Received: 31 December 2019 | Revised: 27 July 2020 | Accepted: 29 July 2020

DOI: 10.1002/pds.5104

COMMENTARY

WILEY

Using real-world evidence to support a changing paradigm for cancer screening: A commentary

Michelle B. Leavy[1] | Kathryn Starzyk[1] | Evan Myers[2] | Gary Curhan[1] | Richard Gliklich[1]

[1]OM1, Inc, Boston, MA

[2]Duke University School of Medicine, Durham, NC

Correspondence
Michelle B. Leavy, 800 Boylston Street, Suite 1410, Boston, MA 02199,
Email: mleavy@om1.com

KEYWORDS: cancer screening, pharmacoepidemiology, real-world data, real-world evidence

1 | INTRODUCTION

Despite enormous investments in research and treatment, cancer continues to be the second leading cause of death in the United States and a significant source of morbidity and economic burden. Population-based screening programs aim to improve patient outcomes by detecting precancerous or early stage cancer in asymptomatic individuals, but these programs must balance the potential risks and benefits of screening. Screening tests must have sufficient sensitivity and specificity to avoid the burden and risks of unnecessary biopsies or other follow-up procedures. Other potential harms of screening include overdiagnosis, procedural complications, and long-term adverse effects (e.g., repeated radiation exposure from mammography).

Currently, routine screening is only performed for a subset of cancers, such as breast cancer, colorectal cancer, and cervical cancer. Even when screening is recommended by professional associations and other organizations, such as the United States Preventive Services Task Force (USPSTF), adherence to guidelines is well below targets, and substantial disparities in access to screening exist.[1] Lack of uptake is due to systemic factors, such as access to care[2] and workflow challenges in identifying which patients are eligible for screening and would most benefit,[3,4] as well as patient preferences, such as avoidance, fear, and potential discomfort.[5]

To address these challenges, substantial resources are devoted to developing new tests for early detection of cancer. Some studies are exploring the potential of liquid biopsies that may allow for early identification of various types of cancer with minimal patient risk and discomfort.[6] In colorectal cancer, the U.S. Food and Drug Administration (FDA) has approved several new products for screening, including fecal occult blood tests and a stool DNA test, that avoid some of the risks and burden of screening with colonoscopy. As the cancer screening paradigm shifts to include more screening options, the need for evidence to support regulatory decision-making and to inform guidelines and clinical and patient decision-making will increase.

2 | SCREENING STUDY DESIGNS AND THE POTENTIAL ROLE OF REAL-WORLD EVIDENCE

Randomized controlled trials (RCTs) are the current gold standard for cancer screening studies, yet these trials are necessarily complex, time-consuming, and costly. While cancer represents an enormous public health burden, the actual prevalence of a specific cancer in a population-based sample is relatively low, making it necessary to include very large numbers of individuals to identify enough cases to achieve narrow confidence intervals around estimates of sensitivity. Patients must be followed for sufficiently long periods to determine that cancers are not missed, and even large trials are often unable to determine the impact of screening on mortality because of the cost and logistical barriers of following patients for many years or even decades. In breast cancer, for example, the National Cancer Institute recently launched the Tomosynthesis Mammographic Imaging Screening Trial (TMIST) to address questions about whether use of three-dimensional mammography, or tomosynthesis, is more effective than convention, two-dimensional mammography at reducing the proportion of women diagnosed with an advanced breast cancer. The trial will follow 165 000 women for 5 years, ending in 2030.[7]

Even large trials with clear findings may fail to change clinical practice. The National Institutes of Health funded the National Lung Screening Trial (NLST), a multicenter RCT of screening with low-dose computed tomography (CT). The trial enrolled 53 454 participants, captured data from 2002 to 2007, and found that annual screening with low-dose CT in a high-risk population was associated with a 20%

reduction in the primary outcome of lung cancer-specific mortality.[8] Many professional organizations used the trial as the basis for lung cancer screening guidelines that include low-dose CT, but actual rates of screening remain low as questions persist about how to replicate the trial findings in community settings.[9,10]

The challenges of relying on RCTs for cancer screening studies are compounded by rapid changes in cancer screening approaches and policies. Clinical decision-making and reimbursement policies around cancer screening are driven largely by guidelines from professional associations and organizations such as the USPSTF. Several factors, such as introduction of new treatments, changes in cancer incidence, identification of new risk factors, or development of new screening products, may result in changes in screening guidelines and in clinical practice. For example, the USPSTF cervical cancer screening recommendation was updated in 2012 and again in 2018 to include a newly approved test and to revise screening interval recommendations.

These challenges point to the need for innovative study designs that can help address questions about screening approaches in a real-world setting in a timely and cost-effective manner. Study designs that use real-world data (RWD) offer a potential tool for the efficient generation of real-world evidence (RWE) to inform regulatory decision-making around cancer screening products. The FDA defines RWD as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records (EHRs); medical claims and billing data; data from product and disease registries; patient-generated data, including from in-home-use settings; and data gathered from other sources that can inform on health status, such as mobile devices. RWE is defined as the clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD."[11]

While the concept of RWE for cancer screening is new, the FDA has used RWE in regulatory decision-making around cancer therapies. For example, blinatumomab was initially approved for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia based on evidence from a single-arm trial combined with historical data extracted from existing patient records.[11] The FDA is also collaborating with several organizations to assess the utility of RWE for different purposes. These projects leverage the many existing high-quality sources of RWD on cancer screening, treatment, and outcomes, including patient registries designed for surveillance, product safety and/or effectiveness, and quality improvement, other non-interventional studies, claims databases, and electronic medical records.[12-14]

Together, these sources of RWD offer the potential to assemble the very large cohorts necessary to assess the sensitivity and specificity of screening tests, calculate the positive predictive value (PPV) and negative predictive value (NPV), and follow patients for many years to examine cancer-specific and all-cause mortality. RWD offer particular promise in the area of assembling sufficiently large and diverse cohorts with potentially variable prevalence of the disease to calculate the PPV and NPV of screening tests in key subpopulations. This information is critical for informing clinical decision-making around who should be screened and how often.

KEY POINTS

- Cancer screening tests are an excellent use case for real-world evidence (RWE) because of the urgent need for new tests and the practical challenges of conducting clinical trials.
- High-quality sources of real-world data (RWD) on cancer screening, treatment, and outcomes already exist and could be used to generate RWE.
- RWD sources are particularly useful for assembling the large and diverse cohorts necessary to assess the sensitivity and specificity of screening tests and to calculate the positive predictive value and negative predictive value.
- The potential for bias, such as verification bias and information bias, must be considered when evaluating RWD sources.

3 | CONSIDERATIONS FOR USING REAL-WORLD EVIDENCE

Real-world studies of cancer screening tests must consider the potential for bias and select study designs and analytic approaches accordingly. In addition, careful evaluations of RWD quality and relevance are necessary before determining that a data source is useful for generating RWE on cancer screening tests. Multiple publications have discussed criteria to assess RWD quality and relevance and methods to evaluate and improve the quality of studies designed to generate RWE.[15,16]

3.1 | Selection bias

The potential for selection bias should be considered when designing real-world cancer screening studies, as the population under study may influence the estimated characteristics of the screening test and the generalizability of the results. For example, a study cohort comprising patients referred to a specialist before screening would likely include more patients with symptoms or risk factors related to a potential cancer diagnosis and may result in verification bias, as the reason for the referral may be associated with the results of the screening test.[17] To address the potential for selection bias, studies should seek to include patients who are representative of the intended population for the screening test. Multi-site studies are useful to include a diverse patient population and to capture variations in screening and follow-up protocols in the real-world setting.

Depending on the type of screening test, multi-site studies may need to account for variability in reading the test result (e.g., interpretation by different radiologists vs reading by a centralized lab). Capture of adequate data on baseline characteristics, such as prior screenings, prior cancer diagnoses, referral to specialists, and risk factors, is also critical to understand the patient population and to identify higher-risk patients. Secondary analyses may be necessary to examine the performance of a screening test generally and within higher-risk patients.

3.2 | Information bias

The potential for information bias also must be considered. In real-world settings, patients may be lost to follow-up in some data sources. Patients with a negative screening test may go on to be diagnosed with cancer at a later date, potentially indicating a false negative screening test, and these will not be captured in the study if patients, for example, change health plans and/or care providers and are lost to follow-up. Patients enrolled in commercial health plans in the United States may switch plans frequently due to changes in employment or other circumstances, making it challenging to track outcomes that occur over long periods.[11] While RCTs may be able to follow up with patients directly or link to other sources, such as death indices, these approaches may not be feasible in some RWD sources. The potential impact of loss to follow-up must be considered in evaluating the appropriateness of RWD sources and when developing the study protocol. Integrated delivery networks, for example, are more likely to retain patients over time, reducing the potential for losses to follow-up. Study protocols should describe clearly how patients who change care providers and/or health plans will be tracked (where feasible) and whether linkages to other sources, such as death indices, are planned to obtain mortality data for patients.

Even when patients remain in the study, data may be missing for key outcomes or other variables. Completeness of data should be reviewed when evaluating the appropriateness of RWD sources, and study protocols should include clear plans for addressing missing outcomes data. For example, what will be done if a patient record indicates that a biopsy was done, but the pathology report is missing? Will any data be extracted from unstructured notes data, and, if so, how? Study protocols should discuss if and how other data sources (e.g., diagnosis codes in place of a pathology report) may be used and whether linkages to other data sources are planned. Studies should also plan for ongoing monitoring of data quality throughout the duration of the study, so that issues can be identified and resolved promptly.

Analysis plans also must consider the potential impact of missing data. In real-world cancer screening studies, analysis plans typically focus on observed specificity and sensitivity. Calculation of specificity can be particularly challenging, as this requires identification of patients with a "true" negative test. Patients with missing data or patients who are lost to follow-up may appear to have a 'true' negative test, when in fact their cancer diagnosis is missing from the data set. To address these issues, analysis plans may require that patients have at least one visit within the follow-up period to verify that the patient is still receiving care from the health system. Analysis plans may also include secondary outcome measures that incorporate additional patients, such as patients with a missing pathology report but relevant diagnosis codes, to assess the robustness of the study findings. Lastly, analysis plans must consider the timeframe for calculating sensitivity and specificity; for example, in a study that follows patients for 5 years after an initial test, it is possible that patients will develop cancer in the follow-up period that was not present at the time of the screening. Descriptive analyses may be useful to describe the average time from the index screening date to diagnosis.

Lastly, study designs should assess the potential for confounding. Real-world screening studies that track outcomes following diagnosis, such as mortality, should aim to capture information on factors that may be related to both the likelihood of screening and the outcome of interest (e.g., lifestyle habits).

3.3 | A case study in cervical cancer

While use of real-world cancer screening studies in the regulatory context is new, real-world studies have provided evidence to support development of clinical guidelines and inform clinical practice. Cervical cancer screening, for example, has evolved in recent years to include three approaches: the high-risk HPV (hrHPV) test alone, cervical cytology alone, or co-testing (hrHPV plus cytology). The availability of multiple approaches introduced questions about their comparative effectiveness and appropriate screening intervals. A large cohort study conducted at Kaiser Permanente Northern California (KPNC) provided evidence of the real-world clinical effectiveness of co-testing in a large, diverse population followed for several years.[18] KPNC is an integrated delivery system that began routine screening with co-testing in 2003. The cohort study captured data on 330 000 women screened with co-testing over 5 years and demonstrated both that co-testing is feasible to implement in routine clinical practice and recommended screening intervals are appropriate.

The KPNC study was designed to mitigate several potential sources of bias. First, the KPNC patient population was similar demographically to the general population in the KPNC region. The study used broad inclusion criteria, and over 90% of eligible women enrolled in co-testing. Data on past history of an abnormal Pap test or abnormal biopsy were available to identify higher risk patients. To mitigate the potential for information bias, the study verified reported cervical cancers with chart review and used a consistent team of pathologists to review abnormal biopsies throughout the study. A computerized system identified abnormal laboratory results without a follow-up procedure and used a series of alerts and alarms to prompt follow-ups with the patient. The RWE generated in this study has been used in the development of cervical cancer screening clinical guidelines and were cited in the USPSTF recommendation statement.[19,20] The steps taken to address the potential for bias in this real-world study could be applied to studies of other cancer screening approaches intended to inform regulatory decision-making.

3.4 | Future directions for real-world studies of cancer screening

As new screening approaches are developed, real-world studies will play an important role in understanding the clinical effectiveness and, in some cases, comparative effectiveness of screening approaches. Studies may be able to take advantage of the introduction of a new screening approach to create a retrospective cohort of patients screened using the older approach and a prospective cohort of patients screened using the newer approach within, for example, the same health system. This approach will address potential concerns about selection bias, where patients at higher risk may be screened using the newer approach. Collection of high-quality data on baseline characteristics and outcomes is critical for real-world studies of cancer screening, and continued efforts to improve the quality of data captured at the point of care are important. Further work on data linkage, ascertaining mortality for patients lost-to-follow-up, and extracting information from unstructured data are also important steps.

4 | CONCLUSIONS

Significant research is devoted to developed and improving cancer screening approaches, but RCTs for cancer screening are challenging. Many high-quality sources of RWD related to cancer screening and outcomes already exist and could be leveraged to generate RWE to inform regulatory decision-making, as has been demonstrated with cancer screening guidelines.

CONFLICT OF INTEREST

The content in this manuscript has not been posted or presented previously. No outside funding was received for this manuscript. Dr. Gliklich, Dr. Curhan, Ms. Starzyk, and Ms. Leavy are employees of OM1, which is involved in issues related to the topic of this commentary. Dr. Myers has been reimbursed by Hologic, Inc as a consultant on real-world evidence for cervical cancer screening.

ORCID

Michelle B. Leavy https://orcid.org/0000-0003-1927-7248
Kathryn Starzyk https://orcid.org/0000-0001-7171-3989

REFERENCES

1. Sabatino SA, White MC, Thompson TD, Klabunde CN. Cancer screening test use - United States. *2013 MMWR*. 2015;64(17):464-468.
2. Reeder-Hayes KE, Anderson BO. Breast cancer disparities at home and abroad: a review of the challenges and opportunities for system-level change. *Clin Cancer Res*. 2017;23(11):2655-2664.
3. Jemal A, Fedewa SA. Lung cancer screening with low-dose computed tomography in the United States—2010 to 2015. *JAMA Oncol*. 2017;3(9):1278-1281.
4. Kinsinger LS, Anderson C, Kim J, et al. Implementation of lung cancer screening in the veterans health administration. *JAMA Intern Med*. 2017;177(3):399-406.
5. Green BB, BlueSpruce J, Tuzzio L, Vernon SW, Aubree Shay L, Catz SL. Reasons for never and intermittent completion of colorectal cancer screening after receiving multiple rounds of mailed fecal tests. *BMC Public Health*. 2017;17(1):531.
6. Hanash SM, Ostrin EJ, Fahrmann JF. Blood based biomarkers beyond genomics for lung cancer screening. *Transl Lung Cancer Res*. 2018;7(3):327-335.
7. Digital Tomosynthesis mammography and digital mammography in screening patients for breast cancer. NCT03233191. *ClinicalTrials.Gov*. https://clinicaltrials.gov/ct2/show/NCT03233191. Accessed March 29, 2020.
8. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New Eng J Med*. 2011;365(5):395-409.
9. Chudgar NP, Bucciarelli PR, Jeffries EM, et al. Results of the national lung cancer screening trial: where are we now? *Thorac Surg Clin*. 2015;25(2):145-153.
10. Triplette M, Thayer JH, Pipavath SN, Crothers K. Poor uptake of lung cancer screening: opportunities for improvement. *J Am Coll Radiol*. 2019;16(4) Pt A:446-450.
11. U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. https://www.fda.gov/media/120060/download. Accessed June 3, 2019.
12. Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. *J Natl Cancer Inst*. 2017;109(11):1-5.
13. Stewart M, Norden AD, Dreyer N, et al. An exploratory analysis of real-world end points for assessing outcomes among immunotherapy-treated patients with advanced non-small-cell lung cancer. *JCO Clin Cancer Inform*. 2019;Jul(3):1-15.
14. INFORMED: Information Exchange and Data Transformation. U.S. Food and Drug Administration. https://www.fda.gov/science-research/informed-information-exchange-and-data-transformation. Accessed December 19, 2019.
15. Gliklich RE, Leavy MB. Assessing real-world data quality: the application of patient registry quality criteria to real-world data and real-world evidence. *Ther Innov Regul Sci*. 2020;54(2):303–307. 2168479019837520.
16. Miksad RA, Abernethy AP. Harnessing the power of real-world evidence (RWE): a checklist to ensure regulatory-grade data quality. *Clin Pharmacol Ther*. 2018;103(2):202-205.
17. Harper R, Henson D, Reeves BC. Appraising evaluations of screening/diagnostic tests: the importance of the study populations. *Br J Ophthalmol*. 2000;84(10):1198-1202.
18. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol*. 2011;12(7):663-672.
19. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol*. 2012;137(4):516-542.
20. Force UPST. Screening for cervical cancer: US preventive services task Force recommendation statement. *JAMA*. 2018;320(7):674-686.

How to cite this article: Leavy MB, Starzyk K, Myers E, Curhan G, Gliklich R. Using real-world evidence to support a changing paradigm for cancer screening: A commentary. *Pharmacoepidemiol Drug Saf*. 2020;1–4. https://doi.org/10.1002/pds.5104