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THE ISRAEL NATIONAL INSTITUTE FOR HEALTH POLICY RESEARCH

Final Report

Title of research (in English)

Future unrelated medical costs and its impact on cost-effectiveness analyses

Title of research (in Hebrew)

עלויות-רקע במהלך הזדקנות, והשפעתן על ניתוחי עלות-תועלת של טכנולוגיות חדשות

Executive Summary- Hebrew

רקע מדעי: הערכת כדאיות כלכלית של טכנולוגיה רפואית לטיפול במחלה כוללת תמיד את אומדן העלויות הקשורות ישירות לטיפול/אי טיפול במחלה, אולם ישנו דיון האם לכלול בהערכה כלכלית זו גם את העלויות שאינן קשורות למחלה אך נצברות בעקבות הארכת תוחלת החיים של החולה (unrelated future medical costs להלן: עלויות נלוות). על-פי הקווים המנחים של ה National Institute for Health and Care Excellence (NICE), אין לכלול את העלויות הנלוות בהערכת הכדאיות הכלכלית של טכנולוגיה רפואית, אולם בארה"ב, שבדיה והולנד ישנה המלצה לכלול את העלויות הללו. מעט ידוע על המידה שבה עלויות נלוות אלה עשויות להשפיע על ההערכת הכדאיות הכלכלית.

מטרות המחקר: 1) לפתח וליישם תהליך לאמידה של עלויות נלוות של טיפול בסרטן שד בישראל; 2) לבחון את ההשפעה של אומדן זה על הערכת כדאיות כלכלית של טיפול בסרטן שד באמצעות trastuzumab כמקרה בוחן (case study) לאמידת ההשפעה של הכללת עלויות נלוות על המסקנה הנובעת מהערכת הכדאיות הכלכלית.

שיטות המחקר: המחקר כלל שני חלקים. חלק א אמד את העלויות הנלוות של חולות בסרטן שד באמצעות נתוני צריכת שירותי בריאות ברמת הפרט. חלק ב בחן את ההשפעה של אומדן העלויות בחלק א על cost-effectiveness analysis (CEA) של טיפול בסרטן שד באמצעות trastuzumab.

חלק א- מחקר עוקבה (cohort) רטרוספקטיבי בוצע בקרב מבוטחות מחוז דרום של שירותי בריאות כלכלית (להלן: כללית) אשר אובחנו לראשונה בסרטן שד בין השנים 2005-2008 והיו מבוטחות פעילות במשך כל תקופת המעקב. למבוטחות אלה הותאמו באופן אקראי מבוטחות ביקורת ממחוז דרום של כללית שאינן חולות בסרטן שד, ביחס 1:4 לפי גיל (±2), מרפאה, מגזר, מצב סוציואקונומי

(±2) ו Charlson comorbidity index (CCI, 2- כיוון שערך המדד בעקבות סרטן שד הוא 2). נתוני צריכת שירותי הבריאות נאמדנו לתקופות של 12 חודשים ממועד האבחון (index date) ועד מוות או תום תקופת המחקר (דצמבר 2019). נתונים אלה כללו: אשפוזים, ניתוחים, אבחונים, תרופות, ביקורים בחדר מיון, אשפוזי יום, ביקורים ברפואה יועצת, טיפול פרא-רפואי, אשפוזי בית, וטיפול אמבולטורי אחר. נתוני העלות הומרו לדולר ארה"ב (USD) לפי שער החליפין הממוצע ל 2019 של 3.56 ₪ ל USD. ניתוח סטטיסטי בוצע בתכנת RStudio. נוסח generalized linear model (GLM) רב משתני לאמידת מנבאים של ההוצאה הממוצעת לשנה בגין צריכת שירותי בריאות. משתנה הליבה הבלתי תלוי היה קבוצת המחקר (חולות בסרטן שד לעומת ביקורת). המודל תוקנן למשתנים מסבירים נוספים כמו מצב חברתי-כלכלי ותחלואה נלווית. Akaike's information criterion (AIC) סייע לבחירת המודל האופטימלי. ערך <0.05 הגדיר מובהקות סטטיסטית.

חלק ב- בהמשך לפרסום קודם של אחד החוקרים הראשיים (YB) ושותפיו[1], ניסחנו מודל מרקוב לאמידת העלויות ושנות החיים המתוקננות לאיכות (quality adjusted life years, QALYs) הקשורות לטיפול כימותרפי ללא trastuzumab וכולל טיפול תרופתי זה, בחולות עם סרטן שד מוקדם מסוג human epidermal growth factor receptor 2 (HER2) חיובי. לכל אסטרטגיה, ביצענו סימולציה בקרב קבוצה היפותטית של 10,000 נשים. בסימולציה הראשונה נכנסו למודל נשים בגיל חציוני של 63 (הגיל החציוני של חולות סרטן שד בישראל). בסימולציה השנייה, נכנסו למודל נשים חשודות לסרטן מוקדם מסוג HER-2 חיובי על-פי צריכת הטיפול התרופתי שלהן כפי שעלה מחלק א של המחקר. נשים אלה נכנסו למודל בגיל הספציפי שבו אובחנו על-פי חלק א של המחקר. כל סימולציה בוצעה פעמיים, לא כולל עלויות נלוות וכולל עלויות נלוות, וערכי incremental cost-effectiveness ratio (ICER) הושוו. במודל הראשון, נכללו עלויות נלוות שנאמדו בחלק א של המחקר כממוצע שנתי של עלות צריכת שירותי הבריאות של המבוטחות בקבוצת הביקורת. במודל השני נאמדו העלויות הנלוות באמצעות מודל ה GLM שנוסח בחלק א של המחקר כך שלכל חולה הותאמו עלויות נלוות בהתאם למאפייניה האישיים. ניתוח רגישות הסתברותי (probabilistic sensitivity analysis) בוצע על מנת לבחון את רגישות הממצאים לשינוי בערכי הפרמטרים של המודל.

הממצאים: *חלק א* של המחקר כלל 696 חולות בסרטן שד ו 2,568 מבוטחות ביקורת. כצפוי, ובשל תהליך ההתאמה של קבוצת המחקר לקבוצת הביקורת, לא היה הבדל בין הקבוצות מבחינת גיל (60.5 לעומת 59.8, p=0.240), מצב חברתי-כלכלי (9.5 לעומת 9.4, p=0.397), וערך CCI בקבוצת המחקר היה גבוה יותר ב 2 מזה שבקבוצת הביקורת (5.7 לעומת 3.7, p<0.001). בנוסף,

[1] Gershon N, Berchenko Y, Hall PS, Goldstein DA. Cost effectiveness and affordability of trastuzumab in sub-Saharan Africa for early stage HER2-positive breast cancer. Cost Effectiveness and Resource Allocation 2019;17(1):1-10

כצפוי, אחוז גבוה יותר מקבוצת המחקר נפטרו בתקופת המעקב (35.4% לעומת 20.6%, p<0.001). העלות הכוללת של צריכת שירותי הבריאות בכל תקופת המעקב הייתה כצפוי גבוהה באוכלוסיית המחקר, בהשוואה לאוכלוסיית הביקורת ($46,470 לעומת $20,100, p<0.001) עיקר ההבדל נבע מצריכת ניתוחים (בעיקר נוירוכירורגיים וקרדיווסקולריים), תרופות (בעיקר antineoplastic and immunomodulating agents), פעילות אמבולטורית אחרת (בעיקר רדיותרפיה), ואשפוזי יום (בעיקר אשפוז יום אונקולוגי). עיקר הפער היה בשנים הראשונה והשנייה שלאחר האבחון. העלות הממוצעת לשנה בקרב קבוצת הביקורת נאמדה ב $2328 ($5662±). ערך זה היווה אומדן לעלויות הנלוות של חולות בסרטן שד שייכלל בניתוח CEA בחלק ב של המחקר. ניתוח GLM העלה שבנוכחות משתנים מסבירים אחרים, העלות הממוצעת לשנה בגין צריכת שירותי הבריאות גבוהה בקרב אוכלוסית המחקר ב $2,445 ($1,677-$2,540, 95% CI: p<0.001).

חלק ב- הסימולציה הראשונה (שלא הייתה מותאמת למאפיינים הייחודיים של מטופלות trastuzumab), העלתה שטיפול ב trastuzumab הוסיף 0.97 QALYs בעלות תוספתית של $40,963, כלומר ICER של $42,638 ל QALY. בהכללת אומדן העלויות הנלוות הממוצע לשנה (כפי שהתקבל בחלק א של המחקר), ICER נאמד ב $48,598. כלומר הטיפול ב trastuzumab נחשב כדאי מבחינה כלכלית בהשוואה לערך התוצר המקומי הגולמי בישראל ב 2019 ($43,600) רק כאשר העלויות הנלוות לא נכללו בניתוח. מגמה דומה של הבדל בערכי ICER התקבלה בסימולציה השנייה שהותאמה למאפיינים הייחודיים של המטופלות ב trastuzumab ושל תאומות הביקורת שלהן, כפי שעלה ממצאי חלק א של המחקר. אולם בסימולציה זו שני ערכי ה ICER הובילו למסקנה דומה לגבי הכדאיות של אימוץ הטכנולוגיה ($28,996 ל QALY ללא עלויות נלוות ו $36,004 ל QALY כולל עלויות נלוות).

מסקנות: טכנולוגיות מתקדמות ויקרות לטיפול בסרטן שד בפיתוח מואץ, לכן יש צורך מתמיד באמידת צריכת שירותי הבריאות של אוכלוסיה זו כמו גם בחינת הכדאיות הכלכלית של אימוץ הטכנולוגיות לטיפול בה. המחקר הנוכחי, נועד לענות על צורך זה. ממצאי המחקר מעלים כי במהלך 14 שנות מעקב, עלות צריכת שירותי הבריאות של החולות גבוה פי 2.3 מתאומות הביקורת. עיקר הפער נובע מהשנתיים הראשונות לאחר האבחון. עוד נמצא כי הכללת העלויות הנלוות עשוי לשנות את המסקנה לגבי מידת הכדאיות הכלכלית של אימוץ הטכנולוגיה. תרומת המחקר היא בניתוח מקיף ומפורט של דפוסים ארוכי טווח של צריכת שירותי בריאות של חולות בסרטן שד, ובכך הוא מצטרף לעדות לגבי הנטל הכלכלי הכרוך במחלה. שנית, המחקר מסייע לאמוד את מידת ההשפעה של העלויות הנלוות על מסקנות הנובעות מהערכת כדאיות כלכלית, ובכך מציף את ההשלכות של התעלמות מהכללת עלויות אלה בניתוח. למיטב ידיעתו, המחקר הוא ראשון מסוגו בישראל, ואף ייחודי בהקשר הבינלאומי מבחינת המתודולוגיה המוצעת לאמידת העלויות הנלוות, ובפרט השימוש

בנתונים ברמת הפרט וכן באמידת ההשלכות שלה על ממצאי ההערכת הכדאיות הכלכלית. מחקר המשך אשר יתקנן את הניתוח לחומרת המחלה ולשלב (disease stage) נדרש על מנת לכייל את הניתוח ואת קבלת ההחלטות בהקשר זה. ניתוח הקשר בין דפוסי טיפול שונים וצריכת שירותי בריאות דורש מחקר המשך גם כן, ויוכל לסייע להבנת ההשפעה של השינוי הטכנולוגי לאורך השנים על דפוסי צריכת שירותי הבריאות והנטל הכלכלי הכרוך במחלה. לבסוף, מחקר המשך אשר יבחן את ההשפעה של אינטראקציה בין מאפייני החולה לעלויות הנלוות, יוכל לכייל גם את אמידת העלויות הנלוות ולכן לכייל את ממצאי ההערכת הכדאיות הכלכלית.

השלכות למדיניות והמלצות למקבל ההחלטות: מערכות בריאות בעולם ניצבות בפני נטל כלכלי כבד הכרוך במחלות כרוניות לא-מדבקות. המצב המתמיד של היעדר משאבים מספקים (תופעת המחסור) מחייב לתעדף טכנולוגיות רפואיות בצורה מיטבית. מכיוון, שכפי שהוכח במחקר הנוכחי, הכללת עלויות נלוות עשויה לשנות את המסקנה הנובעת מהערכת כדאיות כלכלית, אז התעלמות מעלויות אלה עשוי להוביל להטיה לרעת אוכלוסיות ייחודיות (כמו למשל מתמודדי נפש). לכן, תתכן הפרה של מטרת העל של חוק ביטוח בריאות ממלכתי למנוע אפליה בהקצאת שירותי הבריאות לאזרחים. לאור ממצאי המחקר הנוכחי, אנו ממליצים לאמוד את היקף העלויות האלה באופן ייחודי לאוכלוסיות החולים שהטכנולוגיה הנדונה נועדה לסייע להם. אם האומדן משמעותי, אז להכלילו בהערכת הכדאיות הכלכלית כפי שמתחילים לאמץ כעת בארצות הברית, בשבדיה ובהולנד ולא להתעלם ממנו בהתאם לגישה השמרנית המקובלת באנגליה. אי הכללה של עלויות נלוות משולה לקביעה כי ערכן הוא אפס באופן שרירותי. למרות שלכאורה, ניתן לקבוע שתמיד כדאי להכליל עלויות נלוות, בבחינת "כל המרבה הרי זה משובח". ממצאי המחקר שלנו מעלים שזה לא כך. תרומתנו, היא בהעלאת המודעות לסוגיה זו ובאמידת המשמעות של הכללת העלויות הנלוות, אשר חשובים למקבלי ההחלטות במערכת.

Comprehensive scientific report - English

1. Scientific background

One driver of the continuous increase in health expenditure is adoption of new health technologies. Cost effectiveness analysis (CEA) of these technologies may optimize the allocation of the healthcare scarce resources [1,2]. Costs included in CEA may be broadly divided into disease and treatment-related (thus, naturally included in CEA) and *future unrelated* medical costs. These costs derive from the fact that technologies may prolongs life expectancy, thus expose patients to other health conditions (e.g., chronic diseases and injuries). Garber and Phelps [3] defined unrelated costs as those that are independent of the intervention under consideration; moreover, in cases where treatments extend life, costs are defined as unrelated costs if they are independent of treatment but conditional on survival. Conversely, all other costs that are not independent are defined as related. There is an extensive debate around whether *future unrelated* medical costs should be included in CEA [4-8].

The UK's National Institute for Health and Care Excellence (NICE) guidance [9] explicitly recommends that "costs that are considered to be unrelated to the condition or technology of interest should be excluded". It is argued, for example, that the inclusion of future unrelated costs can increase the likelihood of a life-extending technology being categorized as "not cost-effective" even at zero price, which may seem counter-intuitive [5,10]. The second US panel on cost-effectiveness in health and medicine, however, recommends that all current and future, related and unrelated healthcare costs should be included in cost-effectiveness analysis [11]. This reflects a growing consensus that all healthcare costs should be included, particularly in extended years of life [6,11-13]. Indeed, the guidelines employed in the Netherlands and by the LFN (Dental and Pharmaceutical Benefits Board) in Sweden also recommend the inclusion of future unrelated costs [14,15]

The case study addressing the inclusion of unrelated costs will be trastuzumab treatment for breast cancer. Trastuzumab is a humanized monoclonal antibody that

downregulates the extracellular domain of the human epidermal growth factor receptor 2 (HER2) protein. Using trastuzumab to treat women with localized HER2-positive breast cancer has been shown to improve survival. Innovative, effective, and expensive technologies for treating breast cancer continuously emerge. In addition, the incidence of the disease rapidly increases. This emphasizes the importance of articulating the process of prioritization technologies for adoption. The aim of the current research project was to highlight the impact of unrelated future medical costs on the conclusion derived from CEAs, thus on prioritization technologies. The cost-effectiveness of trastuzumab was examined previously in western countries [16-25] and in Sub-Saharan Africa [26]. All studies ignored unrelated future medical costs. In addition, this issue was not analyzed in the Israeli context.

2. Research objectives

The study overall aim was to analyze the impact of inclusion of unrelated future costs in CEA of technology targeted at treatment of breast cancer in Israel. Specifically, our objectives were:

a) To construct and apply procedures for the estimation and assessment of future unrelated medical costs of women with breast cancer in Israel.

b) To ascertain the impact and importance of including unrelated future medical costs in economic evaluations of treating breast cancer with trastuzumab (as a case study).

3. Methodology

This research project was be comprised of two parts. Part A estimated unrelated future medical costs of breast cancer based on patient-level data. Part B examined the influence of these costs on CEA of trastuzumab (treatment of breast cancer as a case study).

3.1. Part A

Study design and setting: A retrospective cohort study was conducted among the Southern District of Clalit Health Services (henceforth: CHS) enrollees. The study was approved by the Institutional Helsinki Committee (0200-19-COM2).

Study population: All female patients who met the following inclusion criteria: 1) enrollees of the Southern District of CHS; 2) newly diagnosed with breast cancer (ICD-9 code 174.9) between 2005-2008; 3) active enrollment during the entire follow-up period (2005-2019). The exclusions criterion for control groups is: patient with no matched control subject.

Control subjects were randomly selected and matched 1:4 to the study population by: age (±2 yrs.), clinic, sector, socioeconomic status (SES, ±2) and Charlson comorbidity index (CCI, -2 since breast cancer patients have CCI of 2). The inclusions criteria for the control group are: 1) enrollees of the Southern District of CHS; 2) active enrollment during the entire follow-up period (2005-2019). The exclusions criterion for the control group is: diagnosis of breast cancer (ICD-9 code 174.9) during the entire follow-up period.

Data source: All study variables were obtained from the Southern District administrative claims database of CHS.

Study procedure: First, demographic, socio-economic and clinical characteristics of study population were extracted from the CHS database. Then we matched control subjects to each breast cancer patient. Finally, we extracted data on healthcare utilization (HCU) for the entire cohort. All data were anonymized.

Healthcare utilization: HCU estimates analyzed in our study included: hospitalizations, surgical procedures, diagnostic procedures, medications, emergency room visits, one-day outpatient care, outpatient specialists' consultation visits, paramedical care, home care and other ambulatory care. Total cost was calculated as the sum of all these estimates. Data on primary care physician visits cost were not available, thus number of visits were analyzed separately. Cost estimates were adjusted to 2019 prices and converted to US dollars (USD) using the 2019 exchange rate of 3.56 Israeli shekels (ILS) per 1 USD.

The diagnosis month was defined as the index date. HCU data were calculated separately for periods of 12 months from the index date and the end of follow-up period or death. The index date for the control subject was identical to the index date of her matched breast cancer patient.

Data analyses: Data were analyzed using RStudio software (version 1.3959, RStudio, PBC, Boston, MA). Continuous variables were presented as mean ±SD,

median and interquartile range (IQR). Dichotomous variables were presented as proportions. The T-test and Mann-Whitney U test were used to determine between-group differences of continuous variable assuming normal or non-normal distribution, respectively. A Chi-squared test was used to examine between-group differences in dichotomous variables.

Multivariable generalized linear models (GLM) were specified for predictors of the average annual HCU costs. The core independent variable was the study group. Both models were adjusted to additional independent variables (e.g., SES and comorbidities), and the best specification of each was determined by the Akaike information criterion (AIC). p values of <0.05 determined statistical significance in all analyses.

3.2. Part B

In this part we examined the impact of unrelated future medical costs on CEA of treating breast cancer with trastuzumab by comparing a CEA that includes only related medical costs with a CEA that includes both related and unrelated future medical costs as derived from part A of the study.

Model structure: Using Rstudio platform and following Gershon et al. [26] we used a Markov model with monthly cycles and lifetime horizon. The model estimated the costs and health outcomes (life years (LYs) and quality adjusted life-years (QALYs)) associated with two strategies, namely chemotherapy [27,28] and chemotherapy with trastuzumab for treating early stage HER2-positive breast cancer.

The inputs of the model were based upon the HERA trial [27-29]. The model is illustrated in Figure 1. It consists of five states: remission (R), locoregional recurrence (LR), distant recurrence (DR) including metastasis, breast cancer death (BCD), and death due to other causes (D). The influence of trastuzumab on the patients was modeled by changing the transition probabilities from R to DR and from LR to DR based on the hazard ratio. The probability of moving from DR to BCD is identical for both model arms since trastuzumab only delays or prevents a patient from moving to the DR state. It was assumed that the effect of trastuzumab lasted 5 years and that there were no cancer recurrences after 20 years of follow-up

[30]. Costs, LYs, and QALYs were discounted at a yearly rate of 3% as recommended by the WHO [31].

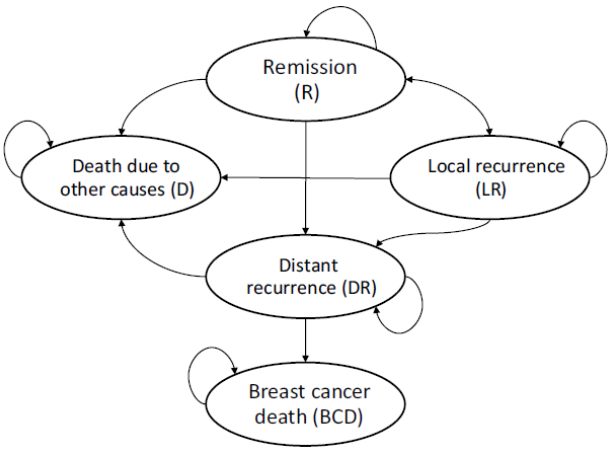

Figure 1. Markov model structure.

Patient population: For each treatment strategy, a hypothetical cohort of 10,000 patients was simulated.

In the first simulation, patients who entered the model were 63 years old based on the median age of breast cancer patients in Israel [32]. Since only 25% of breast cancers are HER2-positive, and only those patients are eligible to receive trastuzumab, in the second simulation, subgroup of patients who were identified in Part A of the study were randomly selected and entered to the model in their exact age.

The background mortality information of the patients was retrieved from the Global Health Observatory [33]

Costs: The total costs for the trastuzumab treatment as well as the costs for the LR and DR states were based on a study of the Southeast Netherlands Breast Cancer Consortium [16]. Following this study, we assumed that there is no cost for the R state. All costs were adjusted to 2019 prices and converted to US dollars (USD) using the July 2019 exchange rate of 1.12 Euro per 1 USD. Unrelated future medical costs were estimated twice based on results of part A of the study. Namely, once as the annual average all-cause healthcare costs of the control subject, and once as predicted values based on the GLM adjusted to patients' characteristics.

Quality adjusted life years: were determined based on extant literature (Table 1), and combined with the costs estimated, enables to calculate the incremental cost-effectiveness ration (ICER).

Sensitivity analyses: To assess the influence of change in parameters' value on the simulation models' results, a one-way probabilistic sensitivity analysis was performed. Each parameter was varied separately based on its distribution as presented in Table 1.

4. Findings

4.1. Part A

Our cohort consisted of 696 patients with breast cancer and 2,568 control subjects (Table 2). As expected and due to the matching algorithm, both groups were comparable with regard to age (p=0.240), SES (p=0.397), and with +2 higher CCI (p<0.001).

In addition, as expected higher proportion of the study group died during follow-up (<0.001). Higher proportion of the study group did not have supplementary health insurance coverage (p<0.001) and had higher prevalence of hyperlipidemia (p=0.005), diabetes (p<0.001), osteoporosis (p=0.029), mental disease (p<0.001), renal failure (p<0.001), and other malignancies (p<0.001). However, both groups were comparable with regard to other comorbidities, namely, arthropathy, hypertension, obesity, CVD, CVA, gastrointestinal diseases, pulmonary disease and dementia (Table 2).

Total all-cause healthcare costs during follow-up by study group is presented in Table 3. These costs were significantly higher in patients with breast cancer ($46,470 vs. $20,100, p<0.001). Most of the difference stem from higher costs of surgical procedures (mainly neurosurgical, and cardiovascular surgical procedures (Table 4)), medications (mainly antineoplastic and immunomodulating agents (Table 4)), other ambulatory care (mainly radiotherapy (Table 4)), diagnostic procedures (mainly mammography and non-cardiac scans (Table 4)), and on-day outpatient care (mainly in the oncology ward (Table 4)).

As illustrated in Figure 2. Most of the difference in HCU costs between the study group and the control subjects during follow-up was at the first and second year after diagnosis. The average annual HCU costs in the control group was estimated at $2328 (±5662) and these were firstly considered unrelated medical costs.

Table 1. Model parameters (base case), distributions and data sources

Parameter	Value	Distribution	Source
Utilities			
Remission (R)	0.94	Beta (89,6)	[23,34]
Locoregional recurrence (LR)	0.82	Beta (77,23)	[28]
Distant recurrence (DR)	0.58	Beta (171, 79)	[28]
Transition probabilities			
R → LR	0.029	Beta (27, 983)	[29]
R → DR	0.087	Beta (102, 1061)	[27,28]
LR → R	0.100	Beta (111, 899)	[28]
LR → DR	0.261	Beta (119, 931)	[28]
DR → BCD	0.325	Beta (15, 20)	[28]
R, DR, LR→D	Age-specific mortality	constant	[33]
Hazard ratio years 1-5	0.59	Log-normal (-0.527,0.089)	[19,28]

Abbreviations: BCD, breast cancer death; D, death due to other causes.

Table 2. Comparison of baseline characteristics by study group**.**

Variable	Breast cancer	Control	P-Value
Observations, % (n)			
Before Matching	100.0% (851)	100.0% (139,142)	
After Matching	81.8% (696)	1.8% (2,568)	
Age at diagnostic [b]	60.50 ± 13.38 (60, 19)	59.77 ± 13.10 (60, 20)	0.240[c]
Year of Diagnosis (%)			0.987[d]
2005	163 (23.4%)	585 (22.8%)	
2006	172 (24.7%)	644 (25.1%)	
2007	163 (23.4%)	607 (23.6%)	
2008	198 (28.4%)	732 (28.5%)	
Socioeconomic Status [b]	9.51 ± 3.20 (9, 5)	9.39 ± 3.19 (9, 5)	0.397[c]
Charlson Comorbidity Index [b]	5.74 ± 2.60 (5, 3)	3.72 ± 2.49 (3, 3)	<0.001[c]
Years of follow-up [b]	9.89 ± 3.95 (11, 6)	11.17 ± 3.04 (12, 2)	<0.001[c]
Survival (%)	443 (63.6%)	2,040 (79.4%)	<0.001[d]
Smoking (%)	104 (14.9%)	483 (18.8%)	0.021[d]
Insurance Coverage			0.003[d]
No Insurance Coverage	259 (37.2%)	787 (30.6%)	
Gold	236 (33.9%)	1,007 (39.2%)	
Platinum	201 (28.9%)	774 (30.1%)	
Hyperlipidemia	546 (78.4%)	1,877 (73.1%)	0.005[d]
Arthropathy	412 (59.2%)	1,486 (57.9%)	0.557[d]
Hypertension	404 (58.0%)	1,430 (55.7%)	0.285[d]
Obesity	311 (44.7%)	1,062 (41.4%)	0.125[d]
Diabetes	261 (37.5%)	777 (30.3%)	<0.001[d]
CVD	246 (35.3%)	885 (34.5%)	0.697[d]
Osteoporosis	230 (33.0%)	737 (28.7%)	0.029[d]
Mental Diseases	228 (32.8%)	667 (26.0%)	<0.001[d]
Gastrointestinal diseases	170 (24.4%)	609 (23.7%)	0.734[d]
Renal Failure	136 (19.5%)	359 (14.0%)	<0.001[d]
Malignancies (excluding breast cancer)	121 (17.4%)	298 (11.6%)	<0.001[d]
Pulmonary Disease	97 (13.9%)	319 (12.4%)	0.318[d]
CVA	92 (13.2%)	283 (11.0%)	0.122[d]
Dementia/Alzheimers/OMS	62 (8.9%)	273 (10.6%)	0.208[d]

[a] t-test
[b] Values are mean ± SD (median, IQR)
[c] Mann-Whitney U test
[d] χ^2 test

Table 3. All-cause healthcare costs during follow-up, by study group

Average costs ($)	Breast Cancer	Control	Difference	P-Value
Total	46,470 ± 42,050 (35,853, 33,772)	20,100 ± 35,979 (9,921, 17,885)	26,370	<0.001[a]
Hospitalization	9,030 ± 17,799 (2,829, 10,304)	6,110 ± 15,945 (647, 5,121)	2,920	<0.001[a]
Surgical procedures	8,958 ± 12,690 (5,806, 10,046)	3,860 ± 9,088 (0, 3,855)	5,098	<0.001[a]
Medications	7,308 ± 16,650 (3,181, 4,413)	2,908 ± 7,711 (1,292, 2,332)	4,400	<0.001[a]
Other ambulatory care	6,513 ± 8,803 (4,972, 5,302)	2,144 ± 18,660 (151, 549)	4,369	<0.001[a]
Diagnostic procedures	5,996 ± 4,851 (5,030, 4,786)	2,166 ± 2,349 (1,455, 2,431)	3,830	<0.001[a]
One-day outpatient care	4,105 ± 8,326 (1,424, 4,955)	357 ± 2,283 (0, 0)	3,748	<0.001[a]
Outpatient specialists' consultation visits	2,839 ± 1,703 (2,689, 2,050)	1,215 ± 1,275 (866, 1,273)	1,624	<0.001[a]
Emergency Room visits	890 ± 1,123 (532, 962)	626 ± 913 (433, 806)	264	<0.001[a]
Paramedical care	648 ± 953 (400, 640)	385 ± 618 (157, 510)	263	<0.001[a]
Home care	183 ± 1,546 (0, 0)	330 ± 4,590 (0, 0)	-147	0.003[a]

Values are mean ± SD (median, IQR)
[a] Mann-Whitney U test

Table 4. All-cause HCU and costs, by study group and type of services

Type of service	Breast cancer (n = 696)	Control (n = 2,568)
Hospitalization in general wards (excluding geriatric, mental and rehabilitation wards	5,145 ± 9,723 (1,607, 5,644)	3,254 ± 9,066 (0, 2,639)
	71.8% (500)	47.5% (1,219)
	2.2 ± 3.3 (1, 3)	1.3 ± 2.4 (0, 1)
Neurosurgical and surgical procedures (subcategory of surgical procedures)	4,463 ± 7,164 (2,078, 5,997)	746 ± 4,361 (0, 0)
	63.5% (442)	7.7% (198)
	0.8 ± 0.8 (1, 1)	0.1 ± 0.3 (0, 0)
Radiotherapy (subcategory of Other ambulatory care)	4,439 ± 4,755 (3,713, 5,641)	155 ± 2,033 (0, 0)
	73.7% (513)	1.3% (33)
	22 ± 16 (26, 35)	0.1 ± 1.9 (0, 0)
Antineoplastic and immunomodulating agents	4,147 ± 15,202 (741, 2,034)	509 ± 6,286 (0, 0)
	89.2% (621)	7.6% (194)
	55 ± 41 (57, 71)	1.3 ± 12 (0, 0)
One-day outpatient care in oncology ward	3,071 ± 5,756 (516, 4,306)	93 ± 1,174 (0, 0)
	50.9% (354)	2.2% (56)
	10 ± 19 (1, 13)	0.2 ± 3 (0, 0)
Outpatient specialists' consultation visits	2,104 ± 1,169 (2,046, 1,432)	810 ± 852 (573, 866)
	99.7% (694)	96.4% (2,476)
	57 ± 34 (54, 46)	29 ± 28 (22, 32)
Non-cardiac diagnostic scans (subcategory of diagnostic procedures)	980 ± 1,632 (476, 918)	113 ± 467 (0, 0)
	80.7% (562)	24.6% (632)
	2 ± 2 (2, 2)	0.4 ± 0.9 (0, 0)
Mammography (subcategory of diagnostic procedures)	951 ± 760 (846, 948)	118 ± 155 (83, 183)
	94.7% (659)	68.0% (1,745)
	6 ± 4 (7, 6)	1.9 ± 1.8 (2, 3)
Cardiovascular surgical procedures (subcategory of surgical procedures)	946 ± 4,470 (0, 0)	553 ± 3,059 (0, 0)
	9.1% (63)	6.0% (153)
	0.1 ± 0.4 (0, 0)	0.1 ± 0.3 (0, 0)

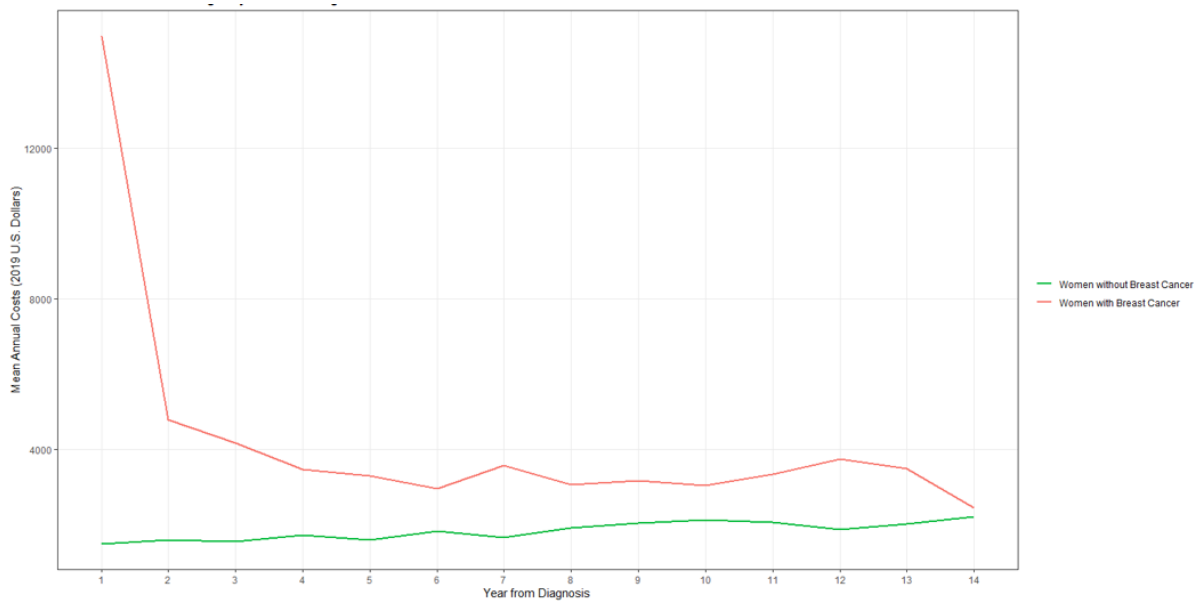

Figure 2. Mean annual HCU costs during follow-up.

Table 5 presents the results of the multivariable GLM for predictors of the annual HCU costs. It reveals that these costs were $2,445 higher (95% CI: $1,677-$2,540, p<0.001) among breast cancer patients compared to control subjects.

Table 5. Multivariable GLM for predictors of the average annual HCU costs.

Explanatory variables		β	β' ($)	(95% CI)	p-value
Intercept		6.96	1,054	(889 -1,249)	<0.001
Study group		1.20	2,445	(1,677 – 2,540)	<0.001
Socioeconomic status	**Lower third**	Ref.			
	Intermediate third	-0.07	-71	(-176 – 74)	0.345
	Upper third	0.01	11	(-101 – 144)	0.845
Malignancies (excluding breast cancer)		0.81	1,315	(814 – 1,480)	<0.001
Diabetes		0.24	286	(103 – 398)	0.000
Hypertension		0.19	220	(64 – 335)	0.003
CVA		0.26	313	(84 – 505)	0.004
Arthropathy		0.13	146	(9 – 252)	0.029
Osteoporosis		0.13	146	(9 – 264)	0.039
Pulmonary Disease		0.24	286	(64 – 451)	0.005
Renal Failure		0.62	905	(519 – 1,050)	<0.001
CVD		0.42	550	(299 – 652)	<0.001
Gastrointestinal diseases		0.22	259	(74 – 373)	0.002
Mental Disease		0.21	246	(74 – 360)	0.001
Has Insurance		-0.48	-402	(-401 – -263)	<0.001

4.2. Part B

In the base case analysis of the first simulation model (not age-specific), trastuzumab yielded a gain of 0.97 QALYs with incremental cost of $40,963, leading to an ICER of $42,638 per QALY (Table 6). Part A of the study revealed that the annual average HCU costs of the control subjects was $2,328. Adding these future unrelated medical costs to the model yielded higher ICER of $48,598 per QALY (Table 6). Hence, trastuzumab was consider cost-effective compared to the threshold of Israel's 2019 GDP per capita of $43,600 [35]only when unrelated future medical costs were excluded. Similar difference between ICERs was observed in the second simulation that was calibrated to the specific characteristics of trastuzumab users and their matched control subjects. Specifically, in this simulation model the unrelated future medical cost were predicted based on results presented in Table 7. Namely, women who entered to the model were randomly selected from the subgroup of trastuzumab users and their corresponding unrelated future medical costs were predicted based on their specific characteristics that are included in the multivariable GLM model. However, in this simulation, both ICERs (excluding/including unrelated future medical costs) led to the conclusion that trastuzumab is a cost-effective technology (Table 8).

Table 6. Mean base case results of the CEA model.

Unrelated future medical costs	**Not included**			**Included**		
	Cost	**QALY**	**ICER ($/QALY)**	**Cost**	**QALY**	**ICER ($/QALY)**
No treatment	77,643	7.20		97,886	7.26	
With treatment	118,606	8.17		139,183	8.11	
ICER			42,638			48,598

Table 7. Multivariable GLM for predictors of the average annual HCU costs of the subgroup of trastuzumab user and match control subject.

Explanatory variables		β	β' ($)	(95% CI)	p-value
Intercept		6.59	728	(488 -1,108)	<0.001
Study Group		1.98	5,543	(2,701 – 7,622)	<0.001
Socioeconomic status	**Lower third**	Ref.			
	Intermediate third	-0.30	-189	(-384 – 118)	0.172
	Upper third	-0.45	-264	(-426 – -22)	0.029
Obesity		-0.24	-155	(-316 – 61)	0.143
Current Smoker		0.28	235	(-101 – 767)	0.187
Dementia/Alzheimers/OMS		0.82	925	(85– 2,913)	0.018
Hypertension		0.56	546	(144 – 1,154)	0.002
CVA		0.42	380	(-95 – 1,311)	0.155
Pulmonary Disease		0.31	264	(-89 – 876)	0.190
Renal Failure		0.44	402	(-69 – 1,331)	0.118
CVD		0.46	425	(69 – 958)	0.021
Mental Disease		0.53	509	(144 – 1,044)	0.004

Table 8. Mean base case results of the age-specific CEA model.

Unrelated future medical costs	**Not included**			**Included**		
	Cost	**QALY**	**ICER ($/QALY)**	**Cost**	**QALY**	**ICER ($/QALY)**
No treatment	85,548	9.14		104,569	9.01	
With treatment	126,630	10.54		149,616	10.26	
ICER			28,996			36,004

5. Discussion and conclusions

Advanced and costly pharmaceutical technologies to treat breast cancer continuously emerge. Thus, it is continuously warranted to estimate patterns of HCU of these patient as well as articulate the methodologies to appraise their cost-effectiveness. The current research project was targeted at these two objectives. It revealed that during 14 years of follow-up HCU of patients with breast cancer is significantly higher than match controls, specifically during the first- and second year following diagnosis. In addition, it revealed that including unrelated future medical costs in CEA may alter the conclusion derived from the analysis, namely, lead to the conclusion that the technology is not cost-effective. These results will be discussed in light of extant literature.

Similar to our results, previous evidence revealed that the first year following diagnosis is considered to be the costliest in terms of HCU [36-39]. In addition, our results substantiate previous results with regard to the significant economic burden associated with breast cancer compared to control subject [36,39-41]. The substantial economic burden was also previously demonstrated in Maccabi Health Services, the second largest HMO in Israel [42].

We found that 38%, and 16% of total costs during follow-up were attributed to inpatient care (hospitalization and surgical procedures) and medication. In a population-based cost analysis across the European Union countries [43] these two components were also the more prominent, however in this analysis medication consist 46% of costs [43] significantly higher than our results. The results with regard to inpatient care were similar to those from the European Union [43] and the US [41], however significantly higher than result from Israel [44]. Nevertheless, the last analyzed the first year following diagnosis, thus, excluded the terminal phase of the disease which is usually costly and includes a high hospitalization rate [38]. It should be noted that, in Israel, patients with breast cancer have mainly the invasive disease [32], thus, it may be assumed that a long-term analysis of HCU during the whole disease course might result in a significant proportion of hospitalizations.

In addition, while outpatient care was relatively negligible in the European Union [43], these costs (including diagnostic procedures (mostly mammography), one-

day outpatient care (mostly visits to the oncology outpatient clinic), outpatient specialists' consultation and other ambulatory care (mostly radiotherapy) consisted 42% of costs.

Our results that are from a mostly publicly financed HMO are also different from those estimated by Allaire et al. for the annual HCU costs during all of the disease course among privately insured women [40], where outpatient care consisted 92% of the total HCU costs for breast cancer. The different utilization of outpatient care portrayed in our study emphasize the fact that HCU patterns are context-specific, thus allocation decision should be context-specific.

Our CEA of trastuzumab revealed higher ICERs than most of current evidence from Europe [16,19,23,24] and even the US [34]. In addition, and as expected the ICER was also higher than a study that referred to low-income country [26] although similar simulation model was conducted. However, it was comparable to that observed in other European countries [17,21,25]. In all analyses [16,17,19,21,23-25,34] as well in the current base case analysis trastuzumab was considered cost-effective based on the GDP per capita threshold, however, all extant analyses [16,17,19,21,23-25,34] ignored the unrelated future medical costs.

As expected, when unrelated future medical costs were included in the model the ICERs increased by ~20%. However, in one out of the two simulations, it led to change in the conclusion derived from the analysis. It is reasonable to assume that the inclusion of unrelated future medical costs may mostly affect the result (thus crucial to be included) as higher is the life-expectancy following treatment and as the expected future costs are non-negligible (as in low-income countries). Our estimation procedure of unrelated future medical cost was unique since it was context-specific, namely estimation of the unrelated future medical costs associated with breast cancer based on patient-level data. Briggs et al. [45] based their estimation on the resource allocation formula which is broadly adjusted solely to age and sex. Van Baal et al. [46] assumed that total healthcare expenditure can be explained by age, sex and time to death, and used 2005 cost-of-illness (COI) data from the Netherlands which covers 107 disease categories. Our analyses were based on comprehensive and detailed information on healthcare utilization including hospitalizations, surgical procedures, diagnostic procedures, medications,

emergency room visits, one-day outpatient care, outpatient specialists' consultation visits, paramedical care, home care and other ambulatory care, while others [45] estimated the relative health expenditure for four care categories (general and acute care, mental health, prescribing, and primary care.

This study has several limitations. First, our analysis relied on financial data that lack clinical information to confirm the disease stage and severity at diagnosis, thus, analyses was not stratified by disease stage that may highly contribute to variability in the HCU estimates. Second, HCU in our study included direct HMO costs and ignored out of pocket costs for medication or other healthcare services. Third, cost estimates of HCU may not be generalizable to other healthcare systems, as practice patterns and tariffs may differ. This limitation, however, does not weaken our analysis since our objective was to describe between-group differences in HCU and the influence of this estimate on the relative ICER rather than to refer to absolute values. Fourth, our CEA was not based on Israeli-specific clinical trial but rather on data gathered from clinical trial in developed countries. Fifth, the treatment costs utilized in the CEA was based on estimates from the Netherlands rather than actual Israel data. However, since these estimates were equally included in both simulations excluding/including unrelated future costs, this limitation only affect the absolute ICER derived from each simulation, yet not the comparison between models, which was the core objective of the current study.

Notwithstanding these limitations, we believe that our research project provides two main contributions. First, it provides a comprehensive description of all-cause HCU of breast cancer patients in Israel, thus, substantiating existing evidence about the economic burden of breast cancer worldwide and leveraging it to estimate unrelated future medical costs. Second, it provides empirical evidence for the influence of these unrelated costs on CEA, thus enable policy makers to appraise the implications of ignoring these costs. This research is not only the first of its kind in Israel, but also quite rare and new globally. Furthermore, its strength is by using patient-level data on HCU. Further research on long-term HCU and health outcomes of patients with breast cancer stratified by disease stage and by pharmaceutical care will enable more in-depth examination and is crucial for CEA of the rapidly emerging technologies. In addition, further research may uncover the

effects of interactions between patients' characteristics on unrelated future medical costs (e.g., the effect of comorbidities of depression and anxiety on future costs of patients with breast cancer).

6. Policy implications and recommendations

Healthcare systems worldwide face major public health challenges from non-communicable diseases and associated financial burden. The continuous state of scarce healthcare resources highlights the need to optimally prioritize medical innovations.

Since inclusion of unrelated future medical costs may alter the conclusion derived from CEA (as was proved in our case study), then ignoring these costs will lead to hidden biases against certain populations (such as the mentally frail). Hence, violating the overall aim of the Israeli National Health Insurance Law to prevent discrimination.

Based on study results we recommend evaluating the magnitude of these costs in the specific context discussed (specific disease and treatment) and if of great magnitude, then applying the model that is emerging in the US and the Netherlands rather than the conservative model used in the UK. Excluding unrelated future medical costs is equivalent to arbitrarily referring to these as equal to zero.

Although one might be tempted to hypothesize the answer to the question whether to include unrelated future costs, is "very important. Always!", it is important to note that this is not universally true as was observed in our study. Our contribution is to raise awareness to this issue and provide the magnitude of effect, both crucial for evidence-based decision-making process.

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