Critical Appraisal of Exercise in Cancer Care of Patients Undergoing Frontline Chemotherapy

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Abstract

Background: Physical activity (exercise) can be adjuvant palliative for cancer patients who are on frontline therapies. This could have cost-effective and quality outcome implications on the target population. This study aimed to critically appraise the economic viability of physical activity in adjuvant cancer treatment (PACT) in a breast and colon cancer sub-population.

Methodology: This was a critical appraisal of a multi-centred randomized controlled study on colon and breast cancer patients. The Critical Appraisal Skills Program economic evaluation checklist was used as a guideline for critical appraisal. The various components in the checklist were used in critical appraisal namely the study validity, the validity of the economic evaluation, comparative cost-effective analysis of the consequences in the test and control population, study results (outcomes), study usefulness, and its application to practice.

Results: Exercise reduced cancer-related fatigue in colon cancer cohorts on adjuvant chemotherapy as evidenced by cost savings of Euro4321 and quality-adjusted life years improvement of 0.03 over an 18-week exercise-research oncology study. However, it was not a cost-effective intervention for the breast cancer group that lost Euro2912 with a QALY improvement of 0.01 (An incremental cost-effective ratio of 0.02 is required to certify cost-effective intervention).

Conclusion: This study has addressed the importance of behavioural activity such as exercise in improving the quality of life of cancer patients on adjuvant chemotherapy. While it is a cost-effective intervention for colon cancer, it is not for breast cancer. Physical activity is a recommendable palliative care intervention in cancer management when all confounding factors are excluded. Exercise can increase cancer patients’ ICER and QALY, improving their life expectancy.

Introduction

One of the major problems of PLWC is fatigue [1]. About 30% of cancer patients report fatigue after treatment and this leads to healthcare-related expenditure and societal costs due to sick leave [2]. There is a paucity of data on the hypothesis surrounding fatigue in cancer patients on frontline chemotherapy and the cost implications. However, it has been postulated that physical activities such as exercise and yoga play a major role in alleviating the fatigue encountered by PLWC following frontline chemotherapeutic treatment [3]. Therefore, physical activities together with other healthy lifestyle variables play a significant role in quality care and cost-effective management of PLWC.
Quality in Medicare begins with the prudent and equitable distribution of financial resources for strategic health conditions [4,5]. Proper health financing impacts favourably on the quality-adjusted life-years, hence, reducing the disability-adjusted life-years of the target population [6]. The hallmark is increased average life expectancy and reduced mortality rate of the target population (Central Intelligence Agency, n.d.). All these revolve around health economics and good health governance. The benefits of the duos are much appraised when strategic disease preventive interventions are institutionalized through the promotion of healthy lifestyle variables such as physical activity (exercise), healthy diet (nutrition), good personal hygiene, periodic screening tests, immunization, good sleeping habits, and avoidance of drug abuse. These public health interventions could be economically valuable when implemented as an upstream approach to primary disease prevention. In addition, they can be adjuvant palliatives for the debilitated who are on frontline therapies.

This study aimed to critically appraise the economic viability of physical activity in adjuvant cancer treatment (PACT) in a breast and colon cancer sub-population.

**Literature Review**

The two major health indices that determine the health status of any nation are the average life expectancy from birth (LE) and the infant mortality rate (IMR) of her population [7]. The healthier a nation becomes the higher the average life expectancy and the lower the IMR of its populace. The social environment which is the place where a person is born, lives, grows, and dies plays a crucial role in the prediction of health outcomes of any population [8]. The availability of favourable social determinants of health makes a social environment conducive to living. Four major determinants of health make an environment health-friendly. They are education, health policy, access to quality health care, and economic empowerment [9]. These social determinants of health are the panacea for improved quality of life of any given populace. This is where health economics and good governance come into play.

Health economics is a science that teaches leadership approaches of prudent allocation of scarce resources to improve healthcare, while good health governance applies health economics to improve clinical practice and public health indices [5]. Governance is a process that uses strategic leadership approaches to coordinate activities for the well-being of society. The term “governance” goes beyond ‘government’. Government in the real sense of it comes under governance because the former is a network of key actors, public and private sectors interacting in a coordinated manner as a team to actualize a common goal for the betterment of society. Both the political and health organizational governance are critical in improving the health indices of any given society [10]. While political governance improves the health indices of a nation by sustaining the major social determinants of health of the entire populace that make up a nation, health organizational governance is saddled with the responsibility of applying health economics to improve the quality of healthcare services which ultimately improve the health outcome of the target population.

The application of Health economics and good health governance becomes very important when dealing with cancer. A cancer cell is a malignant cell that has the capacity of abnormal self-proliferation without achieving any useful purpose in the body. They invade normal cells of the body and cause end-organ failures. Any cell in the body can undergo mutation and become cancerous (i.e., cancer of the breast, cancer of the colon, cancer of the prostate, cancer of the blood). Cancer is a non-communicable disease. In 2007, an estimated number of 6 million cancer-related deaths occurred in 29 million people living with cancer [11,12]. It is projected that cancer-related deaths will rise to 8.32 million in 2030 due to changes in lifestyle variables, especially in low-income and low-middle-income countries of the world [13]. This is indeed a huge global economic burden.

The growing burden of cancer has led to the establishment of different organizational frameworks such as NGOs, and CSOs whose targets are to improve the QoL of PLWC through health promotion, health prevention, and health protection mechanisms. Examples of such bodies include the International Union for Cancer Control (UICC), the Global Cancer Observatory (GLOBOCAN), and the International Agency for Research in Cancer (IARC). Others include the National Comprehensive Cancer Network (NCCN), the European Society of Breast Specialists (EOSOMA), the American Society of Clinical Oncology (ASCO), the Hospice Palliative Care Association (HPCA), the African Palliative Care Association (APCA) and others. These NGOs work in collaboration with multilateral organizations such as the WHO and the World Bank to drive global health issues relating to cancer to reshape the global population and economy [14,15].

In good health organizational governance, several concepts and principles including monitoring, evaluation, auditing, setting standards, use of data, research studies, regulations, risk assessments, quality control, quality assurance, and core competencies of leadership are incorporated in decision-making in public health practice. The hallmark of these applications is to impact a behavioural change that will bring out the desired outcome of the target population [16]. All these concepts are currently incorporated as
palliative care for people living with cancer in modern healthcare practice [15].

Palliative care is an intervention that holistically improves the QoL of a patient suffering from a life-threatening illness such as cancer through the prevention and relief of his sufferings by risk identification, assessment, and management of his conditions which could range from physical, psychosocial, spiritual, and socio-economic problems [17;18]. The palliative care approach is a public health intervention universally accepted and used by many oncology organizations to reduce the DALYs and improve the QALYs of cancer patients. This standard of care uses both the upstream and downstream approaches to impact its target population. A classic example of palliative intervention is the impact of physical activity (exercise) on QALY and the cost of management of PLWC [19].

To improve the quality of palliative care for PLWC, strategic leadership approaches must be taken to achieve the desired outcomes, including improved QoL and average life expectancy of the cancer sub-population. Such approaches include applying leadership models and styles in operational dealings to effect behaviour change. Palliative care believes that modification of lifestyle variables such as diet preferences, body mass index, sleeping habits, personal hygiene, periodic screening tests, physical activity, smoking, and substance abuse can go a long way to prevent non-communicable diseases (i.e., cancer, cardiovascular diseases, obesity, and diabetes) and at the same time improve the QoL of sufferers. Hence, palliative care organizations embark on public health interventions using a health-behavioural theoretical framework to educate their target population to adopt good behaviours that will ultimately bring about the desired outcomes at a cost-effective price.

The value of good governance in the prevention and alleviation of suffering of people living with cancer cannot be overstated. A palliative care organization as an entity can only operate optimally when good governance is embraced. Effective operation in this case requires collaboration with research groups, non-governmental organizations, civil service organizations, and donor agencies passionate about cancer prevention and care. The leadership quality must be patient-centred, visionary, growth-focused, inclusive, and result-oriented. In addition, it must be driven by regulations, accountability, transparency, and effective healthcare services [10]. In addition to this, an effective palliative care organization uses multi-disciplinary and teamwork approaches to improve the QoL of the patients.

A WHO-recommended model of palliative care is supported by four pillars including policy-making, funding, education, and strategic planning [20]. To sustain quality care, funding for capacity building, research, and purchase of essential drugs is necessary. There is a need for collaboration with multi-lateral organizations, NGOs, CSOs, and research organizations on cancer to come up with frameworks and grants that will help to improve the quality of care for cancer patients [21].

Methodology

This was a critical appraisal of a multi-centred randomized controlled research study on colon and breast cancer patients [21]. The study was published in “British Medical Journal Open” in 2017 and authored by May, A.M., Bosch, M.J.C., Velthuis M.J., and other co-authors. The digital object identifier for the study is doi:10.1136/bmjopen-2016-012187. The Critical Appraisal Skills Program economic evaluation checklist was used as a guideline for critical appraisal [22]. The following components of the CASP checklists were used in the critical appraisal and economic evaluation of the impact of physical activities in the cancer population on frontline therapies, the study validity, the validity of the economic evaluation, comparative cost-effective analysis of the consequences in the test and control population, study results (outcomes), study usefulness and its application to practice [22].

Critical Appraisal of the Study Validity

Study Introduction

This was a multi-centred randomized controlled prospective study conducted in the Netherlands between 2010 and 2013 [1]. The study was conducted on 237 adult newly diagnosed breast and colon cancer patients within the age range of 25-75 years who were undergoing adjuvant chemotherapy in the outpatient clinics of 7 hospitals (an academic and 6 general hospitals) in the Netherlands. Ethical approval was given by the institutional review boards of all the participating hospitals while written consent was obtained from each participant.

The study was aimed at determining if there is any cost-effective value of physical activity intervention during cancer therapy. The study design was a CEA with a 36-week time interval (made up of 18 weeks of intervention and 18 weeks of follow-up visitation) in a pragmatic randomized controlled multi-centered prospective study PACT study. PACT in this context is an acronym that connotes Physical Activity during adjuvant Cancer Treatment). Two categories of cancer (breast and colon cancer) were identified and each category was stratified into intervention (experimental) and control groups in an open-labeled study.
The intervention (PACT) was a supervised one-hour aerobic and resistance exercise (two times per week for eighteen weeks) [1] or usual chemotherapy (care) without exercise (C).

The measured consequences (outcome) from the study were costs (including direct and indirect healthcare costs), QALY, and incremental cost-effectiveness ratio (ICER).

The initial outcome measurements were done on the day of recruitment. The patients were subsequently given structured diaries to record weekly recording of the outcomes. Evaluation and weekly reports were done at the end of 18 weeks when the initial diaries were returned and new ones were given for the next 18 weeks post-intervention follow-up periods.

At the end of the 36-week duration of the PACT study, the colon cancer category had a beneficial effect in cost-effectiveness as evidenced by incremental cost savings (I€C= €4321) and QALY improvement of 0.03. In addition, the bootstrapping revealed dominance (cheaper and more effective) of the intervention over the control. This means the probability that the intervention is cost-effective is 100% at every level of willingness to pay (WTP).

On the other hand, the breast cancer category recorded no beneficial effect during CEA as evidenced by a higher incremental cost difference between the intervention and control (I€C=€2912) and QALY of 0.01 (Probability of 2% [0.02] needed to certify that an intervention is cost-effective at Dutch Threshold value of €20,000/QALY). Bootstrapping revealed a higher cost for intervention in all stimulations in the breast cancer category.

In conclusion, PACT intervention was favourable and cost-effective in colon cancer but not for breast cancer. However, this was subject to verification considering other confounding factors during the study.

Study Validity
Did the study address a clear question?
Yes. The title and the aim of this study are clear and aimed to address a critical health issue which is the importance of physical activity (exercise) in improving the quality of life of people living with cancer. The study explored the health and economic benefits of exercise (physical activity) in cancer patients receiving adjuvant chemotherapy. According to the World Health Organization global recommendation, physical activity is a healthy lifestyle variable that is positively linked to reduced incidence of non-communicable diseases including cancer [23]. Other meta-analysis reports showed that exercise mitigates cancer-related fatigue in patients on cytotoxic chemotherapy [2,24]. Cancer-related fatigue can cause decreased QOL, increased number of hospitalizations, and absence from job. However, this study has added advantage over other exercise-oncology research studies because it focused on economic value in addition to the efficacy of the intervention.

Is the Economic Evaluation valid?
Yes and No: I chose to be conservative in the answer based on the strengths, weaknesses, and methodology of this study.

YES:

a) The validity of the economic evaluation of this study could be guaranteed based on its study design (pragmatic randomized-controlled multi-centered progressive study) This design qualifies the research study as a highly high-evidenced based study. The validity of high evidence-based studies is usually higher compared to low evidence-based studies such as cross-sectional, retrospective, or case-controlled studies [25].

b) The economic evaluation is from a societal perspective which is a more valid evaluation compared to the healthcare perspective.

c) In economic evaluation both the costs and outcome measurements are taken into cognizance coupled with a robust comparison of the cost options between the intervention and control groups in both the colon and breast cancers. The various cost options measured include:

- Direct Healthcare Cost (i.e., medication, cancer therapy, radiotherapy, hospital days, day care, consults to medical specialists, and other caregivers, professional home care, and phone consults to other caregivers).
- Indirect Non-health Costs (i.e., unpaid domestic help, paid travel costs, paid own costs).
- Indirect Non-health Costs (i.e., unpaid domestic help and sick leave (in hours)).
- PACT cost
- The outcome (QALY) was conducted using EQSD.
- The time horizon of 36 weeks (9 months) made of 18 weeks intervention period and 18 weeks post-intervention period was objective enough to produce a verifiable result.

These measurements added to the validity of the economic evaluation.

NO:
Some factors can refute the validity of the economic evaluation of this study. These were based on the limitations of the study which include:

- It was not a blinded study and so 50% of the control groups in breast and colon cancers were engaged in high levels of physical activities. This weakness contributed to the underestimation of the intervention.
- The use of diaries instead of administrative data in checking measurements could lead to bias in recording.
- Not all the recruited participants participated due to Non-compliance to research procedures.
- The number of cancers of colon participants was not equal in size matched with their breast cancer counterparts. This could contribute to false positive results of intervention in cancer of the colon category. How were the costs and consequences assessed and compared?

The study had all the relevant resources required to conduct a valid economic evaluation for cost and outcome comparative analysis. The parameters for cost assessment and comparative analysis include:
- Cost data imputed using the Markov Chain Monte Carlo (MCMC) method taking into account <1 year time frame and all cost information (i.e., type of tumour, age, sex, and randomization groups)—no discounting was performed.
- Productivity losses measured using Short Form-Health and Labour Questionnaire (SF-HLQ) imputed in the diaries (measured 4 weekly)
- Data for cancer chemotherapy obtained from medical records.
- Cost prices for resources obtained using the consumer price index of the Netherlands.
- PACT cost derived from the total volume of attendance registrations (measured weekly).
- Patient’s health quality (QALY) was translated into utility value and Dutch EQ5D tariff was used in this conversion. This was encoded in the diary and measured 4 weekly for a total period of 36 weeks. Incremental Cost-Effective Ratio (ICER) was calculated as cost divided by (QALY[I] – QALY[C]) using a bootstrap analysis with 5000 stimulations.

Cost-Effective Plane is produced with bootstrap analysis indicating the efficacy and how expensive intervention is relative to control.

Cost-Effective Acceptability Curve (CEAC) illustrates a decision of uncertainty.

All results were expressed in their appropriate units (examples cost (€); ICER (€/QALY); continuous variables for descriptive analysis (mean/SD and %), EQ5D scores (%), Dominance (%), probability cost-effective (%)). The incremental analyses of cost and outcome of alternatives were performed.

An adequate sensitivity analysis was performed as all areas of uncertainty were considered.

**Results and Discussion**

The results of this study were analyzed into five classical groups namely:
- Baseline characteristics of participants of the PACT study included in the CEA.
- Economic evaluation of the resources and consequences of the study population based on a randomized pattern of administration of interventions.
- Health-related quality assessment of life of participants during the 36-week time horizon of study and QALYs of cancer type and allocation groups.

- CEAC of PACT compared to usual care using bootstrap stimulation.
- Sensitivity analysis of study participants.

The overall results of this randomized controlled study show that exercise is a cheap and effective intervention that can reduce cancer-related fatigue in colon cancer patients on adjuvant chemotherapy as evidenced by a cost savings of €4321 and a QALY improvement of 0.03 over an 18-week exercise-research oncology study.

On the other hand, this is not a cost-effective intervention for the cancer of the breast population on adjuvant chemotherapy as evidenced by a cost loss of €2912 and a QALY improvement of 0.01. A 0.02 ICER is required for certification of a cost-effective intervention.

Although this is a highly evidence-based study, the validity of the result is contestable based on confounding factors in the study design and methodology:
- A compromised controlled study arm made up of mixed interventions (people who engaged in physical activity and those who were only usual care) – this contributed to under-estimation of intervention.
- The number of cancer colon was not standardized with that of cancer of the breast in the study (87 cancer of breast against 14 cancers of the colon in the intervention arm)- number bias which can lead to a false positive result.
- Poor recording technique (use of diaries) which could lead to selection bias. Recorded results will be highly subjective.
- Basic demographic overview of study participants revealed an age-sex mismatch between the two arms of participants.

**Study Usefulness and its Application to Practice**

This study is a multi-centered randomized study design, hence a highly evidence-based study. Therefore, the result could be useful in planning, policy-making, and decision-making [26].

In addition, the study has given insight that physical activity is a healthy lifestyle variable that has cost-effective supportive benefits in chemotherapy-related fatigue in addition to established preventive benefits in reducing obesity and other Noncommunicable diseases as deduced by WHO recommendations [23,24].

The CEA was conducted from a societal perspective and was not narrowed down to only healthcare costs. This approach is strongly recommended for a valid economic evaluation result that could aid in decision-making, policy-making, and planning in public health practice.

The result of this study could be a useful document for health promotion, health surveillance, and as a health protection tool, especially in palliative care of cancer patients where improved quality of life is an essential criterion for a high survival outcome [11].

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economic-constrained settings in low- and low-middle-income countries stand to benefit more from this study because it is an accessible, achievable, and effective intervention. This intervention could be a strategic leadership approach to reshaping the global economy on health expenditure in cancer management [10]. However, based on the confounding factors encountered in this study, reproducibility will be difficult in developing countries due to a lack of compliance in this target population. Health illiteracy is a huge burden in developing countries and a lot of sensitization through advocacy, awareness campaigns, and education would be needed to pull through. Furthermore, it will be a difficult task to assess all the costs and consequences used during the economic evaluation in this study in low-income countries. The reason is that this study was conducted in a developed country (Netherlands) and it is not all the cost parameters that are transferable to the African setting. For instance, the price index of the Netherlands to be the same with other member countries of the European Union, and neither will it be the same with African countries. However, this is worth doing the study because the concept derived from it will act as a useful tool in the prudent allocation of resources for effective clinical management of people living with cancer. This will require collaborations with the principal investigators and leveraging their wealth of experience in economic evaluations in public health practice.

Conclusion
The critical appraisal of this randomized controlled study has addressed a fundamental issue about the importance of physical activity (such as exercise) in improving the QoL of people living with cancer. The economic evaluation of this study was more valid from the societal perspective. The cost and outcome measures were relatively better in the exercise intervention group compared to the control group. Exercise is a cost-effective (reduced cost) intervention and improves the QoL of cancer patients compared to cancer of breast counterparts. Although some confounding factors in the study design and methodology could challenge the validity of the results, physical activity is a recommendable palliative care intervention in cancer management. Exercise can increase cancer patients’ ICER and QALY, improving their life expectancy.

Abbreviations
CASP, critical appraisal skill program; CSO, civil society organization; ICER, DALY, disability-adjusted life years, Incremental cost-effective ratio; NGO, non-governmental organization; PLWC, people living with cancer; QALY, quality-adjusted life years; QALY, quality-adjusted life years; QOL, quality of life; WHO, World Health Organization;

Declaration of Patient Consent
This was not necessary because it is a critical appraisal of an already conducted research study.

Conflicts of interest
There are no conflicts of interest.

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Nil of note.

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