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Health Policy Analysis

Revising the Suspected-Cancer Guidelines: Impacts on Patients' Primary Care Contacts and Costs

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ABSTRACT

Objectives: This study aimed to explore the impact of revising suspected-cancer referral guidelines on primary care contacts and costs.

Methods: Participants had incident cancer (colorectal, n = 2000; ovary, n = 763; and pancreas, n = 597) codes in the Clinical Practice Research Datalink or England cancer registry. Difference-in-differences analyses explored guideline impacts on contact days and nonzero costs between the first cancer feature and diagnosis. Participants were controls ("old National Institute for Health and Care Excellence [NICE]") or "new NICE" if their index feature was introduced during guideline revision. Model assumptions were inspected visually and by falsification tests. Sensitivity analyses reclassified participants who subsequently presented with features in the original guidelines as "old NICE." For colorectal cancer, sensitivity analysis (n = 3481) adjusted for multimorbidity burden.

Results: Median contact days and costs were, respectively, 4 (interquartile range [IQR] 2-7) and £117.69 (IQR £53.23-£206.65) for colorectal, 5 (IQR 3-9) and £156.92 (IQR £78.46-£272.29) for ovary, and 7 (IQR 4-13) and £230.64 (IQR £120.78-£408.34) for pancreas. Revising ovary guidelines may have decreased contact days (incidence rate ratio [IRR] 0.74; 95% confidence interval 0.55-1.00; $P = .05$) with unchanged costs, but parallel trends assumptions were violated. Costs decreased by 13% (equivalent to −£28.05, −£50.43 to −£5.67) after colorectal guidance revision but only in sensitivity analyses adjusting for multimorbidity. Contact days and costs remained unchanged after pancreas guidance revision.

Conclusions: The main analyses of symptomatic patients suggested that prediagnosis primary care costs remained unchanged after guidance revision for pancreatic cancer. For colorectal cancer, contact days and costs decreased in analyses adjusting for multimorbidity. Revising ovarian cancer guidelines may have decreased primary care contact days but not costs, suggesting increased resource-use intensity; nevertheless, there is evidence of confounding.

Keywords: difference-in-differences, early cancer diagnosis, primary care, suspected-cancer policy revision.

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Introduction

Early cancer detection is essential for optimizing patient outcomes and is associated with decreased treatment costs.[1,2] In the UK, patients with health concerns typically first consult primary care. When cancer is suspected, general practitioners (GPs) initiate testing, which may be overseen wholly in primary care or require referral to secondary care. The first suspected-cancer referral guidelines for primary care were published by the National Institute for Health and Care Excellence (NICE) in 2005.[3] The referral criteria consisted of symptoms, signs, or abnormal test results ("features") associated with how cancer presents in primary care. The guidelines were revised in 2011 for ovarian cancer[4] and in 2015 for the remaining cancers.[5] Previous explorations of the suspected-cancer guideline's impact focused on clinical measures, such as time to diagnosis.[6,7] We widen this research by exploring health economics questions: what is the impact of revising the suspected-cancer guidelines on primary care contacts and associated costs in symptomatic patients who are diagnosed of cancer? The findings are relevant to all countries operating a gatekeeper system to cancer testing; for example, Denmark, which implemented a Cancer Patient Pathway in 2007 to 2008.[8,9]

We study cancers whose revised guidelines added primary care tests to identify patients warranting referral because of nonvisible blood in stool (for colorectal cancer) or cancer antigen 125 (Ca125) (a marker of ovarian cancer) in the blood.[4,5] We compare these with pancreatic cancer, whose referral criteria were widened from jaundice to include weight loss, diarrhea, constipation, pain in the back or abdomen, nausea, vomiting, and new-onset diabetes.[5]

Changes in suspected-cancer guidelines are anticipated to decrease primary care consultations for symptomatic patients diagnosed of cancer if the guidelines expedite secondary care referrals. Primary care consultations may increase where guidelines

recommend the GP to conduct triage tests. We conduct 2 analyses to separate changes in the number of contact days (days on which the patient has at least one primary care consultation) from the intensity of resource use and their associated costs on those contact days. In the first analysis, the outcome is the number of contact days between a patient's first recorded cancer feature in primary care and diagnosis. Contacts were defined as GP or nurse consultations (face to face/telephone/home), a blood test, or tests for nonvisible blood in stool or Ca125. The second analysis calculates the costs incurred between the first cancer feature and diagnosis, based on the number and types of consultations and tests.

Methods

Study Design and Setting

Using a difference-in-differences approach, we explored the impact of revising suspected-cancer referral guidelines on primary care contact days and associated costs for symptomatic patients within primary care. Data sources were UK Clinical Practice Research Datalink (CPRD) (GOLD) with linkage (for patients in England) to National Cancer Registration and Analysis Service (NCRAS) (Set 15), and Office for National Statistics Townsend data. The CPRD records all GP and nurse consultations and blood tests in primary care.[10] CPRD GOLD contains prospective, coded, and anonymized medical records from > 600 UK general practices, with 389 having NCRAS linkage.[10] Two cohorts were studied, either side of guideline revision in 2015[5]: (1) pre, August 1, 2012, to December 31, 2014, and (2) post, August 1, 2015, to December 31, 2017. Equivalent cohorts were studied either side of the guideline revision for ovarian cancer in 2011.[4]

Inclusion Criteria

Participants had incident diagnostic codes in the pre- or postperiods for ovarian, colorectal, or pancreatic cancer in NCRAS or in the CPRD where linkage was not available. They were aged ≥ 18 years at diagnosis and registered with their CPRD practice at least 1 year before diagnosis. In the main analyses, participants were from England. In sensitivity analyses for colorectal cancer, participants from Wales and Northern Ireland were added.

Independent Variables

Sex, age, and general practice were identified from CPRD variables. CPRD code lists (available on request) were collated for features of possible ovarian, colorectal, or pancreatic cancer (Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table A1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017).[3–5] Presentations with these features were identified by searching the CPRD records in the year before diagnosis using the code lists. Diagnostic interval was the number of days between the index feature and diagnosis. Dummy variables were created for the period (post vs pre) and guidelines: "new NICE" (index feature was introduced during guidance revision) versus "old NICE" (index feature was listed in the 2005 guidelines). Participants with no coded features of their cancer before diagnosis could not be classified and were omitted from analyses. The Townsend score, obtained from linked Office for National Statistics data for participants in England, represents patient-level material deprivation based on the 2001 census. Multimorbidity was estimated using the Cambridge Multimorbidity General Outcome Score, after searching patient CPRD records for relevant diagnostic and prescription codes and for test results. Estimated as a weighted sum of 37 chronic medical conditions, multimorbidity correlates strongly with primary care consultations and has acceptable predictive validity for primary care utilization.[11] Patients with no recorded conditions were assumed to have no multimorbidity.

Outcome Variables

The outcomes were estimated over the diagnostic interval period:

1. The number of contact days, that is, a day when the patient had at least 1 contact with primary care for a GP or nurse consultation, or for a test. Qualifying GP and nurse consultations occurred face to face, on the telephone, or at home. Tests included full blood count and cancer-specific tests (fecal occult blood test [FOBT] for colorectal cancer and Ca125 test for ovarian cancer). See Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017 and Appendix Tables A2 to A5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017 for CPRD labeling and codes.
2. The total cost of the above-defined contact days. All blood tests, FOBT, and Ca125 tests and all qualifying GP and nurse consultations were costed assuming 2020 unit costs[12] (see assumptions in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table A6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017). Blood tests were costed for the price of the venepuncture plus a full blood count. Patients with no recorded qualifying consultations or tests were considered to have zero costs, and this number is reported.

Analyses

Analyses used a difference-in-differences design and a random intercept for general practice to accommodate differences in guideline adherence.[13,14] The parallel trends assumption was examined visually. We conducted falsification tests to check for existence of confounding, analyzing preperiod data and a placebo date for guideline revision of October 16, 2013 (October 16, 2009, for ovarian cancer).

Sex was entered as a binary covariate (reference category: male) and age as a continuous covariate. Townsend score was entered as quintiles (reference category: least deprived). The interaction term between the guideline and period dummy variables quantified the change in outcome attributable to guideline revision.

Preliminary inspection of the contact-day data revealed overdispersion, so mixed-effects negative binomial regression was used to estimate the mean pre-to-post change in the number of contact days attributable to guideline revision.[15] The variance partition coefficient was estimated to report the percentage of total variation attributable to the general practice level.[14] Cost is a right-skewed, non-negative continuous variable[16] and was modeled using a mixed-effects generalized linear model (gamma family, log link). The regression results and average marginal effects for participants with nonzero costs are presented.

Sensitivity Analyses

In sensitivity analysis 1 of colorectal cancer data, we adjusted for multimorbidity burden, because of its association with primary care consultation rate.[17] Multimorbidity burden was estimated from the Cambridge Multimorbidity Score,[11] entered as a continuous variable. It is estimable for all patients with available prescription and diagnostic codes, enabling inclusion of Wales and

Table 1. Numbers of participants in England provided by the CPRD, with complete Townsend data, and the characteristics of those included in the main analyses.

Characteristic	Ovary	Pancreas	Colorectal
N in England with complete Townsend data	1009	826	3699
N (%) omitted from analysis because they had no coded features of their cancer before diagnosis	246 (24.4)	229 (27.7)	1699 (45.9)
N in main analysis (% female)	763 (100)	597 (50.7)	2000 (47.3)
Mean age, years (SD)	69.6 (13.3)	72.1 (11.4)	65.9 (13.4)
N (%) with old NICE feature	566 (74.2)	76 (12.7)	1208 (60.4)
N (%) in preperiod	399 (52.3)	413 (69.2)	1438 (71.9)
Median diagnostic interval, days (IQR)	60 (28-138)	98 (34-241)	53 (25-120)
Mean diagnostic interval, days (SD)	100.3 (99.5)	139.4 (117.3)	88.1 (88.2)

CPRD indicates Clinical Practice Research Datalink; IQR, interquartile range; NICE, National Institute for Health and Care Excellence.

Northern Ireland data (NICE guidelines do not apply in Scotland). It could not be calculated for pancreatic or ovarian cancer, given that prescription code data for these patients were not available. Multimorbidity is strongly correlated with deprivation,[18] and Townsend score was omitted from these analyses. We included dummy variables for practice location (England = reference category, Wales or Northern Ireland) to account for possible regional differences in NICE guideline implementation.

Sensitivity analysis 2 was conducted for all cancer sites. Patients were classified into old NICE or new NICE groups based on all of their presenting features of possible cancer before diagnosis:

1. Old NICE: patients who presented with at least one old NICE feature before diagnosis
2. New NICE: patients who only ever presented with new NICE features before diagnosis

For new NICE patients reclassified as old NICE, the number of contact days and costs were censored at the date they presented with their first old NICE feature.

Power Calculation

The sample size was determined for the analysis of diagnostic interval.[6] Based on simulation of the outcome distributions, with a 5% type I error rate and the observed distribution of participants across cohorts and NICE grouping, the available sample sizes provided the following power: 90% to detect an 11.3% reduction in contact days associated with revising the referral guidelines for suspected colorectal cancer (n = 2000), 89.8% for an 18% reduction in ovary (n = 763), and 86% for a 36% reduction in pancreas (n = 597). In sensitivity analysis of colorectal cancer, the sample size of 3481 had 90% power to detect an 8.6% reduction.

Results

The numbers of participants in England provided by the CPRD and the characteristics of those included in the main analyses are presented in Table 1. The percentage classified as old NICE ranged from 12.7% in pancreatic cancer to 71.9% in colorectal cancer. The women with ovarian cancer were near-equally divided between pre- and postperiods, whereas a greater percentage of participants with colorectal or pancreatic cancers were in the preperiod than in the postperiod. Diagnostic intervals were longer in pancreatic than in ovarian or colorectal cancers. Old NICE and new NICE participants in the preperiod had similar age and deprivation profiles (Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table A7 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017) and relatively high proportions of women in the new NICE group for pancreatic cancer.

Colorectal Cancer

Overall, the median number of contact days within the diagnostic interval was 4 (interquartile range [IQR] 2-7 days). Median associated costs were £117.69 (IQR £53.23-£206.65), including zero costs recorded for 62 patients (3.1%). The parallel trends assumption appeared well met (Fig. 1A). The falsification test suggested no evidence of confounding (see Appendix Table B1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017).

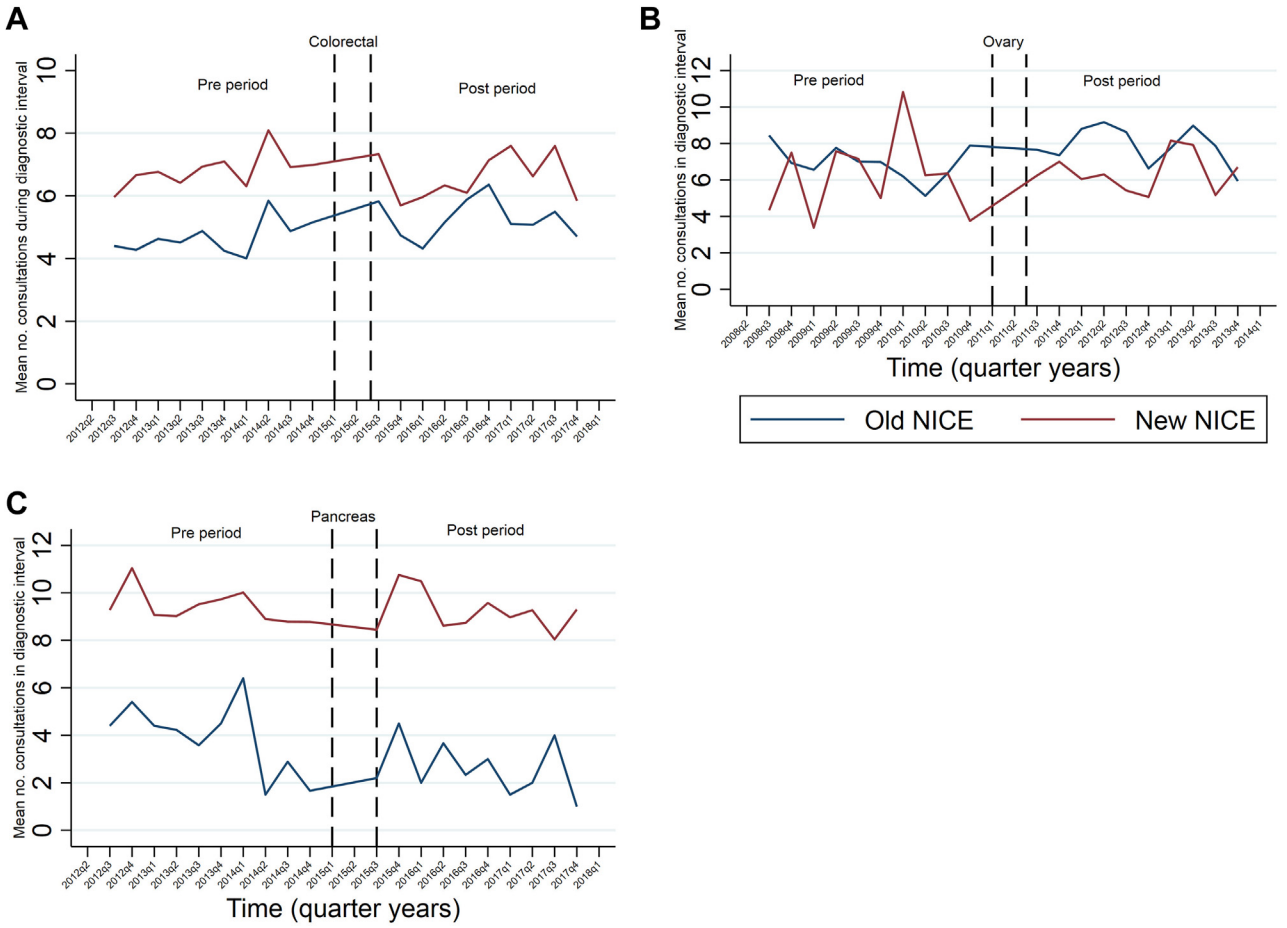
Mixed-effects negative binomial regression identified no effect of guideline revision on contact days, in unadjusted analysis (incidence rate ratio [IRR], 0.99; 95% confidence interval [CI] 0.83-1.18; $P = .880$) or after adjusting for confounders (IRR 0.97; 95% CI 0.81-1.15; $P = .708$) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017). Of the total variation in number of contact days, 5.7% (95% CI 5.2%-6.3% variance partition coefficient) was attributable to the general practice level (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017).

The costs associated with revising the guidelines remained unchanged, both in the unadjusted generalized linear model (exponentiated coefficient 0.89; 95% CI 0.75-1.05; $P = .155$) and after adjusting for confounders (exponentiated coefficient 0.87; 95% CI 0.73-1.03; $P = .104$) (Table 2).

Ovarian Cancer

Overall, the median number of consultation days within the diagnostic interval period was 5 (3-9). Median associated costs were £156.92 (IQR £78.46-£272.29), including zero costs for 17 of 763 patients (2.2%). The falsification test was negative (see

Figure 1. Visualizing the parallel trends assumptions for (A) colorectal, (B) ovarian, and (C) pancreatic cancer. Old NICE: controls; New NICE: patients whose index feature was introduced during guideline revision.



NICE indicates National Institute for Health and Care Excellence.

Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017), and visual inspection suggested that the parallel trends assumption was not met (Fig. 1B).

In mixed-effects negative binomial regression, the contact days associated with revising the guidelines remained unchanged (unadjusted IRR 0.76; 95% CI 0.55-1.04; P = .086). Nevertheless, after adjusting for confounders, there was weak evidence of a 26% reduction (unadjusted IRR 0.74; 95% CI 0.55-1.00; P = .05) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017). The percentage of total variance attributable to the general practice level was 10.2% (95% CI 9.6-10.6) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017).

In the generalized linear model results, the costs associated with guideline revision remained unchanged both in the unadjusted (exponentiated coefficient 0.81; 95% CI 0.60-1.11; P = .190) and adjusted analyses (exponentiated coefficient 0.89; 95% CI 0.72-1.10; P = .281) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017). The predicted mean test costs, adjusted for age and deprivation, have wide CIs (Table 2).

Pancreatic Cancer

The median number of contact days within diagnostic interval was 7 (4-13). The median cost associated with those contact days was £230.64 (£120.78-£408.34), including zero costs recorded for 7 patients (1.2%). The trend in number of contact days within the diagnostic interval period of the new NICE group followed that in the old NICE group in the preperiod, more closely in the earlier part than toward the end (Fig. 1C). The falsification test reported no evidence of confounding (see Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017).

In mixed-effects negative binomial regression, the contact days associated with revising the guidelines remain unchanged in unadjusted (IRR 1.53; 95% CI 0.96-2.43; P = .076) and adjusted analyses (IRR 1.52; 95% CI 0.98-2.36; P = .064) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017). The percentage of total variance attributable to the general practice level was 4.3% (95% CI 3.4-4.4) (Appendix B in Supplemental Materials found at

Table 2. Predicted mean costs for old NICE and new NICE groups in the pre- and postperiods, plus the predicted secular change and change attributable to revising suspected-cancer guidelines for colorectal, ovarian, and pancreatic cancers.

Cancer site	Predicted mean cost for	Margin (£)	95% CI (£)	*P* value
Colon/rectum	Pre, old NICE	129.34	121.28-137.40	< .001
	Pre, new NICE	215.97	200.42-231.53	< .001
	Post, old NICE	144.70	130.20-159.20	< .001
	Post, new NICE	209.75	185.22-234.28	< .001
	Secular change	15.36	−1.29 to 32.00	.071
	Interaction term: period × NICE	−21.58	−51.93 to +8.78	
Ovary	Pre, old NICE	221.05	198.32-243.77	< .001
	Pre, new NICE	196.87	161.02-232.72	< .001
	Post, old NICE	243.02	215.79-270.25	< .001
	Post, new NICE	171.30	135.70-206.90	< .001
	Secular change	21.97	−14.50 to 58.45	.238
	Interaction term: period × NICE	−47.54	−108.58 to 13.50	
Pancreas	Pre, old NICE	142.15	110.31-174.00	< .001
	Pre, new NICE	312.76	289.20-336.31	< .001
	Post, old NICE	103.01	67.00-139.01	< .001
	Post, new NICE	325.70	283.24-368.17	< .001
	Secular change	−39.14	−87.24 to 8.95	.111
	Interaction term: period × NICE	52.10	−12.27 to 116.44	

NICE indicates National Institute for Health and Care Excellence.

https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017).

In the generalized linear model, there was no change in costs associated with guideline revision in either the unadjusted (exponentiated coefficient 1.46; 95% CI 0.95-2.24; *P* = .087) or adjusted models (exponentiated coefficient 1.44; 95% CI 0.94-2.20; *P* = .094) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Table B4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017). The predicted costs have wide CIs (Table 2).

Sensitivity Analyses

The sensitivity analyses are reported in detail in Appendix B found at https://doi.org/10.1016/j.jval.2022.06.017 and are summarized here.

In sensitivity analysis 1, we added multimorbidity to the model in colorectal cancer and omitted Townsend deprivation, allowing us to include patients from the devolved nations. This increased the potential pool of patients to 5467 (England, n = 3699, 67.7%; Wales, n = 1413, 25.8%; and Northern Ireland, n = 355, 6.5%). Of these, 3481 (63.7%) had at least one coded feature of their cancer before diagnosis and were included in the analysis (n = 2566 in England, n = 164 in Northern Ireland, and n = 751 in Wales). Median cost was similar to that in the main analyses (£117.69; IQR £53.23-£206.65, including zero costs for 117 participants [3.4%]). Two findings contrasted with the main analyses. First, there was borderline evidence of a decrease in the number of contact days associated with revising the suspected-cancer guidelines, but only after adjusting for confounding (IRR 0.89; 95% CI 0.79-1.00; *P* = .053). Note that this was not present in unadjusted analyses (IRR 0.89; 95% CI 0.79-1.01; *P* = .071). Second, there was strong evidence of a 13% reduction in costs associated with revising the suspected-cancer guidelines for colorectal cancer in unadjusted analysis (exponentiated coefficient 0.87; 95% CI 0.77-0.98; *P* = .027). This persisted after adjusting for confounding (exponentiated coefficient 0.87; 95% CI 0.77-0.98; *P* = .017) and was equivalent to £28.05 (£5.67-£50.43) (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Tables B5 and B6 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017).

Sensitivity analysis 2, conducted for all cancer sites, reclassified new NICE patients as old NICE based on *all* of their presenting features before diagnosis. The results were similar to the main analyses for colorectal and pancreatic cancers but differed for ovarian cancer (Appendix B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017, Appendix Tables B7 to B12 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.06.017). There was no longer any evidence that guideline revision was associated with reduced contact days.

Discussion

To the best of our knowledge, this is the first study looking at the impact of suspected-cancer guidelines on resource use. We use the difference-in-differences approach to explore the impact of revising suspected-cancer referral guidelines on the number of contact days in primary care and their associated costs for symptomatic patients before their diagnosis of colorectal, ovarian, or pancreatic cancer. Participants were classified based on whether their initial cancer presentation met clinical criteria mentioned in the revised (new NICE) or superseded (old NICE) guidelines.

Overall costs remained the same or decreased within each cancer site. We found no evidence in the main analyses that revising suspected-cancer guidelines affected contact days and

associated costs in patients diagnosed of colorectal or pancreatic cancers. Nevertheless, in sensitivity analyses adjusting for multimorbidity, we found that contact days and costs for colorectal cancer decreased by 11% and 13%, respectively. We report weak evidence of a 26% reduction in primary care contact days before ovarian cancer diagnosis attributable to guideline revision, equating to 2 fewer contact days. Costs after revising the guidelines were unchanged. These ovarian cancer results should be viewed cautiously because of potential confounding (as evidenced by visual inspection of parallel trends) and loss of the effect in sensitivity analyses that reclassified some new NICE participants as old NICE.

Interpretation

Our analysis of contact days can be interpreted in light of previous analyses of time to diagnosis data indicative of expedited referral. Median waiting times decreased for 11 cancers in Denmark after the implementation of their Cancer Patient Pathways in 2008 to 2009.[19] In separate analyses of the data set used in the current study, new NICE patients had shorter diagnostic intervals than old NICE patients around the time of guideline revision for colorectal and ovarian, but not pancreatic, cancers.[6] Therefore, we anticipated that primary care contact days would decrease in ovarian and colorectal, but not pancreatic, cancers. In ovarian cancer, the number of contact days did decrease, but we view these results cautiously because of the weak evidence in the main analyses, violation of the parallel trends assumption, and loss of effect in sensitivity analysis. For colorectal cancer, contact days and costs remained unchanged after guideline revision in the main analysis but decreased by 11% in sensitivity analyses adjusting for multimorbidity. This equates to a reduction of three-quarters of one consultation per patient on an average. From 2015 to 2016, there was a small (1-percentage-point) decrease in the percentage of patients who reported seeing their GP only once or twice about a health problem caused by cancer before testing was initiated.[20]

Unchanging costs in the presence of reducing contact days, as observed for ovarian cancer, suggest that the revised guidelines are associated with increased costs per contact day. This increased resource-use intensity may relate to increased Ca125 testing (each costed at £10.61), requiring nurse consultation at the surgery for venepuncture (£10.50). In the sensitivity analyses for colorectal cancer, we report a 13% decrease in costs, or £28, which is equivalent to the cost of the three-quarters of one GP consultation (each costed at £39.23). FOBTs are cheap (£2.47) and are conducted by the patient at home, with a minimal impact on costs.

There was no evidence that revising pancreatic cancer guidelines affected contact days or costs. This is consistent with our previous analysis finding no impact on diagnostic interval. Furthermore, diagnostic intervals were longer for new NICE than for old NICE participants, consistent with our findings of increased consultations and costs in the new NICE group.[6] The guidelines for patients with "alarm" features of cancer are not always followed by GPs in England.[13] Our study suggests that there is scope for GPs to initiate cancer testing in more of their patients presenting with the nonspecific features of pancreatic cancer added during guideline revision.

Strengths and Limitations

This study's main strength is its primary care setting, where GPs implement the suspected-cancer guidelines. The CPRD is large and generally regarded as having high-quality data on a probability sample of the UK; hence, the findings are generalizable.[10] We used robust methods for identifying cases, their features of cancer, consultations, and costs and for exploring opportunities for early diagnosis (contact days) and resource-use intensity (total resource cost).[12,21]

Although it was not possible to directly observe guideline implementation in our data, we restricted analyses to the patient's "diagnostic window," that is, the time within which GPs might reasonably apply the suspected-cancer guidelines because the patient was reporting cancer features. Our inclusion of a random intercept for general practice was warranted, given that total variance in the number of contact days attributable to the general practice level ranged from 4.3% in pancreatic cancer to 10.2% in ovarian cancer. This is likely to reflect geographical and temporal variation in the structural and behavioral changes required for optimal guideline implementation. NICE guidance is officially applicable in England and Wales but may be implemented in Northern Ireland.[22] To adjust for potential confounding by differences in the extent of guideline implementation, the sensitivity analyses adjusted for location (England, Wales, or Northern Ireland) where appropriate. We defined new NICE patients as having index cancer features that were newly introduced during guideline revision, reasoning that GPs were not legitimized to refer them in the preperiod. Our sensitivity analysis acknowledged that referral would become possible for new NICE patients who subsequently reported a cancer feature in the original guidelines. We suggest that any findings of an impact of guideline revision conferred by those patients would be lost in this sensitivity analyses, and for ovarian cancer, they were.

Although the falsification tests were reassuring, visual inspection of the data suggested that the parallel trends assumption was not met for ovarian and pancreatic cancers. Women were more likely than men to be in the new NICE group, in both pre- and postperiods, particularly for pancreatic cancer. This is consistent with women having a lower threshold for reporting cancer symptoms, particularly the lower risk symptoms introduced during guideline revision.[23] There was no suggestion of self-selection into the NICE grouping based on age or deprivation profile.

Guidance revision expanded the pool of patients eligible for cancer testing by introducing new features. This is reflected by the numbers of 2-week-wait referrals being 11.4% higher in 2015/2016 than in 2014/2015[24] and a fall in the percentage of 2-week-wait referrals that result in a cancer diagnosis.[25] Consequently, increased costs will be accrued from testing more patients who transpire not to have cancer. A limitation of our study was the inability to quantify the additional impacts of guideline revision on symptomatic patients selected for testing who transpire not to have cancer.

We had no data sources to estimate multimorbidity in patients with ovarian and pancreatic cancers. Therefore, our sensitivity analyses were limited to just colorectal cancer.

Recommendations for Policy and Future Research

Future research should aim to quantify the impacts of guideline revision on primary care contact days and costs including all additional patients selected for testing, not just those who transpire to have cancer. The data sources used in this study would be suitable, including data to enable calculation of multimorbidity burden. The inclusion criteria would be patients attending primary care with features of possible cancer, followed up for the outcome of cancer diagnosis. Researchers should explore the potential need to use 2-part models if there are significant nonzero costs.[26] Extension of existing research on guideline adherence is recommended,[13] including variation by geographical region. This requires access to Hospital Episode Statistics referral data and

Cancer Registry Routes to Diagnosis data.[13] Further research into the time-varying impacts of guideline revision is also recommended. Methods could include difference-in-differences analyses, with verification of suspected-cancer guideline application and lagged treatment variables to test for time-varying effects of guideline implementation.[26]

The sensitivity analysis of colorectal cancer data adjusting for multimorbidity is relevant in the wider context of health economics analysis. Adjusting for multimorbidity in cost-effectiveness analysis is uncommon, and guidelines have limited recommendations on how to include multimorbidity in economic models.[27] This is particularly true where patients with comorbid conditions have an increased risk of harm from the intervention being evaluated.[27] We chose to adjust for multimorbidity in sensitivity analysis because multimorbidity is correlated with primary care consultation rate, making interpretation of the final result complex if these correlations are unaccounted for.[11] The sensitivity analysis revealed an association between revised guidelines and decreased consultations and costs. Furthermore, this result was not down to increased power alone, because the main analyses had 90% power to detect an 11.3% reduction in consultations, which is similar to the effect size found in the sensitivity analysis. This result highlights the importance of exploring service use and costs adjusting for multimorbidity in future health economics analyses.

Conclusions

We have shown that difference-in-differences methods can explore the impact on number of contact days separately from intensity of resource use and their associated costs. The main analyses suggested primary care costs after revising the guidelines remained unchanged or decreased for symptomatic patients before their diagnosis with colorectal, ovarian, or pancreatic cancer. For colorectal cancer, the sensitivity analysis adjusting for multimorbidity resulted in decreased consultations and costs. We interpret this as GPs expediting referrals, without any impact on resource-use intensity, possibly because of the low costs involved in FOBT. We report some evidence that revising the suspected-cancer referral guidelines for ovarian cancer decreased primary care contact days with no impact on costs. We interpret this as GPs expediting referrals and increasing resource-use intensity once women present with possible ovarian cancer, possibly through Ca125 testing. The need to consider the impact of guidelines on contacts and costs as well as clinical outcomes is essential if we are to understand the impacts of guideline changes on healthcare resources.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.06.017.

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