6 7–8 9–10	1508 1518 1780 1974 1593	18% 18% 21% 24% 19%	18% 18% 22% 24% 19%	277 294 355 489 394	15% 16% 20% 27% 22%	16% 16% 19% 27% 22%	154 181 247 295 300	13% 15% 21% 25% 25%	13% 15% 20% 25% 27%	232 275 427 556 524	12% 14% 21% 28% 26%	10% 12% 20% 27% 31%	

Abbreviation: Adj = adjusted; LQR = lower quartile range; NZDep = New Zealand Deprivation Index; SEER = Surveillance, Epidemiology, and End Results Program; UQR = upper quartile range. ^aAge standardised to the total New Zealand cancer population, 2006–2008.

^bCochrane–Mantel–Haenzel test for trend, testing that the distribution of the covariates did not change across C3 Index categories.

There was substantial variation in overall comorbidity burden between cancer groups. For example, more than a quarter (26%) of upper GI patients were observed to have the highest level of overall comorbidity (C3 Index category '3'), compared with only 7% of the breast cancer cohort (Supplementary Material 1). The crude prevalence of individual comorbid conditions are presented by cancer group in Supplementary Material 2.

The impact of both overall comorbidity burden and individual comorbid condition on stage of disease at diagnosis is presented in Tables 2 and 3. For the total cohort, the odds of having distant disease (rather than local) increased with rising levels of comorbidity, with higher odds of distant stage for those in C3 Index category '2' (adjusted OR: 1.29, 95% CI 1.06–1.57) and category '3' (1.49, 95% CI 1.26–1.77), compared with patients in C3 Index category '0'. The pattern for individual cancer sites were generally similar to those observed for the total cohort, especially for those in the highest comorbidity category; however, estimates were imprecise for gynaecological, urological and upper GI cancers. Regarding unstaged disease, those with the highest comorbidity burden (C3 Index category '3') had 85% greater odds of being unstaged at diagnosis compared with those without comorbidity (adjusted OR: 1.85, 95% CI 1.59–2.16; Tables 2 and 3).

Several comorbid conditions increased the odds of distant disease at diagnosis, with dementia having the strongest individual impact Table 3). Alcohol abuse disorders, neurological conditions and pulmonary circulation disorders resulted in more than a doubling of the odds of distant disease at diagnosis. Several other conditions increased the odds of distant disease at diagnosis by at least 50%, including cerebrovascular disease, congestive heart failure and major psychiatric disorders. Only chronic viral hepatitis and intestinal disorders appeared to be associated with decreased odds of distant disease at diagnosis. In all, 27 of the 42 investigated comorbid conditions were observed to increase the odds of unstaged disease (Table 3; Supplementary Material 4).

DISCUSSION

This study investigated the degree to which patient comorbidity – the presence of chronic conditions other than the primary tumour – might impact on stage at diagnosis. Our observations among 14096 cancer patients suggest that the presence of patient comorbidity (a) increases the odds of a patient being diagnosed with distant metastases, (b) does not lead to earlier diagnosis and (c) increases the likelihood of a patient receiving no stage of disease at diagnosis.

Contrary to the 'surveillance effect', which suggests that increased contact with health services due to the presence of comorbidity may result in earlier diagnosis, this study found no pattern of earlier stage at diagnosis with higher comorbidity levels. This observation is in contrast to those observed in some contexts, where higher comorbidity levels have been associated with earlier

Table 2. Impact of comorbidity burden on stage of disease at diagnosis (adjusted odds ratios (OR) from multinomial logistic regression models), for the total cohort and by cancer group

Γ	Odds ratio for stage at diagnosis (OR, 95% CI)							
C3 Index category	Local	Regional	Distant	Unknown				
Total cohort ^a								
0	Ref	Ref	Ref	Ref				
1	Ref	0.92 (0.81–1.05)	1.09 (0.93–1.29)	0.91 (0.78–1.08)				
2	Ref	1.01 (0.86–1.18)	1.29 (1.06–1.57)	1.1 (0.91–1.33)				
3	Ref	1.09 (0.95–1.26)	1.49 (1.26–1.77)	1.85 (1.59–2.16)				
Breast ^b								
0	Ref	Ref	Ref	Ref				
1	Ref	0.96 (0.77-1.2)	1.96 (1.22–3.13)	0.81 (0.56–1.19)				
2	Ref	0.95 (0.71–1.28)	2.3 (1.31-4.02)	1.62 (1.12–2.34)				
3	Ref	1.45 (1.09–1.91)	3.86 (2.36–6.3)	2.96 (2.17-4.05)				
Colorectal ^b								
0	Ref	Ref	Ref	Ref				
1	Ref	1.03 (0.84–1.25)	1.25 (0.98–1.6)	0.87 (0.66–1.15)				
2	Ref	1.12 (0.89–1.42)	1.46 (1.1–1.95)	1.08 (0.78–1.48)				
3	Ref	0.93 (0.76–1.13)	1.25 (0.98–1.6)	1.87 (1.47–2.38)				
Gynaecological ^b								
0	Ref	Ref	Ref	Ref				
1	Ref	0.8 (0.5–1.3)	1.01 (0.6–1.7)	1.11 (0.55–2.23)				
2	Ref	0.79 (0.43–1.46)	0.65 (0.33-1.27)	1.5 (0.69–3.29)				
3	Ref	1.28 (0.72–2.25)	1.74 (0.92–3.28)	4.92 (2.72-8.91)				
Upper Gl ^b								
0	Ref	Ref	Ref	Ref				
1	Ref	0.88 (0.41–1.87)	0.6 (0.3–1.17)	0.67 (0.37–1.24)				
2	Ref	0.66 (0.27–1.62)	0.83 (0.38–1.77)	0.78 (0.39–1.58)				
3	Ref	1.67 (0.73–3.86)	1.91 (0.89–4.1)	2.42 (1.17–5.01)				
Urological ^b		I						
0	Ref	Ref	Ref	Ref				
1	Ref	0.65 (0.39–1.11)	0.92 (0.58-1.49)	0.86 (0.52–1.43)				
2	Ref	0.98 (0.54–1.75)	0.89 (0.5–1.57)	0.88 (0.49–1.61)				
3	Ref	1.04 (0.62–1.76)	1.21 (0.75–1.96)	1.55 (0.95–2.53)				

Abbreviations: CI = confidence interval; GI = gastrointestinal; Ref = reference group.

^aAdjusted for age, sex (except for breast and gynaecological cancers), cancer group (e.g., colorectal), ethnicity (Māori/non-Māori) and deprivation (New Zealand Deprivation Index (NZDep) decile).

^bAdjusted for age, sex (except for breast and gynaecological cancers), cancer site (except breast; e.g., colon used as reference for colorectal model), ethnicity (Māori/non-Māori) and deprivation (NZDep decile).

Table 3. Impact of individual comorbidities on stage of disease at diagnosis (adjusted odds ratios (ORs) from multinomial logistic regression models), for the total cohort

Comorbid conditionLocalRegiTotal cohortaAlcohol abuse ('Yes' vs 'No')Ref1.91 (1.0AnaemiaRef1.01 (0.8AnginaRef1.01 (0.8Anxiety and behavioural disordersRef0.97 (0.6Cardiac arrhythmiaRef0.95 (0.7)Cardiac arrhythmiaRef0.95 (0.7)Cardiac arrhythmiaRef0.95 (0.7)Cardiac arrhythmiaRef0.102 (0.7)Congestive heart failureRef1.11 (0.8Congestive heart failureRef1.13 (0.9Congestive heart failureRef0.78 (0.4Congestive heart failureRef0.78 (0.4Connective tissue diseaseRef0.78 (0.4COPDRef0.87 (0.6DementiaRef2.33 (1.2Diabetes no complicationsRef0.9 (0.7Diabetes with complicationsRef1.24 (1.2Diabetes with complicationsRef0.95 (0.4Eye problemsRef0.95 (0.4Eye problemsRef0.23 (0.1GI diseaseRef0.93 (0.8Inflammatory bowel disorderRef0.93 (0.8Inflammatory bowel disorderRef0.78 (0.6Intestinal disordersRef0.78 (0.6Joint or spinal disordersRef0.78 (0.6Joint or spinal disordersRef0.78 (0.6	06-3.46) 2.4 (1.25-4.61) 1-1.23) 0.94 (0.72-1.22) 1-1.27) 0.9 (0.67-1.21) 1-1.54) 1.45 (0.83-2.51)	1.03 (0.81–1.32) 1.16 (0.9–1.5)
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Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; Ref = reference group. A dash (---) denotes a condition for which ORs were not calculated owing to fewer than 10 cases occurring in the given stage strata.

^aOdds ratio of stage among those with the condition compared with those without, adjusted for age, sex (except for breast and gynaecological cancers) and ethnicity (Māori/non-Māori). Statistically significant observations are shown in bold.

stage at diagnosis (Vaeth *et al*, 2000; Gross *et al*, 2006; Zafar *et al*, 2008; Ahn *et al*, 2013). This pattern has most commonly been reported for screen-detected cancers (breast and colorectal), supporting the contention that in some instances a higher number of visits to health clinics may be related to higher rates of screening – particularly where screening coverage rates are related to health service funding or quality indicators, which may encourage the screening of those with high levels of comorbidity (Fisher *et al*, 2005; Walter *et al*, 2009). In the New Zealand context, we found no evidence of this.

By contrast, some of our findings support the so-called 'competing demands' hypothesis, which suggests that the presence of comorbidity can distract patients and/or clinicians to the extent that the early symptoms of tumour growth may go unnoticed (Fleming *et al*, 2005). For example, we observed that breast cancer patients with the highest overall burden of comorbidity had nearly four times greater odds of being diagnosed with distant metastases than those with no comorbidity burden. These findings are consistent with those of several other studies relating to multiple

cancer types (Gonzalez *et al*, 2001; Miller *et al*, 2003; Koppie *et al*, 2008; Tetsche *et al*, 2008; Teppo and Alho, 2009; Sarfati *et al*, 2011; Grann *et al*, 2013).

Some studies have shown that more severe (or 'unstable') comorbid conditions are associated with poorer stage at diagnosis, whilst less severe comorbid conditions are associated with earlier diagnosis (Fleming et al, 2005; Yasmeen et al, 2011). Our own observations support the former, but not the latter - out of the 42 individual comorbid conditions (all of which were included due to their association with non-cancer death in a cancer population; Sarfati et al, 2014) a total of 15 conditions showed increased odds of a patient being diagnosed with distant metastases (OR ranging between 1.27 and 6.25). A further 11 conditions showed similar but non-statistically significant results. By contrast, only two comorbid conditions (hepatitis and intestinal disorders) decreased the likelihood of being diagnosed with advanced disease (OR = 0.42and 0.55, respectively). It is not possible to speculate from the data whether these two exceptions do indeed represent a surveillance effect.

The presence of non-cancerous chronic conditions provides a clinical opportunity for earlier cancer diagnosis and referral for efficacious (and evidence-based) screening. Our observations suggest that it is possible that in some instances we may be missing this opportunity.

We also found strong evidence that the presence of comorbidity, particularly a high overall burden, makes it less likely that a patient will be recorded as staged at diagnosis. This observation is consistent with earlier work (Gurney *et al*, 2013). A possible explanation for this association is that the clinician may decide not to put a patient with severe comorbidity through diagnostic investigation, particularly where that investigation may place the patient at high risk of complication and/or the patient has poor prognosis (as is the case in upper GI cancer, for example). This is, however, speculative.

A major strength of this study is the high-quality nature of the national-level data used. However, there are inherent weaknesses with using administrative data to identify comorbidity. Data may be missing or inaccurate; it can be difficult to differentiate complications of disease from pre-existing conditions; and there may be biases inherent in coding practices. These errors are likely to be non-differential in relation to stage at diagnosis, and are unlikely to account for the associations seen. It is also possible that there may be some differential measurement error, for example, those with later-stage of a given cancer may have been be more likely to have been hospitalised in the period before their diagnosis, resulting in a higher likelihood of their comorbid conditions being recorded. However, we do not believe that this is likely to be a strong effect and thus would be unlikely to have a substantial impact on the general patterns of associations observed here.

The comorbidity status of those treated solely in non-reporting private hospitals may be underestimated, which may result in some bias if there is an association of use of these hospitals with stage of disease at diagnosis. Because we use a 5-year look back period and because for many cancers use of private hospitals for treatment is unusual in New Zealand, we do not think this bias is likely to explain the results. However for cancers for which private hospital care is more common (such as breast and colorectal), we cannot exclude the possibility that the association of lower comorbidity with earlier stage at diagnosis may, at least in part, be explained by this effect.

As we did not correct for multiple comparisons in our analysis of the independent role of each of the 42 comorbid conditions on stage at diagnosis, individual confidence intervals for these conditions should be interpreted with caution; however, we have observed a clear pattern of association across conditions. Finally, it should be noted that the low prevalence of some individual comorbid conditions is likely to have affected our power to detect significant differences for this component of the study.

CONCLUSIONS

We observed that patient comorbidity (a) increases the odds of a patient being diagnosed with distant metastases, (b) does not lead to earlier diagnosis and (c) increases the likelihood of a patient receiving no stage of disease at diagnosis. The strength of these associations varies by cancer type, individual comorbid condition and overall comorbidity burden.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

NOVELTY AND IMPACT OF PAPER

This retrospective cohort study showed that comorbidity among cancer patients (a) increased the odds of being diagnosed with distant metastases, (b) did not lead to earlier diagnosis and (c) increased the likelihood of a patient receiving no stage of disease at diagnosis.

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