Economic Evaluation of Cervical Cancer Screening: Are Costs Outside Health Care Included?

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This thesis originated in challenges I faced while studying the economic evaluation of health care. The authors of different textbooks told me different stories about costs outside of health care, and because of this I felt a personal need to put all of the different stories together in order to make one story about non-health-care costs. In particular, I took special care to present confusing methodological issues in a clear manner. Hopefully these efforts will also be of use to the reader.

Above all, this thesis would never have been possible without persistent support from my supervisor Ivar Sønbø Kristiansen. Even when my thoughts were not well organized or presented, he suggested a clear vision and offered helpful comments as if he had read my mind. I would like to express my deepest appreciation to him. I would also like to thank Emily Burger, for her helpful and considerate comments on the methods of the study. At last, I thank my family and Jaehyung, who have always supported me with heart

Minkyung Shin

ABSTRACTS

BACKGROUND: Economic evaluation of health programs primarily captures costs within the health care system, but may also capture costs that fall on patients, relatives, other public sectors or society in general. Guidelines vary with respect to nomenclature and which costs to be included, and systematic reviews of economic evaluation indicate that this variation carries over to published analyses. For certain health interventions, such as cervical cancer screening, exclusion of non-health-care costs can lead to a biased outcome.

OBJECTIVES: The aim of this thesis was first to explore to what extent economic evaluation of cervical cancer screening includes non-health-care costs, and second, to study the methodological disparities shown in estimation and incorporation of non-health-care costs.

METHODS: A systematic search of three electronic databases was conducted to identify relevant publications on economic evaluation of cervical cancer screening. Included articles were reviewed to explore 1) whether non-health-care costs were included, 2) which cost components were included, and 3) how they were incorporated into estimation. For those studies including non-health-care costs, the magnitude of non-health-care costs compared to health care costs were estimated.

RESULTS: In total, 82 articles were included in the study, and 40 of which included non-health-care costs which were slightly less than half of studies. The studies varied considerably in identification, measurement and valuation of non-health-care costs. Several studies made un unclear distinction between time and productivity costs, and showed low adherence to the recommendations of guidelines. The included studies showed variations in terms of the magnitude of non-health-care costs compared to the health care costs. Travel and time costs account for 0.04-76% of the total screening costs, and 5-48% of cancer treatment costs.

CONCLUSION: Non-health-care costs involved in screening for cervical cancer are not insignificant. Therefore, studies which did not consider such costs may have limited implications for social resource allocation. Consequently, this study calls for more clear and explicit definitions of non-health-care costs, more consistent guidelines and better reporting of economic evaluation.

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1 INTRODUCTION

Resources consumed in one place cannot be used for other use, so we are often faced a prioritization dilemma. In health care, the pressure on health spending becomes greater than ever. As recent series of economic turmoil more strains health care budgets while health care demand becomes more diversified as ageing society emerges, the amount of resources is too limited to meet the growing demands in health care. In this context, the decision makers should make a choice among competing health care programs (health interventions) so as to maximize effectiveness while requiring less cost.

As a tool for the appraisal of health program, economic evaluations support their choices by providing information to facilitate valid comparison of alternative use of limited resources. Drummond defines the economic evaluation as 'the comparative analysis of alternative courses of action in terms of both their costs and consequences'[1]. Since economic evaluation was first introduced in 1960s, its publication has been growing along with its popularity [2, 3]. Economic evaluation is widely applied in health policy in assessment of health programs and its use in decision making also increases [4]. Conducting economic evaluation requires researchers to identify, measure and compare all of the significant positive and negative costs and consequences of alternative programs of addressing a given problem [5].

In estimation of cost effectiveness of each comparator, all relevant costs and effects needs to be estimated in a comprehensive and valid way [6]. Health care programs not only require use of resources within the health care system ("health care costs"), but also entail use of patients' and relatives' 'time' and lost 'productivity' ("non-health-care costs"). Which costs should be included is one of key analytic decisions to be made. In particular, omission of costs outside of health care system has more influence on certain health intervention, for example, cervical cancer screening. Cervical screening program have significant implication that it requires regular day off for young women who are actively participating in labor market. Therefore, time and productivity costs associated with absenteeism and cost savings in added life years as a result of preventive effect of screening are known to be significant compared to other health interventions. In that, failure to fully capture the relevant costs distorts the outcome of studies and lead to suboptimal decisions.

Nevertheless, the disagreement between guidelines of economic evaluation in the way of determining relevant costs and its measurement has led to confusion. A recent systemic review of economic evaluation guidelines finds that there are significant methodological disparities in dealing with costs outside of health care sector [7]. Some of these disparities are attributed to the misunderstanding of the principles of economic evaluation but different opinions on methodological choices are also one of causes [8] . Lack of consensus between guidelines gives more choices for decision analysts which subsequently reduce comparability and transferability of economic evaluations [1]. Misleading study findings could subsequently limit the use of economic evaluation in policy decision making and have opportunity costs because of suboptimal decisions. [9]. This is because it is unclear whether the difference in research outcomes is attributable to the methods being used or actual variation in cost-effectiveness. In order to figure out the question, more information needs to be required, but additional economic evaluation is costly. Therefore, researchers need to ensure that studies are directed properly and their methodological choice on costing is as accurate and valid as possible. Identifying and measuring relevant costs needs careful consideration and transparency in a process.

This study aims to explore to what extent costs outside of health care are considered in economic evaluation studies of cervical cancer screening and how they are incorporated into the economic evaluations. More detailed study question and methods would be further described in the latter part of the study. Basically, this study is composed of five chapters. The introduction part deals with the basic concepts of economic evaluations and theoretical approaches in defining, and estimating non-health-care costs within existing literatures and guidelines. In Chapter 2, the study methods used to analyze current practice of costing non-health-care costs would be described using a flow chart of a systematic review. Chapter 3 presents the results of the studies, to what extent the non-health-care costs were considered, and how they were identified and measured in economic evaluation. In Chapter 4, the discussion related to the results of study would be made. Chapter 5 finally suggests the conclusion of the analysis.

1.1 Cervical Cancer Screening

Cervical cancer is one of the most common causes of cancer deaths in developed countries and its burden to both society and patients is also substantial [10]. Annually, 530,000 women are diagnosed of cervical cancer worldwide, and 270,000 women are died from it, which is around 7% of all women cancer deaths [11]. The incidence of cervical cancer peaks at the age of 30-40 [12]. Cervical cancer is progressed through 4 stages (I-IV) and its treatment and prognosis is dependent on the stage. In a case where cytological abnormalities are suspected in the test result, colposcopy and biopsy are performed additionally for confirmation. Women who are diagnosed of early stage cancer are treated with surgery. Radiotherapy is used for women in more developed stage of cervical cancer. When cervical cancer is progressed to III and IV, survival rate decreases to 39% and 15% respectively.

Conventional Cytology and HPV test

However, cervical cancer is preventable through detection of cancer precursors [13, 14]. Since 1960s, the Papanicolaou (Pap) test has played an important role in detecting premalignant cytological lesion and resulted in significant drop in incidence and mortality of cervical cancer [15]. For countries where health resources and number of trained personnel are limited, visual inspection with acetic acid (VIA) can be an alternative screening method [16] in that the VIA is relatively easy and simple method using 3-5% of acetic acid for observing dysplastic epithelium with unaided eye [17].

In the 1980s, infection of certain human papillomavirus (HPV) types was identified as the cause of cervical cancer [8, 9]. HPV is sexually transmitted infection, and 50-80% of women who are sexually active are exposed to HPV once in a life time. Persistent infection of carcinogenic HPV type is a necessary condition of high grade cervical intraepithelial neoplasia (CIN) which can progress to invasive cervical cancer. In particular, high-risk HPV types 16 and 18 have been identified as being present in approximately 70% of cervical cancers [18].

HPV DNA tests have much higher sensitivity compared to the Pap test, which allows detection of more precursors of cervical cancer in early stage [19]. Because the early detection of precancerous lesions reduces frequency of screening, the HPV DNA test is expected to reduce the additional visits for testing as well as costs of cancer treatment. HPV DNA is

usually detected via cervical and vaginal samples, and these samples can be collected by women themselves. Use of self-collected vaginal specimens can additionally reduce the costs of pelvic evaluation with increasing women's compliance to the screening [20, 21].

Economic evaluation of cervical cancer screening

During the last 40 years, a range of cost effectiveness analyses of cervical screening have been published; this research trend is followed by developing countries where introduction of national screening program is concerned. In the 1980s it was detected that cervical cancer is caused by the HPV, which led to growing interests in HPV test and HPV vaccination. Since then, a number of economic evaluations have been published to estimate the feasibility of introducing HPV DNA testing to replace or supplement current Pap test. Because these new technologies bring additional costs, the number of cost effectiveness studies to compare HPV DNA test and existing cytology is increased. The main issue of recent economic evaluations is whether cost savings in high sensitivity of HPV DNA test is able to offset the added cost. After HPV vaccination was found to be effective to prevent HPV infection primarily, combination of HPV vaccine and regular screening has been also studied.

1.2 Types of Economic Evaluations

In a broad term, economic evaluation includes Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), Cost-Benefit Analysis (CBA), Cost-Minimization Analysis (CMA), Cost Consequence Analysis (CCA), and Cost of Illness Study (COI). But, full economic evaluation requires 1) comparison of alternative health programs and 2) costs and consequences of each health program [1]. In this sense, the study types which fulfill full requirements of economic evaluation are Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA) and Cost-Benefit Analysis (CBA).

Table 1. Unit of cost and effect of economic evaluation

	Unit of Cost	**Unit of Effect**
Cost-Effectiveness Analysis (CEA)	Monetary term	A natural unit (life-years gained, symptom free day, case detected, etc.)
Cost-Utility Analysis (CUA)	Monetary term	Quality Adjusted Life Years (QALY)
Cost-Benefit Analysis (CBA)	Monetary term	Monetary value

CBA is more distinctive form of study in that the valuation of all outcomes of CBA, both costs and consequences, are measured in monetary terms. On the contrary, CUA and CEA are considered more similar types of study [22, 23] since those two are nearly common in dealing with costs and effects and comparing health programs in terms of their cost per unit of effect [1]. The only difference between them is a unit of measuring effects. In measurement of effects of health program, CEA uses natural units such as saved life years, number of symptom free days or number of incidents averted. These units are program specific and it accords with the aim of CEA that makes best choice to maximize health benefits. The consequence of CUA is presented in terms of preference based measures of health, named Quality Adjustment Life Years (QALY). QALY has advantages over natural units in that it combines time and its utility into a single unit which enables comparison between health programs with different outcomes available. In consideration of the similarities between CEA and CUA, some authors uses the term ‘CEA with QALYs’ and include CUA under the CEA

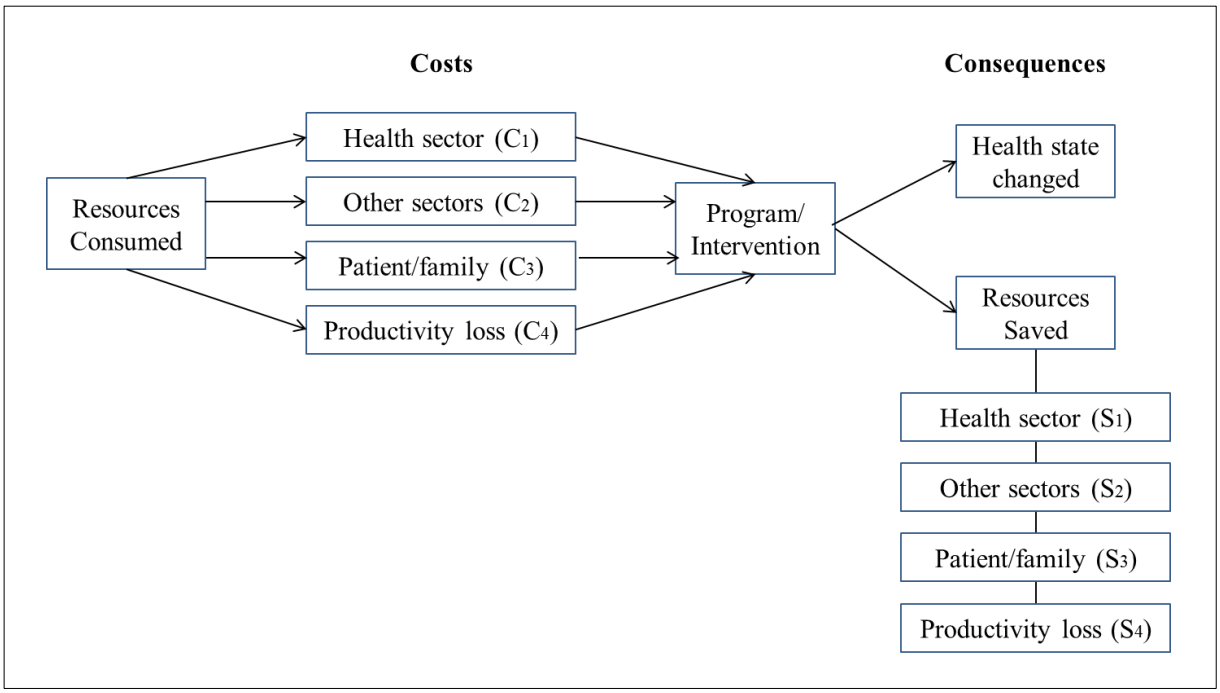
[23, 24]. However, this study maintains the use of the term CUA for further controversy over productivity costs and its reflection on QALYs.

On the other hand, Cost Minimization Analysis (CMA) and Cost of Illness (COI) study are partial economic evaluations since their interests focus more on costs. The application of CMA is limited to the case when the outcomes of alternative health programs are similar so that only cost difference is a subject of interest. COI is used to study economic burden of disease, and thus only involves costs of disease. Cost Consequence Study (CCS) presents its outcome in disaggregated form instead of combining different components of competing health programs in order that users make judgment based on trade- offs between different types of costs and effects.

1.2.1 CEA

Cost Effectiveness Analysis (CEA) presents its results as an incremental ratio of additional costs to additional effects for one health program compared with another [25]. For choice of competing programs, costs effectiveness ratio (C/E ratio) of each program is ranked from the lowest to the highest. From the program with the lowest C/E ratio is selected until all resources are spent or society does not have willingness to pay for the program anymore. Since C/E ratio does not function itself as a standard to make a choice of appropriate program, a 'threshold C/E ratio' is used to assess whether a program is worth being conducted [1]. The threshold is "upper level for accepted cost effectiveness" [26] and mostly reflects societal willingness to pay. On C/E ratio, costs are placed on the numerator while effects are on the denominator. The table below is extracted from the estimation of Drummond [1]. This table identifies costs and savings based on the place where they aroused from.

Figure 1. Costs and consequences of economic evaluation



Costs (C) or savings (S) for the intervention occurred in

C1/S1: in organizing and operating the health intervention

C2/S2: voluntary or public agencies

C3/S3: out-of-pocket money, traveling expenses, expenditures in home, time for seeking and receiving treatment

C4/S4: productivity changes for the treatment, morbidity and mortality

In CEA, possible formulations of economic evaluation can be expressed in two ways as below:

$$(C1 - S1)/E$$

$$[(C1+C2+C3+C4)-(S1+S2+S3+S4)]/E$$

The numerator is the sum of resources consumed and saved. The resources saved are the costs not spent in the alternative program. The denominator is the effects of health care intervention. The formal formula is only concerned with costs and effectiveness in health care sector while the latter is from the societal perspective which takes into account resources consumed in other sectors as well as costs paid by patients themselves.

In CEA, all kinds of non-health-care costs including travel cost, time cost and productivity costs are recommended to be included in the numerator of the C/E ratio.

1.2.2 CUA

Health care intervention is an attempt to extend life both in quality and quantity dimensions throughout "improving the health state and/or prolong the duration of life"[26]. In Cost-Utility Analysis (CUA), effect of health intervention is expressed in terms of QALY. The QALY is a single unit of measurement incorporating both quality and quantity of health changes as a result of health program. Use of QALY has been growing since its first use in 1970s [22]. Its use is to help government organizations to make decision so as to maximize the value of health expenditures in terms of health outcomes [27].

As QALY collapse different types of health effects into a single preference based measure, it enables to analyze health program with more than one kind of health effects and to compare it with other health programs with different types of health effects [24]. QALY is calculated by multiplying a length of life with a quality adjustment weight which is scaled from 0 (dead) to 1 (perfect health). A year of perfect health is, therefore, assumed to be 1 QALY. Death is considered to be 0 QALY.

$$QALY = T * Q$$

T: time (years) Q: quality of life

Quality adjustment weight is based on individual's preference or relative desirability of the health state in question. The measurement of individual preferences is acquired through preference measurement tools such as Time Trade- off (TTO), Visual Analogue Scale (VAS), or Standard Gamble (SG). Self-rated questionnaires, called "health state descriptive systems" or "a generic health state preference instrument" (ex. EQ-5D, 15D or SF 36) assign preference scores to different health states. These measurements are composed of multiple dimensions of health states and levels of improvements so that it measures a multi-attribute utility that reflects individual preference both within and across health dimensions [28].

Formulations for incorporating costs and consequences to CUA are as below:

$$(C1 - S1)/U$$

$$[(C1+C2+C3+C4)-(S1+S2+S3+S4)]/U$$

Costs (C) or savings (S) are same as CEA

U: QALYs

Incorporation of C4 (production loss) in CUA is a controversial issue in that some argues that QALY captures production loss to individuals when it is measured. This issue is more dealt with details in the later part.

Decision making process of CUA is as same as that of CEA. Outcome of CUA is presented as an incremental ratio of additional costs to additional QALY. Program with the least cost per QALY is selected in order so as to maximize the utility until the given budget is exhausted.

1.2.3 CBA

The most distinctive feature of CBA compared to other economic evaluation is that all effects of health intervention are valued in monetary terms. A limitation of CEA and CUA is that they only compares cost effectiveness ratio so that they cannot tell whether a health program is worthwhile of being conducted. However in CBA, the health costs and outcomes of intervention are commensurate so that it can be applied to a wide range of scope. As a result, it enables comparison across programs in other sectors of the economy such as transport and environment [1].

CBA identifies whether the program's benefits are greater than its costs. Therefore, the costs and benefits of competing interventions should be examined [29]. A positive net social benefit of CBA resulting from direct comparison of benefit and cost indicates that the program is worthwhile of being conducted. When several health interventions are considered, the combination which maximizes benefits is chosen. Within a fixed budget, decision rule of CBA allows resources to be allocated in a program where exceeding benefit is the highest.

Benefits from a health intervention are gained improvement in health *per se* and increased productive output [1]. However, undesirability and criticism against monetary valuation of such benefits have tended to limit the use of CBA [5]. As a proxy to value the benefits of health intervention, human capital approach (HC) was introduced by assigning wage rate. However, this approach has been criticized due to its lack of theoretical ground and

discrimination against people outside of labor market. In this respect, willingness to pay approach (contingent valuation) is more welcomed by economists who favor value judgment based on individual's preferences [30]. Individual preferences can be assessed by survey or inferred from decisions actually made that involve tradeoffs between health and money [23]. Respondents are asked to answer hypothetical scenarios about the health intervention and present their maximum value that they are willing to pay for the intervention. In practice, there is a limitation that respondents are strongly influenced by the format and wording of hypothetical questions [26] .

1.3 Types of Costs

Health program requires resources and these resources not only come from health care sector, but also from other part of society such as social services, patients and unpaid informal care givers. When comparing health care programs requiring resources from different sectors, estimating only resources spent in health care sector is not comprehensive. Identification and classification of relevant costs is an important process in conducting analyses.

In terms of cost classification, a dichotomous way of classifying the costs into 'direct' and 'indirect' costs has been widely used [23]. However, reluctance to use such classification was aroused due to its inconsistent use and lack of standard definition. Direct cost refers to the consumed resources in provision of health care program including health services, pharmaceuticals, supplies, and tests [23, 31]. These costs are mainly occurred in health care sector, but the costs aroused in non-health-care sectors and patients in seeking and obtaining the intervention have been also included in the direct costs. On the other hand, costs aroused from patients and informal care givers, outside of the health care sector, are termed indirect costs. The definition of 'indirect' cost is much more inconsistent across literatures. Production loss related to illness or death or time loss of patients and informal care givers mainly related to their working time has been involved in indirect costs [1, 23]. The table below shows various definitions of the 'direct' and 'indirect' costs that each author defined based on existing literatures and their own interpretation.

Table 2. Definition of direct and indirect cost

Source	Direct Cost	Indirect Cost
Luce and Elixhauser (1990) [32]	Actual changes in resource use attributable to the medical technologies under scrutiny	The economic value of any consequence that cannot be counted as a direct cost.
Weinstein (1990)[33]	Costs and savings to the health care delivery system, personal costs to individuals directly related to the implementation of a program, and non-health economic costs and savings	Changes in the productive use of time by patients and others
Gold et al. (1996)	Changes in resources use attributable to the intervention or treatment regimen	Productivity gains or losses related to illness or death
Drummond et al. (2005)	Resources in the health care sector, patient's out of pocket expenses, resources from other statutory agencies and voluntary bodies	Time loss of patients and informal care givers mainly/ Production gains or losses.
Elliott and Payne (2005) [34]	Costs incurred by the health services classified into medical costs (staff time, medical supplies, hotel cost, capital costs, overhead costs) and non-medical costs (patient's out of pocket money and costs occurred in other part of societies)	Costs incurred by reduced productivity of a patient and their family, resulting from illness, death, or treatment.
Olsen (2009) [26]	Costs incurred in health care	Costs incurred in other sectors, most notably the production consequences for the rest of economy

Due to the lack of consensus on a definition of 'direct' and 'indirect' cost, since mid-1990s there has been a tendency towards more detailed sub-classification to avoid confusion aroused from dichotomous cost classification [1, 23]. In order to avoid confusion, Gold and co-workers (1996) re-defines 'direct cost' in a broader term including certain time and productivity cost and renamed other costs which have been termed indirect costs. Drummond (2005) subdivides costs into 4 categories depending on the area where the costs were incurred: health care sector, other sector, family/patient and productivity losses [1]. Johnston and co-workers (1999) also review existing cost classifications and divides costs into 4 categories: direct health care costs, direct non-health-care costs, indirect health care costs (future costs), indirect non-health-care costs throughout a review of existing cost classifications [25].

Table 3. Sub-classification of costs by different authors

Source	Sub-classification of costs
Gold et al. (1996)	- Direct health care costs: the costs of tests, drugs, supplies, health care personnel, and medical facilities - Direct non-health-care costs: informal care giver time cost, child care costs - Patient time costs: travel and waiting time - Productivity costs (morbidity costs, mortality costs): costs associated with lost or impaired ability to work or to engage in leisure
Johnston et al. (1999)[25]	- Direct health care costs: hospital care, drug use, etc. - Direct non-health-care costs: patient travel costs, etc. - Indirect health care costs: costs of health care consumption during added life years - Indirect non-health-care costs: The value of production loss due to illness or treatment; the opportunity cost of time spent
Drummond et al. (2005)	- Health care sector : costs in operating the health intervention - Other sector : voluntary or public agencies - Family/patient : out-of-pocket money, traveling expenses, expenditures in home, time for seeking and receiving treatment - Productivity changes for the treatment, morbidity and mortality

Table 3 shows sub-classification of costs by different authors. If 'direct' and 'indirect' term is ignored, costs can be classified into two categories: health care costs and non-health-care costs. Health care costs involve all costs for medical services and future health care costs in added life years resulting from a health intervention. Resources consumed to produce health services, pharmaceuticals, equipment and facilities, and tests in providing hospital care and community care are referred to health care costs [31]. Thus, the quantities of bed days, overheads, general practitioner or nurse visits, use of ambulance needs to be counted for estimating costs. The costs for treating side effects and additional health care cost occurred during extended life years as a consequence of health intervention is also included in this category as well.

Gold and co-workers (1995) contents that the 'non-health-care costs' is a term including transportation costs consumed in commuting to clinics or hospitals, as well as child care costs if parents need to be away from their children for receiving treatment. Non-health-care costs are mostly occurred in other sectors such as social services, patients and family members. Importantly, the costs paid by other entities of society such as voluntary bodies and patients themselves as a form of out of pocket money in relation to health care services are not

included in non-health-care cost category. Among them, this study focuses mainly on 3 types of non-health-care costs which have important implications in screening: 1) travel costs, 2) time costs, and 3) productivity costs.

1.3.1 Travel Costs

Travel costs are the traveling expenses for commuting health care facilities such as clinics or hospitals. Patients or their company use public transportation, privately owned car or even ambulance to commute health care facilities. The amount of money spent in commuting from and to the site of care is measured and valued in estimation of travel costs.

1.3.2 Time Costs

Because time is uncompensated resources that the patients and unpaid informal care givers spent to receive health care, it should be counted in the economic evaluation at its opportunity cost [8, 31]. The concept of time cost which is distinguished from productivity costs (indirect costs) has been supported by the US panel ("the Washington panel") [8, 35] . However, the distinction is confusing, in that time and productivity cost is overlapped to some extent [36]. The US panel defines time cost as costs of time lost during illness(morbidity time) or while in treatment [23]. The cost associated with this morbidity time, however, has been captured in productivity costs (indirect costs) when patients or unpaid informal caregivers cannot work due to illness.

For maintaining consistency in use of terms, in this study, time cost mainly refers to the cost associated with time loss in treatment. Following the definition, relevant time costs include the value of time spent for traveling to a clinical site, waiting and receiving care of patients and unpaid informal caregivers. In addition, forgone leisure time during morbidity is also included in the time cost, as it is not captured in productivity costs, but it is the real cost to patients and informal caregivers.

In some instances, omission of time costs can lead to a bias in favor of health care intervention that relied on patients' time costs. For example, if one of competing health interventions requires more patients' time- off than the other, a comparison disregarding this time cost cannot be reliable. In particular, screening program requires regular day off for screening, and thus the costs associated with time loss to individuals are significant compared

to other health intervention. The valuation of time costs is inconsistent across guidelines. In principle, time should be valued as its opportunity cost. Thus, whether individuals use time that they would otherwise have been used for working or leisure, valuation of time cost can be differentiated. When valuing time from working hours, wage rate is an acceptable measure of its opportunity cost. However, some guidelines do not agree that wage rate properly reflects opportunity cost of leisure time. The detailed recommendation concerning valuation of time cost would be discussed later.

1.3.3 Productivity Costs

The improved health of people as a consequence of treatment can contribute to increasing their productivity at work place. On the other hand, illness reduces the productivity of labour. Productivity loss is the real cost aroused from health intervention and not transferred from one to another entity in the society. Thus, relevant 'productivity change' due to the morbidity and pre-mature death needs to be taken account in capturing full impact of health intervention. In some occasion, these costs are called morbidity cost and mortality costs respectively [23].

There is no agreed definition of productivity cost [9]. Gold (1996) defines the productivity cost as "the cost aroused from person's impaired ability to work due to the illness or premature death from that illness"[23]. On the other hand, Hunink (2001) describes it as "the societal value of time spent for sickness or lost due to early death"[31]. In this thesis, productivity cost is defined as costs incurred by lost or impaired ability to work due to illness, disability and pre mature death. Based on the definitions, relevant productivity costs which can be included in the economic evaluation are, 1) productivity change by patients and informal care giver from morbidity, mortality, averted illness, and 2) lost productivity while on the job.

In a competitive market, market price can be a good proxy to value items, but there is no available market price corresponding to improvement in productivity. As an alternative, human capital approach (HC) and friction cost approach (FC) have measured productivity costs. The HC approach has been dominant in valuing time and productivity cost by assigning wage rate to value the benefit of health intervention [37]. Reasoning of human capital approach is that health care program is an investment to the human capital and the benefit of this investment can be measured in terms of the individual's improved productivity. Its additional underlying assumption is that wage rate fully reflects productivity of individuals.

The value of wage rate is measured by referring age, sex, occupation and employment rate of beneficiaries of health program in question.

The use of wage rate, however, has been criticized in terms of distributional and ethical concern. The opponents to the HC claim that the HC favors the people who are young, white and socially active and less considers people who are engaging in unpaid work, unemployed or socially vulnerable. Concerning criticism against use of HC, several techniques were developed to count productivity cost of people outside of labor market. For example, the wage of domestic help is employed to value the productivity cost of people who are mostly engaged in housekeeping [32].

The accuracy of HC has also been questioned by the proponents of the friction cost approach (FC) [38-40]. They contend that real production loss is less than the estimates of HC when the vacancy as a result of morbidity and mortality can be replaced by others or covered by patients themselves when they recover. The proponents of the FC emphasize that the time and cost of recovering the reduced production to the initial level is a matter of estimating production loss. In that respect, the FC seems more accurate instrument to estimate the real time and productivity cost. However, FC requires more efforts to estimate the accurate cost at the employer level. In order to estimate FC, average job vacancy duration which is varied by many factors such as market, employer, and employee is necessary to estimate the real cost to the society [9]. Because of the practical problem and lack of theoretical ground, the use of FC in economic evaluations is still limited.

1.4 Guidelines for Economic Evaluation

The guidelines of economic evaluation have methodological disparities over how to treat time cost and productivity cost [7]. Lack of standardization of guideline limits appropriate comparison between health care programs which is the source of decision making in resource allocation. This section overviews varied recommendations of guidelines concerning non-health-care costs and make comparison between them.

1.4.1 US Panel Approach [8, 23, 35, 41, 42]

The US Public Health Service (PHS) convened a project to develop consensus based recommendations for Cost Effectiveness Analysis in 1993. The Panel on Cost Effectiveness in Health and Medicine, so called US panel, attended to the project aiming at publishing methodological guidelines of CEA which comprised of three articles in a row.

The US panel proposed use of standard set of methodological practices (reference case) and societal perspective in order to keep consistency in the accounting of costs and consequences. The societal perspective is most comprehensive in capturing all costs and benefits regardless of to whom it was accrued [1, 8, 23]. Therefore, all costs on the whole society should be incorporated either in the numerator or the denominator of C/E ratio. US panel listed costs components which should be listed in a numerator of C/E ratio as follows: costs of health care services, costs of patient time expended for the intervention, costs associated with care giving (paid or unpaid), other costs associated with illness, such as travel expenses, economic costs borne by the rest of society (including employers) and friction costs due to absenteeism and costs associated, etc.

With respect to non-health-care costs, the US panel distinguishes time cost from other productivity costs. Based on its identification, if the reason for absence from work place is treatment, the amount of production loss is counted as time cost. They contend that time spent by individuals seeking and receiving intervention can be seen as a component of intervention, and therefore this time loss should be valued in monetary terms and incorporated into the numerator of C/E ratio. However, the US panel recommends that productivity cost needs to be incorporated on the denominator of C/E ratio. The panel contended that monetary value for lost life years should not be included in the numerator due to double counting problem. The panel assumed that the effects of morbidity on productive time and leisure are captured by

QALY. They saw that respondents take into account their lost income and reduced productivity when they are asked to measure the utility of given health state.

This recommendation, however, led to a heated debate [8, 35, 43]. The debate started from the different point of view on whether the productivity loss should be considered costs or effects. In response to the opposition, US panel subdivides the productivity cost to three groups depending on the subject of being influenced: 1) individual 2) employers and 3) society [35]. The US Panel agrees that the productivity cost to the employers and the rest of society needs to be included in the numerator. When people get ill, the employer may have to pay additional money to compensate the production loss by recruiting and training new people. This could be seen as productivity cost accrued to the employers. The reduced productivity and income of individuals also have influence on the amount of income taxes and consumptions of other members of society. This is the social cost that other part of society needs to bear. However, the US panel does not amend their initial recommendation that the productivity cost to the individuals needs to be placed on the numerator. They saw that the income loss to the individual is captured by the denominator.

In terms of measurement of non-health-care costs, the US panel recommends valuing spent resources at its opportunity cost. However, in case of non- market items such as time or productivity, direct measurement of opportunity costs is impossible. Productivity costs for working people, therefore, needs to be valued by gross income corresponding to their age and gender. The opportunity cost of individuals who are mostly engaged in leisure such as retirees also can be measured by average wage of labor in similar age and gender. The panel also state that the friction cost can be used to measure the costs that employers and the rest of society need to bear until the lost productivity is recovered.

1.4.2 Erasmus Group Approach [38, 39, 43-46]

With regards to the guideline of US panel, Brouwer (1997) commented that they could not agree with US panel's method on incorporation of time and productivity costs [43]. Because the group of authors is from Erasmus University in Netherlands, these authors are called 'Erasmus group' in general. They gain attention for proposition of 'friction cost' approach to value productivity loss.

The most distinctive disagreement between the US panel and Erasmus group is on whether the productivity loss to individuals needs to be regarded as costs or effects. Erasmus group defines productivity costs as costs associated with production loss and replacement costs due to illness, disability, and death of productive persons, both paid and unpaid [43]. They have emphasized to include both time costs as well as productivity costs to the numerator of the C/E ratio. They argued that incorporation of productivity costs as health effects in the denominator is not correct and only effects on quality of life that cannot be valued in monetary term needs to be include in denominator as health effects [43]. They claim that the recommendation of US panel does not give an accurate estimation of real productivity cost to the society because productivity cost is not included when measuring health related quality of life. They emphasized that most of questionnaires measuring health related quality of life do not contain income factor and individuals do not consider it as much as the US panel expects.

The Erasmus group also raises the potentials of misrepresentation of individual productivity costs. This is because when respondents are asked to incorporate income effect to valuing the health related quality of life, they are more likely to take into account social benefits as well as private insurance. This tendency could result in more variability of responses across countries having different social security system. However, this is an empirical question and more researches on the respondents' consideration when measuring preference of health state needs to be addressed [6].

Erasmus group sees that time and productivity loss due to treatment, morbidity and mortality can be measured in terms of monetary terms. The 'friction cost' method proposed by Erasmus group estimate production loss at the company level. They assume that real productivity loss depends on the friction time that the work loss due to illness, morbidity and mortality becomes recovered to the original level. The friction cost method needs more information on the average duration of absenteeism and its costing method to determine productivity loss. The length of absence is associated with the employee, the employer, or the market and therefore there needs more detailed data to estimate the average length of job vacancy varied by age, sex, occupation and etc. The value of lost productivity is on the other hand determined by internal labor reserve and productivity of people who make up the lost work; their valuation needs more researches.

Concerning changes in individual ability of leisure due to illness and intervention, Erasmus group contended that it can be captured in QALY as an effect and did not give more detailed explanation about the value of lost leisure.

1.4.3 Norwegian Guideline [47]

Norwegian Medicines Agency (NOMA) is an authority to assess whether drug expenses for treatment should be reimbursed in the National Insurance scheme. A recently revised guideline of NOMA in 2012 presents some updated recommendations and requirements of economic evaluations when pharmaceutical companies submitting reimbursement applications. The Norwegian guideline prefers CUA from a societal perspective. In terms of costing, the guideline recommends including all source of resources spent in the provision of the health intervention in question. Identification and valuation of these costs needs to be performed a head of comparison between alternative health interventions. The market price should be used to value unit cost of resources consumed, but VAT is excluded since it is transfer payment from societal perspective.

With regard to time cost, the Norwegian guideline contends that if one of health interventions being compared particularly requires more time, this cost should be included and reported both with and without inclusion of time costs into estimation. The Norwegian guideline specifies two methods in measuring time costs which is varied by the source of time. If time is extracted from working hours, average hourly wage should be attached to value the lost time. The hourly wage includes income tax and employer's shares of social payments. If time use is extracted from leisure time, the average hourly wage after tax is used to value its time cost. This cost is applied to all people regardless of age or employment situation.

The Norwegian guideline acknowledges that methods of dealing with productivity effect are controversial so that it leaves a decision of inclusion to researchers. Inclusion of productivity gains and loss is, therefore, not mandatory; individual researchers can choose any of estimation method as long as they provide with reasonable justification for their choice. Based on the guideline, the time horizon of analyses should be long enough to capture all differences between interventions. Net deadweight cost due to tax funding of treatment should also be excluded. Except these costs, all costs related to the intervention medicine needs to be included in the analysis.

1.4.4 Other Guidelines

WHO guideline [48]

WHO guideline has tendency to capture costs and consequences of health intervention in the social welfare framework. The WHO acknowledges that time and productivity loss should be accounted for the economic evaluation, in particular "where they are likely to be substantial", but it suggests reporting them separately from the main outcomes.

In valuation of time and productivity, the guideline recommends that time cost should be valued in terms of the change in welfare. Thus, ideally, the time should be weighted according to the individual's impact on the production of society and the subjects of consumption externalities. Concerning productivity loss, the WHO guideline basically agrees that productivity costs or gains influencing the consumption of goods and services should be included as well, but it acknowledges that wage rate does not fully reflect changes in productivity. Furthermore, the WHO does not agree with the assumption of the US panel that utility weights for QALY capture the productivity loss to individuals.

UK guideline [49]

In 2013, the UK National Institute for Health and Care Excellence (NICE) published the newest version of guideline for health technology appraisal. The guidance is provided to the National Health Services (NHS) England for publicly funded health program. The NHS guideline presents a reference case that researchers refer to and it contains recommendation that only costs relevant to the NHS and Personal Social Services (PSS) needs to be included.

Concerning time and productivity cost, the informal care giver's time cost should be included but presented separately. The NHS acknowledges the different valuation methods and gives a choice to individual researchers. Individual researchers instead are required to justify their choices and perform sensitivity analysis due to its uncertainty. With regards to the productivity cost, the guideline recommends excluding it since this cost is not relevant from the perspective of NHS and PSS.

1.5 Aims of Study

Against the background of variation in guidelines with regards to the inclusion of non-health-care costs, this study aims to explore to what extent non-health-care costs are considered in economic evaluations. This study does not answer the normative question on how relevant costs should be included and estimated. Instead, it dedicates more on the current practice of individual researchers; how much researchers have varied interpretations about the non-health-care cost in terms of identification, estimation and incorporation will be focused on.

The study, therefore, mainly deals with questions below:

- Whether non-health-care costs are included,
- What types of non-health-care costs are included
- If it does, how they are measured.

A systemic review of cervical screening studies could be a good case study to answer these questions. Identification of non-health-care costs in cervical cancer screening studies is expected 1) to understand the current practices of costing non-health-care resources consumed, 2) to find better way of capturing full range of costs associated with intervention, and 3) to give insight to improve the consistency of the methodology used in economic evaluation analyses.

2 METHODS

A systemic literature search of Pubmed, Embase and Cochrane library up to 19 February 2014 was conducted to identify economic evaluations of cervical cancer screening. The following terms were used for searching: “cervix”, “screening” or “test”, “cost” or “cost effective” or “cost utility”, “economic evaluation” or “analysis” and “cancer”. There were neither language nor publication types restrictions in primary searching.

The full search strategy for each data base is as below:

- Pubmed, N=561
  (cervi*[title]) AND (screening [All Fields] OR test [All Fields]) AND (cost[title/abstract] OR costs[title/abstract] OR cost-effective*[title/abstract] OR cost-utility*[title/abstract]) AND (analysis[All Fields] OR economic evaluation[All Fields]) AND cancer

- Embase, N=646
  (cervi*).ti. and (screen* or test).af. and (cost-effective* or cost-utility*).af. and (analysis or economic evaluation).af. and cancer.af.

- Cochrane library, N=79
  (cervi*) AND (screening OR test) AND (cost OR costs OR cost-effective*OR cost-utility*) AND (cancer) AND (analysis OR “economic evaluation*”)

Study Selection

A primary interest of the study is a practice of costing non-health-care resources consumed. Thus, full economic evaluations of cervical cancer screening were selected for a case. Articles, which did not satisfy the requirements of full economic evaluations or its main intervention is not a cervical screening, were excluded. This means that cost analyses and cost-of-illness analyses were excluded. Articles providing too limited information of costs that it is not available to study what kinds of costs were included were also excluded.

Inclusion Criteria

In order to be included in the systematic review, the article should have the following attributes:

- Original research paper (reviews, conference abstracts were excluded)

- Full economic evaluations (cost analysis or article with no comparison were excluded)
- Articles in English
- Articles with available full texts on the internet
- A study compares both costs and effects of at least two health interventions (including no-screening intervention)
- At least one of interventions is ‘cervical screening’

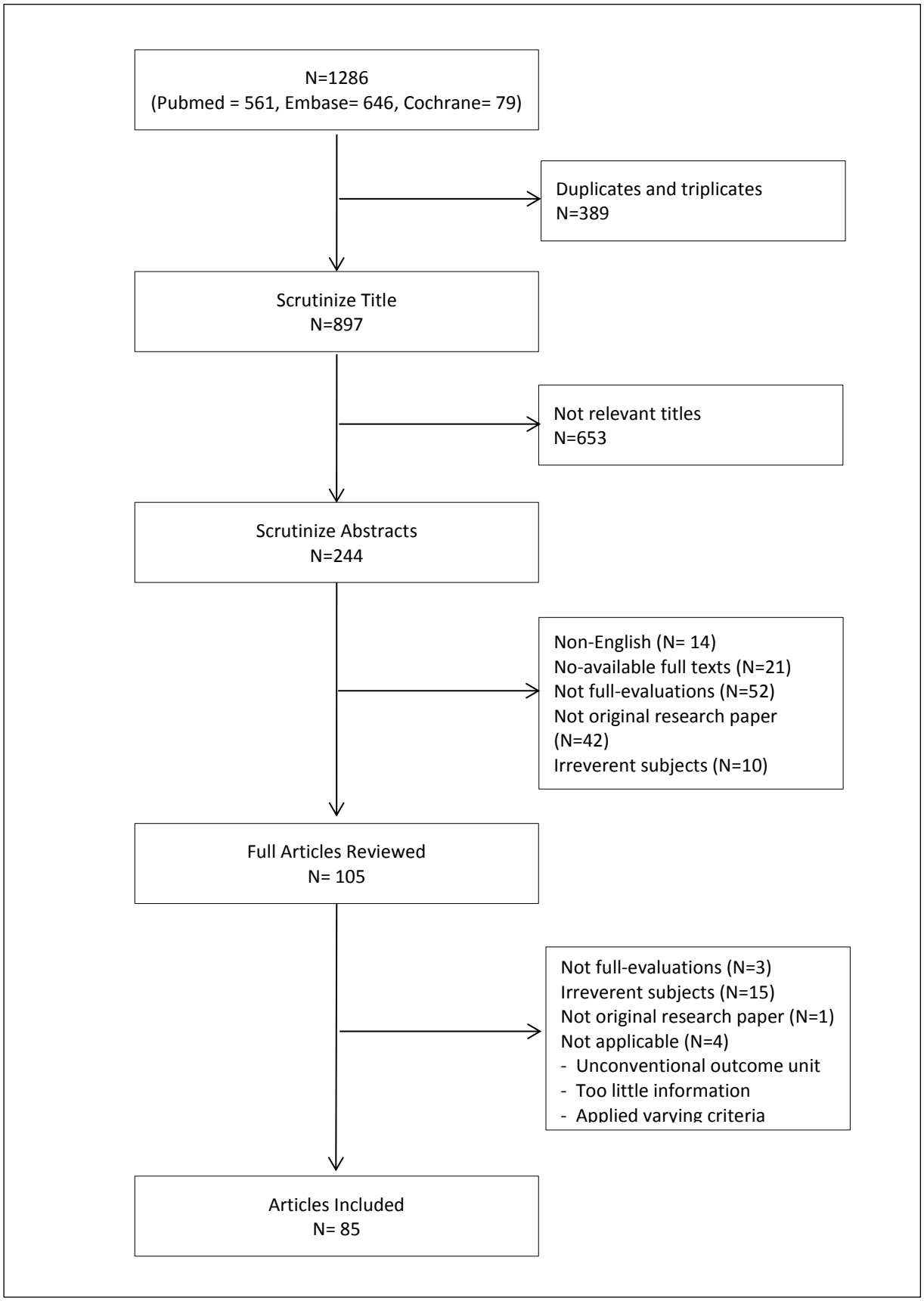
Exclusion Criteria

Articles contain one of those attributes were excluded from the analysis

- Articles which is not available to define which costs were included
- Articles which do not present costs and effects in a conventional unit (ex. Cost saving per life year lost, DALY lost)

Initially, 1286 potentially relevant articles were identified from 3 electronic databases (searched 12.Feb.2014). Excluding duplicates and triplicates (N=389) resulted in 897 unique publications. Throughout screening the titles of the articles, 653 were excluded because the title indicated that the publication was not relevant. Of the 244 articles reviewed in abstracts, 139 publications were excluded based on predefined inclusion and exclusion criteria. For the remaining 105 papers, the full paper was scrutinized, and 23 were excluded based on the same inclusion/exclusion criteria above. Among those excluded, 15 articles were not relevant to the subject of study; three articles were excluded due to the language limitation, and one article was not an original research paper. Four articles were excluded for the following reason: an article presented its outcome in cost saving per life year lost [50], provided too little or inaccessible information to identify what kinds of costs were included [51, 52] and applied varying cost inclusion criteria to each intervention [53]. As a result of screening, total 82 articles were finally selected.

Figure 2. Study selection flow diagram for economic evaluations of cervical cancer screening



Data extraction

To search the degree of concerning non-health-care resources in the economic evaluation, following data were extracted from all original papers.

- Lead author
- Year of publication
- Source of publication
- Types of study
- Main interventions (defined by a study question that authors mainly addressed)
- Country of the study
- Perspective of the study
- Cost classification
- Cost inclusion
- Discounting
- Currency, base year

The data below were additionally extracted only from the articles (n=49) reported non-health-care costs.

- Types of non-health-care costs included
- Method of estimation
- The proportion of non-health-care costs
- Incremental Cost Effectiveness Ratio
- Sensitivity Analysis

Supplementary readings were referred when information is not available in the main article. Extracted data were processed to reach a consistent data base for the review.

3 RESULTS

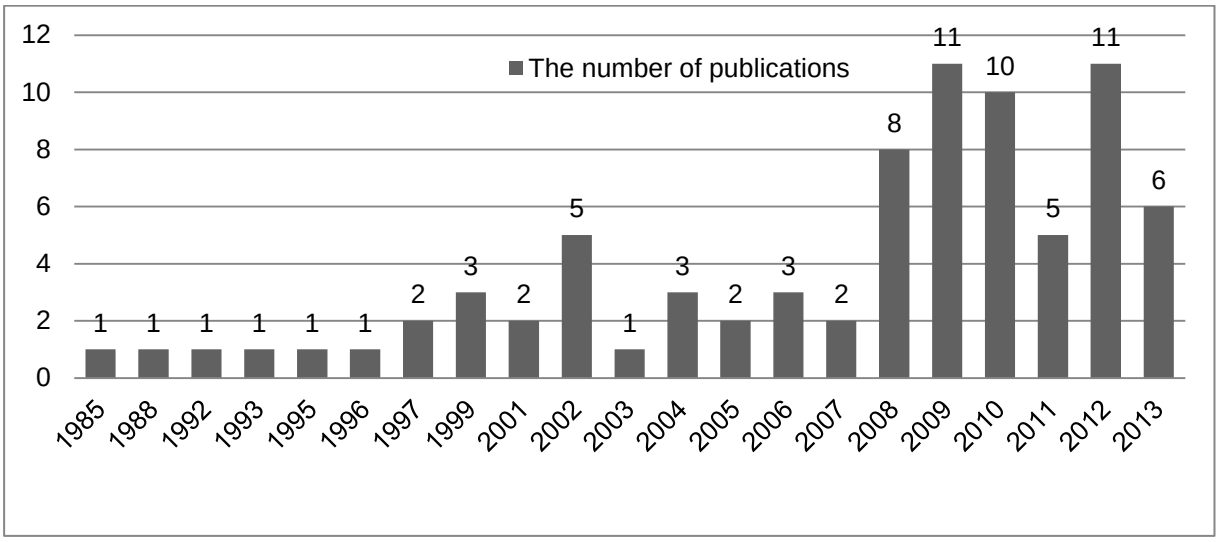
The systematic research yielded 82 economic evaluations of cervical cancer screening from 42 different journals. Characteristics of included articles are described first, and study results concerning non-health-care costs would be provided in the latter part.

3.1 Characteristics of the Studies

Year of publication

The earliest economic evaluation study available on the Internet was one published in 1985 [54]. Even if there were some articles published in 1972, these articles were not available on the Internet, and therefore were excluded from the review. As shown in Figure 3, there was a time trend of the number of studies as well as the subjects of the studies.

Figure 3. The included studies according to publication year



Only few studies were published in the mid-1980s to 1990s. The earlier publications during this period were mostly about the effectiveness of Pap screening in a country where national cervical cancer screening was implemented. Most of these studies compared pap screening with no screening or changed in intervals of screening in order to find the most cost effective screening strategy. Form the late 1990s to early 2000s, the number of publications slightly increased and the subjects of screening studies became varied; different types of screening including Human Papilloma Virus (HPV) test, Liquid Based Cytology (LBC) and visual

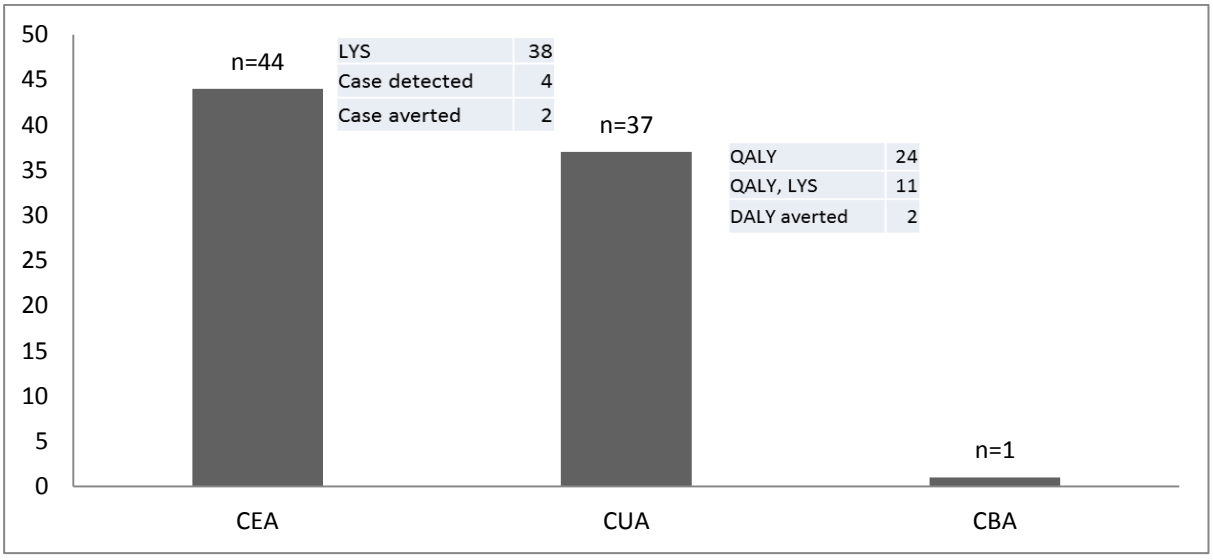
inspection with acetic acid (VIA) were examined. Since the late 2000s, the number of articles has increased again. These articles mainly focused on the cost effectiveness of various types of screening tests in combination with HPV.

Types of economic evaluation

When outcomes were presented in life years saved (LYS) or numbers of detected cases, the studies were classified as cost effectiveness analysis (CEA). Studies, which presented one of its outcomes in QALYs or DALYs, were classified as cost utility analysis (CUA).

The total number of CEA was 44, among which 38 articles reported its effects in terms of LYS, and the rest of six articles used numbers of case detected/averted to express its effects. The number of CUA was 37, among which 24 articles presented its effects in terms of QALY, while 11 articles presented its effects both in LYS and QALY. Two articles of the same lead author used DALY averted as the unit of benefit. There was only one cost benefit analysis (CBA) which presented its outcome in terms of a cost benefit ratio.

Figure 4. Types of economic evaluation

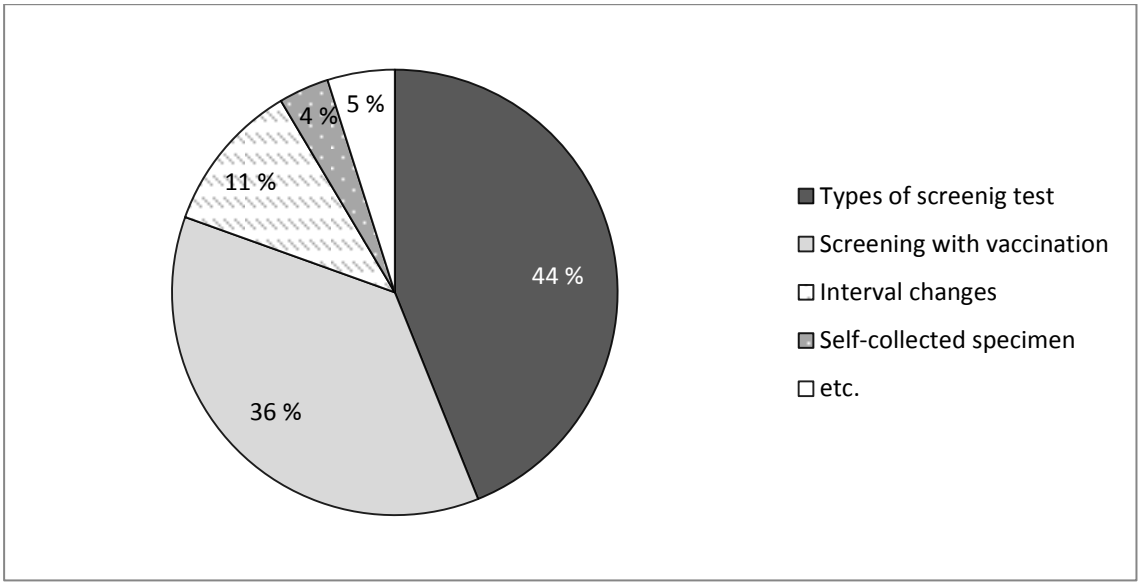


Types of interventions

The included studies explored cost-effectiveness of various screening strategies or combination of screening and vaccination. 36 studies (44% of all) examined the cost-effectiveness of different types of cervical screening test (Pap, LBC and HPV test). Among them, 25 investigated the feasibility of adding HPV triage to the conventional cytology

screening (Pap or LBC) while 11 studied which types of test is the most cost effective when it is implemented in a limited resource setting . There were 30 (36%) studies, which explored the cost-effectiveness of screening in combination with HPV vaccine. Nine (11%) studies compared different intervals of screening. Three (4%) studies explored the feasibility of introducing HPV test using self-collected specimens. Additionally, there were four other studies; those articles were on management alternatives for women with low grade abnormalities [55], comparison of same type of screening provided by different health care facilities [54], cost effectiveness of adding speculoscopy into conventional Pap screening [56] and cost effectiveness of cervical screening in a emergency room at the public hospital [57].

Figure 5. Interventions of the studies



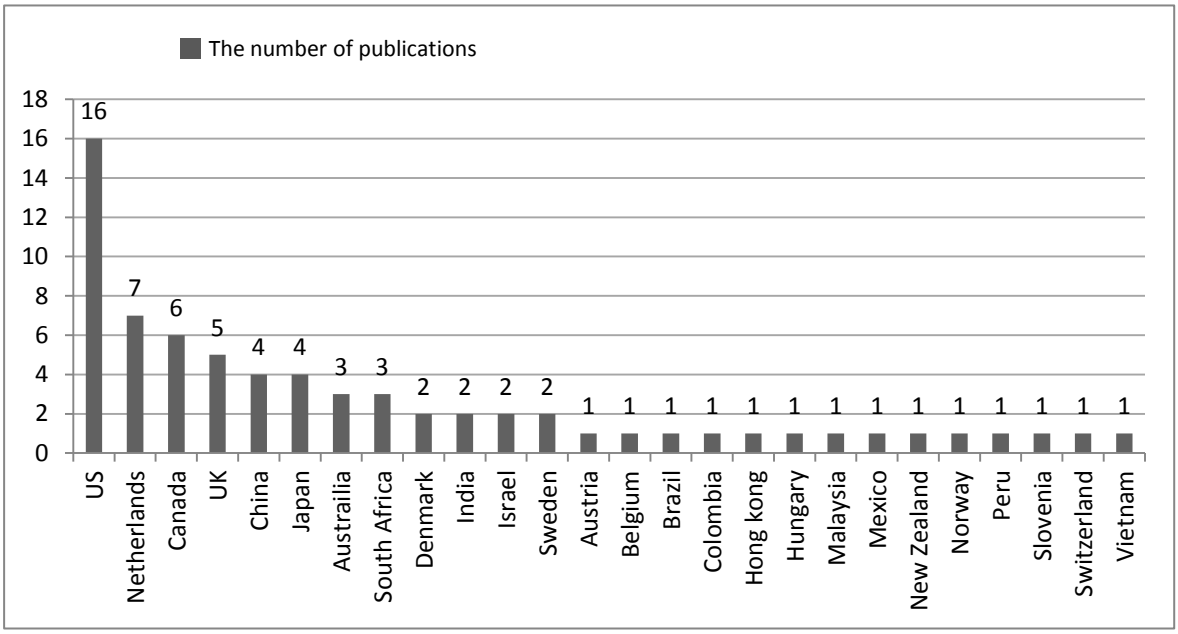
Country of study

There were 8 multi-regional studies and 74 country level studies. Multi regional studies covered screening policies of different countries. The most extensive study in terms of region was the cost effectiveness of cervical cancer screening in a global perspective [58]. Two of multi-regional studies were about different screening policies of European Union (EU), while rests of them studied countries with limited resource settings.

Figure 5 provides the number of publications in terms of the country as a result of analyzing 74 country level studies. 28 countries were subjects of the studies, and 10 studies did not match the country of study and the place where it was conducted. The United States was the most often studied (N=16), followed by the Netherlands (N=7), Canada (N=6), the United

Kingdom (N=5), Japan (N=4) and China (N=4, including Taiwan). According to the country classification of World Bank, the number of studies investigated the middle income countries were 10, those studies explored high income countries was 17 and there was one study investigated low-middle income country.

Figure 6. Country of the study



Study population

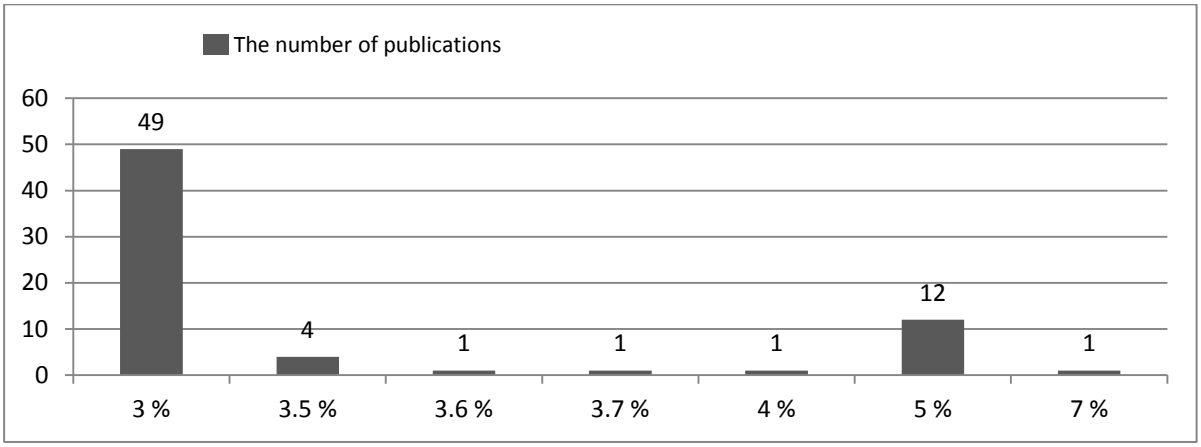
Unlike most studies which examined general female population, there were 19 studies (23%) explored specific population such as women who received abnormal test results from a previous screening (N=6) or cervical cancer patients (N=1). Four studies conducted in US chose low income, elderly or ethnical minority for a study population [57, 59-61]. The other studies investigated a cervical screening of HIV infected women (N=3), women in military services (N=2), kidney transplants (N=1) and pregnant women (N=1).

Discounting

Discounting is a technique to put costs and benefits occurred in the different time points on the same base [62]. Cost effectiveness studies of prevention program are known to be sensitive to the discounting rate because many of the benefits from the cervical screening occur in the future. Based on the result, 92% of studies (N=76) discounted the future costs and benefits (extended life years or QALY). The discount rate was 3-7% varied between the

studies. Among the studies, the discount rate of 3% was the most preferred (71% of studies) followed by 5%. Five studies applied differential discounting to costs and benefits respectively: Canadian and Australian study (5%, 3%), Belgian (3%, 1.5%) and Netherland (4%, 1.5%). Two studies applied three different discount rates to both costs and effects in consideration of the impact of discounting on the cost effectiveness [63, 64].

Figure 7. Discount rate



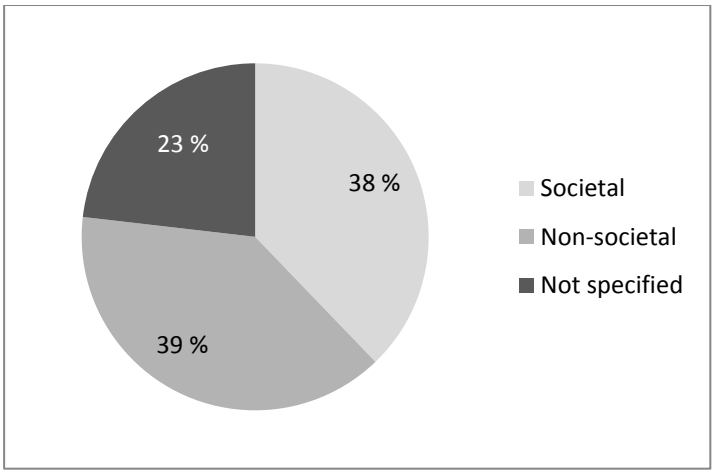
3.2 Non-Health-Care Costs of Cervical Cancer Screening

Despite of the relative importance of non-health-care costs in screening program, only 40 (49%) articles included non-health-care costs, and the other 42(51%) articles ignored its inclusion. Even among the studies including non-health-care costs, they showed varied interpretations about inclusion criteria. The distinction between time and productivity cost introduced by the US panel was not properly understood in practices.

Perspective of the Study

Explicit and clear specification of the perspective is recommended for clear understanding of the analysis [31]. There were 31 (38%) studies adopting a societal perspective. Among them, four studies chose double perspectives (societal and non-societal perspectives), and presented outcomes for each perspective. One study reported an 'adjusted' societal perspective which did not account for productivity costs. Among the other 51 studies, which did not choose societal perspective, 29 chose a perspective of the health care system. 19 (23%) studies did not specify which perspective they chose for the study. It was especially difficult to interpret studies with a lack of explicit perspective as to what kind of costs was included in the analysis. Two studies chose a perspective of Ministry of health and one chose perspective of government in general.

Figure 8. Perspective of the studies



Perspective	N
Societal	31
Health care system	29
Ministry of Health	2
Government in general	1
Not specified	19
Sum	82

Nomenclature for classification of costs

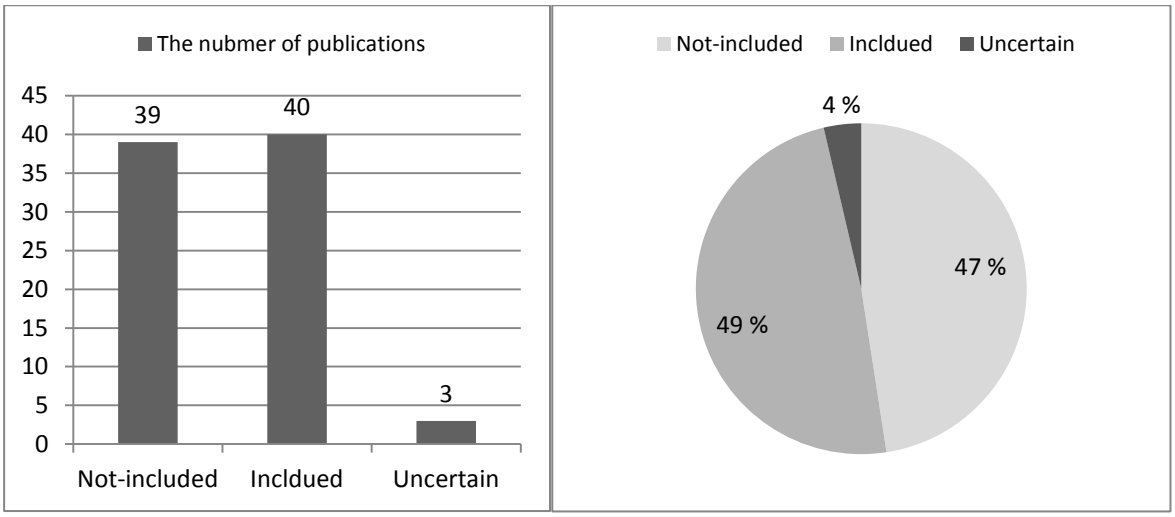
The way of classifying costs into groups differed across studies. A dichotomous taxonomy (indirect versus direct costs) was used in 20 (24% of total publications) studies, most of them published in the 2000s (N=18). There were 33 (39%) studies, which classified costs into more than two categories. The ‘direct medical’ cost was the most preferred term referring to the costs incurred in a health care sector. It denotes all components of costs occurred in test, specimen transport, laboratory process, staff time, office visit and treatment of cancers including treatment for complications and hospitalization. The term ‘health care cost’ was also used in the same meaning of ‘direct medical cost’. In terms of non-health-care costs, ‘Direct non-medical’ or ‘indirect’ costs were often used to refer to the time and travel costs or sometimes costs associated with productivity loss due to morbidity and mortality. 29 studies did not classify the costs with the conventional criteria. These studies, instead, used individual name of costs identified by test/treatment procedure, or progress of disease. One article unusually classified the costs by the budgetary authorities (testing, physicians, inpatient, and outpatient services) [65].

In the following, the terms defined on page 12-15 will be used.

Inclusion of non-health-care costs

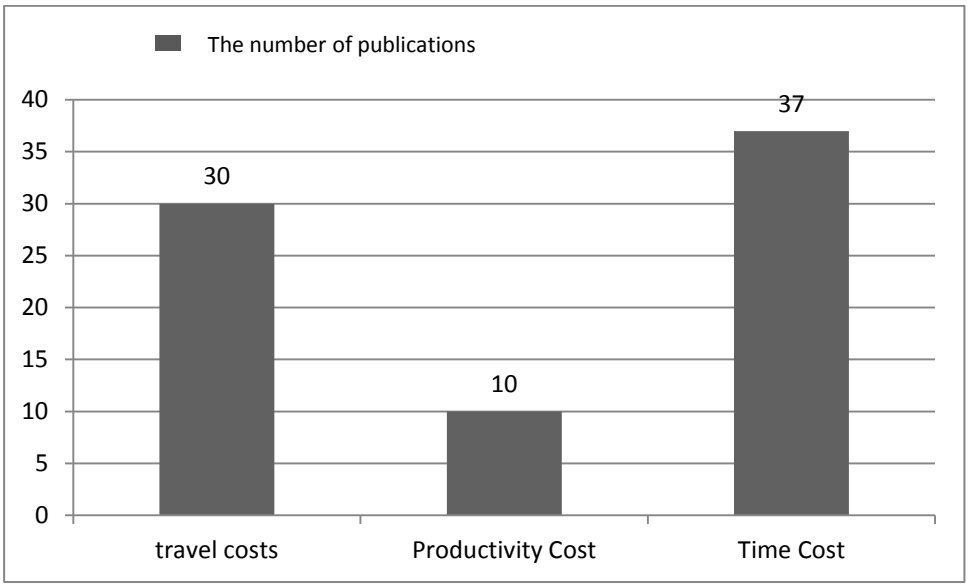
Of the 82 included articles, 40 (49 %) articles included at least one type of non-health-care costs (travel, time and productivity costs). Three articles were unavailable for evaluation because they did not specify the perspective of the study nor their cost classification. The inclusion of non-health-care costs increased over the years. Studies conducted in the Netherlands had a high proportion (six out of seven) with inclusion of non-health-care costs.

Figure 9. Inclusion of non-health-care costs



The extent of inclusion of non-health-care costs varied even in the studies using the same cost classification. Among the 40 articles including non-health-care costs, 37 (93%) included time costs, 30 (75%) included travel costs, and 10 (25%) included productivity costs. It reflected that researchers have varied interpretations of cost components needs to be included into non-health-care costs. Most of articles included time and travel costs only, and very few studies took productivity costs into account. Only four articles included all types of non-health-care costs, of which three articles were from the same lead author [55, 66-68].

Figure 10. Inclusion of non-health-care cost components



Identification and estimation

This of the following is a result of the study of 40 articles including at least one type of non-health-care costs.

Travel costs

In published articles, travel cost was defined as a cost for patients to commute to the clinical site for a screening, diagnosis and further treatments. Most of studies measured round trip-transportation to the clinical site made by women being subjects of care with an assumption that women used public transportation. Only one study included travel costs of a companion [55].

Measurement and valuation of traveling cost varied. Travel costs were measured by the level of health care facilities, or purpose of traveling, whether it was aiming at screening, diagnosis, further treatment for detected abnormalities, or treatment for advanced cervical cancer. The latter travel cost, for cancer treatments, was much higher than for other types of care. In almost all studies, travel expenses for round trip were used to value the travel costs. Most of travel cost data stemmed from the study's own patient level costing, survey or other literatures. The data extracted from other literature were extrapolated using country specific data referring to the density of health care facilities, percentage of urban/rural population and road infrastructure. In the cost table provided by the studies, travel costs were reported separately or in a combination with time costs.

Time costs

Time cost mostly denoted patients time spent for traveling to and from the clinical site, waiting, and receiving care. It included all visits of patients in screening, diagnosis, and treatment for complications and hospitalization. The variation in time costs was greater for travel than for time spent in testing or treatment. Depending on the availability of transportation and accessibility to the health care facilities, travel time was varied from 30 to 230 minutes per episode of screening. In countries with only few health care facilities for treating advanced cancers or low population density, travel times were greater. The waiting time was also varied from 15 to 90 minutes. As a result, a total time (including 2 way round trip, waiting and receiving care) spent per episode of screening was varied from 55 (US) to 325 (Kenya) minutes. However, even within a studies examining same country (US), the time

variation appeared [56, 69]. The time data mostly originated from patient level costing or the literature. One study simply applied an assumption made by the authors [56].

All studies employed a wage rate to value the time costs which indicates that human capital approach is widely accepted. However, each study used different types of wage rates: average wage rate (N=7), average gross income adjusted for social benefits (N=1), median wage rate (N=3), minimum wage (N=2), salary varying by military rank and adjusted for fringe benefits such allowable housing costs (N=1). One study used both average and minimum wage varying employment status of women [70]. A number of studies adjusted wage rate for the characteristics of the each groups of population which varied by age, income level, a place of work (public/private or formal/informal), and employment rate. Unusually, one study valued time costs in terms of utilities [71]. This study assumed that the utility of patients is likely to decrease due to the anxiety and inconvenience from spending time to care. Reporting of time cost also varied by study; some studies measured time spent in traveling, waiting and receiving screening separately, while others measured in an aggregated form.

Productivity costs

To some extent, the definition of productivity cost used in studies was overlapped with time cost. Unlike the time cost which was almost similarly used between the studies, researchers had varied interpretations about the productivity cost (mostly referred to production loss or indirect costs). In most of guidelines, productivity cost is defined as production loss resulting from morbidity and mortality. Some studies, however, defined it as "production loss absence from work due to complications and after effect"[55] or the value of time that "a patient is either physically incapable of or otherwise unavailable to perform employment related activities" [69]. A cost benefit analysis (CBA) defined it as discounted current value for future earnings, labor day loss for treatment [54].

In valuation of productivity costs, assigning wage rate to the value was most commonly used (N=5 among 11 studies). However, each study used different types of wage rate: median (N=2), average (N=2), salary (N=1). The time away from work due to illness was not specified in the articles. Only, Taylor and co-workers (2000) assumed that it takes 1.6 days per year for treating Low-grade Squamous Intraepithelial lesion (LSIL) and High-grade Squamous Intraepithelial lesion (HSIL), while cervical cancer requires 35.4 days per year for treatment [56]. There were no studies including friction costs into costing. With regards to

the incorporation of the productivity costs, three out of ten studies described explicitly that productivity costs to the individuals is captured in terms of 'reduced utilities' [64, 72, 73]. Some studies recognized productivity cost as real costs and put them on the numerator of ICER [55, 56, 74]. Three studies did not specify the methods in valuing productivity costs [66-68].

The magnitude of non-health-care costs

There was considerable variation in terms of the proportion of non-health-care costs of total screening costs. No study reported all types of non-health-care costs including time, travel, and productivity cost. The results in terms of the magnitude of non-health-care costs are, therefore, limited to the proportion of time and travel costs to the health care costs. The time and travel cost accounted for 0.04-76% of total costs per screening (pap: 0.12-76%, HPV test: 0.05-42%). In terms of its ratio to the health care costs, two studies reported 0.17: 1 and 1.47:1 respectively [75, 76].

It is uncertain whether the proportion of non-health-care costs is greater for the screening itself than the subsequent treatment of cervical cancer that is not prevented by the screening. The study conducted by Praditsitthikorn and co-workers (2011) demonstrated that the proportion of non-health-care costs was greater for the cancer treatment than the screening *per se* [76]. Other studies found that the time and travel costs accounted for 5-48% of cancer treatment costs [77, 78]. Here, the ratio of these types of non-health-care costs to health care costs was 1: 1.17-4.5 with no discounting (1: 0.2-1.19 with discounting).

Table 4. Proportion of time and travel costs to health care costs

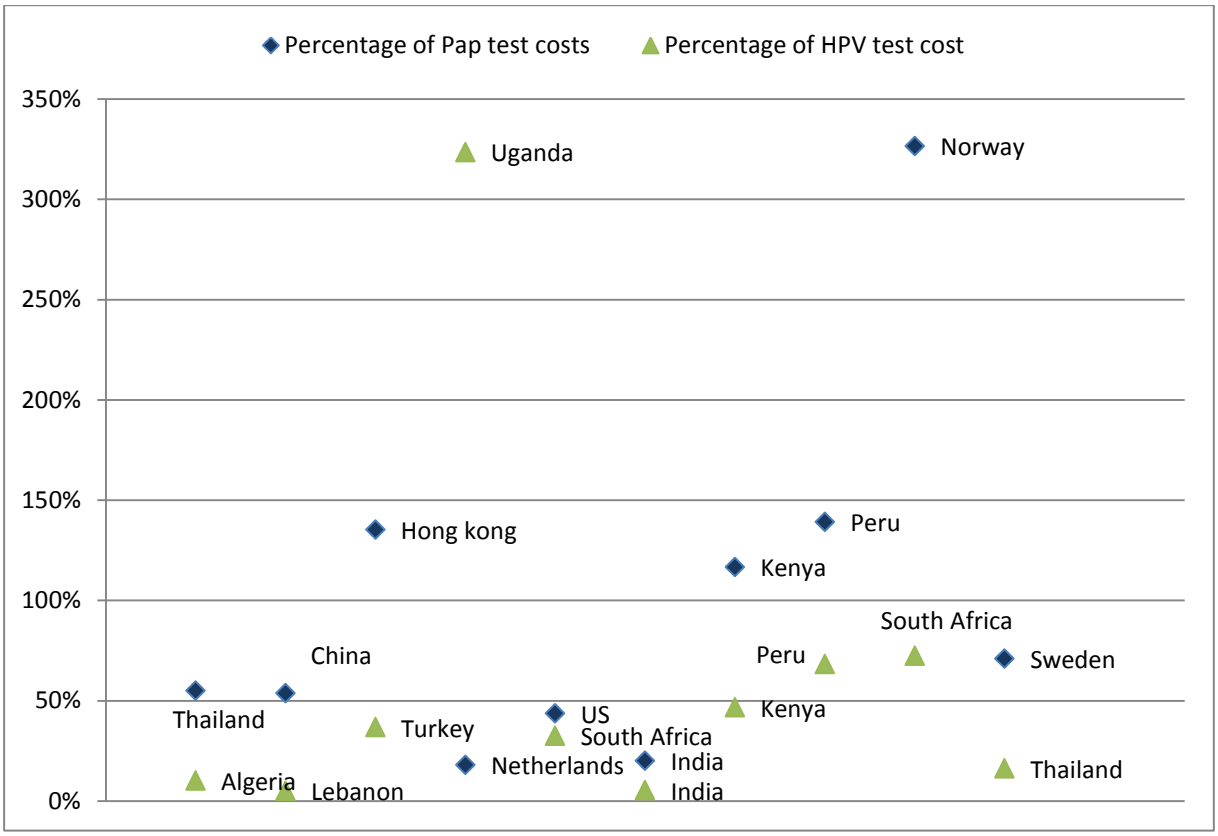
	Screening cost	**Cancer treatment cost**
Proportion of non-health-care costs (time and travel)	0.04-76%	5-48%
Ratio of non-health-care costs (time and travel) to health care costs	0.2-1.47 : 1	1.17-4.5 : 1

Figure 11 presents the time and travel costs as a percentage of the health care costs in screening (costs of the tests, office visits and laboratory costs) excluding cancer treatment

costs. The percentage ranged from 18% to 327% (time cost: 5%- 139%, travel cost: 1%-106%) of the health care costs per pap screening. Norway reported the biggest estimates (327%) [79], while the smallest was reported in Netherlands (18%) [71, 80].

In the studies which explored HPV test of low and middle income countries, the time and travel cost was amounted to 5-324% (time cost: 10 -285 %, travel cost: 0-52%) of the health care costs per screening. Due to the geographical disadvantage in rural areas and low accessibility to the health care facilities, the time spent for traveling and waiting was the largest in Uganda (324%). In five studies, the magnitude of time and travel costs was greater than health care costs for screening.

Figure 11. Time and travel costs as a percentage of health care costs



Impact of non-health-care costs

Among the 40 studies including non-health-care costs, 19 presented sensitivity analyses of costs (screening, diagnosis and treatment of pre-invasive lesions and cancer). Among them, 12 (63%) were sensitive to variation in at least one type of costs. Six studies conducted sensitivity analysis to determine whether the inclusion of non-health-care costs would affect

the results of the study. One of studies showed that inclusion/exclusion of non-health-care costs would reverse the rankings of the strategies [70]. Goldie and co-workers (2005) demonstrated that when they included the productivity costs from cancer treatment, screening became cost saving or more cost effective. In their study, countries where non-health-care costs accounted for most of screening costs, the incremental cost effectiveness ratio (ICER) was, as expected, more sensitive to variation in the non-health-care costs.

The results of the other five studies were robust, but the ICERs were influenced by the inclusion of non-health-care costs. Only three studies were available to estimate the effect of inclusion/exclusion of time and travel costs on the ICER [55, 74, 75]. When including them, the ICER decreased by 21-41% on average.

4 DISCUSSION

Like other review articles [81-84], this study also revealed that there is considerable variation in the guidelines for economic evaluation of health care programs (health interventions) and in the identification, measurement and valuation of non-health-care costs in practices. The non-health-care costs have tended to be ignored, but our findings indicate non-health-care costs may represent a considerable proportion of the total program costs, and omitting them will consequently bias the results.

Strengths and limitations of the study

To the best of our knowledge, this is the first study to review the costing practices of non-health-care costs within the context of screening for cervical cancer. Inclusion of non-health-care costs has been mainly concerned in cost-of-illness studies (COI) [85-89], while relatively little concern has been directed to full economic evaluations (CEA/CUA/CBA). This study differs from other studies in that it solely focused on non-health-care costs in full economic evaluations. By limiting the subject of study to cervical cancer screening, our study focused on methodological disparities within studies for a similar condition (ex. population, comparator, research question). The systematic way of searching contributed to the finding of as many relevant articles as possible. In terms of generalizability, this study has meaningful findings concerning inconsistent treatments over the non-health-care costs in the published articles.

This study, however, has several limitations. First, even if there was partial assistance from the thesis supervisor, only one person scrutinized all titles, abstracts and contents. As a result, individual judgment could have been more involved in the data collection, which may lead to selection as well as information bias. Second, due to the limited number of words in most published papers, many articles lacked details so that the authors' original costing may have been misinterpreted. In case where authors did not provide any details on how they measured and estimated costs, some pieces of information had to be omitted in our analysis. Third, by restricting languages only to English, 14 articles were excluded due to the language restriction. This may have limited the number of informative studies.

Study findings

Discrepancy between theories and practices

Our finding demonstrates discrepancies between the theories and practices. Researchers may prefer more simple and practical methods instead of theoretically valid ones. In this sense, theory seems to be ahead of practice. Non-health-care costs have been ignored in a number of studies. Concerning the nomenclature of costs, a number of studies still classify costs into direct and indirect costs [55, 56, 66-69, 73, 74, 90, 91], which have been recommended against in the literatures. In valuation of productivity and time costs, no study adopted the friction cost approach, while human capital approach was still used despite of the theoretical and ethical controversies.

In terms of measurement, time loss from unpaid informal caregivers (ex. family, relatives) was not considered. Omission of such cost may underestimate the societal resources consumed in treatment of cervical cancer, particularly in a country where public social services for ill people are not well established. In such countries, care for seriously ill patients is largely dependent on those unpaid informal caregivers so that inclusion of the time or productivity cost of unpaid informal care giver would make cervical cancer screening more socially favorable.

Furthermore, loss of leisure due to the patients' or informal care givers' time spent for treatment or during illness was not captured in any of the studies. Theoretically, this time which otherwise could have been spent on leisure if a patient were healthy, should have counted as opportunity costs of treatment, but it was not reflected in published studies.

Inconsistency in costing of non-health-care costs

Our study showed that most of studies included time and travel costs only, and very few studies included productivity costs. Because our study distinguished time costs from productivity costs, it may be seen that the productivity loss associated with health interventions is less considered in included articles. However, such an interpretation is partially incorrect as productivity loss to individuals has been captured in time costs.

Whether the distinction between time and productivity is accurate is a controversial issue, as time spent for treatment or during illness may be productive time to the working population.

This time has been recognized in relation to the productivity loss, so that it is not easy to conceptually distinguish the time cost from productivity cost. With regards to the confusion, the US panel comments that time should be understood as real input of individuals to the treatment, and therefore it should be counted as real costs, while productivity loss to individuals should be counted in lost utilities [8, 23, 35, 41, 42]. The Erasmus group, however, claimed to such argument in that the US panel's approach does not comply with the principles of societal perspective [45].

In the published articles, different authors showed varied interpretation associated with the distinction between time and productivity costs. Among the included studies in our analysis, time cost was first included and distinguished from productivity costs in 1999 [64]. The study followed the US panel's recommendation and counted time costs as real costs, while productivity costs to individuals were assumed to be lost utilities in the denominator of the ICER. However, the study did not describe how they treated productivity costs to the employers and society. Some later published studies even omit the descriptions on how they dealt with productivity costs to individuals.

The inconsistency over the valuation of non-health-care costs seems to be country specific. Depending on the women's labor participation rate and industrial structure of the studied country, researchers adjusted their valuation of non-health-care costs. For example, in developing countries, large proportions of women are unemployed or engaging in work in informal sectors. The studies exploring such countries tend to use minimum wage or agricultural wage as a proxy for the productivity losses. For the developed countries, the average wage rate is often used with adjustment of the amount of social benefits (allowances for sick leave) and high income tax. In a country such as Norway, high income taxes are imposed to the working population, and therefore ignorance of the tax effect could affect the value of women's time and productivity costs.

Impact of including non-health-care costs

The magnitude of non-health-care costs and its impact of inclusion varied significantly among studies. When including all types of non-health-care costs, the ICER was reduced by 22-41%. However, we cannot generalize the statement that inclusion of non-health-care costs necessarily reduces ICER.

The formulation of ICER of cervical cancer screening is as below.

$$(\text{Screening costs } (\Delta H + \Delta NH) - \text{averted treatment costs } (\Delta H + \Delta NH))/ \text{ Effect}$$

ΔH: Increase in health care costs,

ΔNH: Increase in non-health-care costs

Assuming that effect is given, the cost effectiveness of cervical screening is dependent on the trade-off between screening costs and averted treatment costs. If non-health-care costs in screening are greater than that of treatment costs, ICER can be greater. For example, if health intervention requires large amounts of time for traveling, waiting and receiving care as well as travel costs, health interventions become less cost-effective. Moreover, if productivity of patients is low valued, like in developing countries, so that the intervention do not avert large amount of productivity costs, its inclusion may increase ICER.

The proportion of non-health-care cost in health intervention was country specific. For example, the estimation of time cost is a function of wage rate and time for traveling, receiving screening and treatment. Relatively greater time costs were reported in the studies of Norway and Rwanda. However, main cost driver is different between two countries. In case of Norway, the high wage rate drove up the time costs while long traveling time was the main cause of increasing time costs in Rwanda.

Furthermore, it was evident that fewer visits reduced the time and travel cost, but no study provided a magnitude of its effect when extending screening intervals. Only one study identified that screening costs are increasing less than proportionally with the number of examinations [80]. Another study found that when a longer period of time is applied to the study, inclusion of non-health-care costs lowers the ICER [74]. This is because greater amounts of productivity costs are averted assuming that the effect of treatment (in our study, preventive effect) lasts longer.

Distributional consequences

Since monetary value is assigned to the time and productivity of individuals, inclusion of non-health-care costs will unavoidably have distributional implications. An ethical concern surrounding inclusion of non-health-care costs has been raised since it advantages health interventions targeting employed people. When including non-health-care costs, health intervention for the people with higher wage *rates – ceteris paribus* - becomes more preferable than those for others. This is because the greater amount of productivity costs is saved, the more cost effective the outcome is.

Our study reconfirms that wage rate is most commonly used in valuation of time and productivity in practice (53% of studies including non-health-care costs). Use of wage rates has a potential risk to bring current discrimination and inequality problem of market income into the decision making in health care. Bidus and co-workers (2006) provided different estimates of time costs varied by rank in military service [69]. Based on the estimates, the value of time for the women at the highest rank was 250% higher than the lowest. Furthermore, time and productivity losses for women in developing countries are more underestimated than those from developing countries. Three studies used minimum wage to value the time and productivity loss of women in developing countries, which is much lower than medium or average wage [70, 92, 93]. Practical limitation can be one of reasons for inducing underestimation since it may not be easy to value the time and productivity of women doing domestic chores in rural area.

Discrimination is also appeared when valuing time costs for people having different occupations. A study conducted by Goldie and co-workers (2005) varied wage rate by the types of employment, whether the women working in informal employment (without secure contracts, worker benefits, or social protection) or formal employment [70]. As a result, the time cost for the formal employed was greater than the others. Such estimate indicates that economic evaluation values more on the time for people who have more money and secured job.

Quality of reporting costs in the economic evaluation

Even though the study complies with the standardized method, low quality of reporting raises a question of validity of the study. Many of studies showed low adherence to the guidelines in

presentation of cost data and costing methods. First, the perspective of study needs to be stated explicitly, so that the readers clearly identify what kinds of costs are considered into the study. However, in our study, 23% of all included articles did not state the perspective of study, which makes more difficult to identify included costs. If a study did not use the proper nomenclature (ex. direct non-medical, time cost, etc.) either, it becomes difficult to identify the included cost components of the analysis. Second, many studies did not state the costing methods in an explicit manner so that it was more difficult to identify the methods of measurement and valuation of relevant costs. Third, guidelines suggested reporting unit and value of cost respectively, but many of studies did not comply with this requirement. It made more difficult to identify which value was used to estimate the costs. Fourth, guidelines state that researchers should provide further justification concerning their inclusion or exclusion of non-health-care costs. However, no study explicitly specified their reason for including/excluding such costs.

Policy recommendation

Since the dispute between the US panel and Erasmus group in the late 1990s, the controversies related to the inclusion of non-health-care costs have not been settled. The discussion was an attempt to standardize methods in economic evaluations, but there was no visible improvement in this area since then. In this context, our study empirically indicates that it is still room for improvement in defining, estimating and incorporating non-health-care costs.

For the improvement, the development of standardized form is one of solutions. Here, major journal could play an important role in leading theoretical discussion for standardization, and ensuring the high standards of reporting by calling for more adherences to the standardized form when publishing the studies. The journals need to put an effort to develop agreed definition of costs and its measurement; these should be specified and detailed enough to apply to different study setting (country, disease, health intervention and population examined). They should mandate researchers to provide clear description of included costs and justification of researcher's determination. Unclear language in guidelines may lead to varied interpretations of researchers. Therefore, more specified guideline is required to reduce inconsistency which appeared in costing methods. Most of all, more research on

inconsistencies within economic evaluations would contribute to developing theoretically correct and practically applicable guideline.

Concerning distributional implication in valuation of time and productivity, researchers are in dilemma between their responsibility to reflect economic reality and the desire to support equitable resource allocation. It is inevitable to include ‘productivity’ of patients since it is fact that health intervention improves individual life as well as their working ability. Therefore, time and productivity cost need to be separately reported so that the decision would be left to the decision makers and the society.

5 CONCLUSION

In 1992, Jefferson stated, “there is a long way to go before economic evaluations can be regarded as good enough to justify their use in decision making”[94]. Even though many attempts have been made to standardize methods as well as reporting, the findings of this study indicate that Jefferson still may have a point. To resolve the issue, we need to look back to the basic principles of economic evaluations. Definition of certain terms needs to be clarified; inconsistency in costing methods should be avoided; standardized costing methods should be discussed in consideration of distributional concern. Furthermore, researchers themselves should be aware of the possible implications of the analytic choices they made. As long as uncertainty associated with impact of inclusion/exclusion of non-health-care costs remains, researchers should report non-health-care costs separately so as to ensure the transparency of the study. Above all, an attempt to standardize and to justify the methods we use in the analysis need to be prioritized in order to keep transparency and comparability across studies.

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