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Title: Differences in breast cancer diagnosis by patient presentation in Ontario: a retrospective cohort study
Authors: Steven Habbous PhD, Esha Homenauth MSc, Andriana Barisic MSc, Sharmilaa Kandasamy BSc, Vicky Majpruz MA, Katharina Forster PhD MD, Marta Yurcan MHSc, Anna M. Chiarelli PhD, Patti Groome PhD, Claire Holloway PhD MD, Andrea Eisen MD

Reviewer 1
General comments (author response in bold)

Comment #1: Can you elaborate on the QA method that ensures screening mammograms confirming so-called interval cancers can be retrospectively reviewed to ensure that individual OBAS's are not outliers with regards to missed diagnoses?
Thank you for this interesting question. The Ontario Breast Screening Program (OBSP) conducts annual linkages with the Ontario Cancer Registry to monitor interval cancer rates. The OBSP also has a QA mechanism for radiologists and screening sites, which examines the incidence of interval cancers to establish whether any individual radiologist or OBSP screening site (rather than O-BAS) are outliers with regards to missed diagnoses. An example of this is published as Cancer Care Ontario's Cancer Screening Performance Report and is reported by geography (https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOCancerScreeningPerformanceReport.pdf). It is not currently possible to report interval cancer rates in the O-BAS as defined in our study, but this would be an important quality indicator to capture as O-BAS become a universal standard for breast assessment of both screen-detected and symptomatic breast cancers.

Comment #2: Why was Stage 0 excluded (or at least a very low number included in the sample). No mention of DCIS, which would make up a large proportion of screen-detected disease.
DCIS was out of scope of the present study, because it is generally asymptomatic. A small number of invasive breast cancers were classified as stage 0 by the Ontario Cancer Registry (rather than in situ); it is possible that these were misclassified as stage 0 by the Ontario Cancer Registry since the proportion of stage 0 cases did not differ between screening and symptomatic subgroups. We added a statement to the limitations section about the generalizability to the DCIS population.

Comment #3: How was lead-time bias allowed for in the analysis when comparing O-BAS diagnosed patients to the other groups?
This is a great point. In the current revision, we adjust for lead-time bias in the OBSP-screen-detected subgroup of patients using the correction factor suggested by Duffy et al (2008) and a mean sojourn time of 2 years. The overall survival time for the OBSP-screened group was reduced as a result, but our conclusions remain unchanged. We updated the figures and all survival analyses accordingly.

Comment #4: Can you specify the fail-safe mechanisms in place to ensure that all positive diagnoses are conveyed back to family doctors in a timely manner, or better still,

is there a way in which BIRADS-5 lesions can bypass the GP and be referred by the radiologist straight to a surgical team to allow for timely intervention?
The reviewer's suggestion is an important potential avenue for improving the diagnostic phase for both screened and symptomatic women. The purpose of this study was to document differences in diagnostic wait times and survival outcomes between women with screen-detected and symptomatic breast cancer. Having done so, the next steps would be to develop a plan for implementation of a system approach to the diagnostic evaluation of all women with breast cancer regardless of the mode of presentation. Facilitated referral may well prove to be an important aspect of that plan.

Comment #5: This database is an excellent resource, and represents an invaluable snapshot of screening practices in Canada. Consequently, was breast density recorded, and did this have an influence on oncological outcomes?
We fully agree that such a database would be an excellent resource. Breast density was only available for OBSP-patients and used to identify women with high breast density (>= 75%) for annual (rather than biennial) screening. Thus, we would only have this information on breast density for OBSP screened women and would not be able to fully address this question. The OBSP is in the process of implementing an enhanced reporting system for breast density, so perhaps the association between breast density and cancer outcome can be assessed in future studies.

Reviewer 2
General comments (author response in bold)

Comment #1: Would appreciate a defined portion of your discussion on highlighting more of the health care utilization component. Especially some discussion on total dollars saved for tests that were not required (ie CT scan etc). This is extremely timely with all provinces now with ever heightened scrutiny on overall health care costs.
Thank you for your comment. The impact of O-BAS on health care costs was beyond the scope of the current study. We examined utilization of mammography, ultrasound, and consultation with various specialists, but a comprehensive analysis of the cost-effectiveness of O-BAS would require identification and costing of a more extensive menu of healthcare encounters. The fact that women diagnosed at an O-BAS had more duplicate breast ultrasound examinations but fewer staging tests for distant disease suggest that there are differences worthy of further study. Our group is currently conducting a separate study of the relationship between concordance with published pathways and healthcare costs. Understanding the drivers behind higher health system costs would be a critical factor to inform quality improvement initiatives. We have added healthcare utilization to the discussion, demonstrating the potential efficiency gains of a provincial-program.
"However, a more standardized diagnostic assessment pathway may also reduce repeated imaging and unnecessary testing, which is also expected to reduce costs.37 A 2018 environmental scan of national and regional cancer diagnostic improvement initiatives described reported costs and cost savings, but formal cost effectiveness analyses were not available.[5]"

Reviewer 3

General comments (author response in bold)

This paper reports on a very interesting analysis of data on women with breast cancer from 2013-2017 in the Ontario Cancer Registry. The authors determined which of these patients had complete diagnostic and pretreatment assessment at an Ontario Breast Cancer Assessment Centre (O-BAS) and those who were diagnosed and assessed outside of this system. They then analyzed the effect of diagnosis at an O-BAS (vs Non O-BAS) on those who were diagnosed through screening or presentation with symptoms on breast cancer stage, wait-times, patterns of healthcare utilization, and overall survival.
The assumptions and cohort development were reasonable except for comorbidity.
The investigators identified 51,460 breast cancer patients with a mean age of 63 at diagnosis, 86% had no comorbidity, 3,845 (7%) had a prior breast cancer and 42,598 (83%) were diagnosed in an O-BAS. A total 28,107 were symptomatic, 13,615 were OBSP-screened, and 9,738 were GP screened. Most patients had stage 1 (n=21,218; 42%) or stage 2 (n=18,568; 37%) breast cancer.
Also compared with symptomatic patients the diagnostic interval was 25 days shorter for OBSP-screened patients and 6 days longer for GP-screened patients. After adjustment overall survival of patients managed by the O-BAS was better than either those who were GP screened or those who were symptomatic. Patients who were older or from a lower income neighbourhood had worse outcomes.

Comment #1: This is a very thorough and well done analysis and makes for a compelling argument to have the O-BAS be the care model for all women who have symptoms or are suspected of having breast cancer. There are limitations to this particularly for women who live a long distance from an O-BAS. It is unclear whether there would be capacity issues if this were to occur and may result in longer wait times. It may also result in some 'de-skilling' of GPs and others in managing women who present with breast cancer symptoms.
Thank you for the comment. O-BAS is becoming the model of care for all women with screen-detected breast cancer, and we argue that this should also be the standard for all women with symptomatic breast cancer (referral to an O-BAS is less likely for symptomatic women simply due to the organizational structure of the referral system in place). We agree that understanding capacity issues of O-BAS is a limitation of the study, as increased referrals may strain the O-BAS and prolong wait-times. We have added this point to the discussion.

Comment #2: A couple of suggestions: The research questions were not explicitly stated for this project and that would be helpful upfront. I also found it confusing to try and follow the different groups and whether the cohort was symptomatic or not. If the main conclusion of this paper is to make a case for women with symptoms of breast cancer to be managed through O-BAS then perhaps the paper should focus on that as a direct comparison. While the GP screening group is also an important consideration, adding this group caused confusion for me.
Thank you for the suggestions, and we agree that we should have made this clearer. We revised the introduction to make it more streamlined and focused. The purpose of the study was to measure diagnostic wait-times and survival among patients with breast cancer and to identify potential areas for improvement in care, with a particular focus on the breast assessment process. The main conclusion of the paper indeed makes the case for women with symptomatic breast cancer to be managed by O-BAS by potentially leveraging the organization

of the OBSP at the time of presentation. However, this conclusion was not known at the outset of the study, nor was it initially hypothesized. Only by characterizing the patients as OBSP-screened, GP-screened, and symptomatic, measuring their wait-times, comparing their referral patterns, and comparing their overall survival did this conclusion become apparent. This approach demonstrates the utility of examining a patient population more broadly instead of honing in a specific subset, which may mask the problem (e.g. focusing only on the symptomatic patients). Differences in the processes and outcomes of diagnostic assessment for screening and symptomatic presentations of breast cancer should be considered when exploring new models of care, as they raise issues related to vertical inequity.

Comment #3: A minor point is that assessing comorbidity using only hospital databases will miss many people with chronic disease since most are managed in primary care and may not be hospitalized (eg. Diabetes, hypertension, depression etc.)
Thank you, this is a good point. We provided additional references regarding the utility of the Charlson comorbidity index, which despite its limitations, is fairly robust at capturing comorbidity. Those without any hospital encounter will likely have well-managed comorbidity that may be less prognostic (e.g. people with well-controlled diabetes may have similar medium-term survival as those who have no diabetes at all).