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Brief Communication

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BRIEF COMMUNICATION

Comparing Survival After Recurrent vs De Novo Stage IV Advanced Breast, Lung, and Colorectal Cancer

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Abstract

The treatments provided to and survival of patients with recurrent vs de novo stage IV advanced breast, lung, and colorectal cancer may differ but have not been well studied. Using population-based data from the Cancer Research Network for 4510 patients with advanced breast, lung, or colorectal cancer, we matched recurrent/de novo patients on demographic factors. We found longer survival for recurrent vs de novo lung cancer (182 matched pairs); no significant difference for colorectal cancer (332 matched pairs); and shorter survival for recurrent vs de novo breast cancer (219 matched pairs). Compared with recurrent cases, chemotherapy use and radiation therapy use were more common among de novo cases. Differences in treatment and survival between recurrent and de novo advanced cancer patients could inform prognostic estimates and clinical trial design.

Most cancer deaths occur because of advanced disease, which can be present either when a cancer is first diagnosed (ie, de novo stage IV) or represent recurrence of a previously treated nonmetastatic (ie, stage I–III) diagnosis (1). Patients with recurrent cancer may differ from those with de novo metastatic disease because of differences in tumor behavior, cancer therapy, or treatment preferences. We sought to compare the treatments provided for and survival duration after the development of advanced disease for recurrent vs de novo breast, colorectal, and lung cancer using a large sample of community-treated patients.

The Cancer Research Network (CRN) is a consortium of large health care systems affiliated with the National Cancer Institute (2). Two CRN sites (Kaiser-Permanente Colorado, Denver, CO, and Kaiser-Permanente Northwest, Portland, OR) have tumor registries that collect high-quality recurrence data, and therefore could contribute patients. The analysis relied on the CRN's Virtual Data Warehouse (VDW), which links health plan eligibility, demographics, tumor registry, diagnosis and procedure codes from EPIC-based electronic medical records, and claims for services delivered by external contract providers (3,4). Institutional review boards from Dana-Farber and participating CRN sites approved the study.

Among patients diagnosed (2000–2011) with primary invasive breast (BC), colorectal (CRC), or lung cancer (LC), we selected those who had one of two types of advanced cancer: 1) Recurrent patients were a) originally diagnosed with stage I–III cancer (excluding IIIc LC); b) completed definitive therapy within one year of the original diagnosis (ie, surgery for most patients; chemotherapy/radiation for stage IIIa LC); and c) subsequently developed regional/distant recurrence. 2) De novo metastatic patients were diagnosed with stage IV disease. To balance characteristics, advanced cancer patients were matched 1:1 based on their propensity for having recurrent vs de novo disease as follows. First, we fit a logistic regression model where the dependent variable was recurrent vs de novo metastatic disease, and the independent variables were age, sex, race, marital status, smoking status, income, comorbidity score, and year of advanced disease. From this model, we calculated each patient's log odds of having distant recurrence. Next, we used nearest neighbor matching on the log odds of having distant recurrence using a caliper of 20% of the pooled standard deviation of the log odds between the two groups (5,6). Patients were followed through death, health plan disenrollment, or study end (December 31, 2012).

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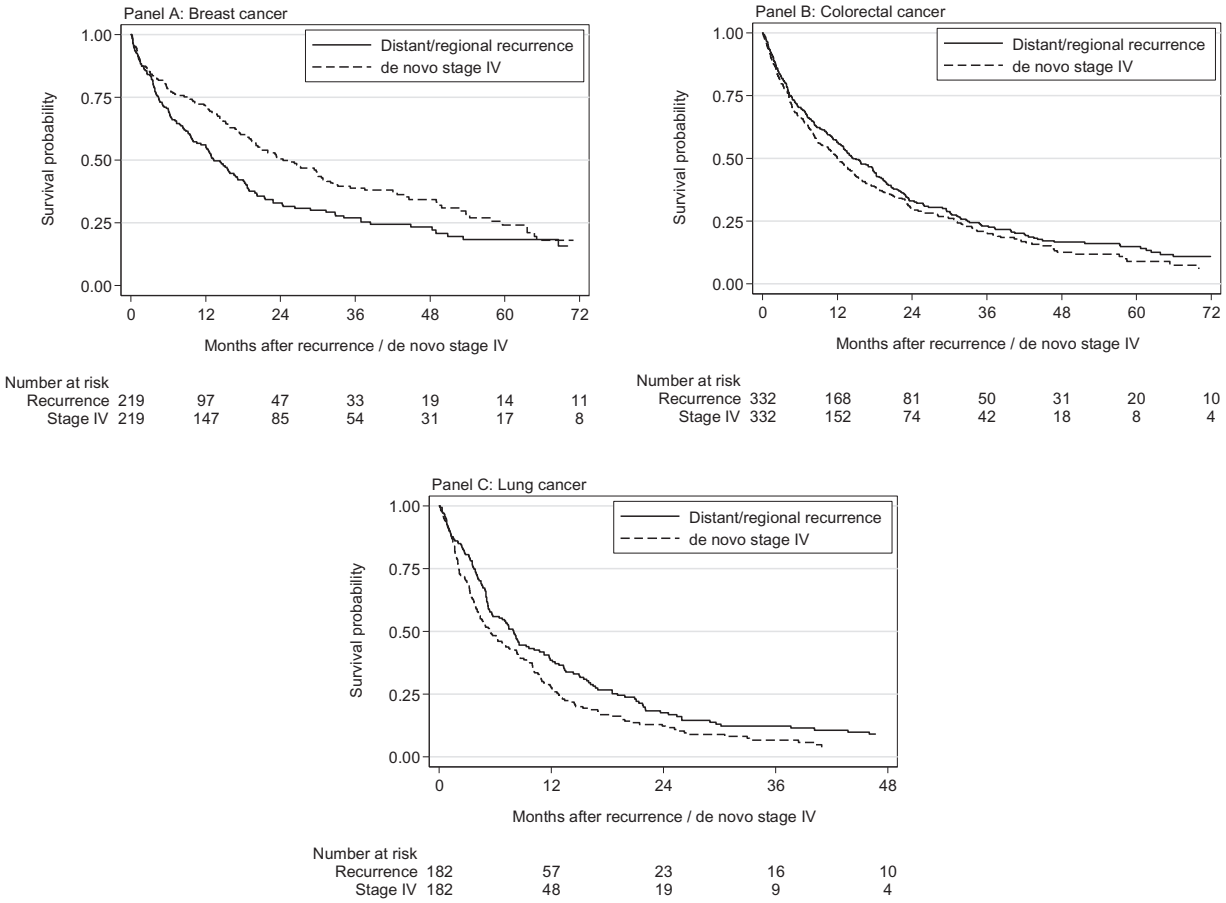

Figure 1. Kaplan-Meier plot of overall survival following a diagnosis of recurrent vs de novo stage IV metastatic cancer (propensity score–matched sample). Propensity score was matched on age, sex, race, marital status, smoking status, income, comorbidity score, and diagnosis year.

The primary outcome—survival duration after advanced cancer diagnosis—was summarized using a Kaplan-Meier plot and restricted mean survival time (RMST) through 48 months. RMST provides a clinically interpretable value that does not rely on modeling assumptions (ie, proportional hazards) (7–9). A senstivity analysis that focused only on patients with distant recurrence (ie, excluding regional recurrences) matched to those with de novo metastatic disease was also performed. All analyses were conducted separately for each cancer type.

We identified 410 recurrent and 219 de novo BCs, 332 recurrent and 705 de novo CRCs, and 182 recurrent and 2662 de novo LCs. After matching, there were 219 BC pairs, 332 CRC pairs, and 182 LC pairs. Standardized differences after matching were less than 6% for all independent variables included in the propensity score model, suggesting that these characteristics were well balanced (Supplement). Kaplan-Meier plots appear in Figure 1. Multivariable models demonstrated a 6.8-month advantage for de novo vs recurrent BC, a 3.4-month disadvantage for de novo vs recurrent LC, and no significant difference for de novo vs recurrent CRC (Table 1). As expected, older age and higher comorbidity (10) were associated with shorter survival. Developing advanced cancer in a more recent year was typically associated with longer survival. Among LC patients, current smoking was associated with an 8.1-month survival disadvantage vs never smokers. Chemotherapy was more common after a de novo vs recurrent diagnosis (BC: 85% vs 65%; CRC: 78% vs 64%; LC: 86% vs 56%), perhaps because some recurrent patients received adjuvant chemotherapy for their original cancer. Radiotherapy was also more common after a de novo vs recurrent diagnosis (BC: 50% vs 38%; CRC: 19% vs 9%; LC: 59% vs 33%).

A sensitivity analysis comparing patients with de novo vs distant recurrent cancer (supplement) revealed longer survival in patients with BC (9.1 months, $P < .001$), but no significant differences for patients with CRC (–1.2 months, $P = .39$) or LC (–1.8 months, $P = .28$). This occurred because excluding regional recurrences modestly shortened survival estimates for the recurrent cohorts.

Few studies have compared the treatments provided to or outcomes experienced by patients with recurrent vs de novo metastatic disease, and clinical trial reports do not usually distinguish between distinct types of advanced cancer. Similar to our findings, an analysis of 643 women with de novo stage IV and 2881 women with relapsed BC found that median survival was 12 months longer for de novo patients (11). However, this study only included patients treated at a large comprehensive cancer center, and median follow-up was just 19 months. Two other investigations demonstrated that recurrent metastatic BC conferred a survival disadvantage (12,13), but an analysis of human epidermal growth factor receptor 2–positive BC patients treated with trastuzumab found no survival difference for those with recurrent vs de novo disease (14). Among patients with metastatic LC, recurrence conferred a six-month survival advantage among those with a KRAS but not an EGFR mutation (15).

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Table 1. Multivariable models for restricted mean survival time through 48 months among matched recurrent and de novo metastatic breast, colorectal, and lung cancer patients*

	Breast		Colorectal		Lung	
	Coef (95% CI) (n = 219 matched pairs)	*P*	Coef (95% CI) (n = 332 matched pairs)	*P*	Coef (95% CI) (n = 182 matched pairs)	*P*
Intercept	22.2†		25.4†		22.3†	
Age at recurrent/de novo diagnosis, y						
21–54	0.0		0.0		0.0	
55–69	–2.1 (–6.5 to 2.4)	.36	–2.0 (–5.8 to 1.8)	.31	–4.1 (–9.8 to 1.5)	.15
≥70	–8.1† (–13.1 to –3.1)	.002	–9.4† (–13.3 to –5.6)	<.001	–6.0† (–11.7 to –0.2)	.04
Sex						
Male	na	na	0.0		0.0	
Female	na	na	0.8 (–2.0 to 3.5)	.59	1.3 (–1.7 to 4.4)	.39
Race/ethnicity						
Non-Hispanic white	0.0		0.0		0.0	
Nonwhite or Hispanic	4.0 (–2.2 to 10.2)	.20	–1.6 (–6.0 to 2.8)	.47	–0.2 (–5.6 to 5.3)	.95
Unknown	–1.0 (–7.5 to 5.6)	.77	–1.9 (–6.2 to 2.3)	.37	–3.4 (–9.2 to 2.4)	.26
Marital status‡						
Married/living with partner	0.0		0.0		0.0	
Not married/living with partner	–0.7 (–4.9 to 3.5)	.74	–3.2† (–6.4 to –0.0)	.05	–0.7 (–4.1 to 2.8)	.70
Unknown	0.0 (–5.6 to 5.7)	.99	–2.7 (–7.0 to 1.6)	.22	–2.3† (–7.6 to 3.0)	.39
Smoking status§						
Never	0.0		0.0		0.0	
Former	–3.3 (–7.3 to 0.8)	.12	0.2 (–2.8 to 3.1)	.91	–4.6† (–9.0 to –0.2)	.04
Current	–0.6 (–6.9 to 5.6)	.84	0.5 (–3.7 to 4.8)	.80	–8.1† (–12.8 to –3.3)	.001
Unknown	–6.7 (–15.3 to 1.9)	.13	–1.0 (–8.7 to 6.6)	.79	–6.4 (–16.6 to 3.8)	.22
Annual income, US$‖						
<40 000	0.0		0.0		0.0	
40 000 to <60 000	–2.1 (–10.2 to 6.0)	.61	–2.5 (–7.4 to 2.3)	.30	–1.3 (–6.0 to 3.4)	.59
≥60 000	–1.0 (–8.9 to 6.9)	.80	–2.0 (–6.6 to 2.7)	.40	–0.7 (–5.2 to 3.8)	.75
Unknown	0.0 (–10.9 to 10.9)	.99	–6.0 (–13.1 to 1.2)	.10	–3.8 (–10.4 to 2.7)	.25
Comorbidity score¶						
0	0.0		0.0		0.0	
1	–0.8 (–5.3 to 3.7)	.73	–2.1 (–5.3 to 1.2)	.21	–2.6 (–6.0 to 0.8)	.14
2+	–6.2† (–11.5 to –0.9)	.02	–5.1† (–8.5 to –1.7)	.00	–4.7† (–8.6 to –0.9)	.02
Year of recurrence/de novo#						
2000–2003	0.0		0.0		0.0	
2004–2005	3.0 (–3.5 to 9.4)	.37	2.5 (–1.8 to 6.8)	.26	6.4† (1.6 to 11.1)	.01
2006–2012	7.7† (3.0 to 12.5)	.001	6.1† (2.6 to 9.6)	.004	5.1† (1.0 to 9.1)	.01
Recurrent vs de novo#						
Recurrent	0.0		0.0		0.0	
De novo	6.8† (3.2 to 10.3)	<.001	–1.6 (–4.2 to 1.0)	.22	–3.4† (–6.2 to –0.6)	.02

*Coefficients were derived from three separate multivariable models—one for each cancer type. They represent the average number of months survived through 48 months of follow-up. To derive the average survival for a specific group, add the intercept coefficient and subgroup coefficient values. For example, a de novo breast cancer patient with two comorbidities and referent categories for all other covariates survived 22.8 months (ie, 22.2–6.2 + 6.8 months). All variables (age, sex, race/ethnicity, marital status, smoking status, annual income, comorbidity index, and year of recurrence/de novo diagnosis) were included in the multivariable models, regardless of their statistical significance on bivariate analysis. Coef = coefficient; CI = confidence interval; na = not applicable.

†Statistically significant coefficients ($P < .05$).

‡Marital status was obtained from the Virtual Data Warehouse (VDW) tumor registry.

§Smoking status was obtained from the VDW social history files.

‖Income data were obtained from block-level Census data in the VDW.

¶Comorbidity score was derived using methods developed by Klabunde and colleagues (9), excluding cancer diagnoses.

#Stage was based on American Joint Committee on Cancer, version 7.

Advantages of our analysis include the large, contemporary, community-treated cohort; using a common data source to study three cancer types simultaneously; using propensity score matching to balance observed covariates; including all patient types rather than a biomarker-selected subset; and incorporating treatment data. That said, some potentially important variables that could be associated with treatments/outcomes and may have been imbalanced between the recurrent/de novo cohorts, such as extent of disease, preferences for treatment/hospice, and tumor biomarkers, were not available. Also, a larger sample could have provided greater power to detect statistically significant effects.

Considering that the relationship between type of advanced cancer and survival varied by cancer type, the observed survival differences are most likely attributable to a combination of factors, including the cancer's intrinsic biology/behavior, previous

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receipt of cancer-directed therapy, and patient preferences. For example, de novo metastatic cancer may have a greater facility to spread/invade compared with cancer that is nonmetastatic at first presentation. Patients with recurrent BC or CRC could have fewer treatment options at the time of recurrence because they previously received adjuvant therapy, or past treatment(s) could have exerted selective pressure such that the recurrence had some degree of treatment resistance when it was discovered (eg, the BC patients who recurred while taking adjuvant anti-estrogens). For any cancer type, a patient who had prior therapy for localized disease could have less desire for aggressive treatment of a recurrence. Regardless of the reasons, these findings could inform estimates of prognosis and encourage clinical trials to stratify by or control for type of advanced disease.

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Notes

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