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Long-Term Recurrence Risk in HR+/HER2− Early Breast Cancer: Evidence from a Canadian Cohort

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ABSTRACT

Breast carcinoma constitutes the most common malignancy and ranks as the second most frequent cause of cancer-associated death among women in Canada. Approximately two-thirds of all occurrences fall under the HR+/HER2 subtype. This real-world evidence investigation was designed to deliver a thorough assessment of treatment sequences and clinical results in Canadian individuals diagnosed with early-stage HR+/HER2− breast carcinoma. This retrospective, longitudinal cohort evaluation included 541 participants from the pan-Canadian cancer patient database, PMT (Personalize My Treatment). The cohort covered individuals having newly identified or relapsed stage II or III HR+/HER2− breast carcinoma between January 1st, 1992, and May 31st, 2022. Descriptive statistics were used to capture treatment sequences, and the Kaplan-Meier method was applied to evaluate clinical outcomes. In the adjuvant setting, the study found that ET was administered to 75.6% of participants, with a notable preference for pairing ET with cytotoxic drugs, particularly in stage III individuals. Furthermore, neoadjuvant intervention, chiefly employing cytotoxic drugs, was more frequent in stage III individuals, and those undergoing neoadjuvant treatment showed a greater likelihood of proceeding with ET as adjuvant therapy. The median duration of adjuvant ET was 4.5 years. In the adjuvant-treated group, recurrence rates increased progressively over time: 13.2% after 2 years, 21.4% after 3 years, 30.3% after 5 years, and culminating at 58.4% after 10 years. The median time to recurrence in the ET-treated group was 7.76 years. OS figures for ET-treated individuals reached 94.6% at 5 years and 78.3% at 10 years. This investigation brings to light the considerable unmet requirement in stage II and stage III breast carcinoma, with 1 out of 3 individuals relapsing after 5 years, and over half relapsing after 10 years despite adjuvant ET alone. This spotlights the demand for more potent and tolerable therapeutic choices to confront disease recurrence across both short- and long-term horizons for eBC HR+/HER2− patients in Canada.

Keywords: Real-world data, Real-world evidence, HR+/HER2-eBC, Recurrence rate, Endocrine therapy, PMT registry

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Introduction

Within the sphere of oncologic illnesses impacting women, breast carcinoma stands as the leading challenge, holding the position of the most frequently identified cancer among females and the second greatest contributor to female cancer deaths [1]. Canadian women encounter a lifetime probability of breast carcinoma development of 12.8% (one in 8) and a lifetime chance of dying from it of 2.8% (one in 36) [2]. Projections for 2024 indicate 30,500 Canadian women will receive a breast carcinoma diagnosis, with an estimated 5,500 perishing from the condition [3]. Early-stage presentations account for a significant share of first-time diagnoses [4]. The curative-driven fight against early-stage breast carcinoma rests on a strategically layered foundation, incorporating surgical, radiotherapeutic, and medical oncologic disciplines. Turning to molecular classification, breast

carcinoma is classified by hormone receptor (HR) status and human epidermal growth factor receptor 2 (HER2) expression, determined by immunohistochemistry. Cases fall into 4 categories: Luminal A, Luminal B, HER2-enriched, and basal-like, each with distinct prognostic outcomes and therapeutic approaches [5]. Conventionally, breast carcinoma is grouped into 3 principal categories: HER2-positive (irrespective of hormone receptor status), HR+/HER2− (hormone receptor-positive/HER2-negative), and triple-negative breast carcinoma [5-8]. Every category has its own prognosis and treatment options [9].

The dominance of HR+/HER2− breast carcinoma is conspicuous, comprising roughly two-thirds of all instances [10]. The care pathway for this category is intricate, involving surgical tumor extraction and lymph node appraisal [11, 12]. Preoperative chemotherapy may permit breast-conserving procedures and lessen surgical morbidity. It is especially indicated for individuals presenting with bulky tumors, substantial axillary lymph node burden, and those having advanced stages or aggressive categories, most notably triple-negative breast carcinomas [11, 12]. After surgical removal, adjuvant endocrine-based treatment targeting HR to reduce relapse hazards is endorsed as standard care spanning 5-10 years, with radiotherapy and chemotherapy set aside for high-risk profiles [13, 14]. The selection of therapy and its duration are customized, weighing relapse risk, patient preferences, and other factors such as tolerability and treatment compliance [15]. Moreover, cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) have been absorbed into therapeutic protocols for HR+/HER2− breast carcinoma. Abemaciclib holds worldwide approval for adjuvant management of node-positive individuals at elevated relapse risk [16-18]. In contrast, ribociclib has secured approval in the United States and Europe for combined use with an aromatase inhibitor in the adjuvant management of early-stage individuals at elevated relapse risk. In Canada, ribociclib is authorized for advanced or metastatic HR+/HER2− breast carcinoma, while its application for early-stage illness remains under regulatory review [19].

Despite this all-encompassing therapeutic methodology, illness recurrence [20] occurs in 13% to 41% of individuals [21-24] and, contingent upon contributing elements, close to 30% of diagnosed individuals will experience a recurrence [20], advancing many toward late-stage illness. Clinical characteristics associated with heightened risk include large primary tumor dimensions, elevated tumor grade, advanced stage, degree of axillary lymph node involvement, Ki-67 index, and additional multi-gene assay-derived proliferative indices; these components collectively inform prognostic assessment and therapeutic decision-making [25-28]. Delineating elevated recurrence risk in early breast carcinoma is intrinsically difficult owing to interpatient diversity and the uneven accessibility of prognostic instruments across clinical landscapes. Although certain guidelines include defined risk cutoffs to guide therapeutic decisions, their adoption is inconsistent, frequently hampered by disparities in resource availability and tool access. Furthermore, real-world applications may deviate from guideline recommendations due to variability across healthcare systems, clinician judgment, and patient-specific circumstances. It is equally vital to recognize that reliance on specific cutoffs or prognostic techniques may yield false-negative categorizations at times, risking under-recognition of individuals who might benefit from more intensive intervention [25-29].

The present study records the clinical trajectories of Canadian individuals confronting early-stage breast carcinoma, investigating recurrence incidence following endocrine therapy commencement. This undertaking is anticipated to expand the knowledge base on early breast carcinoma management, encouraging improved treatment frameworks and advancing patient expectations within the Canadian healthcare milieu.

Materials and Methods

Study design

This investigation utilizes a retrospective, longitudinal cohort design, drawing on real-world secondary data from the pan-Canadian Personalize My Treatment (PMT) cancer registry [30], operated by Exactis Innovation. The cohort approach was adopted to evaluate temporal shifts in therapeutic practices alongside longitudinal endpoints, including overall survival (OS) and recurrence rates. This longitudinal oncology repository operates with Research Ethics Board (REB) clearance, whereby cancer patients provide consent for access to their medical documentation for data extraction and are prospectively monitored throughout their cancer course (NCT02355171). The PMT registry currently houses de-identified clinical and molecular records from upwards of 2,644 Canadian breast cancer participants, with enrollment steadily expanding. The dataset captures a broad range of details, primarily encompassing patient and tumor profiles, clinical outcomes, and therapeutic trajectories.

The investigation encompasses all HR+/HER2− early breast cancer (eBC) patients contained within the PMT registry who were given a stage II or III diagnosis between January 1, 1992, and May 31, 2022, and who had at least 1 year of follow-up. The index date for this work was set as the date of first diagnosis for HR+/HER2− early breast cancer, and patients were tracked from the index date through to the close of the study's designated observation window (May 31, 2023), through to death, or through to loss to follow-up within the PMT registry. Should patients become lost to follow-up, they were censored at the time point of their most recent available records. This situation could arise from relocation or transition to care centers outside the PMT infrastructure. The PMT registry undergoes annual data refreshes; however, for this specific research effort, the cohort's records were updated through to the observation window's conclusion by designated PMT coordinators stationed at the respective sites. The logic underpinning the capture of 30 years of data is to secure a larger population sample, thereby optimizing the opportunity to trace the evolution of the Canadian therapeutic landscape in relation to recurrence risk across 20 years. This rationale is likewise congruent with a parallel analysis from a US database investigation conducted by O'Shaughnessy *et al*. [24].

Study population and data collection

The cohort incorporated every patient listed in the PMT registry with a diagnosis of HR+/HER2− early breast cancer between January 1, 1992, and May 31, 2022, who satisfied the eligibility conditions outlined hereafter. Patients exceeded the age of 18 years at the moment of their early breast cancer diagnosis. They had been assigned a stage II or stage III breast cancer diagnosis within the stated interval and had undergone adjuvant and/or neoadjuvant intervention. Patient staging is captured in the PMT repository in accordance with the stage unequivocally noted in the patient's medical chart. Patients were required to exhibit HR+/HER2− status as established from the pathology report, with HER2− defined by IHC 0 or 1+, or IHC2+/ISH negative, and HR+ defined by ER-positive or PR-positive designation. Patients for whom HER2 testing results at primary diagnosis were missing or unobtainable were omitted from the investigation. Only patients with confirmed HER2-negative status were retained. Where multiple assays for hormone receptor expression were undertaken, those performed nearest in time to the diagnosis date were regarded. Patients harboring a concurrent primary malignancy at the point of initial early breast cancer diagnosis were omitted from the investigation.

By May 2023, among 2,644 breast cancer patients in the PMT registry, 551 met the study selection criteria specified above. During the data monitoring stage, a further 10 patients were identified as not meeting the eligibility criteria and were consequently removed. Hence, the final analytical work rested on a rigorously assembled cohort of 541 patients .

Demographic particulars, tumor features, treatment schedules, and clinical outcomes were extracted retrospectively through a combination of electronic health platforms, paper-based files, and inpatient hospitalization records. Every variable was collected precisely as documented in the patient's medical file. Where a variable was missing, it was recorded as unknown. The collated information was systematically encoded and securely maintained within our cloud-hosted PMT repository. Upon completion of the observation period, all data entries underwent a stringent centralized verification workflow. Inconsistencies within the data were identified and raised as data queries, which were subsequently investigated and confirmed by the PMT coordinators to ensure correctness and verification.

Statistical analysis

Data imputation procedures were applied to partial dates concerning the following variables: birth, death, diagnosis, disease progression, surgery, radiation, and systemic therapy. The imputation protocols are described in detail within the supplementary information document. Additionally, variable definitions, along with the categorization frameworks for therapy groups and subgroups, are likewise furnished in the supplementary information document.

This investigation remains fundamentally descriptive, and accordingly, no formal hypothesis testing has been conducted. Continuous variables were summarized using the number of observations (N) and the median, where appropriate. Categorical variables were summarized employing the count of observations (N) and the percentage (%) attributable to each category. No statistical testing was performed for the descriptive analysis of treatments administered in this cohort.

The Kaplan-Meier approach was employed to ascertain recurrence probabilities at 2, 3, 5, and 10 years post-endocrine therapy (ET) commencement. A recurrence event was marked by either the earliest recorded disease

advancement following a disease-free documentation, or any progression date after the initial surgical procedure at first diagnosis. Percentage-based rates accompanied by 95% confidence intervals (CIs) were reported. The recurrence evaluation included only individuals who received ET in the adjuvant setting.

To describe treatment regimens and the clinical and demographic profiles of HR+/HER2− early breast cancer cases within the registry, descriptive statistical methods were applied. Categorical parameters were conveyed through absolute frequencies (n) and percentages (%), where appropriate. Numerical parameters were characterized via medians alongside their corresponding ranges and/or means accompanied by standard deviations. Unadjusted Kaplan-Meier (K-M) methodology was used to evaluate ET exposure duration, time to recurrence, recurrence frequency, and overall survival (OS) measured from diagnosis. Medians and 95% CIs accompanied K-M plots or cumulative incidence plots, or were presented as the percentage of events at the 2-, 3-, 5-, and 10-year landmarks with 95% CI.

In every time-to-event assessment, participants who were lost to follow-up were censored at the time of their final documented medical chart activity.

To preserve patient privacy in secondary health data use, a suppression rule was applied to all outputs: any cell count below 5 was concealed.

Compliance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines for observational research reporting was maintained, and the completed checklist is presented in [31].

Results and Discussion

Demographic and clinicopathological features of the cohort

Our investigation captured individuals undergoing either adjuvant or neoadjuvant regimens for newly identified or relapsed stage II or III HR+ HER2− breast carcinoma between January 1, 1992, and May 31, 2022. At the point of study launch, a total of 541 patients were registered in our PMT database, and the median surveillance interval for the cohort reached 8.1 years. As depicted in **Table 1**, a pronounced clustering of participants from Quebec accounted for 84.8% of the 541 enrolled subjects, with CHUQ, CHUM, and JGH as the principal contributing centers. Other provinces, including Ontario, New Brunswick, and Alberta, contributed smaller patient shares.

Table 1. Study population distribution by sites and provinces.

	% of patients	**# of patients**
Alberta	< **1**	< **5**
TBCC	< 1	< 5
New Brunswick	**1.5**	**8**
DGLDUHC	1.1	6
TMH	< 1	< 5
Ontario	**13.1**	**71**
SHSC	6.7	36
TOH	6.5	35
Quebec	**84.8**	**459**
CHUQ	31.1	168
CHUM	26.1	141
JGH	18.5	100
CHUS	6.8	37
CIUSSS MCQ	2.4	13
Grand Total	**100.0**	**541**

Abbreviations: TBCC = Tom Baker Cancer Center, TOH = The Ottawa Hospital; JGH = Jewish General Hospital; CHUM = Center hospitalier de l'Université de Montréal; CIUSSS MCQ = Center intégré universitaire de santé et de services sociaux de la Mauricie-et-du-Center-du-Québec; CHUQ = Center hospitalier de Québec; TMH = The Moncton Hospital; DGLDUHC = Dr. Georges.-L.-Dumont University Hospital Center; CHUS = Center hospitalier universitaire de Sherbrooke, SHSC = Sunnybrook Health Sciences Center.

The assembled cohort contained 307 individuals with stage II and 234 with stage III breast cancer; the median age upon diagnosis stood at 53 years (interquartile range [IQR] = 44, 61) **(Table 2).** Assessment of tumor

morphology identified infiltrating duct carcinoma as the foremost subtype, making up 68% of all instances. Lobular carcinoma was detected in 15% of subjects. High-grade malignancy affected 31% of the collective group, whereas intermediate-grade tumors were the most widespread, appearing in 50% of participants. Low-grade tumors occurred less often, were present in 13% overall, and were more frequent in the stage II subgroup (15%) than in stage III (9.4%).

Table 2. Patient demographic and clinical characteristics.

Clinical–pathological variable	Stage III (n = 234)	Stage II (n = 307)	Overall (n = 541)
Age at diagnosis	52 (44, 60)	53 (45, 62)	53 (44, 61)
Sex			
Female	233 (100%)	304 (99%)	537 (99%)
Male	< 5	< 5	< 5
Stage at initial diagnosis			
Stage 0 (in situ)	0 (0%)	< 5	< 5
Stage I	< 5	< 5	7 (1.3%)
Stage II	0 (0%)	302 (98%)	302 (56%)
Stage III	229 (98%)	0 (0%)	229 (42%)
Unknown	< 5	< 5	< 5
Tumor grade			
High grade	75 (32%)	93 (30%)	168 (31.1%)
Intermediate grade	120 (51%)	153 (50%)	273 (50%)
Low grade	22 (9.4%)	46 (15%)	68 (13%)
Unknown	17 (7.2%)	15 (4.9%)	32 (5.9%)
Histological subtype (morphology)			
Ductal	161 (68.8%)	226 (73.6%)	387 (71.5%)
Lobular	38 (16%)	43 (14%)	81 (15%)
Mixed	15 (6.4%)	16 (5.2%)	31 (5.7%)
Other	20 (8.5%)	22 (7.2%)	42 (7.8%)
Lymph node status			
Negative	< 5	61 (20%)	65 (12%)
Positive	218 (93%)	209 (68%)	427 (79%)
Unknown	12 (5%)	37 (12%)	49 (9%)
Estrogen receptor (ER) status			
Negative	< 5	10 (3%)	12 (2%)
Positive	232 (99%)	297 (97%)	529 (98%)
Progesterone receptor (PR) status			
Unknown	< 5	< 5	< 5
Negative	13 (5.6%)	43 (14%)	56 (10%)
Positive	220 (94%)	261 (85%)	481 (89%)
HER2 status			
Negative	234 (100%)	307 (100%)	541 (100%)
Positive	0	0	0
Ki-67 category			
<20%	18 (7.7%)	24 (7.8%)	42 (7.8%)
>20%	26 (11%)	48 (16%)	74 (14%)
Not tested	190 (81%)	235 (77%)	425 (79%)
BRCA1 testing status	66 (28%)	94 (31%)	160 (30%)
BRCA2 testing status	68 (29%)	96 (31%)	164 (30%)
BRCA1/2 mutation status	10 (4.3%)	25 (8.1%)	35 (6.5%)

[a]Median (IQR); n (%).

Lymph node involvement was documented in 79% of the entire group, with stage III exhibiting a markedly elevated rate (93%) versus stage II (68%). Owing to this substantial imbalance favoring node-positive (N+) over

node-negative (N0) cases, further division into N0 and N+ strata for subsequent investigations of therapy patterns and outcomes was not feasible. The Ki-67 proliferation biomarker was divided into two groups: < 20% and ≥ 20%. A large segment of patients (425, 79%) lacked Ki67 evaluation. Among the tested minority, 42 patients (7.8%) had a Ki67 value < 20%, and 74 patients (14%) had a Ki67 value ≥ 20%. BRCA1 and BRCA2 genetic screening was conducted for 30% across the population. Pathogenic variants in BRCA were confirmed in 35 individuals (6.5% of the total cohort).

Treatment landscape

The therapeutic sequences administered across the cohort were systematically cataloged, with a synopsis provided in **Table 3.** This overview breaks down the uptake of neoadjuvant, operative, and first-line adjuvant interventions according to disease extent (stage II versus stage III). Neoadjuvant approaches recorded in the study fell into three analytical clusters: "cytotoxic," "other," and "no" neoadjuvant delivery. The "cytotoxic" cluster comprised individuals treated with cytotoxic drugs, whether as single agents or in multi-agent cytotoxic protocols. The "other" cluster captured all remaining neoadjuvant combinations and types, spanning cytotoxic plus endocrine regimens, radiotherapy, investigational trials, VEGFi, anti-HER2 agents, CDK4/6 inhibitors, and assorted mixtures thereof. Individuals who bypassed neoadjuvant intervention entirely were placed in the "no" cluster. This grouping structure permits a simplified comparative overview of differing management strategies within the cohort. A majority of individuals forewent neoadjuvant management, with 63.2% of stage II and 51.7% of stage III patients not pursuing this route. Within the subset who received neoadjuvant treatment, cytotoxic compounds were the most commonly used, administered to 23.5% of stage II and 35.5% of stage III individuals. Among the 155 subjects given cytotoxic agents, cyclophosphamide ranked highest in usage, delivered to 148 patients (95.5%), with paclitaxel and doxorubicin following, received by 91 and 90 patients (58.7% and 58.1%), Operative management was virtually universal: 97.7% of stage II and 91.0% of stage III patients underwent resection of the primary lesion and/or regional lymph nodes. This finding reinforces the role of surgery as a foundational pillar in the management of early-stage HR+/HER2− breast carcinoma, irrespective of stage.

Table 3. Summary of treatment patterns received by HR+/HER2− early breast cancer patient population.

Treatment category	Total (n = 541)	Stage III (n = 234)	Stage II (n = 307)
Neoadjuvant therapy			
None	315 (58.2%)	121 (51.7%)	194 (63.2%)
Cytotoxic (monotherapy or combination)	155 (28.7%)	83 (35.5%)	72 (23.5%)
Other therapies[a]	71 (13.1%)	30 (12.8%)	41 (13.4%)
Surgery	513 (94.8%)	213 (91.0%)	300 (97.7%)
Adjuvant therapy			
Cytotoxic + endocrine therapy ± other therapies[b]	212 (39.2%)	101 (43.1%)	111 (36.1%)
Endocrine therapy ± other therapies[c]	167 (30.9%)	61 (26.1%)	106 (34.5%)
No adjuvant therapy	83 (15.3%)	38 (16.2%)	45 (14.7%)
Clinical trial ± other therapies	34 (6.3%)	19 (8.1%)	15 (4.9%)
Cytotoxic ± other therapies	27 (5.0%)	9 (3.9%)	18 (5.9%)
Radiation only	18 (3.3%)	6 (2.6%)	12 (3.9%)
Total patients	541 (100.0%)	234 (100.0%)	307 (100.0%)

[a]Include cytotoxic therapy combined with endocrine therapy, radiation, clinical trials, targeted therapies, and various combinations of these treatments.

[b]Other therapies include CDK4/6, radiation, anti-HER2 therapy, and various combinations of these treatments.

[c]Other therapies include CDK4/6 inhibitors, radiation, anti-HER2 therapies, VEGF inhibitors, and various combinations of these treatments.

For first-line therapy delivered after surgery, the approaches we documented were organized into six groups: "cytotoxic + ET ± other therapies," "ET ± other therapies," "clinical trial ± any other therapy," "cytotoxic ± other therapies," "radiation," and "no" adjuvant therapy. The cluster labeled "cytotoxic + ET ± other therapies" captured every instance where a cytotoxic drug was paired with endocrine therapy, provided the patient was not concurrently enrolled in a clinical study. When a regimen was built around endocrine therapy but did not incorporate either a cytotoxic component or a clinical trial, it was placed in the "ET ± other therapies" cluster.

Any treatment course that involved investigational study participation, no matter what other modalities it included, was assigned to the "clinical trial ± any other therapy" group. Regimens featuring a cytotoxic backbone that were not paired with ET or a clinical trial were grouped under "cytotoxic ± other therapies." The "radiation" designation was reserved for cases in which radiotherapy alone constituted the adjuvant plan. Finally, subjects for whom no adjuvant treatment was recorded were classified under "no."

Looking at the adjuvant phase, a considerable segment of the population was treated with a cytotoxic plus ET backbone, with or without additional modalities (36.2% for stage II, 43.2% for stage III). Within this specific segment, a clear majority (174 of 212, 82.1%) received a tri-modal regimen comprising a cytotoxic agent, endocrine therapy, and radiation. Once again, cyclophosphamide was the dominant cytotoxic drug in this context, administered to 199 of the 212 individuals (93.9%).

Endocrine therapy, whether as a standalone treatment or combined with other non-cytotoxic approaches, was the chosen path for 34.5% of stage II and 26.1% of stage III patients. A key observation is that, for the large majority of these individuals (123 of 167, 73.6%), radiation was delivered alongside endocrine therapy. The endocrine agents most frequently prescribed to this group were tamoxifen and anastrozole, given to 81 and 66 of the 167 patients, respectively. A smaller subset of the cohort did not receive any adjuvant treatment, a pattern observed in 14.7% of patients with stage II and 16.2% with stage III disease. Additionally, participation in a clinical study as part of adjuvant care was documented in 4.9% of the stage II group and 8.1% of the stage III group, reflecting a tangible level of engagement with experimental therapeutics. Radiation delivered as the only adjuvant modality was an uncommon choice, applied to only 3.9% of stage II and 2.6% of stage III patients. This breakdown of practice patterns shows that the predominant strategy for patients with stage III disease was the combination of cytotoxic agents and endocrine therapy. Patients with stage II disease, however, were distributed almost equally between an endocrine therapy approach combined with cytotoxics and one without them. The more intensive adjuvant profile seen in stage III, which couples cytotoxics with ET for those at elevated risk, aligns with expectations. The factors driving the roughly 50/50 split in adjuvant management for stage II patients are not fully explained, mainly because other recognized high-risk markers—such as nodal status, Ki-67 index, tumor size, and gene panel profiles—were insufficiently available or absent from the records for this cohort.

We also mapped out the sequences in which therapies were administered. Of the 315 patients (58.2%) whose care pathway did not include neoadjuvant treatment, almost all (312, 99%) advanced to surgery. From there, a large portion (198, 62.9%) subsequently received an adjuvant combination of endocrine therapy and cytotoxic drugs **(Table 4).** Among those who did start with neoadjuvant treatment, particularly the cytotoxic type, the transition to surgery was also very high (96.1%). Their subsequent adjuvant care pathways, however, looked quite different. They were steered toward endocrine therapy without a cytotoxic partner at a much higher rate (54.4% vs 22.1%), and a larger fraction received no adjuvant therapy at all (21.5 vs ≤ 1%). Conversely, the rate of receiving a combination of cytotoxics plus ET plummeted in this group (6% vs 63.5%). For the subset of patients whose neoadjuvant therapy was classified as "other," a smaller percentage proceeded to surgery (73.2%, n = 52), and their subsequent adjuvant management followed a much more scattered distribution: 38.5% (n = 20) had no adjuvant therapy, 32.7% (n = 17) were prescribed ET without cytotoxics, 11.5% (n = 6) received radiation exclusively, and 9.6% (n = 5) were treated with ET plus cytotoxic therapy **(Table 4; Figure 1).**

Table 4. Distribution of patients by treatment categories and subsequent therapies.

	Proportion of patients (%)[a]	Number of patients (N)
Neoadjuvant therapy = No	**58.2**	**315**
Surgery = Yes	**99.0**	**312**
Adjuvant therapy = Cytotoxic + ET ± other therapies	63.5	198
Adjuvant therapy = ET ± Other therapies	22.1	69
Adjuvant therapy = Clinical Trial	6.7	21
Adjuvant therapy = Cytotoxic ± other therapies	5.8	18
Adjuvant therapy = Radiation alone		< 5
Adjuvant therapy = No		< 5
Surgery = No		< **5**
Adjuvant therapy = No	100	< 5
Neoadjuvant therapy = Cytotoxic	**28.7**	**155**

Surgery = Yes	**96.1**	**149**
Adjuvant therapy = ET ± Other therapies	54.4	81
Adjuvant therapy = No	21.5	32
Adjuvant therapy = Clinical Trial	8.7	13
Adjuvant therapy = Radiation alone	6.0	9
Adjuvant therapy = Cytotoxic + ET ± other therapies	6.0	9
Adjuvant therapy = Cytotoxic ± other therapies	3.4	5
Surgery = No	**3.9**	**6**
Adjuvant therapy = No	100	6
Neoadjuvant therapy = Any other therapies	**13.1**	**71**
Surgery = Yes	**73.2**	**52**
Adjuvant therapy = No	38.5	20
Adjuvant therapy = ET ± Other therapies	32.7	17
Adjuvant therapy = Radiation alone	11.5	6
Adjuvant therapy = Cytotoxic + ET ± other therapies	9.6	5
Adjuvant therapy = Cytotoxic ± other therapies		< 5
Surgery = No	**26.8**	**19**
Adjuvant therapy = No	100	19
Grand Total	**541**	**541**

[a]The proportion is calculated from the parent group using this sequence of events: neoadjuvant therapy, surgery, and adjuvant therapy.

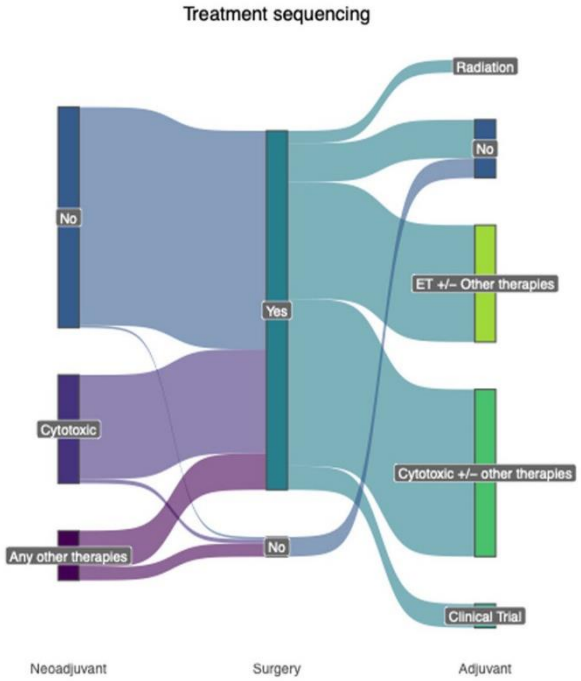


Figure 1. Sankey diagram for treatment sequencing in HR+/HER2− early BC patients.

This analysis encompasses the entire spectrum of treatment modalities from neoadjuvant through to adjuvant stages for our cohort of HR+/HER2− early breast cancer Canadian patients. The term "Cytotoxic" encompasses all forms of chemotherapy. "Endocrine" refers to all endocrine therapies. The category "No" denotes patients who did not receive any neoadjuvant, surgery, or adjuvant treatment. The term "Adjuvant" includes all forms of treatment administered post-surgery. This comprehensive categorization offers a clear and detailed overview of the treatment journey for breast cancer patients in this specific cohort.

Adjuvant endocrine therapy treatment exposure and discontinuation rate

Our attention turned to a more granular investigation of the endocrine therapy modality in the adjuvant setting, analyzed independently of other interventions. This involved quantifying the overall rate of ET uptake, measuring the duration of treatment, and determining the frequency of premature cessation.

The data showed a closely comparable proportion of patients in each stage group for whom adjuvant ET was part of the treatment plan: 75.2% among stage II and 76.1% among stage III patients, yielding a combined total of 75.6% across the entire study population **(Table 5).** The median time spent on adjuvant ET was also consistent across the two groups. A median of 4.5 years (IQR = 3.8-5.0 years) was documented for stage II patients, and a median of 4.6 years (IQR = 3.8-5.2 years) for stage III patients. For the cohort as a whole, the median therapy duration was 4.5 years (IQR = 4.0-5.0 years). These results affirm that the likelihood of being placed on and continuing adjuvant ET, as well as the typical treatment span, is essentially the same for patients diagnosed with stage II and stage III breast cancer.

Table 5. Endocrine treatment exposure in the patient cohort.

Clinical characteristic	Overall (n = 541) N (%)	Stage III (n = 234) N (%)	Stage II (n = 307) N (%)
Received adjuvant endocrine therapy (ET)	409 (75.6%)	178 (76.1%)	231 (75.2%)
Duration of adjuvant ET (years)	4.5 (4.0–5.0)	4.6 (3.8–5.2)	4.5 (3.8–5.0)

Median (95% CI), n (%).

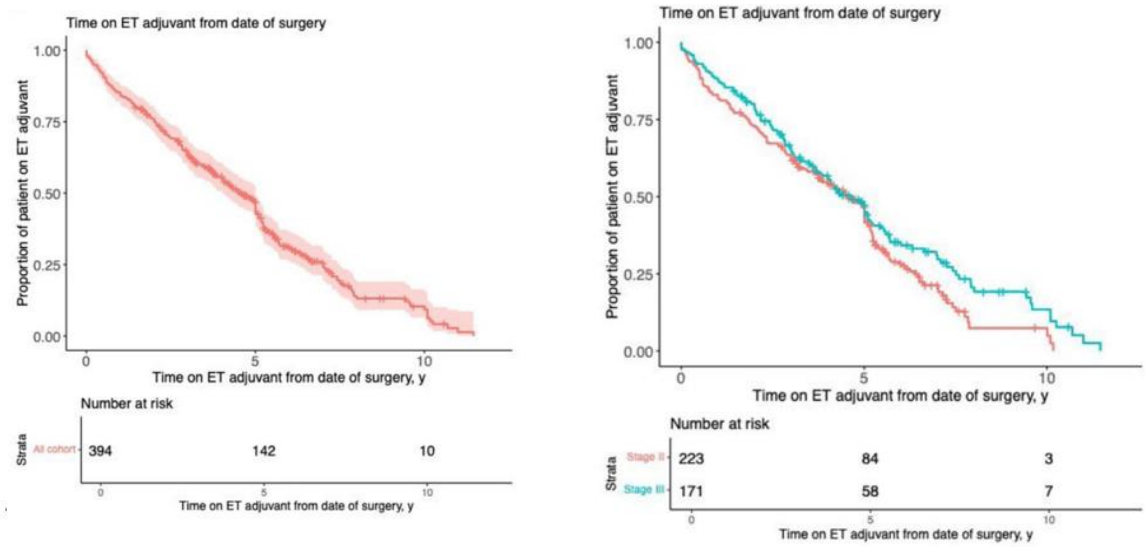
When we looked at how patients were distributed by the length of time they remained on endocrine therapy, we found a large drop-off early on. Nearly half of the cohort (48.3%) stopped their adjuvant ET before the 3-year mark, while an additional 21.3% discontinued their treatment between 3 and 5 years. A much smaller slice of the population, just 19.6%, continued their therapy into the 5-to-7-year window, and persistence beyond that was rare; only 3.1% remained on treatment for longer than a decade **(Table 6).** These numbers cast a sharp light on the real-world difficulty of sustaining long-term adherence to adjuvant ET and also reflect the changing expert recommendations over time that have progressively pushed for longer courses of therapy.

Table 6. Distribution of patients by duration of adjuvant endocrine therapy.

Duration of adjuvant ET	Percentage (%)	Number of patients (n)
Less than 3 years	48.3%	138
3 to 5 years	21.3%	61
5 to 7 years	19.6%	56
7 to 10 years	7.7%	22
Over 10 years	3.1%	9

[a]Patients with missing ET treatment end date and patients with still ongoing adjuvant ET were excluded from the analysis.

Kaplan-Meier plots within **Figure 2** illustrate the persistence of adjuvant endocrine therapy, with data presented for the entire cohort **(Figure 2a)** and then separately by stage **(Figure 2b).** A distinct and prominent bend in the survival curves becomes visible around the 5-year time point, marking a period of concentrated treatment withdrawal. This pattern is consistent with prevailing clinical practice guidelines, which advise a course of endocrine therapy of at least 5 years [32]. This time point functions as a critical adherence threshold for our study population, as the curves for the stage II and stage III groups notably begin to separate after it. Specifically, the visual evidence in **Figure 2b** indicates that patients with stage III cancer are more likely to stay on their adjuvant ET longer before finally stopping, relative to patients with stage II cancer.



a) b)

Figure 2. Kaplan-Meier curves for time on adjuvant ET from the date of surgery in cohort patients.

Panel A shows the overall proportion of patients on ET adjuvant therapy over time, with 95% confidence intervals. Panel B compares the durations of patients with stage II (red curve) and stage III (blue curve) disease, with censoring events indicated by ticks on the x-axis. The x-axis represents time on ET adjuvant therapy in years, and the y-axis shows the proportion of patients remaining on the therapy. The tables below each panel indicate the number of patients at risk at various time points.

The final part of our analysis involved calculating the rate of early discontinuation of adjuvant endocrine therapy **(Table 7).** We set an arbitrary, non-evidence-based cutoff of 5 years to indicate whether a full course of ET had been completed. Any patient whose documented time on treatment was shorter than this was considered to have discontinued their therapy. In the stage II subgroup, 30.7% (51 of 166) completed the full 5-year course, while 69.3% (115 of 166) stopped before reaching this point. For stage III patients, the results were very similar: 30% (36 of 120) completed the therapy, and 70% (84 of 120) did not. Looking at the combined group, only 30.4% (87 of 286) completed their prescribed ET course, whereas a substantial majority (69.6%; 199 of 286) discontinued. These stark figures confirm that failing to complete the full prescribed course of adjuvant ET is a widespread issue affecting the vast majority of patients across both the stage II and stage III cohorts, highlighting a critical barrier to durable adherence in the endocrine management of breast cancer.

Table 7. Endocrine treatment discontinuation rate in the adjuvant setting.

	Overall		**Stage III**		**Stage II**	
	N	**%**	**N**	**%**	**N**	**%**
ET completed	87	30.4%	36	30%	51	30.7%
ET Discontinued	199	69.6%	84	70%	115	69.3%
Grand Total	286[a]	100%	120	100%	166	100%

[a]Patients with missing ET treatment end date and patients with still ongoing adjuvant ET were excluded from the analysis.

Recurrence rate and time to recurrence

With the panoramic treatment patterning and the core characteristics of adjuvant ET delivery within our cohort delineated, inquiry pivoted to how these therapeutic selections translated into downstream patient outcomes. Owing to the limited size of several comparator arms, the window of recurrence analysis was narrowed to patients whose care included chemotherapy in combination with ET, those managed with ET in the absence of any cytotoxic agent, and the pooled recurrence experience across all patients exposed to ET regardless of concurrent modalities.

Estimates of the probability of disease reappearance at a series of temporal landmarks, each anchored to the commencement of adjuvant therapy, are presented in **Tables 8 and 9**, stratified by treatment category and disease

burden. At every single time point under examination, the subset whose treatment incorporated a chemotherapy-plus-ET backbone—whether or not additional therapies were included—demonstrated recurrence figures that were lower than those documented in the subset whose treatment revolved around ET, delivered either in isolation or augmented with non-cytotoxic therapies (2 years: 10.4% vs 16.8%; 3 years: 18.4% vs 25.3%; 5 years: 23.1% vs 39.6%).

Table 8. Recurrence rate stratified by therapy group in the adjuvant setting.

Follow-up time	ET ± other			Chemotherapy + ET ± other		
	N	95% CI	Recurrence rate (%)	N	95% CI	Recurrence rate (%)
2 years	138	10.9–22.3	16.8	189	6.2–14.4	10.4
3 years	122	18.4–31.6	25.3	170	13–23.5	18.4
5 years	81	31.5–46.7	39.6	134	17.1–28.6	23.1

Table 9. Recurrence rate after initiation of endocrine therapy.

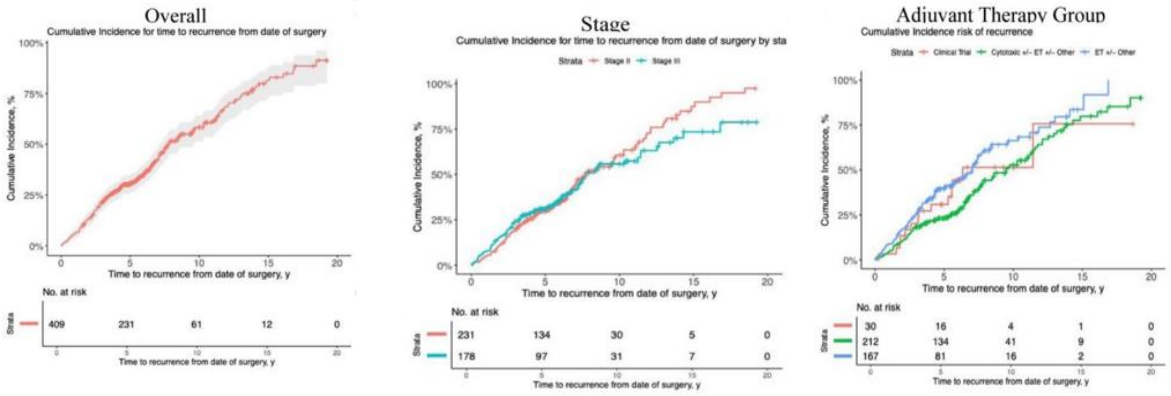
Follow-up time	Overall			Stage III			Stage II		
	N	95% CI	Recurrence rate (%)	N	95% CI	Recurrence rate (%)	N	95% CI	Recurrence rate (%)
2 years	353	9.9–16.4	13.2	149	10.2–20.9	15.7	204	7.1–15.3	11.3
3 years	315	17.3–25.3	21.4	131	17.2–29.7	23.7	184	14.3–24.5	19.6
5 years	231	25.7–34.7	30.3	97	23.8–37.6	31.0	134	23.5–35.5	29.8

Taking the cohort as an undivided whole, the actuarial recurrence burden clocked from ET initiation spanned from a low of 13.2% at the 2-year assessment to a high of 58.4% when the 10-year threshold was reached. For stage II patients, in whom the quantity of data rendered estimation feasible, a progressive accumulation of recurrence risk over time was unmasked: the observed rate sat at 11.3% at 2 years, swelled to 19.6% at 3 years, and climbed further to 29.8% at the 5-year mark. Stage III patients exhibited recurrence rates that ran modestly higher across these same three intervals: 15.7%, 23.7%, and 31%.

The median interval separating surgical intervention from a recurrence event, examined through the dual lenses of adjuvant treatment assignment and time elapsed from ET initiation, is summarized in **Table 10**. In the aggregate, half of the cohort had recurred by 7.76 years post-surgery (CI = 7.14 to 9.61 years). The median values calculated for the stage II and stage III strata were closely comparable, coming in at 7.7 years (CI [6.93-9.76 years]) and 7.78 years (CI = 7.21 to 11.45 years), respectively. However, when the data were sliced by adjuvant treatment category, substantial divergence emerged. For patients who had been treated with a chemotherapy-ET combination, the median time to recurrence stretched to 9.51 years (95% CI [7.76-11.45]). Among those whose adjuvant regimen was built around ET with or without other therapies, this metric contracted to 7.01 years (95% CI [5.72-7.84]). Among the clinical trial enrollees, the median was further abbreviated to 6.34 years (95% CI [5.29-NA]). The cumulative incidence landscapes corresponding to these recurrence dynamics are shown in **Figure 3**, encompassing the overall cohort **(Figure 3a),** split by disease stage **(Figure 3b),** and disaggregated by adjuvant therapy group **(Figure 3c).**

Table 10. Time to recurrence from date of surgery stratified by stage and adjuvant therapy.

Grouping	Subgroup	95% CI	Median time to recurrence (years)	N
Overall	Overall	7.14–9.61	7.76	409
By stage	Stage II	6.93–9.76	7.7	231
	Stage III	7.21–11.45	7.78	178
By therapy group	ET ± other	5.72–7.84	7.01	167
	Chemotherapy + ET ± other	7.76–11.45	9.51	212
	Clinical trial	5.29–NA	6.34	30

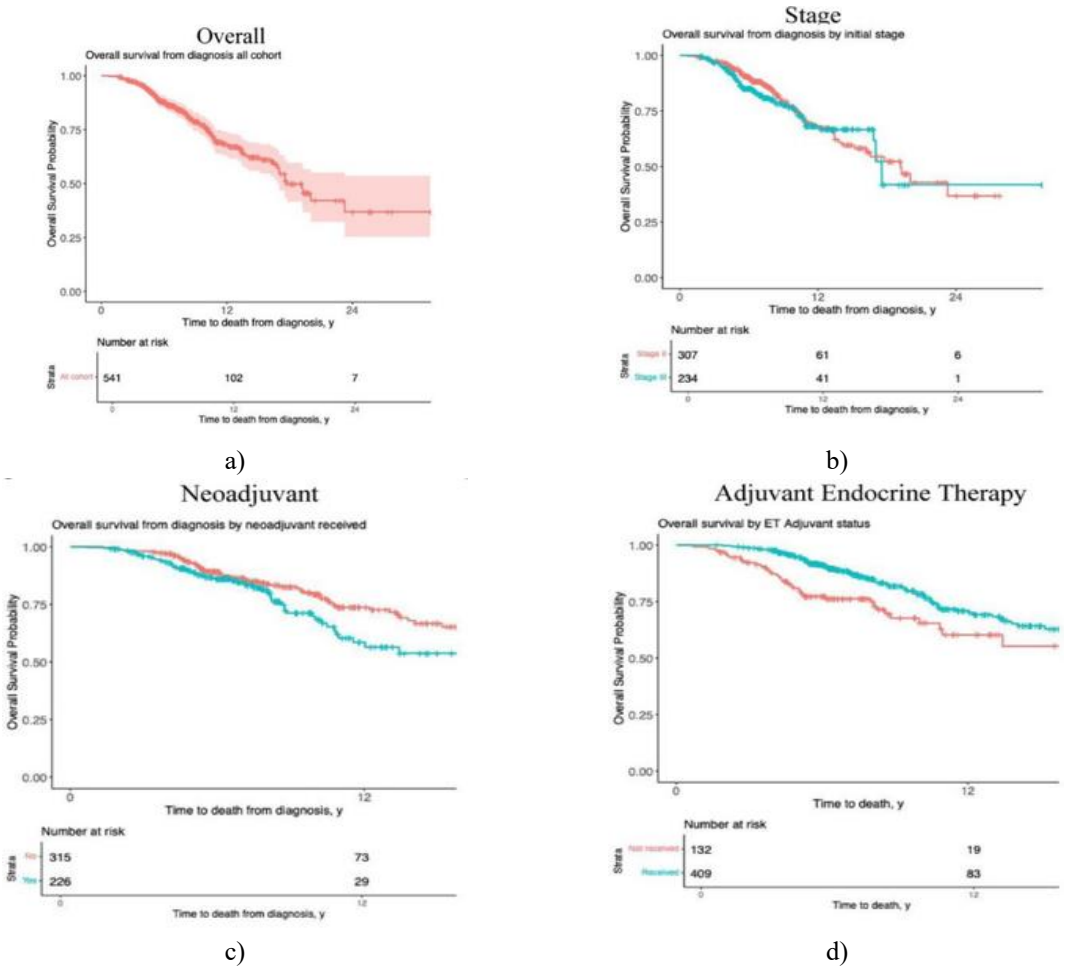


a) b) c)

Figure 3. Cumulative incidence Curves for Time to Recurrence in cohort patients: (a) shows the overall recurrence over time, with 95% confidence intervals; (b) compares recurrence between stage II (red curve) and stage III (blue curve) patients, highlighting the censoring events on the x-axis; (c) depicts recurrence for different treatment groups: ET ± other therapies (blue), Cytotoxic ± other therapies (green), and patients in clinical trials (red), with censoring events indicated on the x-axis. The x-axis represents time to recurrence in years, and the y-axis shows the cumulative incidence of recurrence.

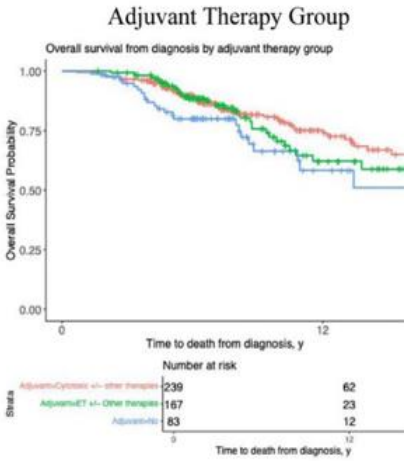
OS from early-stage diagnosis

Bringing the outcome evaluation to its final component, overall survival measured from the point of early-stage diagnosis was assessed; the median OS registered for the cohort was 17.77 years. Kaplan-Meier representations of survival experience are furnished in **Figure 4**, depicting the entire cohort **(Figure 4a)** and the stage-stratified comparison **(Figure 4b).**



a) b)

c) d)



e)

Figure 4. Kaplan-Meier curves for OS from early-stage diagnosis by various factors.
This figure presents Kaplan-Meier curves for time-to-death across various patient groups: (a) shows the overall survival curve for all patients, including a 95% confidence interval; (b) contrasts survival between patients with stage II (red curve) and stage III (blue curve) disease, with censoring events indicated by ticks on the x-axis; (c) compares survival between patients with (blue curve) and without (red curve) neoadjuvant therapy, also highlighting censoring events; (d) illustrates survival for patients who received adjuvant endocrine therapy (blue curve) versus those who did not (red curve), with censoring events marked on the x-axis; (e) depicts survival by adjuvant therapy group: no adjuvant therapy (blue curve), ET ± other therapies (green curve), cytotoxic ± other therapies (red curve), with ticks indicating censoring events. The x-axis represents time to death in years, and the y-axis shows the cumulative incidence of death.

Survival probabilities anchored at the 5-year and 10-year milestones are tabulated in **Table 11**. For the population considered in its entirety, 91.4% (95% CI [89.0%-93.9%]) were alive at 5 years, with this fraction declining to 75.3% (95% CI [70.8%-80.1%]) at 10 years. Splitting by stage revealed a survival differential favoring stage II at the earlier landmark: 93.6% (95% CI [90.9%-96.4%]) for stage II, compared with 88.5% (95% CI [84.3%-92.9%]) for stage III. Strikingly, the long-range picture showed these trajectories coalescing. At 10 years, stage II patients exhibited a survival rate of 75.1% (95% CI [69.0%-81.8%]), while stage III patients posted a nearly identical 75.3% (95% CI [68.9%-82.4%]), consistent with a closing of the survival gap over extended follow-up.

Table 11. 5-year and 10-year survival rates by various factors.

Category	Subgroup	95% CI	10-year survival rate (%)	N (10-year)	95% CI	5-year survival rate (%)	N (5-year)
Overall	Overall	70.8–80.1	75.3	158	89–93.9	91.4	434
By stage	Stage II	69–81.8	75.1	89	90.9–96.4	93.6	257
	Stage III	68.9–82.4	75.3	69	84.3–92.9	88.5	177
By adjuvant ET	ET adjuvant	73.4–83.6	78.3	129	92.4–96.9	94.6	345
	No ET adjuvant	NA	NA	29	74.4–88.4	81.1	89
By adjuvant therapy	ET ± other	61.4–81.2	70.6	39	89.9–97.5	93.7	138
	Cytotoxic ± other	73.2–85.4	79.1	87	88.7–95.7	92.2	196
	No adjuvant therapy	NA	NA	18	74.6–91.8	82.8	58
By neoadjuvant therapy	No neoadjuvant	74–84.7	79.2	110	89.9–95.7	92.8	267
	Neoadjuvant	60.2–77.6	68.4	48	85–93.8	89.5	167

Attention was then channeled specifically toward neoadjuvant and adjuvant treatment exposure **(Table 11).** Approximately 2 in 5 patients—roughly 40%—had a neoadjuvant phase incorporated into their care pathway. Among this subset, the likelihood of surviving to the 5-year point was 89.5% (95% CI [85.0%-93.8%], n = 167).

By contrast, those whose journey did not include neoadjuvant therapy registered a higher 5-year survival probability of 92.8% (95% CI [89.9%-95.7%], n = 267). This gap was magnified when the 10-year data were inspected. The survival rate among neoadjuvant-exposed patients had fallen to 68.4% (95% CI [60.2%-77.7%], n = 48), whereas the rate for the no-neoadjuvant comparator sat at 79.2% (95% CI [74.0%-84.7%], n = 110). The Kaplan-Meier plots for these time-to-death analyses are shown in **Figure 4c.** A probable explanation for this observed disparity lies in selection factors governing treatment assignment. The neoadjuvant subgroup contained an equal admixture of stage II and stage III cases (50% each). In contrast, the subgroup that was not exposed to neoadjuvant therapy skewed more heavily toward stage II disease (61.6% stage II vs 38.4% stage III). This compositional difference strongly suggests that neoadjuvant therapy was preferentially deployed in those with greater disease burden, and this pre-existing prognostic imbalance plausibly accounts for the attenuated long-term survival seen in the neoadjuvant group rather than any deleterious effect of the treatment itself.

A further observation of substantial weight concerned the imprint of adjuvant ET on survival duration. A pronounced survival advantage was conferred upon patients who received ET. At the 5-year point, 94.6% (95% CI [92.4%-96.9%]) of ET-exposed patients were alive, a proportion that comfortably exceeded the 81.1% (95% CI [74.4%-88.4%]) observed among those without ET exposure. This separation in survival experience remained apparent at the 10-year milestone: ET recipients had a 78.3% (95% CI [73.4%-83.6%]) survival rate. For the group that did not receive ET, a 10-year estimate could not be reconstructed owing to an inadequate sample size at that duration **(Table 11; Figure 4d).**

The final analytical layer involved examining survival as a function of the specific adjuvant treatment category. Only three groupings yielded patient numbers sufficient to permit estimation: those treated with ET alone or in combination with other therapies; those treated with a chemotherapy-ET combination alone or in combination with other therapies; and those who did not receive any adjuvant therapy. At the 5-year mark, survival troughed at 82.8% among the patients who underwent no adjuvant therapy, while the other two groupings posted nearly equivalent 5-year survival values (ET ± other therapy: 93.7%; chemotherapy + ET ± other therapy: 92.2%). At the 10-year point, only two of these groups retained sufficient patient counts for reporting, and a clear distinction had crystallized. The chemotherapy-plus-ET ± other therapy group registered a survival rate of 79.1%, whereas the ET ± other therapy group lagged at 70.6% **(Table 11; Figure 4e).** The pattern emerging from these data suggests that an adjuvant strategy embedding chemotherapy alongside ET may yield more durable disease containment, reflected in superior survival and a more pronounced suppression of recurrence when combined with therapies outside the cytotoxic class. That said, this signal demands tempered interpretation. Uncontrolled confounders—among which are high-risk disease features, disparities in the fidelity with which ET was adhered to between the two arms, sociodemographic covariates, and the extent of exposure to CDK4/6 inhibitors—were not incorporated into this analysis. Uptake of CDK4/6 inhibitors in the adjuvant setting across this cohort was, in fact, exceedingly sparse: ribociclib was prescribed to 1.2% of patients, palbociclib to 4.1%, and abemaciclib to fewer than 1%. Only through additional investigation designed to adjust for these variables systematically can the suggestion of a meaningful benefit from the chemotherapy-ET coupling be either substantiated or called into question.

The central aim of the present investigation was to map therapeutic approaches, characterize the risk of relapse, and describe overall survival among HR+/HER2− early breast cancer patients, drawing on real-world evidence from four Canadian provinces. Adjuvant endocrine therapy has constituted the established benchmark of care for HR+/HER2− early breast cancer since the dawn of the 1990s [18-20]. Our work assesses the full spectrum of treatment strategies used for these patients in the adjuvant setting, with particular emphasis on those receiving endocrine therapy. It examines how these strategies modulate the likelihood of disease recurrence.

A scrutiny of treatment patterns revealed several observations regarding real-world therapeutic practice and its alignment with published clinical practice recommendations. To begin with, the data show that a sizable segment of patients foregoes neoadjuvant intervention altogether: no presurgical treatment was administered to 63.2% of individuals with stage II disease and 51.7% of those with stage III disease. This pattern may reflect clinical decision-making shaped by goals of downstaging, tumor biological aggressiveness, the extent of lymph node involvement, and patients' preferences. Adding further complexity, the value of neoadjuvant therapy in the HR+/HER2− early breast cancer population has been a matter of ongoing debate [33, 34]. Among patients for whom a neoadjuvant course was chosen, cytotoxic chemotherapy held a dominant position, especially within the stage III subgroup, signaling a willingness to adopt a more intensive treatment philosophy when confronting locally advanced presentations. Once in the adjuvant phase, a backbone of cytotoxic agents combined with

endocrine therapy emerged as the primary therapeutic option, and this doublet was commonly augmented with radiation. The uptake of this strategy was higher in stage III than in stage II, underscoring its centrality in the management of more extensive disease. Conversely, endocrine therapy—whether deployed as a single agent or in tandem with non-cytotoxic modalities—found greater utilization in stage II than in stage III. Our results brought to light a marked disparity: a considerably larger fraction of patients who had undergone neoadjuvant therapy, and especially those whose neoadjuvant regimen featured cytotoxic drugs, subsequently either transitioned to endocrine therapy as their adjuvant treatment or went without any adjuvant therapy whatsoever, relative to patients whose treatment trajectory did not include a neoadjuvant phase. In concrete terms, 54.4% of neoadjuvant recipients proceeded to adjuvant endocrine therapy, a proportion that stands in sharp relief to the mere 22.1% documented among those with no neoadjuvant exposure.

This pronounced difference suggests that the upfront deployment of cytotoxic agents in the neoadjuvant window—a choice very likely driven by the tumor's aggressive biological features at initial presentation—may shape subsequent therapeutic decisions. An element this manuscript does not address, yet which is highly relevant, is the integration of prognostic assays such as Oncotype DX. These tools have profoundly reshaped how risk is stratified and how treatment pathways are selected within HR+ breast cancer. The observed patterns reinforce the imperative of devising individualized care plans that account for a patient's response to neoadjuvant therapy and underscore the need for vigilant surveillance, coupled with customized therapeutic strategies to maximize patient outcomes. Uptake of CDK4/6 inhibitors as a component of adjuvant therapy in our study cohort was exceedingly limited: ribociclib, palbociclib, and abemaciclib accounted for a mere 1.2%, 4.1%, and less than 1% of treatments, respectively. It is critical to contextualize this finding by noting that, at the juncture when this analysis was conducted, ribociclib, abemaciclib, and palbociclib all held regulatory approval in Canada for the advanced breast cancer setting; palbociclib had generated unfavorable findings in its adjuvant trial and consequently lacked an adjuvant indication; and abemaciclib had secured approval for adjuvant use within a narrowly defined subset of the population encompassed by our analysis—specifically, node-positive, early-stage breast cancer patients categorized as being at elevated recurrence risk based on their clinicopathological characteristics. In light of the evidence assembled here, the future therapeutic landscape for HR+ breast cancer appears to be pivoting toward an optimization of endocrine therapy, offered either as monotherapy or in conjunction with CDK4/6 inhibitors within the adjuvant arena. This evolving paradigm mirrors an ongoing effort to strike a balance between therapeutic efficacy and toxicity, a pursuit currently being interrogated by multiple prospective trials designed to clarify the contribution of CDK4/6 inhibitors to reducing the probability of relapse in high-risk populations.

When considered in aggregate, adjuvant ET was prescribed to 75.6% of the patient cohort, a figure that bespeaks an unequivocal preference for this modality over alternative approaches. This pattern is broadly congruent with the international consensus governing the management of HR+/HER2− early breast cancer. The in-depth examination of adjuvant ET exposure within this cohort yields several instructive insights into the realities of treatment adherence outside the confines of clinical trials and the obstacles inherent to it. The overall median duration of ET landed at 4.5 years, a value that aligns closely with the 5-year treatment course enshrined in guideline recommendations. Yet, despite the strong impetus to initiate therapy documented by our data, the study also highlights the formidable challenges of sustaining long-term adherence to adjuvant ET. Close to half of all patients—48.3%—had ceased treatment before reaching the 3-year milestone. When the completion of a prescribed ET course was evaluated, the picture that emerged was sobering: a mere 30.4% of patients saw their full course through to the end, a statistic that speaks to a profound and pervasive struggle with long-term therapeutic persistence and that underscores the pressing obligation of healthcare providers to identify and dismantle the barriers that stand in the way of sustained ET use. A constraint inherent to our study is the absence of any documentation of the specific reasons driving treatment cessation; this lacuna forecloses any thorough understanding or nuanced interpretation of the elevated discontinuation rate we observed. Among the plausible contributors are the side-effect burden associated with treatment, frank disease progression, the quality and extent of patient education, individual patient preferences, financial hardship, and the lack of robust psychosocial support structures. The evidence emerging from our cohort reinforces the call for purposeful interventions tailored to bolster adherence and to accompany patients across the entire arc of their ET experience. Subsequent research should focus on both pinpointing and mitigating the factors that precipitate premature treatment discontinuation, with the ultimate objective of optimizing therapeutic outcomes and reducing the risk of cancer recurrence.

What motivated this investigation above all was the objective of describing, with real-world evidence harvested from four Canadian provinces, the landscape of treatment practices, the probability of disease returning, and

overall survival figures for patients diagnosed with HR+/HER2− early breast cancer. Since the early 1990s, the bedrock of care in this population has been adjuvant endocrine therapy [18-20]. Our analysis appraises the totality of adjuvant-phase management approaches for these patients, focusing on those who received endocrine therapy and probing its influence on the likelihood of relapse.

Several insights into how real-world therapeutic behavior aligns with—or fails to align with—clinical practice guidelines emerged from our analysis of treatment patterns. A particularly striking observation was the extent to which neoadjuvant treatment was bypassed entirely: 63.2% of stage II patients and 51.7% of stage III patients received no presurgical therapy. Factors plausibly shaping such decisions include the intent to achieve tumor downstaging, the malignancy's inherent aggressiveness, the status of lymph node basins, and the choices of individual patients. Compounding this, the utility of neoadjuvant intervention in HR+/HER2− early breast cancer has long been a terrain of dispute [33, 34]. Where neoadjuvant therapy was utilized, the dominant paradigm—most markedly in stage III cases—was cytotoxic chemotherapy. This pattern signals a predilection for intensified treatment in the face of more locally extensive disease. Postoperatively, the central pillar of adjuvant management proved to be a cytotoxic-endocrine doublet, very frequently supplemented with radiation. That this combined approach was more heavily drawn upon among stage III than stage II patients underscores its perceived value when confronting greater disease burdens.

In contrast, endocrine therapy, delivered either as a single agent or in combination with non-cytotoxic modalities, was more widely applied in the stage II subset. Our data brought into sharp relief a notable divergence: a substantially larger percentage of patients who had passed through a neoadjuvant treatment sequence, particularly those whose neoadjuvant course contained cytotoxic agents, either stepped directly onto adjuvant endocrine therapy or went on to receive no adjuvant therapy at all, relative to patients whose care omitted a neoadjuvant phase from the outset. In numerical terms, 54.4% of neoadjuvant-exposed patients transitioned to adjuvant endocrine therapy. This proportion exceeds the 22.1% observed among patients who did not receive neoadjuvant therapy.

Such a gap intimates that choices made early—specifically the initiation of cytotoxic drugs preoperatively, a step presumably shaped by the tumor's presenting biological profile—cast a long shadow over downstream therapeutic plans. What remains unaddressed in this manuscript, yet is of considerable relevance, is the incorporation of prognostic gene expression assays, such as Oncotype DX. The widespread adoption of these tools has fundamentally reconfigured how risk is gauged and how treatment pathways are selected in HR+ breast cancer. The trends we document reinforce the centrality of individualized therapeutic design, calibrated to how a given patient responds to neoadjuvant treatment, and they accentuate the need both for meticulous longitudinal surveillance and for bespoke strategies engineered to maximize long-term outcomes. Adjuvant CDK4/6 inhibitor prescribing in our dataset was vanishingly rare: ribociclib, palbociclib, and abemaciclib accounted for 1.2%, 4.1%, and < 1% of all treatments, respectively. Contextualizing this finding requires acknowledgment that, at the time this analysis was undertaken, all three agents held Canadian regulatory authorization solely for advanced breast cancer; palbociclib's adjuvant pivotal study had yielded unfavorable results, rendering it without an adjuvant indication; and abemaciclib had been greenlit for adjuvant deployment in a narrow sliver of the population captured by our analysis—node-positive, early-stage patients whose clinicopathological features placed them at elevated risk for disease return. Against this backdrop, the trajectory of therapeutic advance for HR+ breast cancer appears increasingly oriented toward refining endocrine therapy, either in its own right or partnered with CDK4/6 inhibitors within the adjuvant arena. This shifting paradigm captures the ongoing calibration of efficacy against toxicity, a tension actively being parsed by multiple prospective studies seeking to define precisely the contribution CDK4/6 inhibitors can make toward reducing recurrence risk in those most vulnerable to relapse.

Across the entire cohort, adjuvant ET was prescribed to 75.6% of participants, leaving little doubt about where clinical preference lies. This observation is consonant with the corpus of international guidance on the management of HR+/HER2− early breast cancer. A deeper dive into the dynamics of adjuvant ET exposure in this cohort furnishes instructive lessons about how therapeutic adherence plays out under real-world conditions and the hurdles that attend it. The overall central tendency for treatment duration was 4.5 years, close to the 5-year minimum endorsed by guidelines. At the same time, and notwithstanding the strong momentum toward treatment initiation, the durability of commitment to adjuvant ET emerged as a formidable challenge. The fraction of patients who had already terminated therapy by the 3-year point approached one-half—specifically, 48.3%. An examination of ET course completion revealed a sobering statistic: only 30.4% of patients completed the full prescribed course. This figure illuminates a deep-rooted predicament of long-term therapeutic persistence. It

highlights the duty borne by healthcare teams to identify, understand, and dismantle the obstacles that undermine sustained engagement with ET. A weakness inherent to our study is that the specific precipitants behind treatment cessation were not captured, foreclosing any rich or nuanced interpretation of the elevated discontinuation rate we documented. Among the candidate drivers, one can plausibly list treatment-emergent side effects, outright disease progression, inadequacies in patient counseling and health literacy, personal preference, economic hardship, and a thin or absent scaffold of psychosocial support. The patterns emerging from our cohort amplify the call for interventions purpose-built to shore up adherence and to walk alongside patients through every chapter of their ET journey. The agenda for future scholarship should be directed squarely at both illuminating and softening the variables that prompt premature treatment cessation, with the larger ambition of delivering superior therapeutic outcomes and reducing the long-term risk of cancer recurrence.

The initial outcome placed under the microscope was the real-world recurrence rate documented within our study cohort. It was apparent that the recurrence figures we recorded were substantially higher than those reported in seminal clinical trials (5-year recurrence rate: 30.3% in the present study versus 9%-12.1%) [35]. Fresh data from the MonarchE trial pegged the 5-year invasive disease-free survival (IDFS) rate at 83.6% for the arm receiving adjuvant abemaciclib alongside ET, a result that contrasts with the 76% rate observed with ET alone [36]. In parallel, findings from the NATALEE study reported a 3-year IDFS rate of 90.4% in the ribociclib-plus-ET arm, compared with 87.1% in the ET monotherapy arm [37, 38].

A likely explanation for this gap between real-world and trial-based estimates resides in the more inclusive operational definition of recurrence that real-world data sources necessitate, coupled with temporal shifts in the recurrence evaluation window. Such temporal variation captures, in part, the evolution of the therapeutic armamentarium over the decades and the considerably more variegated treatment patterns found outside the highly regimented environment of randomized controlled trials. Yet these recurrence rates, by virtue of encompassing patients who were either never rendered disease-free or who progressed rapidly upon embarking on adjuvant endocrine therapy, bear witness to legitimate unmet needs that persist in everyday practice. They constitute a forceful argument for the development of more efficacious therapeutic options. In a separate real-world investigation that mined the US-based Flatiron Health electronic health record database, applying a recurrence definition closely aligned with our own, 2- and 5-year recurrence rates of 11.9% and 29.8% were reported—figures that sit comfortably alongside our own estimates of 13.2% and 30.3% [39]. A constellation of factors may conspire to produce the divergence between recurrence outcomes recorded in clinical trials and those observed in real-world cohorts. Among them are shortfalls in treatment adherence, including the premature abandonment of adjuvant ET; demographic and clinical differences between the patient populations being compared; and differences in the intensity with which surveillance and follow-up are pursued in the two environments. When we benchmarked the 10-year mortality rate in our cohort against a pooled analysis of adjuvant tamoxifen and aromatase inhibitor trials, the outcomes were notably congruent (this study: 21.7% vs 21.3%-24%) [35]. Patients whose adjuvant regimen bundled chemotherapy with ET, with or without other therapies, carried a lighter recurrence burden than those for whom chemotherapy was omitted (5-year recurrence rate: 23.1% vs 39.6%). This contrast was reflected in the median time from surgery to recurrence, which was 9.51 years in the chemotherapy-exposed group versus 7.01 years in the unexposed—a signal that integrating chemotherapy into the adjuvant ET framework may, for a subset of patients, constitute a more durable long-term strategy. The proviso, of course, is that this inference is offered tentatively, given that a host of confounding variables were not adjusted for.

Across the cohort, the median interval to recurrence was 7.76 years. The observation that patients with a heavier disease burden tended to continue adjuvant endocrine therapy beyond the guideline-specified 5-year threshold may help explain why the recurrence rates we observed in the stage II and stage III subgroups did not differ materially. This pattern aligns with a body of prior work indicating that stretching adjuvant ET from 5 to 10 years—as the American Society of Clinical Oncology (ASCO) advocates for patients at elevated risk [32]—confers meaningful benefit in HR+/HER2− early breast cancer with documented nodal involvement. Notwithstanding these guidelines and the fact that nodal positivity was present in a striking 86% of our study cohort, the median duration of adjuvant ET we recorded was just 4.5 years, a value that closely mirrors the 4.8-year median reported in another real-world study [40]. While the survival advantage of completing at least 5 years of adjuvant ET in HR+/HER2− early breast cancer is well substantiated in the literature, multiple investigations have documented a pervasive tendency toward early cessation in everyday practice [41-44]. A review examining ET treatment persistence outside the clinical trial context found that 31%-73% of patients discontinued ET within the 5-year window [45]. Echoing this body of evidence, our data showed that 69.6% of patients had abandoned

adjuvant ET before completing the prescribed 5-year course. A diverse array of influences—sociodemographic characteristics, co-prescribed medications, and the toxicities patients endure—likely conspire to produce treatment cessation. All the same, the magnitude of its impact on recurrence risk creates an imperative to redouble efforts to enable patients to complete their intended therapy. Investigations into the association between premature ET discontinuation and overall survival outcomes would be a valuable addition to the research agenda in the years ahead.

When overall survival was scrutinized across the study population, stage-based subgroup comparisons generated only trivial differences. This may, however, be an artifact of the difficulty inherent in assessing survival beyond the 10- or 12-year horizon, compounded by a limited total cohort size and the restricted pool of patients with adequately extended follow-up records. Juxtaposing those who underwent adjuvant ET against those who did not reaffirmed the survival dividend that endocrine therapy delivers in the adjuvant context. A further force bearing upon overall survival, particularly germane to patients whose disease transitions to the metastatic state, is the advent of newer therapeutic agents in that space, with CDK4/6 inhibitors being a prominent example.

When weighing the conclusions of this study, several constraints warrant careful consideration. First among them is the cohort's geographical concentration, with patients from Quebec accounting for 84.8% of the total; this regional dominance inevitably limits the extent to which our observations can be generalized to the broader Canadian context or to international settings. Second, genomic assays that would have permitted stratification of patients by recurrence risk were not applied, a gap that could color both treatment selection and the outcomes that ensued. Additionally, the menopausal status of participants—a variable that exerts a known influence on both therapeutic decisions and prognosis in breast cancer—was unavailable for our cohort. This missing dimension may leave our understanding of treatment patterns incomplete. Another limitation of considerable weight is the absence of any outcome analysis broken down by the specific endocrine therapy class used (tamoxifen vs aromatase inhibitors). This deficiency impedes a full appreciation of how the therapeutic shifts across three decades have shaped patient trajectories. The temporal distribution of diagnoses was itself skewed: 12 of the 541 patients were diagnosed before 2000, 284 within 2000–2015, and 245 after 2015, an uneven spread that could influence the generalizability of results across diagnostic eras. Finally, while a median follow-up of 8.1 years represents a substantial period of observation, it may nonetheless fall short of what is required to capture the full arc of late-occurring recurrences, events of particular salience in hormone receptor-positive breast cancer.

Conclusion

Condensing our findings, a portrait emerges of recurrence rates that mount in a stepwise fashion over time: 13.2% at the 2-year landmark, 21.4% by 3 years, 30.3% at the 5-year mark, and reaching a zenith of 58.4% once a full decade has passed. This trajectory leaves little room for doubt about the acute need for more effective treatment options across the entire population included in this analysis.

Our mapping of adjuvant and neoadjuvant therapy patterns lays bare an oncological care landscape that is in flux for HR+/HER2− breast cancer. The particulars underline a stark unmet medical deficit in stage II and stage III disease: despite exposure to adjuvant ET alone, one in every three patients will develop recurrent disease within 5 years, and by the 10-year point, more than half will have recurred. These realities demand that the field prioritize the search for therapeutic alternatives that are simultaneously more potent and more tolerable—agents capable of peeling back both near-term and distant recurrence rates while prolonging survival.

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