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Advanced stage cancer and time to diagnosis: an International Cancer Benchmarking Partnership (ICBP) cross-sectional study

Running head: ICBP-M4: Advanced stage cancer with longer diagnostic intervals

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ADDITIONAL INFORMATION

Collaborators

*Online supplementary file VII contains a list of the full ICBP Module 4 Working Group.

Contributors

MT and AZ analysed the data and together with HJ produced the first versions of this manuscript. DW, PV and UM are lead investigators on ICBP-M4. CA, AZ, EOF, RD, WL, HJ and IR are involved in the central co-ordination of ICBP-M4 and made significant contributions to the paper, including the provision of technical information. AG, EG, ML, R-JL, MM, RDN, JK, DT and VW have lead roles in their individual jurisdictions and also contributed substantially to the paper. The ICBP-M4 working group contributed to the study through

data collection, technical support and other activities essential to the production of this paper. Every author takes responsibility for the entire content of the manuscript.

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Competing interests

David Weller is editor-in-chief of European J of Cancer Care.

Ethics approval

For each local data collection, specific procedures and approvals were required. This included anonymised data transfer to University College London and Aarhus University (Supplementary file 5). Approvals were received from the following institutions: Cancer Council Victoria Human Research Ethics Committee [HREC 1125]; Health Research Ethics Board, University of Manitoba [HS15227 (H2012:105)]; Research Resource Ethics Committee, CancerCare Manitoba [RRIC#28-2012]; University of Toronto Research Ethics Board [27881]; the Danish Data Protection Agency [2013-41-2030]; the Swedish Ethics Review Board, Uppsala [2013/306]; Norwegian regional committees for medical and health research ethics [2013/136/REK nord]; England, Wales and Scotland, NRES Committee East Midlands – Derby 2, local R&D for each health board [11/EM/0420]; Northern Ireland ORECNI Ethical approval, local governance for each health Trust [11/EM/0420].

ABSTRACT

Objective

To investigate the relationship between tumour stage at diagnosis and selected components of primary and secondary care in the diagnostic interval for breast, colorectal, lung and ovarian cancers.

Methods

Observational study based on data from 6,162 newly diagnosed symptomatic cancer patients from Module 4 of the International Cancer Benchmarking Partnership. We analysed the odds of advanced stage of cancer as a flexible function of the length of primary care interval (days from first presentation to referral) and secondary care interval (days from referral to diagnosis), respectively, using logistic regression with restricted cubic splines.

Results

The association between time intervals and stage was similar for each type of cancer. A statistically significant U-shaped association was seen between the secondary care interval and the diagnosis of advanced rather than localised cancer; odds decreasing from the first day onwards and increasing around three and a half months. A different pattern was seen for the primary care interval; flat trends for colorectal and lung cancers and a slightly curved association for ovarian cancer, although not statistically significant.

Conclusion

The results confirm previous findings that some cancers may progress even within the relatively short time frame of regulated diagnostic intervals. The study supports the current emphasis on expediting symptomatic diagnosis of cancer.

Keywords: Early Detection of Cancer, Diagnosis, Time Factors, Delayed Diagnosis, Waiting Lists, Breast Neoplasms, Colorectal Neoplasms, Lung Neoplasms, Ovarian Neoplasms, Primary Health Care, Bias.

INTRODUCTION

The waiting time from the first presentation of symptoms in primary care to cancer diagnosis, herein referred to as the *diagnostic interval*, is a major concern for patients, healthcare providers and the healthcare system. Delayed diagnosis at several different sites has been suggested to impact cancer survival.(Moller et al., 2015; Neal et al., 2015; S Walters et al., 2015) From the system and provider perspective, the length of the diagnostic interval is becoming a benchmark for the quality of cancer care. From the patient perspective, the diagnostic interval has been associated with increasing anxiety and fear of cancer progression during the waiting time.(Eskander et al., 2013; Oudhoff, Timmermans, Knol, Bijnen, & van der Wal, 2007; Ringbaek, Borgeskov, Lange, & Viskum, 1999)

Despite limited high-quality evidence on waiting-time outcomes, many healthcare systems have developed recommendations on “acceptable” diagnostic intervals. The guidelines by the National Institute for Health and Care Excellence (NICE) in the England and Wales state that patients suspected of cancer must be assessed within two weeks after referral from primary care.(Emery & Vedsted, 2015) Similar benchmarks have been adopted elsewhere, e.g. the Cancer Care Ontario Standards, the Scottish Cancer Referral Guidelines, the Victorian Optimal Care Pathways, and the Cancer Patient Pathways across Scandinavia.(“Optimal Care Pathways - Cancer Council Victoria,” n.d.; Probst, Hussain, & Andersen, 2012; SIGN, 2003; Wilkens, Thulesius, Schmidt, & Carlsson, 2016)

Although the benefits of expedited diagnosis of symptomatic cancer cannot be experimentally tested, some evidence exists from observational studies. These have reported increasing mortality and advanced stage of disease with longer diagnostic intervals for breast cancer,(Ermiah et al., 2012; A R Jensen, Madsen, & Overgaard, 2008; Richards, Westcombe, Love, Littlejohns, & Ramirez, 1999; Warner et al., 2012) colorectal cancer,(Corley et al., 2017; Tørring et al., 2011; Tørring, Frydenberg, Hansen, Olesen, & Vedsted, 2012) head and neck cancers,(Chen, King, Pearcey, Kerba, & Mackillop, 2008; Liang et al., 2017; Murphy et al., 2016) endometrical cancer,(Dolly et al., 2016) and lung cancer.(Anni R Jensen, Mainz, & Overgaard, 2002; Olsson, Schultz, & Gould, 2009; Wang, Mahasittiwat, Wong, Quint, & Kong, 2012) Nevertheless, most of these findings need to be replicated using analytical methods that address many of the problems associated with previous studies of this nature.(Neal et al., 2015)

The International Cancer Benchmarking Partnership (ICBP) is a major international collaboration aimed at exploring differences in cancer outcomes between countries with comparable wealth, access to universal healthcare and high-quality cancer registration.(Sarah Walters et al., 2013) The ICBP Module 4 (ICBP-M4) study was set up to describe cancer pathways and investigate the association between the diagnostic interval and outcomes of breast, colorectal, lung and ovarian cancers.(David Weller et al., 2016)

The aim of this study was to investigate the relationship between tumour stage at diagnosis and selected components of primary and secondary care in the diagnostic interval for breast, colorectal, lung and ovarian cancers. To address confounding by indication, which could explain previous equivocal findings, we analysed stage of cancer as a flexible function of the length of time under primary and secondary care, respectively.

METHODS

We conducted a cohort study and calculated the odds of finding advanced stage cancer as the primary outcome while using the length of the diagnostic interval (defined as the time from the first presentation of symptoms in primary care to the date of diagnosis) as the exposure variable.

Setting and population

The ICBP-M4 study included all patients with newly diagnosed breast, colorectal, lung or ovarian cancers from cancer registries and hospital registries in 10 jurisdictions across the UK (Wales, England, Scotland, Northern Ireland), Scandinavia (Denmark, Sweden, Norway), Canada (Ontario, Manitoba) and Australia (Victoria) during 2013-2015. Patients below the age of 40 years with a prior history of cancer in the same site, or two or more primary cancers, were excluded. In the present study, patients from Sweden and Norway were ineligible due to lack of information on date of referral in the Swedish data and low participation in the Norwegian survey.

Data collection

Local ICBP-M4 teams sent a questionnaire to eligible patients, their primary care physician (PCP) and the main cancer treatment specialist (CTS), who provided a detailed description of the route to diagnosis, milestone dates, cancer-specific symptoms (yes/no), chronic morbidity, types of clinical investigations and tumour stage. In addition, the teams obtained information on date of diagnosis and tumour stage from cancer registries and clinical databases. Using registry data, we subsequently excluded patients with screen-detected (i.e. non-symptomatic) cancer and patients with missing information on gender, age, date of consent and diagnosis. To avoid recall bias, we also excluded patients who completed the questionnaire more than nine months after diagnosis. In Manitoba, data on specialists were not collected. In Northern Ireland and Denmark, data on specialists were collected solely from clinical databases and registries. Data collection and data management has been described in further detail elsewhere.(David Weller et al., 2016)

Defining exposures, outcome and covariates

Dates encompassing the diagnostic interval were defined in line with the Aarhus Statement as the date of first presentation to a health professional and the date of diagnosis.(D Weller et al., 2012) We prioritised

PCP-reported over patient-reported date of first presentation, as this date is known to be more reliable.(Larsen, Hansen, Sokolowski, & Vedsted, 2014) Date of referral was only provided by PCPs. We prioritised registry-recorded date of diagnosis over survey reports and defined diagnosis as histological confirmation of the malignancy. We defined and calculated three exposure variables as illustrated in Figure 1: (a) the primary care interval (days from first presentation to referral to a CTS); (b) the secondary care interval (days from referral to diagnosis); and (c) the diagnostic interval (days from first presentation to diagnosis). All corresponding dates were validated manually in case of inconsistencies, and negative intervals were set to zero days. All intervals were truncated at 365 days. Outlier and missing dates were imputed based on specific rules to ensure that the direction of a possible misclassification bias was known (Supplementary material, Appendix I).

The primary outcome of the study was tumour stage classified as stage I, II, III or IV according to the TNM staging system or according to the Dukes' or FIGO staging system for colorectal cancer and ovarian cancer, respectively (see Appendix II). We ranked registry-based over CTS-reported staging and re-categorised the identified cases into a binary variable of advanced (stage III+IV) vs. localised (stage I+II) cancer (Appendix II).

We obtained information on age and gender and patient-reported comorbidity defined as suffering from either heart disease, stroke, lung disease and/or diabetes (none=0; medium=1-2; high=3-4). Age was modelled as a categorical variable with three categories based on tertiles for each cancer type.

Statistical analysis

We analysed each cancer separately and modelled the data in two ways. First, we treated the care interval as a continuous variable using restricted cubic splines to make efficient use of within-category information.(Durrleman & Simon, 1989; Greenland, 1995) We used three knots according to Harrell's recommended percentiles (Harrells, 2001) and chose an a priori reference of 30 days. We used logistic regression to estimate the odds ratio (OR) of being diagnosed with an advanced vs. localised cancer as a function of length of each diagnostic interval. Second, to confirm spline trends by a categorical analysis, we grouped intervals by allocating patients roughly based on their cancer and interval-specific percentiles ('short': below 0.75; 'medium': between 0.75 and 0.90; 'long': above 0.90) and calculated the adjusted OR for short or long vs. medium length of diagnostic intervals. In both models, we adjusted for age, gender, comorbidity and jurisdiction to allow for between-jurisdiction variability. Several sensitivity and agreement analyses tested the robustness of the models (Appendix VI).

We calculated 95% confidence intervals (CIs) for all estimates and tested each model against a model with no diagnostic interval term using the likelihood-ratio test. A two-sided P-value of 0.05 or less was defined as statistically significant. Statistical analyses were carried out using Stata statistical software (version 14).

Patient and public involvement

The research questions for the survey, which this study is based, drew on an extensive literature relating to diagnosis and treatment delays leading to negative patient experiences. Patients were involved in the piloting of study instruments to ascertain if recruitment and questionnaire content and dissemination strategies were appropriate, described elsewhere (David Weller et al., 2016).

RESULTS

The flow of patient identification, responses and exclusion is outlined in Figure 2. The flow for each type of cancer is shown in the supplementary material (Appendix III: Figures A1-A4). A total of 6,162 patients fulfilled the inclusion criteria. Of these, 2,544 patients (41%) were excluded due to missing time intervals. Finally, 3,618 (59%) patient questionnaires were included in the analyses. Additionally, 3,618 (59%) PCP questionnaires and 1,974 (32%) CTS questionnaires were included.

Patient description

Patients with breast cancer were generally younger, suffered from less comorbidity, experienced much shorter diagnostic intervals (58% had no primary care delay) and were diagnosed with earlier tumour stages compared to patients with colorectal, lung and ovarian cancer. Ovarian cancer patients had the longest secondary care interval and were more likely to be diagnosed with an advanced cancer than patients with other types of cancer. Lung cancer patients had more comorbidity and generally experienced longer primary care intervals than patients with other types of cancer (Table 1). The clinical features were similar for each jurisdiction, except for the proportion diagnosed with advanced cancer, which tended to be highest in Northern Ireland and Denmark and lowest in Victoria and Canada depending on cancer site (Appendix IV: Table A1).

Diagnostic interval and cancer stage

The association between both primary and secondary care intervals and staging was similar for each type of cancer, but we observed opposite trends for the two intervals. For the primary care interval, we generally saw a flat trend, but a slightly concave or n-shaped association was seen for ovarian cancer with increasing and subsequently decreasing odds of advanced cancer with longer primary care intervals. However, these associations were not statistically significant (Figure 3, Table 2 and Appendix V: Figure A5-A7). For the secondary care interval, we observed a convex or U-shaped association with decreasing and subsequently increasing odds of advanced cancer with longer secondary care intervals. The U-shaped association was

statistically significant for colorectal cancer ($P=0.005$), lung cancer ($P<0.001$) and ovarian cancer ($P<0.001$) and tended to be statistically significant for breast cancer ($p=0.071$). The crude curve estimates were similar to the adjusted estimates (Appendix V: Figure A8-A11).

The pointwise estimates showed that the adjusted odds of being diagnosed with an advanced stage colorectal cancer decreased from the first day until the bottom point of 104 days, where it was around 27% lower than the odds for patients who waited 30 days from referral to diagnosis ($OR=0.73$; 95% CI: 0.59-0.89) (Figure 4 and Appendix V: Figure A8-A11). For breast cancer, the bottom point corresponded to 31 days ($OR=1.00$; 95% CI: 0.99-1.00); for lung cancer to 93 days ($OR=0.52$; 95% CI: 0.42-0.64); and for ovarian cancer to 104 days ($OR=0.56$; 95% CI: 0.43-0.76). The observed trends of the spline regression were confirmed by categorical analyses comparing short or long vs. medium secondary care intervals (Table 2).

More equivocal trends were noted across the individual cancers for the diagnostic interval, and the associations were not statistically significant for lung and ovarian cancer (Appendix V: Figure A12).

Our sensitivity analyses (Appendix VI) overall displayed similar findings as the main analysis, except when we included only PCP data as this decreased the U-shaped trend seen in the secondary care interval for breast and ovarian cancers.

DISCUSSION

While we found statistically significant associations between the length of time interval and cancer stage for all four types of cancer, the observed U-shaped trends only pertained to the secondary care component of the diagnostic interval. The trends for the primary care component were either flat or slightly n-shaped, but these were not statistically significant.

Strengths of the study

A main strength of the present population-based cohort study of 3,618 patients with incident colorectal, lung, breast or ovarian cancer is that selection and information bias was reduced owing to the use of highly reliable cancer registries with histological data on diagnoses and staging. The ICBP-M4 survey drew on state-of-the-art instruments and went through extensive cognitive testing, piloting, translation and adaptation to ensure a high-quality, standardised and clinically validated dataset on diagnostic routes. (David Weller et al., 2016) Additionally, we used benchmarked registries and approaches to produce comparable stage information. (Benitez-Majano, Fowler, Maringe, Di Girolamo, & Rachet, 2016; Deleuran et al., 2012; Ording et al., 2012; Ostensfeld et al., 2012; Tucker C, Howe L, & Weir K, 1999; Sarah Walters et al., 2013) By excluding

screen-detected patients, we ensured a highly homogeneous group with respect to confounders and obtained better internal validity and relevance for all healthcare systems with a gatekeeper function. Furthermore, a main analytical strength of the study is that it addressed confounding by indication by making interval-specific models and by using restricted cubic splines, which allowed for a flexible relationship between exposure and outcome.

Limitations of the study

A number of limitations exist due to the cross-sectional study design, which does not permit direct inference of causality. This may also hold a risk of selection and information bias and of residual confounding.

Firstly, the recruitment process in the ICBP-M4 required the patient to be alive for at least 3-4 months after diagnosis and for some up to 6 months after diagnosis.(David Weller et al., 2016) Bias is conceivable due to the exclusion of more advanced cases in some jurisdictions, which is likely to reflect patients who died during admission or treatment. This problem was perhaps most apparent for the jurisdiction of Victoria, which only included patients with less advanced stages of lung cancer who could be treated by surgery. The main effect of such information bias would be increased variation and fewer cases with short intervals and advanced stages; this would most likely have biased the results towards no association between time and stage. Hence, our estimates may have underestimated the true association.

Secondly, 41% (2,544) of the study population could not be included in the final analyses due to missing information on time intervals; this was primarily due to missing PCP-reported date of referral. Compared to the 3,618 included, excluded study subjects had more early stage cancer and less comorbidity, but, differences were so small they can hardly have influenced the overall results (Appendix IV, Table A2).

The length of the diagnostic interval may be subject to differential misclassification; this could be due to e.g. non-random recalling of dates when symptoms are vague, which is often the case for colorectal, lung and ovarian cancers.(Lyratzopoulos, Neal, Barbiere, Rubin, & Abel, 2012; Lyratzopoulos, Wardle, & Rubin, 2014) Furthermore, missing information is likely to confound all studies on staging and may have biased results if the quality of staging was associated with drop-out and/or diagnostic timeliness. Given the observed U-shaped and n-shaped trends, it is difficult to predict the direction of potential selection and information bias. However, we compared the dates of first presentation to primary care between PCP and patient, and we also compared the date of diagnosis between all data sources available. These comparisons showed adequate agreement (CCC=0.92 and CCC≥0.95, respectively), which indicates that the bias raised is very limited.

Unmeasured confounding by factors such as tumour grade/aggressiveness and socioeconomic status (including ethnicity and education), which were not universally available, may have influenced the results.

We reduced this risk by adjusting for comorbidity and age, but residual confounding may still have resulted from imperfect adjustment and misclassification of other diseases. We observed no major changes in the estimates when controlling for measured comorbidity and age, and this speaks against the presence of residual confounding.

Despite differences in data sources and construction, the clinical features of the patients were remarkably similar across cancer types and the eight jurisdictions. We obtained strikingly similar results, which suggests that selection and information bias cannot explain the observed trends.

Finally, although stratification procedure, spline regression and interval-specific models were used to limit the risk of confounding and selection bias, this approach also reduced the statistical precision of the study. A larger study is needed to assess the cancer- and jurisdiction-specific effects.

Comparison with findings from other studies

Previous studies have reported that the so-called waiting-time paradox shows poor outcomes for patients with very short diagnostic intervals for various types of cancer.(Neal et al., 2015) Maguire and colleagues explicitly warned that failure to consider a non-linear effect may partly explain previous inconclusive findings.(Maguire et al., 1994) Our results confirm previous findings of a non-monotonic relationship (i.e. not constantly increasing (or decreasing) association) between the length of time intervals and mortality or staging for breast, colorectal, lung, skin, prostate and ovarian cancers.(Murchie et al., 2014; Redaniel, Martin, Cawthorn, Wade, & Jeffreys, 2013; Tørring et al., 2013) The authors analysed the staging of colorectal cancer as a function of the length of time under PCP care and specialist care, respectively, and found an n-shaped and a U-shaped association. This study confirms these findings for other types of cancers, jurisdictions and data sources and thus consolidates two important points made by Crawford et al. and Afzelius et al. several years ago; the basis for assignment of waiting time (the sorting of patients) changes during the diagnostic pathway, and the interval-specific models are necessary to achieve valid comparisons.(Afzelius, Zedeler, Sommer, Mouridsen, & Blichert-Toft, 1994; Crawford et al., 2002; Tørring et al., 2017)

Underlying mechanisms

We believe that the finding of the waiting-time paradox reflects confounding by indication; a bias stemming from the inherent difference in the prognosis of patients given different medical priority (i.e. the very sick patients are prioritised, but due to their advanced disease they are more prone to succumb). The diverse trends for both primary care intervals and secondary care intervals support the assumption that symptomatic cancer patients are classified and diagnosed at different pace, which is based on their gradually changing clinical indications and on the diagnostic tools available in primary and secondary care.

The observed decreasing odds with longer secondary care intervals correspond well with a clinical reality in which patients are offered specialist care after primary care triage; this increases the probability of finding advanced stage tumours among expedited patients. Furthermore, in secondary care, the greater clinical experience of patients with cancer and ready access to hospital-based investigations ensure that patients with advanced disease who attend a specialist service are diagnosed very quickly, whereas patients with less clear symptoms and less advanced disease progression are managed less urgently. Hence, negative bias (where the observed effect is lower than the true value) is likely to explain the decreasing odds of advanced cancer with time. As a final tentative point, we propose that the observation of increasing odds of advanced cancer with secondary care intervals longer than approximately three and a half months could reflect the effect of false-negative tests or unnecessary delays in the investigation and/or treatment. Thus, health systems should focus on the effectiveness of the pathways after referral of patients from primary care.

As with previous studies, we found no statistically significant association between the primary care interval and cancer stage. This is presumably due to potential bias from selection, information and confounding as well as confounding by indication inherited from the study designs, which are likely to have caused negative bias. Still, this does not indicate that time does not matter in primary care. It merely indicates the complex clinical and organisational process of selecting patients for referral to specialised investigation for cancer.

The equivocal findings for the diagnostic interval and disease stage (Appendix V: Figure A12) underscore the central argument of the study: When we mix the waiting times for primary care and secondary care (Hansen et al., 2011; Helsper, van Erp, Peeters, & de Wit, 2017; Swann et al., 2018), we do not only fail to acknowledge the complex and differential processes that shape the duration of primary care and secondary care; we also make the study vulnerable to type two errors and may even fail to reject a null hypothesis that is actually false.

Clinical implications

Our consistent findings of U-shaped associations are likely evidence of advanced stage cancer with longer diagnostic intervals. In many previous studies, the authors have seemed unprepared for meeting contradictory results. Instead of questioning their study design, many have ignored statistically significant reverse effects and claimed that the time duration of both diagnostic and treatment processes is too short to have any clinical relevance. (Brasme et al., 2012; Flemming et al., 2017; Iversen, Antonsen, Laurberg, & Lautrup, 2009; Nagle et al., 2011; Polissar, Sim, & Francis, 1981; Porta, Gallen, Malats, & Planas, 1991; Rupassara, Ponnusamy, Withanage, & Milewski, 2006; Sainsbury, Johnston, & Haward, 1999) We believe such conclusions to be erroneous, because clinical triage will inherently result in selecting the very ill patients to be prioritised. Even if most patients will experience necessary and/or unavoidable waiting time during

their diagnostic interval, no 'safe' amount of delay can be defined, at least not by an observational study. The inclusion of data from eight different jurisdictions across the globe emphasises the universal implications of these findings.

Thus, the present study substantiates that observational studies are not ideal for testing whether waiting time matters or not on the patient's prognosis. It shows that wrong conclusions will be drawn from studies applying a simple linear or dichotomous model. On the backdrop of this, future studies should at least account for the inherent risk of different referral practices (such as fast-tracking more seriously ill patients) and strong confounders such as heterogeneity of the patient population, the heterogeneity of tumours and the rate of progression of the tumour.

CONCLUSION

We found that the waiting-time paradox is seen across different types of cancer, and we confirmed that the U-shaped association between waiting time and tumour stage is uniquely related to the secondary care component of the diagnostic interval. The study provides evidence that longer care intervals are associated with more advanced cancer staging; this is seen even in highly regulated universal healthcare systems with diagnostic guidelines and standardised procedures, including fast-track referrals. The study thereby supports efforts to shorten the clinical pathway.

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ADDITIONAL INFORMATION

List of abbreviations

CI	Confidence interval
CRC	Colorectal cancer
CTS	Cancer treatment specialist
ICBP-M4	International Cancer Benchmarking Partnership, Module 4
IQI	Interquartile interval
NA	Not available
NICE	National Institute for Health and Care Excellence
PCP	Primary care physician
SIGN	Scottish Intercollegiate Guidelines Network

Availability of data and material

The data that support the findings of this study are available from the named authors from each ICBP jurisdiction, but restrictions apply to the availability of these data and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the ICBP Programme Board.

Tables and table legends

Table 1: Clinical features for symptomatic patients aged 40 YEARS or over with the first diagnosis of cancer displayed for each cancer (n (%)) if nothing else is stated)

	Breast cancer (N=1058)	CRC (N=1069)	Lung cancer (N=890)	Ovarian cancer (N=601)	Total (N=3618)
Age (years), Median (IQR)	61 (50,73)	70 (61,78)	69 (64,75)	64 (56,72)	67 (58,75)
Gender, Male, among CRC and Lung cancer patients	-	611 (57)	470 (53)	-	1,082 (55)
Comorbidity¹					
None	729 (69)	577 (54)	357 (40)	421 (70)	2,038 (58)
Medium	314 (30)	463 (43)	485 (54)	175 (29)	1,437 (40)
High	10 (1)	27 (3)	48 (5)	5 (1)	90 (2)
Missing	5 (1)	2 (1)	0 (0)	0 (0)	7 (1)
Tumour stage²					
I	353 (33)	179 (17)	218 (24)	165 (27)	914 (25)
II	489 (46)	349 (33)	138 (16)	52 (9)	1,028 (28)
III	135 (13)	357 (33)	249 (28)	261 (43)	1,002 (28)
IV	35 (3)	146 (14)	248 (28)	82 (14)	511 (14)
Missing	46 (4)	38 (4)	37 (4)	41 (7)	163 (5)
Time interval, Median (IQR) days					
Primary care interval	0 (0,7)	2 (0,21)	14 (3,42)	7 (0,24)	4 (0,22)
Secondary care interval	13 (6,21)	29 (14,70)	27 (13,59)	35 (14,62)	21 (10,51)
Diagnostic interval	16 (9,30)	44 (21,97)	50 (26,108)	48 (26,97)	35 (15,79)

¹Comorbidity coded as none=none reported, medium=1-2 reported and high=3+ reported; IQR: inter-quartile interval

² TNM classification for breast and lung cancers, TNM or Duke's classification for CRC, TNM or FIGO classification for ovarian cancer

Table 2: Estimated odds ratios for tumour stage III-IV vs. I-II as a function of secondary- and primary care intervals, adjusted for jurisdiction, age, comorbidity and gender (Lung, CRC). The time intervals were treated as categorical variables.

Time interval	Cancer	Time interval categories, days	N	Advanced stage %	Crude OR (95% CI)	Adjusted OR (95% CI)
Primary Care	Breast	0-15	836	16	0.82 (0.46-1.45)	0.63 (0.33-1.19)
		16-30	84	19	1 (ref.)	1 (ref.)
		>30	92	21	1.11 (0.53-2.32)	1.04 (0.49-2.22)
	CRC	0-30	829	48	0.92 (0.62-1.37)	0.93 (0.62-1.39)
		31-90	110	50	1 (ref.)	1 (ref.)
		>90	92	54	1.19 (0.68-2.07)	1.11 (0.63-1.97)
	Lung	0-30	568	61	1.36 (0.99-1.89)	1.29 (0.91-1.83)
		31-90	200	54	1 (ref.)	1 (ref.)
		>90	85	51	0.89 (0.54-1.48)	0.96 (0.56-1.65)
	Ovarian	0-30	444	60	0.69 (0.40-1.19)	0.60 (0.34-1.07)
		31-90	67	69	1 (ref.)	1 (ref.)
		>90	49	61	0.72 (0.33-1.56)	0.65 (0.29-1.47)
Secondary Care	Breast	0-15	628	18	1.25 (0.87-1.81)	1.27 (0.86-1.89)
		16-60	329	15	1 (ref.)	1 (ref.)
		60	55	15	0.97 (0.43-2.18)	1.08 (0.47-2.47)
	CRC	0-60	727	51	1.52 (1.08-2.13)	1.71 (1.20-2.44)
		61-120	171	41	1 (ref.)	1 (ref.)
		>120	133	45	1.19 (0.75-1.87)	1.20 (0.75-1.92)
	Lung	0-60	644	63	2.49 (1.67-3.70)	2.14 (1.40-3.28)
		61-120	121	41	1 (ref.)	1 (ref.)
		>120	88	49	1.40 (0.81-2.44)	1.35 (0.75-2.44)
	Ovarian	0-60	415	63	1.55 (0.99-2.41)	1.65 (1.03-2.64)
		61-120	99	53	1 (ref.)	1 (ref.)
		>120	46	63	1.54 (0.75-3.16)	1.33 (0.63-2.82)

Bold numbers indicate statistically significant result at $p < 0.05$ or less.

FIGURE LEGENDS

Figure 1: Definition of exposure variables. The three exposure variables based on date of first presentation of symptoms in primary care (B); date of referral to a cancer specialist centre (C); and date of diagnosis (D): “The primary care interval” as B-C = time from first presentation to referral to a cancer specialist centre, “The secondary care interval” as C-D = time from referral to diagnosis and “The diagnostic interval” as B-D = time from first presentation to diagnosis.

Figure 2: Flowchart of patient inclusion. Boxes on the left indicate exclusion of patients, while boxes on the right indicate drop-outs.

Figure 3: The odds of being diagnosed with advanced cancer as a function of primary care interval (time from presentation to referral). Estimated odds ratios of being diagnosed with advanced (stage III+IV) vs. localised (stage I+II) cancer as a function of the length of the primary care interval analysed for each type of cancer. We adjusted for age, gender (for lung and colorectal cancer), comorbidity and jurisdiction. The horizontal line indicates the chosen reference point of 30 days (see logistic regression details in Appendix V). Comparisons within breast cancer patients were not justified because more than half experienced no primary care delay.

Figure 4: The risk of being diagnosed with advanced cancer as a function of secondary care interval (time from referral to diagnosis). Estimated odds ratios of being diagnosed with advanced (stage III+IV) vs. localised (stage I+II) cancer as a function of the length of the secondary care interval analysed for each type of cancer. We adjusted for age, gender (for lung and colorectal cancer), comorbidity and jurisdiction. The horizontal line indicates the chosen reference point of 30 days (see logistic regression details in Appendix V).

FIGURES

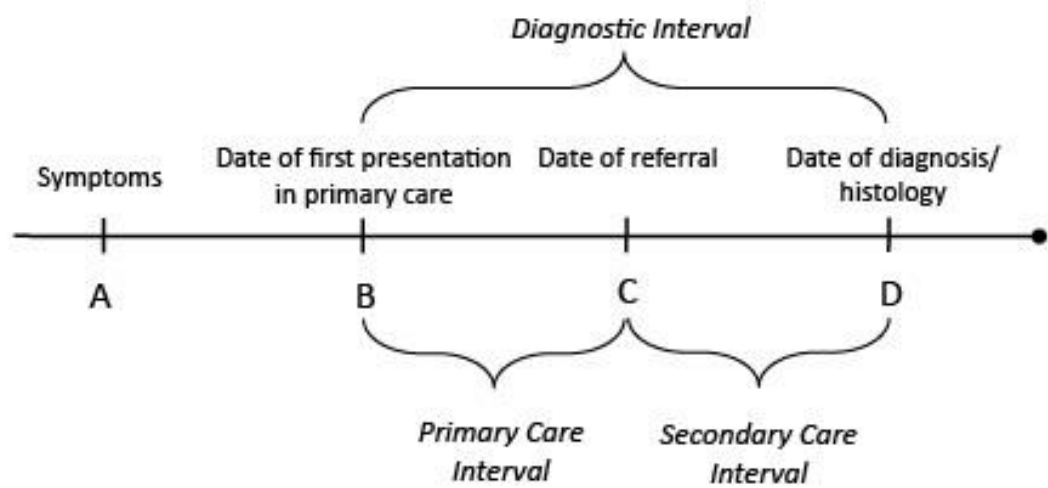
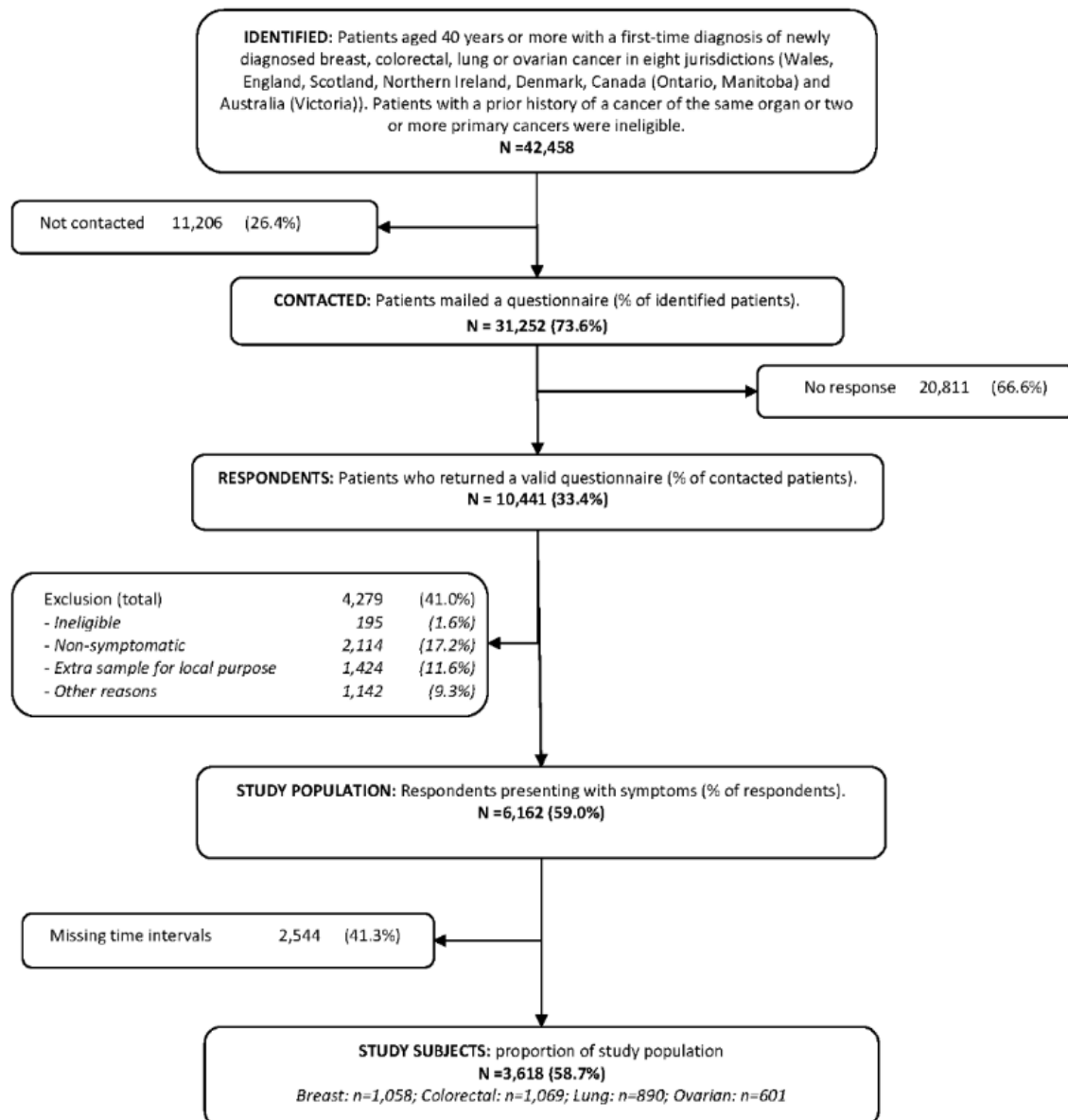
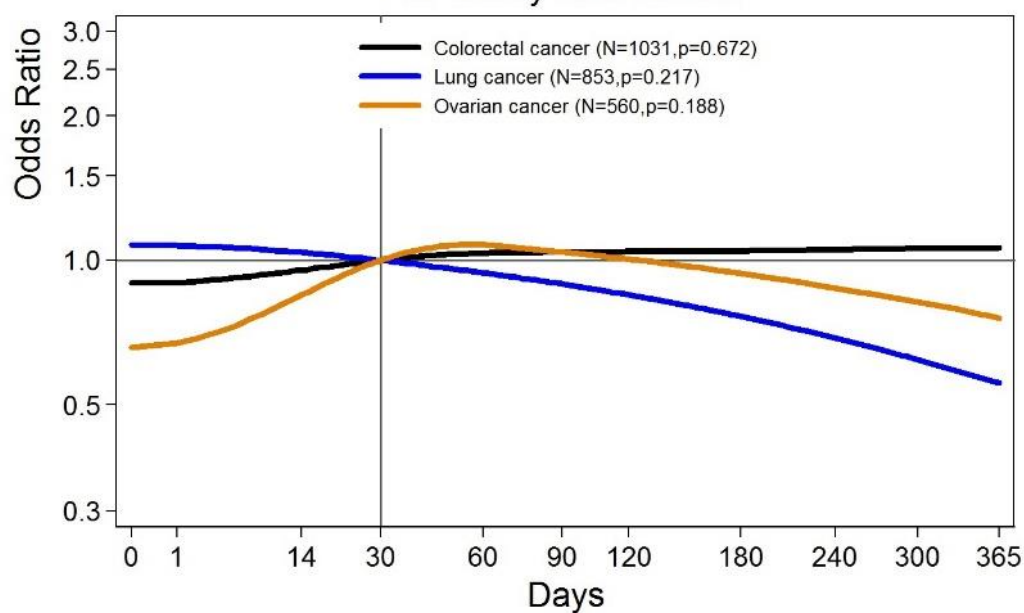


FIGURE 1: DEFINITION OF EXPOSURE VARIABLES
The three exposure variables based on date of first presentation of symptoms in primary care (B); date of referral to a cancer specialist centre (C); and date of diagnosis (D): "The primary care interval" as B-C = time from first presentation to referral to a cancer specialist centre, "The secondary care interval" as C-D = time from referral to diagnosis and "The diagnostic interval" as B-D = time from first presentation to diagnosis.



B: Primary care interval



A: Secondary care interval

