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ORIGINAL ARTICLE

Bayesian synthesis using prior information on fracture risk from randomized trials to analyze post-market data

Ava John-Baptiste[a,b,c,*], Taryn Becker[c,d], Kinwah Fung[e], Lorraine L. Lipscombe[c,f,g], Peter C. Austin[e,h,i], Geoffrey M. Anderson[c,e,j]

[a]*Departments of Anesthesia & Perioperative Medicine, Epidemiology & Biostatistics, Interfaculty Program in Public Health, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada*
[b]*Centre for Medical Evidence, Decision Integrity & Clinical Impact, London, Ontario, Canada*
[c]*Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada*
[d]*The Scarborough Hospital, Toronto, Ontario, Canada*
[e]*Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada*
[f]*Department of Medicine, University of Toronto, Toronto, Ontario, Canada*
[g]*Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*
[h]*Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada*
[i]*Sunnybrook Health Sciences Centre, Toronto, Canada*
[j]*Institute of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada*

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Abstract

Objective: To conduct a Bayesian evidence synthesis using commonly available statistical procedures to estimate fracture risk for postmenopausal women undergoing hormonal therapy for breast cancer.

Study Design and Setting: Using linked administrative data, we conducted a retrospective cohort study of women aged 66 years or older diagnosed with stage I to III breast cancer in Ontario, Canada, between April 1, 2003, and February 28, 2010. We used data augmentation to perform Bayesian Cox regression of the hazard of a hip, spine, or wrist/forearm fracture, adjusting for age, history of fragility fracture, corticosteroid use, osteoporosis, rheumatoid arthritis, dementia, or diabetes diagnoses.

Results: Of 10,259 included in the sample, 3,733 initiated on tamoxifen and 6,526 on an aromatase inhibitor. Posterior probabilities that the hazard ratio (HR) exceeded 1 for aromatase inhibitor compared with tamoxifen were 46% (HR = 0.99, 95% credible interval [CrI] 0.71, 1.25), 35% (HR = 0.94, 95% CrI 0.78, 1.26), and 76% (HR = 1.08, 95% CrI 0.88, 1.32) with an uninformative prior, and 63% (HR = 1.04, 95% CrI 0.83, 1.3), 84% (HR = 1.12, 95% CrI 0.89, 1.4), and 89% (HR = 1.13, 95% CrI 0.93, 1.36) with an informative prior, for hip, spine, and wrist/forearm fractures, respectively.

Conclusions: Prior information resulted in higher posterior probabilities. The strength of evidence for increased risk varied by fracture site.

Keywords: Breast cancer; Fractures; Bayesian evidence synthesis; Aromatase inhibitors; Tamoxifen; Data augmentation

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Conflict of interest: None.

* Corresponding author. Dr Ava John-Baptiste, Western University, Rm 4111, 1465 Richmond Street, London, Ontario N6G 2M1, Canada. Tel.: 519-661-2111; fax: 519-850-2958.

E-mail address: ajohnbap@uwo.ca (A. John-Baptiste).

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What is new?

Key findings

- Using Bayesian evidence synthesis, we incorporated prior information on fracture risk from trials into an analysis of postmarket data.
- Incorporating prior information from trials resulted in higher probabilities of fracture risk when comparing aromatase inhibitors (AIs) with tamoxifen.
- Although we found little evidence to support increased hip fracture risk with AIs, the probability of increased risk of spine and wrist/forearm fractures with AIs requires further investigation.

What this adds to what was known?

- We demonstrated a simple approach to evidence synthesis that can be implemented in commonly used statistical software to enhance the analysis of observational postmarket data.

What is the implication and what should change now?

- Bayesian evidence synthesis should be used more widely to incorporate trial data into post-market analysis of drug safety.

1. Background

In Canada, the 5-year survival rate following diagnosis with early-stage breast cancer is 87% [1]. Hormonal therapies reduce the risk of breast cancer recurrence for postmenopausal women, with stage I or II, estrogen or progesterone receptor–positive tumors [2–4]. Therapeutic options include selective estrogen receptor modulators, such as tamoxifen and aromatase inhibitors (AIs) such as anastrozole, letrozole, or exemestane. AIs have been shown to reduce recurrence of breast cancer when compared with tamoxifen and to increase disease-free survival. The treatments have different risk profiles. AIs may lead to arthralgias and increased fracture risk compared with tamoxifen. Tamoxifen is associated with an increased risk of endometrial cancer and venous thromboembolism [5].

Our objectives were to use an observational data set to estimate the relative risk of fractures for AIs compared with tamoxifen for postmenopausal women diagnosed with breast cancer. We used a simple approach to evidence synthesis that can be implemented in commonly used statistical software to enhance the analysis of observational postmarket data. In the Bayesian paradigm, belief about an unknown quantity is expressed using probabilities. New evidence can be used to update knowledge and make new inference about the probabilities of clinical events. We augmented postmarket data from an observational cohort with a prior data set that was based on estimates from randomized controlled trials (RCTs) to make inference about the probability of hip, spine, and wrist/forearm fractures. The Bayesian approach can enhance the analysis of observational data supplementing RCT findings by directly incorporating prior information from RCTs into the analysis. The other benefit of the Bayesian approach is that it allows researchers to make inference using direct probability statements.

We used data augmentation to implement Bayesian evidence synthesis. Data augmentation makes use of basic statistical procedures to produce similar results to Markov Chain Monte Carlo simulations [6].

2. Methods

We conducted a retrospective observational cohort study using the following Ontario administrative databases: the Ontario Cancer Registry, the Canadian Institute of Health Information Discharge Abstract Database, the National Ambulatory Care Reporting System database, the Ontario Drug Benefit Formulary database, the Ontario Health Insurance Plan (OHIP) database, the Ontario Diabetes Database [7], and the Registered Persons Database. These data sets were linked using unique encoded identifiers derived from the OHIP number and analyzed at the Institute for Clinical Evaluative Sciences. This number is required to access hospital and physician services, diagnostic tests, and pharmaceuticals, which are publicly financed.

Using the Ontario Cancer Registry, we identified women diagnosed with stage I to III invasive breast cancer between April 1, 2003, and February 28, 2010, who were 66 years or older at the time of diagnosis and filled a prescription for an AI or tamoxifen within 12 months following the date of diagnosis. In Ontario, women aged 65 years and older are eligible for drug benefits covering the cost of hormonal therapies and other drugs. Women were considered exposed to the drug therapy if they filled a second script for the same drug within 150% of the days supplied of the initial drug. We excluded women with exposure to tamoxifen or an AI in the year preceding the date of diagnosis. The follow-up period ended on February 29, 2012.

Information on the breast cancer stage at diagnosis was available from the Ontario Cancer Registry for a subset of women diagnosed in the final 2 years of the cohort. For these women, those diagnosed with stage IV tumors were excluded from the analysis. For women diagnosed before the availability of staging information in the Ontario Cancer Registry, we excluded women with diagnostic or procedure codes indicating metastatic cancer, multiple myeloma, or pathological fracture within 5 years preceding diagnosis. We also excluded women with a diagnosis of carcinoma in situ (Supplementary Data File 1).